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Sudden deafness

Edited by
Maoli Duan, Jun Yang and Lisheng Yu

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Sudden deafness

Topic editors
Maoli Duan — Karolinska Institutet (KI), Sweden
Jun Yang — Shanghai Jiaotong University School of Medicine, China
Lisheng Yu — Peking University People's Hospital, China

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EDITED AND REVIEWED BY
Michael Strupp,
Ludwig Maximilian University of Munich, Germany

*CORRESPONDENCE
Maoli Duan
maoli.duan@ki.se
Jun Yang
yangjun@xinhuamed.com.cn

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Editorial: Sudden deafness

Jun Yang[1,2,3]*, Yupeng Liu[1,2,3], Lisheng Yu[4] and Maoli Duan[5,6]*

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Shanghai Jiaotong University School of Medicine Ear Institute, Shanghai, China, [3]Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China, [4]Department of Otorhinolaryngology-Head and Neck Surgery, People's Hospital of Peking University, Beijing, China, [5]Ear Nose and Throat Patient Area, Trauma and Reparative Medicine Theme, Karolinska University Hospital, Stockholm, Sweden, [6]Division of Ear, Nose and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

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Editorial on the Research Topic
Sudden deafness

Introduction

Sudden sensorineural hearing loss (SSNHL) is an otologic emergency characterized by a rapid onset of hearing loss, typically within 72 h, affecting three or more consecutive frequencies by 30 dB or more (1). The global incidence of SSNHL ranges from 5 to 400 per 100,000 individuals annually, with a rising trend worldwide (2). Although viral infections, autoimmune diseases, and vascular abnormalities are acknowledged as potential etiological factors, the pathophysiology of SSNHL remains unclear in the majority of cases (3). Current treatment strategies focus on the use of corticosteroids-either systemic or intratympanic-as the primary therapy to reduce inflammation and restore hearing (4). Additional treatments such as hyperbaric oxygen therapy, traditional Chinese medicine (TCM), and vasodilators have been explored but with inconsistent evidences. However, the effectiveness of alternative therapies continues to be the subject of ongoing debate. Accurately predicting hearing recovery is essential for patient counseling, as factors such as delayed treatment initiation, vestibular function impairment, and comorbid health conditions are associated with poorer prognoses. This Research Topic "*Sudden deafness*" consists of 16 original articles and two reviews. We summarized these articles within the following categories: overview of SSNHL in China, comorbidities and laboratory changes, special types of SSNHL, therapeutic regimen and prognostic factors. Further understanding of SSNHL through this Research Topic will benefit SSNHL patients and their families, thus decreasing the economic load for the society.

Overview of SSNHL in china

Chen N. et al. provides a comprehensive overview of the contemporary clinical approaches to diagnosing and treating SSNHL in China. The study evaluated the factors influencing these practices, such as hospital grade and regional economic differences. The study highlighted the heterogeneity in SSNHL diagnosis and treatment in China. There is a need for more standardized practices and higher-quality RCT studies to ensure better outcomes.

The widespread use of post-auricular injections and combination therapies in China is noted as a distinct practice, which may inform future international research and treatment guidelines.

Comorbidities and laboratory changes

Certain comorbidities are recognized as risk factors for SSNHL, and specific laboratory findings may offer insights into the etiology of SSNHL. Xie, Karpeta, Tong et al. provided a review focuses on the etiological comorbidities and laboratory changes of SSNHL. They concluded that various etiological comorbidities have been associated with SSNHL, including cardiovascular diseases, metabolic diseases, autoimmune diseases, et al. They also pointed out that abnormal laboratory tests, including blood coagulation, endothelial dysfunction and inflammation, were reported in SSNHL patients. The review emphasizes the need for further research into the comorbidities and laboratory findings related to SSNHL to develop more effective and targeted treatments. Chen J. et al. investigates the causal relationship between thyroid function and SSNHL using Mendelian randomization (MR). The results suggest that genetically predicted elevated FT4 levels may reduce the risk of SSNHL, while no significant association was found between TSH levels and SSNHL. Zeng et al. developed and validated a predictive model for SSNHL. The model identified thrombin time (TT), red blood cell (RBC) count, and granulocyte-lymphocyte ratio (GLR) as key predictors. This prediction model could aid in early diagnosis and treatment decisions for SSNHL. Zhang J. et al. found that miRNAs may be closely related to SSNHL pathogenesis and could serve as potential biomarkers for early diagnosis and prognosis. do Amaral et al. explored the relationship between inflammatory markers, metabolic parameters, and hearing recovery in SSNHL patients. Key findings included a significant decrease in cytokines such as TNF-α and IFN-γ over time, which correlated with hearing improvement. Zhong et al. explored the association between SSNHL and stroke, particularly posterior circulation strokes. The study emphasizes the importance of early audiometric and vascular assessments in SSNHL patients to detect and prevent stroke, particularly in high-risk individuals. These studies collectively contribute to a better understanding of SSNHL by exploring its association with thyroid function, miRNA profiles, stroke risk, and inflammatory processes.

Special types of SSNHL

Special populations and unique categories of SSNHL garnered insufficient attention yet, and clinical research in this domain remains limited. In contrast to common forms of SSNHL, these specific cases demonstrated differences in both etiology and prognosis. Liu et al. investigated the clinical features and prognosis of SSNHL in single-sided deafness (SSD) patients. The SSD group had poorer hearing recovery outcomes and lower hearing gains after treatment. Patients with SSNHL in the sole hearing ear face significant challenges in recovery, emphasizing the need for optimized treatment strategies. He et al. focused on bilateral sudden sensorineural hearing loss (BSSNHL). The study found that patients with BSSNHL tend to have more severe hearing loss and worse prognosis than those with unilateral SSNHL. The overall treatment efficacy was 32%, with those having profound hearing loss showing worse outcomes. Wang et al. also evaluates the clinical characteristics and prognosis of BSSNHL compared with unilateral SSNHL. BSSNHL patients showed poorer hearing recovery and more severe symptoms. Prognostic factors included the audiogram curve type, with sloping-type audiograms being linked to worse outcomes. Li et al. conducted a bi-center retrospective study analyzed 145 pediatric SSNHL patients to identify factors influencing prognosis. Children with ascending and flat form of audiogram configurations had better recovery, while descending ones were associated with worse outcomes. The study also found that higher platelet-to-lymphocyte ratios (PLR) and lower lymphocyte counts were related to worse initial hearing loss, highlighting the role of systemic inflammation in pediatric SSNHL. Further clinical research is imperative to investigate the underlying mechanisms and treatment strategies for these cases to enhance patient outcomes.

Therapeutic regimen

The established effective treatment for SSNHL involves the systemic administration and intratympanic injection of corticosteroids. However, the efficacy of alternative administration methods, including post auricular injections, repetitive systemic corticosteroid administration, and TCM, requires further investigation. Xie, Karpeta, Liu et al. investigated whether adding intratympanic or post auricular subperiosteal corticosteroid injections to systemic corticosteroid treatment improves hearing recovery in patients with SSNHL. The study found no significant difference in hearing recovery between the groups, indicating that local corticosteroid injections do not significantly improve outcomes when added to systemic corticosteroids. Yamamoto et al. compared patients who received repetitive treatment with those who only received one round of therapy. Although the final hearing outcomes did not differ significantly between the groups, early and sufficient corticosteroid dosing was found to be crucial for better hearing recovery. Although repetitive corticosteroid therapy may play a supplementary role, the study emphasizes the importance of early, aggressive treatment to improve outcomes. Zhao et al. used network pharmacology and molecular docking techniques to investigate the molecular mechanisms by which the TCM Erlongjiaonang (ELJN) acts in the treatment of SSNHL. The study suggests that ELJN may reduce inflammation and improve inner ear blood circulation, providing a molecular basis for its effectiveness in treating SSNHL.

Prognostic factors

The prognosis of SSNHL is generally influenced by factors including the patient's age, the severity of the initial hearing loss, the timing of treatment initiation, and the presence of vestibular function impairment. Prior research examining the correlation between vestibular function impairment and the prognosis of SSNHL remains limited. Chen L. et al. explored the prognosis of patients with SNHL who also had inner ear malformations

involving the lateral semicircular canal (LSCC). Compared with patients without LSCC malformation, the recovery outcomes were poorer, with only 40% of patients LSCC malformation showing hearing improvement. The study suggests that LSCC malformation is a risk factor for poor prognosis in SSNHL. Shen et al. examined the functional status of the vestibular otolith and conductive pathways in unilateral SSNHL patients using vestibular evoked myogenic potentials (VEMPs). The study found that patients with normal VEMPs had better hearing recovery than those with abnormalities. The study highlights the importance of evaluating both the otolith and vestibular nerve pathways to predict hearing outcomes. Yang et al. investigated the relationship between vestibular function and prognosis in patients with severe and profound SSNHL. The findings suggest that vestibular ischemia caused by corresponding vascular circulation disorder affect both the cochlea and posterior semicircular canal, may contribute to poor outcomes in these patients. These studies focus on the impact of vestibular function and inner ear abnormalities on the prognosis of patients with SSNHL, emphasizing the need for comprehensive vestibular assessment to better understand and predict recovery outcomes. In addition, cardiovascular disease, diabetes, hypercholesterolemia and hypertension have been found to be poor prognostic factors. However, randomized double blind placebo control study has not been investigated until now. Thus, it is difficult to say that these factors affect SSNHL's prognosis.

Prospect

SSNHL, an otologic emergency, has a wide incidence globally, and its pathophysiology remains largely unknown. Therefore, future research in SSNHL should focus on uncovering the underlying pathophysiology. Advancements in molecular biology, genetics, and bioinformatics could provide deeper insights into the causes of SSNHL. Studies investigating biomarkers, including miRNAs, inflammatory markers, and genetic factors, could help identify high-risk individuals and improve early diagnosis. Additionally, more high-quality, randomized double blind placebo controlled trials are needed to validate the effectiveness of alternative therapies like TCM and novel drug combinations.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Andrés Soto-Varela,
Complejo Hospitalario Universitario de Santiago, Spain

REVIEWED BY
Manuel Oliva Domínguez,
Hospital Costa del Sol, Spain
Andrea Castellucci,
Azienda USL – IRCCS di Reggio Emilia, Italy

*CORRESPONDENCE
Jianyong Chen
✉ chenjianyong@xinhuamed.com.cn
Maoli Duan
✉ maoli.duan@ki.se
Jun Yang
✉ yangjun@xinhuamed.com.cn

†These authors have contributed equally to this work and share first authorship

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Abnormal posterior semicircular canal function may predict poor prognosis in patients with severe and profound ISSNHL

Yang Yang[1,2,3†], Dekun Gao[1,2,3†], Xiaobao Ma[1,2,3†], Jiali Shen[1,2,3], Qin Zhang[1,2,3], Xiangping Chen[1,2,3], Qing Zhang[1,2,3], Yulian Jin[1,2,3], Jianyong Chen[1,2,3*], Maoli Duan[4*] and Jun Yang[1,2,3*]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Shanghai Jiaotong University School of Medicine Ear Institute, Shanghai, China, [3]Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China, [4]Division of Ear, Nose and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

Background: Severe and profound idiopathic sudden sensorineural hearing loss (ISSNHL) generally leads to unfavorable prognosis, and has a considerable impact on patient quality of life. However, related prognostic factors remain controversial.

Objective: To elaborate the relationship between vestibular function impairment and the prognosis of patients with severe and profound ISSNHL, and investigated the relevant factors affecting prognosis.

Methods: Forty-nine patients with severe and profound ISSNHL were divided into good outcome group [GO group, pure tone average (PTA) improvement $>$ 30 dB] and poor outcome group (PO group, PTA improvement $\leq$30 dB) according to hearing outcomes. The clinical characteristics and the proportion of abnormal vestibular function tests in these two groups were analyzed by univariate analysis, and multivariable logistic regression analysis was performed for parameters with significant differences.

Results: Forty-six patients had abnormal vestibular function test results (46/49, 93.88%). The number of vestibular organ injuries was 1.82 $\pm$ 1.29 in all patients, with higher mean numbers in PO group (2.22 $\pm$ 1.37) than in GO group (1.32 $\pm$ 0.99). Univariate analysis revealed no statistical differences between the GO and PO groups in terms of gender, age, side of the affected ear, vestibular symptoms, delayed treatment, instantaneous gain value of horizontal semicircular canal, regression gain value of vertical semicircular canal, abnormal rates of oVEMP, cVEMP, caloric test and vHIT in anterior and horizontal semicircular canal, however, significant differences were found in the initial hearing loss and abnormal vHIT of posterior semicircular canal (PSC). Multivariable analysis revealed that only PSC injury was an independent risk factor for predicting the prognosis of patients with severe and profound ISSNHL. Patients with abnormal PSC function had worse initial hearing impairment and prognosis than patients with normal PSC function. The sensitivity of abnormal PSC function in predicting poor prognosis in patients with severe and profound ISSNHL was 66.67%, specificity was 95.45%, and positive and negative likelihood ratios were 14.65 and 0.35, respectively.

Conclusion: Abnormal PSC function is an independent risk factor for poor prognosis in patients with severe and profound ISSNHL. Ischemia in the branches of the internal auditory artery supplying the cochlea and PSC may be the underlying mechanism.

KEYWORDS

severe and profound, idiopathic sudden sensorineural hearing loss, prognosis, vHIT, posterior semicircular canal

1. Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as an otologic emergency in which three or more consecutive frequency hearing thresholds rise suddenly by 30 dB or more within 72 h, accompanied by tinnitus and concurrent or delayed vestibular symptoms in some patients (1). Previous studies have reported spontaneous recovery in a proportion of patients with ISSNHL (2); however, the outcome is often poor in some patients with severe-to-profound ISSNHL (3, 4). Severe and profound unilateral hearing loss may lead to speech communication impairment, particularly in noisy environments, and difficulty in localizing sound sources, which has a considerable impact on the long-term quality of life and mental status of patients (5, 6).

There is no consensus on the prognostic factors of ISSNHL and various factors have been identified including the degree of initial hearing loss, age at onset, presence of vestibular symptoms, classification of hearing loss, and time of intervention (7–9). Recent studies have found that the results of a series of vestibular function tests can predict the outcomes of patients with ISSNHL to some extent (10, 11). However, there are relatively few studies on the prognosis of patients with severe or profound ISSNHL. The purpose of this study was to elucidate the relationship between vestibular function impairment and the prognosis of patients with severe and profound ISSNHL, and to further investigate the relevant factors affecting prognosis.

2. Methods

2.1. Patients and study design

A retrospective study was performed on patients with ISSNHL who were hospitalized at the Department of Otolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine between September 2020 and September 2022. This study was approved by the Institutional Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University (NM: XHEC-D-2022-259), and all patients provided consent for their data to be used for this research.

The following inclusion criteria applied: patients with unilateral ISSNHL, PTA (0.5, 1,2, 4 k Hz) $\geq$ 65 dB in the affected ear, and normal hearing in the opposite ear; intact tympanic and Type A tympanogram in both ears; complete patient medical record data and records of pure tone audiometry (performed on the first day of admission and the day before discharge), ocular vestibular-evoked myogenic potential test (oVEMP), cervical vestibular-evoked myogenic potential test (cVEMP), caloric test, and video head impulse test (vHIT). Exclusion criteria were as follows: a history of genetic disorders associated with familial deafness; sensorineural hearing loss secondary to noise exposure or ototoxic drugs; space-occupying lesions of the internal auditory canal, central organic pathology, and external and middle ear disease; a malignant tumor; inability to complete the course of treatment or audiology-vestibular function test due to liver or kidney disease or other reasons.

