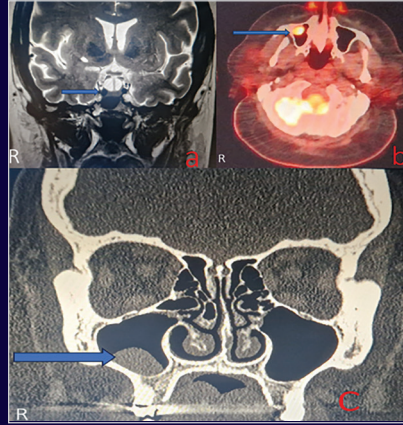


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34093 İstanbul, Türkiye

Phone: +90 (530) 177 30 97 / +90 (539) 307 32 03

E-mail: info@galenos.com.tr/yayin@galenos.com.tr

Web: www.galenos.com.tr

Publisher Certificate Number: 14521

Publication Date: September 2026

E-ISSN: 2667-7474

International scientific journal published quarterly.



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Turkish Archives of Otorhinolaryngology is indexed in PubMed, PubMed Central, Web of Science (Emerging Sources Citation Index), Scopus, DOAJ, ULAKBIM TR Index, EBSCO, Embase, GALE, J-Gate, CNKI, Ideonline, Sudoc and ProQuest.

The journal is published online.

Owner: Turkish Otorhinolaryngology Head and Neck Surgery Society

Responsible Manager: Taner Kemal Erdağ



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Turk Arch Otorhinolaryngol 2026; 64(3): 137-143

DOI: 10.4274/tao.2026-4-9

Prospective Exploratory Evaluation of Audiovestibular Function in Patients Receiving Oral Isotretinoin Using Audiometry and Videonystagmography

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Abstract

Objective: To prospectively evaluate possible audiovestibular changes associated with short-term oral isotretinoin therapy using pure-tone audiometry and selected videonystagmography (VNG)-based vestibular assessments.

Methods: Participants older than 18 years receiving oral isotretinoin therapy constituted the study group. All participants underwent detailed otorhinolaryngological examination, along with pure-tone audiometry and tympanometric analysis, prior to treatment initiation and after three months of therapy. Vestibular assessment included VNG-based spontaneous nystagmus analysis, gaze testing, positional testing, and oculomotor evaluations.

Results: Thirty-three patients were included in the analysis (11 males and 22 females). The median age was 20.0 years (interquartile range: 3.0). Comparison of pre- and post-treatment audiometric data demonstrated no significant changes across frequencies ranging from 250 to 8000 Hz, nor in pure-tone average, high-frequency average, or low-frequency average pure-tone average, high-frequency average, or low-frequency average values. A significant change was observed at 6000 Hz in the right ear; however, this finding was not clinically meaningful and likely reflected minor distributional variation between paired measurements. Selected VNG-based vestibular assessments, including spontaneous nystagmus, gaze, positional, and oculomotor testing, remained within normal limits throughout the study period.

Conclusion: Within the limitations of this exploratory pilot study, short-term oral isotretinoin therapy did not demonstrate clinically significant abnormalities in audiometric measurements or selected VNG-based vestibular assessments.

Keywords: Acne vulgaris, isotretinoin, audiometry, vestibular function tests

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Cite this article as: Yüksel F, Yavuz C, Kahraman ME. Prospective exploratory evaluation of audiovestibular function in patients receiving oral isotretinoin using audiometry and videonystagmography. Turk Arch Otorhinolaryngol. 2026; 64(3): 137-143

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Received Date: 11.06.2026

Accepted Date: 03.08.2026

Epub: 22.09.2026

Publication Date: 30.09.2026



Introduction

Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit with a multifactorial pathogenesis, involving increased sebum production, follicular hyperkeratinization, microbial proliferation, and downstream inflammatory responses (1). The condition most commonly involves the face, neck, chest, and back, and frequently affects adolescents and young adults, leading not only to cosmetic concerns but also to significant psychosocial burden. Therefore, early and effective therapeutic intervention is essential to minimize the risk of permanent scarring.

Oral isotretinoin remains one of the most effective therapeutic options for acne vulgaris due to its ability to target multiple pathogenic mechanisms simultaneously (1). Although initially reserved for severe nodulocystic acne, its use has expanded to include selected moderate cases with appropriate monitoring and individualized dosing strategies. Despite its well-established efficacy, isotretinoin therapy is associated with a broad spectrum of adverse effects, including mucocutaneous dryness, epistaxis, musculoskeletal complaints, mood alterations, visual disturbances, and teratogenicity (2-5). Less frequently, neurological and sensory symptoms such as dizziness, tinnitus, nausea, and vertigo have also been reported (2,6,7).

The relationship between isotretinoin and audiovestibular dysfunction remains controversial. Previous studies investigating auditory effects have yielded inconsistent results, while vestibular data remain extremely limited (8-11). Furthermore, vestibular adverse effects may be underrecognized because mild or transient symptoms are often evaluated subjectively and objective vestibular testing is rarely performed.

Videonystagmography (VNG) is a diagnostic modality utilized in the assessment of vestibular function, enabling objective recording and analysis of eye movements through infrared-based video technology (12). By tracking pupillary movements with high precision, VNG provides real-time evaluation of oculomotor responses and allows for subsequent data storage and detailed analysis. Unlike traditional methods, VNG is not significantly influenced by ambient lighting conditions or certain ocular limitations, and it offers the additional advantage of detecting torsional eye movements. In clinical practice, this capability facilitates the diagnosis of vestibular disorders, including benign paroxysmal positional vertigo (12). In addition, pure-tone audiometry provides objective assessment of cochlear function and hearing thresholds.

To date, only one study has evaluated vestibular function during isotretinoin therapy using the video head impulse test (vHIT) (8). In addition, literature regarding VNG-based vestibular assessment during isotretinoin treatment remains

scarce. Therefore, this prospective exploratory study aimed to investigate possible subclinical audiovestibular alterations during short-term oral isotretinoin therapy using audiometry and selected VNG-based vestibular assessments.

Methods

Thirty-three patients older than 18 years who presented to the Dermatology Outpatient Clinic of Konya City Hospital with a complaint of “acne vulgaris” and were started on oral isotretinoin (0.5-1 mg/kg/day) constituted the study population (13). The study was designed as an exploratory pilot investigation evaluating possible audiovestibular alterations before and after isotretinoin exposure within the same cohort. All participants received detailed information regarding the study protocol, and written informed consent was obtained from all individuals prior to participation. Ethical approval was granted by the Necmettin Erbakan University Research on Non-Drug and Medical Device Products Ethics Committee (approval no: 2021/3484, date: 05.11.2021). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Participants with documented conductive or sensorineural hearing loss, diagnosed vestibular disorders, abnormal otoscopic findings, neurological or psychiatric disorders, systemic diseases potentially affecting vestibular function, or a history of otologic surgery were excluded from the study.

All participants underwent comprehensive otorhinolaryngological examination before testing. Hearing evaluation was performed using a clinical audiometer (Interacoustics AC 40, Assens, Denmark) and tympanometry device (Interacoustics AT 235, Assens, Denmark). Air- and bone-conduction thresholds were assessed at frequencies ranging from 250 to 8000 Hz. Tympanometric findings and acoustic reflex responses were recorded. Pure-tone average (PTA) was calculated using air-conduction thresholds at 500, 1000, 2000, and 4000 Hz. High-frequency average (HFA) values were calculated from 4000, 6000, and 8000 Hz, whereas low-frequency average (LFA) values were derived from 250, 500, and 1000 Hz. Audiometric evaluations were performed before treatment initiation and repeated at the third month of therapy.

Participants were questioned regarding vestibular-related symptoms, including dizziness, vertigo, imbalance, tinnitus, nausea, and vomiting, at baseline and during follow-up. Bedside vestibular examination included assessment of spontaneous nystagmus, the bedside HIT, head-shaking nystagmus, tandem gait, the Fukuda stepping test, the Romberg test, and evaluation for skew deviation.

Selected VNG-based vestibular assessments were performed using a VNG system (Micro Medical, Interacoustics A/S, VisualEyes 505, Assens, Denmark) before treatment initiation

and after three months of oral isotretinoin therapy. The VNG protocol included spontaneous nystagmus analysis, gaze testing, positional and positioning tests comprising the Dix-Hallpike maneuver, straight head-hanging maneuver, and supine roll maneuver, as well as quantitative oculomotor testing.

The quantitative oculomotor test battery included smooth pursuit, saccadic, and optokinetic evaluations. Smooth pursuit gain was recorded separately for rightward and leftward tracking at target frequencies of 0.2 and 0.4 Hz. Saccadic testing included direction-specific measurements of latency (ms), velocity ($^{\circ}$ /s), and accuracy (%). Optokinetic gain was assessed separately for rightward and leftward stimulation at a stimulus velocity of 20° /s. Because binocular eye movements are physiologically conjugate, the values recorded from the right and left eyes were averaged to obtain a single representative value for each stimulus direction and participant. Directional symmetry of smooth pursuit responses was evaluated by comparing rightward and leftward gain values in each assessment session. Caloric testing was not included in the predefined study protocol, which was limited to a focused non-invasive vestibular test battery.

Statistical Analysis

Descriptive statistics were used to summarize the demographic, treatment-related, audiometric, and VNG findings. The distribution of continuous variables and paired differences was assessed using the Kolmogorov-Smirnov and the Shapiro-Wilk tests. Categorical variables were expressed as number (n) and percentage (%). Because several audiometric variables were not normally distributed, these data were presented as median and interquartile range (IQR), and pre-treatment and third-month measurements were compared using the Wilcoxon signed-rank test.

Quantitative VNG parameters were presented as mean $\pm$ standard deviation together with minimum and maximum values. Pre-treatment and third-month VNG measurements were compared using the paired-samples t-test when the distribution of paired differences was normal and the Wilcoxon signed-rank test when the normality assumption was not met. Directional symmetry was evaluated by comparing rightward and leftward smooth pursuit gain values within each assessment session using the paired-samples t-test or the Wilcoxon signed-rank test, as appropriate. Given the exploratory nature of the study, no formal adjustment for multiple comparisons was applied; therefore, isolated statistically significant findings were interpreted cautiously and in conjunction with their clinical relevance. Statistical analyses were performed using the Statistical Package for the Social Sciences software, version 22.0 (IBM Corp., Armonk, NY, USA). All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

The study included 33 patients (11 males, 33.3%; 22 females, 66.7%). The median age was 20.0 years (IQR: 3.0). Based on the Global Acne Grading System, none of the patients were classified as stage 1, whereas 8 (24.2%) were stage 2, 18 (54.5%) were stage 3, and 7 (21.2%) were stage 4. Regarding treatment dosage, 17 patients (51.5%) received 30 mg/day, 15 (45.5%) received 40 mg/day, and 1 patient (3.0%) was treated with 50 mg/day isotretinoin (Table 1).

Otorhinolaryngological examination findings were unremarkable in all participants. Audiological assessments were performed separately for the right and left ears. Tympanometric measurements were within normal limits in all cases, and speech discrimination scores did not indicate any impairment. Comparative analysis of audiometric parameters revealed no statistically significant differences between pre-treatment and third-month measurements at frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz, as well as in PTA, HFA, and LFA values. An isolated statistically significant difference was observed at 6000 Hz in the right ear ($p = 0.043$). Although median threshold values remained unchanged, this finding likely reflected minor distributional shifts among paired measurements rather than a clinically meaningful hearing threshold deterioration (Table 2).

None of the participants reported newly developed vestibular or audiological symptoms, including vertigo, dizziness, imbalance, tinnitus, nausea, or vomiting, during the study period. No spontaneous, gaze-evoked, or positional nystagmus was detected either before treatment or at the third-month assessment.

Quantitative analysis of the VNG-based oculomotor parameters revealed no statistically significant changes after three months of oral isotretinoin therapy. Smooth pursuit gain at 0.2 and 0.4 Hz remained stable for both rightward and leftward tracking, with all time-effect p-values ranging from 0.451 to 0.692. No significant differences between rightward and leftward smooth pursuit gains were identified at either

Table 1. Demographic and treatment characteristics of the study population

Variable	Value
Sex, n (%)	
Male	11 (33.3)
Female	22 (66.7)
Age (years), median (IQR)	20.0 (3.0)
Daily isotretinoin dose, n (%)	
30 mg	17 (51.5)
40 mg	15 (45.5)
50 mg	1 (3.0)

IQR: Interquartile range

Table 2. Pre- and post-treatment pure-tone audiometry outcomes

Frequency (Hz)	Ear	Pre-treatment (median, IQR)	Post-treatment (median, IQR)	p-value
250	Right	15.0 (10.0)	15.0 (5.0)	0.083
	Left	10.0 (7.5)	15.0 (5.0)	0.731
500	Right	10.0 (5.0)	10.0 (7.5)	0.980
	Left	10.0 (10.0)	10.0 (7.5)	0.568
1000	Right	10.0 (10.0)	10.0 (5.0)	0.550
	Left	10.0 (10.0)	10.0 (10.0)	0.985
2000	Right	10.0 (5.0)	5.0 (5.0)	0.573
	Left	10.0 (10.0)	10.0 (5.0)	0.642
4000	Right	10.0 (5.0)	10.0 (7.5)	0.451
	Left	10.0 (10.0)	10.0 (10.0)	0.898
6000	Right	10.0 (10.0)	10.0 (12.5)	0.043
	Left	10.0 (5.0)	15.0 (5.0)	0.812
8000	Right	15.0 (10.0)	10.0 (7.5)	0.107
	Left	10.0 (5.0)	15.0 (7.5)	0.460
PTA	Right	8.75 (6.3)	8.75 (5.0)	0.922
	Left	8.75 (6.3)	10.0 (5.0)	0.866
HFA	Right	13.33 (8.3)	11.66 (5.0)	0.098
	Left	13.33 (8.3)	11.66 (8.3)	0.326
LFA	Right	11.66 (6.7)	10.0 (6.7)	0.211
	Left	10.0 (5.8)	11.66 (5.8)	0.930

PTA: Pure-tone average (500, 1000, 2000, and 4000 Hz), HFA: High-frequency average (4000, 6000, and 8000 Hz), LFA: Low-frequency average (250, 500, and 1000 Hz), IQR: Interquartile range

assessment, indicating preserved directional symmetry at both frequencies before and after treatment (all symmetry p-values ranging from 0.184 to 0.812).

Saccadic latency, velocity, and accuracy did not differ significantly between the pre-treatment and third-month evaluations in either direction, with p-values ranging from 0.435 to 0.925. Similarly, optokinetic gain at a stimulus velocity of 20°/s remained unchanged for both rightward (p=0.627) and leftward stimulation (p=0.942). The mean $\pm$ standard deviation and minimum-maximum values for all quantitative VNG parameters are presented in Table 3.

Discussion

The presented prospective exploratory study evaluated possible audiovestibular alterations associated with short-term oral isotretinoin therapy using objective audiometric and selected VNG-based vestibular assessments. The findings demonstrated no clinically meaningful deterioration in hearing thresholds or abnormalities in the selected VNG-based vestibular assessments during the three-month treatment period.

Oral isotretinoin remains a cornerstone in acne vulgaris management because of its established efficacy across

multiple pathogenic pathways (13). However, concerns regarding adverse effects involving neurological, sensory, and vestibular systems continue to be discussed in the literature (2-7). Although complaints such as dizziness and vertigo have occasionally been reported, objective vestibular investigations evaluating possible vestibulotoxicity remain limited. Vestibular adverse effects associated with isotretinoin appear to be rare and inconsistently reported. In one study involving 150 isotretinoin-treated patients, vertigo was reported in only one patient (2). However, objective vestibular assessment findings and detailed otolaryngological evaluation data were not provided, limiting interpretation of the clinical significance and causality of these symptoms.

The presented study was not designed as a pharmacovigilance prevalence investigation or as a study intended to establish a causal relationship between isotretinoin and vestibular dysfunction. Instead, it was planned as an exploratory pilot study aimed at objectively evaluating possible subclinical audiovestibular alterations during isotretinoin therapy.

Previous studies evaluating hearing outcomes during isotretinoin treatment have produced inconsistent results. Karabulut et al. (9) reported statistically significant short-term changes in PTAs at different frequency ranges and interpreted these findings as an improvement in hearing levels during treatment. In contrast, Kemeriz et al. (11) observed bilateral hearing threshold changes during isotretinoin therapy that improved after treatment discontinuation, suggesting that these alterations may be reversible. Experimental evidence has provided a different perspective, with an animal study suggesting that isotretinoin may exert a protective effect against cisplatin-induced ototoxicity (14). Akdag et al. (15) reported significant bilateral changes in hearing thresholds at frequencies between 1000 and 6000 Hz, although no corresponding significant alterations were detected in transient-evoked otoacoustic emission responses. Conversely, Yaldiz et al. (16) found no significant deterioration in bilateral hearing thresholds during oral isotretinoin treatment.

Electrophysiological and clinical observations have also yielded variable findings. Nikiforidis et al. (17) found no statistically significant group-level changes in auditory brainstem responses after isotretinoin administration; however, marked increases in latencies and interpeak latencies together with reductions in amplitudes were observed bilaterally in three patients, raising the possibility of subclinical effects on auditory neural transmission. In addition, Rosende et al. (18) reported an isolated case of hypoacusis and tinnitus developing during isotretinoin treatment, with rapid improvement after discontinuation of the drug. Although a single case report cannot establish causality, it highlights the importance of clinical awareness of newly developed auditory symptoms during treatment.

Table 3. Comparison of VNG test parameters before and after systemic isotretinoin treatment (n=33)

Parameters	Pre-treatment (mean ± SD) [min-max]	Post-treatment (mean ± SD) [min-max]	p-value ¹ (time effect)
Smooth pursuit gain (%)			
0.2 Hz-rightward	98.67±8.65 [77.5-118.0]	98.15±8.35 [75.0-116.0]	0.692
0.2 Hz-leftward	95.55±10.32 [68.0-114.5]	96.82±8.84 [77.5-117.0]	0.451
p-value² (symmetry)	0.184	0.495	
0.4 Hz-rightward	93.00±12.87 [60.5-113.0]	94.61±11.23 [62.0-114.0]	0.473
0.4 Hz-leftward	96.12±10.15 [70.0-116.0]	95.27±10.22 [69.5-115.5]	0.624
p-value² (symmetry)	0.278	0.812	
Saccade			
Latency (ms)-rightward	143.76±17.56 [112.0-188.0]	143.45±15.65 [116.0-182.0]	0.925
Latency (ms)-leftward	137.64±15.42 [110.0-171.0]	138.27±12.98 [113.0-164.0]	0.814
Velocity (°/s)-rightward	350.55±48.75 [256.0-455.0]	351.64±46.21 [232.0-441.0]	0.898
Velocity (°/s)-leftward	362.58±42.18 [278.0-461.0]	356.45±36.87 [289.0-432.0]	0.435
Accuracy (%) -rightward	95.73±10.34 [69.0-112.0]	96.61±8.12 [77.0-111.0]	0.618
Accuracy (%) -leftward	95.39±8.92 [74.5-111.0]	94.45±7.95 [77.0-109.5]	0.540
Optokinetic nystagmus			
Gain (%) at 20°/s-rightward	93.61±10.85 [72.0-114.0]	92.67±10.12 [68.0-113.0]	0.627
Gain (%) at 20°/s-leftward	93.88±10.42 [70.5-114.5]	93.76±9.85 [71.5-117.0]	0.942

Continuous variables are expressed as mean ± SD [min-max]. Statistical significance was defined as p<0.05

p-value¹: Evaluated using the paired samples t-test (or Wilcoxon signed-rank test based on normality), comparing pre-treatment and post-treatment values within the same cohort

p-value²: Represents the Directional Symmetry p-value, evaluating the physiological balance between rightward and leftward tracking responses within the same session

Data reduction: because binocular eye movements are physiologically conjugate, values recorded from the right and left eyes were averaged to obtain a single representative value for each stimulus direction and participant

Hz: Hertz, ms: Milliseconds, °/s: Degrees per second, SD: Standard deviation, VNG: Videonystagmography

Overall, the available evidence does not demonstrate a consistent pattern of clinically relevant isotretinoin-related auditory toxicity, and differences among studies may be related to treatment duration, cumulative dose, sample characteristics, and the audiological methods used.

In the presented study, audiometric thresholds remained stable throughout the treatment period except for an isolated statistically significant difference at 6000 Hz in the right ear. Because this finding was unilateral, not accompanied by clinically relevant hearing loss, and not reflected in averaged hearing parameters, it was interpreted cautiously and considered more likely related to minor statistical variation than true cochlear toxicity.

Objective studies investigating the possible vestibular effects of isotretinoin are considerably more limited. Kocak et al. (8) prospectively evaluated 30 patients using vHIT before treatment and after three months of isotretinoin therapy. They detected no overt or covert corrective saccades or spontaneous nystagmus and reported no significant changes in semicircular canal gain or asymmetry measurements. These findings suggested that short-term isotretinoin therapy did not adversely affect the peripheral vestibular system or vestibulo-ocular reflex pathways. The presented

study complements these limited data by providing quantitative VNG-based smooth pursuit, saccadic, and optokinetic measurements before and after treatment. Regarding vestibular evaluation, none of the participants reported dizziness, vertigo, or imbalance during follow-up. In addition, selected VNG-based assessments demonstrated normal findings in all participants. These findings are generally consistent with the limited existing vestibular literature regarding isotretinoin therapy.

The absence of caloric testing represents the main limitation of the vestibular assessment in the presented study. Although VNG-based positional and oculomotor assessments were normal, caloric testing was not included in the study protocol. Therefore, these results do not allow a definitive exclusion of subtle vestibular dysfunction or vestibulotoxic effects. The vestibular assessment in this study was limited to a focused test battery within the scope of an exploratory pilot design.

Study Limitations

The study has several additional limitations. Firstly, the relatively small sample size and absence of a control group may limit the generalizability of the findings. Secondly, the follow-up duration was limited to three months, precluding assessment of long-term audiovestibular effects. Finally,

asymptomatic patients were evaluated, and rare vestibular adverse effects may not be detectable in a relatively small cohort.

Despite these limitations, the presented study provides prospective objective audiometric and selected VNG-based vestibular data regarding short-term isotretinoin therapy, an area in which available literature remains limited. Future studies involving larger patient populations, longer follow-up durations, and more comprehensive vestibular assessment protocols, potentially including electrophysiological and experimental investigations, are needed to further clarify the effects of isotretinoin on auditory and vestibular function.

Conclusion

Within the limitations of this prospective exploratory pilot study, short-term oral isotretinoin therapy did not demonstrate clinically significant abnormalities in audiometric measurements or selected VNG-based vestibular assessments in this cohort. Selected VNG-based vestibular assessments and audiometric measurements remained stable throughout the study period. Larger controlled studies with longer follow-up durations and comprehensive vestibular testing are required before definitive conclusions regarding vestibulotoxicity can be established.

Main Points

- Short-term oral isotretinoin therapy did not demonstrate clinically significant audiovestibular abnormalities in this cohort.
- No clinically meaningful deterioration was observed in pure-tone audiometric thresholds during the study period.
- Selected videonystagmography-based vestibular assessments remained within normal limits throughout treatment.
- Larger controlled studies with longer follow-up and comprehensive vestibular testing are needed.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Necmettin Erbakan University Research on Non-Drug and Medical Device Products Ethics Committee (approval no: 2021/3484, date: 05.11.2021).

Informed Consent: All participants received detailed information regarding the study protocol, and written informed consent was obtained from all individuals prior to participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.Y., C.Y., M.E.K., Concept: F.Y., C.Y., M.E.K., Design: F.Y., C.Y., M.E.K., Data Collection

and/or Processing: F.Y., C.Y., Analysis or Interpretation: C.Y., M.E.K., Literature Search: F.Y., Writing: F.Y.

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.

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Original Investigation



Turk Arch Otorhinolaryngol 2026; 64(3): 144-153

DOI: 10.4274/tao.2026-5-6

Videofluoroscopic Analysis of Swallowing Biomechanics in Parkinson's Disease

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Abstract

Objective: To quantitatively assess maximum hyoid displacement, laryngeal displacement, pharyngeal constriction, and upper esophageal sphincter opening in patients with Parkinson's disease and compare these measures with those of controls with normal videofluoroscopic swallowing findings.

Methods: This retrospective observational study included 32 videofluoroscopic swallowing examinations: 16 from patients with Parkinson's disease and 16 from controls. Thin liquid, paste, and solid consistencies were evaluated. Measurements were obtained using ImageJ after image calibration, and between-group comparisons were performed using Student's t-test or the Mann-Whitney U test according to data distribution.

Results: The groups had similar mean ages. Patients with Parkinson's disease demonstrated significantly reduced laryngeal displacement across all consistencies and poorer pharyngeal constriction with thin liquids, as indicated by a larger residual pharyngeal area. No significant between-group differences were observed in maximum hyoid displacement or upper esophageal sphincter opening.

Conclusion: In this sample, Parkinson's disease was primarily associated with impaired laryngeal displacement and pharyngeal constriction, potentially affecting airway protection and pharyngeal clearance. Quantitative videofluoroscopic analysis may help identify biomechanical swallowing alterations in this population.

Keywords: Parkinson disease, deglutition disorders, fluoroscopy, hyoid bone, larynx

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Cite this article as: Gonçalves MIR, Neto ICO, Lederman H, Zica GM. Videofluoroscopic analysis of swallowing biomechanics in Parkinson's disease. Turk Arch Otorhinolaryngol. 2026; 64(3): 144-153

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Received Date: 15.05.2026

Accepted Date: 18.08.2026

Epub: 28.09.2026

Publication Date: 30.09.2026

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder involving basal ganglia circuits and reduced dopaminergic transmission. It is characterized by motor signs such as resting tremor, muscle rigidity, and bradykinesia (1,2). Although pharmacological treatment and newer surgical interventions help control symptoms, no intervention has been shown to definitively halt disease progression (1-3).

Among non-motor manifestations and complications related to disease progression, dysphagia is clinically relevant because of its functional impact and association with silent aspiration and aspiration pneumonia (4,5). Swallowing abnormalities may occur even in early stages and include slowed oral transit, delayed swallowing response, reduced anteriorization and laryngeal elevation, and increased pharyngeal residue (5-7).

The pharyngeal phase of swallowing depends on coordinated hyoid displacement, laryngeal elevation, pharyngeal constriction, and upper esophageal sphincter opening. Alterations in these events may compromise swallowing safety and efficiency, increasing the risk of penetration, aspiration, and post-swallow residue. In neurological diseases, spatial displacement, velocity, timing, and movement sequence are all relevant determinants of swallowing risk (8-10).

The videofluoroscopic swallowing study (VFSS) is considered the reference examination for dysphagia assessment because it allows dynamic visualization of structures, identification of the timing of penetration/aspiration, and extraction of quantitative displacement, time, and velocity measures (5,10,11). Despite its widespread use, standardized quantitative measures in PD remain heterogeneous, with differences in protocols, volumes, and consistencies that hinder direct comparisons between studies. In addition, few studies involving this patient group have been conducted in Latin America, which limits the generalizability of international findings.

In this context, this study aimed to quantitatively analyze maximum hyoid bone displacement, laryngeal elevation, pharyngeal constriction, and the extent of upper esophageal sphincter opening in patients with PD and compare them with a control group with normal swallowing in a Brazilian public service.

Methods

Ethical Aspects

This study was approved by the Research Ethics Committee of the Federal University of Sao Paulo-Unifesp/Hospital Sao Paulo, under approval no: 820.360, date: October 06, 2014. All patients had previously signed the informed consent form at the time of the videofluoroscopic swallowing examination, authorizing the use of their data for scientific purposes according to the institutional protocol.

Study Design

This was an observational, retrospective, analytical study with random selection of medical records, conducted through analysis of reports and images from videofluoroscopic swallowing examinations.

Data were obtained from the videofluoroscopic swallowing archive of the Functional Swallowing Rehabilitation Sector, Department of Speech-Language Pathology and Audiology, Escola Paulista de Medicina, Universidade Federal de São Paulo. The examinations analyzed were performed in the Diagnostic Imaging Sector of Hospital São Paulo, Universidade Federal de São Paulo, from 2010 to 2020.

Sample Selection and Group Allocation

The institutional database for the period analyzed contained 37 examinations of patients diagnosed with PD and 54 examinations of patients with videofluoroscopic reports indicating normal swallowing.

The sample size was defined pragmatically according to the retrospective availability of eligible VFSS examinations and image quality. No a priori sample size calculation was performed. Although the database included 37 examinations of patients with PD and 54 examinations with normal VFSS reports, only examinations meeting the eligibility criteria and allowing quantitative analysis of the selected biomechanical variables were included. A balanced sample of 16 examinations per group was therefore obtained.

For sample composition, stratified random selection by group was performed in Microsoft Excel. Eligible reports were organized according to clinical condition, numerically identified, and randomly selected without replacement until 16 reports were obtained in each group.

The final sample consisted of 32 VFSS reports: 16 from patients with PD and 16 from individuals with normal swallowing according to the videofluoroscopic report.

The reports were distributed into two groups: Group 1, patients with PD; and Group 2, individuals with normal VFSS findings. Random selection aimed to reduce selection bias within the available database.

Eligibility Criteria

Inclusion Criteria

- Group 1: Patients with a clinical diagnosis of PD who had sufficient oral feeding conditions to undergo the VFSS.
- Group 2: Individuals without PD or other central or peripheral neurological disorders, without a history of head and neck tumors, resections, surgery, or oncological treatment, and with normal swallowing on VFSS. These individuals were referred from different clinical or surgical departments for indications such as odynophagia, reflux-related symptoms, gastrointestinal complaints, or evaluation of suspected fistula but showed no evidence of oropharyngeal dysphagia according to the institutional VFSS report. This group should be interpreted as a clinically referred comparison group with normal VFSS findings, rather than as healthy volunteers.

Exclusion Criteria

Patients diagnosed with other neurological diseases associated with PD were excluded, as were those with a history of tumors in the head and neck region, or who had undergone

treatment for such tumors. Patients whose examinations revealed poor visualization of anatomical structures, which compromised the analysis and quantification of the variables studied, were also excluded.

PD severity was classified using the Hoehn and Yahr (12) scale, which stratifies patients into stages I to V according to symptom laterality, balance impairment, and functional independence (13). In this study, staging was performed before data collection by hospital neurologists during routine clinical assessment.

All patients with PD were under regular neurological follow-up and were considered clinically stable at the time of VFSS. Clinical stability was defined as the absence of acute neurological or systemic decompensation recorded at the time of examination, no indication of acute hospitalization related to neurological worsening, and sufficient clinical condition to undergo VFSS with oral intake according to the institutional protocol. However, because of the study's retrospective design, the institutional database did not systematically record the specific dopaminergic medication status at the time of examination, including whether patients were evaluated on or off medication. Therefore, we could not include this variable in the statistical analysis.

Videofluoroscopic Swallowing Procedures

All VFSS examinations were performed in the Diagnostic Imaging Sector of Hospital São Paulo, Hospital Universitário da Universidade Federal de São Paulo, preceded by anamnesis and clinical assessment, and followed the protocol described by Gonçalves et al. (14).

The VFSS evaluated individuals in an upright position in left lateral, frontal, and, when necessary, oblique views. Patients were instructed to keep their head straight during the examination and were identified by the initials of their first and last names, recorded at the beginning of the examination together with the date.

Patients who did not have the motor conditions required to remain upright were accommodated in a VESS CHAIR®, a chair developed to adapt patients with positioning difficulties on the fluoroscopy table, providing comfort, safety, and appropriate examination performance.

The procedure began with the recording of a resting image in lateral view. The individuals were then asked to swallow the following volumes and consistencies:

- 1 mL, 3 mL, 5 mL, and free sips of thin liquid (water with contrast) and thickened liquid;
- 3 mL and 5 mL of paste consistency (petit suisse yogurt), offered by spoon;

- One portion of solid food (wafer cookie) soaked in contrast.

The examinations were performed in a shielded X-ray room using Medicore radiological equipment with seriography, tilting table, triphasic system, capacity of 500 mA and automatic 120 kV, image intensifier, and closed-circuit television. The images were digitized, transferred to a computer, and subsequently recorded on DVD.

The equipment was operated by a radiology technician with the assistance of a speech-language pathologist experienced in performing videofluoroscopic swallowing examinations. The examinations were analyzed independently by another experienced speech-language pathologist and by a radiologist, with reports classified as mild dysphagia, moderate dysphagia, severe dysphagia, or normal swallowing, as described by Gonçalves et al. (14).

Image Extraction and Measurement of Variables

Images from VFSS examinations recorded in DVD format were used to extract the measures. The images were captured, selected, and inserted into ImageJ software for measurement. The data obtained were organized in electronic spreadsheets for subsequent tabulation and statistical analysis.

All measurements were performed by graduate researchers trained in quantitative VFSS image analysis using ImageJ. Training was conducted within institutional graduate-level swallowing research activities and supervised by an experienced faculty advisor. Before data extraction, the examiners underwent a standardization process that included review of the measurement protocol, discussion of anatomical landmarks, calibration procedures, selection of the swallowing frame of interest, and pilot measurements using representative VFSS images. The same anatomical landmarks, calibration procedures, and measurement criteria were applied throughout the analysis to improve consistency.

The following consistencies and volumes were analyzed:

- 5 mL of thin liquid;
- 5 mL of paste consistency;
- Solid food (wafer cookie soaked in contrast).

Because this was a retrospective study based on clinically indicated VFSS examinations, not all consistencies or volumes were available for all patients. Some consistencies were not administered because of clinical safety concerns, and some images, although adequate for clinical interpretation, did not allow reliable quantitative measurement because of limited visualization of anatomical structures, patient positioning, movement artifacts, or image quality. Therefore, the number of observations varied across variables according to image availability and measurement suitability.

