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Volume quantification of endolymphatic hydrops in patients with vestibular schwannoma

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ABSTRACT

Objective: The origin of vestibular symptoms in patients with vestibular schwannoma (VS) is uncertain. We used intratympanic gadolinium-enhanced magnetic resonance imaging (MRI) to confirm the labyrinthine lesions in patients with VS and to explore the features of endolymphatic hydrops (EH) in these patients.

Methods: In total, 66 patients diagnosed with unilateral VS were enrolled in this study and underwent intratympanic gadolinium-enhanced MRI. The borders of the vestibule and endolymph were mapped on the axial MRI images, and the area and volume of vestibule and endolymph were automatically calculated using Osirix software, and the area and volume percentage of vestibular endolymph were obtained.

Results: The area and volume percentages of vestibular endolymph on the affected side were significantly larger than those on the healthy side (both $p < 0.001$). Using Kendall's W test, we found that the area and volume percentages of vestibular endolymph on the affected side were consistent ($p < 0.001$), but the consistency was moderate ($k = 0.574$). The healthy side was also consistent ($p < 0.001$), and the degree of consistency was moderate ($k = 0.444$). We used 19.1% as the cut-off point to distinguish the presence or absence of vestibular EH; that is, the volume percentage of vestibular endolymph that was more than 19.1% were defined as the subgroup with hydrops, while the subgroup without hydrops included patients with a baseline level below 19.1%. No volume classification for vestibular EH was proposed. Based on this standard, 11/66 (16.7%) of the patients with VS in this study had vestibular EH. Conclusions.

The volume percentage of the vestibular endolymph was more accurate than the area percentage for assessing vestibular EH. Using 19.1% as the cut-off point to distinguish the presence or absence of vestibular EH, we found that 16.7% of patients with VS had varying degrees of vestibular EH. We believe that the vestibular symptoms in patients with VS may originate from the peripheral lesions.

1. Introduction

Vestibular schwannoma (VS), a benign tumor arising from the eighth cranial nerve, is a commonly observed cerebellopontine angle (CPA) tumor (Myrseth et al., 2007; Wang et al., 2019). Common symptoms of VS are unilateral hearing loss, tinnitus, poor speech discrimination, and vestibular symptoms. These symptoms are attributed to a combination of compressional/neurotoxic effects on vestibular nerve afferents and/or a compromised vascular supply to the inner ear (Eliezer et al., 2019; Fujiwara et al., 2019; Myrseth et al., 2006; Taylor et al., 2015; Tsutsumi et al., 2000; Ushio et al., 2009; von Kirschbaum and Gürkov, 2016). In general, the slow progressive reduction of vestibular function results it the gradual implementation of central adaptive mechanisms, which minimize VS-related symptoms and clinical signs (Curthoys, 2000; Fujiwara et al., 2019). Despite this, vestibular symptoms are still the most painful clinical symptoms for patients with VS (von Kirschbaum

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and Gürkov, 2016). Previous studies have also shown that 30% to 75% of patients with VS report at least one vestibular symptom when diagnosed, ranging from dizziness, disequilibrium, directional pulsion, positional to severe spontaneous vertigo, and vestibular crisis events (Andersen et al., 2015; Carlson et al., 2015; Hızlı et al., 2016; Taylor et al., 2013).

Endolymphatic hydrops (EH) is an inner ear disease that can cause vertigo attacks and is typified by excessive accumulation of endolymph (Ralli et al., 2017; Slattery et al., 2015). In addition to vertigo, other features of EH are tinnitus, fluctuating hearing loss, ear fullness, and progressive loss of audiovestibular function (Ralli et al., 2017; Slattery et al., 2015). With the development and progression of magnetic resonance imaging (MRI), many technical difficulties have been overcome, resulting in MRI being used to identify several tumor characteristics, such as size, blood supply, and nature. Contrast-enhanced MRI has recently become a well-established method, which can be used to directly visualize EH in vivo via intratympanic injection of gadolinium-based contrast media (GBCM) (Nakashima et al., 2007; Wang et al., 2020). As the GBCM diffuses through the round and oval windows into the inner ear, the perilymphatic space surrounding the endolymph can be successfully visualized as a bright signal, while the endolymph space appears dark (Wang et al., 2020). To date, few cases have confirmed the presence of coexisting ipsilateral VS and vestibular EH using MRI (Dispenza et al., 2008; Morrison and Sterkers, 1996; Naganawa et al., 2011; Ralli et al., 2017).