A total of 49 patients were included in this study. All enrolled patients underwent an audiology-vestibular function test on the first day of admission, and hearing was retested the day before discharge after one course of treatment. The treatment protocol was as follows: (i) daily intravenous dexamethasone 10 mg, (ii) daily intratympanic injection of dexamethasone (5 mg), and (iii) daily hyperbaric oxygen therapy. The completion of 10 days of treatment was considered completion of the course of treatment.

2.2. Audiometry

Pure tone audiometry was performed using the MADSEN Astera clinical diagnostic audiometry system (GN Otometrics, Denmark). The binaural PTA was taken as the mean of the four frequencies of 500, 1,000, 2,000, and 4,000 Hz. Severe hearing loss was defined as a pretreatment hearing level between 65 and 80 dB HL, and profound hearing loss was defined as a pretreatment hearing level $\geq$ 80 dB HL, according to the latest standards of the World Health Organization (12).

2.3. Vestibular function tests

2.3.1. vHIT

An EyeSeeCam head tosser (Interacoustics Company) was used for the testing. The patient wore an eye patch containing a head velocity monitoring sensor and was placed in the sitting position with the head held still and the eyes focused on a fixed point (target point) 1.5 m in front of them. The examiner stood behind the patient and calibrated the target point before examining the horizontal and vertical semicircular canals in the conjugate plane of each of the three pairs of semicircular canals following the standard vHIT technique. The EyeSeeCamTM software objectively recorded the 60 ms instantaneous gain value of the horizontal semicircular canal, regression gain value of the vertical semicircular canal, asymmetry ratio of the three pairs of conjugate semicircular canals, and refixation saccades from the beginning to the end of the head impulse. Any one of the following conditions was considered abnormal: (i) an instantaneous gain value of the horizontal semicircular canal $<$0.8 and a regression gain value of the vertical semicircular canal $<$0.7; and (ii) 10 or more refixation saccades with a peak angular velocity $>$100°/s in 20 head impulses (13).

2.3.2. Caloric test

The patient was placed in the supine position, with the head in forward flexion at 30° to ensure that the horizontal semicircular canal was perpendicular to the floor. Cold air (24°C) and hot air (50°C) were instilled into the patient's ears separately for 60 s each time. The patient's electronystagmogram was recorded for 1 min after instillation, with the interval between instillations being 5 min after the disappearance of the previous nystagmus. The average slow-phase velocity (SPV) during the strongest period of temperature-induced nystagmus was recorded, and canal paresis (CP) was calculated using the Jongkees formula, which reflects the asymmetry of the horizontal semicircular canal bilaterally. A CP value $>$25% was considered abnormal and indicated a relative reduction in ipsilateral horizontal semicircular canal function. The dominant preponderance ratio (DP) was calculated to determine the lateral preponderance of nystagmus, and a DP value $>$30% was considered abnormal.

2.3.3. Air conducted sound cVEMP

The Biologic Navigator Pro Auditory Evoked Potential (Biologic Auditory Evoked Potential Software Ver.7.3.1, Denmark) was used to perform the test. The reference electrode was placed between the clavicular joints, the ground electrode was placed between the two eyebrows of the forehead, and the left and right test electrodes were placed in the middle of the sternocleidomastoid muscle on the left and right sides, respectively, with an electrode impedance of $\leq$5 kΩ. The stimulation signal was 500 Hz, with 90 dB nHL short tone bursts, 1 ms rise/fall time, 2 ms duration at peak, 5 Hz stimulation rate, and 50 superimposed times. The stimulation sound was delivered using air conduction insert earphones to elicit a VEMP response. The patient was instructed to lift the head off the pillow after hearing the unilateral stimulation sound and to elevate the head 30° in the supine position to keep the sternocleidomastoid muscle tense until the stimulation sound stopped, before returning to the original lying position.

2.3.4. Air conducted sound oVEMP

The equipment and relevant parameters used for the testing were the same as those described above. The reference electrode was placed on the lower jaw, ground electrode was placed between the two eyebrows on the forehead, and test electrode was placed 1 cm below the central part of the contralateral eyelid. The patient was instructed to gaze upward after hearing the unilateral stimulation sound, keeping the eye position at 25–30° and blinking as little as possible to maintain the lower oblique muscle tone until the stimulation sound stopped.

The interwave amplitude of P1-N1 was recorded as the vertical distance between the apex of the N1 and P1 waves. The amplitude asymmetry ratio (AR) was calculated as the ratio of the absolute value of the difference between the amplitudes of the two sides to the sum of the wave amplitudes of the two sides. Abnormal VEMP was defined as a waveform not elicited or an AR of >29% (14).

2.4. Grouping according to therapeutic outcomes

According to the Chinese Medical Association of Otolaryngology criteria, the return of the hearing threshold of the damaged frequencies to normal, healthy ear, or pre-disease levels was considered complete recovery; partial recovery was defined as hearing improvement > 30 dB HL; slight recovery was defined as hearing improvement between 15 and 30 dB HL, and no recovery was defined as hearing improvement of <15 dB HL (15).

Based on the degree of hearing recovery, forty-nine patients with severe and profound ISSNHL were divided into two groups: the good outcome group (GO group, including complete and partial recovery, PTA improvement >30 dB) and the poor outcome group (PO group, including slight and no recovery, PTA improvement $\leq$ 30 dB).

2.5. Statistical analysis

SPSS software (version 26.0) was used to analyze the data. Measurement data were expressed as mean ± standard deviation (M ± SD), and count data were expressed as percentages. The Shapiro-Wilks test was performed to test the normal distribution of the measurement data, the independent *t*-test was used for data that was normally distributed, and the rank sum test was used for data that was not normally distributed. The differences between groups were analyzed using univariable logistic regression analysis, and those parameters with significant differences were analyzed using multivariable logistic regression analysis. Differences were considered statistically significant at $P < 0.05$.

3. Results

3.1. Clinical data for all patients

This study enrolled 49 patients (25 males and 24 females, 48.69 ± 18.63 years old) were enrolled in this study, with 17 right ears and 32 left ears. Twenty-six patients had vestibular symptoms at the time of the consultation (26/49, 53.06%). The mean timeframe between the onset of symptoms and treatment was 5.94 ± 4.64 (1–21 days). Severe hearing loss was observed in 14 ears and profound hearing loss was observed in 35 ears. The mean hearing threshold of the affected

TABLE 1 Clinical data of all patients included in this study.

Variable	Statistical data ($N = 49$)
Gender	
Male	25 (51.02%)
Female	24 (48.98%)
Affected side	
Left	32 (65.31%)
Right	17 (34.69%)
Age	48.69 ± 18.63
vestibular symptoms	26 (53.06%)
Onset of treatment (days)	5.94 ± 4.64
Hearing loss	
Severe hearing loss	14 (28.57%)
Profound hearing loss	35 (71.43%)
Initial hearing threshold (dB HL)	92.09 ± 18.05
Hearing threshold after-treatment (dB HL)	66.76 ± 33.32
Hearing recovery	
GO group	22 (44.90%)
PO group	27 (55.10%)
Abnormal vestibular function tests	46 (93.88%)
Abnormal oVEMP	29 (59.18%)
Abnormal cVEMP	28 (57.14%)
Abnormal caloric test	25 (51.02%)
Abnormal vHIT	23 (46.94%)
Abnormal horizontal canal	12 (24.49%)
Abnormal anterior canal	1 (2.04%)
Abnormal posterior canal	19 (38.78%)

ear was 92.09 ± 18.05 dB HL before treatment and 66.76 ± 33.32 dB HL after treatment. Of the 46 patients who underwent abnormal vestibular function tests (46/49, 93.88%), 29 had abnormal oVEMP (29/49, 59.18%), 28 had abnormal cVEMP (28/49, 57.14%), 25 had abnormal caloric tests (25/49, 51.02%), and 23 had abnormal vHIT tests (23/49, 46.94%), including 19 (19/49, 38.78%) with abnormal posterior semicircular canal (PSC) function, 12 (12/49, 24.49%) with abnormal horizontal semicircular canal function, and one (1/49, 2.04%) with abnormal anterior semicircular canal function (Table 1).

3.2. GO group vs. PO group

3.2.1. Clinical characteristics

There were 22 patients (12 males and 10 females, 45.91 ± 20.31 years old) in the GO group, including 16 left ears and six right ears, of which nine had vestibular symptoms at the time of the consultation. The mean hearing threshold of the affected ear was 85.00 ± 17.47 dB HL before treatment, and 38.18 ± 19.17 dB HL after treatment.

There were 27 patients (13 males and 14 females participants, 50.96 ± 17.20 years old) in PO group, including 16 left ears and 11 right ears, in which 17 patients had vestibular symptoms at the time of the consultation. The mean hearing threshold of the affected ear was 97.87 ± 16.67 dB HL before treatment, and 90.05 ± 22.32 dB HL after treatment. A comparison of clinical data between the two groups is shown in Table 2.

3.2.2. Vestibular function test

In the vestibular function test results in the GO group, the abnormality rate of oVEMP was the highest (14/22, 63.64%), followed by cVEMP (10/22, 45.45%), caloric test (10/22, 45.45%), horizontal semicircular canal (4/22, 18.18%), and PSC (1/22, 4.54%). No anterior semicircular canal dysfunction was observed.

In the vestibular function examination results in the PO group, the abnormality rate of cVEMP (18/27, 66.67%) and PSC (18/27, 66.67%) was the highest, followed by the oVEMP (15/27, 55.56%), caloric test (15/27, 55.56%), horizontal semicircular canal (8/27, 29.63%), and anterior semicircular canal (1/27, 3.70%). The differences in the vestibular function tests between the two groups are shown in Figure 1.

The number of vestibular organ injuries was 1.82 ± 1.29 in all patients, with higher mean numbers in the PO group (2.22 ± 1.37) than in the GO group (1.32 ± 0.99). The difference in the number of vestibular organ injuries between the two groups is shown in Figure 2A. The linear fitting curve between the number of vestibular organ injuries and the average percentage increase in PTA is shown in Figure 2B. The results showed that the average increased percentage of PTA was linearly and negatively correlated with the number of vestibular organ injuries. ($R^2 = 0.8597$; the linear equation was $y = -0.1025x + 0.4925$). The specific modes of vestibular organs injuries between GO group and PO group were shown in Figure 2C.

3.2.3. Univariable and multivariable logistic regression analysis of prognostic factors for hearing recovery

Univariable logistic regression analysis of clinical characteristics and vestibular function test revealed that there were significant differences in the initial hearing threshold ($P = 0.016$) and abnormal vHIT result in PSC ($P = 0.001$) between the GO and PO groups; there was no significant difference in gender, age, side of the affected ear,

TABLE 2 Univariate and multivariate analysis of prognostic factors in patients with severe and profound ISSNHL.

	Group		Univariate analysis	Multivariate analysis	
	GO group ($n = 22$)	PO group ($n = 27$)	*P*-value	*P*-value	Exp (B)
Gender, male	12 (54.55%)	13 (48.15%)	0.656		
Age	45.91 ± 20.31	50.96 ± 17.20	0.344		
Affected side, left	16 (72.73%)	16 (59.26%)	0.327		
vestibular symptoms	9 (40.91%)	17 (62.96%)	0.127		
Onset of treatment (days)	6.09 ± 5.43	5.81 ± 4.00	0.835		
Initial hearing threshold (dB)	85.00 ± 17.47	97.87 ± 16.67	0.016	0.382	1.02
Abnormal cVEMP	10 (45.45%)	18 (66.67%)	0.139		
Abnormal oVEMP	14 (63.64%)	15 (55.56%)	0.568		
Abnormal Caloric test	10 (45.45%)	15 (55.56%)	0.483		
vHIT					
Abnormal horizontal canal	4 (18.18%)	8 (29.63%)	0.358		
Instantaneous gain value	1.11 ± 0.17	1.02 ± 0.19	0.111		
Abnormal posterior canal	1 (4.54%)	18 (66.67%)	0.001	0.002	33.009
Regression gain value	1.17 ± 0.21	0.98 ± 0.40	0.065		
Abnormal anterior canal	0 (0)	1 (3.70%)	1		
Regression gain value	1.29 ± 0.27	1.40 ± 0.32	0.191		

Exp (B), odds ratio.

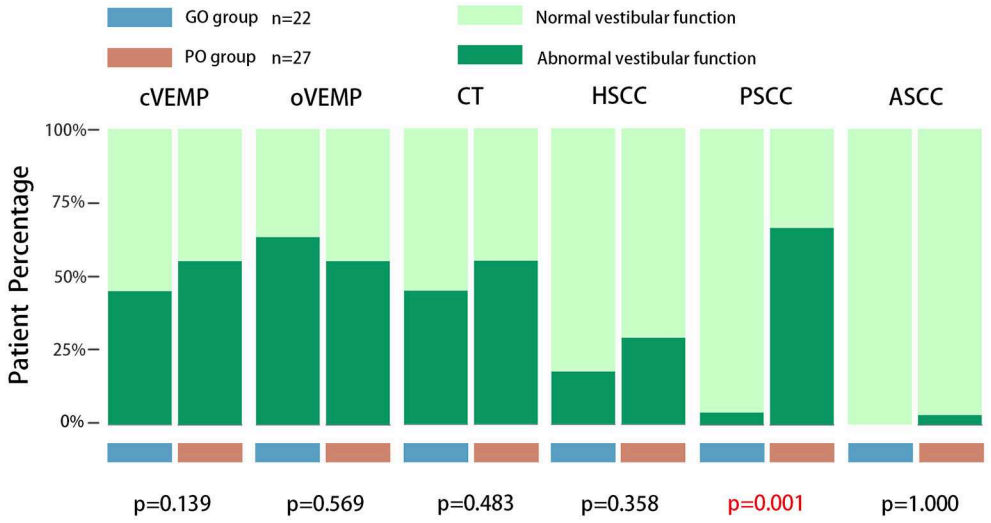

FIGURE 1
The comparison of vestibular function between the GO group and PO group. There was no significant difference in terms of the abnormal rates of oVEMP, cVEMP, caloric test, and vHIT in anterior and horizontal semicircular canals by univariate logistic regression analysis, and only a significant difference in the posterior semicircular canals was observed. CT, caloric test; HSCC, vHIT results in horizontal direction semicircular canal; PSCC, vHIT result in posterior semicircular canal; ASCC, vHIT result in anterior semicircular canal.

vestibular symptoms, delayed treatment, instantaneous gain value of the horizontal semicircular canal, regression gain value of the vertical semicircular canal, abnormal rates of oVEMP, cVEMP, caloric test, and vHIT in the anterior and horizontal semicircular canals between these two groups. Multivariable logistic regression analysis of the parameters with significant differences showed that the significance of initial hearing loss disappeared, and only PSC injury was an independent risk factor for prognosis [$P = 0.002$, Exp (B) = 33.009]. These are listed in Table 2.

3.3. Abnormal vs. normal posterior semicircular canal function

The sensitivity, specificity, and positive and negative likelihood ratios were calculated. The sensitivity of abnormal PSC function in predicting poor prognosis in patients with severe and profound ISSNHL was 66.67%, specificity was 95.45%, and positive and negative likelihood ratios were 14.65 and 0.35, respectively. Patients with abnormal PSC function had worse initial hearing loss and prognosis than those with normal PSC function (Table 3).

4. Discussion

The incidence of ISSNHL is ~5–20/100,000 people per year, and it has been gradually increasing with recent reports that younger populations are being affected (1). The percentage of patients with severe and profound hearing loss is ~41–74.2% (16). Unilateral severe to profound hearing loss inevitably affects a person's spatial hearing and speech recognition abilities, particularly in a long-term noise environment. The function of the auditory center of the cerebral cortex may degenerate, which can have a serious impact on the life, work, and psychology of the patient (17). In general, most patients with severe and profound ISSNHL have a negative prognosis due to the severity of their hearing loss. Age, initial hearing level, vestibular symptoms, and treatment onset have been previously reported in the literature as relevant indicators of prognosis in patients with ISSNHL (8). However, in our study, we found no significant relationship between gender, age, affected side, vestibular symptoms, delayed treatment, and poor hearing outcomes in patients with severe and profound ISSNHL.