Measurement Procedure

Tongue mobility, pharyngeal constriction, and hyoid and laryngeal displacement measures were obtained using ImageJ software, as described by Gonçalves and Leonard (11). ImageJ is an image analysis program developed by the National Institutes of Health and freely available (<http://rsb.info.nih.gov/nih-image/>). It allows adjustments of contrast and brightness, rotation, inversion, resizing, tracing, and calculation of distances, areas, and angles.

Before the measurements were performed, the software was calibrated using the known diameter of a metallic marker positioned over the mastoid process of the patient's temporal bone (a one-centavo Brazilian Real coin). A line was drawn along the diameter of the coin, allowing conversion from pixels to centimeters.

Variables Analyzed

Maximum Hyoid Bone Displacement

Maximum hyoid bone displacement was measured from the intersection between a line tangent to the anterior portion of the hyoid bone and another line tangent to its inferior margin. A right angle was then drawn using the same cervical vertebrae as a reference. The resting image was superimposed on the image of maximum hyoid bone excursion, and the distance between the intersections was calculated by ImageJ, representing maximum displacement (10).

Maximum Laryngeal Displacement (Cricoid Cartilage)

For measurement of laryngeal displacement, the anterior portion of the cricoid cartilage was considered. Two tangent lines were drawn: one at the level of the free edge of the vocal folds and another at the anterior wall of the trachea immediately below the larynx. The intersection of these lines was associated with a 90° angle fixed to a cervical vertebra. The same procedure was performed on the resting image and on the image of maximum laryngeal elevation, using the same vertebra as reference. The images were superimposed, allowing measurement of cricoid cartilage displacement (10).

Pharyngeal Constriction

Pharyngeal constriction measurements were performed from lateral-view images obtained at rest and at the moment of maximum pharyngeal constriction. The resting pharyngeal area was manually outlined in ImageJ using the freehand selection tool, from the posterior pharyngeal wall at the level of the anterior tubercle of the atlas vertebra to the height of the upper border of the arytenoid cartilage. The contour included the arytenoid cartilages, epiglottis, valleculae, tongue base, and soft palate up to the posterior nasal spine of the palatine bone. The upper border was defined by a straight line between the posterior nasal spine and the anterior tubercle of the atlas vertebra. The area was

automatically calculated in square centimeters, following the fluoroscopic pharyngeal area measurement principles described by Leonard et al. (15).

Upper Esophageal Sphincter Opening

The extent of upper esophageal sphincter opening was measured during swallowing of the largest contrast volume. The image showing the greatest displacement of the cricoid cartilage was captured, and, considering the previous calibration, the distance between the anterior and posterior esophageal walls was measured 1 cm below the lower border of the cricoid cartilage, as described in the literature (10,11).

Reliability Analysis

To assess reliability, a subset of VFSS examinations was remeasured using the same anatomical landmarks and calibration procedures. Measurement reliability was calculated using the intraclass correlation coefficient (ICC), based on a two-way mixed-effects model for absolute agreement using single measurements. This model was selected because the biomechanical variables were continuous manual measurements obtained from calibrated VFSS images.

Statistical Analysis

Data were initially analyzed descriptively. Categorical variables were presented as absolute and relative frequencies, whereas numerical variables were presented as mean, median, minimum and maximum values, and standard deviation.

The distribution of numerical variables was assessed to determine whether they followed a normal (Gaussian) distribution. The Shapiro-Wilk test was used for variables with up to 30 observations, whereas the Kolmogorov-Smirnov test was used for variables with more than 30 observations. For between-group comparisons, Student's t-test for independent samples was applied when variables showed normal distribution. When the assumption of normality was not met, the non-parametric Mann-Whitney U test was used.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). The level of statistical significance was set at 5% ($p < 0.05$). An exploratory post hoc power analysis was performed using G*Power software, version 3.1.9.7, for the main biomechanical outcomes. The analysis was based on the statistical test used for each between-group comparison, the observed between-group effect size, the final number of observations available for each variable, and a two-sided alpha level of 0.05. This analysis was conducted to contextualize the probability of detecting the observed effects in this retrospective sample and was not interpreted as a substitute for an a priori sample size calculation.

Because multiple between-group comparisons were performed across biomechanical variables and consistencies, a sensitivity analysis was conducted using the Benjamini-Hochberg false discovery rate (FDR) procedure. This approach was chosen because the swallowing measures were physiologically related and not fully independent.

Results

The total sample consisted of 32 participants, equally distributed by sex. In the PD group, early disease stages predominated: 50.0% were classified as Hoehn and Yahr (12) stage I, 12.5% as stage II, and 25.0% as stage II-III. Only two patients were in advanced stages: one in stage IV and one in stage V (Table 1).

Mean age was similar between the control and PD groups (67.75 and 67.25 years, respectively). In the PD group, mean disease duration was 3.56 years, ranging from 1 to 9 years (Table 2).

Participants aged 60 years or older predominated in both groups, corresponding to 87.5% of controls and 81.3% of patients with PD. The small number of participants aged 59 years or younger limited age-stratified analyses (Table 3).

Normality testing showed that most variables were compatible with normal distribution. Hyoid displacement for paste and

pharyngeal constriction for thin liquid showed non-normal distribution, supporting the use of parametric or non-parametric tests according to each variable distribution (Table 4).

Reliability analysis showed good agreement for the ImageJ-based measurements (ICC=0.83). Between-group comparisons showed significantly reduced laryngeal displacement in the PD group for thin liquid, paste, and solid consistencies ($p<0.05$). Pharyngeal constriction for thin liquid was also significantly altered, with a larger residual pharyngeal area in the PD group. No significant between-group differences were identified for hyoid displacement or upper esophageal sphincter opening (Table 5). After Benjamini-Hochberg FDR adjustment, the main differences remained significant for laryngeal displacement across all consistencies and pharyngeal constriction for thin liquid.

A descriptive stratification of the swallowing biomechanical variables according to Hoehn and Yahr (12) stage is shown in Table 6. Given the limited number of participants within each disease stage, particularly in stages II, IV, and V, inferential statistical comparisons were not performed for this subgroup analysis. Therefore, this data should be interpreted as exploratory and descriptive.

Overall, the stratified descriptive analysis suggested a gradual reduction in laryngeal displacement and an increase

Table 1. Numerical and percentage distribution of patients with Parkinson's disease according to disease stage

Disease stage	n	%
I	8	50
II	2	12.5
II to III	4	25
IV	1	6.25
V	1	6.25
Total	16	100.0

Disease stage according to the Hoehn and Yahr (12) scale (1967)

Table 2. Mean, median, and standard deviation values for age in both groups, and disease duration in the Parkinson's disease group

Variable	Measure	Normal	Parkinson
Age	Mean	67.75	67.25
	Median	67.50	67.00
	Minimum	50	50
	Maximum	93	79
	Standard deviation	10.38	8.40
	n	16	16
Disease duration (years)	Mean		3.56
	Median		4.00
	Minimum		1
	Maximum		9
	Standard deviation		2.50
	n		16

in residual pharyngeal area for thin liquid swallowing with greater motor severity. Hyoid displacement and upper esophageal sphincter opening remained comparatively preserved across stages.

Discussion

The results indicate a predominant pattern of impairment in pharyngeal contraction and laryngeal elevation mechanisms during swallowing in patients with PD, with reduced laryngeal displacement across all consistencies and poorer pharyngeal constriction performance for thin liquid. This finding is consistent with the literature indicating that laryngeal elevation and the effectiveness of vestibular closure are central determinants of airway protection and aspiration reduction in neurological populations (1-3,16,17).

In PD, detailed kinematic studies suggest that swallowing deficits may manifest both as reduced movement amplitude and as reduced velocity and impaired muscle coordination. Lee et al. (9) observed reduced horizontal displacement and velocity of the hyoid bone in patients with PD compared with older adults in the control group, highlighting combined effects of disease and aging.

Alves et al. (18) described seven physiological hyoid displacement patterns in healthy individuals, which may explain the absence of a statistically significant difference in maximum hyoid displacement in the presented study. The varied findings in swallowing considered normal suggest

that, in PD, swallowing deficits may be less related to reduced maximum movement amplitude and more associated with temporal and coordination changes, such as decreased velocity and hyolaryngeal incoordination. Although these kinematic aspects are fundamental for effective laryngeal elevation and airway protection, isolated spatial measures do not fully capture them, reinforcing the need for analyses that integrate temporal and functional parameters in swallowing assessment in neurological populations (10,18).

In a review conducted by Wei et al. (8), it is possible to understand that kinematic analysis of the hyoid bone should consider both spatial and temporal components, because velocity changes may occur even when amplitude is preserved, especially in neurodegenerative diseases. Thus, peak velocity, time to peak, and coordination with laryngeal vestibule closure may be more sensitive measures for detecting early changes in PD, which is consistent with methodological gaps recognized in recent literature (1,2,5).

Laryngeal Elevation and Implications for Swallowing Safety

Reduced laryngeal displacement is clinically relevant because laryngeal elevation contributes to laryngeal vestibule closure and airway protection during bolus passage. Lower displacement may indicate less effective airway closure and greater vulnerability to penetration or aspiration, particularly with thin liquids, which require rapid and coordinated pharyngeal and laryngeal responses. In PD, this

Table 3. Numerical and percentage distribution of age range in both groups

Age range	Normal n	Normal %	Parkinson n	Parkinson %	Total n	Total %
≤59	2	12.5	3	18.8	5	15.6
60+	14	87.5	13	81.3	27	84.4
Total	16	100.0	16	100.0	32	100.0

Table 4. Normality analysis of numerical variables

Variable	Kolmogorov-Smirnov statistic	df	Sig. (p)
HD Liq	0.138	32	0.123
HD P	0.164	32	0.028*
HD S	0.115	31	0.200
LD Liq	0.092	30	0.200
LD P	0.121	31	0.200
LD S	0.138	30	0.151
PC Liq	0.247	31	<0.001*
PC P	0.206	15	0.086
PC S	0.193	14	0.168
UESO Liq	0.089	32	0.200
UESO P	0.108	32	0.200
UESO S	0.084	32	0.200

*: Statistically significant non-normal distribution ($p < 0.05$). HD: Hyoid displacement, LD: Laryngeal displacement, PC: Pharyngeal constriction, UESO: Upper esophageal sphincter opening, Liq: Liquid, P: Paste, S: Solid

impairment may be influenced by bradykinesia, rigidity, delayed swallowing response, fatigue, and reduced sensory feedback. Although aspiration was not the primary outcome of this study, reduced laryngeal displacement may represent

a useful marker for identifying patients who require closer instrumental monitoring and individualized swallowing management (10,16,17).

Table 5. Comparison of mean, median, and standard deviation values for the analyzed variables (hyoid displacement, laryngeal displacement, pharyngeal constriction, and upper esophageal sphincter opening) in both study groups

Variable	Measure	Normal	Parkinson	Total	p	Result
HD Liq	Mean	2.51	2.70	2.60	0.517	Normal=Parkinson
	Median	2.41	2.47	2.41		
	Standard deviation	0.75	0.85	0.79		
	n	16	16	32		
HD P	Mean	2.55	2.48	2.51	0.724	Normal=Parkinson
	Median	2.46	2.41	2.42		
	Standard deviation	0.74	0.56	0.64		
	n	16	16	32		
HD S	Mean	2.56	2.93	2.74	0.206	Normal=Parkinson
	Median	2.22	2.97	2.75		
	Standard deviation	0.91	0.69	0.82		
	n	16	15	31		
LD Liq	Mean	2.95	2.13	2.57	0.002*	Normal>Parkinson
	Median	2.99	2.02	2.55		
	Standard deviation	0.69	0.61	0.76		
	n	16	14	30		
LD P	Mean	2.80	2.00	2.41	0.011*	Normal>Parkinson
	Median	2.63	1.87	2.31		
	Standard deviation	0.93	0.66	0.90		
	n	16	15	31		
LD S	Mean	2.98	2.18	2.60	0.008*	Normal>Parkinson
	Median	2.91	2.15	2.44		
	Standard deviation	0.92	0.55	0.86		
	n	16	14	30		
PC Liq	Mean	0.03	1.06	0.53	<0.001*	Normal<Parkinson
	Median	0.02	0.88	0.11		
	Standard deviation	0.03	0.61	0.67		
	n	16	15	31		
UESO Liq	Mean	0.95	0.84	0.89	0.358	Normal=Parkinson
	Median	0.92	0.91	0.91		
	Standard deviation	0.37	0.29	0.33		
	n	16	16	32		
UESO P	Mean	0.95	0.97	0.96	0.857	Normal=Parkinson
	Median	0.98	0.97	0.97		
	Standard deviation	0.33	0.25	0.29		
	n	16	16	32		
UESO S	Mean	0.97	1.20	1.08	0.086	Normal=Parkinson
	Median	0.92	1.21	1.10		
	Standard deviation	0.36	0.39	0.39		
	n	16	16	32		

* Statistically significant difference (p<0.05). FDR-adjusted sensitivity analysis was performed using the Benjamini-Hochberg procedure for multiple between-group comparisons. Parametric Student's t-test and non-parametric Mann-Whitney U test. HD: Hyoid displacement, LD: Laryngeal displacement, PC: Pharyngeal constriction, UESO: Upper esophageal sphincter opening, Liq: Liquid, P: Paste, S: Solid

The reduction in laryngeal displacement across all consistencies reinforces its potential clinical value. Previous studies in mild PD have sometimes reported measures close to those of controls, possibly because of differences in disease stage, consistency, volume, and measurement criteria (19,20). In the presented sample, the consistent difference across consistencies suggests that laryngeal elevation may be affected even when other spatial measures remain unchanged.

Pharyngeal Constriction, Residue, and Efficiency

Poorer pharyngeal constriction for thin liquid, reflected by a larger residual pharyngeal area, indicates reduced pharyngeal clearance efficiency. This finding is clinically important because pharyngeal residue may increase the risk of post-swallow airway invasion, especially in patients with fatigue, sensory impairment, or reduced spontaneous clearing swallows. The direction of this result is consistent with evidence that impaired pharyngeal constriction is associated with residue and aspiration risk in dysphagic populations (16,21).

The fact that this difference was observed for thin liquid may reflect the greater sensitivity of this consistency to deficits in timing, pressure generation, and airway protection. More viscous consistencies may slow bolus flow and allow compensatory adjustments, which could reduce between-group differences in a small retrospective sample.

Upper Esophageal Sphincter Opening and Interpretation of Findings

Upper esophageal sphincter opening did not differ significantly between groups, suggesting that maximum anteroposterior opening was relatively preserved in this sample. However, preserved opening extent does not exclude abnormalities in opening duration, timing, pressure generation, or coordination with hyolaryngeal elevation.

These parameters were not assessed and should be included in future studies.

Implications for Speech-Language Pathology Practice

Clinically, these findings support early instrumental assessment in PD, even in patients with limited complaints, because swallowing impairment may be silent or underestimated. The observed pattern suggests that therapeutic planning should consider strategies to improve airway protection, laryngeal elevation, and pharyngeal clearance, with individualized decisions about bolus volume, consistency, pacing, and compensatory maneuvers. Quantitative VFSS may also help monitor treatment response over time.

As an exploratory descriptive analysis, stratification by Hoehn and Yahr (12) stage suggested a gradual reduction in laryngeal displacement and an increase in residual pharyngeal area for thin liquid swallowing with greater motor severity. In contrast, hyoid displacement and upper esophageal sphincter opening remained relatively preserved across stages. These findings should be interpreted cautiously because of the small and uneven number of participants in each stratum, particularly in advanced stages.

Study Limitations

This study has limitations. First, the sample size was small and was not based on an a priori sample size calculation, but on the retrospective design, the availability of eligible patients with PD, and the requirement for VFSS images suitable for quantitative analysis. Although exploratory post hoc power estimates indicated adequate power for the significant findings, non-significant results, particularly for hyoid displacement and upper esophageal sphincter opening, should be interpreted cautiously and not as evidence of equivalence between groups.

Table 6. Descriptive stratification of swallowing biomechanical variables according to Hoehn and Yahr (12) stage in patients with Parkinson's disease

Biomechanical variable	Consistency	H&Y I (n=8)	H&Y II (n=2)	H&Y II-III (n=4)	H&Y IV (n=1)	H&Y V (n=1)
HD	Thin liquid 5 mL	2.85±0.72	2.70±0.68	2.55±0.82	2.20	2.05
HD	Paste 5 mL	2.60±0.50	2.50±0.45	2.35±0.58	2.15	2.00
HD	Solid	3.05±0.60	2.95±0.65	2.85±0.72	2.55	2.35
LD	Thin liquid 5 mL	2.35±0.48	2.15±0.50	1.95±0.56	1.60	1.35
LD	Paste 5 mL	2.20±0.52	2.00±0.45	1.80±0.58	1.55	1.30
LD	Solid	2.40±0.50	2.20±0.46	2.00±0.52	1.70	1.45
PC	Thin liquid 5 mL	0.75±0.38	0.95±0.42	1.25±0.55	1.70	2.05
UESO	Thin liquid 5 mL	0.90±0.25	0.85±0.22	0.80±0.30	0.75	0.70
UESO	Paste 5 mL	1.00±0.22	0.98±0.20	0.95±0.25	0.90	0.85
UESO	Solid	1.25±0.36	1.20±0.34	1.15±0.40	1.05	0.95

Values are expressed in centimeters for displacement/opening measures and in square centimeters for pharyngeal residual area. HD: Hyoid displacement, LD: Laryngeal displacement, PC: Pharyngeal constriction, UESO: Upper esophageal sphincter opening, H&Y: Hoehn and Yahr (12)

Second, most patients with PD were in early Hoehn and Yahr (12) stages, whereas advanced stages were underrepresented. Therefore, the findings may not be generalizable to patients with advanced disease, in whom swallowing biomechanics may be more severely impaired. The descriptive stratification by Hoehn and Yahr (12) stage was included for clinical context but should be interpreted as exploratory.

Finally, because of the retrospective design, clinically relevant variables were not systematically controlled, including dopaminergic medication state, cognitive status, respiratory function, and nutritional status. Although all patients were under regular neurological follow-up and clinically stable at the time of VFSS, the database did not record whether examinations were performed during the on or off medication state. In addition, the analysis focused on maximum spatial measures and did not include temporal, velocity, or pressure-related parameters, which may be more sensitive to swallowing impairment in PD.

Conclusion

In this retrospective quantitative VFSS study, patients with PD showed reduced laryngeal displacement across thin liquid, paste, and solid consistencies and poorer pharyngeal constriction for thin liquid swallowing. Maximum hyoid displacement and upper esophageal sphincter opening did not differ significantly between the groups. These findings suggest that impairment of laryngeal elevation and pharyngeal constriction may be predominant biomechanical features of swallowing dysfunction in PD, with potential implications for airway protection and pharyngeal clearance.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Federal University of Sao Paulo-Unifesp/Hospital Sao Paulo, under approval no: 820.360, date: October 06, 2014.

Informed Consent: All patients had previously signed the informed consent form at the time of the videofluoroscopic swallowing examination, authorizing the use of their data for scientific purposes according to the institutional protocol.

Footnotes

Authorship Contributions

Concept: M.I.R.G., I.C.O.N., G.M.Z., Design: M.I.R.G., I.C.O.N., G.M.Z., Data Collection and/or Processing: M.I.R.G., I.C.O.N., G.M.Z., Analysis or Interpretation: M.I.R.G., I.C.O.N., G.M.Z., Writing: M.I.R.G., I.C.O.N., H.L., G.M.Z.

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

- Patients with Parkinson's disease showed reduced laryngeal displacement during swallowing across thin liquid, paste, and solid consistencies.
- Pharyngeal constriction was impaired for thin liquid swallowing in the Parkinson's disease group.
- Maximum hyoid displacement and upper esophageal sphincter opening did not differ significantly between groups.
- Quantitative videofluoroscopy may support early identification of pharyngeal and laryngeal biomechanical changes in Parkinson's disease.

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Original Investigation



Turk Arch Otorhinolaryngol 2026; 64(3): 154-162

DOI: 10.4274/tao.2026.2026-6-32

Benign Sinonasal Tumors: A 17-Year Single Center Experience

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Abstract

Objective: This study evaluated demographic characteristics, histopathological distribution, surgical approaches, residual disease, complications, and recurrence patterns in patients surgically treated for benign sinonasal tumors.

Methods: Medical records of patients who underwent surgery for benign sinonasal tumors at a single tertiary center between January 2007 and December 2024 were retrospectively reviewed. Patients with less than three months of follow-up were excluded. Demographic, histological, surgical, complication, residual disease, follow-up, and recurrence data were analyzed according to tumor type.

Results: A total of 368 patients were included. The median age was 42.5 years, and 260 patients (70.7%) were male. The most common histological groups were sinonasal papilloma (34.2%), osseous lesions (22.6%), and juvenile nasopharyngeal angiofibroma (19.0%). Surgical approach differed significantly by tumor type ($p<0.001$), with endoscopic surgery used most frequently overall (74.5%). Residual disease also differed significantly among tumor types ($p=0.011$) and was most common in osseous lesions. Complications occurred in 17.4% of patients; complication types varied significantly across tumor groups ($p=0.035$). Recurrence data were available for 326 patients, and recurrence occurred in 40 patients (12.3%), most frequently in juvenile nasopharyngeal angiofibroma (23.4%; $p=0.010$).

Conclusion: Histological subtype was associated with surgical approach, residual disease, complication pattern, and recurrence. These findings support individualized surgical planning and histology-specific follow-up in benign sinonasal tumors.

Keywords: Sinonasal neoplasms, sinonasal papilloma, juvenile nasopharyngeal angiofibroma, osteoma, endoscopic surgery, recurrence

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Cite this article as: Kara H, Avcı K, Alayoğlu VE, Olgun F, Öcal YB, Aydemir L, et al. Benign sinonasal tumors: a 17-year single center experience. Turk Arch Otorhinolaryngol. 2026; 64(3): 154-162

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Received Date: 30.06.2026

Accepted Date: 22.09.2026

Epub: 29.09.2026

Publication Date: 30.09.2026

Introduction

Benign sinonasal tumors represent a clinically diverse group of lesions, including epithelial, vascular, fibro-osseous, and other histopathological entities with markedly different biological behavior (1). Although these tumors are benign, their management can be challenging because of tumor-related factors such as local aggressiveness, vascularity, proximity to the orbit and skull base, and the potential for residual or recurrent disease.

Among sinonasal tumors, sinonasal papilloma, juvenile nasopharyngeal angiofibroma (JNA), and osseous tumors constitute key histological subgroups with distinct management considerations. Sinonasal papilloma is notable for its potential of recurrence and its recognized risk of malignant transformation (2). JNA is a highly vascular tumor affecting predominantly adolescent males, in which bleeding control and recurrence prevention remain central concerns (3). Osseous lesions, including osteoma, fibrous dysplasia and ossifying fibroma, differ substantially in clinical behavior and treatment goals, ranging from observation to complete excision (4).

Advances in endoscopic surgery have transformed the treatment of benign sinonasal tumors, allowing effective resection with reduced morbidity in many cases (5,6). However, open and combined approaches remain necessary in selected cases depending on histopathological subtype and anatomical extension (4,7). Although many studies have focused on individual benign sinonasal tumor entities (4,8-10), studies evaluating different tumor subtypes within a large cohort remain limited. Therefore, this study aimed to evaluate a large single-center surgical cohort of benign sinonasal tumors and to compare demographic features, surgical approaches, complications, residual disease, and recurrent disease status across tumor subtypes.

Methods

A single-center retrospective cohort study was conducted and approved by the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee (approval no: 08, date: 18.04.2025). Written informed consent for surgery and for the use of anonymized clinical data for scientific purposes was obtained as part of the institutional general surgical consent process. The requirement for additional study-specific informed consent was waived due to the retrospective design of the study. Medical records of patients diagnosed with benign sinonasal tumors who underwent endoscopic, open, or combined surgical procedures between January 2007 and December 2024 were reviewed (n=403). Patients with less than three months of follow-up were excluded from the study (n=35).

Data on demographics (gender and age at surgery), histological tumor type, surgical approach, primary versus revision surgery status, presence of residual disease after surgery, perioperative and postoperative complications, follow-up duration, and recurrence were extracted from patients' electronic medical records.

JNAs were staged according to the Radkowski classification (11), and inverted papillomas were staged according to the Krouse classification (12).

The primary objectives of this study were as follows: (i) to perform a descriptive analysis of all collected variables, (ii) to compare surgical approach, residual disease, complication, and recurrence rates across different histological tumor types, and (iii) to compare complication and recurrence rates between primary and revision cases.

Statistical Analysis

Descriptive analyses were performed for all variables. Q-Q plots were used to assess the normality of continuous variables. Continuous variables are presented as mean (standard deviation) or median [interquartile range (IQR)] according to their distribution. Categorical variables are reported as counts (percentages). The Kruskal-Wallis test was applied for between-group comparisons. Associations between categorical variables were evaluated using chi-square tests; however, Fisher's exact test was performed when more than 25% of cells had an expected count of fewer than five.

Data analyses were conducted using SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY). A p-value of <0.05 was considered statistically significant for all analyses.

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (13).

Use of Artificial Intelligence-Assisted Technologies

AI-assisted tools were used solely for grammar, spelling, and language editing. No AI-assisted technology was used for data collection, statistical analysis, interpretation of results, or generation of scientific conclusions. The authors reviewed and approved the final manuscript and take full responsibility for its content.

Results

Demographics

A total of 368 patients with benign sinonasal tumors were included in the study. The age distribution of patients at the time of surgery exhibited a bimodal pattern, with peaks observed in late adolescence to early adulthood and in the fifth to sixth decades of life (Figure 1). The median age was 42.5 years (IQR: 18-56), with a range of 0 to 84 years. Of the 368 patients, 108 (29.3%) were female and 260 (70.7%) were male. The mean follow-up duration was 42.8 ± 40.6 months (range: 3-209 months).

Histological Tumor Types

Sinonasal papilloma was diagnosed in 126 cases (34.2%), osseous lesions in 83 cases (22.6%), and JNA in 70 cases (19.0%). The remaining 89 cases (24.2%) were classified as

other benign sinonasal tumors. The histological subtypes are detailed in Table 1. The age distribution of patients differed significantly across tumor types ($p<0.001$). Patients with JNA were the youngest, with a median age of 16 years (IQR: 14-19), whereas patients with sinonasal papilloma had the highest median age of 55.5 years (IQR: 49-64). Patients with osseous lesions had a median age of 30 years (IQR: 18-43), and patients in the “other” category had a median age of 44 years (IQR: 32-59). Post-hoc pairwise comparisons confirmed statistically significant differences between all groups after Bonferroni correction (adjusted $p<0.05$ for all comparisons). A significant association was observed between gender and tumor type ($\chi^2=59.57$, $df=3$, $p<0.001$). JNA showed a male predominance (95.7% male), while sinonasal papilloma also occurred more frequently in males (82.5% male). In contrast, osseous lesions and tumors classified as other displayed a more balanced gender distribution (male: 53.0% and 50.6%, respectively). The detailed histopathological distribution of the 89 tumors in the other benign sinonasal tumor category is presented in Table 2.

Staging data were available for all 70 patients with JNA and all 106 patients with inverted papilloma. According to the Radkowski classification (11), stage IIA was the most frequent JNA stage (23/70, 32.9%), followed by stage IIIA (14/70, 20.0%). According to the Krouse classification (12), T3 was the most frequent inverted papilloma stage (47/106, 44.3%), followed by T2 (41/106, 38.7%) (Table 3).

A significant association was found between surgical approach and tumor type ($\chi^2=52.41$, $df=6$, $p<0.001$). The endoscopic approach was the most frequently employed technique overall (74.5%), particularly in sinonasal papilloma (88.1%), JNA (75.7%), and other tumors (78.7%). In contrast, osseous lesions had a higher proportion of open surgery (37.3%) compared with other groups. Combined

approaches were less common overall (9.8%) but were used across all tumor types (Table 4).

There was no significant difference in the distribution of primary versus revision surgeries across tumor types ($p=0.129$). Revision surgeries constituted 16.6% of the total cases.

A statistically significant difference was observed in the rate of residual disease left during surgery among tumor types ($\chi^2=16.64$, $df=6$, $p=0.011$). Residual disease was most frequent in osseous lesions (21.7%), whereas it was less common in sinonasal papilloma (6.3%), JNA (8.6%), and other tumors (13.5%). Overall, 85.6% of all cases were reported to have no residual disease at the end of surgery. Among 43 patients with documented residual disease, 23 patients (53.5%) were managed with observation alone, 14 patients (32.6%) underwent additional surgery, and 6 patients (14.0%) had no documented follow-up data regarding residual management. By tumor type, surgery rates were 22.2% in osseous lesions (4/18), 71.4% in sinonasal papilloma (5/7), 50.0% in JNA (3/6), and 16.7% in other tumors (2/12) ($p=0.102$). Within the osseous group, residual disease was present in 6 of 39 osteomas (15.4%), 6 of 24 fibrous dysplasia cases (25.0%), 5 of 15 ossifying fibromas (33.3%), and 1 of 5 aneurysmal bone cysts (20.0%) (Table 5).

Perioperative or postoperative complications occurred in 17.4% ($n=64$) of patients, with no statistically significant difference in complication rates between tumor types ($p=0.108$). The most frequent complication was epistaxis requiring intervention (53.1%), followed by cerebrospinal fluid (CSF) leak (15.6%), orbital penetration (6.3%), orbital hematoma (3.1%), and oroantral fistula (3.1%) (Figure 2). Subgroup analysis of complication types showed a statistically significant variation

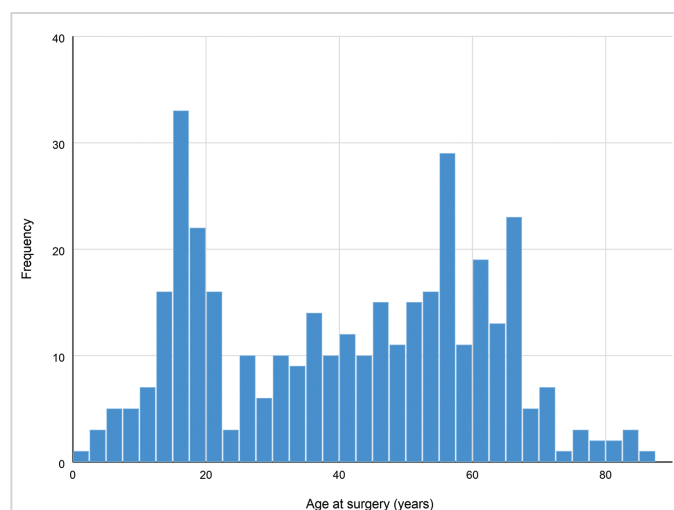


Figure 1. Age distribution of patients at the time of surgery

Table 1. Histological distribution of benign sinonasal tumors

Histological group/subtype	No.	%
Osseous lesions	83	22.6
Osteoma	39	47.0
Fibrous dysplasia	24	28.9
Ossifying fibroma	15	18.1
Aneurysmal bone cyst	5	6.0
Sinonasal papilloma	126	34.2
Inverted papilloma	106	84.1
Oncocytic papilloma	17	13.5
Exophytic papilloma	2	1.6
Mixed papilloma	1	0.8
Juvenile nasopharyngeal angiofibroma	70	19.0
Other benign sinonasal tumors	89	24.2
Total	368	100.0

Percentages for major histological groups are calculated among the total cohort ($n=368$); percentages for indented subtypes are calculated within the respective histological group

across tumor groups ($p=0.035$) driven primarily by the high frequency of epistaxis in JNA patients (47.1% of all epistaxis

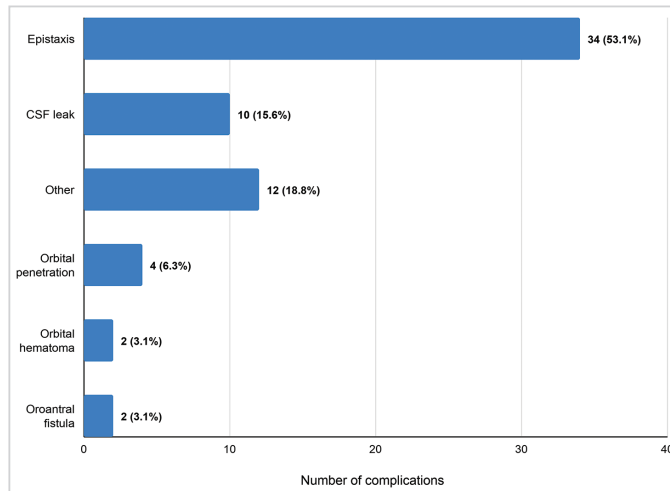


Figure 2. Distribution of perioperative and postoperative complications
CSF: Cerebrospinal fluid

Table 2. Histopathological distribution of other benign sinonasal tumors and their subtypes

Histopathological diagnosis	n (%)
Hemangioma	33 (37.1)
Lobular capillary hemangioma	15 (45.5)
Cavernous hemangioma	8 (24.2)
Epithelioid hemangioma	1 (3.0)
Hemangioma, not specified	9 (27.3)
Hamartoma	16 (18.0)
Respiratory epithelial adenomatoid hamartoma	13 (81.2)
Seromucinous hamartoma	3 (18.8)
Ameloblastoma	7 (7.9)
Central giant cell granuloma	7 (7.9)
Odontogenic myxoma/fibromyxoma	5 (5.6)
Schwannoma	4 (4.5)
Meningioma	2 (2.2)
Mature teratoma	2 (2.2)
Solitary fibrous tumor	2 (2.2)
Langerhans cell histiocytoma	2 (2.2)
Benign spindle cell neoplasm, not specified	2 (2.2)
Sinonasal glomangiopericytoma	2 (2.2)
Pleomorphic adenoma	2 (2.2)
Aneurysmal bone cyst	1 (1.1)
Chondroma	1 (1.1)
Paraganglioma	1 (1.1)
Total	89 (100.0)

Data are presented as n (%). Percentages for main diagnoses were calculated among the 89 tumors classified as other benign sinonasal tumors; percentages for the indented hemangioma and hamartoma subtypes were calculated within their respective parent diagnoses

cases). CSF leaks were predominantly observed in osseous lesions (40%) and sinonasal papilloma (40%). Further details of complication distribution by tumor type are presented in Figure 3. Complication rates were 16.9% ($n=51$) in primary surgeries and 21.3% ($n=13$) in revision surgeries, with no statistically significant difference ($\chi^2=0.665$, $p=0.415$).