The origin of vestibular symptoms in patients with VS is uncertain. Traditionally, vestibular dysfunction and symptomatology have been ascribed to retrolabyrinthine sources (Hızlı et al., 2016; Tringali et al., 2008). However, whether labyrinthine pathology contributes to vestibular dysfunction and symptomatology is unclear. Previous studies have either described the severity of vestibular EH by roughly estimating the area of vestibular endolymph, used non-contrast-enhanced 3D-FLAIR images, or were case reports only (Jerin et al., 2015; Naganawa et al., 2011). This study aimed to confirm the labyrinthine lesions in patients with VS using intratympanic gadolinium-enhanced MRI, calculate the volume percentage of the vestibular endolymph to assess vestibular EH more accurately, and explore the features of vestibular EH in patients with VS.

2. Materials and methods

2.1. Ethical considerations

This study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study protocol was approved by the Institutional Review Board of the Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China. All study methods were performed in accordance with the relevant guidelines and regulations. All participants provided informed consent prior to study enrollment.

2.2. Study design

In total, 66 patients diagnosed with unilateral VS were enrolled, between January 2019 and November 2020, in this study. All patients underwent intratympanic gadolinium-enhanced MRI. The exclusion criteria included (1) contraindication to intratympanic injection or MRI examination and (2) poor compliance and inability to complete the study.

2.3. Intratympanic injection

Patients were seated on a treatment chair with their heads and faces at an angle of approximately 45° to the sagittal line, with the affected ear facing the injector (Yang et al., 2018). The external ear canal was disinfected twice with 75% medicinal alcohol, and lidocaine aerosol was used for topical anesthesia. The position of the posterior-superior quadrant of the tympanic membrane was confirmed using an endoscope. Next, 0.3 to 0.5 mL gadopentetate dimeglumine (Gd-DTPA), diluted fourfold with saline (v/v 1:4), was injected into the tympanic cavity using a 1-mL syringe (Yang et al., 2018). The patients were asked to hold the injected ear upward for 15 min and avoid swallowing or coughing (Yang et al., 2018). No patients experienced any discomfort.

2.4. MRI measurements

All MRI scans were performed using a 3.0 T MRI scanner (Verio, Siemens Medical Solutions, Erlangen, Germany) equipped with a 32-channel phased-array head coil. The inner ear image was acquired 24 h after intratympanic Gd-DTPA injection. The T2-weighted turbo spin-echo (T2 TSE) sequence was used to acquire inner ear images that emphasized the fluid-filled compartments: echo time (TE), 78 ms; repetition time (TR), 3,000 ms; matrix, 269 × 384; 190 contiguous 1 mm thick slices; and acquisition time of 53 s. 3D-FLAIR was used to image the Gd-DTPA in the inner ear: TE, 181 ms; TR, 5,000 ms; flip angle, TSE with 180° refocusing flip angle; echo train length, 23; matrix size, 384 × 384; 12 axial 0.8 mm thick slices; and scan time of 14 min 50 s. Based on the radiologic evaluation, patients were classified according to the Koos classification scale for VS: grade I, purely intracanalicular tumor; grade II, small tumor with protrusion into the CPA without brainstem contact; grade III, tumor filling the CPA cistern with no brain stem displacement; and grade IV, large tumor with brain stem compression (Fujiwara et al., 2019; Koos et al., 1998; von Kirschbaum and Gürkov, 2016).