The presence of vestibular symptoms in patients with sudden deafness is often considered an influential factor in poor hearing recovery; however, Wen et al. (18) found that patients with profound ISSNHL have worse hearing improvement, regardless of the presence of vestibular symptoms. Yu and Li (19) conducted a large sample size study on vestibular symptoms and hearing outcomes in patients with sudden deafness using a meta-analysis and found that vestibular symptoms may be negatively associated with hearing recovery, except in the group treated with intra-tympanic corticosteroid injections. Each patient in the current study was treated with intra-tympanic dexamethasone injections, which may be one of the reasons for our inconsistency with the results of previous studies. Meanwhile, our study showed no significant effect of the time of delayed treatment on hearing recovery, which may be because most of our patients (46/49) underwent timely treatment within 2 weeks, which is the therapeutic response period of treatment (1).

Due to the close anatomical and developmental relationship between the cochlea and vestibule, patients with severe and profound ISSNHL often have abnormal vestibular function, in addition to more damaged cochlear hair cells that are more difficult to recover (20). In this study, 26 of the 49 patients (26/49, 53.06%) presented with vestibular symptoms, and 46 patients (46/49, 93.88%) presented with abnormalities in vestibular function. Almost all patients had abnormalities in the objective tests of vestibular function. Meanwhile, our results showed that the average number of vestibular organ injuries was higher in the PO group than in the GO group. This suggests that the greater the extent of inner ear damage in patients

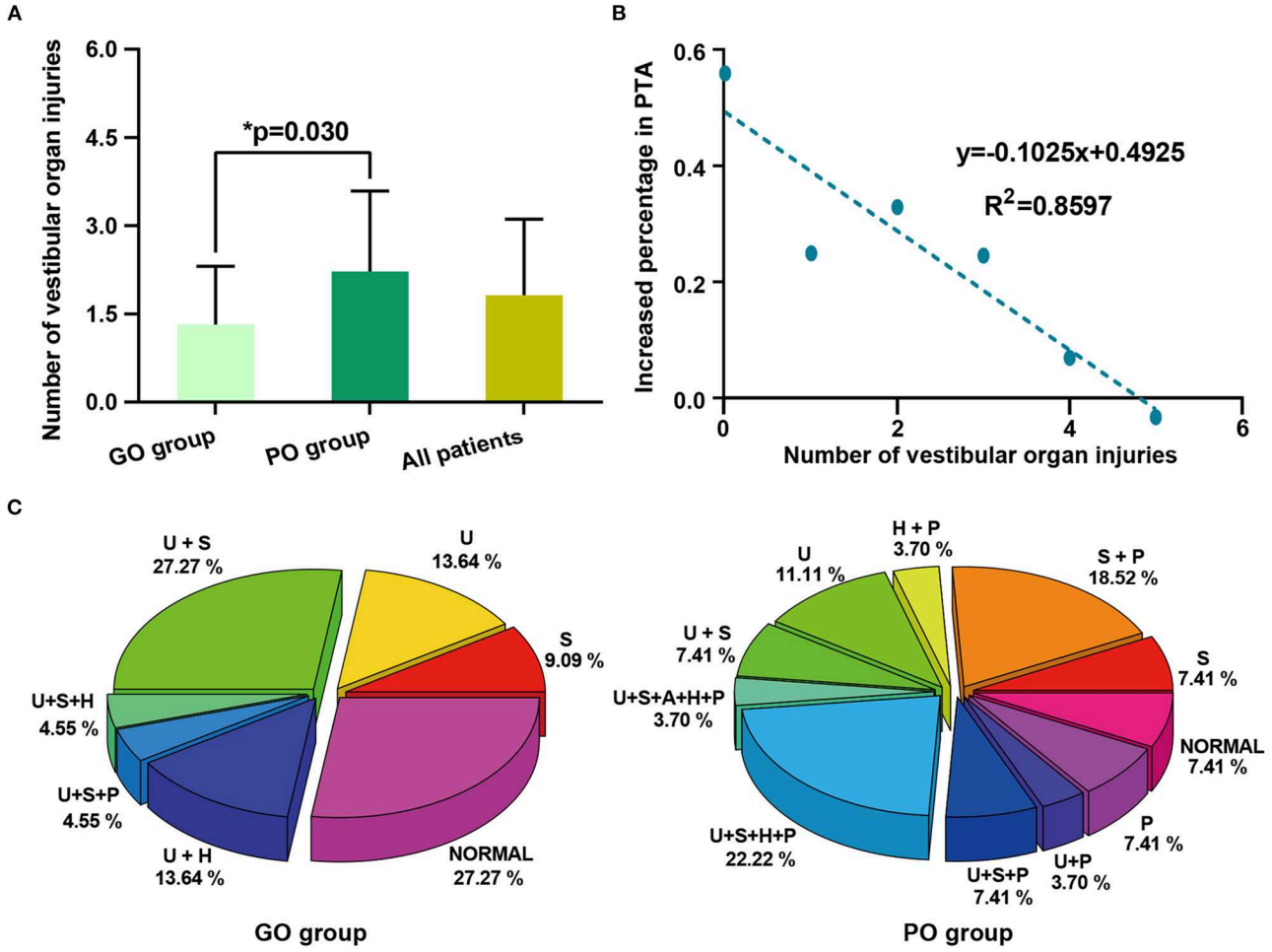

FIGURE 2
The comparison of vestibular organ injuries between the GO group and PO group. **(A)** The number of vestibular organ injuries between the GO group and PO group. **(B)** The linear fitting curve between the number of vestibular organ injuries and the average increased percentage in PTA. Each point on the figure was not a single patient, but the average increased percentage in PTA of all patients in the vestibular organ injury group. The results showed that the average increased percentage in PTA is linearly negatively correlated with the number of vestibular organ injuries ($R^2 = 0.8597$, the linear equation was $y = -0.1025x + 0.4925$). **(C)** The specific modes of vestibular organs injuries between GO group and PO group. U, utricle dysfunction; S, saccule dysfunction; A, anterior semicircular canal dysfunction; H, horizontal semicircular canal dysfunction; P, posterior semicircular canal dysfunction. In the above statistical data on vestibular organ injuries, the results of the caloric test were not included.

TABLE 3 Abnormal vs. normal posterior semicircular canal function.

	Hearing outcome		Initial hearing loss	Hearing improvement
	PO group ($n = 27$)	GO group ($n = 22$)		
Abnormal posterior canal	18	1	101.58 ± 15.62 dB	10.86 ± 15.75 dB
Normal posterior canal	9	21	86.08 ± 17.08 dB	34.50 ± 23.49 dB
	Sensitivity = 66.67%	Specificity = 95.45%	$P = 0.002$	$P < 0.001$
	NLR = 0.35	PLR = 14.65		

NLR, negative likelihood ratios; PLR, positive likelihood ratios.

with ISSNHL, the worse the prognosis, which is consistent with the results of previous research (21).

Previous studies have shown that abnormal VEMP is indicative of poor prognosis regardless of the onset of vestibular symptoms in patients with sudden deafness (22, 23). Shih et al. found that abnormal caloric test results were significantly associated with poor prognosis in patients with sudden deafness and that CP values were significantly associated with hearing recovery in patients with abnormal caloric test (24). However, no correlation was observed in the current study between vestibular test abnormalities and the prognosis of patients with severe and profound ISSNHL. Liang et al. (25) investigated the relationship between vestibular function and prognosis in patients with sudden deafness using a battery of vestibular function tests and showed that VEMPs may be a valid predictor of prognosis. While the results of the caloric test and vHIT test had no significant effect on hearing recovery, they did

not correlate the abnormal results of the three semicircular canals on the affected side in vHIT with prognosis separately. However, the results of Guan et al. (26), in contrast to those of Liang et al. (25), revealed that the prognosis of patients with ISSNHL was only related to horizontal semicircular canal function impairment, but the study did not group the patients according to the degree of initial hearing loss.

Recently, Seo et al. found that higher initial hearing impairment and PSC abnormalities were associated with poor hearing prognosis in patients with profound sudden deafness (27). Our study is partially consistent with these results; however, the present study targeted a subgroup of patients with severe and profound hearing deafness, and the results of the prediction model showed that only abnormal PSC was an independent risk factor for poor prognosis in this subgroup. We found that patients with PSC injury had higher initial hearing impairment; therefore, the degree of initial hearing loss before treatment may have a collinearity relationship with PSC dysfunction. It is indirectly associated with prognostic outcome through its association with PSC functional loss; therefore, the significance of initial hearing loss disappeared in the multivariate analysis. PSC injury is likely to be a key factor in predicting prognosis. Almost all patients with ISSNHL with PSC impairment had a poor curative effect following treatment, with a specificity of 95.45% and a positive likelihood ratio of 14.65 for predicting poor outcome. Therefore, the results suggest that the vHIT can provide a preliminary assessment of patient prognosis and better respond to their consultation.

Currently, the pathogenesis of sudden deafness has not yet been ascertained, and microcirculatory disorders in the inner ear have been considered one of the main etiologies of ISSNHL (1). In previous reports, selective PSC dysfunction on vHIT was often associated with vestibulo-cochlear disorders such as vestibular neuritis and Meniere's disease, but it has rarely been mentioned in ISSNHL (28, 29). In 2005, Rambold et al. (30) found that 53% of patients with ISSNHL with vestibular lesions had a characteristic vestibulocochlear lesion pattern with combined injury of the cochlear and ipsilateral PSC, which may point to the vascular etiology of ISSNHL. In addition, Lee et al. and Yao et al. investigated vestibular function impairment in patients with ISSNHL and found that the abnormality rate of PSC was significantly higher than that of the anterior semicircular canal and horizontal semicircular canal (31, 32). Recently, several studies hypothesized that the mechanism of abnormal PSC function associated with poor hearing recovery may be related to the fact that the cochlea and PSC share a common branch artery for blood supply (27, 33, 34).

The internal auditory artery is the terminal artery supplying the labyrinth of the inner ear and is divided into the anterior vestibular artery and the common cochlear artery. The latter is further divided into the main cochlear and vestibulo-cochlear arteries, which provide blood supply to the cochlea. The vestibulocochlear artery supplies the basal turn of the cochlea, utricle, saccule, and PSC simultaneously. When the microcirculation of the vestibular cochlear artery or common cochlear artery is impaired and the cochlear blood supply is reduced, PSC also faces the risk of ischemia, while the utricle and saccule still have some blood from the anterior vestibular artery to compensate (35–39). Studies in animal models have found that vestibular and cochlear hair cell ischemia from various causes for more than 30 min is likely to cause permanent damage (40, 41). Based on these studies, we hypothesized that patients with severe and profound ISSNHL with abnormal PSC function may have impaired vascular supply to the vestibule and cochlea and that ischemia of the branches of the internal auditory artery supplying the cochlea and PSC may provide a possible explanation for the poor hearing prognosis in these patients.

Recently, Castellucci et al. (42) reported a case of a patient with multiple cardiovascular risk factors who had oriented the etiological hypothesis toward a possible common cochlear artery ischemia based on clinical symptoms and vestibular examination but found that only the PSC in vestibular end organs had imaging manifestations of post-ischemic fibrosis on steady-state gradient-echo MRI. Comacchio et al. (43) also reported a case of a patient with acute vestibular loss whose clinical manifestations and examinations mimicked inferior vestibular neuritis. The patient developed PSC ossification during follow-up. The authors speculated that the underlying etiology in this patient may have been posterior vestibular artery occlusion, although no other imaging manifestations of vestibular end-organ ischemia were detected on brain CT during the follow-up. In occlusion of the common cochlear artery or its inferior branches, the PSC appears to be at a greater risk of ischemia than other vestibular organs because of the lack of a dual blood supply. The imaging evidence in the above case report may strengthen the assumption of vascular pathomechanisms underlying the poor prognosis of patients with ISSNHL with PSC dysfunction.

However, despite the fact that the abnormal rate of PSC was the most prominent in the PO group, we found that the rates of utricle and saccule injury were also noticeable. This could be because patients in the PO group without PSC dysfunction seemed to have different patterns of vestibular damage, which may have increased the abnormal rates of oVEMP and cVEMP. If the above hypothesis is reasonable, early administration of blood-circulation-improving drugs or fibrinolytic drugs may improve the prognosis of patients with severe and profound sudden deafness with PSC injury; however, the effectiveness and efficacy of these drugs need to be further investigated.

However, there is one potential limitation to our study. When evaluating the prognosis of patients with ISSNHL, we did not assess the speech audiometry of patients after treatment, and only used PTA as the sole standard. As emphasized in the article, the significant decline in hearing function in patients with severe and profound ISSNHL will bring many obstacles to social life, and the speech discrimination score is also critical in evaluating the quality of hearing function in life.

In conclusion, abnormal PSC function is an independent risk factor for poor prognosis in patients with severe and profound ISSNHL. Patients with severe and profound ISSNHL and PSC abnormalities have higher initial hearing impairment and poorer prognosis. Ischemia in the branches of the internal auditory artery supplying the cochlea and PSC may be the underlying mechanism of poor hearing prognosis in patients with ISSNHL with PSC abnormalities.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University (NM: XHEC-D-2022-259). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JC, MD, and JY contributed to the study design. XM, JS, and QinZ preformed VEMPs, caloric test, and vHIT. YY and DG contributed to statistical analysis and manuscript draft. All authors helped to perform the analysis and to revise the manuscript with constructive discussions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Michael Strupp,
Ludwig Maximilian University of Munich, Germany

REVIEWED BY
Yujuan Yang,
Qingdao University, China
Takefumi Kamakura,
Osaka University, Japan

*CORRESPONDENCE
Lisheng Yu
✉ yulish68@163.com
Maoli Duan
✉ maoli.duan@ki.se

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Diagnosis, differential diagnosis, and treatment for sudden sensorineural hearing loss: Current otolaryngology practices in China

Nishan Chen[1], Niki Karpeta[2], Xin Ma[1], Xianhui Ning[3], Xiaoling Liu[4], Jijun Song[5], Zigang Jiang[6], Xiulan Ma[7], Xiuli Liu[8], Shixun Zhong[9], Qing Sun[10], Jun Liu[11], Ganggang Chen[12], Maoli Duan[13]* and Lisheng Yu[1]*

[1]Department of Otolaryngology, Head, and Neck Surgery, Peking University People's Hospital, Beijing, China, [2]Department of Otolaryngology, Head, and Neck Surgery, Karolinska University, Solna, Sweden, [3]Department of Otolaryngology, Head, and Neck Surgery, Zhongshan Hospital, Shanghai, China, [4]Department of Otolaryngology, Inner Mongolia People's Hospital, Hohhot, Inner Mongolia, China, [5]Department of Otolaryngology, Zhoukou Central Hospital, Zhoukou, China, [6]Department of Otolaryngology, First Hospital of Qinhuangdao, Qinhuangdao, China, [7]Department of Otolaryngology, Head, and Neck Surgery, Sheng Jing Hospital, Shenyang, China, [8]Department of Otolaryngology, First Affiliated Hospital of Dalian Medical University, Dalian, China, [9]Department of Otolaryngology, First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [10]Department of Otolaryngology, Head, and Neck Surgery, Third Medical Center of PLA General Hospital, Beijing, China, [11]Department of Otolaryngology, Head, and Neck Surgery, Chinese PLA General Hospital, Beijing, China, [12]Department of Otolaryngology, Head, and Neck Surgery, First Hospital of Shanxi Medical University, Taiyuan, China, [13]Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden

Introduction: Although sudden sensorineural hearing loss (SSNHL) has been attempted to be understood for 70 years, diagnosis and treatment strategies still have strong heterogeneity worldwide, which are reflected in the guidelines issued by countries and the clinical practice of otolaryngologists.