As shown in Figure 3, epistaxis requiring intervention occurred in 5 of 18 patients with complications in the osseous group (27.8%), 9 of 18 in the sinonasal papilloma group (50.0%), 16 of 17 in the JNA group (94.1%), and 4 of 11 in the other benign tumor group (36.4%). CSF leak occurred in

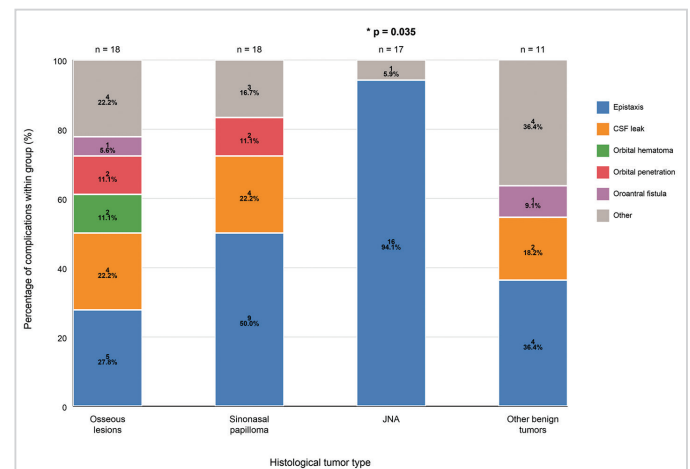


Figure 3. Distribution of complication types according to histological tumor type
CSF: Cerebrospinal fluid, JNA: Juvenile nasopharyngeal angiofibroma

Table 3. Tumor staging of juvenile nasopharyngeal angiofibroma and inverted papilloma

Tumor type	Staging system	Stage	n (%)
Juvenile nasopharyngeal angiofibroma	Radkowski	IA	7 (10.0)
		IB	9 (12.9)
		IIA	23 (32.9)
		IIB	7 (10.0)
		IIC	7 (10.0)
		IIIA	14 (20.0)
		IIIB	3 (4.3)
		Total	70 (100.0)
Inverted papilloma	Krouse	T1	13 (12.3)
		T2	41 (38.7)
		T3	47 (44.3)
		T4	5 (4.7)
		Total	106 (100.0)

Data are presented as n (%). Percentages were calculated within each tumor type. JNA was staged according to the Radkowski classification (11), and inverted papilloma was staged according to the Krouse classification (12). JNA: Juvenile nasopharyngeal angiofibroma

four osseous lesion cases, four sinonasal papilloma cases, and two other benign tumor cases. Orbital hematoma occurred only in the osseous group, orbital penetration occurred in the osseous and sinonasal papilloma groups, and oroantral fistula occurred in one osseous lesion case and one other benign tumor case.

Recurrence

Recurrence status was available for 326 patients. Of these, 40 patients (12.3%) experienced recurrence, whereas 286 patients (87.7%) showed no evidence of recurrence. Recurrence rates varied significantly across tumor types ($\chi^2=11.39$, $df=3$, $p=0.010$), with the highest recurrence observed in JNA (23.4%) compared to osseous lesions (5.8%), sinonasal papilloma (8.9%), and other tumors (13.6%) (Table 6). Recurrence was observed in 29 of 269 primary surgeries (10.8%) and 11 of 57 revision surgeries (19.3%), while no recurrence was documented in 240 primary cases (89.2%) and 46 revision cases (80.7%), with no statistically significant difference ($\chi^2=3.17$, $df=1$, $p=0.075$).

The median time to recurrence was 26.2 months (IQR: 13.6-44.4 months). There was no statistically significant difference in time to recurrence across tumor types ($H=6.46$, $df=3$, $p=0.091$) (Figure 4).

Among patients with recurrence, 35 (87.5%) underwent revision surgery, whereas 5 (12.5%) were managed with observation alone. Surgery was the most common management strategy across all tumor types, with rates of 75.0% for osseous lesions (3/4), 100.0% for sinonasal papilloma (10/10), 80.0% for JNA (12/15), and 90.9% for other tumors (10/11) ($p>0.05$). Representative radiological images of selected tumors, postoperative findings, and recurrence are presented in Figure 5.

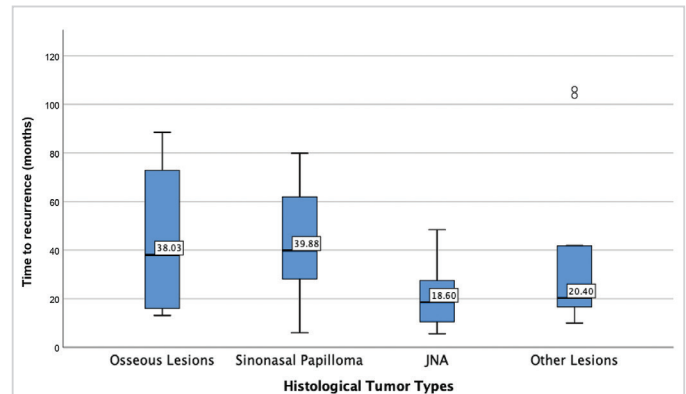


Figure 4. Time to recurrence according to histological tumor type
JNA: Juvenile nasopharyngeal angiofibroma

Table 4. Surgical approaches according to histological tumor type

Surgical approach	Osseous lesions (n=83)	Sinonasal papilloma (n=126)	JNA (n=70)	Other benign tumors (n=89)	Total (n=368)
Endoscopic	40 (48.2)	111 (88.1)	53 (75.7)	70 (78.7)	274 (74.5)
Open	31 (37.3)	4 (3.2)	9 (12.9)	14 (15.7)	58 (15.8)
Combined	12 (14.5)	11 (8.7)	8 (11.4)	5 (5.6)	36 (9.8)

Data are presented as n (%). Percentages are column percentages. Overall association between surgical approach and histological tumor type: chi-square=52.41, $df=6$, $p<0.001$. JNA: Juvenile nasopharyngeal angiofibroma

Table 5. Residual disease according to osseous lesion subtype

Osseous lesion subtype	No. of patients	Residual disease, n (%)
Osteoma	39	6 (15.4)
Fibrous dysplasia	24	6 (25.0)
Ossifying fibroma	15	5 (33.3)
Aneurysmal bone cyst	5	1 (20.0)
Total	83	18 (21.7)

Data are presented as n (%). Percentages were calculated within each osseous lesion subtype

Table 6. Recurrence according to histological tumor type

Recurrence status	Osseous lesions (n=69)	Sinonasal papilloma (n=112)	JNA (n=64)	Other benign tumors (n=81)	Total (n=326)
No recurrence	65 (94.2)	102 (91.1)	49 (76.6)	70 (86.4)	286 (87.7)
Recurrence	4 (5.8)	10 (8.9)	15 (23.4)	11 (13.6)	40 (12.3)

Data are presented as n (%). Percentages are column percentages among patients with available recurrence data. Overall association between recurrence and histological tumor type: chi-square =11.39, $df=3$, $p=0.010$. JNA: Juvenile nasopharyngeal angiofibroma

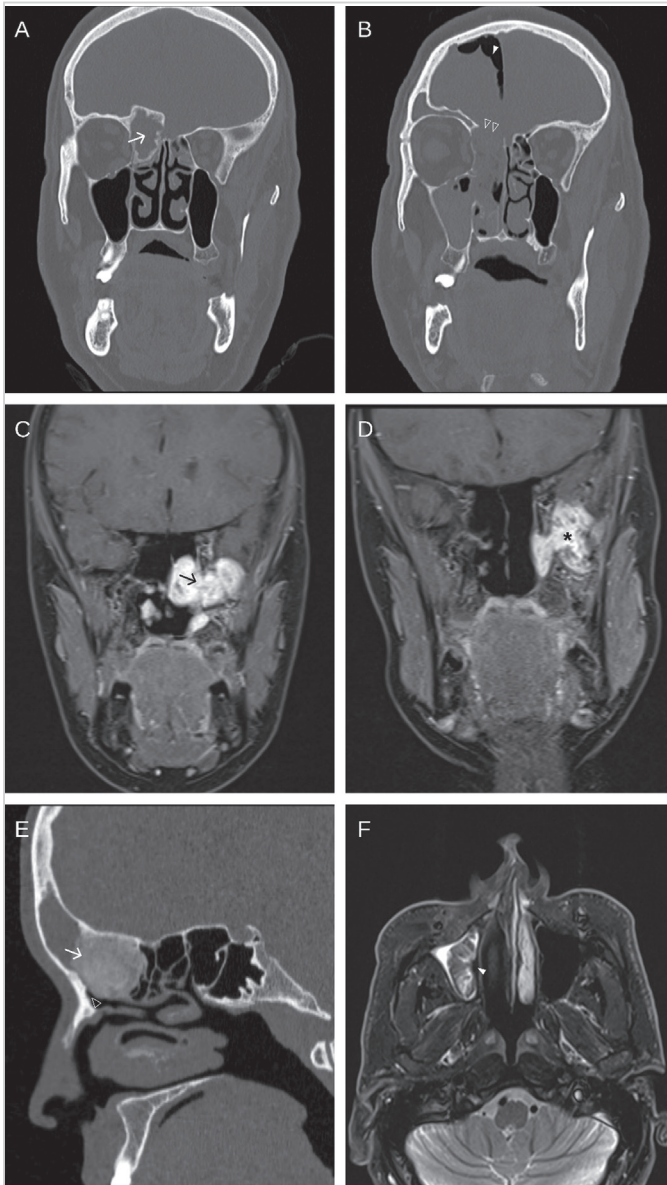


Figure 5. Representative cases of surgically treated benign sinonasal tumors. (A) Preoperative coronal computed tomography showing an ossifying fibroma displacing the right lamina papyracea and anterior skull base. (B) Coronal computed tomography obtained on postoperative day 1 in the same patient, who developed headache after excision and fascia lata skull base repair, demonstrating the bony skull base defect and pneumocephalus. (C) Preoperative coronal magnetic resonance imaging of a recurrent juvenile nasopharyngeal angiofibroma in the left infratemporal fossa. (D) Follow-up coronal magnetic resonance imaging of the same patient showing further recurrence at the same site. (E) Sagittal computed tomography of a frontoethmoidal osteoma narrowing the frontal recess. (F) Axial magnetic resonance imaging showing a convoluted cerebriform pattern consistent with inverted papilloma in the maxillary sinus; the site of origin was suggested to be the medial maxillary wall and confirmed intraoperatively

Discussion

Benign sinonasal tumors encompass a broad spectrum of histopathological subtypes with differing biological behavior and distinct implications for diagnostic evaluation, treatment, and surveillance (1). In our cohort of 368 surgically treated benign sinonasal tumors, histological subtype was associated with clinically meaningful differences in patient demographics, surgical approach, residual disease, complication patterns and recurrence. The demographic distribution across tumor subtypes was consistent with the established epidemiology of these lesions. Sinonasal papilloma typically presents in middle-aged adults with a male predominance, whereas JNA characteristically affects adolescent males; a similar pattern was observed in our cohort (2,3).

The significant association between histological subtype and surgical approach in our cohort suggests that operative strategy was driven primarily by lesion-specific anatomical and biological characteristics. Endoscopic surgery predominated overall, particularly in sinonasal papilloma and JNA, which is in line with prior series showing that endoscopic resection has become the preferred approach for most sinonasal papillomas and is effective in appropriately selected JNA cases (5,6,14). The more frequent use of open surgery in osseous lesions is therefore clinically plausible. This approach is consistent with previous reports on sinonasal fibro-osseous lesions, in which external or combined approaches were required in selected cases according to lesion site and extent, particularly when the orbit, frontal sinus, or skull base was involved (4,9). Although used in a limited number of patients, combined approaches were observed across multiple histological groups in our series. The presence of combined approaches across histological groups supports the view that endoscopic and open techniques should be regarded as complementary rather than mutually exclusive when managing benign sinonasal tumors.

Residual disease also differed significantly across histological subtypes, with the highest rate observed in osseous lesions. This finding should be interpreted cautiously, as the osseous group comprises entities with distinct biological behavior and different therapeutic goals. In ossifying fibroma, particularly in juvenile variants, complete excision is generally pursued whenever feasible because these lesions may behave in a locally aggressive manner (9). By contrast, fibrous dysplasia is typically regarded as a developmental fibro-osseous disorder rather than a true neoplasm, and management is often conservative unless there are compressive symptoms, functional impairment, or progressive deformity (15,16). Osteomas likewise differ from both ossifying fibroma and fibrous dysplasia in that they are usually slow-growing and frequently asymptomatic; accordingly, observation may be appropriate in selected cases, whereas surgery is generally

reserved for symptomatic lesions or for tumors whose size and location create a risk of orbital, skull base, or frontal sinus-related complications (16-18). Taken together, these considerations suggest that the higher rate of residual disease in osseous lesions in our cohort reflects not only technical constraints of resection but also biological and management heterogeneity within this group. Residual disease was identified in 6.3% of our sinonasal papilloma cases, and 71.4% of these patients underwent additional surgery. In sinonasal papilloma, complete resection remains the operative goal because these tumors are locally aggressive and have potential for malignant transformation (10), limiting the suitability of observation in the presence of residual disease. In JNA, the residual disease rate in our cohort (8.6%) was comparable to the pooled residual tumor rate reported in a systematic review of exclusively endoscopic series (7.7%, 95% confidence interval 5.4%-10.1%), although the comparability of these figures is limited by the fact that our cohort was not managed exclusively with an endoscopic approach (19). Among our patients with residual JNA, half underwent additional surgery, whereas the remainder were followed without immediate reintervention. This variable management pattern may reflect that residual JNA is not managed uniformly in clinical practice; rather, decisions are often guided by serial imaging findings, lesion location, and the balance between the risk of progression and the morbidity of further intervention (14).

Perioperative and postoperative complications occurred in 17.4% of our cohort, and although the overall complication rate was not significantly associated with histological subtype, complication types varied across tumor groups. Epistaxis requiring intervention was the dominant complication and was especially common in JNA, which accounted for 47.1% of all epistaxis events. At our institution, preoperative embolization is routinely utilized 24-48 hours before surgery in all patients with JNA unless there is a contraindication for the procedure. This practice is consistent with the literature, in which preoperative embolization is commonly performed 24-48 hours before surgery and has been associated with lower intraoperative blood loss and reduced transfusion requirements (20-24). The prominence of epistaxis as a complication in our JNA group underscores the intrinsic vascularity of this tumor rather than the absence of a preventive preoperative strategy. CSF leak, in contrast, was seen mainly in osseous lesions and sinonasal papilloma, a pattern that may reflect the need for dissection near the skull base and frontal sinus. Complication rates were higher in revision cases than in primary procedures in our cohort (21.3% vs. 16.9%), but this difference did not reach statistical significance. This may indicate that perioperative morbidity in benign sinonasal tumors is influenced more by lesion-specific anatomical surgical demands rather than revision status alone, but the relatively small number of revision cases in our series should also be considered.

Recurrence also varied by histological subtype in our cohort, with the highest rate observed in JNA (23.4%), followed by other tumors (13.6%), sinonasal papilloma (8.9%), and osseous lesions (5.8%). In JNA, the recurrence rate in our series was similar to the 24.5% overall recurrence rate reported in a meta-analysis by Reyes et al. (25) including both endoscopic and open approaches. McCombe et al. (26) reported an association between preoperative embolization and recurrence in JNA however, more recent literature has suggested that embolization may be correlated with lower recurrence rates (21,27,28). In a recurrence analysis by Attya et al. (29), embolization was associated with recurrence on univariable analysis, whereas only age and tumor size remained independent predictors on multivariable analysis. Taken together, these findings imply that recurrence in JNA may be more strongly related to tumor-driven factors. The recurrence rate observed in sinonasal papilloma in our cases (8.9%) was lower than that reported in many recent series, in which recurrence is generally described in the range of 15% to 20% (10,30,31). In these studies, recurrence was linked to revision cases, more extensive tumors, and technically challenging sites such as the frontal sinus although these associations have not been uniform across all series. Our comparatively low recurrence rate in sinonasal papilloma may be attributable to the differences in tumor extent and location. Recurrence in general was numerically more frequent in revision cases than in primary cases (19.3%-10.8%), but this difference did not reach statistical significance. The median time to recurrence was 26.2 months, with no substantial variation across tumor groups. This time course supports sustained postoperative surveillance, particularly because both JNA and sinonasal papilloma may recur beyond the early postoperative period (10,32).

Study Limitations

Our study has several strengths. It represents a relatively large single-center surgical cohort of benign sinonasal tumors, encompassing a broad histopathological spectrum. The mean follow-up duration was substantial, allowing assessment of both early and late postoperative outcomes. At the same time, several limitations should be acknowledged, including the retrospective design, the long study period with possible temporal variation in imaging, surgical technique, postoperative management, and follow-up, and biological heterogeneity within the osseous lesions and other tumor groups.

Conclusion

In this large single-center retrospective cohort of surgically treated benign sinonasal tumors, histological subtype was associated with meaningful differences in patient demographics, surgical approach, residual disease, complication patterns, and recurrence. Endoscopic surgery

was the predominant approach overall, particularly for sinonasal papilloma and JNA, whereas osseous lesions more frequently required open or combined approaches and had higher rates of residual disease. Although the overall complication rate did not differ significantly between tumor groups, complication types varied according to histology, with epistaxis being the most common complication, especially in patients with JNA. Recurrence occurred in a minority of patients but was most frequent in JNA, emphasizing the need for long-term, tumor-specific surveillance. These findings support individualized surgical planning and follow-up strategies based on histopathological subtype in patients with benign sinonasal tumors.

Ethics

Ethics Committee Approval: A single-center retrospective cohort study was conducted and approved by the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee (approval no: 08, date: 18.04.2025).

Informed Consent: Written informed consent for surgery and for the use of anonymized clinical data for scientific purposes was obtained as part of the institutional general surgical consent process.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.K., L.A., Ş.Ç., M.N.K.T., Concept: H.K., L.A., Ş.Ç., M.N.K.T., Design: H.K., K.A., L.A., Data Collection and/or Processing: V.E.A., F.O., Y.B.Ö., Analysis or Interpretation: H.K., K.A., L.A., Ş.Ç., M.N.K.T., Literature Search: K.A., V.E.A., F.O., Y.B.Ö., Writing: H.K., K.A., V.E.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

- Histological subtype was associated with surgical approach, residual disease, and recurrence in surgically treated benign sinonasal tumors.
- Endoscopic surgery was the predominant approach overall, but open or combined approaches remained important, particularly for osseous lesions.
- Recurrence occurred in 12.3% of patients with available follow-up and was most frequent in juvenile nasopharyngeal angiofibroma.
- Tumor-specific surgical planning and long-term surveillance are warranted in benign sinonasal tumors.

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Original Investigation



Turk Arch Otorhinolaryngol 2026; 64(3): 163-170

DOI: 10.4274/tao.2026.2026-6-13

Burnout and Work Engagement among Otorhinolaryngologists in Türkiye: A Multicenter Cross-Sectional Survey

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Abstract

Objective: Burnout and reduced work engagement are recognized occupational concerns among physicians; however, specialty-specific data on otorhinolaryngology (ORL) practice in Türkiye are limited. This multicenter study evaluated burnout and work engagement among otorhinolaryngologists and examined their associations with sociodemographic characteristics and institutional settings.

Methods: This cross-sectional online survey included 120 otorhinolaryngologists working in different cities and institutional settings across Türkiye, including tertiary city hospitals, university hospitals, training and research hospitals, state hospitals, and private clinics. Burnout was assessed using the Maslach Burnout Inventory (MBI), comprising the emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (PA) subscales. Work engagement was assessed using the nine-item Utrecht Work Engagement Scale (UWES-9). Multivariable median regression analyses were performed to identify factors independently associated with the study outcomes.

Results: Based on the predefined MBI thresholds, 65.8% of participants scored within the high range for EE, and 41.7% scored within the high ranges for both EE and DP. Female participants had higher EE and DP scores than male participants (both $p \leq 0.001$). Increasing age was associated with lower DP and higher PA scores. In the unadjusted analyses, physicians working in city hospitals had higher DP scores than those working in university hospitals ($p = 0.016$). In the multivariable median regression analyses, female sex was the only factor independently associated with higher EE ($p < 0.001$) and DP ($p = 0.034$) scores. The total UWES-9 score was negatively correlated with EE and DP and positively correlated with PA (all $p < 0.001$).

Conclusion: Burnout-related dimensions, particularly EE and DP, were frequently observed among otorhinolaryngologists in Türkiye. Female sex was independently associated with higher EE and DP scores. These findings highlight the need to monitor occupational well-being among ORL physicians and may inform the development of institution-level initiatives aimed at improving workplace support and organization.

Keywords: Burnout, professional, work engagement, occupational stress, otolaryngologists

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Cite this article as: Akbal Çufalı Ş, Güneş MM, Şahin ÇE. Burnout and work engagement among otorhinolaryngologists in Türkiye: a multicenter cross-sectional survey. Turk Arch Otorhinolaryngol. 2026; 64(3): 163-170

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Received Date: 11.06.2026

Accepted Date: 04.08.2026

Epub: 28.09.2026

Publication Date: 30.09.2026



Introduction

Physicians face chronic occupational stress from multiple directions: patient volume, administrative load, high-stakes clinical decisions, and repeated exposure to distressing situations. These pressures accumulate across training and practice, and their effects on professional well-being have become increasingly difficult to ignore (1,2). Burnout has received particular attention due to its associations with job dissatisfaction, reduced empathy, intention to leave practice, and risks to the quality and safety of patient care (1-4).

Burnout is defined by three dimensions: emotional exhaustion (EE), depersonalization (DP) or cynicism, and reduced personal accomplishment (PA). Although these are sometimes discussed alongside related constructs such as compassion fatigue or compassion satisfaction, they are conceptually distinct. Using a burnout-specific instrument and interpreting its subscales separately remains important when evaluating occupational well-being in clinical populations.

Burnout captures what is depleted in professional life, whereas work engagement reflects the positive dimensions that may sustain it. Defined by vigor, dedication, and absorption, high engagement has been associated with resilience, motivation, and more sustainable professional functioning (5). Assessing both constructs together offers a more complete picture of occupational well-being than assessing either construct alone.

Surgical specialties carry a specific occupational burden: long hours, operative responsibility, urgent decisions, medicolegal exposure, and the emotional weight of high-stakes care (6,7). Otorhinolaryngology (ORL) combines this with high outpatient volume, emergency airway management, oncologic and functional surgery, and continuous patient contact across acute and chronic conditions (8). Despite this workload profile, burnout, and work engagement in otolaryngologists have received limited study. Systematic reviews of ORL trainee burnout have reported prevalence ranging from 29.7% to 86%, with female sex and working hours consistently identified as risk factors (9,10). Broader data from Türkiye show elevated burnout rates among primary care physicians, including during the pandemic period, yet specialty-specific data for ORL practitioners remain absent, and no prior study has examined institution-based differences within this specialty (11).

To our knowledge, this is the first study to assess burnout and work engagement specifically among otolaryngologists in Türkiye, with comparison across institution types. This study aimed to evaluate these dimensions using the Maslach Burnout Inventory (MBI) and Utrecht Work Engagement Scale-9 (UWES-9), and to examine their associations with sociodemographic characteristics and institution type.

Methods

This study was designed as a multicenter, cross-sectional online survey of otorhinolaryngologists practicing in Türkiye. The study was initiated after approval from University of Health Sciences Türkiye, Ankara Bilkent City Hospital Scientific and Ethical Evaluation Board for Medical Research (approval no: TABED 2/1621/2025, date: 21.01.2026).

The survey was distributed to otorhinolaryngologists across seven Turkish cities (Ankara, İstanbul, Konya, Kayseri, Kocaeli, Van, and Malatya), located in the Marmara, Central Anatolia, and Eastern Anatolia regions, encompassing tertiary city hospitals, university hospitals, training and research hospitals, secondary-care state hospitals, and private clinics. Participants were recruited through a two-stage strategy: (i) an open invitation announcement posted on the official website of the Turkish Otorhinolaryngology Head and Neck Surgery Society, followed by (ii) targeted individual outreach via instant messaging applications to otorhinolaryngologists practicing in the target institutions. The survey link was delivered through an online platform (Google Forms). A non-probability convenience sampling strategy was adopted. Rather than targeting a predetermined sample size, the study sought to recruit as many eligible otorhinolaryngologists as possible during the predefined six-month recruitment period. Accordingly, no formal a priori sample-size calculation or power analysis was performed. Given the voluntary, convenience-based recruitment, the sample was not intended to provide statistically representative estimates for the entire otorhinolaryngologist population in Türkiye. Participation was voluntary and anonymous, and informed consent was obtained electronically before participation.

ORL residents and actively practicing ORL specialists were eligible for inclusion. Participants provided sociodemographic and professional information, including age, sex, institution type, duration of professional experience, marital status, and tobacco use. Institution type was categorized as city hospital (high-volume tertiary public hospital), university hospital, training and research hospital, secondary-care state hospital, or private hospital/clinic. Professional experience was recorded as less than 1 year, 1-5 years, 6-10 years, 11-15 years, or more than 15 years. Marital status and tobacco use were also recorded using predefined categories.

Burnout was assessed using the Turkish version of the MBI, adapted and validated by Ergin (12), which includes three subscales: EE, DP, and PA (13,14). Higher EE and DP scores indicate greater burnout, whereas lower PA scores indicate a lower sense of PA. In the presented study, PA is reported in its original direction, with higher scores indicating a greater sense of PA. For descriptive purposes, MBI subscale scores were categorized using thresholds from the third edition of the MBI manual (13). These cut-offs have since been criticized

by the scale authors and removed from the fourth edition, as they were derived by splitting a normative population into tertiles rather than defining a validated clinical threshold; prevalence estimates based on them should be interpreted accordingly.

Work engagement was assessed using the nine-item UWES-9, originally developed by Schaufeli et al. (5). The scale comprises three dimensions—vigor, dedication, and absorption—with three items in each dimension. The Turkish validity and reliability of the nine-item form were evaluated by Özkalp and Meydan (15), and this validated Turkish version was used in the presented study. Subscale and total scores were calculated according to the scale structure, with higher scores indicating greater work engagement.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation or median (minimum-maximum), as appropriate, whereas categorical variables were summarized as frequencies and percentages. Normality of continuous variables was assessed using the Shapiro-Wilk test. Because the main scale scores were not normally distributed, comparisons between two groups were performed using the Mann-Whitney U test, whereas comparisons among more than two groups were performed using the Kruskal-Wallis test. When the Kruskal-Wallis test indicated an overall significant difference, post-hoc pairwise comparisons were performed using Dunn's test with Holm correction for multiple testing. Effect sizes were reported as the rank-biserial correlation (r) for Mann-Whitney U tests and eta-squared based on the Kruskal-Wallis H statistic ($\eta^2[H]$) for Kruskal-Wallis analyses. Associations between continuous variables were evaluated using Spearman's rank correlation coefficient (ρ). To identify factors independently associated with EE and DP, multivariable median regression models were constructed including sex, age, institution type, professional experience, marital status, and tobacco use as covariates. All statistical analyses were performed using R software (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

A total of 120 otorhinolaryngologists were included. The mean age was 29.5 ± 5.32 years, and the median age was 28 years (range, 25-60 years). Seventy-three participants (60.8%) were men and 47 (39.2%) were women. Regarding institution types, 49 participants (40.8%) worked in city hospitals (high-volume public hospitals), 47 (39.2%) in university hospitals, 14 (11.7%) in training and research hospitals, 7 (5.8%) in secondary-care state hospitals, and 3 (2.5%) in private hospitals or clinics. The most common professional experience category was 1-5 years (68.3%).

The largest marital status group was single without children (52.5%). Tobacco use was reported as never used by 49.2%, formerly used by 7.5%, occasional use by 15.0%, and daily use by 28.3% of participants.

The mean MBI subscale scores were 33.4 ± 15.2 for EE, 13.3 ± 8.4 for DP, and 28.9 ± 11.0 for PA. The corresponding median scores were 33 (range, 0-54), 12 (range, 0-30), and 30 (range, 0-48), respectively (Table 1). Cronbach's alpha values were 0.941 for EE, 0.937 for DP, and 0.943 for PA, indicating high internal consistency for all three subscales.

When MBI subscores were classified according to the standard thresholds defined by Maslach et al. (13), 79 physicians (65.8%) showed high EE, 57 (47.5%) showed high DP, and 68 (56.7%) showed low PA. Fifty physicians (41.7%) met the criteria for high scores on both EE and DP simultaneously, reflecting a pattern consistent with advanced occupational burnout.

Age was not significantly correlated with EE ($\rho = -0.131$, $p = 0.153$). However, increasing age was associated with lower DP ($\rho = -0.248$, $p = 0.006$) and higher PA ($\rho = 0.237$, $p = 0.009$). In sex-based comparisons, women had significantly higher EE scores than men ($p < 0.001$, $r = 0.382$) and significantly higher DP scores ($p = 0.001$, $r = 0.290$). PA did not differ significantly between women and men ($p = 0.919$, $r = 0.010$) (Table 2).

Table 1. Participant characteristics and scale scores

Variable	n (%) or mean $\pm$ SD	Median (range)
Age, years	29.5 ± 5.32	28 (25-60)
Female sex	47 (39.2)	
Male sex	73 (60.8)	
City hospital	49 (40.8)	
University hospital	47 (39.2)	
Training and research hospital	14 (11.7)	
Secondary-care state hospital	7 (5.8)	
Private hospital/clinic	3 (2.5)	
Never used tobacco	59 (49.2)	
Former tobacco use	9 (7.5)	
Occasional tobacco use	18 (15.0)	
Daily tobacco use	34 (28.3)	
Emotional exhaustion	33.4 ± 15.2	33 (0-54)
Depersonalization	13.3 ± 8.4	12 (0-30)
Personal accomplishment	28.9 ± 11.0	30 (0-48)
UWES vigor	2.39 ± 1.51	
UWES dedication	3.16 ± 1.66	
UWES absorption	2.88 ± 1.71	
UWES total score	2.81 ± 1.43	

SD: Standard deviation, UWES: Utrecht Work Engagement Scale

Institution type was associated with differences in EE and DP scores. For EE, the overall Kruskal-Wallis test score was significant ($p=0.0445$, $\eta^2[H]=0.050$), indicating a small effect. Post-hoc pairwise comparisons for EE did not yield significant differences between groups with sufficient sample size. The private hospital/clinic subgroup ($n=3$) was excluded from pairwise comparisons due to insufficient sample size. For DP, the overall difference was also significant ($p=0.00095$, $\eta^2[H]=0.127$), indicating a medium effect. Post-hoc analysis showed that physicians working in city hospitals had higher DP scores than those working in university hospitals ($p=0.016$). PA did not differ significantly by institution type ($p=0.498$) (Table 3).

The mean UWES-9 scores were 2.39 ± 1.51 for vigor, 3.16 ± 1.66 for dedication, 2.88 ± 1.71 for absorption, and 2.81 ± 1.43 for the total UWES score. UWES scores did not

differ significantly by sex or age group. In institution-based comparisons, dedication ($p=0.024$) and total UWES score ($p=0.044$) showed significant overall differences; however, none of the pairwise comparisons remained significant after Dunn-Holm correction. Vigor and absorption did not differ significantly by institution type ($p=0.192$ and $p=0.066$, respectively) (Table 4).

UWES subscale and total scores were correlated with MBI dimensions in the expected directions. The UWES total score correlated negatively with EE ($r=-0.346$, $p<0.001$) and DP ($r=-0.393$, $p<0.001$), and positively with PA ($r=0.623$, $p<0.001$). Vigor and dedication were negatively associated with EE and DP and positively associated with PA. Absorption was positively correlated with PA but was not significantly correlated with EE or DP (Table 5).