2.5. Image analysis

The MRI images were processed by OsiriX software (v. 10.0.3, Pixmeo SARL, Switzerland). The image window level and width were set to 400/1000 before contouring the vestibular regions on the axial images. Regions of interest (ROIs) were manually mapped around the perilymphatic space with an enhanced Gd-DTPA signal, and the endolymphatic space with negative signal in each slice. Two senior radiologists and one experienced otologist, blinded to the patients' information, independently drawn the borders of the vestibule and endolymph. Interobserver discrepancies were resolved by consensus. For the vestibular ROIs, all visible vestibular slices were selected, excluding the semicircular canal and ampulla (Fig. 1). The OsiriX software was used to calculate the area and volume of the vestibule and endolymph, and the area and volume percentages of vestibular endolymph were obtained. We measured the endolymphatic volume and quantified the extent of vestibular endolymph as the percentage of the volume of endolymph in relation to the vestibule, that is, the volume percentage of vestibular endolymph = (the volume of the negative signal representing the ROIs of the endolymph/the total volume of the enhanced and negative signals in these ROIs) × 100% (Wang et al., 2020).

2.6. Statistical analyses

We used SPSS statistical software (version 20 for Windows; IBM Corp., Armonk, NY, USA) to analyze all data. Continuous variables conforming to a normal distribution were expressed as mean values ± standard deviations, and continuous variables not conforming to the normal distribution were expressed as median (interquartile range). Categorical variables are presented as percentages. An analysis of variance and Kruskal–Wallis test were performed to assess data across the classifications for normal and non-normal distributed data, respectively. The Mann–Whitney *U* test was applied to analyze the tumor size, pure-tone audiometry, disease duration, and the volume percentage of vestibular endolymph in vertigo and non-vertigo groups, and to compare the area and volume percentage of vestibular endolymph between the affected and healthy sides. Kendall's W test was used to compare the consistency of area and volume percentages of vestibular

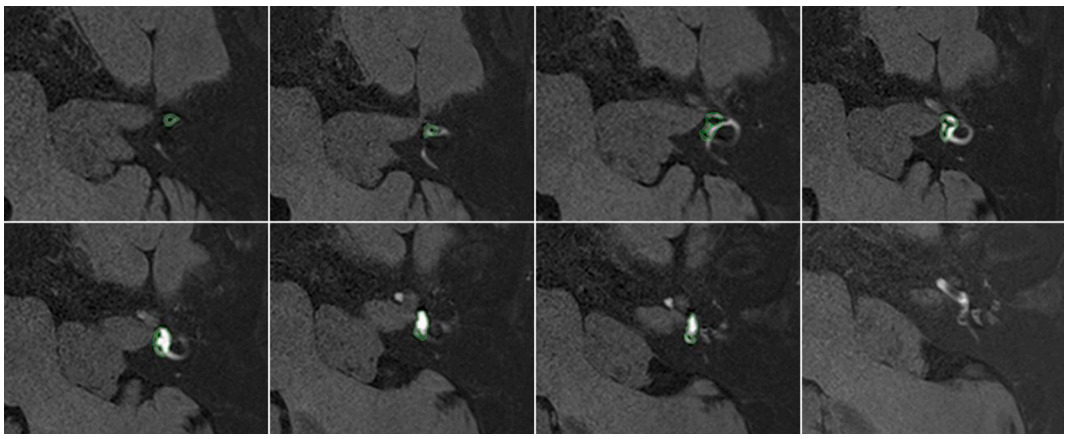

Fig. 1. The process of contouring the ROIs on the 3D-FLAIR MR images to draw the borders of the vestibule and endolymph. All visible vestibular slices were contoured.

endolymph. The K-means clustering algorithm was used to cluster the volume percentage of vestibular endolymph on the affected side and to explore a new method for evaluation of vestibular EH. P-values < 0.05 were considered statistically significant for all analyses.