Methods: Questionnaires were sent to registered otolaryngologists nationwide *via* an online questionnaire system. We investigated the current views and clinical practices of otolaryngologists in mainland China about the diagnosis, examination, and treatment strategies of SSNHL.

Results: Most otolaryngologists supported diagnostic classification *via* audiograms. Regional economic situation and hospital grade affected application strategies for differential diagnosis. Regarding corticosteroid therapy, 54.9% of respondents opted to discontinue the drug 5 days after systemic administration. Both intratympanic therapy and post-auricular injections were selected by more than half of the respondents as initial and salvage treatments.

Discussion: Chinese otolaryngologists exhibit heterogeneity in clinical practices for SSNHL, including distinct approaches to combination therapy and local application of steroids. This study pointed out Chinese doctors' similarities, differences, and unique strategies in diagnosing and treating SSNHL and analyzed the possible reasons to help the world understand the current otolaryngology practices in China.

KEYWORDS

sudden sensorineural hearing loss (SSNHL), otolaryngologists, corticosteroids (CS), survey questionnaire, hospital grade, differential diagnosis

1. Introduction

The concept of sudden sensorineural hearing loss (SSNHL) was first proposed in 1944 (1). SSNHL is defined as an unexplained sensorineural hearing loss occurring within 72 h (2). Numerous clinical and basic studies have examined the etiology, diagnostic criteria, diagnostic tests, and treatments such as corticosteroids for SSNHL. Further, several countries have updated the guidelines for SSNHL in recent years (3–9). Nevertheless, there are significant differences in diagnostic and treatment strategies due to the low quality of available evidence.

We focused on guidelines published by China, the US, Japan, the UK, Germany, Spain, and other countries and found large differences in diagnostic criteria (Table 1). In addition, some countries recommend the clinical classification of SSNHL based on the pure-tone test (2, 4), while others do not (6, 8). Regarding supplementary examination, the recommendations of guidelines are also different. Although glucocorticoids are recognized as an effective treatment of SSNHL, the recommended route of delivery, dosage, and period of administration still have heterogeneity. Moreover, the effectiveness of hemorheological drugs remains controversial. As a result of these differences, clinicians may hold personal views and follow different instructions in their clinical practice, which is not conducive to standardized treatment and high-quality RCT research. For example, the inclusion and exclusion criteria may be inconsistent, caused by the differences in diagnostic criteria and clinical classification. As a result, the conclusions of similar RCT studies deviate considerably. Similarly, different dosages and treatment periods make it difficult to include similar research in meta-analyses.

As China is large and the most populated country, applying the guidelines to different levels of hospitals in 31 provincial bureaus is difficult. The guidelines only provide basic diagnosis and treatment proposals in most cases; local hospitals and otolaryngologists should also make necessary adjustments according to their conditions and the personalized needs of patients. Thus, it is necessary to understand individual preferences and local practices of otolaryngologists in China nationwide. These types of surveys in the UK, US, Germany, and Austria have been published (10, 11). Regarding these questionnaires, we modified a survey to Chinese-specific situations. Our survey focused on the current preferences and opinions of Chinese otolaryngologists regarding the diagnosis and treatment of SSNHL. According to the Ministry of Health of China, hospitals in China are classified into primary (Level 1), secondary (Level 2), and tertiary (Level 3) hospitals according to their standards of medical care, education, and research. Further, secondary (Level 2) and tertiary (Level 3) hospitals are classified into Grades A, B, and C based on their size, technology, equipment, and management. Otolaryngologists in different hospitals may employ divergent medical strategies. We explored potential factors influencing their clinical decisions and compared our results with those of other countries (10, 11).

At present, the uniqueness of the SSNHL practice in China has not been well-known worldwide. We believe that our findings revealed the current practice of Chinese physicians and provided new information, including the proposal and application of post-aural steroid delivery and the combination therapy of hemorheology drugs. We hope this information could arouse the interest of peers worldwide and provide future research ideas for RCT research design.

2. Materials and methods

Our questionnaire (Supplementary material 1) was originally based on the design of Sutton et al. (10) and Lechner et al. (11), and was modified according to Chinese-specific situations and the uniqueness of clinical practice. An online questionnaire system sent a survey link to otolaryngologists in mainland China. The survey was performed in accordance with relevant regulations in China and was approved by the Ethics Committee of Peking University People's Hospital (2019PHB109-01). All participants received an informed consent form on the front page of the questionnaire, and participants could not fill in the questionnaire until they signed it. The inclusion criteria were otorhinolaryngologists who hold a practicing certificate issued by the government health department. The exclusion criteria were doctors who could not use intelligent communication devices, doctors who were not qualified for various reasons, and doctors who had not done actual medical work within 1 year.

China has vast national land and uneven population distribution with complex governmental divisions and developing informational networks. Currently, the government's complete contact lists of otolaryngologists in China are unavailable. Thus, we sent our survey link to every provincial organization of physicians and received responses from all interviewees. Although the exact number of doctors who received the questionnaire was difficult to quantify, our survey was considered to approximate nationwide research.

In total, 2015 respondents participated in the survey and completed all questionnaires. The survey was divided into several parts, encompassing basic information, diagnostic criteria, systemic and local steroid therapy, and combination therapy. The interviewed otolaryngologists were required to respond in view of their clinical practice.

All topics were presented as single- or multi-choice questions. In cases where the respondent perceived no optimal option, they were allowed to select "other" and fill in the content autonomously. The responses were submitted and included in statistical analysis upon completing the questionnaire.

Categorical variables were expressed as count and percentage. Univariable ordinal logistic regression models and a multivariable ordinal logistic regression model were performed to evaluate factors influencing classification diagnosis. All these statistical analyses were performed using SPSS 23.0 software (SPSS Inc, Chicago, IL, USA). All P-values were 2-tailed, and $P < 0.05$ was considered statistically significant. The power of statistical analysis was calculated using PASS 23.0 software. Graphs were generated using GraphPad Prism 7.

3. Results

3.1. Questionnaire recovery and distribution

China is the most populated country, and its mainland is divided into 31 provincial bureaus. The sample sizes

TABLE 1 Comparison of key information in SSNHL guidelines.

Nation	China	United States	Germany
Agency	CMA	AAO-HNS	AWMF
Year of publication	2015	2019	2014
Audiological criteria	A decrease ≥20 dB affecting at least 2 consecutive frequencies	A decrease ≥30 dB affecting at least 3 consecutive frequencies	Not specified
Classification	Classified into four types by frequency and severity of hearing loss	Not specified	Classified into five types by frequency and severity of hearing loss
Supporting test	*Necessary*: Otoscopy, Tuning fork test/Pure tone test, Nystagmus examination (when accompanied by vertigo) *As required*: OAE/ABR /ECochG, Imaging examination, Laboratory testing.	*Recommendation*: History and physical examination, Audiometry, Retrocochlear pathology (MRI/ABR) *Strong recommendation against:* CT of the head, Laboratory tests	*Necessary*: History, Otoscopy, Tuning fork test/Pure tone test, Nystagmus examination *As required*: OAE/Stapedius reflex, Cervical spine, Imaging examination, Laboratory testing. ASSR, etc.
Steroid therapy	*Systemic application:* prednisone at 1 mg/kg/d for 3-5 days *Local application*: ITS/PAS as salvage treatment	*Systemic application*: prednisone at 1 mg/kg/d for 7-14 days, then taper over *Local application*: ITS as initial or salvage treatment	*Systemic application*: prednisolone at 250mg/d for 3 days *Local application*: ITS as salvage treatment
Combination therapy	*Recommendation*: Vasodilators and Hemorheology *Against*: Hyperbaric oxygen therapy	*Optional*: Hyperbaric oxygen therapy *Strong recommendation against*: Other pharmacologic therapy	*Optional*: Vasodilators and Hemorheology *Not specified*: Hyperbaric oxygen therapy *Against*: Hydroxyethyl starch

CMA, Chinese Medical Association; AAO-HNS, American Academy of Otolaryngology-Head and Neck Surgery; AWMF, Arbeitsgemeinschaft Wissenschaftlich Medizinischer Fachgesellschaften (Association of Scientific Medical Societies in Germany); OAE, Otoacoustic emission; ECochG, electrocochleogram.

TABLE 2 Number of questionnaires in different provinces of China.

Province	Number	Province	Number
Beijing	107	Hainan	8
Shanghai	69	Henan	120
Tianjin	15	Xinjiang	71
Jiangsu	66	Sichuan	208
Zhejiang	102	Hebei	179
Fujian	89	Qinghai	14
Guangdong	98	Anhui	47
Shandong	72	Jiangxi	17
Inner Mongolia	72	Shanxi	117
Hubei	31	Heilongjiang	61
Chongqing	72	Tibet	8
Shaanxi	33	Guangxi	36
Liaoning	131	Guizhou	13
Jilin	29	Yunnan	39
Ningxia	58	Gansu	10
Hunan	23	**Total**	**2015**

of each province are presented in Table 2 and mapped in Supplementary material 2. The total number of licensed otolaryngologists in mainland China is ~30,000. The sample size of this study was considered sufficient, given that the effective number of questionnaires collected in this study was 2015, which achieves 100% power to detect logistic regression models by a posteriori validation. All required questions were answered in each questionnaire, but some questions were skipped automatically by the predesigned logic system. Thus, the number of valid answers varied among questions.

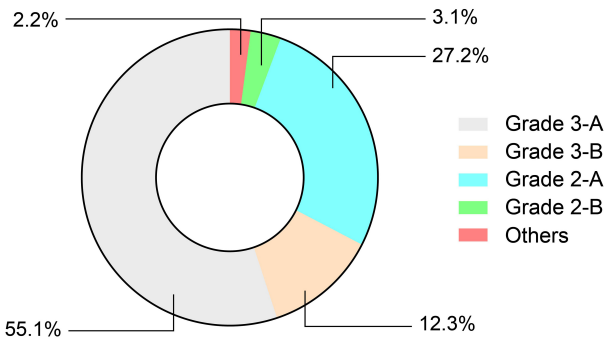

FIGURE 1
Distribution of hospital grade.

Most of the 2015 respondents were from 3-A hospitals (55.1%, $n = 1{,}110$) and 2-A hospitals (27.2%, $n = 549$). Other respondents were from 3-B hospitals, 2-B hospitals, and other types of hospitals (Figure 1). Otolaryngologists reported different clinical experiences and professional titles in China. Of respondents, 13.6% ($n = 275$) were within 5 years of employment, 17.4% ($n = 350$) were within 5–10 years, 34.1% ($n = 688$) were within 10–20 years, 31.9% ($n = 642$) were within 20–35 years, and 3.0% ($n = 60$) had been employed for more than 35 years. In terms of professional titles, the percentages of residents, specialists, senior consultants, and consultants were 14.6% ($n = 295$), 32.1% ($n = 646$), 32.7% ($n = 660$), and 19.1% ($n = 384$), respectively.

Regarding specific research fields, most respondents were general otolaryngologists (68.7%; $n = 1384$) without specific subspecialties. Approximately one-third ($n = 469$) of these doctors indicated that their clinical work was predominantly in otology. Of the respondents, 25.7% ($n = 517$) declared a sub-disciplinary research field; 256 were otologists, and the others worked in the nasal, throat, or neck surgery field. Among otologists, 37.8% were in surgery, 49.6% were in otology and audiology, 6.1% were in basic

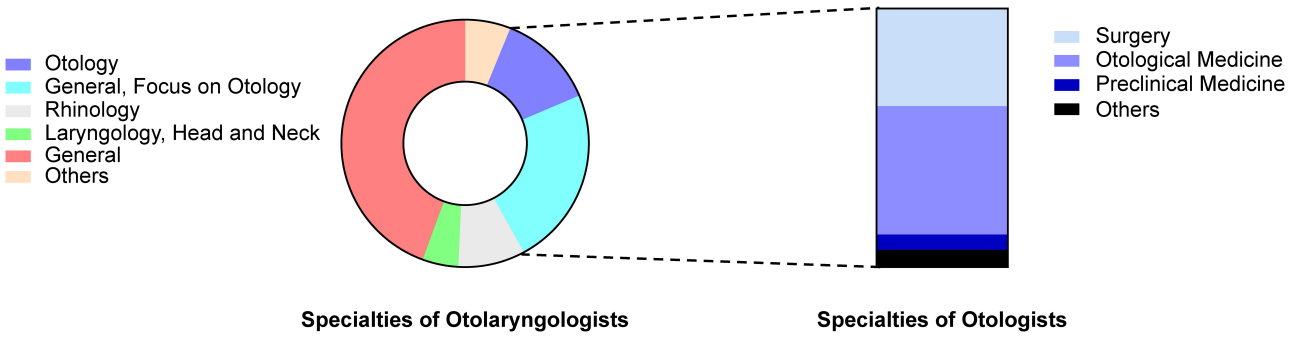

FIGURE 2
Distribution of research fields of respondents.

medical sciences, and 6.5% were in other fields, such as hearing detection, neuroscience, and Chinese medicine (Figure 2).

As a developing country, the economic situation in China varies among regions, which is a key factor causing unbalanced medical resources across the country. To assess the regional representativeness of the survey, we calculated the population composition ratio in different economic regions and compared it with our sample composition ratio using a Chi-square test (Table 3). The sample distribution in this study was slightly lower than expected in developed regions, was higher than expected in moderately developed regions, and was in line with the expected value in less developed regions.

3.2. Diagnostic criteria and classification

Most doctors (93.1%, n = 1,875) had sufficient clinical experience in SSNHL and handled at least 2–3 cases of SSNHL per month. More than half of the doctors responded that the most commonly encountered consultations were for patients with sudden hearing loss occurring within 14 days and without prior treatment (58.1%, n = 1171). In contrast, one-third of the doctors responded that consultation time varied substantially (32.5%, n = 655).

Chinese doctors reported different opinions regarding SSNHL diagnosis. Of respondents, 32.7% (n = 659) defined SSNHL based on the latest Chinese guidelines, i.e., ≥ 20 dB of hearing loss in two consecutive frequencies. Of doctors, 20.3% (n = 409) supported the criteria of AAO-HNS, i.e., hearing loss ≥ 30 dB in three continuous frequencies (Table 1). The definition of cases with "hearing loss ≥ 20 dB in at least three frequencies" received the most recognition (35.3%, n = 712); this definition falls between the Chinese and American criteria but is not mentioned in any guidelines. Less than one-tenth of doctors defined SSNHL as cases with hearing loss of 30 dB or 20 dB at any frequency. Other rare opinions included a 15 dB or 40 dB hearing loss or based on patient complaints only (Figure 3).

Respondents generally agreed on the key role of classification in SSNHL diagnosis and treatment. In a multi-choice questionnaire, 72.9% (n = 1,470) of respondents indicated that clinical classification helped them to explain the possible pathogenesis to patients, 76.7% (n = 1,546) indicated that classification helped estimate patient outcomes, and 72.7% (n = 1,465) indicated that they would choose different treatment strategies based on different classifications. Only 6.2% (n = 124) of respondents indicated that classification had no significant effect on clinical practice. However, classification diagnosis remains to be implemented in actual clinical practice. Our survey revealed that only 37.2% (n = 749) of physicians performed the classification procedure for every patient, and 33.8% (n = 680) were able to classify the most handled cases. Of physicians, only 13.5% (n = 273) performed classification occasionally, and 15.5% (n = 313) respondents never classified any SSNHL cases.