Table 2. Associations of age and sex with Maslach Burnout Inventory subscales

Variable	Test/statistic	p-value	Direction
Age-emotional exhaustion	Spearman rho=-0.131	0.153	Not significant
Age-depersonalization	Spearman rho=-0.248	0.006	Older age, lower DP
Age-personal accomplishment	Spearman rho=0.237	0.009	Older age, higher PA
Sex-emotional exhaustion	$r=0.382$	<0.001	Higher in women
Sex-depersonalization	$r=0.290$	0.001	Higher in women
Sex-personal accomplishment	$r=0.010$	0.919	Not significant

Age associations were assessed with Spearman rank correlation. Sex comparisons were assessed with the Mann-Whitney U test; r indicates rank-biserial effect size
DP: Depersonalization, PA: Personal accomplishment

Table 3. Institution-based comparison of emotional exhaustion and depersonalization scores

Institution type	EE, median (IQR)	DP, median (IQR)
Secondary-care state hospital	30 (18-43)	8 (4.5-16.5)
Training and research hospital	40.5 (28-45)	12 (7.75-23.8)
Private hospital/clinic	2 (2-2)	1 (0.5-1)
City hospital	33 (25-51)	15 (12-22)
University hospital	31 (18-45)	9 (6-16.5)
Overall p-value	0.0445	0.00095
Effect size	$\eta^2[H]=0.050$	$\eta^2[H]=0.127$

Kruskal-Wallis test was used for overall comparisons. Dunn post-hoc tests with Holm correction were used for pairwise comparisons. The city hospital group had higher depersonalization than the university hospital group in post-hoc pairwise comparison ($p=0.016$). The private hospital/clinic subgroup ($n=3$) was excluded from pairwise comparisons

EE: Emotional exhaustion, DP: Depersonalization, IQR: Interquartile range

Table 4. Institution-based comparison of UWES-9 subscales and total score

Variable	City hospital	University	Training/research	Other	H	p-value
Vigor	2.17 ± 1.32	2.65 ± 1.43	2.93 ± 1.31	3.37 ± 1.81	4.739	0.192
Dedication	2.43 ± 1.41	3.71 ± 1.69	3.79 ± 1.11	3.87 ± 2.03	9.426	0.024
Absorption	2.29 ± 1.48	3.48 ± 1.70	3.40 ± 1.39	3.47 ± 1.84	7.185	0.066
UWES total	2.30 ± 1.25	3.28 ± 1.52	3.37 ± 1.10	3.57 ± 1.85	8.095	0.044

Values are mean $\pm$ standard deviation. Kruskal-Wallis test was used for overall comparisons. Although dedication and UWES total score showed significant overall differences, no pairwise comparison remained significant after Dunn-Holm correction. "Other" includes secondary-care state hospitals and private hospital/clinic

UWES: Utrecht Work Engagement Scale

In multivariable median regression models, female sex remained independently associated with higher EE and DP scores. For EE, female sex was associated with higher median EE [coefficient=15.62, 95% confidence interval (CI): 7.84-23.40, $p<0.001$]. For DP, female sex was significantly associated with higher median DP (coefficient=4.40, 95% CI: 0.34-8.46, $p=0.034$) (Table 6).

Discussion

This multicenter survey evaluated burnout and work engagement among Turkish otorhinolaryngologists. Using standard MBI thresholds, 65.8% of participants had high EE, 47.5% had high DP, and 41.7% met both criteria simultaneously, indicating a substantial burden of burnout among participating physicians. Increasing age was associated with lower DP, and higher PA. Female sex was independently associated with higher EE and DP in multivariable regression. In unadjusted comparisons, physicians in city hospitals showed higher DP than those in university hospitals. Work engagement correlated inversely with EE and DP, and positively with PA. Since the study population predominantly consisted of physicians in the early stages of their careers, these findings should primarily be interpreted within the context of early-career ORL practice rather than as representative of the entire ORL workforce in Türkiye.

Table 5. Correlations between UWES-9 and Maslach Burnout Inventory dimensions

UWES dimension	Emotional exhaustion	Depersonalization	Personal accomplishment
Vigor	-0.441***	-0.391***	0.539***
Dedication	-0.342***	-0.506***	0.641***
Absorption	-0.148	-0.151	0.469***
UWES total	-0.346***	-0.393***	0.623***

Values are Spearman rank correlation coefficients. Negative coefficients indicate lower burnout dimension scores with higher work engagement; positive coefficients indicate higher personal accomplishment with higher work engagement.

***: $p<0.001$, UWES: Utrecht Work Engagement Scale

These rates are consistent with the broader ORL and surgical burnout literature. Systematic reviews of ORL trainees have documented burnout prevalence of 29.7% to 86%, and the presented findings suggest that this substantial burden is also evident in a predominantly early-career ORL physician sample in Türkiye (9,10). Operative responsibility, workload, and organizational pressures create conditions for burnout rather than individual weakness (6,7). ORL adds its own pressures to this picture: emergency airway decisions, oncologic and functional surgery, high outpatient volume, and uninterrupted patient contact across both acute and chronic care. The burnout observed here is not surprising given these demands, but its prevalence warrants attention.

The simultaneous assessment of burnout and engagement produced one pattern worth noting: dedication scores were relatively higher than vigor and absorption scores, suggesting that many physicians still find their work meaningful even when energy and immersion are depleted. The correlations between UWES total score and all three MBI dimensions ran in the expected directions and were consistent with the view that engagement is not simply the absence of burnout, but a distinct positive component of occupational well-being (5).

Age associations followed a recognizable pattern. Older physicians had lower DP and higher PA, while EE showed no significant age correlation. The findings should be interpreted in light of the career-stage distribution of the sample. More than two-thirds of the participants had one to five years of professional experience with a median age of 28 years; therefore, the presented study predominantly reflects the experiences of trainees and early-career ORL physicians. This observation is consistent with previous evidence indicating that residency and the transition to independent practice represent particularly demanding stages of surgical careers. Systematic reviews of otolaryngology trainees have reported burnout prevalences ranging from 29.7% to 86%, with longer working hours, female sex, educational demands, and limited professional autonomy identified as important contributors to physician distress (9,10). Accordingly, the

Table 6. Multivariable median regression models for emotional exhaustion and depersonalization

Variable	EE Coef.	95% CI	p	DP Coef.	95% CI	p
Female sex ¹	15.62	7.84-23.40	<0.001	4.40	0.34-8.46	0.034
Age, years	0.04	-1.22-1.29	0.955	-0.40	-1.06-0.26	0.230
City hospital ²	-1.91	-11.93-8.12	0.707	3.20	-2.04-8.44	0.228
University hospital ²	1.49	-8.67-11.66	0.772	-3.00	-8.31-2.31	0.265
Training and research hospital ²	1.05	-11.65-13.75	0.870	2.40	-4.23-9.03	0.475
Professional experience ³	-3.24	-11.03-4.55	0.412	0.40	-3.67-4.47	0.846
Married ⁴	-0.71	-9.28-7.87	0.870	-0.20	-4.68-4.28	0.930
Tobacco use ⁵	-1.76	-9.26-5.74	0.642	1.00	-2.92-4.92	0.614

Multivariable median regression models. Coefficients represent the change in the median outcome relative to the reference category

¹: Reference: male sex, ²: Reference: secondary-care state hospital; the private hospital/clinic subgroup (n=3) was excluded due to insufficient sample size, ³: Reference: less than 1 year,

⁴: Reference: single, ⁵: Reference: never use. Coef.: Median regression coefficient, CI: Confidence interval, EE: Emotional exhaustion, DP: Depersonalization

associations observed between younger age, DP, and PA in the presented study may partly reflect the occupational challenges inherent to training and early career development rather than age alone. Because career stage was not evenly represented in our sample, these findings should not be interpreted as definitive differences between residents, early-career specialists, and senior specialists.

Female sex was the only independent predictor of both EE and DP in the adjusted models. Similar concerns have been reported across surgical populations. Studies examining compassion fatigue in female surgeons and pediatric surgeons have found that women are disproportionately affected by EE and secondary traumatic stress, with similar patterns described in trauma surgery populations, and burnout-specific findings in female head and neck surgeons point in the same direction (16-19). There are likely to be multiple mechanisms at play, such as role expectations, work-family conflict, sex-related professional stressors, and differences in emotional labor. However, this study was not designed to disentangle them. The presented findings suggest that female otorhinolaryngologists may carry a disproportionate burnout burden, and this observation warrants targeted attention in future research and institutional policy.

In unadjusted comparisons, physicians in city hospitals had higher DP scores than those in university hospitals, with a medium effect size. This finding should be interpreted cautiously because institution types may overlap with other factors, including career stage, workload intensity, patient volume, duty frequency, and professional autonomy. Nevertheless, the observed institution-based pattern suggests that organizational context may be relevant to physician well-being and should be examined in larger studies incorporating direct workload indicators. Because institution types may also be associated with career stages, the observed differences may partially reflect the overrepresentation of early-career physicians within some institution categories. This possibility could not be fully evaluated in the presented study and warrants investigation in future multicenter studies.

The practical implication is straightforward. Burnout at this prevalence is unlikely to be addressed by resilience training alone. Workload distribution, duty scheduling, mentorship for early-career physicians, psychosocial support, and participatory management are the kinds of structural changes that address the conditions producing burnout rather than the individuals experiencing it (20). Female physicians appear to be the group most consistently in need of such measures.

This study has several methodological strengths. The simultaneous evaluation of burnout and work engagement using validated instruments and the multicenter design—spanning seven Turkish cities and multiple institution types,

including three major tertiary city hospitals—improves the geographic and institutional diversity of the sample and provides a broad snapshot of participating ORL physicians across different healthcare settings in Türkiye. To our knowledge, this is the first multicenter assessment of burnout and work engagement focused on Turkish ORL physicians.

Study Limitations

Several limitations should also be acknowledged. The cross-sectional design precludes causal inference. The MBI cut-offs used for categorical classification were derived from the third edition of the MBI manual and have been criticized by the scale authors as statistically arbitrary, having been generated by tertile-splitting a normative population rather than by clinical validation; consequently, the prevalence figures reported here should not be read as defining clinical burnout with precision (13). Recruitment combined an open call through the national ORL society website with targeted instant-messaging outreach, which constitutes non-probability convenience sampling; the denominator of invited physicians could not be determined, and a formal response rate cannot be calculated. As participants self-selected, volunteer bias toward more engaged or more distressed physicians cannot be excluded. In addition, participating centers are located in seven cities across three of Türkiye's seven geographical regions (Marmara, Central Anatolia, and Eastern Anatolia); therefore, the geographic distribution of centers limits the generalizability of the findings to the entire country. Although multiple independent centers contributed to the sample, clustering of responses within hospitals was not modelled, which may have led to under-estimated standard errors; future analyses using multilevel models would be valuable. Furthermore, because 68.3% of participants had one to five years of professional experience, the sample disproportionately represented trainees and early-career physicians. Consequently, the results may not fully reflect the experiences of senior ORL specialists and should not be interpreted as establishing differences between residents and specialists. The private-practice subgroup ($n=3$) was too small for inferential comparison and was excluded from post-hoc analyses. Finally, workload indicators such as weekly hours, night-call frequency, and operative volume were not captured; their absence from the adjusted models represents a meaningful gap that future studies should address directly.

Future research should include larger, multicenter samples with more balanced representation of institution types and should incorporate objective or semi-objective workload indicators. Longitudinal designs would be valuable to clarify whether work engagement protects against later burnout or whether burnout reduces engagement over time. Interventional studies are also needed to test whether organizational changes can reduce burnout and improve work engagement among surgical physicians (1-20).

The institution-based differences observed in unadjusted comparisons suggest that workload and organizational variables, such as duty frequency, outpatient volume, and perceived professional autonomy, may contribute to burnout patterns. Future studies should incorporate these variables directly to clarify how institutional conditions may shape occupational well-being in ORL practice.

Conclusion

In this multicenter sample of otorhinolaryngologists in Türkiye, burnout was common, particularly in the dimensions of EE and DP. Female sex was independently associated with higher EE and DP scores. Work engagement was closely related to burnout dimensions, suggesting that occupational well-being in ORL practice should be evaluated not only through burnout but also through positive professional engagement. Given the predominance of early-career physicians in the study population, these findings are particularly relevant for physician well-being initiatives targeting residency training and the transition to independent clinical practice. These findings highlight the need for continued monitoring of physician well-being and support institution-level strategies focusing on workload organization, psychosocial support, and mentorship in ORL practice.

Ethics

Ethics Committee Approval: The study was initiated after approval from University of Health Sciences Türkiye, Ankara Bilkent City Hospital Scientific and Ethical Evaluation Board for Medical Research (approval no: TABED 2/1621/2025, date: 21.01.2026).

Informed Consent: Participation was voluntary and anonymous, and informed consent was obtained electronically before participation.

Footnotes

Authorship Contributions

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

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

- In this multicenter cross-sectional survey of 120 otorhinolaryngologists in Türkiye, 65.8% showed high emotional exhaustion and 41.7% met the criteria for high

scores on both emotional exhaustion and depersonalization simultaneously.

- Female sex was the only independent predictor of both emotional exhaustion and depersonalization in multivariable median regression, after adjustment for age, institution type, professional experience, marital status, and tobacco use.
- Institution-based differences in depersonalization were observed in unadjusted analyses, particularly between city hospitals and university hospitals, suggesting that organizational and workload-related factors may warrant further investigation.
- Work engagement was inversely associated with emotional exhaustion and depersonalization, and positively associated with personal accomplishment, supporting the view that engagement and burnout represent distinct but related dimensions of occupational well-being.

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Original Investigation



Turk Arch Otorhinolaryngol 2026; 64(3): 171-179

DOI: 10.4274/tao.2026.2026-3-26

Risk Factors for Post-Tonsillectomy Hemorrhage: A 10-Year Retrospective Cohort Study at a Tertiary Military Hospital in Thailand

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Abstract

Objective: Tonsillectomy is one of the most frequently performed surgical procedures worldwide, and several patient—and procedure—related factors have been associated with post-tonsillectomy hemorrhage (PTH). Severe hemorrhage may require reoperation under general anesthesia to achieve hemostasis. The aim of this retrospective cohort study was to identify pre-, intra-, and postoperative factors associated with PTH.

Methods: Records of 549 patients who underwent tonsillectomy at a tertiary military hospital in Thailand between 2010 and 2020 were reviewed, with PTH ascertained by detailed manual chart review.

Results: The mean age was 26.89 ± 15.69 years. PTH occurred in 56 patients (10.2%), most commonly on postoperative day 6. Multivariate logistic regression identified the following independent risk factors: male sex [$p=0.039$; adjusted odds ratio (aOR) 2.11, 95% confidence interval (CI) 1.04-4.30], age <19 years ($p=0.016$; aOR 7.96, 95% CI 1.46-43.27), age 19-45 years ($p=0.024$; aOR 5.74, 95% CI 1.26-26.11), surgeon experience <15 years ($p=0.023$; aOR 2.85, 95% CI 1.16-7.01), elevated mean arterial pressure (MAP) ($p=0.002$; aOR 1.04 per mmHg, 95% CI 1.02-1.07), intravenous (IV) antibiotic prescription ($p=0.036$; aOR 2.03, 95% CI 1.05-3.92), and a day-1 pain score >5 ($p=0.037$; aOR 2.25, 95% CI 1.05-4.81). As the >45-year reference group had few events, the age odds ratios were imprecise; a Firth-penalized pediatric estimate was 6.33 (95% CI 1.52-37.37), and a pooled age <45 versus ≥ 45 contrast gave aOR 5.07 (95% CI 1.56-26.00).

Conclusion: Male sex, age under 45 years, and surgeon experience less than 15 years were the principal independent predictors of PTH; elevated postoperative MAP, a day-1 pain score above 5, and IV antibiotic prescription further characterized higher-risk patients.

Keywords: Tonsillectomy, postoperative hemorrhage, risk factors, retrospective studies, postoperative complications, blood pressure, pain measurement

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Cite this article as: Mounghthong J, Pilakasiri A. Risk factors for post-tonsillectomy hemorrhage: a 10-year retrospective cohort study at a tertiary military hospital in Thailand. Turk Arch Otorhinolaryngol. 2026; 64(3): 171-179

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Received Date: 03.04.2026

Accepted Date: 14.07.2026

Epub: 22.09.2026

Publication Date: 30.09.2026



Introduction

The palatine tonsils are paired lymphoid organs lying within the tonsillar fossae, delimited anteriorly by the palatoglossal arch and posteriorly by the palatopharyngeal arch (1). As components of Waldeyer's ring, they participate in mucosal immune defense and antigen sampling (1). When these tonsils become chronically infected or hypertrophic, tonsillectomy is undertaken for recurrent or chronic tonsillar disease, upper-airway obstruction, or suspected malignancy (2).

Among postoperative complications including pain, hemorrhage, airway obstruction, pulmonary edema, velopharyngeal insufficiency, nasopharyngeal stenosis, and the rare Eagle's syndrome, post-tonsillectomy hemorrhage (PTH) carries the greatest clinical consequence, as extensive blood loss may necessitate reoperation under general anesthesia or blood transfusion, and in severe cases may result in death from airway obstruction, anemia, or hemorrhagic shock.

Muninnobpamasa et al. (3) reported a PTH incidence of 4% among 481 patients at our institution between 2003 and 2006. Østvoll et al. (4) demonstrated a rising national trend in readmission for post-tonsillectomy bleeding from approximately 1% in 1987 to 5% in 2013. At our institution, internal audit data for 2017-2019 recorded PTH rates of 10% (7/68), 15% (10/66), and 8% (6/76) in successive years, yielding an aggregate rate of 11% over the three-year period (23 of 210 patients). This increasing trend prompted the present investigation.

Lechner et al. (5) reported that chronic tonsillitis as a surgical indication was associated with higher PTH incidence, with bipolar cautery being the most widely used technique. Wulu et al. (6) suggested that tonsillar pillar suturing may reduce hemorrhage when electrocautery techniques are used. In contrast, Galindo Torres et al. (7) found no statistically significant association between tonsillectomy indication and PTH. Manimaran et al. (8) identified preoperative factors and surgeon experience as significant contributors. The prevalence of PTH worldwide ranges from approximately 1.5% to 21.8%, with regional variations: 3.16-16.1% in the United States (9-11), 1.5-9.2% in the United Kingdom (12-14), 5.21% in Spain (7), 2.86-6% in Germany (15,16), 2.2% in Taiwan (17), and 11.6-21.84% in Japan (18,19). The global mean prevalence has been estimated at 6.44%. A recent United States pediatric study by Johnson et al. (20) also noted a 2.18% rate of return to the emergency department for postoperative bleeding.

Given the rising incidence at our institution and the divergence between local rates and the published benchmarks, this study aimed to identify the prevalence and independent risk factors for PTH and evaluate the pre-, intra-, and postoperative risk factors associated with this complication at our institution over a 10-year period.

Methods

Study Design and Population

This was a retrospective cohort study. The study population comprised patients who underwent tonsillectomy at the department of otolaryngology in a tertiary military hospital, Thailand, between 2010 and 2020. The study protocol was reviewed and approved by the Institutional Review Board of the Royal Thai Army Medical Department (approval no: R085h/63_Exp, date: 13 June 2020). Informed consent was waived due to the retrospective nature of the study, in accordance with the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Patients who were admitted for tonsillectomy and operated on by attending physicians or residents between 2010 and 2020, and whose records were retrievable from the hospital database were included. Patients whose records were incomplete or missing, and those who were referred from other hospitals specifically for management of PTH were excluded.

Data Collection and Sampling

Data were retrieved using hospital numbers from the hospital database using ICD-9-CM procedure codes 28.2 (tonsillectomy without adenoidectomy), 28.3 (tonsillectomy with adenoidectomy), and 28.7 (control of hemorrhage after tonsillectomy and adenoidectomy). Using the corrected formula $n = Z^2 P(1-P)/d^2$ ($Z=1.96$ for 95% confidence level, $p=0.06$ based on prior literature, $d=0.02$ for precision), the minimum required sample size was 542 patients (4). From the 1,481 eligible cases, 549 records were selected for detailed review. Two levels of case ascertainment were applied. For the full cohort of 1,481 patients, PTH status was derived from ICD-9-CM procedure code 28.7 (control of hemorrhage after tonsillectomy and adenoidectomy), yielding a rate of 6.14%. Because code 28.7 identifies only patients who underwent a procedure to control hemorrhage, this figure represents the rate of procedurally treated, administratively identified hemorrhage rather than the overall PTH rate; administrative coding was recognized to under-ascertain PTH, as conservatively managed or jointly coded bleeds were omitted, so this figure represents a conservative lower bound rather than the true event frequency. In the 549-patient subset, PTH was ascertained by detailed manual chart review, which captured the bleeding episodes missed by coding and yielded a higher, more complete rate of 10.2%. This subset rate is corroborated by our institutional morbidity-and-mortality audit (11%; 23 of 210 patients, 2017-2019), which was likewise chart-based. The two rates therefore reflect differing ascertainment methods rather than sampling bias, and the 549-patient rate is not intended to estimate the administratively coded cohort figure.

Variables Analyzed

Preoperative: Sex, age group, body mass index (BMI; kg/m²) or ideal body weight for patients aged ≤18 years, comorbidities, current medications, baseline vital signs, occupation, tonsillar size, and indication for surgery.

Intraoperative: Surgical technique (cold dissection, dissection with snare, or electrocautery), use of suturing, anesthetic technique, intubation route (transoral vs. transnasal), operative time, and surgeon experience (Category I: attending surgeon ≥15 years of ear, nose and throat training; Category II: attending surgeon <15 years and/or with resident assistance; Category III: primary and assisting surgeons both residents).

Postoperative: Vital signs in the first 24 hours and at discharge, daily pain scores, analgesic and antibiotic type and dose (classified as: no antibiotics; oral antibiotics only; intravenous antibiotics), length of hospital stay, oral hygiene protocol, and histopathology report.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using STATA/MP version 12 (StataCorp LP, College Station, TX, USA). Frequencies with percentages summarized categorical data, whereas continuous data were reported as mean ± standard deviation or as median with interquartile range according to their distribution, which was examined with the Shapiro-Wilk test. Continuous variables were compared between groups using the Student's t-test when the distribution was normal and the Mann-Whitney U test when it was not, while categorical variables were compared using the chi-square or Fisher's exact test as appropriate. Records containing missing values were handled by complete-case analysis. Univariate analyses were performed initially to identify factors potentially associated with PTH. Variables entered in the multivariable logistic regression model were selected based on univariate analysis results ($p < 0.05$), literature review, and clinical relevance. Results from logistic regression analyses are reported as adjusted odds ratio (aOR) with 95% confidence interval (CI). Statistical significance was defined as a two-tailed p -value < 0.05 . Specifically, the following variables were entered into the multivariable model: sex, age group (<19 years, 19-45 years, and >45 years as the reference category), surgeon experience category (Category I, II, and III), postoperative mean arterial pressure (MAP), postoperative day-1 pain score, intubation route, antibiotic type (none, oral, or intravenous), and oral hygiene protocol all of which demonstrated statistical significance on univariate analysis or were deemed clinically relevant a priori based on the literature. Given the small number of bleeding events in the oldest age stratum (>45 years, two events) and the resulting events-per-variable ratio, we performed pre-specified sensitivity analyses to assess model stability: a Firth penalized logistic regression, re-specification of the age reference category (19-45 years), collapse of age into a

binary contrast (<45 vs. ≥45 years), and modelling of age as a continuous variable.

Results

Of the 1,481 patients who underwent tonsillectomy between 2010 and 2020, procedurally treated PTH identified by ICD-9-CM procedure code 28.7 occurred in 6.14%; this administratively identified rate does not capture conservatively managed bleeding episodes. A subset of 549 patients was analyzed by detailed chart review, with approximately equal numbers per year (Table 1). In this chart-reviewed subset, 56 patients (10.2%) had PTH; this higher rate reflects more complete case detection by chart review, corroborated by the institutional audit (11%), rather than sampling bias, as described in the methods section and the limitations. The mean participant age was 26.89 ± 15.69 years (median 24 years, interquartile range 15-37 years, range 3-72 years). The Shapiro-Wilk test confirmed a non-normal age distribution ($p < 0.001$), indicating a heterogeneous cohort comprising both pediatric and adult patients, consistent with the military-hospital setting. PTH occurred in 56 patients (10.2%), most commonly on postoperative day 6.

On univariate analysis, sex and age group were significantly associated with PTH ($p < 0.05$). BMI, body weight, comorbidities, current medications, and tonsillar size were not statistically significant. Chronic tonsillitis as the surgical indication, intraoperative and postoperative factors, including surgeon experience, intubation route, postoperative pain scores, antibiotic administration, and oral hygiene protocol, showed significant differences between groups (Tables 2 and 3). Surgical technique, use of suturing, operative duration, anesthetic agents, and perioperative vital signs other than MAP were not significantly associated with PTH.

Multivariate logistic regression (Table 4) identified the following independent risk factors for PTH: male sex: 13.27% incidence; aOR 2.11 (95% CI 1.04-4.30); $p = 0.039$. Age <19 years (pediatric group): 7.14% incidence; aOR 7.96 (95% CI 1.46-43.27); $p = 0.016$. Age 19-45 years (young adult group): 13.44% incidence; aOR 5.74 (95% CI 1.26-26.11); $p = 0.024$. Surgeon experience (Category II, attending surgeon experience <15 years): 14.9% incidence; aOR 2.85 (95% CI 1.16-7.01); $p = 0.023$. Category III (both surgeons as residents) did not reach statistical significance on multivariate analysis (aOR 1.94, 95% CI 0.80-4.69; $p = 0.142$). Elevated postoperative MAP: mean 90.00 ± 13.15 mmHg; aOR 1.04 per 1-mmHg increase (95% CI 1.02-1.07); $p = 0.002$. Postoperative day 1 pain score >5: 18.67% incidence; aOR 2.25 (95% CI 1.05-4.81); $p = 0.037$. Intravenous antibiotic administration: 18.67% incidence (oral antibiotics only: 64.8%; no antibiotics: 16.5%); aOR 2.03 (95% CI 1.05-3.92); $p = 0.036$.

Table 1. Demographic data

Variables	No hemorrhage (n=493)	Hemorrhage (n=56)	p-value
Gender			0.004
Female	212 (94.22%)	13 (5.78%)	
Male	281 (86.73%)	43 (13.27%)	
Age group			0.007
≤18 years	143 (92.86%)	11 (7.14%)	
19-45 years	277 (86.56%)	43 (13.44%)	
>45 years	73 (97.33%)	2 (2.67%)	
IBW (children) BMI			0.079
<P5 <18.5	27 (100.00%)	-	
P5-P95 18.5-24.9	256 (87.67%)	36 (12.33%)	
>P95 ≥25	210 (91.30%)	20 (8.70%)	
Occupation			0.056
Student	179 (90.86%)	18 (9.14%)	
Government officer	139 (90.85%)	14 (9.15%)	
Military officer	40 (75.47%)	13 (24.53%)	
Employee	91 (89.21%)	11 (10.78%)	
Other	44 (100.00%)	-	
DM			0.709
Negative	475 (89.62%)	55 (10.38%)	
Positive	18 (94.74%)	1 (5.26%)	
HT			0.816
Negative	445 (89.90%)	50 (10.10%)	
Positive	48 (88.89%)	6 (11.11%)	
Snoring			0.105
Negative	355 (88.53%)	46 (11.47%)	
Positive	138 (93.24%)	10 (6.76%)	
Anticoagulants			1.000 [†]
Negative	490 (89.74%)	56 (10.26%)	
Positive	3 (100.00%)	-	
Left tonsil grading			0.706
Small (grade 1-2)	251 (89.32%)	30 (10.68%)	
Large (grade 3-4)	242 (90.30%)	26 (9.70%)	
Right tonsil grading			0.874
Small (grade 1-2)	241 (89.59%)	28 (10.41%)	
Large (grade 3-4)	252 (90.00%)	28 (10.00%)	
Indication			
CHT	348 (88.32%)	46 (11.68%)	
Snoring/OSA	120 (95.24%)	6 (4.76%)	
Unilateral/CA	15 (93.75%)	1 (6.25%)	
Peritonsillar abscess	10 (76.92%)	3 (23.08%)	

[†]: Fisher's exact test, BMI: Body mass index, CA: Carcinoma, CHT: Chronic hypertrophic tonsillitis, DM: Diabetes mellitus, HT: Hypertension, IBW: Ideal body weight, OSA: Obstructive sleep apnea

Table 2. Intraoperative factors

Variables	No hemorrhage (n=493)	Hemorrhage (n=56)	p-value
Operation			0.013
Tonsillectomy	351 (87.31%)	51 (12.69%)	
T&A	62 (98.41%)	1 (1.59%)	
UPPP+Tonsil	70 (94.59%)	4 (5.41%)	
Other	10 (100.00%)	-	
Technique			0.689
Cautery	388 (90.23%)	42 (9.77%)	
Cold/snare	105 (88.98%)	13 (11.02%)	
Suture			0.105
Negative	189 (92.65%)	15 (7.35%)	
Positive	303 (88.34%)	40 (11.66%)	
Surgeon experience			0.003
Category I	192 (95.52%)	9 (4.48%)	
Category II	128 (85.91%)	21 (14.09%)	
Category III	173 (86.93%)	26 (13.07%)	
Duration range			0.560
Short (≤90 min)	349 (89.49%)	41 (10.51%)	
Long (>90 min)	144 (91.14%)	14 (8.86%)	
Route of intubation			0.045
Nasal	301 (87.76%)	42 (12.24%)	
Oral	190 (93.14%)	14 (6.86%)	
Induction drug			0.160
Propofol	173 (86.07%)	28 (13.93%)	
Thiopental	315 (92.11%)	27 (7.89%)	
Other	2 (100.00%)	-	
Intubation drug			0.367
Succinyl	233 (92.09%)	20 (7.91%)	
Tracrium	85 (85.00%)	15 (15.00%)	
Nimbex	167 (88.83%)	21 (11.17%)	
Pavulon and none	5 (100.00%)	-	
Analgesic drug			0.363
Fentanyl	483 (89.78%)	55 (10.22%)	
Morphine or Pethidine	7 (100.00%)	-	
None	1 (50.00%)	1 (50.00%)	
Sedate drug			0.318
Dormicum	148 (88.62%)	19 (11.38%)	
Propofol	2 (66.67%)	1 (33.33%)	
Valium	8 (100.00%)	-	
None	333 (90.49%)	35 (9.51%)	
Reverse drug			0.622
Atropine+Prostigmine	321 (88.92%)	40 (11.08%)	
Neostigmine+Atropine	8 (88.89%)	1 (11.11%)	
Atropine	1 (100.00%)	-	
None	161 (91.48%)	15 (8.52%)	

Table 2. Continued

Variables	No hemorrhage (n=493)	Hemorrhage (n=56)	p-value
Dexamethasone IV			0.074
Negative	28 (80.00%)	7 (20.00%)	
Positive	465 (90.47%)	49 (9.53%)	
Parecoxib IV			0.530
Negative	350 (89.29%)	42 (10.71%)	
Positive	143 (91.08%)	14 (8.92%)	

Surgeon experience: Category I =main surgeon with ENT training at least 15 years; Category II =main surgeon with <15 years' experience and/or assisted by residents; Category III =main and assisted surgeons are residents. IV: Intravenous, T&A: Tonsillectomy and adenoidectomy, UPPP: Uvulopalatopharyngoplasty, ENT: Ear, nose and throat

Table 3. Postoperative factors

Variables	No hemorrhage (n=493)	Hemorrhage (n=56)	p-value
Admission day (days)			0.636
Mean $\pm$ SD	3.16 $\pm$ 1.97	3.29 $\pm$ 1.24	
Median (min-max)	3 (2-32)	3 (2-7)	
Temperature ($^{\circ}$C)			0.818
Mean $\pm$ SD	36.83 $\pm$ 0.47	36.85 $\pm$ 0.50	
Median (min-max)	36.8 (35.8-38.5)	36.9 (35.9-38.0)	
Postoperative fever			0.772
$\leq 37.5^{\circ}$ C	462 (89.88%)	52 (10.12%)	
$> 37.5^{\circ}$ C	31 (88.57%)	4 (11.43%)	
Postoperative BP (mmHg)			0.078
Normal	437 (91.04%)	43 (8.96%)	
Hypotension ($\leq 90/60$)	1 (100.00%)	-	
Hypertension ($> 140/90$)	55 (82.09%)	12 (17.91%)	
Postoperative MAP (mmHg)			0.001
Mean $\pm$ SD	84.58 $\pm$ 11.74	90.00 $\pm$ 13.15	
Median (min-max)	83.33 (57.0-123.3)	88.0 (65.7-127.3)	
Postoperative HR (bpm)			0.760
Mean $\pm$ SD	83.35 $\pm$ 15.88	82.65 $\pm$ 16.92	
Median (min-max)	82 (50-152)	80 (54-147)	
Postoperative HR group			0.890
< 60 bpm	16 (88.89%)	2 (11.11%)	
60-120 bpm	465 (89.94%)	52 (10.06%)	
> 120 bpm	12 (92.31%)	1 (7.69%)	
Pain score			0.009
Mild ($\leq 5/10$)	432 (91.14%)	42 (8.86%)	
Severe ($> 5/10$)	61 (81.33%)	14 (18.67%)	
NSAID drug			0.806
Negative	448 (89.78%)	51 (10.22%)	
Positive	45 (91.84%)	4 (8.16%)	

Table 3. Continued

Variables	No hemorrhage (n=493)	Hemorrhage (n=56)	p-value
IV antibiotics			0.030
Negative	374 (91.44%)	35 (8.56%)	
Positive	119 (85.00%)	21 (15.00%)	
Oral care			0.036
None	267 (90.51%)	28 (9.49%)	
SMW	57 (95.00%)	3 (5.00%)	
NSS	116 (90.63%)	12 (9.38%)	
Both	53 (80.30%)	13 (19.70%)	
Pathology report			0.625
ACT/AET	285 (89.62%)	33 (10.38%)	
CHT/RT/LH	152 (89.94%)	17 (10.06%)	
SCCA/NHL	4 (80.00%)	1 (20.00%)	
Colonization			0.784
Negative	173 (90.10%)	19 (9.90%)	
Actinomycete	268 (89.33%)	32 (10.67%)	

ACT: Acute on chronic tonsillitis, AET: Acute exudative tonsillitis, BP: Blood pressure, CHT: Chronic hypertrophic tonsillitis, HR: Heart rate, LH: Lymphoid hypertrophy, MAP: Mean arterial pressure, NHL: Non-Hodgkin lymphoma, NSS: Normal saline, RT: Recurrent tonsillitis, SCCA: Squamous cell carcinoma, SMW: Special mouth wash, IV: Intravenous, SD: Standard deviation, NSAID: Non-steroidal anti-inflammatory drug

Discussion

Our overall figure of 10.2% falls within the upper range of published global estimates (1.5-21.84%), a rate that warrants targeted institutional intervention. This rate is notably higher than that reported in Taiwan (2.2%) and comparable to rates observed in Japan (11.6-21.84%) and the upper range reported in the United States (3.16-16.1%), suggesting that our institutional rate reflects a pattern consistent with higher-volume Asian teaching-hospital settings (9-11,17-19).