3. Results

Among the 66 patients with VS that enrolled, 42(63.6%) were female and 24(36.4%) were male, aged between 27 and 73 years. VS occurred on the right side in 38 cases and on the left side in 28 cases. The tumor was cystic in 42 cases and solid in 24, and 30 patients had vestibular symptoms. Tinnitus was present in 54 of the patients, and a history of sudden deafness was noted in 21 cases. There was no significant difference in tumor size, pure-tone audiometry, and disease duration between the vertigo and non-vertigo groups ($p > 0.05$). In Table 1, demographic variables are presented for each Koos classification.

The average area percentage of vestibular endolymph was considerably larger, at 19.0%, on the affected side vs. 6.2% on the healthy side ($p < 0.001$). Similarly, the average volume percentage of vestibular endolymph on the affected side was significantly larger than that on the healthy side (12.6% vs. 5.5%, $p < 0.001$) (Fig. 2). Using Kendall's W test, the area and volume percentage of vestibular endolymph on the affected side were found to be consistent ($p < 0.001$), but the consistency was moderate ($k = 0.574$). The measurements on the healthy side were also consistent ($p < 0.001$), and the degree of consistency was moderate ($k = 0.444$).

The average area percentage of vestibular endolymph on the affected side without and with vestibular symptoms was 17.8% and 19.5%, respectively; the difference was not significant ($p = 0.584$). The average volume percentage of vestibular endolymph on the affected side without and with vestibular symptoms was 12.3% and 13.8%, respectively; the difference was not significant ($p = 0.974$).

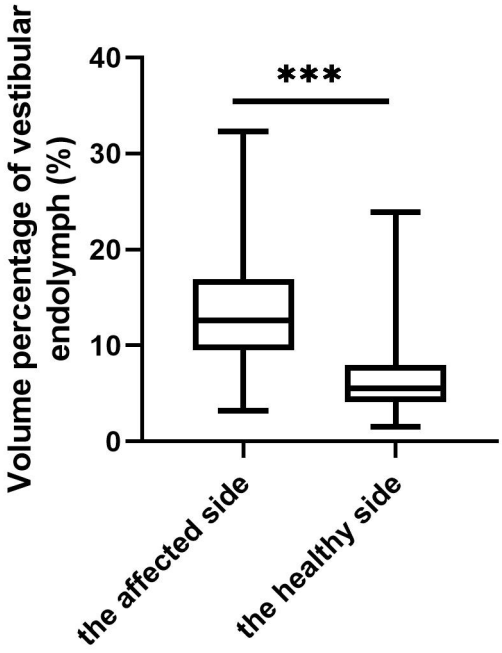

Fig. 2. Volume percentage of vestibular endolymph (%) between the affected side and the healthy side.

The average area percentage of vestibular endolymph was 6.3% on the healthy side, and 17.8% on the affected side without vestibular symptoms, the difference was significant ($p < 0.001$). The average volume percentage of vestibular endolymph was 5.5% on the healthy

Table 1
Comparison of clinical features.

Characteristics	Total(N = 66)	Koos classifications				P1	vestibular symptoms		P2
		Koos I(n = 8)	Koos II(n = 33)	Koos III(n = 18)	Koos IV(n = 7)		Without vertigo (n = 36)	with vertigo(n = 30)	
Mean age, y	50.7 ± 11.2	50.4 ± 10.5	52.3 ± 11.0	49.1 ± 12.3	47.7 ± 11.0	0.77	48.9 ± 10.8	52.9 ± 11.5	0.664
Female/Male, (n/n)	42/24	4/4	18/15	14/4	6/1	0.161	20/16	22/8	0.135
Symptom duration, m	12(58)	2.5(27)	12(28)	12(58)	60(108)	0.109	8.5(32)	12(57)	0.216
Tinnitus (n, %)	54(81.8)	6(75.0)	29(87.9)	13(72.2)	6(75.0)	0.532	29(80.6)	25(83.3)	0.771
History of sudden deafness (n, %)	21(31.8)	2(25.0)	11(33.3)	6(33.3)	2(28.6)	0.966	13(36.1)	8(26.7)	0.412

P1: Comparison of clinical features in vestibular schwannoma patients of different Koos classifications. P2: Comparison of clinical features in vestibular schwannoma patients without and with vertigo.

side, and 12.3% on the affected side without vestibular symptoms, the difference was also significant ($p < 0.001$).