The division of economic regions was based on the Gross Domestic Product (GDP) rankings and populations of provinces issued by the National Bureau of Statistics in 2018. We calculated the per capita GDP of each province: regions ranked in the top 1–10 were classified as economically developed, regions ranked 11–20 were classified as moderately developed regions, and regions classified in the bottom 21–31 were classified as less developed regions (Table 4). We conducted a logistic regression analysis using SPSS 23.0 (Table 5) to investigate further the factors influencing classification diagnosis. In multivariate regression analysis, hospital grade, economic region, working experiences of doctors, and professional titles were considered. Hospital level was the only independent factor influencing clinical classification. Compared to top-level hospitals, respondents from lower-level hospitals were more likely to perform less or no classification in their clinical practice (OR = 0.452, 95% CI = 0.283–0.722, p = 0.001). The economic region, working experience, and professional title did not affect the inclination for classification.

3.3. Supporting tests

More than 80% of physicians always performed otoscopy, pure tone test, and acoustic impedance examinations; only 36.3% (n = 732) used imaging as part of routine examinations. A small proportion of physicians used ABR (23.9%, n = 481), electrocochleography (3.4%, n = 67), and vestibular function (7.8%, n = 157) in routine examinations. Only a few physicians (2.0%, n = 39) based their diagnoses on patients' complaints without

TABLE 3 Demographic distribution of surveys.

Economic pattern	Population (10, 000)	Observed N./Proportion	Expected N./proportion	Chi-square
Developed	53,711	721/35.8%	860.0/41.4%	50.57
Moderately developed	42,983	753/37.4%	621.1/29.9%	
Less developed	40,322	541/26.8%	533.9/25.7%	

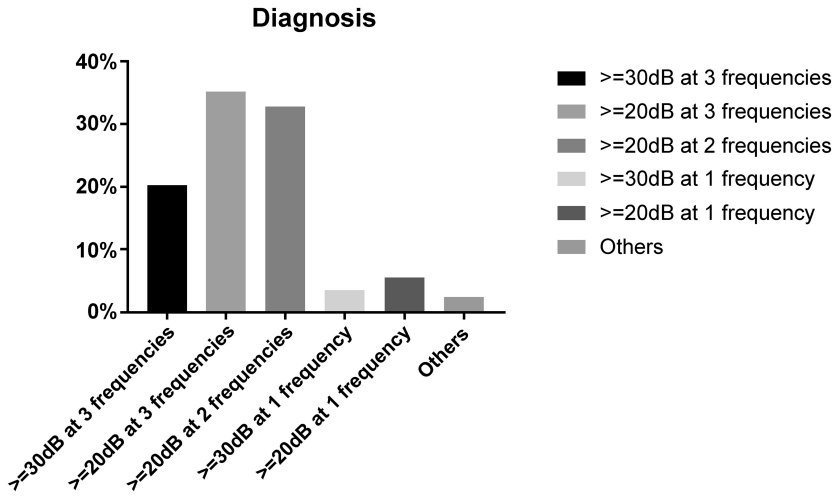

FIGURE 3
Criteria used to define sudden sensorineural hearing loss (SSNHL).

TABLE 4 Regional economic patterns of China.

Economic pattern	Regions
Developed	Beijing, Shanghai, Tianjin, Jiangsu, Zhejiang, Fujian, Guangdong, Shandong, Inner Mongolia, Hubei
Moderately developed	Chongqing, Shaanxi, Liaoning, Jilin, Ningxia, Hunan, Hainan, Henan, Xinjiang, Sichuan
Less developed	Hebei, Qinghai, Anhui, Jiangxi, Shanxi, Heilongjiang, Tibet, Guangxi, Guizhou, Yunnan, Gansu

TABLE 5 Multi-factor analysis of diagnosis type.

Factor		OR	95% CI		*P*
			Lower	Upper	
Hospital grade	1	0.452	0.283	0.722	0.001*
	2	0.677	0.409	1.123	0.131
	3	0.884	0.549	1.423	0.611
	4	/	/	/	/
Region	1	0.997	0.806	1.232	0.975
	2	0.950	0.771	1.171	0.630
	3	/	/	/	/
Working experience	1	0.589	0.309	1.124	0.109
	2	0.793	0.516	1.217	0.288
	3	0.909	0.615	1.342	0.630
	4	0.823	0.573	1.184	0.294
	5	/	/	/	/
Professional titles	1	1.041	0.667	1.623	0.860
	2	1.004	0.678	1.488	0.983
	3	1.327	0.943	1.866	0.104
	4	/	/	/	/

*$p < 0.05$.

examining them. In addition, several respondents indicated that otoacoustic emissions, extended high-frequency audiometry, and Eustachian tube function tests were included in their routine examinations (Figure 4).

Binary logistic regression analysis revealed that hospital level and economic situation were independent factors that affected whether doctors routinely performed ABR tests and cochlear electrogram examinations, respectively. Doctors in 3-A hospitals were more inclined to perform ABR tests than other hospitals (OR = 3.488, 95% CI = 1.365–8.915, $p = 0.009$). Doctors in less developed regions performed fewer audiology tests than those in more developed regions (OR = 0.517, 95% CI = 0.285–0.938, $p = 0.030$). Professional title and working experience did not significantly affect clinical decisions. For imaging examinations, none of these factors influenced whether MRI was performed. For the choice of 'no tests,' only the professional title was an independent factor. Compared to consultants, lower-level doctors were more inclined to make diagnoses based solely on patients' complaints without performing any tests, which goes strongly

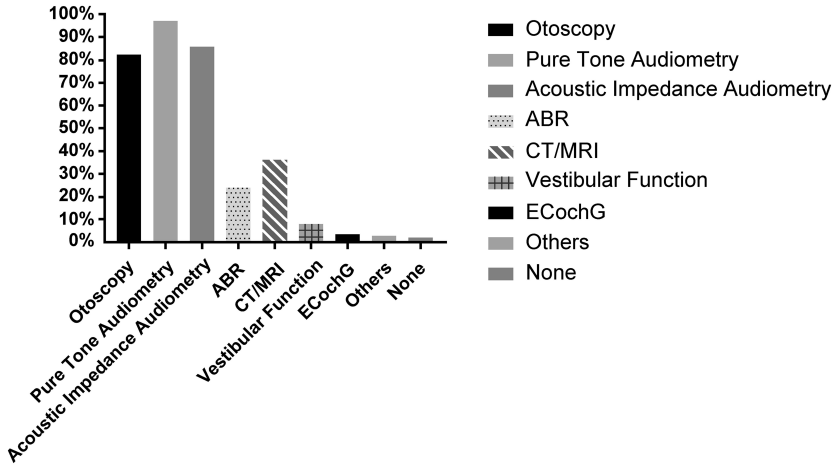

FIGURE 4
Support tests for differential diagnosis.

TABLE 6 Binary logistic regression analysis of differential diagnosis.

Test	Factor		OR	95% CI		*P*
				Lower	Upper	
ABR	Hospital grade	1	3.488	1.365	8.915	0.009*
		2	2.020	0.758	5.383	0.160
		3	1.466	0.562	3.820	0.434
		4	/	/	/	/
ECochG	Region	1	0.517	0.285	0.938	0.030*
		2	0.545	0.305	0.974	0.040*
		3	/	/	/	/
No tests	Professional titles	1	0.141	0.025	0.800	0.027*
		2	0.134	0.026	0.686	0.016*
		3	0.131	0.026	0.669	0.015*
		4	/	/	/	/

*$p < 0.05$.

against recommended guidelines (OR = 0.141, 95% CI = 0.025–0.800, $p = 0.027$) (Table 6).

It is worth mentioning that the medical system in China is significantly different from those in Europe and the United States. For example, most patients in China directly turn to the otorhinolaryngology department of general hospitals, while European and American patients tend to make the first consultation in the community. Thus, there were certain differences between support tests in the first screening, which may affect doctors' judgment and treatment.

3.4. Treatments

3.4.1. Steroid therapies

Our survey investigated the current applications of steroid therapies by Chinese otolaryngologists. When using systemic steroids, the most popular protocol was discontinuing the treatment after 5 days of intravenous application (40.5%, $n = 816$). Of respondents, 18.9% ($n = 380$) typically administered steroids orally and discontinued the medication after 5 days. The Chinese guidelines recommend both protocols. Some respondents selected intravenous application for 5 days and gradually reduced the dosage (24.8%, $n = 499$), whereas others preferred intravenous-oral sequential administration (10.4%, $n = 210$) and oral administration (5.5%, $n = 110$), followed by a gradual dosage reduction. With regard to the variety of steroids, methylprednisolone (54.4%, $n = 1096$) and dexamethasone (65.9%, $n = 1328$) were the most commonly used types of intravenous steroids. In comparison, prednisone (77.4%, $n = 1560$) and methylprednisolone (26.1%, $n = 527$) were the most commonly used types of oral steroids. Since respondents were allowed to select more than one type of drug, the total percentage exceeded 100%.

Our survey also investigated the current applications of local steroid administration. The results indicated that 52.8% ($n = 1664$) of Chinese otolaryngologists had attempted ITS therapy, predominantly used as a salvage treatment. Specifically, 54.2% ($n = 577$) applied the treatment in patients who failed initial treatment; 24.5% ($n = 261$) preferred to attempt salvage treatment in all patients who failed initial treatment. Of the respondents, 34.8% ($n = 370$) used ITS as an initial treatment in specific patients, while 10.7% ($n = 114$) of respondents used it as an initial treatment for all patients (Figure 5).

Besides ITS, another local drug delivery approach widely used in China was post-aural steroids (PAS) therapy. The procedure is operated by an injector that enters vertically from the skin at the mid-point of the retroauricular groove, delivering drugs into the periosteum of the mastoid process (12). Our survey is the first to investigate the use of PAS therapy by Chinese otolaryngologists. Of the respondents, 59.1% ($n = 1919$) had attempted post-auricular injections in their clinical practice, which exceeded the number of respondents who had used ITS, highlighting the convenience and popularity of post-auricular injections. Similarly, most doctors used PAS as a salvage treatment; 45.7% ($n = 544$) used it in a

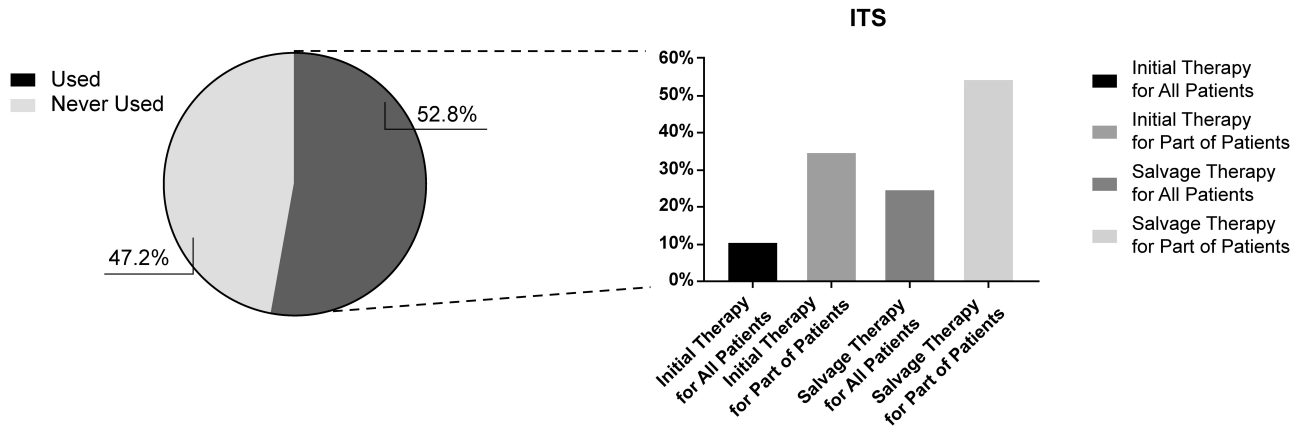

FIGURE 5
Application of intratympanic steroid injections.

proportion of patients who failed initial treatment, and 23.7% (n = 282) attempted it in all patients who failed initial treatment. Of the respondents, 40.0% (n = 477) used it as an initial treatment in specific patients, and 13.8% (n = 165) used it as an initial treatment in all patients (Figure 6).

3.4.2. Hemorheology treatment

Despite the vital role of steroid treatment for SSNHL, most Chinese doctors tended to use vasoactive and rheologic agents as combination treatments. Of the respondents, 61.7% (n = 1,243) reported using at least one type of combination medicine. In the investigation of SSNHL pathogenesis, cochlear ischemia, embolism, and vasospasm were approved by almost all physicians (97.1%, n = 1,957). Therefore, hemorheology treatment was considered a key treatment for SSNHL in China. Our survey investigated hemorheology drugs commonly used by Chinese otolaryngologists, which are listed in Table 7. Results of the multi-choice questionnaire revealed that extracts of *Ginkgo biloba* leaves (EGB) (91.2%, n = 1,134), alprostadil (55.6%, n = 691), and batroxobin (51.5%, n = 640) were favored by more than half of Chinese physicians. Thrombus (26.2%, n = 326), vinpocetine (22.5%, n = 280), and ShuXueTong (a type of herbal medicine) (6.4%, n = 80) were preferred by a proportion of physicians.

In terms of efficacy evaluation, results were similar to those reported above, i.e., from high-efficacy to low-efficacy: EGB (85.8%, n = 1,066), batroxobin (57.8%, n = 718), alprostadil (52.1%, n = 648), thrombus (14.9%, n = 185), vinpocetine (14.9%, n = 185) and Shu Xuetong (3.7%, n = 46) (Figure 7). In particular, although batroxobin ranked third in usage frequency, it ranked higher in the efficacy evaluation. This could be due to the lack of reimbursement in some regions, cost, the complexity of the clinical application, and follow-up difficulties.

3.4.3. Nutritional neurological drugs

Neurogenic drugs were also considered a key treatment due to the risk of secondary neurological damage in SSNHL pathogenesis. Of the respondents, 80.7% (n = 1,626) included neurotrophic drugs as a combination treatment. The types of drugs are listed in Table 8. Almost all respondents indicated that mecobalamin should be included as a treatment for SSNHL (92.0%, n = 1,816). Approximately one-fourth of respondents suggested cobamamide (24.2%, n = 497) and GM-1 (21.6%, n = 426) as treatments. Less than one-tenth of respondents preferred mouse nerve growth factor and edaravone (Figure 8).

4. Discussion

4.1. Analogical diagnostic criteria

The current criteria for SSNHL are not uniform internationally. Japan (4) and the European International Federation of Otorhinolaryngology Societies (IFOS) Conference (5) defined SSNHL as $\geq$ 30 dB hearing loss in at least three consecutive frequencies, whereas the clinical guidelines of the United States (6) and Spain (7) have expanded these criteria. In contrast, the clinical guidelines of Germany and the United Kingdom (8) do not specify a hearing loss threshold for SSNHL diagnosis. China initiated a multi-center randomized controlled trial (RCT) in 2008; the results were reported in 2015 (13). In the same year, a new edition of the guidelines (9) was published with reference to the latest international literature and the RCT results reported by Yu and Yang [13]. Based on these data, the diagnostic criteria were defined as hearing loss $\geq$ 20 dB in two consecutive frequencies, occurring within 72 h.