Male sex and age were confirmed as independent risk factors in two distinct groups: patients aged under 19 years (pediatric group; aOR 7.96, 95% CI 1.46-43.27) and those aged 19-45 years (young adult group; aOR 5.74, 95% CI 1.26-26.11), consistent with findings by Ikoma et al. (18) and Inuzuka et al. (19). The observation that the pediatric group had a lower crude bleeding rate (7.14%) yet the highest aOR is consistent with negative confounding (a suppression effect): younger patients more frequently presented with protective covariates, notably lower baseline MAP and a higher proportion of obstructive sleep apnea as the surgical indication, that attenuated the crude association. After adjustment for these covariates, the underlying age-related risk was unmasked, raising the aOR. This estimate must nonetheless be interpreted with caution. The reference category (age >45 years) contained only two bleeding events, and the ratio of events to model parameters was low; both conditions produce sparse-data instability and account for the wide CIs (pediatric group, 95% CI 1.46-43.27).

Table 4. Univariate and multivariate analysis

Variables	No hemorrhage n (%)	Hemorrhage n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
1. Preoperative factors						
Gender						
Female	212 (94.22)	13 (5.78)	1		1	
Male	281 (86.73)	43 (13.27)	2.50 (1.31-4.76)	0.005	2.11 (1.04-4.30)	0.039
Age group						
>45 years	73 (97.33)	2 (2.67)	1		1	
≤18 years	143 (92.86)	11 (7.14)	2.81 (0.61-13.00)	0.187	7.96 (1.46-43.27)	0.016
19-45 years	277 (86.56)	43 (13.44)	5.67 (1.34-23.94)	0.018	5.74 (1.26-26.11)	0.024
2. Indication						
Snoring/OSA	120 (95.24)	6 (4.76)	1			
CHT	348 (88.32)	46 (11.68)	2.64 (1.10-6.35)	0.030		
Unilateral/CA	15 (93.75)	1 (6.25)	1.33 (0.15-11.84)	0.796		
Peritonsillar abscess	10 (76.92)	3 (23.08)	6.00 (1.30-27.67)	0.022		
3. Intraoperative factors						
Route of intubation						
Oral	190 (93.14)	14 (6.86)	1			
Nasal	301 (87.76)	42 (12.24)	1.89 (1.01-3.56)	0.048		
Dexamethasone IV						
Yes	465 (90.47)	49 (9.53)	1			
No	28 (80.00)	7 (20.00)	0.42 (0.18-1.02)	0.054		
Operation						
T&A	62 (98.41)	1 (1.59)	1			
Tonsillectomy	351 (87.31)	51 (12.69)	9.01 (1.22-66.39)	0.031	7.48 (0.92-61.00)	0.060
UPPP+Tonsil	70 (94.59)	4 (5.41)	3.54 (0.39-32.55)	0.264	1.79 (0.16-19.46)	0.634
Other	10 (100.00)	-	N/A	N/A	N/A	N/A
Surgeon experience						
Category I	192 (95.52)	9 (4.48)	1		1	
Category II	128 (85.91)	21 (14.09)	3.50 (1.55-7.89)	0.003	2.85 (1.16-7.01)	0.023
Category III	173 (86.93)	26 (13.07)	3.21 (1.46-7.03)	0.004	1.94 (0.80-4.69)	0.142
4. Postoperative factors						
MAP (mmHg)						
Mean ± SD	84.58±11.74	90.00±13.15	1.04 (1.01-1.06)	0.002	1.04 (1.02-1.07)	0.002
Pain score						
Mild (≤5/10)	432 (91.14)	42 (8.86)	1		1	
Severe (>5/10)	61 (81.33)	14 (18.67)	2.36 (1.22-4.58)	0.011	2.25 (1.05-4.81)	0.037
IV antibiotics						
Negative	374 (91.44)	35 (8.56)	1		1	
Positive	119 (85.00)	21 (15.00)	1.89 (1.06-3.37)	0.032	2.03 (1.05-3.92)	0.036
Oral care						
None	267 (90.51)	28 (9.49)	1			
SMW	57 (95.00)	3 (5.00)	0.50 (0.15-1.71)	0.270		
NSS	116 (90.63)	12 (9.38)	0.99 (0.49-2.01)	0.970		
Both	53 (80.30)	13 (19.70)	2.34 (1.14-4.81)	0.021		

The "other" operation category (n=10, with no bleeding events) produced quasi-complete separation and could not be estimated in the multivariable model; its adjusted odds ratio and p-value are therefore reported as N/A. CA: Carcinoma, CHT: Chronic hypertrophic tonsillitis, IV: Intravenous, MAP: Mean arterial pressure, OSA: Obstructive sleep apnea, SMW: Special mouth wash, T&A: Tonsillectomy and adenoidectomy, UPPP: Uvulopalatopharyngoplasty, SD: Standard deviation, NSS: Normal saline, N/A: Not applicable, OR: Odds ratio, CI: Confidence interval

Table 5. Sensitivity analyses for the age-PTH association using Firth penalized logistic regression

Variable	aOR	95% CI	p
Panel A. Firth penalized model (reference age category >45 years)			
Male sex	2.02	1.03-4.16	0.044
Age ≤18 years (vs. >45)	6.33	1.52-37.37	0.018
Age 19-45 years (vs. >45)	4.46	1.35-23.11	0.029
Surgeon Category II	2.69	1.15-6.66	0.022
Surgeon Category III	1.90	0.83-4.66	0.132
Postoperative MAP (per mmHg)	1.04	1.01-1.07	0.003
Day-1 pain score >5	2.25	1.05-4.65	0.031
Intravenous antibiotic	2.04	1.06-3.86	0.029
Panel B. Alternative age parameterizations (Firth)			
Age ≤18 vs. 19-45 (reference)	1.42	0.61-3.13	0.391
Age >45 vs. 19-45 (reference)	0.22	0.04-0.74	0.029
Age <45 vs. ≥45 years	5.07	1.56-26.00	0.016
Age (continuous, per year)	0.97	0.94-1.00	0.038

Panel A is adjusted for all listed covariates plus operation type; Firth penalization was applied to address the small number of events in the >45-year reference category and quasi-complete separation in the operation variable. In Panel B, each row is a separate age parameterization within the same adjusted model. aOR: Adjusted odds ratio, CI: Confidence interval (profile penalized likelihood), MAP: Mean arterial pressure, PTH: Post-tonsillectomy hemorrhage

The CIs for the pediatric and young-adult estimates overlap substantially and are statistically indistinguishable. The direction and significance of the age association are therefore robust, but the precise magnitude of the pediatric aOR should be regarded as hypothesis-generating rather than definitive. These interpretations are supported by sensitivity analyses (Table 5). A Firth penalized logistic regression attenuated the pediatric aOR from 7.96 to 6.33 (95% CI 1.52-37.37) while retaining statistical significance; re-specifying the reference category as the 19-45-year age group rendered the pediatric and young-adult estimates statistically indistinguishable (aOR 1.42, 95% CI 0.61-3.13; $p=0.391$); and modelling age continuously demonstrated a modest decrease in the odds of PTH with increasing age (aOR 0.97 per year, 95% CI 0.94-1.00; $p=0.038$). Together, these analyses indicate that the apparent primacy of the pediatric group is largely an artifact of the sparse reference category rather than a genuinely greater risk than in young adults. The robust signal is instead one of higher risk among patients aged under 45 years. Clinically, the elevated risk in younger patients may additionally reflect differences in tonsillar vascularity, lower baseline blood pressure that may mask early hemorrhage warning signs, and the challenges of postoperative monitoring in this group, hypotheses that merit prospective evaluation.

Surgeon experience less than 15 years (Category II: attending surgeon with <15 years of ENT training, with or without resident assistance) was an independent predictor of PTH (aOR 2.85, 95% CI 1.16-7.01; $p=0.023$), whereas Category III (both primary and assisting surgeons as residents) did

not reach statistical significance (aOR 1.94, 95% CI 0.80-4.69; $p=0.142$). This aligns with Manimaran et al. (8), Ikoma et al. (18), and Windfuhr et al. (15), all of whom identified surgeon-related variables as contributors to PTH in teaching-hospital settings. Structured operative supervision and standardized hemostatic training for residents therefore merit institutional priority. The 15-year threshold reflects the institutional credentialing policy at our institution, which classifies surgeons as junior or senior faculty for supervision purposes; this classification is institution-specific and may not be generalizable.

Elevated postoperative MAP independently predicted PTH (aOR 1.04 per mmHg). Although the per-unit odds ratio appears modest, the wide range of MAP values (90.00 ± 13.15 mmHg) represents a clinically relevant cumulative risk across the observed MAP range, supporting close postoperative blood-pressure monitoring, particularly in hypertensive patients. These findings are consistent with prior studies reporting an association between elevated postoperative blood pressure and PTH; because the present data are observational, a causal mechanism cannot be established, and residual confounding cannot be excluded (8).

Elevated day-1 pain scores (>5) and intravenous antibiotic prescription were also independent predictors. As this is a retrospective observational study, these associations should not be interpreted causally. Severe pain more plausibly serves as a clinical marker of extensive intraoperative tissue trauma or difficult dissection—subject to confounding by indication—than as a direct mechanical cause of hemorrhage (19). In our cohort, intravenous antibiotics were prescribed selectively for patients with clinical signs of postoperative infection (fever >38.3 °C, purulent exudate) or marked intraoperative tissue trauma, at the attending surgeon's discretion. Both infection and trauma predispose to premature separation of the tonsillar eschar and secondary hemorrhage (9). While routine postoperative antibiotic use following tonsillectomy is not currently recommended by evidence-based guidelines, the intravenous antibiotic group in this study likely represents a higher-risk subgroup defined by disease severity rather than antibiotic exposure per se (2).

A comparison of smoking habits among adult patients was not feasible in the present study, as smoking status was inconsistently documented in retrospective records across the 10-year period (complete data available in approximately 60% of cases). Smoking is a recognized risk factor for impaired wound healing and secondary hemorrhage (19); future prospective studies should include systematic recording of smoking history.

Study Limitations

This study has several limitations. First, PTH ascertainment differed between the full cohort (ICD-9-CM procedure code

28.7, which identifies only procedurally treated hemorrhage) and the analyzed subset (detailed manual chart review). Administrative coding is known to under-ascertain PTH, so the cohort rate (6.14%) represents a conservative lower bound, whereas the chart-based subset rate (10.2%)—consistent with our prospective institutional audit—more completely captures the true event frequency. Detailed risk-factor analyses were necessarily confined to the chart-reviewed subset; although its rate aligns with independent audit data, residual differences between the subset and the source cohort in unmeasured characteristics cannot be fully excluded. Second, the single-center design limits generalizability to institutions with different surgical training paradigms or patient demographics. Third, smoking status was incompletely recorded, precluding its inclusion as a covariate. Fourth, the 15-year surgeon experience threshold is institution-specific and was not derived from a data-driven cut-point analysis. Fifth, as a single military-hospital cohort with a predominantly male and occupationally selected population, the case mix may differ from that of general hospitals, potentially limiting generalizability. Sixth, preoperative and intraoperative variables (relevant to preoperative risk stratification) and postoperative variables (relevant to postoperative monitoring) were combined in a single model; as some postoperative factors may lie on the causal pathway to hemorrhage, a degree of over-adjustment cannot be excluded, and the two groups of predictors are best interpreted according to their distinct clinical roles. A multicenter prospective study capturing patient behavioral data, microbiological findings, and a standardized smoking history would clarify the associations identified here.

Conclusion

This 10-year institutional analysis identifies male sex, patients aged under 19 years (pediatric group) and those aged 19-45 years (young adult group), and surgeon experience less than 15 years as the principal independent predictors of PTH. In particular, patients aged under 45 years—comprising both the pediatric (age < 19 years) and young-adult (age 19-45 years) groups—carry significantly elevated adjusted odds of PTH; because the CIs for these two estimates are wide and overlapping, they should not be ranked against one another, but both warrant heightened postoperative surveillance. Elevated postoperative MAP, a day-1 pain score above 5, and intravenous antibiotic prescription further characterize patients at heightened risk. Careful documentation of pain scores and MAP, close monitoring of patients receiving intravenous antibiotics, and comprehensive postoperative patient education are recommended to reduce the incidence of PTH at our institution.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Institutional Review Board of the Royal Thai Army Medical Department (approval no: R085h/63_Exp, date: 13 June 2020).

Informed Consent: Informed consent was waived due to the retrospective nature of the study, in accordance with the Declaration of Helsinki.

Acknowledgements

The authors thank Dr. Anupong Sirirungreung and Miss Worarachanee Imjaijitt for their assistance with the data analysis and for their valuable statistical advice.

Footnotes

Authorship Contributions

Concept: J.M., A.P., Design: J.M., A.P., Data Collection and/or Processing: J.M., Analysis or Interpretation: J.M., A.P., Literature Search: J.M., A.P., Writing: J.M., A.P.

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

- Post-tonsillectomy hemorrhage (PTH) is one of the most clinically significant complications of tonsillectomy, with an institutional incidence of 10.2% in this 10-year study.
- Independent risk factors for PTH include male sex, age under 19 years [pediatric group; adjusted odds ratio (aOR) 7.96] and 19-45 years (young adult group; aOR 5.74), surgeon experience less than 15 years, elevated postoperative mean arterial pressure, day-1 pain score >5, and intravenous antibiotic prescription.
- Patients aged under 45 years—both the pediatric (aOR 7.96) and young-adult (aOR 5.74) groups—show elevated adjusted odds of PTH; the wide, overlapping confidence intervals preclude ranking the two groups, and both warrant targeted postoperative surveillance.

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Original Investigation



Turk Arch Otorhinolaryngol 2026; 64(3): 180-185

DOI: 10.4274/tao.2026.2026-6-14

Machine Learning-Based Multiclass Classification of Benign Vocal Fold Lesions Using Acoustic, Clinical, and Patient-Reported Features

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Abstract

Objective: To develop and evaluate a multiclass random forest classifier for distinguishing among five types of benign vocal fold lesions using acoustic and phonatory parameters, patient-reported outcomes (PROs), demographic characteristics, and occupational voice demands.

Methods: This retrospective study included 217 adults with confirmed diagnoses of vocal fold nodules, vocal fold polyps, intracordal cysts, Reinke's edema, or sulcus vocalis at a tertiary otolaryngology center. Features included five acoustic parameters (fundamental frequency, jitter, shimmer, maximum phonation time, s/z ratio), three PRO instruments, the voice handicap index, voice-related quality of life, and reflux symptom index (RSI), and demographic and occupational variables. A class-weighted random forest classifier was evaluated using stratified five-fold cross-validation with bootstrap-derived 95% confidence intervals; multinomial logistic regression and linear support vector machine served as comparators.

Results: The random forest classifier outperformed the comparator models, achieving accuracy of 0.576, balanced accuracy of 0.476, macro-F1 of 0.479, and a macro-averaged area under the receiver operating characteristic curve of 0.76. The highest class-level F1 scores were observed for sulcus vocalis (0.703) and vocal fold polyps (0.625); intracordal cysts showed the lowest recall (0.111), reflecting acoustic overlap with vocal fold polyps. Top 2 accuracy was approximately 74%. Fundamental frequency, RSI, and maximum phonation time were the highest-ranked predictors.

Conclusion: A multidimensional random forest framework incorporating acoustic measures, PROs, and occupational voice demand demonstrated potential for classifying benign vocal fold lesions. Acoustic parameters alone may not adequately distinguish among these lesions, and the inclusion of patient-reported data may improve model performance. A top 2 accuracy of 74% supports utility as a pre-endoscopic decision-support tool.

Keywords: Dysphonia, machine learning, patient-reported outcome measures, random forest, vocal cords, voice disorders

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Cite this article as: Karakaya Gojayev E, Çiler Büyükkatalay Z, Öksüz A, Dursun G. Machine learning-based multiclass classification of benign vocal fold lesions integrating acoustic and patient-reported features. Turk Arch Otorhinolaryngol. 2026; 64(3): 180-185

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Received Date: 11.06.2026

Accepted Date: 03.08.2026

Epub: 25.09.2026

Publication Date: 30.09.2026



Introduction

Voice is a fundamental component of communication and social interaction, and its impairment significantly affects an individual's quality of life and functional capacity. Although dysphonia has a prevalence of approximately 1% in treatment-seeking populations, population-based studies have shown that the lifetime risk of voice disorders may reach up to 30%, with higher prevalence observed among women and older adults. Benign vocal fold lesions, including vocal nodules, polyps, Reinke's edema, intracordal cysts, and sulcus vocalis, are among the most common causes of dysphonia and represent a substantial clinical burden. Limited awareness of dysphonia may lead to hoarseness being perceived as a transient condition, resulting in diagnostic delays (1).

In current clinical practice, the diagnosis of benign vocal fold lesions relies primarily on laryngoscopic or videolaryngostroboscopic evaluation. Although these minimally invasive office-based procedures provide the diagnostic reference standard, they require specialized equipment and expertise and are therefore not well suited for large-scale screening, highlighting the need for complementary pre-endoscopic assessment approaches. Acoustic voice analysis has long been used for objective evaluation, and parameters such as fundamental frequency (f_0), jitter, shimmer, maximum phonation time (MPT), and the s/z ratio have been associated with various laryngeal pathologies. However, the isolated evaluation of individual acoustic parameters provides limited discriminatory power, underscoring the need for multivariate analytical approaches (2,3).

In recent years, machine learning-based methods have been increasingly applied to the detection and classification of voice disorders. Among these, random forest is an ensemble-based algorithm that combines multiple decision trees, offering robustness against overfitting and the ability to model complex, non-linear relationships (4). Most previous studies have focused on binary classification (pathological versus healthy voice), while multiclass differentiation of benign vocal fold lesions remains underexplored. Moreover, existing models rely predominantly on acoustic features and insufficiently incorporate clinical variables reflecting the functional and demographic context of voice disorders.

Voice disorders cannot be fully characterized by acoustic measurements alone. Patient-reported outcomes (PROs) measures, such as the voice handicap index (VHI), voice-related quality of life (VRQoL), and reflux symptom index (RSI), provide important information regarding functional impact and disease burden. Occupational voice demand classified as high, moderate, or low based on daily vocal use has also been shown to be associated with clinical risk among professional voice users (5-7).

The aim of this study is to develop a random forest-based multiclass machine learning model integrating acoustic parameters, PROs, demographic characteristics, and occupational voice demand, and to evaluate its diagnostic performance in distinguishing benign vocal fold lesions.

Methods

Study Design and Participants

This retrospective observational study was conducted using routinely collected clinical data from adult patients presenting with dysphonia to the Otolaryngology Clinic at Ankara University Faculty of Medicine. Patients evaluated between January 2010 and January 2020 were eligible for inclusion. All patients underwent comprehensive voice assessment and videolaryngostroboscopic examination as part of the routine diagnostic protocol. The reference diagnosis for each patient was established independently by two experienced otolaryngologists based on videolaryngostroboscopic findings. These diagnoses served as the ground-truth labels used for machine learning model development and evaluation.

Patients diagnosed with one of the five most common benign vocal fold lesions were included: vocal fold nodules, vocal fold polyps, intracordal cysts, Reinke's edema, and sulcus vocalis. Patients with rare, malignant, neurological, or inflammatory laryngeal disorders were excluded to ensure adequate sample size per class for multiclass modeling. The final analytic dataset consisted of 217 patients.

Data Collection and Variables

Demographic variables included age, sex (binary: female/male), and smoking status (current smoker versus non-smoker). Occupational voice demand was categorized as high, moderate, or low according to daily vocal load (5-7). High-demand occupations included teachers, singers, imams, call-center workers, and actors; low-demand occupations included homemakers, retirees, and students; all others were categorized as moderate.

PRO instruments included the VHI, RSI, and VRQoL, all administered as part of routine clinical evaluation.

Acoustic Voice Recording and Analysis

Voice recordings were obtained under standardized conditions. Patients were instructed to produce a sustained vowel /a/ for approximately 6 seconds in modal voice at comfortable pitch and loudness. Recordings were performed using a condenser microphone (EM-616, Shure, Chicago, IL) positioned at 20 cm from the mouth in a quiet examination room; ambient noise levels were maintained below 45 dB sound pressure level. Acoustic analysis was conducted using commercially available software (Vocal Assessment,

Dr. Speech, Tigers Inc., Seattle, WA). Parameters extracted included fundamental frequency (f0; Hz), jitter (%), shimmer (dB), and s/z ratio. MPT was measured separately as the duration of sustained /a/ phonation following maximum inspiration. All endoscopic diagnoses were made by two experienced otolaryngologists and cases with diagnostic disagreement were resolved by consensus.

Statistical Analysis

All analyses were performed using Python (version 3.10) with the scikit-learn, NumPy, and SciPy libraries. Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables as counts and percentages.

The outcome variable was benign lesion category (five classes). The 12 input features were age, sex, smoking status, occupational voice demand, VHI, RSI, VRQoL, f0, MPT, jitter, shimmer, and s/z ratio. Physiologically implausible f0 values were excluded (range: 60-500 Hz). Missing values were handled using median imputation for continuous and most-frequent imputation for categorical variables. All preprocessing steps were implemented within the cross-validation pipeline to prevent data leakage.

Multiclass classification was performed using a class-weighted random forest classifier (n_estimators=500, max_features='sqrt', class_weight='balanced'; all remaining parameters were kept at their scikit-learn default settings) to account for class imbalance. The use of 500 decision trees was a deliberate modeling choice to improve the stability of ensemble predictions and feature importance estimates while reducing model variance. No formal hyperparameter optimization was performed because the primary objective was to evaluate a robust and clinically interpretable baseline model rather than maximize predictive performance. Multinomial logistic regression and linear support vector machine models served as comparators under identical preprocessing and validation conditions. Model performance was evaluated using stratified five-fold cross-validation. Overall performance metrics included accuracy, balanced accuracy, macro-averaged F1-score, and macro one-vs-rest receiver operating characteristic (ROC)-area under the curve (AUC). Non-parametric bootstrap resampling (1,000 iterations) was performed to derive 95% confidence intervals. Top-2 accuracy was additionally calculated. Feature importance was estimated using normalized impurity-based scores and complemented by permutation importance analysis performed within the cross-validation loop to prevent data leakage.

This study was approved by the Ankara University Human Research Ethics Committee (approval no: İ04-493-26, date: 12.05.2026) and conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective study design.

Results

A total of 217 patients were included. Their mean age was 43.2 ± 12.6 years, with a slight predominance of female patients (55.3%). Current smoking was present in 56.7%. Occupational voice demand was classified as high in 12.4%, moderate in 42.9%, and low in 44.7%. Vocal fold polyps (33.6%) and sulcus vocalis (23.9%) were the most common diagnoses, followed by Reinke's edema (23.0%), vocal fold nodules (11.1%), and intracordal cysts (8.3%) (Table 1).

The effect of occupational voice demand on model performance is presented in Table 2. Adding occupational voice demand increased overall accuracy slightly (0.567 to 0.576), while balanced accuracy remained unchanged (0.476) and macro-F1 decreased marginally (0.486 to 0.479). Overlapping bootstrap confidence intervals indicated no statistically meaningful global improvement, suggesting a lesion-specific rather than global effect.

Comparative model performance is summarized in Table 3. Random forest achieved the highest accuracy (0.576), balanced accuracy (0.476), macro-F1 (0.479), and macro-ROC-AUC (0.76) among evaluated algorithms. Top 2

Table 1. Demographic and diagnostic characteristics of the study cohort (n=217)

Variable	Value
Age, mean $\pm$ SD (years)	43.2 $\pm$ 12.6
Sex, female	120 (55.3%)
Sex, male	97 (44.7%)
Current smoker	123 (56.7%)
High voice demand occupation	27 (12.4%)
Moderate voice demand occupation	93 (42.9%)
Low voice demand occupation	97 (44.7%)
Vocal fold nodule	24 (11.1%)
Vocal fold polyp	73 (33.6%)
Intracordal cyst	18 (8.3%)
Reinke's edema	50 (23.0%)
Sulcus vocalis	52 (23.9%)

Values are presented as mean $\pm$ SD for continuous variables and n (%) for categorical variables. SD: Standard deviation

Table 2. Effect of occupational voice demand on random forest performance

Model	Accuracy	Balanced accuracy	Macro-F1
Random forest (without occupational voice demand)	0.567	0.476	0.486
Random forest (with occupational voice demand)	0.576	0.476	0.479

Values represent stratified five-fold cross-validation performance; 95% CIs estimated by bootstrap resampling. CIs: Confidence intervals

accuracy reached approximately 74%, indicating that the correct diagnosis was captured within the two highest predicted probabilities in nearly three of four cases.

Class-specific performance is presented in Table 4. The highest F1-scores were observed for sulcus vocalis (0.703) and vocal fold polyps (0.625). Reinke's edema demonstrated intermediate performance (F1: 0.545). Vocal fold nodules were more challenging to classify (F1: 0.368), and intracordal cysts showed the lowest recall (0.111) and F1-score (0.154), reflecting substantial acoustic overlap with polyps (Figure 1). Occupational voice demand improved recall for polyps (0.671 to 0.685) and Reinke's edema (0.500 to 0.540). In contrast, recall for intracordal cysts decreased slightly after inclusion of occupational voice demand. This finding is likely attributable to the small number of cyst cases (n=18) and the relatively weak association between occupational voice demand and intracordal cysts, which may have introduced additional variability into this subgroup.

Feature importance analysis is presented in Table 5. Fundamental frequency (f0; 0.120), RSI (0.119), and MPT (0.105) were the leading predictors. VRQoL (0.097) and VHI (0.097) also contributed substantially. Permutation-based importance yielded a comparable ranking, supporting predictor robustness.

Discussion

The random forest model developed in this study offers a multidimensional approach to the classification of

benign vocal fold lesions, extending beyond acoustic-only frameworks by integrating PROs and contextual clinical variables. Although overall balanced accuracy (0.476) and macro-F1 (0.479) indicated moderate class-wise discrimination, reflecting the inherent acoustic overlap among benign lesion types, the macro-ROC-AUC of 0.76 suggests meaningful probabilistic ranking ability across lesion categories. In multiclass clinical settings, ROC-AUC and top-2 accuracy is arguably more informative than strict top 1 accuracy, as the clinical objective is not definitive pre-endoscopic diagnosis but rather probability-guided triage

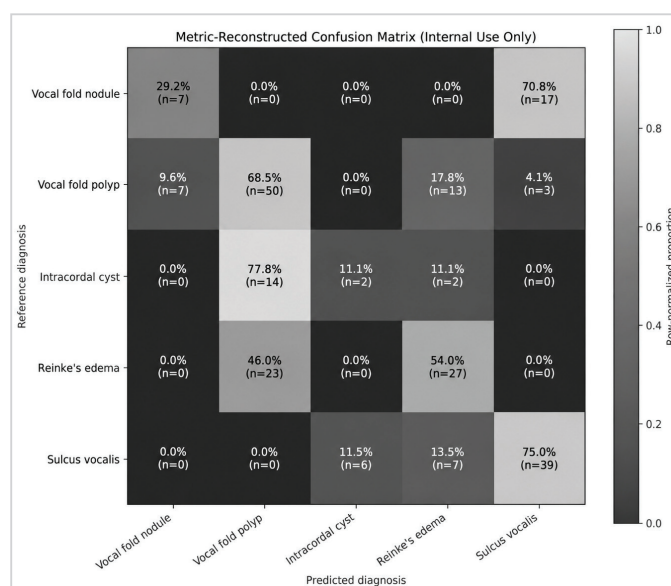


Figure 1. Normalized confusion matrix of the final random forest classifier evaluated using stratified five-fold cross-validation. Rows represent the reference diagnoses and columns represent the predicted diagnoses. Each cell displays the row-normalized proportion together with the corresponding number of patients assigned to each diagnostic category

Table 3. Comparison of classification algorithms (with occupational voice demand)

Model	Accuracy	Balanced acc	Macro-F1	Macro ROC-AUC
Logistic regression	0.51	0.41	0.39	0.72
Linear SVM	0.53	0.42	0.41	0.74
Random forest	0.576	0.476	0.479	0.76

Metrics derived from stratified five-fold cross-validation. Macro ROC-AUC calculated using a one-vs-rest approach. ROC-AUC: Receiver operating characteristic-area under the curve, SVM: Support vector machine

Table 4. Class-specific performance of the final random forest model

Diagnosis	Precision	Recall (without occ.)	Recall (with occ.)	F1-score
Vocal fold nodule	0.500	0.292	0.292	0.368
Vocal fold polyp	0.575	0.671	0.685	0.625
Intracordal cyst	0.250	0.167	0.111	0.154
Reinke's edema	0.551	0.500	0.540	0.545
Sulcus vocalis	0.661	0.750	0.750	0.703

Values derived from stratified five-fold cross-validation of the class-weighted random forest model. Occ.: Occupational voice demand

Table 5. Feature importance ranking (random forest model)

Predictor	Relative importance
Fundamental frequency (f0)	0.120
Reflux symptom index	0.119
Maximum phonation time	0.105
Voice-related quality of life	0.097
Voice handicap index	0.097
Shimmer	0.091
s/z ratio	0.091
Jitter	0.072
Age	0.065
Occupational voice demand	0.052
Smoking	0.051
Sex	0.041

Normalized impurity-based (mean decrease in impurity) scores; values sum to 1.0

that can narrow the differential before laryngoscopy. A model with balanced accuracy below 0.50 in a five-class problem should not be interpreted as performing at chance level; rather, class-weighted training and the inherent difficulty of acoustically overlapping benign lesions set a naturally lower performance ceiling than binary classification tasks.

Most previous machine learning studies in voice pathology have focused on binary classification, primarily distinguishing healthy voices from pathological ones, rather than differentiating among multiple benign vocal fold lesions. Consequently, the high accuracy values reported in these studies (approximately 86-96%) are not directly comparable with the presented study because binary classification represents a substantially less complex task than multiclass classification involving five diagnostically overlapping lesion categories (2,3). In contrast, our model addressed the clinically more challenging problem of discriminating among vocal fold nodules, polyps, intracordal cysts, Reinke's edema, and sulcus vocalis, all of which may exhibit similar acoustic characteristics. Therefore, the moderate overall classification performance observed in the presented study should be interpreted within the context of this considerably greater classification complexity rather than compared directly with binary classification studies. This distinction is clinically important because the aim of our model is not simply to distinguish healthy voices from pathological ones, but to support the pre-endoscopic differential diagnosis of benign vocal fold lesions encountered in routine laryngology practice.

The high importance scores of VRQoL, RSI, and VHI in the model indicate that PROs capture diagnostically informative dimensions beyond what acoustic parameters alone can provide (8,9). Notably, RSI emerged as the second most important predictor overall. This finding is biologically plausible: laryngopharyngeal reflux is differentially associated with specific lesion types, particularly Reinke's edema and vocal fold polyps, and RSI scores may therefore carry lesion-specific signal beyond generic voice handicap measures (6). The superior classification of sulcus vocalis, reflected in the highest F1-score, is consistent with the distinctive effects of this pathology on phonation efficiency and patient-perceived voice quality. The lesion-specific recall improvements attributed to occupational voice demand support prior findings associating high vocal load with phonotraumatic lesion development among teachers and professional voice users (5-7).

Random forest's performance advantage over linear comparators reflects its capacity to model non-linear interactions among acoustic, patient-reported, and demographic variables (4). The top 2 accuracy of approximately 74% is particularly relevant clinically: by narrowing the differential diagnosis to two likely categories

in nearly three of four cases, the model may support pre-endoscopic patient counseling and prioritization of specialist referral.

Importantly, the proposed model is not intended to establish an autonomous diagnosis or replace comprehensive clinical evaluation. Rather, it is designed as a clinical decision-support tool that complements detailed history taking, physical examination, videolaryngostroboscopic assessment, and physician expertise. The final diagnosis should always be established through comprehensive otolaryngological evaluation.

The relatively low proportion of vocal fold nodules compared with sulcus vocalis likely reflects the referral pattern of our university-based tertiary laryngology clinic. Patients with uncomplicated phonotraumatic nodules are frequently diagnosed and managed conservatively in primary or secondary care, whereas patients with persistent dysphonia, diagnostic uncertainty, recurrent symptoms, or suspected structural vocal fold abnormalities are more likely to be referred to our center. Consequently, sulcus vocalis and other structurally complex lesions may have been relatively overrepresented in our study cohort.

Study Limitations

This study has several limitations. The retrospective single-center design may limit generalizability, although standardized protocols and routine clinical data enhance ecological validity. Model performance was assessed using internal cross-validation without external validation. Therefore, external validation using independent patient cohorts from different institutions, recording devices, and recording environments is essential before clinical implementation. Such validation will help determine the generalizability, robustness, and transportability of the proposed model across diverse clinical settings. Notably, the intracordal cyst subgroup consisted of only 18 patients (8.3%), resulting in fewer than four cases per cross-validation fold on average; class-specific metrics for this group should therefore be interpreted with caution, as they carry substantial statistical uncertainty. The analysis was restricted to five common benign lesions and did not encompass rare or malignant pathologies. A normalized confusion matrix illustrating class-specific prediction patterns is provided as Figure 1. Finally, acoustic analysis was based on sustained vowel phonation, which may not fully represent voice behavior during connected speech.