There was no difference in the area percentage of vestibular endolymph in VS with different Koos grades ($p = 0.055$). However, the volume percentage of vestibular endolymph in different Koos grades was significantly different on the affected side ($p = 0.011$) (Fig. 3). Additionally, the volume percentage of vestibular endolymph in Koos grade I patients was significantly higher than that of Koos grades III and IV ($p = 0.036$ and $p = 0.024$, respectively).

No volume classification of the vestibular EH was proposed. We used the k-means clustering algorithm and divided the patients into two subgroups according to vestibular endolymph (Fig. 4). We used 19.1% as the cut-off point to distinguish the presence or absence of vestibular EH; that is, patients with a volume percentage of vestibular endolymph that was $\geq$ 19.1% were defined as the subgroup with hydrops, while the subgroup without hydrops included patients with a baseline level below 19.1%. Based on this cut-off point, 1/6 (16.7%) of the patients with VS in our study had vestibular EH.

4. Discussion

This study is the first to use intratympanic gadolinium-enhanced MRI to quantify the volume percentage of vestibular EH and to confirm peripheral lesions in patients with VS. In this study, we used the volume percentage of the endolymphatic space to reflect the degree of vestibular EH on the VS side and found varying degrees of vestibular EH when compared to the healthy side.

The origin of the audiovestibular symptoms in patients with VS remains controversial (Jerin et al., 2015). It is still unclear whether the onset of vertigo in patients with VS is caused by the stimulation of the nerve by the tumor or the local compression of the tumor causing inner ear disease (EH, for example) (Naganawa et al., 2011). Clinicians usually ascribe the dysfunction of the vestibular nerve to VS-associated vertigo. Supporting this contention is histopathologic evidence of the destruction of vestibular nerve fibers from pressure atrophy or tumor invasion. Larger tumors may also cause centrally mediated vestibular symptoms by compressing the cerebellum and brainstem (Hızlı et al., 2016; Tringali et al., 2008). Several studies have discussed the origin of vestibular

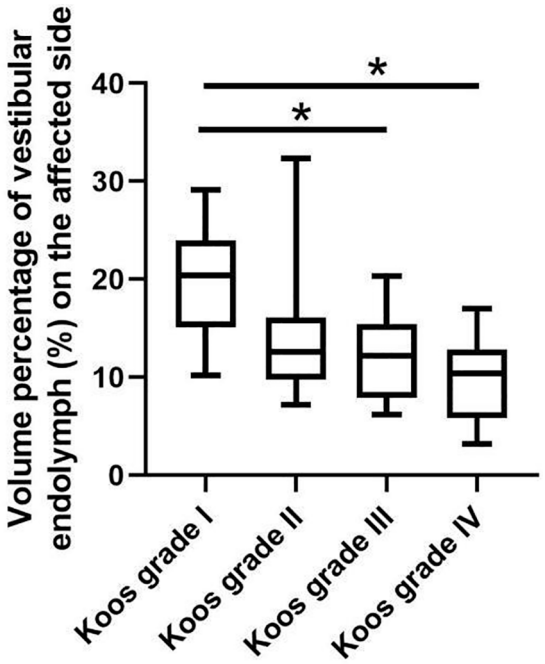

Fig. 3. Volume percentage of vestibular endolymph (%) of different Koos grades on the affected side.