Our survey revealed that Chinese otologists exhibited strong heterogeneity in SSNHL diagnosis. When asked about the audiological criteria, one-third and one-fifth of the respondents diagnosed SSNHL based on the guidelines of China and the USA, respectively. However, when asked, "In which situation will you apply treatment to patients who suffer from sudden hearing loss," more respondents (42.7%) selected the Chinese guidelines for audiological criteria, which is milder than American standards, showing a mismatch between diagnostic criteria and treatment criteria. Comparison with surveys in the UK exhibited a relatively

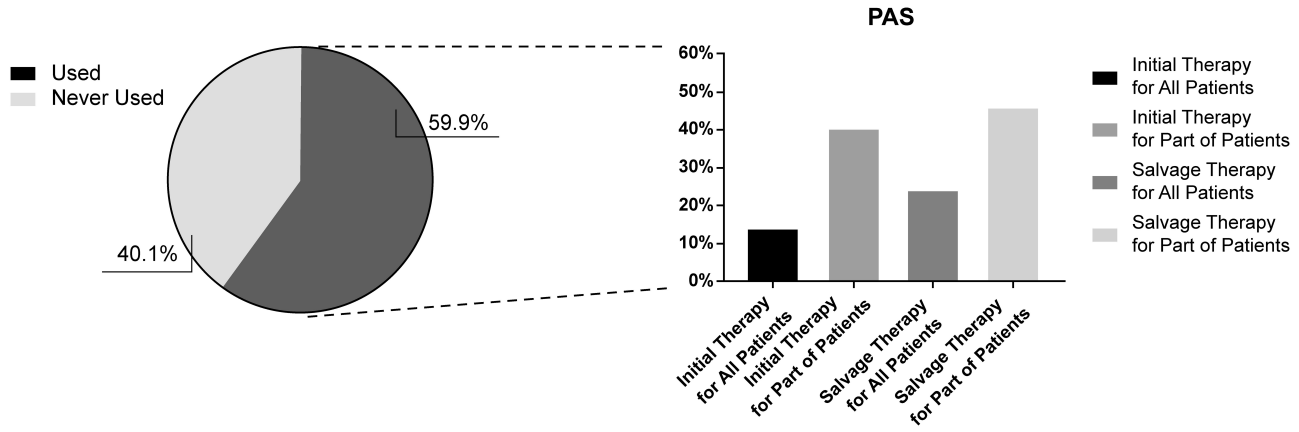

FIGURE 6
Application of post-aural steroid injections.

TABLE 7 Hemorheology drugs used by Chinese otolaryngologists.

Drugs	Description
GB 761®	Extract of Ginkgo biloba Leaves tablets used for microcirculatory disturbances
Alprostadil	Prostaglandin E1, which has vasodilatory properties.
Batroxobin	A snake venom enzyme used as a defibrinogenating agent.
Vinpocetine	A synthetic derivative of the vinca alkaloid vincamine. Mechanisms include blockage of sodium channels and antioxidant activity.
Shu Xuetong	A traditional Chinese drug used to ameliorate stagnation of blood flow.
Panax Notoginsenosidum	A traditional Chinese drug extract from *P. notoginseng* used for microcirculatory disturbances

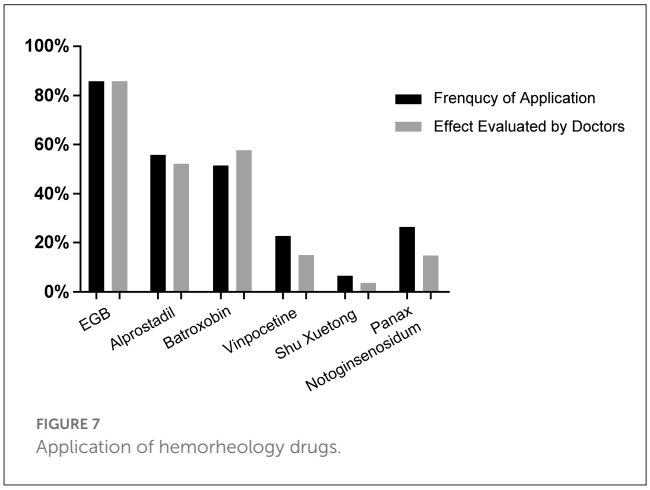

FIGURE 7
Application of hemorheology drugs.

TABLE 8 Neurogenic drugs used by Chinese otolaryngologists.

Drugs	Description
Mecobalamin	A form of vitamin B12 used for peripheral neuropathy.
Cobamamide	An active form of vitamin B12 used for peripheral neuropathy.
Mouse nerve GF	Isolated from mouse submaxillary glands and used for regulating neuronal survival and development.
Edaravone	An antioxidant used as a free radical scavenger.
GM-1	Monosialotetrahexosylganglioside, a member of the ganglio series used for neuronal plasticity and repair.

consistent opinion regarding diagnosis. The majority (70%) of respondents defined SSNHL according to the criteria in the relevant guidelines. The reasons underlying the heterogeneity in diagnosis warrant further exploration, but the inconsistencies in audiological diagnostic criteria may reduce the quality of evidence of RCTs in China. When using milder criteria, the outcome of RCTs may become better than those who used the severer criteria, for the higher probability of self-recovery in mild cases.

4.2. Clinical classification

With a deeper understanding of SSNHL pathogenesis, clinical classification has become crucial. The German and Japanese guidelines classify SSNHL into five and four types, respectively. Similar to the Japanese guidelines, the Chinese guidelines classify SSNHL into four types based on clinical practice and recommend different treatment options and prognostic evaluations for each type. Although guidelines in the US, UK, and Spain do not propose specific classifications, possibly due to the lack of high-quality clinical evidence and cost of diagnostic tests, the IFOS Conference (5) has clearly emphasized the heterogeneity of SSNHL. Our survey revealed that most of the respondents supported the classification of the SSNHL, but the number of doctors who performed classification diagnoses in clinical practice was limited. Since clinical classification is predominantly based on PTA, which only requires basic medical equipment, the key factor affecting doctors'

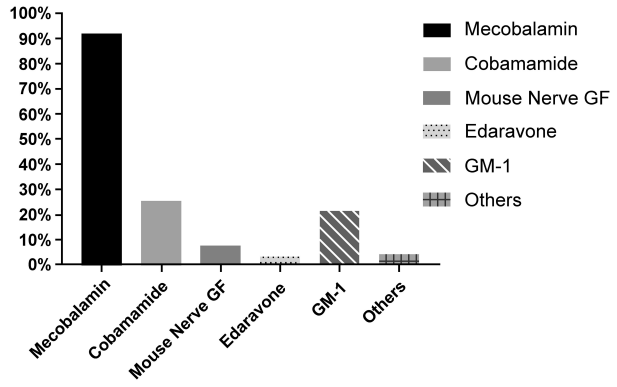

FIGURE 8
Application of neurotrophic drugs.

practices may not be the lack of devices caused by economic differences; rather, it may be due to insufficient understanding of the discipline in lower-level hospitals. We speculate that an appropriate classification could make the treatment more targeted and help to get more valuable results in clinical research because the prognosis of patients with different types could vary wildly.

4.3. Steroid therapies

Corticosteroids are a common treatment for SSNHL. A previous RCT (14) demonstrated the effectiveness of the systemic application of steroids for SSNHL. In contrast, Nosrati and Cinamon reported no significant difference in efficacy between steroid-treated and control groups (15), highlighting the need to verify the effectiveness of steroid treatment for SSNHL. In consideration of steroid efficacy and the consequences of permanent hearing loss, guidelines in most countries still recommend steroids as a treatment of choice. Nevertheless, the dose, timing, and frequency of treatment vary among countries. Chinese guidelines recommend the administration of prednisone at 1 mg/kg/d for 3 days, continuing for 2 additional days if effective, and tapering is not recommended. The heterogeneity of RCTs is a key factor resulting in the inconsistent systemic application of steroids.

Local administration of steroids in the inner ear remains a challenging field of research. Intratympanic steroids (ITS) have become the most commonly used local drug delivery system internationally (16). However, the strength of recommendations and treatment protocols vary among countries. ITS was commonly used as salvage treatment (17) but has recently been trialed as an initial treatment for SSNHL (18).

Compared with ITS, PAS is considered more economical, more convenient, minimally invasive, and has no inferiority compared with ITS (12). As first proposed and widely used by Chinese doctors, PAS constitutes a novel approach for local inner ear drug delivery. Clinical trials have reported satisfactory efficacy of PAS therapy, especially for intractable low-frequency sudden hearing loss, though the evidence remains insufficient due to defective trial design (19).

MRI assessments have demonstrated that the signal intensities of gadolinium-enhanced images of the cochlea were higher and longer following PAS administration compared to those following intravenous injection in guinea pigs (12). Recent studies have reported that PAS administration resulted in higher dexamethasone concentrations and longer durations in perilymph compared to systemic administration (20, 21). Notably, ITS administration and PAS resulted in greater fluorescence intensity in the basal portions of the organ of Corti and the scala media in the apical portions and stria vascularis, respectively. Theoretically, drugs injected post-auricularly may enter the inner ear through various pathways, such as circulation, tissue channels, and the sigmoid sinus (22–24). In contrast, for ITS, the drug enters the inner ear predominantly *via* the round window and oval window (25). Thus, different administration routes of local drug delivery may act on distinct targets in the inner ear, resulting in different clinical outcomes.

In China, both intratympanic and post-aural administration is recommended as a salvage option after systemic administration of corticosteroids. The use of steroid therapies by Chinese physicians was heterogeneous, especially in local applications. ITS was widely used as a salvage or initial treatment program. Despite not being recommended as an initial treatment in Chinese guideline (9), studies have reported its potential effectiveness (26, 27). In this survey, more Chinese physicians used post-auricular injection of steroids as a local drug delivery treatment instead of ITS. Clinical studies have demonstrated the effectiveness of post-auricular administration as a salvage treatment (28) and initial treatment (29) for SSNHL. Our results exhibited a similar or superior efficacy to systemic administration, especially for cases with low-frequency hearing loss. In this regard, post-auricular injections may replace or supplement ITS in China.

4.4. Combination therapy

The combination of other treatments with steroid therapy for SSNHL treatment remains controversial. A Cochrane systematic review reported inconclusive findings regarding hemorheology and vasodilators (30), predominantly due to inadequate RCTs. References have a strong heterogeneity with regard to drug types and efficacy assessments, making the interpretation of outcomes difficult. There is currently insufficient evidence to recommend drugs other than glucocorticoids for SSNHL treatment. Nevertheless, Chinese otolaryngologists still tended to select a combination treatment significantly different from the recommendations of US guidelines. In this survey, nearly all physicians indicated that cochlear ischemia and/or vasospasms were key factors in SSNHL pathogenesis. Ginkgo biloba extract and batroxobin were the most popular drugs applied by Chinese otolaryngologists. Most of the clinical studies supporting the efficacy of these drugs were performed by Chinese researchers, but the quality of studies included in the meta-analysis was low (31–33). Therefore, higher-quality RCTs assessing the effectiveness of hemorheological drugs are warranted.

4.5. Significance and limitations

Our survey was the first to investigate current opinions and clinical practices of SSNHL in China. We found that PAS therapy was widely used in China as a simple and practical choice, which costs significantly lower than ITS, and has better effects than ITS in the lower frequency of hearing threshold. Besides, otolaryngologists in China supported that the combination therapy of hemorheology drugs could improve the prognosis of SSNHL.

However, due to China's complex and wild regional distribution, the sample distribution in this study was slightly lower than expected in developed regions and higher than expected in moderately developed regions. These differences may slightly affect the accuracy of the results. In order to improve research quality, we conducted multifactorial analysis according to hospital level, physician level, and other aspects to reduce the impact of bias on the sample distribution.

5. Conclusions

This survey revealed Chinese otolaryngologists' views and clinical practices in the diagnosis and treatment of SSNHL. Chinese physicians exhibit substantial heterogeneity in SSNHL diagnostic criteria. Physicians generally support clinical classifications, but this requires improvements in actual clinical practice. In terms of steroid therapy, commonly used systemic administration strategies by Chinese physicians include short-term (5-day) therapy. For local administration, physicians generally employ ITS and PAS treatments as a salvage or initial protocol. The combination of hemorheology and neurotrophic drugs is widely used among Chinese physicians.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Peking University People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NC, NK, and XinM wrote the main manuscript text. XN, XiaL, JS, ZJ, and XiuM prepared Figures 1–8. XiuL, SZ, QS, JL, and GC prepared Tables 1–6. MD and LY designed the questionnaire. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1121324/full#supplementary-material

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EDITED BY
Lisheng Yu,
Peking University People's Hospital, China

REVIEWED BY
Dongzhen Yu,
Shanghai Jiao Tong University, China
Dekun Gao,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Dan Bing
✉ didibing1981@aliyun.com

†These authors have contributed equally to this work and share first authorship

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Clinical features and prognosis of pediatric idiopathic sudden sensorineural hearing loss: A bi-center retrospective study

Yingqiang Li[1†], Xiaowei Zhou[2†], Zhiyong Dou[3], Dongzhou Deng[1] and Dan Bing[1*]

[1]Department of Otolaryngology-Head and Neck Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [2]Otological Department, The First People's Hospital of Foshan, Foshan, China, [3]School of Electronic Information and Communications, Huazhong University of Science and Technology, Wuhan, China

Objective: Limited research has focused on the clinical features of sudden sensorineural hearing loss (SSNHL) in pediatric patients. This study is aimed to investigate the relationship between clinical features and the baseline hearing severity and outcomes of SSNHL in the pediatric population.

Method: We conducted a bi-center retrospective observational study in 145 SSNHL patients aged no more than 18 years who were recruited between November 2013 and October 2022. Data extracted from medical records, audiograms, complete blood count (CBC) and coagulation tests have been assessed for the relationship with the severity (the thresholds of the initial hearing) and outcomes (recovery rate, hearing gain and the thresholds of the final hearing).

Results: A lower lymphocyte count ($P = 0.004$) and a higher platelet-to-lymphocyte ratio (PLR) ($P = 0.041$) were found in the patient group with profound initial hearing than in the less severe group. Vertigo ($\beta = 13.932$, 95%CI: 4.082–23.782, $P = 0.007$) and lymphocyte count ($\beta = -6.686$, 95%CI: −10.919 to −2.454, $P = 0.003$) showed significant associations with the threshold of the initial hearing. In the multivariate logistic model, the probability of recovery was higher for patients with ascending and flat audiograms compared to those with descending audiograms (ascending: OR 8.168, 95% CI 1.450–70.143, $P = 0.029$; flat: OR 3.966, 95% CI 1.341–12.651, $P = 0.015$). Patients with tinnitus had a 3.2-fold increase in the probability of recovery (OR 3.222, 95% CI 1.241–8.907, $P = 0.019$), while the baseline hearing threshold (OR 0.968, 95% CI 0.936–0.998, $P = 0.047$) and duration to the onset of therapy (OR 0.942, 95% CI 0.890–0.977, $P = 0.010$) were negatively associated with the odds of recovery.

Conclusions: The present study showed that accompanying tinnitus, the severity of initial hearing loss, the time elapse and the audiogram configuration might be related to the prognosis of pediatric SSNHL. Meanwhile, the presence of vertigo, lower lymphocytes and higher PLR were associated with worse severity.

KEYWORDS

pediatric, audiogram, tinnitus, sudden sensorineural hearing loss (SSNHL), complete blood count (CBC)

1. Introduction

Sudden sensorineural hearing loss (SSNHL) is an urgent otologic condition that should be managed promptly. The frequency of SSNHL in adults is expected to range from 5 to 27 cases per 100,000 per year (1), primarily affecting those aged 40–50 years (2–4). Nevertheless, the incidence of SSNHL is 10- to 20-fold lower in children and adolescents than in adults (5), with only 3.5–10% of patients aged <18 years (6).