Conclusion

This study demonstrates that a multidimensional random forest model integrating acoustic biomarkers, PROs, demographic variables, and occupational voice demand provides a more clinically comprehensive framework

for benign vocal fold lesion classification than acoustic-only approaches. Although class-wise performance was moderate, lesion-specific improvements and a top 2 accuracy of 74% indicate that the proposed framework has potential as an adjunctive pre-endoscopic clinical decision-support tool. Future prospective multicenter validation studies are required before routine clinical implementation. Importantly, the proposed model should be regarded as a complementary clinical decision-support tool rather than a replacement for comprehensive otolaryngological evaluation, including detailed history taking, physical examination, videolaryngostroboscopic assessment, and physician judgment.

Ethics

Ethics Committee Approval: This study was approved by the Ankara University Human Research Ethics Committee (approval no: İ04-493-26, date: 12.05.2026).

Informed Consent: The requirement for informed consent was waived because of the retrospective study design.

Footnotes

Authorship Contributions

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

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

- Distinguishing benign vocal fold lesions before laryngoscopy remains a clinical challenge; machine learning offers a promising diagnostic support approach.
- A random forest classifier trained on acoustic parameters combined with patient-reported outcomes (voice handicap index, voice-related quality of life, reflux symptom index) achieved a macro-receiver operating characteristic-area under the curve of 0.76 and top 2 accuracy of ~74% in 217 dysphonic patients.
- Integration of patient-reported data significantly improved classification performance over acoustic features alone, particularly for sulcus vocalis and Reinke's edema.
- This model may serve as a practical pre-laryngoscopic triage tool in tertiary otolaryngology settings.

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Original Investigation



Turk Arch Otorhinolaryngol 2026; 64(3): 186-195

DOI: 10.4274/tao.2026.2026-8-4

Incremental Value of Multimodality Imaging for Preoperative Localization in Primary Hyperparathyroidism: A Stepwise Strategy for Focused Parathyroidectomy

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Abstract

Objective: Accurate preoperative localization of the affected parathyroid gland is important for focused parathyroidectomy in primary hyperparathyroidism, yet no single imaging modality is uniformly reliable. This study evaluated the incremental localization benefit of combining ultrasonography (US), ^{99m}Tc-sestamibi scintigraphy (MIBI), and four-dimensional computed tomography (4D-CT) and assessed agreement between imaging-measured and histopathological adenoma size.

Methods: This retrospective, single-center study included 118 patients with histopathologically confirmed parathyroid adenoma who underwent parathyroidectomy between 2015 and 2025. Imaging-based localization was compared with the surgically confirmed location of the adenoma. Sensitivity, positive predictive value, and incremental localization accuracy were calculated. Size agreement was assessed using Bland-Altman analysis, and US sensitivity was examined according to gland location.

Results: Site-level sensitivity was 71.8% for US, 72.8% for MIBI, 66.7% for CT, and 60.0% for 4D-CT, with no significant pairwise differences (all $p>0.05$). Adding MIBI to US significantly increased localization accuracy from 71.7% to 84.1% ($n=113$, McNemar $p<0.001$); adding 4D-CT to US+MIBI further raised accuracy from 73.5% to 79.4% in a smaller cohort ($n=34$), though this increment was not statistically significant ($p=0.50$). US sensitivity fell sharply with anatomical difficulty, from 80.9% for inferior glands to 61.1% for superior and 16.7% for ectopic glands. US also systematically underestimated adenoma size, particularly for larger lesions (bias -10.8 mm; 95% limits of agreement -50.1 to 28.5 mm).

Conclusion: Combining US with MIBI improved localization accuracy. The addition of 4D-CT yielded a further, statistically non-significant increase in the smaller cohort studied. These findings support a stepwise approach to preoperative imaging for focused parathyroidectomy.

Keywords: Hyperparathyroidism, parathyroid neoplasms, ultrasonography, technetium tc 99m sestamibi, four-dimensional computed tomography, parathyroidectomy

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Cite this article as: Özgür E, Savaş Ö, Bayrak AF, Çapa Kaya G, Atakan Ç, Özdemir Başer Ö, et al. Incremental value of multimodality imaging for preoperative localization in primary hyperparathyroidism: a stepwise strategy for focused parathyroidectomy. Turk Arch Otorhinolaryngol. 2026; 64(3): 186-195

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Received Date: 07.08.2026

Accepted Date: 14.09.2026

Epub: 29.09.2026

Publication Date: 30.09.2026



Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder caused, in the great majority of cases, by a single hyperfunctioning parathyroid adenoma (1,2). Surgery remains the only curative treatment, and the shift from bilateral neck exploration toward minimally invasive parathyroidectomy (MIP) has made accurate preoperative localization a prerequisite for successful, low-morbidity surgery rather than an optional adjunct (3,4). When localization fails or is discordant, surgeons are left to choose between an unguided bilateral exploration and a targeted approach built on imperfect information, and either choice carries real consequences for operative time, gland preservation, and complication risk, particularly in patients with ectopic glands, coexisting thyroid pathology, or prior neck surgery.

PHPT is now most often diagnosed incidentally on routine biochemical screening rather than through overt symptoms of hypercalcemia, and this shift has increased the proportion of patients presenting with smaller, more subtle adenomas that are inherently harder to localize (1). As MIP has become the default surgical approach for these patients, the practical burden of imaging has shifted from simply confirming the diagnosis to reliably guiding a focused operative plan, so that any gain in localization accuracy translates directly into fewer converted or extended explorations. The purpose of preoperative imaging in this setting is therefore not to diagnose PHPT, which is already established biochemically before any scan is ordered, but to facilitate focused, minimally invasive surgery by telling the surgeon precisely where to look.

Ultrasonography (US) and ^{99m}Tc -sestamibi scintigraphy (MIBI) are the two most widely used first-line modalities, and four-dimensional computed tomography (4D-CT) has increasingly been adopted as a problem-solving tool when first-line imaging is negative or inconclusive. Reported diagnostic performance, however, varies markedly between series, and much of this variability appears to reflect differences in operator experience, patient selection, and how “correct localization” is defined rather than a genuine, reproducible superiority of one modality. Individual series and meta-analyses disagree on which modality performs better, with reported US sensitivities ranging as low as 76% (5-7). This inconsistency suggests that the clinically relevant question may not be which single modality is superior, but whether combining modalities changes management-relevant accuracy in a way that individual head-to-head comparisons cannot capture.

4D-CT, introduced in 2006 (8), has been proposed as an alternative to routine scintigraphy (9), with pooled per-patient sensitivity of 75-81% (10). Because 4D-CT is typically reserved for cases with negative or discordant first-

line imaging, however, its reported performance is difficult to interpret in isolation and is likely affected by the selection of an inherently harder subgroup of patients; its added radiation exposure and cost further argue for a selective rather than routine role. Evidence on agreement between imaging-measured and true histopathological adenoma size is similarly limited and conflicting, ranging from strong correlation (11) to essentially none (12), raising the question of whether imaging-based size estimates can be trusted for surgical planning.

Our own center previously reported clinical and surgical outcomes in a related cohort of 112 patients, including single-modality sensitivities for US, MIBI, and computed tomography (CT), but did not evaluate 4D-CT, combined-modality performance, or size agreement (13). We hypothesized that the sequential addition of imaging modalities would improve localization accuracy beyond what any single test could achieve, and that this incremental benefit, rather than head-to-head superiority of one modality, is the more clinically actionable question for surgical planning. The present study was designed to determine whether integrating commonly used imaging modalities provides incremental localization benefit over single-modality imaging in patients undergoing surgery for PHPT, and to characterize the agreement between imaging-based and histopathological adenoma size measurements.

Methods

Study Design and Setting

This retrospective single-center study was conducted at the Department of Otorhinolaryngology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye. All patients who underwent parathyroidectomy for PHPT between January 1, 2015 and December 31, 2025 were identified through the institutional electronic medical record system. Although our institution has previously reported the clinical outcomes of parathyroid surgery in a broader PHPT cohort (13), the present study was designed to address a distinct research question focusing on the incremental value of multimodality imaging for preoperative localization and included only patients with histopathologically confirmed parathyroid adenoma. The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval date: June 1, 2026; decision no. 2026/20-46). Given the retrospective study design, the requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki.

Patients and Eligibility

Inclusion criteria were: (i) parathyroidectomy for PHPT performed at the study center within the defined period; (ii) at least one preoperative localization study (US, MIBI,

and/or 4D-CT); and (iii) histopathological confirmation of parathyroid adenoma. Patients with a final histopathological diagnosis other than adenoma (hyperplasia, carcinoma, atypical neoplasia, reactive lymph node) or with missing pathology data were excluded, since the study question specifically concerns localization of solitary adenomas rather than multigland or malignant disease, which follow different surgical algorithms. Of 132 patients initially identified, 14 were excluded (9 hyperplasia, 2 carcinoma, 1 atypical parathyroid neoplasia, 1 reactive lymph node, 1 indeterminate pathology), leaving 118 patients with histopathologically confirmed adenoma for analysis. The patient selection process is summarized in Figure 1.

Data Collection

Demographic data (age, sex, and year of surgery), preoperative biochemical parameters [serum parathyroid hormone (PTH) and calcium levels], imaging findings for each modality, intraoperative findings (location of the excised gland and whether autotransplantation was performed), and histopathological findings (diagnosis, maximum specimen dimension, and weight) were obtained from the electronic medical records through a review of surgical, radiology, and pathology reports.

Imaging Classification

Because imaging reports were recorded as free text rather than structured fields, each modality (US, MIBI, CT, 4D-CT) was coded into one of three categories: not performed (excluded from that modality's denominator), negative (no lesion identified, considered a localization failure), or positive (a lesion described). Positive findings were compared against the surgically confirmed gland at two levels of agreement: site-level (concordance of both side and quadrant/pole, the stricter and clinically more relevant definition for focused surgical planning) and side-level (concordance of side only, a more lenient definition comparable to some prior reports). Reported dimensions, expressed in mixed units and decimal notations, were converted to a single maximal diameter in millimeters for each lesion; when more than one dimension or lesion was recorded, the largest reported value was used.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation or median [interquartile range (IQR)], as appropriate; categorical variables as number (%). For each modality, sensitivity, positive predictive value (PPV), and accuracy were calculated among patients who underwent that test, with Wilson 95% confidence intervals (CIs) calculated for the anatomical subgroup sensitivities of US. Pairwise and incremental comparisons between modalities used McNemar's test rather than unpaired methods, because the same patients typically underwent more than one imaging study and outcomes were therefore correlated

within individual; each comparison was restricted to the paired subcohort in which both compared modalities (or modality combinations) had actually been performed, so that denominators varied across comparisons. Incremental (stepwise) accuracy was defined as the proportion of patients correctly localized by at least one modality when a second or third modality was added sequentially (US alone, then US+MIBI, then US+MIBI+4D-CT), with each increment tested against the preceding step using McNemar's test within the relevant paired subcohort. Agreement between imaging-measured and histopathological maximal diameter was assessed with Pearson and Spearman correlation coefficients and with Bland-Altman analysis (mean bias and 95% limits of agreement). A two-sided $p < 0.05$ was considered statistically significant throughout, and no correction for multiple comparisons was applied given the hypothesis-generating nature of the secondary analyses. All analyses were performed in Python (pandas, SciPy, statsmodels). Given the exploratory nature of several secondary analyses and the modest size of certain subgroups, particularly the 4D-CT cohort, results are reported with exact sample sizes throughout so that readers can independently gauge the precision underlying each estimate.

Results

Patient Characteristics

Of 132 patients screened, 118 (89.4%) had histopathologically confirmed parathyroid adenoma and were included in the analysis (Figure 1). Mean age was 56.2 ± 13.5 years, and 96 patients (81.4%) were female. Mean preoperative PTH was 232.4 ± 233.9 pg/mL, and median excised adenoma weight was 1.2 g (IQR 0.6-2.2 g; $n=102$ with recorded weight). Mean histopathological maximal adenoma diameter was 27.6 ± 19.1 mm (Table 1). Surgery dates spanned the full 2015-2025 study period.

Single-Modality Localization Performance

US was performed in 117 patients (site-level sensitivity 71.8%, PPV 78.5%), MIBI in 114 patients (sensitivity 72.8%, PPV 82.2%), CT in 63 patients (sensitivity 66.7%, PPV 79.2%), and 4D-CT in 35 patients (sensitivity 60.0%, PPV 70.0%) (Table 2). Side-level sensitivities, a more lenient definition, were correspondingly higher for all modalities (82.9-83.3% for US and MIBI). Pairwise McNemar comparisons showed no statistically significant difference between any two modalities (all $p > 0.05$), with the US-versus-CT comparison approaching but not reaching significance ($p=0.077$).

Incremental Localization Accuracy

In the subcohort of 113 patients who underwent both US and MIBI, US alone correctly localized the adenoma in 71.7% of cases; adding MIBI increased accuracy to 84.1%, a statistically significant improvement (exact McNemar

$p < 0.001$) driven by 14 patients in whom MIBI succeeded where US had failed. In the smaller subcohort of 34 patients who underwent all three modalities, accuracy rose stepwise from 58.8% with US alone to 73.5% with US+MIBI (5 net gains, exact McNemar $p = 0.063$) and to 79.4% with US+MIBI+4D-CT (exact McNemar $p = 0.50$ for this final increment); neither step reached statistical significance in this smaller subgroup, in contrast to the larger 113-patient cohort, reflecting both the reduced sample size available for these comparisons and the selective use of 4D-CT in more difficult cases (Table 3, Figure 2).

Agreement Between Imaging and Histopathological Size

Among 105 patients with paired US and histopathological measurements, US correlated weakly with histopathological

size (Spearman $\rho = 0.233$, $p = 0.017$; Pearson $r = 0.194$, $p = 0.047$). US systematically underestimated adenoma size, with a mean bias of -10.8 mm (95% limits of agreement -50.1 to 28.5 mm; paired t-test and Wilcoxon test both $p < 0.0001$); US underestimated size in 70.5% of cases and overestimated it in 23.8%. This underestimation was most pronounced for larger adenomas: mean bias was +1.4 mm in the smallest size tertile, -7.4 mm in the middle tertile, and -31.3 mm in the largest tertile, indicating that US-based size estimates become progressively less reliable as adenomas grow larger. Agreement within a clinically tolerable margin was limited: only 45.7% of US measurements fell within ± 5 mm of the histopathological value, and 65.7% fell within ± 10 mm. CT ($n = 52$) showed a similarly weak, non-significant correlation (Spearman $\rho = 0.230$, $p = 0.101$; bias -12.0 mm), while 4D-CT

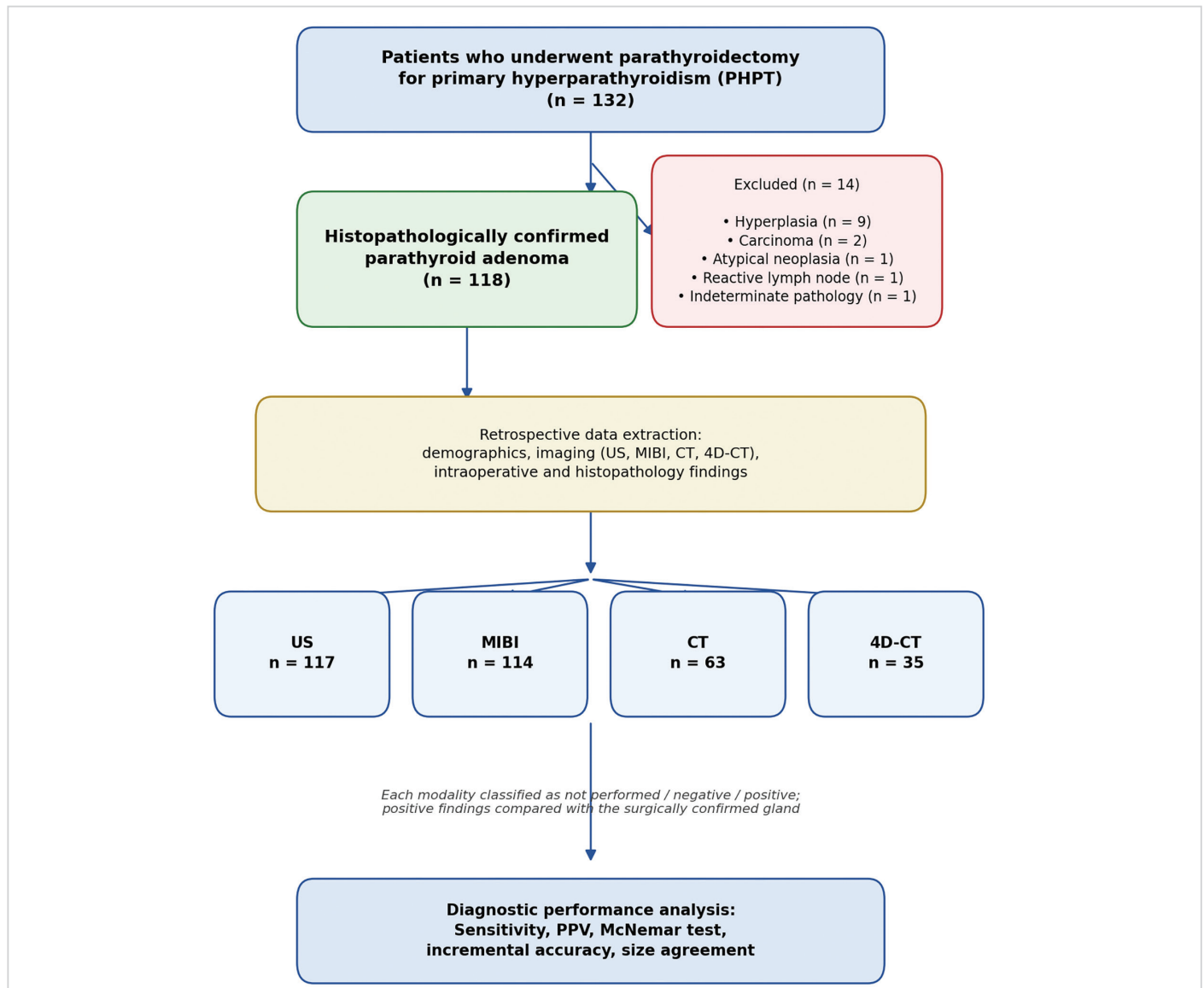


Figure 1. Patient selection flow diagram

US: Ultrasonography, MIBI: ^{99m}Tc -sestamibi scintigraphy, CT: Computed tomography, 4D-CT: Four-dimensional computed tomography, PPV: Positive predictive value

(n=31) showed a stronger correlation than either US or CT (Spearman $\rho=0.474$, $p=0.007$; Pearson $r=0.551$, $p=0.001$; bias -7.2 mm), although this finding should be interpreted cautiously given the smaller, non-randomly selected 4D-CT subgroup (Table 4, Figure 3).

Modality Concordance and Anatomical Subgroup Performance

Among the 113 patients who underwent both US and MIBI, both modalities were positive in 90 (79.6%), US alone was positive in 13 (11.5%), MIBI alone was positive in 10 (8.8%),

Table 1. Patient demographic, biochemical, and histopathological characteristics (n=118)

Variable	Value
Age, years (mean $\pm$ SD)	56.2 $\pm$ 13.5
Sex, female / male, n (%)	96 (81.4)/22 (18.6)
Preoperative PTH, pg/mL (mean $\pm$ SD)	232.4 $\pm$ 233.9
Excised adenoma weight, g, median (IQR), (n=102)	1.2 (0.6-2.2)
Histopathological maximal diameter, mm (mean $\pm$ SD)	27.6 $\pm$ 19.1

SD: Standard deviation, PTH: Parathyroid hormone, IQR: Interquartile range

Table 2. Single-modality diagnostic performance for adenoma localization

Modality	N tested	Negative	Positive	Correct (site-level)	Sensitivity % (site-level)	Sensitivity % (side-level)	PPV % (site-level)	PPV % (side-level)
US	117	10	107	84	71.8	82.9	78.5	90.7
MIBI	114	13	101	83	72.8	83.3	82.2	94.1
CT	63	10	53	42	66.7	79.4	79.2	94.3
4D-CT	35	5	30	21	60.0	77.1	70.0	90.0

No pairwise McNemar comparison between modalities reached statistical significance (all $p>0.05$); US vs. CT was closest to significance ($p=0.077$). US: Ultrasonography, MIBI: ^{99m}Tc -sestamibi scintigraphy, CT: Computed tomography, 4D-CT: Four-dimensional computed tomography, PPV: Positive predictive value, N: Number of patients

Table 3. Incremental (stepwise) localization accuracy

Cohort	Step	N	Accuracy %	McNemar p (vs. previous step)
A: US+MIBI performed	US alone	113	71.7	—
A: US+MIBI performed	+ MIBI	113	84.1	<0.001
B: US+MIBI+4D-CT performed	US alone	34	58.8	—
B: US+MIBI+4D-CT performed	+ MIBI	34	73.5	0.063
B: US+MIBI+4D-CT performed	+ 4D-CT	34	79.4	0.50

US: Ultrasonography, MIBI: ^{99m}Tc -sestamibi scintigraphy, 4D-CT: Four-dimensional computed tomography

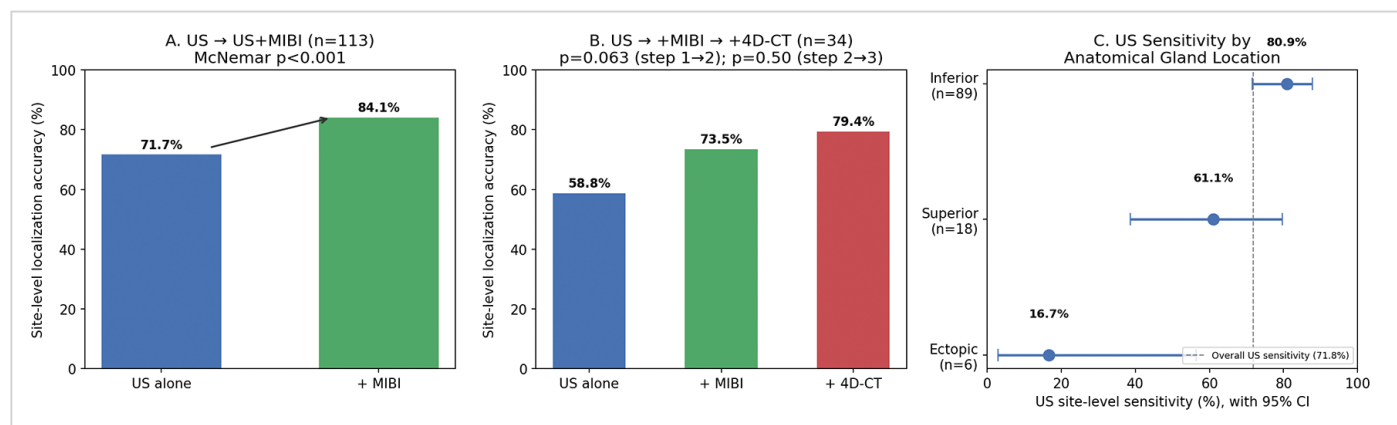
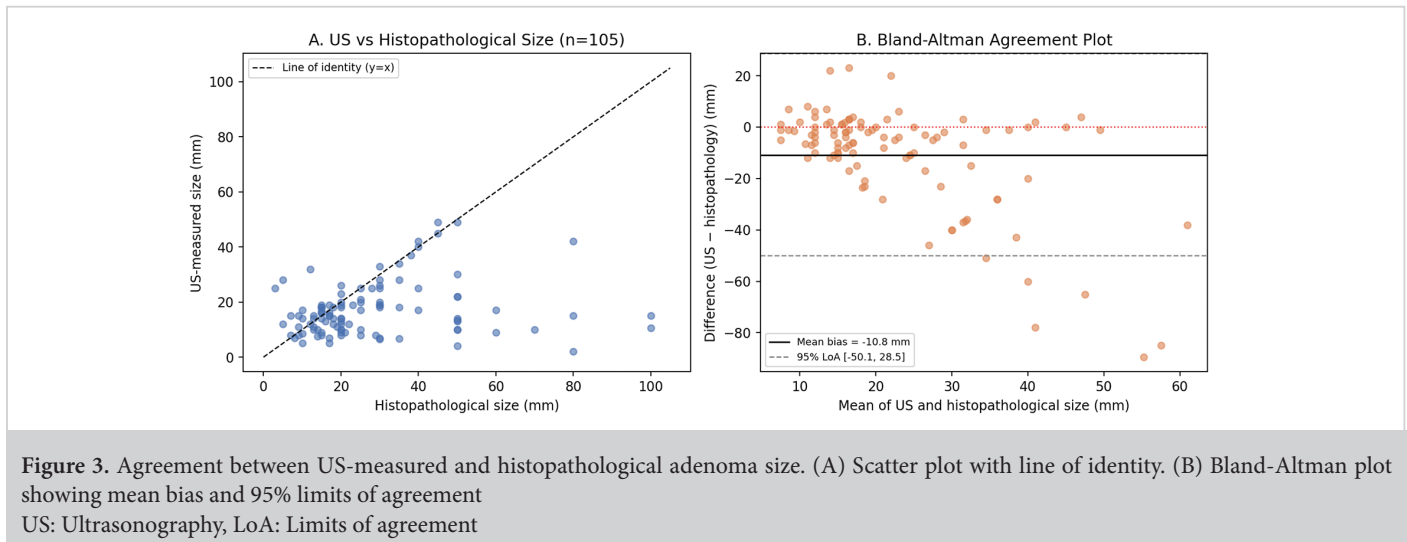


Figure 2. Incremental (stepwise) localization accuracy and anatomical determinants of US performance. (A) Addition of MIBI to US in patients who underwent both tests. (B) Sequential addition of MIBI and 4D-CT in patients who underwent all three modalities. (C) Forest plot of US site-level sensitivity by anatomical gland location, with 95% Wilson CIs; dashed line indicates overall US sensitivity
US: Ultrasonography, MIBI: ^{99m}Tc -sestamibi scintigraphy, 4D-CT: Four-dimensional computed tomography, CI: Confidence interval

Table 4. Agreement between imaging-measured and histopathological adenoma size

Modality	N	Pearson r (p)	Spearman rho (p)	Mean bias, mm	95% limits of agreement, mm
US	105	0.194 (0.047)	0.233 (0.017)	-10.8	-50.1 to 28.5
CT	52	0.161 (0.255)	0.230 (0.101)	-12.0	-53.9 to 29.9
4D-CT	31	0.551 (0.001)	0.474 (0.007)	-7.2	-32.6 to 18.3

US: Ultrasonography, CT: Computed tomography, 4D-CT: Four-dimensional computed tomography, r: Pearson correlation coefficient, rho: Spearman rank correlation coefficient



and both were negative in none, indicating that discordant single-positive findings occurred in roughly one in five patients and that a purely single-modality strategy would have missed a positive finding altogether in 8.8-11.5% of cases depending on which test was omitted. US sensitivity varied markedly by anatomical location of the pathological gland: 80.9% for inferior glands (n=89, 95% CI 71.5-87.7%), 61.1% for superior glands (n=18, 95% CI 38.6-79.7%), and only 16.7% for ectopic glands (n=6, 95% CI 3.0-56.4%) (Figure 2C). This location-based gradient was steeper than the difference between any two imaging modalities reported above, indicating that anatomical location, rather than choice of first-line test, was the strongest single determinant of US localization success in this cohort. The wide CI around the ectopic-gland estimate reflects the small number of such cases, but the point estimate and its direction were consistent with the well-established difficulty of sonographically visualizing deep, mediastinal, or retroesophageal glands.

Combined-Modality Strategies

When any two or three modalities were considered jointly (localization considered successful if at least one modality was concordant), US+MIBI achieved 83.9% accuracy (n=118), and the three-modality combination of US+MIBI+4D-CT achieved the highest overall accuracy at 85.6% (n=118), compared with 71.8-72.8% for the best-performing single modality. These combined-modality accuracies consistently

exceeded single-modality sensitivities, reinforcing that sequential, rather than single, imaging is associated with materially higher localization accuracy in this cohort. Taken together, the site-level, side-level, incremental, and anatomical-subgroup analyses converge on a consistent picture: individual modalities perform comparably but incompletely, and their combination, rather than substitution of one for another, accounts for most of the achievable gain in localization accuracy.

Discussion

The principal finding of this study is that no single imaging modality was clearly superior, whereas sequential multimodality imaging provided clinically meaningful incremental localization benefit. Specifically, adding MIBI to US increased localization accuracy from 71.7% to 84.1% (p<0.001). In a smaller subgroup, the subsequent addition of 4D-CT increased accuracy to 79.4%, although this improvement did not reach statistical significance. The combined use of all three modalities yielded the highest overall localization accuracy (85.6%). The purpose of preoperative imaging in PHPT is not to establish the diagnosis, but to facilitate focused minimally invasive surgery. Our findings suggest that this aim may be achieved more effectively through a stepwise imaging approach rather than reliance on a single preferred modality. The combined

use of imaging modalities produced incremental gains in localization success and supports the adoption of a stepwise preoperative imaging strategy before MIP.

The sensitivities observed for the individual modalities in our cohort—71.8% for US, 72.8% for MIBI, and 66.7% for CT—were within the broad range reported in the literature, although closer to the lower limits. Meta-analyses have likewise failed to demonstrate a consistent superiority of US over MIBI or vice versa (6,7). Interestingly, the direction of superiority between these modalities has also been inconsistent across individual studies. In a series of 104 patients, US was markedly more sensitive than MIBI with single-photon emission computed tomography (SPECT), at 75% vs. 57% (14), and a separate series of 156 patients likewise found ultrasound superior to scintigraphy for predicting adenoma location (15), whereas other series have reported the opposite (5). This inconsistency indicates that there is insufficient evidence to support an institutional or individual preference for a single “best” imaging modality. From a surgical planning perspective, the more relevant question is how much additional confidence is gained by adding a second modality after the first examination. Rather than debating which single modality should be preferred, it may therefore be more useful to standardize the circumstances in which a second imaging test should be introduced.

In our cohort, that second modality was almost always MIBI. MIBI correctly localized the pathological gland in 14 patients in whom US had failed. Thus, MIBI did not merely confirm the US finding; it identified a true pathological focus that had not been demonstrated by US. This finding is consistent with the substantial increase in sensitivity reported when the two modalities are used together (11). Accordingly, when US is non-localizing, proceeding to MIBI may be more appropriate than repeating or overinterpreting the ultrasound examination.

The increase in localization success obtained by adding 4D-CT to the US and MIBI combination, from 73.5% to 79.4%, did not reach statistical significance. Moreover, the finding that 4D-CT had the lowest standalone sensitivity in our cohort (60.0%) appears at first to conflict with the 75-88% sensitivities reported in the literature (10,16). Indeed, in a recent larger meta-analysis including 23 studies and 5,845 patients, 4D-CT had a sensitivity of 81% and a specificity of 89%, with sensitivity substantially exceeding the 65% reported for sestamibi SPECT/CT (17). Nevertheless, we believe that the lower rate observed in our series reflects selection bias rather than inadequate performance of the modality itself. Only 35 of 118 patients (30%) underwent 4D-CT, most likely because the examination was reserved for more challenging cases with negative or discordant first-line imaging. In addition to selection bias, reader dependence may

also explain differences in reported 4D-CT performance. In a series of 95 patients, the sensitivity of surgeon-interpreted 4D-CT was 71%, increasing to 76% when combined with radiology interpretation (18). Thus, the “true” performance of 4D-CT may depend not only on the patient population in which it is used, but also on who interprets the examination and how it is reviewed. Therefore, 4D-CT should be assessed within its role as a problem-solving modality and interpreted by experienced readers rather than being benchmarked as a routine first-line examination. Considering radiation exposure and cost, our findings support selective use of 4D-CT in patients with negative or discordant US and MIBI findings rather than its routine application (9).

The anatomical subgroup analysis revealed what we consider the most surgically applicable finding of the study. The sensitivity of US was not a fixed characteristic of the modality, but decreased progressively as the anatomical difficulty of the target gland increased: 80.9% for inferior glands, 61.1% for superior glands, and only 16.7% for ectopic glands (Figure 2C). This finding indicates that the overall sensitivity commonly reported for US is essentially a population-weighted average and may misrepresent performance at both ends of the anatomical spectrum. It may overestimate the expected success for superior or ectopic glands while underestimating the degree of confidence that may be reasonable when a typical inferior gland is clearly identified. A similar gradient of difficulty also appears to apply to adenoma size. In one study, 4D-CT achieved 100% sensitivity for adenomas smaller than 2 cm, whereas US reached only 76.2% in the same subgroup (16). This suggests that small size and atypical localization represent separate but related dimensions of difficulty that challenge the limits of US. In clinical practice, these findings imply that the need for additional imaging should not be determined solely by an institution's overall sensitivity rate, but should also take into account the suspected anatomical location and size of the adenoma. An equivocal or suspicious US finding in a superior or paratracheal location should lower the threshold for adding MIBI or 4D-CT more than a similarly uncertain finding in a typical inferior location. The near-complete failure of US in ectopic disease, with correct localization in only 1 of 6 patients, further emphasizes the importance of cross-sectional imaging in the group in whom unguided bilateral exploration may also be most challenging.

Adenoma sizes measured by both US and CT showed poor agreement with histopathological measurements, and this disagreement was not random. US systematically underestimated size, particularly in larger adenomas. Whereas no meaningful bias was observed in the smallest tertile, the mean bias reached -31.3 mm in the largest tertile. Strong correlations between US and histopathological size have been reported, but primarily in series in which US

was performed by highly experienced endocrinologists (11). In contrast, a study using contrast-enhanced US found no correlation at all (12). It has also been reported that correctly lateralized adenomas are significantly larger than those not detected by US or scintigraphy (14). This finding further highlights that larger adenomas may be easier to detect, while accurate measurement of their size remains a separate challenge. Surgeons should therefore not expect US to provide an accurate estimate of true adenoma size, particularly for larger lesions, and should instead anticipate a tendency toward underestimation.