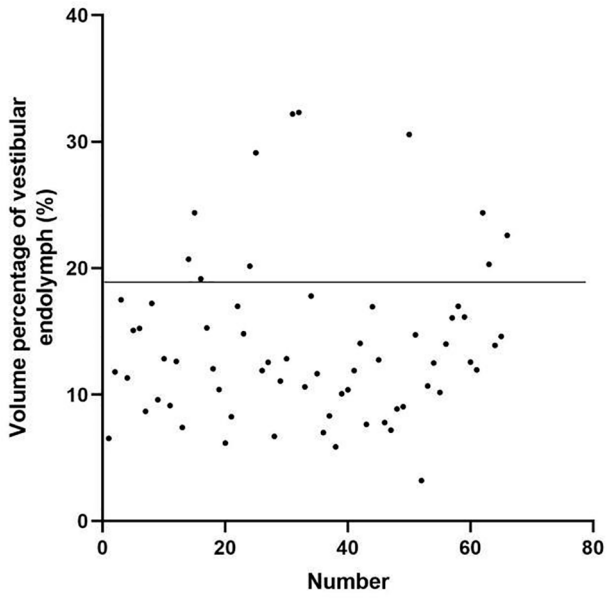

Fig. 4. Volume percentage of vestibular endolymph (%) in each patient with vestibular schwannoma.

symptoms in patients with VS, suggesting that vertigo may also have a peripheral origin, possibly induced by tumor-related vascular alterations of the inner ear, rather than being exclusively linked to direct pressure of the tumor on the vestibulocochlear nerves (Gouveris et al., 2007; Ralli et al., 2017; Roosli et al., 2012). Giannuzzi et al. reported that three out of four patients with VS, treated with gentamicin, had no more intractable vertigo, which supports the idea that vertigo in VS is partly due to a dysfunction of the inner ear (Giannuzzi et al., 2013). Owing to advances in MRI technology and the intratympanic application of a contrast medium, we were able to visualize vestibular EH in patients (Dispenza et al., 2008; Morrison and Sterkers, 1996; Naganawa et al., 2011; Ralli et al., 2017). Jerin et al. showed signs of vestibular EH in a patient with VS (Jerin et al., 2015). In our study, we used intratympanic gadolinium-enhanced MRI to confirm the peripheral origin of the vestibular lesions in patients with VS. Furthermore, we found no correlation between vertigo and disease duration, which also indicates the peripheral origin of vestibular symptoms.

Nakashima et al. proposed a three-grading classification of vestibular EH for a simple assessment of its severity in the vestibule (Nakashima et al., 2007). However, this indexing method determined the degree of vestibular EH by roughly estimating the area of the endolymph by the vestibule (Nakashima et al., 2007). Hence, Nakashima et al. suggested that the volume percentage of the vestibular endolymph should be calculated to assess vestibular EH more accurately (Nakashima et al., 2007). Our results show that although the area and volume percentage of the affected side were significantly larger than those of the healthy side, and for both the affected and the healthy sides, the area and volume percentages of vestibular endolymph were consistent, but the consistency was not strong, indicating that the volume percentage of the vestibular endolymph seems to be more accurate than the area percentage in evaluating vestibular EH.

Currently, there is no research to quantify the volume of vestibular EH in patients with VS. Our study found no difference in the area percentage of vestibular endolymph of different Koos grades. However, the volume percentage of vestibular endolymph with different Koos grades was significantly different, which also suggests that measurement of the volume percentage may be more sensitive than that of the area percentage to evaluate vestibular EH. The association between hydrops and VS has been described by Naganawa et al., but they still used the area percentage for classification (Naganawa et al., 2011). Furthermore, their

study used non-contrast-enhanced 3D-FLAIR images (Naganawa et al., 2011). In these MR images, the endolymphatic space was not demarcated from the perilymphatic space as clearly and distinctly as it was in gadolinium contrast-enhanced inner ear MRI. Jerin et al. adopted locally enhanced inner ear MRI, but they examined only one case (Jerin et al., 2015). Our study included a larger sample size and used intratympanic gadolinium-enhanced MRI to confirm the presence of vestibular EH.