To date, there have been a limited number of studies focusing on pediatric patients with SSNHL. It is probably due to the low prevalence. It is common knowledge that children are not "small" adults. Thus, accurately describing the symptoms and relevant medical history is not easy for them. Hearing loss, especially unilateral hearing loss, is sometimes a less perceptible symptom. Thus, it can be difficult to clarify whether a child's hearing loss occurs "suddenly" or in the long run. Another unanswered question is whether SSNHL in children is the same as that observed in adults. Previous study found differences with respect to the recovery rate and audiogram configuration between adult and pediatric patients with SSNHL (6, 7). However, the genesis and progression of SSNHL remain unknown (8). Laboratory tests to explore the etiology, including viral infection (5, 9) and inflammatory biomarkers [neutrophil and lymphocyte count, mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)] (10–12), were investigated in children, with results that were not entirely similar to those of adults (13–15). Interestingly, we paid more attention to the mental effect of sudden hearing loss on children and their parents. Therefore, data-driven and easy-to-interpret prognostic prediction models are needed to communicate effectively with parents who may be highly anxious to learn about their child's prognosis.

Among the existing studies on pediatric SSNHL, there were some inadequacies. First, the small sample size reduced the power of the statistical analysis. Second, most of the previous studies were conducted in a single center, which made them more susceptible to bias; and third, the statistical methods used were commonly limited to univariate analysis, which was not able to exclude confounding factors to identify adequately independent correlations.

In the present study, we analyzed the clinical parameters associated with the severity and prognosis of SSNHL in children and developed interpretable prognostic prediction models to improve counseling.

2. Materials and methods

2.1. Study design

We conducted a retrospective analysis of pediatric patients with SSNHL aged ≤ 18 years who consecutively visited two Chinese tertiary centers (Tongji Hospital, Hubei and The First People's Hospital of Foshan, Guangdong) between November 2013 and October 2022. All the patients underwent a comprehensive clinical assessment, including a neurotological physical examination, audiometry, and imaging. The follow-up visit was conducted in person at the hospital, and 145 patients (85 from Tongji Hospital and 60 from the First People's Hospital of Foshan) were included in the study (Figure 1). We utilized the hospital information system (HIS) and conducted manual screening to collect and review the medical data. The inclusion criteria were as follows: age ≤ 18 years; diagnosed with SSNHL by an otologic specialist based on the criteria outlined in the Chinese guideline (16), i.e. unilateral or bilateral sensorineural hearing loss of >20-decibel hearing levels (dB HL) involving at least two continuous test frequencies developing within 72 h. Participants were excluded if they met any of the following exclusion criteria: (1) had congenital or genetic deafness; (2) had acoustic trauma; (3) had current otitis media; (4) had Meniere's disease; (5) had migraine; (6) had a history of ear surgery; (7) had a history of ototoxic medications; (8) had structural or retrocochlear pathology based on computed tomographic scanning or magnetic resonance (MR) imaging; and (9) were lost to follow-up. The clinical information collected included demographic data, medical records (e.g., the affected ear, accompanying symptoms, time from symptom onset to treatment, and treatment), and laboratory tests (e.g., complete blood count and coagulation tests).

2.2. Assessment

The participants enrolled were assessed using pure-tone audiometry. Pure-tone air and bone conduction thresholds at 0.25, 0.5, 1, 2, 4, and 8 kHz were examined based on the standard audiometric methodology. The average baseline hearing threshold was calculated at the affected frequencies of air conduction (frequencies with hearing loss >20 dB HL). The severity of initial hearing loss was classified as follows: mild hearing loss: 20–40 dB HL; moderate hearing loss: 41–60 dB HL; severe hearing loss: 61–80 dB HL; and profound hearing loss: >80 dB HL. We categorized the configurations of the audiogram into four types as described in our earlier study (17): ascending, descending, flat, and cophosis. The results of hearing recovery were estimated using Siegel's criterion (18). Four grades of hearing recovery were referred to as complete recovery (CR, the final hearing level is better than 25 dB HL), partial recovery (PR, the mean threshold for the final hearing levels is between 25 and 45 dB HL and more than 15 dB HL of hearing gain), slight recovery (SR, the final hearing level is worse than 45 dB HL and more than 15 dB HL of hearing gain), and no improvement (NI, <15 dB HL of hearing gain). Hearing outcomes were also assessed based on the final hearing threshold (calculating the mean of thresholds at the affected frequencies) and hearing gain (the difference between the final and initial hearing thresholds). Before therapy, patients received complete blood counts and underwent coagulation tests. Values of the absolute neutrophil counts, absolute lymphocyte counts, absolute monocyte counts, absolute platelet counts, and mean platelet volume (MPV) were obtained. The absolute neutrophil count divided by the absolute lymphocyte count was used to compute the neutrophil-to-lymphocyte ratio (NLR). By dividing the absolute platelet counts by the absolute lymphocyte count, the platelet-to-lymphocyte ratio (PLR) was determined. The coagulation function parameters included the values of activated partial thromboplastin clotting time (APTT), thrombin time (TT), prothrombin time test (PT), and concentration of fibrinogen. All

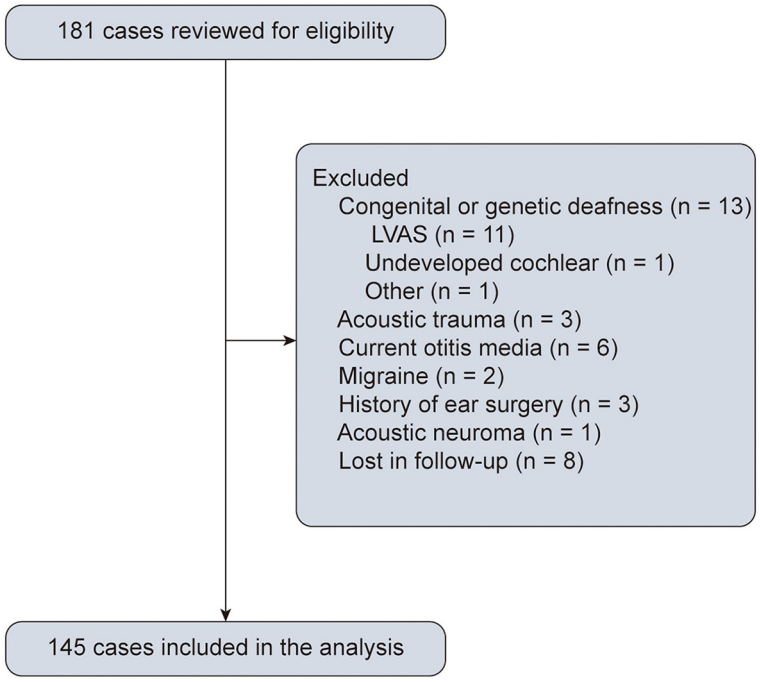

FIGURE 1
A flowchart depicting the process of study selection through the application of predetermined inclusion and exclusion criteria.

145 patients underwent 14 days of treatment containing systemic corticosteroids (prednisolone 1 mg/kg/day, tapered progressively every 4 days) and vasoactive medications.

2.3. Statistical analyses

We analyzed the initial severity of hearing loss and hearing outcomes based on Siegel's criterion. The patients with an average baseline hearing threshold graded as profound (>80 dB HL) were allocated to the profound group, whereas those with less severe baseline hearing were assigned to the not profound group. According to Siegel's criterion, patients whose hearing outcomes were classified as CR or PR were allocated to the recovery group, and the remaining patients were assigned to the non-recovery group. The Shapiro–Wilk test was used to determine if a continuous variable was normally distributed. Continuous data with a normal distribution were given as the mean and standard deviation, whereas non-normal data were presented as the median and interquartile range. The frequency and proportion were used to characterize nominal variables. Subgrouping comparisons were performed using appropriate statistical tests, such as the Mann–Whitney *U*-test, Fischer's exact test, and the Student's *t*-test, between the two subgroups. The Kruskal–Wallis test was applied to the ordinal variables for the group comparison. In addition, *post-hoc* pair-wise comparisons were used where there were more than two subgroups. The "glm" package was used to fit multivariate models to explore the factors that affected either the initial hearing or the hearing outcomes. The multivariate linear regression included the baseline hearing threshold as the response variable. Based on the variables having significance in the comparison between groups, the presence of vertigo, the lymphocyte count, and the monocyte count should be incorporated into the model. However, the analysis (Pearson correlation coefficient) revealed a significant linear correlation between the lymphocyte count, the monocyte count, and PLR. Furthermore, when these variables were included in the model, high variance inflation factor (VIF) values were observed. Therefore, we only chose the lymphocyte count to avoid potential collinearity. To analyze factors affecting hearing outcomes, a binomial categorical variable (recovery vs. non-recovery) and a continuous variable (final hearing threshold) were utilized as dependent variables. Significant variables from the univariate analysis for hearing recovery were included in the multivariate linear and logistic regression models, adjusted for age, sex, and time to the onset of therapy. To include nominal variables in the linear regression, a dummy variable was developed with a value of 1 if the case matched the description and 0 otherwise. Regression coefficients, standard regression coefficients, 95% confidence intervals, and odds ratios were calculated using regression models. All analyses were conducted using RStudio (Version: 2022.07.2+576, RStudio, Inc., Boston, MA) and R (http://www.R-project.org). A two-sided p-value of <0.05 was deemed statistically significant.

‘

3. Results

3.1. Characteristics of patients with SSNHL based on their initial hearing level

Table 1 summarizes the demographic and clinical characteristics and hearing outcomes for all enrolled patients,

TABLE 1 Clinical characteristics and recovery situation grouped by the initial hearing level.

	Overall ($N = 145$)	Initial hearing level		P
		Not profound ($N = 90$)	Profound ($N = 55$)	
Age (y)*	14.0 (11.0–16.0)	14.0 (11.0–17.0)	13.0 (11.0–16.0)	0.260[a]
Sex F:M*	65:80	41:49	24:31	0.864[b]
Side of SSNHL				
Unilateral: bilateral*	140:5	85:5	55:0	0.157[b]
L:R (150 ears)	81:69	52:43	29:26	0.866[b]
Accompanying symptoms				
Tinnitus*	74 (51.0%)	47 (52.2%)	27 (49.1%)	0.735[b]
Vertigo*	30 (20.7%)	13 (14.4%)	17 (30.9%)	0.021[b]
Onset of treatment* ($N = 124$)	4.0 (3.0–10.0)	5.0 (3.0–10.0)	4.0 (2.0–8.5)	0.628[a]
Initial configuration (150 ears)				0.001[b]
Ascending	16 (10.7%)	16 (16.8%)	0 (0%)	
Descending	33 (22.0%)	29 (30.5%)	4 (7.3%)	
Flat	58 (38.7%)	50 (52.6%)	8 (14.5%)	
Cophosis	43 (28.7%)	0 (0%)	43 (78.2%)	
Complete blood count ($N = 81$)				
Neutrophil (10^9/L)*	5.8 (4.8–7.2)	5.7 (4.6–7.5)	5.8 (5.1–6.8)	0.737[a]
Lymphocyte (10^9/L)*	1.8 (1.2–2.5)	2.1 (1.4–2.6)	1.3 (1.0–2.0)	0.004[a]
Monocyte (10^9/L)*	0.4 (0.2–0.6)	0.5 (0.3–0.7)	0.3 (0.1–0.5)	0.009[a]
Platelet (10^9/L)*	297.6 (72.4)	303.1 (67.5)	288.8 (80.2)	0.414[c]
MPV (fl)*	10 (1.2)	9.8 (1.1)	10.3 (1.4)	0.122[c]
NLR*	3.5 (2.0–5.3)	3.1 (1.8–5.1)	4.7 (2.4–5.6)	0.066[a]
PLR*	167.6 (110.2–234.4)	142.2 (105.2–216.8)	218.7 (126.2–263.4)	0.041[a]
Coagulation function ($N = 83$)				
APTT (s)*	29.0 (12.2–36.6)	28.1 (12.2–36.3)	30.2 (12.3–36.7)	0.856[a]
FIB (g)*	2.3 (2.0–2.7)	2.4 (2.1–2.7)	2.2 (1.7–2.6)	0.148[a]
PT (s)*	14.1 (12.9–23.1)	13.7 (12.9–23.3)	14.4 (13.1–21.0)	0.592[a]
TT (s)*	17.6 (16.8–18.7)	17.6 (17.0–18.4)	17.7 (16.7–20.1)	0.637[a]
Follow-up days*	14.0 (12.0–90.0)	14.0 (11.2–90.0)	14.0 (13.5–76.5)	0.667[a]
Hearing recovery (150 ears)				
Recovery[#]	65 (43.3%)	56 (58.9%)	9 (16.4%)	<0.001[b]
Hearing gain (dB HL)	21.5 (7.1–35.8)	21.7 (8.3–35.8)	19.2 (6.3–36.7)	0.641[a]
Final hearing (dB HL)	42.7 (19.4–75.8)	28.3 (15.8–46.2)	81.7 (55.0–95.4)	<0.001[a]

Continuous variables were presented as mean (standard deviation) for normal distribution or medians (interquartile range) for non-normal distribution. Categorical variables were presented as n (%).

Subjects with one or more affected ears estimated as profound level hearing loss (average hearing threshold ≥ 80 dBHL) were assigned to the profound group.

Hearing gain and final hearing were evaluated by the hearing thresholds at frequencies affected (frequencies with initial hearing threshold > 20 dBHL).

*These were subject-specific covariates, while the rest were ear-specific covariates.

[#]According to Siegel's criteria, hearing recovery was defined as complete recovery (CR) and partial recovery (PR).

[a]Mann-Whitney U-test.

[b]Fischer's exact test.

[c]Student t-test.

MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; APTT, activated partial thromboplastin time; FIB, fibrinogen; PT, prothrombin time test; TT, thrombin time.

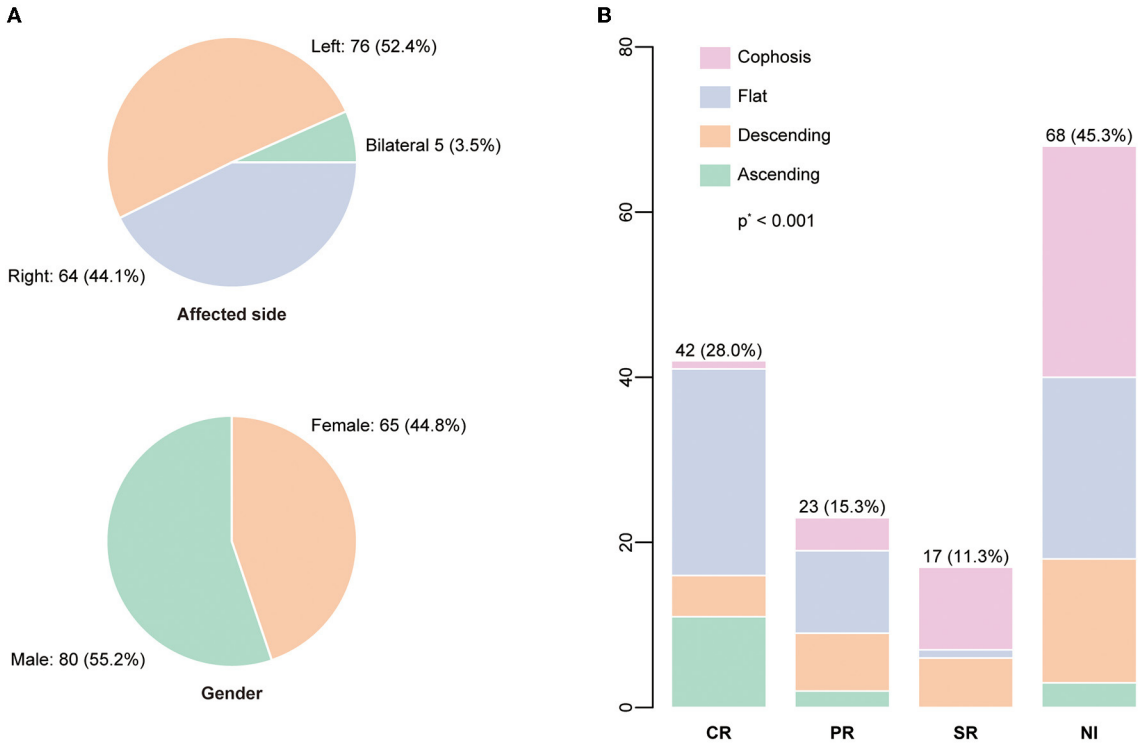

FIGURE 2
(A) The distributions of the affected side and gender were displayed. **(B)** The audiogram configuration distribution according to the recovery status based on Siegel's criteria. *P*-value was calculated by the Kruskal-Wallis test.

according to their baseline hearing level. The study comprised 145 patients (150 ears), of whom 65 were women (44.8%). The characteristics of the affected side and gender are displayed in Figure 2A. At the commencement of SSNHL, tinnitus was present in more than half of the patients (74/145, 51.0%). In contrast, only 30 patients had vertigo (20.7%), with a statistical difference between the baseline hearing groups ($P = 0.021$). Regarding the configurations of the initial audiogram, the flat configuration was the most common (58/150, 38.7%), and a significant difference in the initial hearing was detected among groups ($P = 0.001$). Eighty-one patients had complete blood count (CBC) test results, and 83 patients had coagulation factor test findings. The study found that patients with profound initial hearing loss had a significantly lower absolute lymphocyte count compared to those without [the profound group: 1.3 (1.0–2.0); the non-profound: 2.1 (1.4–2.6); $p = 0.004$]. The patients in the profound group had a higher level of PLR and a lower level of monocytes than their counterparts with less severe hearing loss.