The gap between quadrant-level (site-level) and side-level accuracy observed in our cohort has also been described at other institutions. In a series of 437 patients comparing US and 4D-CT against surgical outcome, US sensitivity for correct quadrant fell to 37.7%, well below its 55.7% sensitivity for correct side alone; 4D-CT showed the same pattern, 52.2% by quadrant versus 69.2% by side (19). Our own results move in the same direction—US site-level sensitivity of 71.8% against a side-level 82.9%—at a higher absolute level and with a smaller but directionally consistent gap. This suggests that the quadrant-versus-side distinction is not an artifact of our dataset but a structural feature of how these tests are validated, and reinforces that future studies should state explicitly which definition of “correct localization” they are reporting rather than leaving readers to assume comparability across series.

Study Limitations

This study has limitations. These include its retrospective, single-center design; the possibility of misclassification of rare anatomical descriptions because free-text imaging reports required rule-based standardization; and the relatively small, non-random subgroup of patients who underwent 4D-CT, which limited both the precision of its standalone performance estimate and the statistical power of the sequential imaging analyses. Nevertheless, the study also has important strengths. These include a 10-year cohort treated by a single surgical team, histopathological confirmation in all cases, and simultaneous evaluation of four imaging modalities within the same patient population. Unlike previous comparative studies, the present analysis did not merely compare the isolated performance of individual modalities, but quantitatively assessed the additional contribution of a sequential imaging strategy. It therefore addressed a question that is more directly relevant to surgical decision-making. Because our findings reflect the experience of a single tertiary referral center, they may not be directly generalizable to institutions with different imaging technology, operator expertise, or case mix. Prospective multicenter validation of the proposed stepwise imaging algorithm is therefore warranted.

Conclusion

Based on our findings, we propose the stepwise preoperative imaging algorithm shown in Figure 4. US should be used as the first-line modality. MIBI should be added when US is negative, discordant, or anatomically uncertain. When both first-line modalities remain negative or discordant, particularly in patients with suspected superior or ectopic glands, 4D-CT should be used selectively as a problem-solving examination. In conclusion, no single imaging modality can reliably localize all parathyroid adenomas. However, the stepwise and complementary use of US, MIBI, and selectively applied 4D-CT provides a practical framework for preoperative planning before MIP.

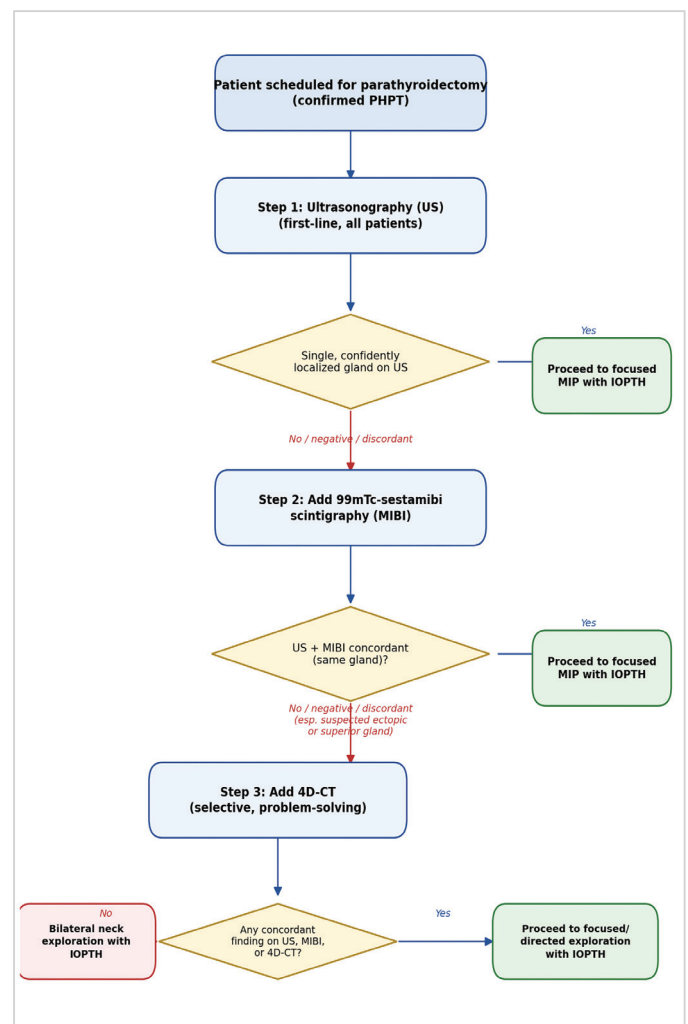


Figure 4. Proposed stepwise preoperative imaging algorithm for primary hyperparathyroidism
IOPTH: Intraoperative parathyroid hormone monitoring, MIP: Minimally invasive parathyroidectomy, PHPT: Primary hyperparathyroidism, 4D-CT: Four-dimensional computed tomography

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval date: June 1, 2026; decision no. 2026/20-46).

Informed Consent: Given the retrospective study design, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ö., Ö.S., A.F.B., Concept: E.Ö., N.K., Design: E.Ö., N.K., Data Collection and/or Processing: E.Ö., Ö.S., A.F.B., G.Ç.K., Ç.A., Ö.Ö.B., N.K., Analysis or Interpretation: E.Ö., Ç.A., Literature Search: E.Ö., G.Ç.K., N.K., Writing: E.Ö., Ö.S.

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

- No single imaging modality—ultrasonography, sestamibi scintigraphy, or four-dimensional computed tomography (4D-CT)—reliably localizes all parathyroid adenomas in primary hyperparathyroidism.
- Adding sestamibi scintigraphy to ultrasonography significantly increases localization accuracy (71.7% to 84.1%, $p < 0.001$), demonstrating a genuine incremental rather than merely confirmatory benefit.
- Ultrasonography sensitivity is strongly dependent on anatomical gland location, ranging from 80.9% for inferior glands to only 16.7% for ectopic glands.
- Ultrasonography systematically underestimates adenoma size, particularly for larger lesions, and should not be relied upon alone for surgical planning.
- A stepwise multimodal imaging strategy—adding sestamibi scintigraphy and, selectively, 4D-CT when first-line imaging is negative or discordant—is recommended before minimally invasive parathyroidectomy.

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Video Article



Turk Arch Otorhinolaryngol 2026; 64(3): 196-199

DOI: 10.4274/tao.2026.2026-3-24

Reversible Horizontal Semicircular Canalith Jam Mimicking Acute Vestibular Syndrome: Diagnosis and Treatment with Head-Shaking and Gufoni Maneuvers

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Abstract

A 72-year-old man presented with a 3-day history of positional rotational vertigo that progressed to continuous vertigo with one episode of vomiting, mimicking acute vestibular syndrome (AVS). Bedside examination revealed spontaneous right-beating horizontal nystagmus and findings consistent with a peripheral pattern on the head impulse, nystagmus, test of skew (HINTS) examination: a positive head impulse test (HIT), unidirectional nystagmus, and no skew deviation. Head shaking with the head flexed forward by 30° reversed the nystagmus to left-beating, and the HIT became positive on rightward impulses. The head yaw test subsequently elicited apogeotropic horizontal positional nystagmus, which converted to a geotropic pattern after repeated head yaw testing and head shaking. Following the Gufoni maneuver, nystagmus and vertigo resolved within one hour. This case demonstrates reversible right horizontal semicircular canal (HSC) canalith jam, a rare benign paroxysmal positional vertigo (BPPV) variant caused by otoconial obstruction of endolymph flow, producing persistent nystagmus and fluctuating sequential labyrinthine hypofunction. Head-shaking maneuver induced a previously unreported bidirectional switch between sustained excitatory and inhibitory cupular deflections within the same canal. Simple bedside maneuvers enabled rapid diagnosis and cure without imaging or drugs. Clinicians should consider HSC canalith jam in AVS with peripheral HINTS when history suggests BPPV.

Keywords: Canalith jam, benign paroxysmal positional vertigo, semicircular canals, nystagmus, Gufoni maneuver

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Cite this article as: Vats AK, Kothari S, Vundavilli P. Reversible horizontal semicircular canalith jam mimicking acute vestibular syndrome: diagnosis and treatment with head-shaking and Gufoni maneuvers. Turk Arch Otorhinolaryngol. 2026; 64(3): 196-199

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Received Date: 04.04.2026

Accepted Date: 23.06.2026

Epub: 30.09.2026

Publication Date: 30.09.2026

Introduction

Benign paroxysmal positional vertigo (BPPV) is the most common vestibular disorder, with horizontal semicircular canal (HSC) involvement in 46 percent of cases (1). A rare variant is canalith jam (CJ), in which displaced otoconial debris becomes impacted within the canal lumen, obstructing endolymph flow and producing fixed cupular deflection. This results in persistent direction-fixed spontaneous nystagmus that can mimic acute vestibular syndrome (AVS) of either peripheral or central origin, often leading to unnecessary imaging or hospital admission (2).

The head impulse, nystagmus, test of skew (HINTS) battery [head impulse test (HIT), nystagmus, test of skew] is highly sensitive for distinguishing central from peripheral AVS (3). However, in HSC-CJ, findings may falsely suggest a fixed peripheral vestibulopathy despite a purely mechanical reversible etiology. Head-shaking maneuver (HSM) can disperse the jam and convert the pattern into canalolithiasis which then responds to

repositioning maneuvers such as the Gufoni maneuver (4). Recognition of this reversible condition is essential for accurate bedside diagnosis. We report a case of right HSC-CJ diagnosed and treated using dynamic positional testing and maneuvers.

Case Presentation

A 72-year-old man presented in February 2026 with a 3-day history of rotational vertigo that began on rising from bed. Initially positional, it occurred during supine to sitting transitions and during lateral recumbency. Over the preceding day, vertigo became continuous and was associated with one episode of vomiting. Examination showed blood pressure of 130/80 mm Hg without postural drop, normal limb power, and no appendicular or gait ataxia. Oculovestibular examination, as demonstrated in this video case report, revealed spontaneous direction-fixed right-beating horizontal nystagmus. HIT was positive on head thrust to left and test of skew was negative. All three HINTS components suggested peripheral AVS in a patient with a history consistent with BPPV, raising suspicion of CJ.

HSM with 30-degree cervical anteflexion reversed spontaneous nystagmus to left-beating. Repeat HIT then showed a catch-up saccade on rightward head impulses, indicating right-sided labyrinth hypofunction and aligning all HINTS components with right peripheral vestibulopathy. Supine head yaw test (HYT) initially produced right-beating lying-down nystagmus. Yaw to either side elicited persistent apogeotropic horizontal positional nystagmus lasting more than one minute, weaker on right head yaw, suggesting debris in the short anterior ampullary arm of the right HSC. Repeated yawing followed by repeated HSM were carried out. Subsequent HYT showed left-beating lying-down nystagmus with geotropic positional nystagmus stronger on right head yaw, indicating transformation to the long posterior non-ampullary arm HSC canalolithiasis. The Gufoni maneuver was then performed. One hour later, spontaneous and positional nystagmus had been resolved and the patient was asymptomatic. The patient was telephonically followed up for 4 weeks and he remained symptom-free. Written informed consent was obtained.

Discussion

CJ is a rare mechanical form of BPPV in which otoconial debris becomes impacted within a semicircular canal, most often the HSC, producing sustained cupular deflection due to obstruction of endolymph flow (2). The deflection may be ampullopetal, producing excitation of the HSC, or ampullofugal, which is inhibitory, depending on the direction of the trapped endolymphatic force. This results in persistent direction-fixed spontaneous nystagmus and

may simulate AVS (5). The most distinctive feature of this case is the sequential transformation from a fixed excitatory ampullopetal deflection of the right HSC cupula to a fixed inhibitory ampullofugal deflection following a single head-shaking maneuver. Initially, right-beating spontaneous nystagmus with a positive HIT to the left indicated persistent excitatory ampullopetal deflection due to CJ. After the head-shaking maneuver, reversal to left-beating nystagmus and emergence of a positive right HIT indicated conversion to an inhibitory cupular deflection (6). Such a bidirectional switch between sustained excitatory and inhibitory cupular deflections within the same canal during a single episode has not been previously reported. It provides direct clinical evidence of the mechanical basis of CJ. This suggests a dynamic reconfiguration of the obstruction rather than simple resolution. It demonstrates that the same labyrinth can transiently simulate both hyperfunction and hypofunction depending on the direction of cupular bias. HSM likely generated high-velocity endolymphatic currents that fragmented or displaced the impacted debris, temporarily reversing the net force on the cupula before complete release (7). This intermediate state explains the observed reversal of spontaneous nystagmus and changes in HIT findings. Further positional testing clarified the evolution. Initial apogeotropic positional nystagmus indicated debris in the short anterior ampullary arm (8). Repeated HYT resulted in conversion to geotropic nystagmus, reflecting migration into the long posterior non-ampullary arm (9). This progression from jammed obstruction to mobile debris highlights the dynamic nature of HSC-CJ (Figure 1). Resolution after the Gufoni maneuver (Figure 2) confirms the mechanical etiology. The rapid disappearance of symptoms and signs within one hour supports successful repositioning of debris into the utricle.

This case illustrates an important diagnostic pitfall. A peripheral HINTS pattern in a patient with BPPV-like history may lead to misdiagnosis as vestibular neuritis. However, positional onset, direction-fixed nystagmus, and rapid reversibility with mechanical maneuvers favor CJ. The presence of alternating fixed excitatory and inhibitory states further distinguishes this condition from true neurogenic acute unilateral peripheral vestibular loss. Previous reports have described CJ presenting with spontaneous nystagmus and apparent canal hypofunction that resolves after physical therapy and/or repositioning (10). The presented case extends this understanding by demonstrating reversible switching between opposite fixed cupular deflections within a single episode. From a clinical perspective, dynamic bedside testing is essential. HSM can both diagnose and modify the pathological state, converting a misleading fixed pattern into recognizable canalolithiasis. This approach can avoid unnecessary imaging and treatment.

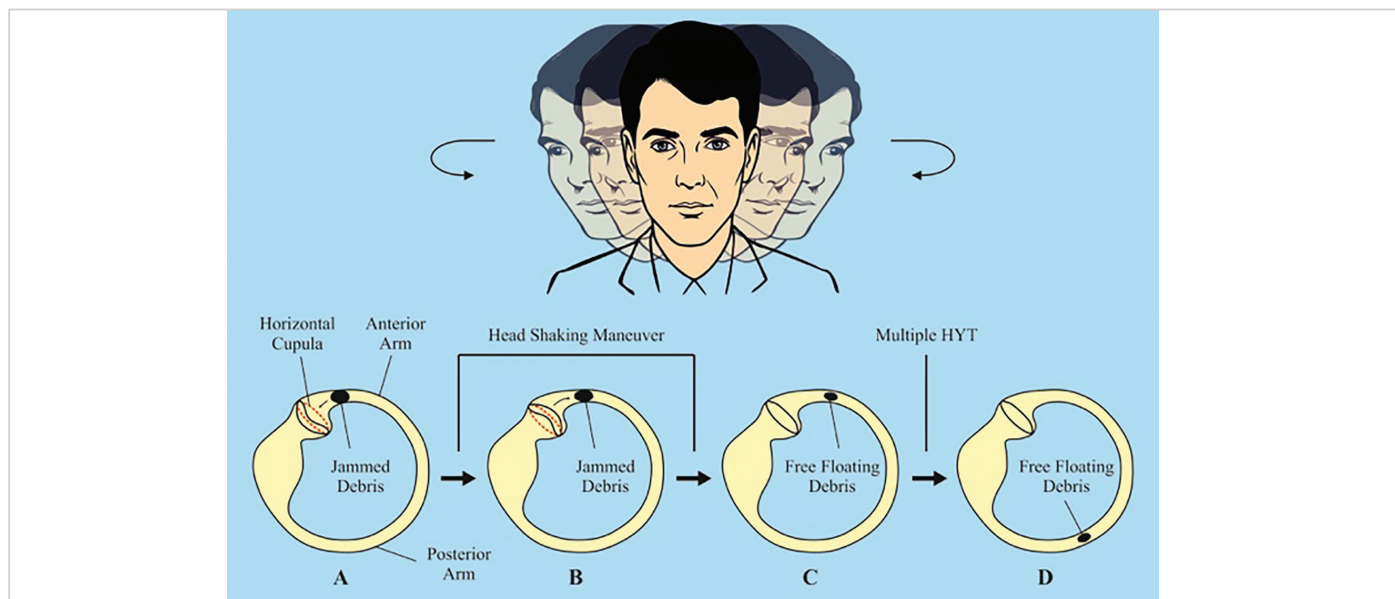


Figure 1. Evolution of right horizontal semicircular canal canalith jam with persistent ampullopetal cupular deflection (A) to persistent ampulofugal deflection (B), followed by canalolithiasis in the short anterior arm (C) and migration of debris to the posterior arm (D), geotropic conversion of the disorder with staged head shaking maneuvers and multiple head yaw tests (HYTs)

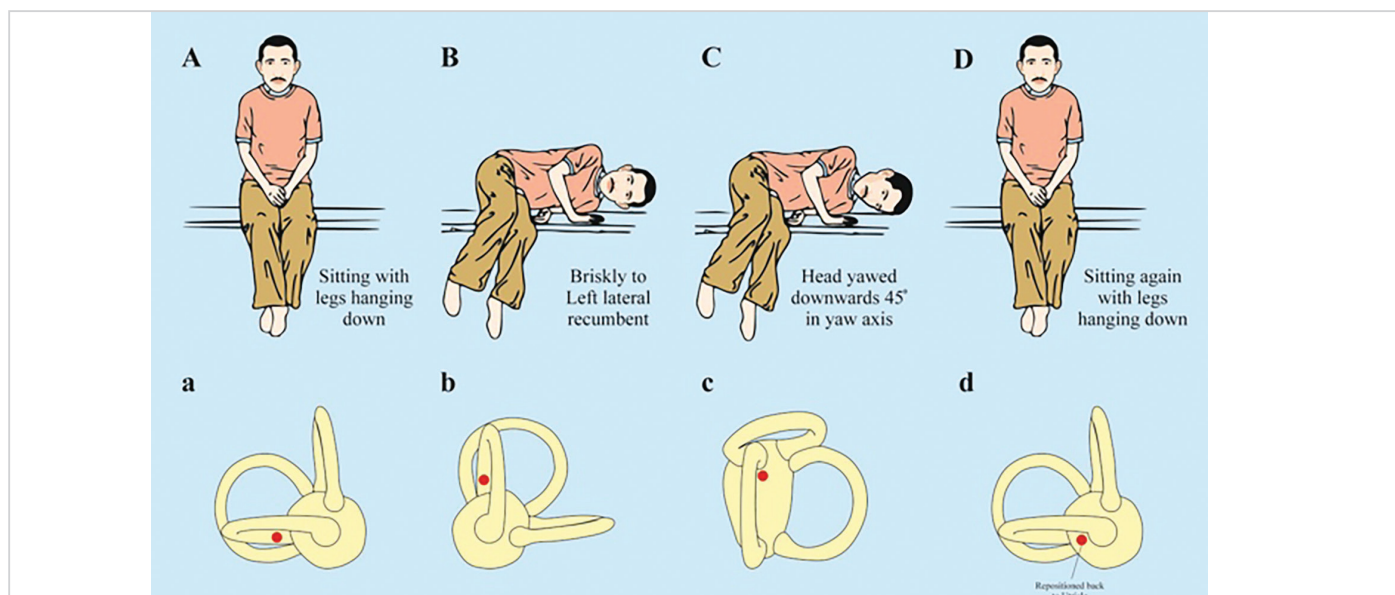


Figure 2. Gufoni maneuver: from short sitting (A), the patient is rapidly moved to the lateral recumbent position on the non-involved side for 1 minute (B). The head is then rotated 45° downward for 2 minutes (C) and returned to upright (D). Lower panel (a-d) shows otoconial debris moving from the long posterior non-ampullary arm of the right horizontal semicircular canal into the utricle

Study Limitations

This report describes a single case of reversible HSC-CJ. As with any single case report, the findings may not be generalizable to all patients with similar presentations. The diagnosis and treatment were based on clinical bedside examination and maneuvers; no imaging or laboratory tests were performed to exclude other causes. Long-term follow-up beyond four weeks was not conducted. Video recording

and telephone follow-up provided supportive data, but objective vestibular testing such as video HIT or caloric testing was not available.

Conclusion

In conclusion, this case demonstrates an unusual presentation of HSC-CJ characterized by sequential fixed excitatory and inhibitory cupular deflections induced by HSM. Recognition

of such patterns expands the spectrum of BPPV variants and emphasizes the importance of vestibular biomechanics in clinical practice.

Ethics

Informed Consent: Written informed consent was obtained.

Acknowledgments

The authors acknowledge Mr. Renith Kurian for video recording of diagnostic and therapeutic maneuvers and accurately documenting the nystagmus during the entire diagnostic and treatment period. The authors also extend thanks to Mr. Ashraf Hussain for creating Figure 1 using CorelDraw graphics suite 2019.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K.V., S.K., P.V., Concept: A.K.V., S.K., P.V., Design: A.K.V., S.K., P.V., Data Collection and/or Processing: A.K.V., S.K., P.V., Analysis or Interpretation: A.K.V., S.K., P.V., Literature Search: A.K.V., S.K., P.V., Writing: A.K.V.

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.



Video link: https://youtu.be/xw4-61_lp1s

Main Points

- A 72-year-old man presented with positional vertigo that rapidly progressed to continuous spontaneous vertigo with vomiting, mimicking acute vestibular syndrome.
- Bedside examination revealed spontaneous right-beating horizontal nystagmus with a peripheral head impulse, nystagmus, test of skew pattern; head-shaking maneuver (HSM) reversed the nystagmus direction and switched the side of positive head impulse test.
- Repeated HSM and head yaw test converted the initial apogeotropic positional nystagmus to geotropic nystagmus, indicating transition from right horizontal semicircular canal (HSC)-canalith jam (CJ) to canalolithiasis.
- The Gufoni maneuver resulted in complete resolution of nystagmus and vertigo within one hour, confirming the mechanical nature of the reversible CJ.
- This case demonstrates bidirectional switching between sustained excitatory and inhibitory cupular deflections in the same horizontal canal induced by HSM, an unreported finding that highlights the importance of dynamic bedside testing in suspected HSC-benign paroxysmal positional vertigo variants.

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Case Report



Turk Arch Otorhinolaryngol 2026; 64(3): 200-203

DOI: 10.4274/tao.2026.2026-4-18

Primary Burkitt Lymphoma of the Maxillary Sinus in an Immunocompetent Adult: A Case Report

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Abstract

Primary Burkitt lymphoma (BL) of the maxillary sinus is rare, particularly in immunocompetent adults, and only a few cases have been reported in the literature. Its clinical presentation may mimic benign conditions, such as chronic rhinosinusitis or neuropathic facial pain, potentially resulting in diagnostic delay. We present the case of a 38-year-old male with a five-month history of isolated left-sided facial pain. Comprehensive clinical, radiological, and histopathological evaluation established the diagnosis of BL, and the patient subsequently received systemic chemotherapy. This case highlights the importance of considering BL in the differential diagnosis of persistent or atypical sinonasal symptoms, particularly those unresponsive to empirical treatment. Prompt biopsy and histopathological and immunohistochemical evaluation are essential for establishing the diagnosis and initiating appropriate treatment without delay.

Keywords: Burkitt lymphoma, paranasal sinus neoplasms, maxillary sinus, immunocompetence, rhinology, case report

Introduction

Burkitt lymphoma (BL) is a non-cleaved B-cell non-Hodgkin lymphoma that accounts for less than 5% of adult lymphoma cases (1,2). Sinonasal lymphomas are generally uncommon, representing less than 1% of all malignancies in the head and neck region. Although BL predominantly affects children and immunocompromised individuals, its occurrence in immunocompetent adults is uncommon, and involvement of the sinonasal region is exceedingly rare. The association between viral infections and lymphoid malignancies is well established, with Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) recognized as key etiological factors in BL. Characterized by an extraordinary proliferation rate, BL typically exhibits rapid local expansion and early dissemination, often leading to swift clinical deterioration and facial deformities in cases involving the head and neck region (3). Given its rarity confined to the paranasal sinuses, particularly in non-immunocompromised adults, we present an extremely rare case of BL originating from and limited to the left maxillary sinus in an immunocompetent adult, highlighting the diagnostic challenges and the need for heightened clinical suspicion.

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Cite this article as: Chaidas K, Zarkadi A, Tepelenis N, Papouliakos S. Primary Burkitt lymphoma of the maxillary sinus in an immunocompetent adult: a case report. Turk Arch Otorhinolaryngol. 2026; 64(3): 200-203

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Received Date: 05.05.2026

Accepted Date: 22.05.2026

Epub: 23.09.2026

Publication Date: 30.09.2026



Case Presentation

A 38-year-old Caucasian male presented to the otorhinolaryngology outpatient clinic with a five-month history of progressively worsening left-sided facial pain associated with numbness over the left cheek. The patient reported no other symptoms. There was no relevant medical or surgical history. Clinical examination did not reveal any abnormality such as nasal obstruction or cervical lymphadenopathy. There was normal function of all cranial nerves.

A computed tomography (CT) scan of the paranasal sinuses revealed a soft-tissue mass within the left maxillary sinus with erosion of the posterior wall and possible compression of the infraorbital nerve (Figure 1). A subsequent magnetic resonance imaging (MRI) demonstrated similar findings, with a soft-tissue mass partially occupying the left maxillary sinus and extending posteriorly into the adjacent pterygopalatine fossa.

Considering the above findings, the patient underwent left-sided endoscopic middle meatal antrostomy and diagnostic tumor biopsy. Intraoperatively, a white, round, and friable tumor within the maxillary sinus was seen (Figure 2).

Histopathological evaluation demonstrated the presence of a monomorphic infiltrative population of medium-to-large-sized lymphoid cells exhibiting a classic “starry-sky” pattern, characterized by numerous tangible-body macrophages scattered amongst the highly proliferative neoplastic B-lymphocytes (Figure 3). Immunohistochemical staining yielded the following profile: the neoplastic cells were positive for Pan-B markers (L26/CD20, CD10, CD79a, and Bcl-6) and negative for CD3, CD5, CD23, CD30, and BCL-2. A notably high Ki-67 proliferative index of 98% was documented, confirming the diagnosis of BL. Serological

testing for EBV, HIV, and hepatitis B and C was negative. Further imaging to determine disease staging, including contrast-enhanced CT of the chest, abdomen, and pelvis, as well as a bone scan, revealed no evidence of metastatic disease (Ann Arbor Stage IE).

The patient was promptly referred to the Haematology department and initiated on an intensive, short-course chemotherapy regimen following the R-CODOX-M/IVAC protocol, comprising rituximab in combination with cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, and cytarabine. The patient completed four cycles of therapy, without major complications. A follow-up CT scan performed two months after treatment demonstrating complete remission. A positron-emission tomography (PET)/CT scan at one-year follow-up was also unremarkable. At the two-year follow-up, the patient remains clinically and radiologically free of disease recurrence.

Informed consent was obtained from the patient.

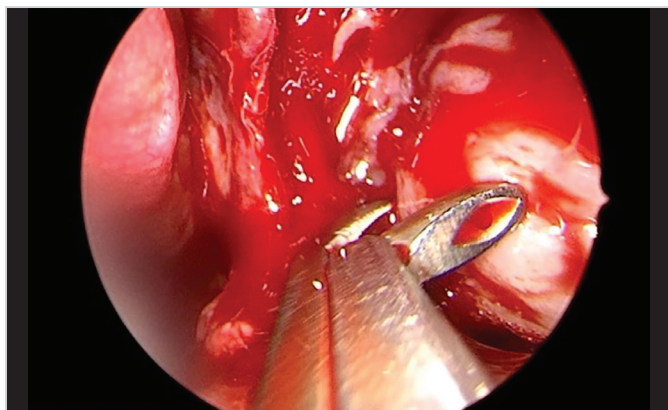


Figure 2. Intraoperative imaging of the left maxillary sinus showing the presence of a white, friable lesion

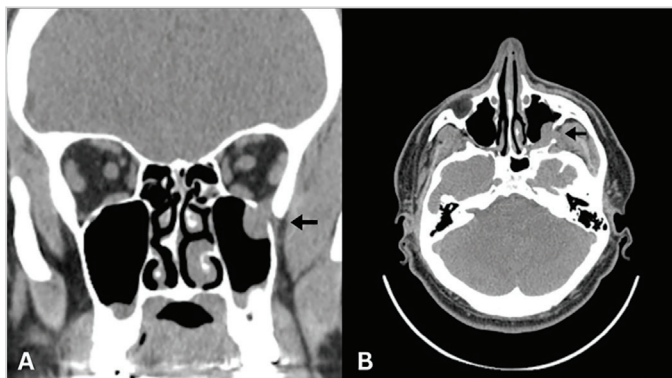


Figure 1. Coronal (A) and axial (B) view of a computed tomography showing partial opacification of the left maxillary sinus by a soft-tissue mass originating from the superior and lateral walls. The mass exhibited locally aggressive characteristics causing erosion of the posterior sinus wall and possible compression of the infraorbital nerve

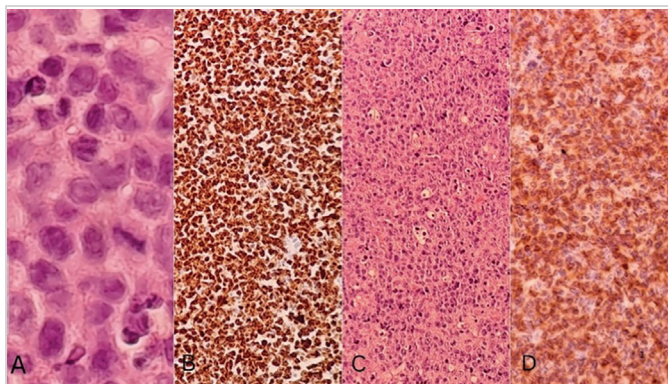


Figure 3. A. There is a lymphoid population of Burkitt-like cells featuring an atypical mitosis; B. BCL2 immunostain with dim expression; C. The proliferation rate of the lymphoma is almost 100% with the Ki67 immunostain; D. There exists an evident Starry sky pattern among the lymphoid cells

Discussion

BL was first described in Central Africa by Denis Burkitt in 1958 and is recognized as one of the most aggressive B-cell non-Hodgkin lymphomas. Although BL was historically classified into three clinical subtypes (endemic, sporadic, and immunodeficiency-associated), the recent 5th edition of the World Health Organization classification employed a molecular classification based on EBV status, distinguishing EBV-positive from EBV-negative BL (4).

In the head and neck region, BL most commonly presents as cervical lymphadenopathy (3); however, primary extranodal involvement of the paranasal sinuses is extremely rare, especially in the absence of immunosuppression. To the best of our knowledge, only a few cases of BL primarily affecting the maxillary sinus have been reported in the literature until now (3,5).

The diagnostic challenge of BL in otorhinolaryngology resides in its non-specific clinical presentation. Symptoms such as nasal obstruction, facial swelling, or headache frequently mimic benign conditions such as chronic rhinosinusitis or nasal polyposis, often resulting in diagnostic and therapeutic delay—an issue of critical importance given the tumor's exceptionally rapid doubling time of 24-48 hours (5,6). The present case illustrates a particularly atypical presentation, wherein neuropathic facial pain caused by infraorbital nerve encasement was the sole symptom. Such a subtle manifestation, particularly in the absence of typical sinonasal complaints, highlights the importance of considering BL in the assessment of rapidly progressive or atypical sinonasal lesions.

Therefore, diagnostic evaluation must be thorough and expeditious (7). Cross-sectional imaging utilizing contrast-enhanced CT and MRI is vital for delineating local disease extent, while PET-CT is recommended for systemic staging. Laboratory investigations should include a complete blood count, serum lactate dehydrogenase (LDH), renal and hepatic function tests, tumor lysis parameters, and viral serology for HIV, EBV, and hepatitis B and C. A surgical biopsy remains the preferred diagnostic method, providing tissue for histopathological and immunohistochemical analysis. Lumbar puncture is essential to exclude central nervous system involvement, with bone marrow assessment reserved for cases demonstrating clinical or laboratory indications of leukemic transformation.

Management of BL requires intensive, short-course, multi-agent chemotherapy, frequently including rituximab, an anti-CD20 monoclonal antibody. The selection of treatment protocols depends on tumor burden, serum LDH levels, performance status, and disease stage (1). The currently used chemotherapy regimens in patients with disease limited to the head and neck have yielded 90% long-term survival (3).

Conclusion

This case highlights the significance of sustaining a heightened level of suspicion for BL in patients presenting with persistent, unilateral sinonasal symptoms that do not respond to conventional therapy. Early imaging, prompt biopsy, and multidisciplinary management are crucial for facilitating a timely diagnosis and curative intervention, even among immunocompetent individuals who are HIV- and EBV-negative, considering the tumor's highly aggressive characteristics.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

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

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

- Primary Burkitt lymphoma of the maxillary sinus is a quite rare entity in immunocompetent adults, yet it should be included in the differential diagnosis of rapidly progressive or atypical sinonasal lesions.
- Early recognition supported by advanced imaging and definitive histopathological and immunohistochemical confirmation is crucial for avoiding diagnostic delay.
- Short-course, multi-agent chemotherapy regimens have demonstrated favorable outcomes and represent the cornerstone of effective management, offering a promising prognosis when initiated early.