Since no studies have been conducted to calculate the volume percentage of the endolymphatic space to allow classification of vestibular EH, we proposed 19.1% as the cut-off point to distinguish the presence or absence of vestibular EH; that is, patients with a vestibular endolymph ratio of $\geq$ 19.1% were defined as the subgroup with hydrops, while the subgroup without hydrops included patients with a baseline level below 19.1%. Based on this, 11/66 (16.7%) of the patients with VS in our study had vestibular EH.

Naganawa et al. also sought to verify whether vertigo in patients with VS correlated with vestibular EH, and reported vestibular hydrops in 4/15 cases; however, no significant correlation between vertigo and hydrops was found (Naganawa et al., 2011). Our findings were consistent with their study; we did not find a correlation between vertigo and vestibular EH, and there was no significant difference in the volume percentage of vestibular endolymph between the vertigo group and the non-vertigo group. Additionally, vertigo has been reported to be one of the risk factors for the growth of VS (Artz et al., 2009). However, our study did not find a significant difference in tumor size between the vertigo and non-vertigo groups.

Similarly, previous studies have demonstrated that the hearing level does not correlate with the size of the VS, indicating that compression of the cochlear nerve within the internal auditory canal may not be the only mechanism of hearing loss. In other words, commonly observed hearing loss of pure tones (in the absence of poor speech scores) in patients with VS may be caused by cochlear mechanisms rather than retrocochlear dysfunction. In our study, neither tumor diameter nor tumor volume was associated with the preoperative pure-tone audiometry.

This study has several limitations, most notably, its small sample size, which restricts the generalizability of the study findings to all patients with VS. We also did not use scales such as the Dizziness Handicap Inventory questionnaire to assess the severity of vertigo in patients with VS. As such, additional studies with larger sample sizes and proper vertigo severity assessments are necessary to confirm and expand our findings. In the present study, most patients underwent translabyrinthine microsurgery because their preoperative hearing was already unserviceable, or the size of tumor was too large for hearing to be preserved. In future research, we will focus on the changes of preoperative and postoperative hydrops in patients undergoing hearing-preserving surgeries.

5. Conclusions

In conclusion, the volume percentage of the endolymphatic space was more accurate than the area percentage for assessing vestibular EH. In view of the fact that there is no such research on this topic, we have proposed a new two-grading classification of vestibular EH according to the volume percentage of the vestibular endolymph. We used 19.1% as the cut-off point to distinguish the presence or absence of vestibular EH, and found that 16.7% of the patients with VS had varying degrees of vestibular EH. We believe that the vestibular symptoms experienced by some patients with VS may originate from peripheral lesions.

CRediT authorship contribution statement

Jingjing Wang: Conceptualization, Methodology, Software, Writing - original draft, Writing - review & editing. **Chunyan Li:** Writing - review & editing. **Yaoqian Liu:** Data curation, Writing - original draft, Software. **Yuxin Tian:** Data curation, Formal analysis. **Yuanping Xiong:** Data curation, Software. **Yanmei Feng:** Conceptualization, Methodology, Writing - review & editing. **Dongzhen Yu:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Funding acquisition. **Zhengnong Chen:** Writing - review & editing, Supervision, Funding acquisition. **Shankai Yin:** Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

J.J.W., Y.M.F. and D.Z.Y. designed the experiments. Y.Q.L., Y.X.T. and Y.P.X analysed the data. J.J.W. and D.Z.Y. wrote the original draft. Y.Q.L. prepared table and figures. C.Y.L., Y.M.F., Z.N.C. and S.K.Y. edited and revised the manuscript. Y.M.F., D.Z.Y., Z.N.C. and S.K.Y. provided funding acquisition. All authors have approved the final copy of this manuscript.

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