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Case Report



Turk Arch Otorhinolaryngol 2026; 64(3): 204-208

DOI: 10.4274/tao.2026.2025-12-4

Deep Neck Infection Complicated by Internal Carotid Pseudoaneurysm: A Diagnostic and Therapeutic Challenge

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Abstract

Parapharyngeal infections may result in a pseudoaneurysm of the internal carotid artery, a rare but potentially fatal condition. Early recognition and multidisciplinary management are crucial to avoid catastrophic outcomes. We present a case of a twenty-two-year-old man with a parapharyngeal abscess complicated by an internal carotid artery pseudoaneurysm. The patient presented with painful left neck swelling, fever, dysphagia, and hoarseness. Examination revealed oropharyngeal asymmetry, ipsilateral vocal cord paralysis, and shoulder weakness findings consistent with jugular foramen syndrome. Imaging demonstrated a parapharyngeal abscess with a surrounding hematoma encasing the distal internal carotid artery, which appeared aneurysmal and was confirmed as pseudoaneurysm. Despite appropriate antibiotic therapy, the patient's neck pain progressively worsened, and repeat imaging demonstrated enlargement of the lesion. Urgent endovascular coil embolization was successfully performed. The patient was discharged on the second postoperative day and remained neurologically stable at six-month follow-up, with radiological improvement. Carotid pseudoaneurysm secondary to deep neck infection is exceedingly rare. Infection may spread from the parapharyngeal space to the carotid sheath, causing progressive arterial wall erosion. Early identification is crucial, as rupture carries high mortality without intervention. Recent evidence supports endovascular management as a safe and effective alternative to open surgery, particularly for lesions involving the skull base or petrous segment, where surgical exposure is hazardous. This case underscores that deep neck infections presenting with cranial neuropathies or opioid-refractory pain warrant prompt vascular imaging, and that endovascular occlusion represents a safe and effective treatment when collateral circulation is sufficient.

Keywords: Parapharyngeal abscess, carotid artery, aneurysm, jugular foramen syndrome, embolization, case report

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Cite this article as: Vural Camalan B, Güneş Küçük T, Uyanık SA, Özlügedik S. Deep neck infection complicated by internal carotid pseudoaneurysm: a diagnostic and therapeutic challenge. Turk Arch Otorhinolaryngol. 2026; 64(3): 204-208

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Received Date: 10.12.2025

Accepted Date: 14.04.2026

Epub: 23.09.2026

Publication Date: 30.09.2026

Introduction

Deep neck infection (DNI) remains a potentially life-threatening condition. The parapharyngeal space is particularly critical, as infection may extend to the carotid sheath, risking airway obstruction and vascular erosion. Although mycotic aneurysms account for less than 1% of all aneurysms, they carry a mortality rate of approximately 20% (1). Erosion of the carotid artery due to infection is exceedingly rare, with pseudoaneurysm formation reported only in isolated cases.

Cross-sectional imaging is crucial. Computed tomography (CT) is often first-line, while magnetic resonance imaging (MRI) better delineates soft tissue and vascular involvement. When vascular injury is suspected, angiography remains the diagnostic gold standard (2). With advances in interventional radiology, endovascular therapy has become a viable option when surgical management carries prohibitive risk. Here, we describe a rare case

of internal carotid artery (ICA) pseudoaneurysm secondary to a parapharyngeal abscess, successfully treated with endovascular coil embolization.

Case Presentation

A 22-year-old male presented to the emergency department with left-sided neck swelling, severe pain, fever, hoarseness, and dysphagia. He had no significant comorbidities aside from remote tonsillectomy and a five pack-year smoking history. At an outside facility, he had received clindamycin intramuscularly for five days, then oral amoxicillin-clavulanate for two weeks, without improvement. The patient was referred to our otolaryngology department from the emergency department with a three-week history of persistent symptoms that had failed to improve despite antibiotic therapy. Physical examination revealed left-sided neck swelling, and the patient was subsequently admitted for further diagnostic evaluation and treatment.

At presentation, he exhibited left vocal cord paralysis, ptosis, and miosis, consistent with Horner's syndrome. The presence of oropharyngeal asymmetry accompanied by unilateral vocal cord paralysis and limitation of shoulder movements on the same side indicates involvement of cranial nerves IX, X, and XI, consistent with jugular foramen syndrome. These two neurological findings reflected involvement of distinct anatomical pathways. Horner's syndrome represents dysfunction of the cervical sympathetic chain coursing along the ICA, whereas jugular foramen syndrome results from impairment of the lower cranial nerves (IX, X, and XI) as they traverse the jugular foramen at the skull base. Laboratory studies showed leukocytosis and elevated C-reactive protein. On initial contrast-enhanced CT obtained at admission, an 80×50×50 mm parapharyngeal abscess was demonstrated, along with a 12-mm aneurysmal dilation of the distal cervical ICA (Figure 1a). MRI confirmed the collection and raised

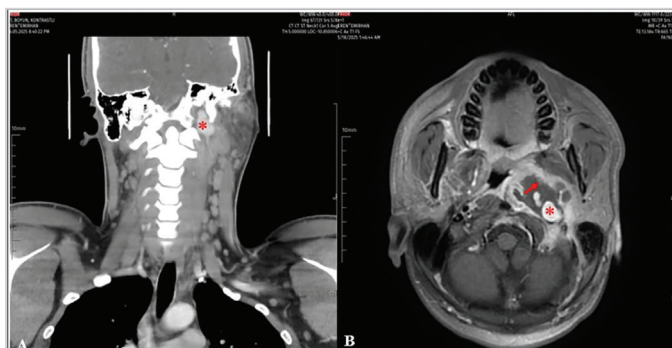


Figure 1. Pre-embolization images. A. Coronal contrast-enhanced CT showing a left parapharyngeal abscess and adjacent internal carotid artery pseudoaneurysm (asterisk), B. Axial contrast-enhanced T1-weighted MRI showing the pseudoaneurysm (asterisk) surrounded by hematoma (arrow)
CT: Computed tomography, MRI: Magnetic resonance imaging

suspicion of pseudoaneurysm (Figure 1b). Surgical drainage of the parapharyngeal abscess was deliberately avoided because of the close anatomical relationship between the abscess cavity and the ICA pseudoaneurysm, which posed a high risk of catastrophic hemorrhage in the event of inadvertent vascular injury.

Extensive evaluation excluded infective endocarditis, vasculitis, syphilis, and tuberculosis. Blood and abscess cultures were not obtained due to prior prolonged antibiotic therapy, and invasive diagnostic procedures were avoided because an ICA pseudoaneurysm was identified on initial imaging. Following consultation with the infectious diseases team, empirical intravenous therapy with ampicillin-sulbactam was initiated and continued throughout hospitalization. By hospital day 10, the patient developed disproportionate worsening neck pain despite opioid therapy. Accordingly, repeat CT angiography showed aneurysm enlargement by 1.5 cm. Angiography revealed narrowing of the cervical ICA with aneurysmal filling extending to the petrous segment, without distal opacification. In light of aneurysm progression and given the high risk of rupture together with evidence of sufficient collateral circulation, a multidisciplinary council decided to proceed with endovascular coil embolization of the ICA (Figure 2a, b). The procedure was uneventful. The patient was discharged on postoperative day two with oral ampicillin-sulbactam therapy prescribed for an additional two weeks and remained neurologically intact during six-months of follow-up. MRI at one month confirmed radiological improvement (Figure 3). Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Discussion

Early recognition and treatment of DNIs are essential to reduce morbidity and mortality. The most frequent complication is airway obstruction, reported in 14.2% of cases (3). Rare complications include unilateral vocal cord paralysis and infectious carotid pseudoaneurysm secondary

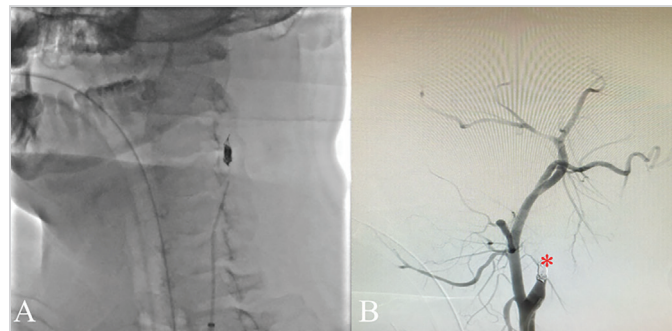


Figure 2. Endovascular findings. A. Selective left carotid angiography showing coil placement within the distal internal carotid artery. B. Post-embolization angiogram demonstrating absence of flow distal to the occluded segment (asterisk)

to parapharyngeal abscess (4). The incidence of vocal cord paralysis in DNI is approximately 1.5%, attributed to the involvement of the pharyngeal branch of the vagus nerve (3).

The term mycotic aneurysm, introduced by William Osler, refers to any infection-related aneurysm (1). Carotid involvement is particularly rare. In the pre-antibiotic era, syphilis, tuberculosis, and endocarditis were the predominant causes, whereas today hematogenous seeding and direct invasion from adjacent infection are recognized mechanisms (1,5). In our case, pseudoaneurysm formation may have resulted from direct extension of the parapharyngeal abscess. Fernández et al. (6) provided a comprehensive anatomical and pathophysiological explanation of how parapharyngeal infections may extend into the carotid sheath through progressive adventitial invasion, ultimately compromising the arterial wall. They further identified Horner's syndrome, severe dysphagia, and disproportionate pain as early clinical indicators of carotid space involvement findings that closely parallel the neurological presentation observed in our patient. Reported predisposing factors include immunosuppression, malignancy, corticosteroid therapy, and diabetes, of which none were present in our patient, adding to the case's uniqueness (6). Pirvu et al. (7), reported that most extracranial mycotic aneurysms occur in older or immunocompromised patients, with *Staphylococcus aureus*, *Salmonella*, and *Streptococcus* species as the leading pathogens. Our patient's lack of systemic comorbidity further underscores the exceptional nature of infection-

induced pseudoaneurysm in an otherwise healthy host. This distinction becomes more evident when the presented case is viewed in the context of age and immune status reported in literature. Reported adult cases predominantly involve older individuals, often in the sixth to eighth decades of life, with significant systemic comorbidities such as uncontrolled diabetes mellitus, hypertension, or recent surgical or traumatic vascular injury (1,2,4,6). In the pediatric population, infection-related carotid pseudoaneurysms have also been described (8). In contrast, this case suggests that severe vascular complications of DNIs can also be encountered in young, immunocompetent patients, despite the absence of traditional risk factors.

Management is complicated by a potential risk of embolization and rupture, which results in high morbidity and mortality. To our knowledge, there are no available guidelines recommending the best treatment option. Conservative therapy is discouraged due to the high risk of fatal complications (7). The definitive treatment of carotid mycotic aneurysms is surgical resection of the aneurysm with reestablishment of arterial flow, aiming to eliminate the infected aneurysm, prevent ischemic complications, and evacuate any associated hematoma (9). However, surgical ligation of the ICA carries a 30-60% risk of ischemic infarction, as reported by Nader et al. (2) and Fernández et al. (6), particularly in older or high-risk patients. Although grafts and anastomosis have been described, endovascular therapy is increasingly favored in anatomically complex or high-risk lesions. Stent grafts, flow diverters, and coil embolization have been reported as safe and effective alternatives (10). Antibiotic therapy remains the cornerstone of management; Knouse et al. (1) and Pirvu et al. (7) recommend a minimum of 6 weeks of targeted intravenous antibiotics, extendable to 6 months in persistent infections or immunocompromised hosts.

In our patient, the aneurysm extended to the petrous ICA, where surgical resection was technically challenging and hazardous. A multidisciplinary council composed of specialists from interventional radiology, infectious diseases, otolaryngology, and neurosurgery concluded that endovascular coil embolization was the safest strategy, supported by evidence of adequate collateral circulation. The procedure was successful, and the patient remained free of complications at six-month follow-up. Clinically, disproportionate pain resistant to opioids and multiple cranial neuropathies were the most striking findings. Worsening pain and new anisocoria prompted repeat imaging, which revealed aneurysm enlargement and necessitated urgent intervention. Mismanagement of such lesions as conventional DNIs, with surgical drainage attempted before vascular evaluation, may result in catastrophic hemorrhage secondary to pseudoaneurysm rupture. In our case, a staged management strategy was adopted, prioritizing



Figure 3. Post-embolization image. Axial contrast-enhanced T1-weighted fat-suppressed MRI showing marked resolution of the internal carotid artery pseudoaneurysm in the left parapharyngeal space
MRI: Magnetic resonance imaging

vascular stabilization before any attempt to address the abscess. Because surgical manipulation in close proximity to the pseudoaneurysm carried a high risk of catastrophic hemorrhage, immediate drainage was avoided; instead, the patient was managed with close radiological and clinical follow-up and appropriate antimicrobial therapy, while the vascular lesion was secured by endovascular intervention. We believe that this cautious and multidisciplinary approach may be appropriate in similar high-risk clinical scenarios. Following this staged approach, vascular risk was first controlled, and in the absence of clinical deterioration during close follow-up, additional surgical drainage was not deemed necessary. Therefore, clinicians should maintain a high index of suspicion when atypical neurological symptoms, opioid-refractory pain, or unexplained hematoma are present.

A key limitation in this case is the absence of microbiological confirmation, as reliable culture results could not be obtained due to prior empirical antibiotic therapy. While clinical and radiological findings were suggestive of an infectious process, including radiological evidence of a parapharyngeal abscess, elevated inflammatory markers, and clinical improvement following antimicrobial therapy, a direct causal relationship between the infection and pseudoaneurysm formation cannot be definitively established. Furthermore, extensive evaluation excluded other potential causes, including infective endocarditis, syphilis, tuberculosis, and rheumatological conditions such as vasculitis. Therefore, infection is considered the most likely underlying mechanism; however, causality cannot be definitively established, and close clinical follow-up is warranted, with attention to findings suggestive of alternative etiologies.

Conclusion

This case emphasizes the need for a multidisciplinary approach in managing rare cervical aneurysms, where unusual findings such as disproportionate pain or cranial neuropathies should raise suspicion. Early recognition should prompt vascular imaging to rule out aneurysmal disease. Mismanagement of such lesions as conventional DNIs, with surgical drainage attempted before vascular evaluation, may result in catastrophic hemorrhage secondary to pseudoaneurysm rupture. In high-risk anatomical sites, endovascular coil embolization can be a safe and effective alternative to surgery, enabling rapid recovery. The unclear etiology, despite thorough evaluation, highlights the importance of continued surveillance and further studies on these uncommon but serious conditions.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A.U., Concept: B.V.C., S.Ö., Design: B.V.C., Data Collection and/or Processing: T.G.K., S.A.U., Analysis or Interpretation: B.V.C., S.Ö., Literature Search: T.G.K., Writing: B.V.C., T.G.K.

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

- Deep neck infections can rarely lead to life-threatening vascular complications such as internal carotid artery pseudoaneurysm, and early recognition is essential to prevent catastrophic hemorrhage.
- The presence of cranial neuropathies or progressive, treatment-refractory neck pain in parapharyngeal infections should prompt immediate vascular imaging to exclude carotid involvement.
- Multidisciplinary collaboration is essential throughout both the diagnostic and the therapeutic processes in managing rare vascular complications of deep neck infections.
- Endovascular management represents a safe and effective treatment option for carotid pseudoaneurysms when adequate collateral circulation is present, especially in anatomically challenging regions.

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Case Report



Turk Arch Otorhinolaryngol 2026; 64(3): 209-213

DOI: 10.4274/tao.2026.2025-5-3

Ectopic ACTH-Secreting Pituitary Adenoma of the Maxillary Sinus: A Rare Cause of Cushing's Syndrome

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Abstract

We describe a rare case of Cushing's syndrome caused by an ectopic adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma located in the maxillary sinus and outline the diagnostic and therapeutic challenges. A 41-year-old woman presented with an eight-year history of progressive weight gain, fatigue, type 2 diabetes mellitus, and hypertension, leading to a diagnosis of Cushing's syndrome. Inferior petrosal sinus sampling confirmed an ectopic ACTH source. Fluorodeoxyglucose-positron emission tomography demonstrated a 12-mm lesion in the right maxillary sinus, which was successfully removed via an endonasal approach. Postoperatively, cortisol levels normalized and her symptoms resolved. The patient remains in remission 2.5 years following surgery. This case highlights the importance of considering ectopic ACTH-secreting adenomas in patients with Cushing's syndrome without a sellar mass and emphasizes the need for thorough diagnostic evaluation to ensure accurate tumor localization and optimal surgical management.

Keywords: Cushing's syndrome, adrenocorticotrophic hormone (ACTH), pituitary neoplasms, paranasal sinuses, maxillary sinus, endoscopic sinus surgery, case report

Introduction

Ectopic pituitary adenomas are exceedingly rare benign neoplasms of pituitary origin that arise outside the sella turcica, without any involvement of the sellar region (1). These tumors are frequently misdiagnosed as other neuroendocrine or epithelial neoplasms that may arise in similar anatomical locations. The current literature on ectopic pituitary adenomas is limited to isolated case reports and small case series, which collectively highlight the heterogeneous presentation of these lesions in terms of anatomical location, radiological features, and biochemical functionality. This variability often complicates timely diagnosis and management.

The majority of patients with adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome (CS) have an ACTH-secreting pituitary adenoma located within the sella turcica. However, prolonged investigation reveals an ectopic ACTH-secreting pituitary adenoma situated along the embryological migratory path of Rathke's pouch in exceedingly rare instances. Despite the suggestion of surgery as the first-line treatment in these cases, evidence to guide long-term management, surveillance, and recurrence prediction remains limited.

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Cite this article as: Wordsworth G, Karagöz T, Lonnen K, Bennett W, Bates T. Ectopic ACTH-secreting pituitary adenoma of the maxillary sinus: a rare cause of Cushing's syndrome. *Turk Arch Otorhinolaryngol.* 2026; 64(3): 209-213

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Received Date: 03.08.2025

Accepted Date: 03.03.2026

Epub: 20.08.2026

Publication Date: 30.09.2026



To our knowledge, only a small number of ectopic pituitary adenomas located in the maxillary sinus have been reported (2). Here, we report a patient with a longstanding history of Cushingoid features, whose workup revealed an ectopic ACTH-secreting pituitary adenoma in the right maxillary sinus. This case underscores the diagnostic and therapeutic challenges posed by these rare tumors and contributes to the growing body of literature aimed at guiding their management.

Case Presentation

A 41-year-old woman with an eight-year history of progressive weight gain, fatigue, type 2 diabetes mellitus, and hypertension was referred to the endocrine clinic. She had no other significant past medical history and had previously been told that her symptoms were consistent with fibromyalgia. She had undertaken research on the internet and had noted several fibromyalgia forums referencing CS. She felt her symptoms and physical features were consistent with this diagnosis. She had no history of exogenous steroid use and no cause for physiological hypercortisolism. Clinical assessment confirmed signs consistent with CS (facial plethora, obesity, dorsocervical fat pad, proximal myopathy, and hirsutism). A review of old photographs demonstrated a marked change in the patient's physical appearance over the preceding five years.

Initial diagnostic investigations confirmed CS. A non-suppressed ACTH level of 39.1 ng/L confirmed ACTH-dependent CS (Table 1). Concurrent findings of secondary hypothyroidism initially suggested a pituitary source. Subsequently, she underwent corticotropin-releasing hormone stimulation testing, which yielded indeterminate results for a pituitary source. A contrast-enhanced magnetic resonance imaging (MRI) of the pituitary gland revealed a possible right-sided microadenoma (Figure 1a). She

was discussed at the regional pituitary multidisciplinary team (MDT) meeting and inferior petrosal sinus sampling (IPSS) was recommended. IPSS favored an ectopic rather than pituitary source of ACTH. Based on these findings, she underwent cross-sectional imaging. A computed tomography (CT) scan of her neck/thorax/abdomen and pelvis was unremarkable. Fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging revealed a 12-mm right maxillary sinus lesion with avid tracer uptake (SUV_{max} 11.9) (Figure 1b). There were no areas of FDG tracer uptake in the brain or pituitary gland.

Following biochemical confirmation of CS, she was prescribed prophylactic low molecular weight heparin (enoxaparin 40 mg once daily). In view of escalating hyperglycemia (HbA1c 108 mmol/mol) and in anticipation of surgery, she was commenced on the maximum tolerated dose of metyrapone (500 mg twice daily). Dose adjustments were guided by regular early morning serum cortisol assessment (target mean 150-300 nmol/L) (3). Her diabetes was managed with basal-bolus insulin therapy (insulin glargine U-300 and insulin aspart) and metformin 1 g twice daily. Her hypertension was treated with two agents (lisinopril 20 mg once daily and amlodipine 10 mg once daily). She was referred to the ear, nose and throat MDT meeting and following a CT (Figure 1c), which confirmed the lesion's presence, the decision was made to proceed with surgery. She underwent endonasal resection of the lesion from the right anterior maxillary sinus wall using a pre-lacrimal approach. Through the nasal cavity, an incision was made anterior to the inferior turbinate along the lateral nasal wall. The mucosa was elevated, and the medial wall of the maxillary sinus was drilled anterior to the nasolacrimal duct, creating a wide surgical window into the maxillary sinus. This approach provided direct access to the anterior, lateral, and inferior walls of the maxillary sinus while preserving the lacrimal drainage system. After complete excision of the lesion, the mucosal flap was repositioned.

Table 1. Laboratory test results

Test	Result	Reference range
24-hour urinary free cortisol (1)	934 nmol/24 hrs	<120 nmol/24 hrs
24-hour urinary free cortisol (2)	906 nmol/24 hrs	<120 nmol/24 hrs
Overnight dexamethasone suppression test	221 nmol/L	Suppression expected
ACTH	39.1 ng/L	
TSH	1.68 mIU/L	
Free T4	8.2 pmol/L	12-22 pmol/L
CRH stimulation test (ACTH)	24.1 to 86.5 ng/L	>50% increase
CRH stimulation test (cortisol)	783 to 806 nmol/L	>20% increase
IPSS (central-to-peripheral ratio pre-CRH)	<2	
IPSS (central-to-peripheral ratio post-CRH)	<3	
IPSS (prolactin-normalized ratio)	0.4	

CRH: Corticotropin-releasing hormone, IPSS: Inferior petrosal sinus sampling, TSH: Thyroid stimulating hormone, ACTH: Adrenocorticotrophic hormone

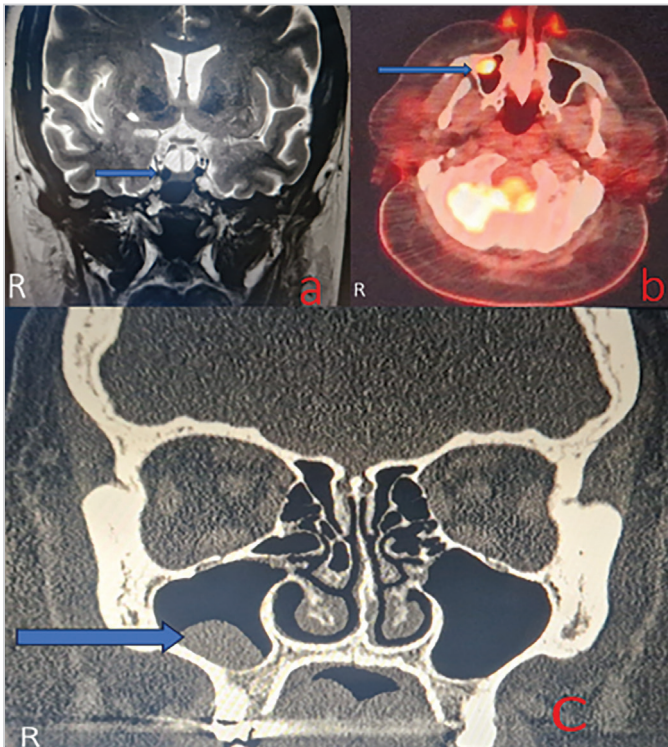


Figure 1. a) Coronal MRI of the pituitary with gadolinium shows a partially empty sella and a small non-enhancing focus in the right anterior pituitary (blue arrow), b) The blue arrow highlights a rounded polypoid lesion arising from the anterior wall of the right maxillary antrum, demonstrating marked FDG uptake (SUV_{max} 11.9), c) Coronal CT reveals a well-defined low-density lesion at the base of the right maxillary antrum (blue arrow)
MRI: Magnetic resonance imaging, FDG: Fluorodeoxyglucose, CT: Computed tomography

Macroscopic examination revealed a 28×20×8 mm tumor arising from the right maxillary sinus. Histological examination demonstrated respiratory-type sinonasal mucosa infiltrated by a pituitary adenoma (Figure 2). No cytologic atypia or evidence of tumor apoplexy was identified. Immunohistochemical analysis showed diffuse positivity for ACTH, synaptophysin, chromogranin, and TPIT, confirming the diagnosis of a corticotroph adenoma. The Ki-67 proliferation index was low (<1%), indicating low proliferative activity. An independent second histopathological review confirmed the diagnosis of an ectopic ACTH-secreting pituitary adenoma (ectopic corticotropinoma).

A 9 a.m. serum cortisol level of 34 nmol/L on the first postoperative day was consistent with early biochemical remission. Hydrocortisone replacement therapy was initiated at a dose of 10 mg on waking, 5 mg at lunchtime, and 5 mg in the afternoon. At 2.5-year follow-up, she remains in clinical and biochemical remission. Antihypertensive therapy has been discontinued, and she no longer requires glucose-

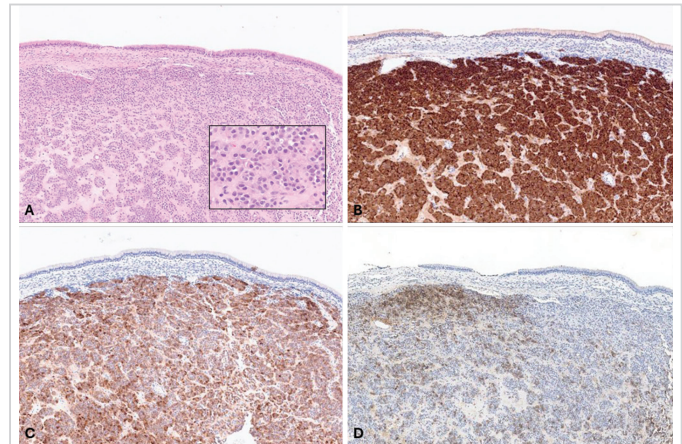


Figure 2. Histopathological images. A) H&E shows sinonasal mucosa lined by respiratory epithelium. The lamina propria contains small tumor cells arranged in sheets, nests, and trabeculae. The tumor cells have pale amphophilic cytoplasm and small nuclei (insert). Insert: ×400 magnification, B) Synaptophysin is strongly positive, C) Chromogranin is also positive, D) ACTH shows patchy positivity, A-D) ×50 magnification
H&E: Hematoxylin and eosin, ACTH: Adrenocorticotrophic hormone

lowering medication. A recent HbA1c of 38 mmol/mol is consistent with sustained diabetes remission. She has also lost 20 kg since surgery.

The patient provided written informed consent for the publication of clinical details and images.

Discussion

Pituitary adenomas are among the most common intracranial tumors, typically benign and confined to the sella turcica. Approximately 15% of these tumors secrete ACTH, giving rise to the clinical picture of CS (4). In contrast, ectopic pituitary adenomas arising outside the sella are exceptionally rare, with only a small number of cases reported in the literature. The published cases reveal marked variability in clinical presentation, imaging features, and hormone secretion profiles (5). Unusual sites for ectopic pituitary adenomas include the ethmoid sinus, the temporal bone, the nasal bridge, Meckel's cave and even the thalamus (6).

Ectopic pituitary adenomas originate from the remnants of normal pituitary tissue derived from Rathke's pouch during embryological development. They are most commonly found along this migratory pathway, in regions such as the sphenoid sinus, the suprasellar region, the clivus, the cavernous sinus, and the nasopharynx (2). Zhu et al. (7) reported that among 180 patients with ectopic pituitary adenomas, the most common locations were the sphenoid sinus (34.4%) and the suprasellar region (25.6%), followed by the clivus (15.6%), the cavernous sinus (13.3%) and the nasopharynx (5.6%). These lesions can also establish vascular supply and endocrine communication with the hypothalamus. Although the exact

factors influencing their location and development remain unclear, the presence of an ectopic pituitary adenoma in the maxillary sinus—as seen in this case—is notably atypical, lying well off this midline migratory route and distinct from the ethmoid sinus, temporal bone, nasal bridge, Meckel's cave, and thalamus reported as other rare, non-midline sites.

The clinical presentation of ectopic pituitary adenomas often correlates with their anatomical location. Patients with suprasellar ectopic pituitary adenomas are more likely to present with menstrual disorders and visual changes, while those with clival ectopic pituitary adenomas are more likely to suffer from headaches (7). The diverse locations and non-specific symptoms of ectopic pituitary adenomas make their diagnosis challenging, often leading to misdiagnosis and delayed treatment.

Several case reports of ectopic pituitary adenoma located within or adjacent to the maxillary sinus have been described in the literature. Sindoni et al. (6) describe a 49-year-old man with ACTH-dependent CS who underwent further imaging following an unsuccessful surgical attempt to resect a presumed pituitary adenoma. An 18F-choline PET/CT scan demonstrated avid uptake in a nodule within the left maxillary sinus. Subsequent transnasal endoscopic resection and histological analysis confirmed the diagnosis of an ectopic ACTH-secreting pituitary adenoma. Both our case and the one reported by Sindoni et al. (6) presented with ACTH-dependent CS and were successfully treated with surgical resection. However, our case utilized FDG-PET for localization, while Sindoni et al. (6) used 18F-choline PET/CT. This highlights the utility of different imaging modalities in localizing these rare tumors. Additionally, both patients achieved biochemical remission following surgical resection, demonstrating the effectiveness of surgery as the primary treatment modality for these rare tumors.

Our case highlights the diagnostic challenges involved in the work-up of CS and underscores the importance of a thorough, stepwise approach to investigating patients with hypercortisolemia. Ectopic pituitary adenomas are rare and diverse in location and presentation; they may frequently be overlooked in the differential diagnosis of CS. Campana et al. (5) describe an apparent higher prevalence of clinically functioning ectopic pituitary adenomas when compared to sellar-located pituitary adenomas. On review of the literature, positive staining for ACTH was described in 36% of cases, 13% of which were clinically silent. Given that ectopic pituitary adenomas are often misdiagnosed, it is essential to screen any patient presenting with hypercortisolemia and no clear source for the possibility of an ectopic pituitary adenoma. The presence of a pituitary adenoma within the sella turcica should not exclude the consideration of an ectopic pituitary adenoma, especially if the biochemical findings are discordant.

Surgical removal is the treatment of choice for ectopic pituitary adenomas and allows further evaluation of the roof of the sinus to guide any additional management (8). The use of various medical therapies has been described, including dopamine agonists for prolactin secreting ectopic pituitary tumors (9). However, these treatments are non-curative and are likely to result in re-growth once stopped. The use of radiotherapy both as an initial treatment and post-operatively has also been reported (8). Often such adjuvant therapy was recommended because of an incorrect initial diagnosis and brings with it similar risks seen with radiation to the pituitary fossa.

The dilemma in a rare case such as this is the natural history of the tumor following surgical resection both in terms of tumor growth and/or recurrence. In the case series reported by Thompson et al. (8), 29 of 32 patients with sphenoid sinus ectopic pituitary adenomas had available follow-up data. The average follow-up duration was 10.2 years post-surgical resection. Four patients had recurrence or persistence of the tumor after surgery. Two of these patients were given adjuvant radiotherapy and are now disease free. Seltzer et al. (10) also suggest favorable outcomes with the possibility of long-term remission from CS for functional ectopic pituitary adenomas resected from the sphenoid sinus. Given their rarity, however, no formal evidence-based treatment pathways exist for the investigation and management of ectopic pituitary adenomas. This is particularly the case for a tumor located away from the midline and anatomically distant from the pituitary gland.

Correct localization of an ectopic pituitary adenoma in this case to the maxillary sinus, ensured the patient did not undergo unnecessary investigation or treatment. Given the increased mortality associated with CS even after successful treatment, the case highlights the need for prompt tumor identification to reduce a patient's long-term exposure to hypercortisolemia. Our patient remains in biochemical remission 2.5 years post-surgery and as a result has benefited from improvements in blood pressure and glycemic control. However, the potential for recurrence in this very rare case is largely unknown. In the absence of any long-term surveillance data in the literature, we will need to assess the extent to which that strategy is appropriate, having opted for biochemical surveillance. We hope this will help better inform future clinicians in how to manage these rare tumors.

Conclusion

This case underscores the diagnostic and therapeutic challenges posed by ectopic pituitary adenomas, particularly those located outside the typical embryological migratory path, such as within the maxillary sinus. This underscores the importance of maintaining a broad differential diagnosis in patients with ACTH-dependent CS who have discordant

imaging and biochemical findings, even when an apparent sellar lesion is present. Accurate localization in this case prevented unnecessary treatments and led to successful surgical resection, with the patient achieving biochemical remission and clinical improvement. However, the long-term behavior of such rare tumors remains uncertain. In the absence of established guidelines, careful biochemical surveillance and case reporting will be essential to improving future recognition, management strategies, and outcomes for patients with ectopic pituitary adenomas.

Ethics

Informed Consent: The patient provided written informed consent for the publication of clinical details and images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.W., K.L., W.B., Design: G.W., Data Collection and/or Processing: T.K., K.L., T.B., Analysis or Interpretation: T.K., K.L., W.B., Literature Search: G.W., T.K. Writing: G.W., T.K.

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

- Cushing's syndrome is commonly caused by an adrenocorticotrophic hormone secreting pituitary adenoma. In very rare cases, the pituitary gland can be separate from the sellar turcica and ectopically located.
- Ectopic pituitary adenomas are most commonly found in areas linked to the development of the pituitary gland such as the midline sinuses.
- Any patient presenting with hypercortisolemia and no clear source should be screened for an ectopic pituitary adenoma.
- Surgery is the first line treatment for ectopic pituitary adenomas with favorable outcomes reported in the literature.

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