3.2. Hearing outcome prognostic factor analysis using a subgroup comparison

Figure 2B depicts the percentage and number of ears for each Siegel's recovery grade. Tinnitus was reported by 61.3% (38/62) of patients in the recovery group and 43.3% (36/83) in the patient group without recovery. The difference in accompanying tinnitus between the two outcome groups was statistically significant ($P = 0.044$) (Table 2). There were significant differences in the baseline threshold average between the non-recovery group and the recovery group [non-recovery: 84.0 (68.3–104.2); recovery: 60.8 (43.8–72.9), $P = <0.001$] and in the subgroups separated by initial severity ($P = 0.037$). The configurations of the audiograms were significantly different across the groups ($P = <0.001$). Patients with cophosis figures had significantly different recovery than those with descending ($P = 0.020$), ascending ($P < 0.001$), and flat figures ($P < 0.001$). Patients with descending figures had significantly different recovery than those with ascending ($P = 0.011$) and flat figures ($P = 0.038$) after *post-hoc* comparison. The thresholds for the initial and final hearing comparison, sorted by the initial configuration, are shown in Figure 3. There were significant differences in the final hearing between the cophosis configuration and the other three groups, respectively (ascending: $P = <0.001$; descending: $P = <0.001$; flat: $P = <0.001$). A worse final hearing was found in patients with descending figures than with ascending ($P = <0.001$) and flat ($P = 0.016$) figures, respectively. The threshold for a final hearing with ascending figures was similarly lower than for that with the flat figure ($P = 0.019$). No statistical difference was found in complete blood cell and coagulation test biomarkers across the recovery group and the non-recovery group.

3.3. Factors related to initial hearing and final hearing which were analyzed using the multivariate regression models

In the linear models, the factors related to the initial hearing level included vertigo (β = 13.932, 95% CI: 4.082–23.782, $P =$

TABLE 2 Clinical characteristics, laboratory tests, and audiograms related to hearing recovery.

	Hearing outcomes		
	Non-recovery ($N = 83$)	Recovery[#] ($N = 62$)	*P*
Age (y)*	14.0 (11.0–16.0)	14.0 (11.0–16.8)	0.386[a]
Sex F:M*	40:43	25:37	0.400[b]
Side of SSNHL			
Unilateral: bilateral*	81:2	59:3	0.651[b]
L:R (150 ears)	46:39	35:30	1.000[b]
Accompanying symptoms			
Tinnitus*	36 (43.4%)	38 (61.3%)	0.044[b]
Vertigo*	19 (22.9%)	11 (17.7%)	0.536[b]
Onset of treatment* ($N = 124$)	5.0 (3.0–12.0)	4.0 (2.0–7.0)	0.359[a]
Follow-up*	14.0 (12.0–54.0)	14.0 (13.2–90.0)	0.333[a]
Baseline hearing profiles (150 ears)			
Baseline threshold average (dB HL)	84.0 (68.3–104.2)	60.8 (43.8–72.9)	<0.001[a]
Initial severity			0.037[d]
Mild	7 (8.2%)	15 (23.1%)	
Moderate	11 (12.9%)	20 (30.8%)	
Severe	21 (24.7%)	21 (32.3%)	
Profound	46 (54.1%)	9 (13.8%)	[e]
Initial configuration			<0.001[b]
Ascending	3 (3.5%)	13 (20.0%)	
Descending	21 (24.7%)	12 (18.5%)	[f]
Flat	23 (27.1%)	35 (53.8%)	
Cophosis	38 (44.7%)	5 (7.7%)	[g]
Complete blood count ($N = 81$)			
Neutrophil (10^9/L)*	5.6 (4.7–6.8)	6.0 (5.2–7.8)	0.197[a]
Lymphocyte (10^9/L)*	1.5 (1.1–2.3)	2.1 (1.4–2.6)	0.057[a]
Monocyte (10^9/L)*	0.4 (0.1–0.5)	0.5 (0.3–0.6)	0.224[a]
Platelet (10^9/L)*	296.7 (79.7)	298.5 (65.9)	0.913[c]
MPV (fl)*	10.2 (1.4)	9.8 (1.1)	0.092[c]
NLR*	4.4 (2.1–5.6)	3.1 (1.8–5.2)	0.232[a]
PLR*	184.1 (132.3–247.9)	142.2 (101.8–223.5)	0.129[a]
Coagulation function ($N = 83$)			
APTT (s)*	32.0 (13.1–37.0)	26.3 (12.1–35.8)	0.156[a]
FIB (g)*	2.4 (1.9–2.8)	2.3 (2.0–2.6)	0.543[a]
PT (s)*	13.9 (12.9–16.6)	14.8 (13.1–23.3)	0.312[a]
TT (s)*	17.6 (16.7–19.5)	17.7 (16.9–18.4)	0.876[a]

Continuous variables were presented as mean (standard deviation) for normal distribution or medians (interquartile range) for non-normal distribution. Categorical variables were presented as *n* (%).

The baseline threshold average was evaluated by the hearing thresholds at frequencies affected (frequencies with initial hearing threshold > 20 dBHL).

Subjects with one or more affected ears estimated as not recovered based on Siegel's criteria were assigned to the non-recovery group.

*These were subject-specific covariates, while the rest were ear-specific covariates.

[#]According to Siegel's criteria, hearing recovery was defined as CR and PR.

[a]Mann-Whitney *U*-test.

[b]Fischer's exact test.

[c]Student *t*-test.

[d]Kruskal-Wallis test.

[e]Significant differences were found between profound and the other three groups after a *post-hoc* comparison in initial severity grouping.

[f]Significant differences were found between descending and the other three groups after a *post-hoc* comparison in initial configuration grouping.

[g]Significant differences were found between cophosis and the other three groups after a *post-hoc* comparison in initial configuration grouping.

MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; APTT, activated partial thromboplastin time; FIB, fibrinogen; PT, prothrombin time test; TT, thrombin time.

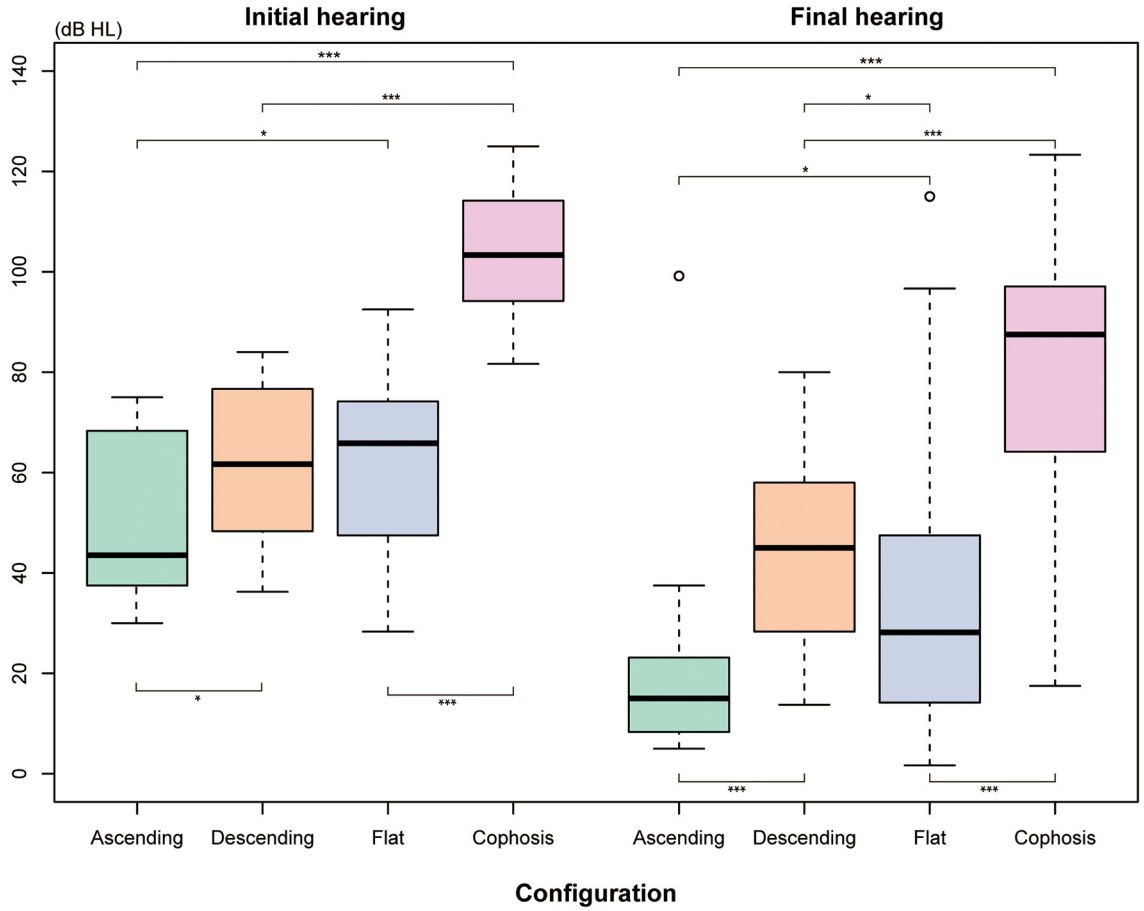

FIGURE 3
The means thresholds of the initial and final hearing with different audiogram configurations. The Mann-Whitney *U*-test was used for comparison. *Indicates that $P \leq 0.05$. ***Indicates that $P \leq 0.001$.

0.007), lymphocyte count (β = −6.686, 95% CI: −10.919 to −2.454, $P = 0.003$) (Table 3), and independent predictors for the threshold for the final hearing, which comprised the onset of therapy (β = 0.313 95% CI: 0.125–0.502, $P = 0.001$), baseline hearing (β = 0.772, 95% CI: 0.563–0.980, $P = <0.001$), and configurations (Table 4). In the multivariate logistic model adjusted for age, sex, and time to the onset of treatment (Table 5), the patients with ascending and flat audiograms were more likely to recover than the patients with descending audiograms (ascending: OR 8.168, 95% CI 1.450–70.143, $P = 0.029$; flat: OR 3.966, 95% CI 1.341–12.651, $P = 0.015$). The odds of recovery were 3.2 times higher for patients with tinnitus than for those without tinnitus (OR 3.222, 95% CI 1.241–8.907, $P = 0.019$). The threshold for baseline hearing (OR 0.968, 95% CI 0.936–0.998, $P = 0.047$) and the onset of therapy (OR 0.942, 95% CI 0.890–0.977, $P = 0.010$) were negatively associated with the odds of recovery. To predict the hearing outcomes of pediatric patients with SSNHL, a nomogram was established by incorporating the following parameters: tinnitus, the onset of therapy, baseline hearing, and configuration (Figure 4).

4. Discussion

The present bi-center study found some predictive factors of hearing outcomes in pediatric patients with SSNHL, including tinnitus, the time elapsed from the onset of the symptoms to the commencement of the treatment, initial audiogram configuration, and hearing levels. We observed a higher proportion of accompanying vertigo, a greater degree of inflammatory biomarkers (lower the concentration of lymphocytes. and a higher level of PLR), and worse hearing outcomes (lower recovery rate and increased final hearing thresholds) in patients with more severe initial hearing loss. Meanwhile, according to the multivariate linear regression model, we developed a nomograph as a simple predictive tool for the final hearing threshold.

The coexisting symptoms of vertigo (29–56%) and tinnitus (41–90%) were frequently observed in adult patients with SSNHL (19, 20). The incidence rate of both symptoms is similar in pediatric patients with SSNHL, as reported in a previous study (21). We noticed that tinnitus is independently associated with

TABLE 3 Correlation between baseline characteristics and threshold of the initial hearing.

	B	SE	*β*	Lower limit	Higher limit	*P*
Age (y)	−1.134	0.699	−0.161	−2.503	0.235	0.109
Sex male	10.700	4.702	0.225	1.484	19.916	0.026
Vertigo	13.932	5.026	0.273	4.082	23.782	0.007
Lymphocyte (10^9/L)	−6.686	2.159	−0.306	−10.919	−2.454	0.003

B, unstandardized coefficient; SE, standard error; β, standardized coefficient; lower limit, lower limit of 95% confidence interval for unstandardized coefficient; higher limit, higher limit of 95% confidence interval for unstandardized coefficient.
The correlation was analyzed by multivariate linear regression analysis adjusted by age and sex.

TABLE 4 Correlation between baseline characteristics and threshold of the final hearing.

	B	SE	*β*	Lower limit	Higher limit	*P*
Age (y)	−0.541	0.523	−0.056	−1.565	0.484	0.303
Sex men	−5.252	3.357	−0.079	−11.832	1.329	0.120
Tinnitus	−6.232	3.427	−0.094	−12.949	0.485	0.072
Onset of treatment (d)	0.313	0.096	0.165	0.125	0.502	0.001
Baseline hearing (dB HL)	0.772	0.106	0.601	0.563	0.980	<0.001
Configuration						
Descending	Ref					
Ascending	−16.123	6.364	−0.153	−28.596	−3.650	0.013
Flat	−12.182	4.460	−0.180	−20.924	−3.440	0.007
Cophosis	7.037	6.561	0.096	−5.822	19.896	0.286

B, unstandardized coefficient; SE, standard error; β, standardized coefficient; lower limit, lower limit of 95% confidence interval for unstandardized coefficient; higher limit, higher limit of 95% confidence interval for unstandardized coefficient.
The correlation was analyzed by multivariate regression analysis adjusted by age, sex, and the onset of treatment.

TABLE 5 Correlation between baseline characteristics and hearing recovery (recovery vs. non-recovery).

	B	Odds ratio	Lower limit	Higher limit	*P*
Age (y)	0.006	1.006	0.866	1.168	0.938
Sex men	0.889	2.433	0.923	6.899	0.080
Tinnitus	1.170	3.222	1.241	8.907	0.019
Onset of treatment (*d*)	−0.059	0.942	0.890	0.977	0.010
Baseline hearing (dB HL)	−0.032	0.968	0.936	0.998	0.047
Configuration					
Descending	Ref				
Ascending	2.100	8.168	1.450	70.143	0.029
Flat	1.378	3.966	1.341	12.651	0.015
Cophosis	−1.197	0.302	0.032	2.153	0.250

B, unstandardized coefficient; lower limit, lower limit of 95% confidence interval for odds ratio; higher limit, higher limit of 95% confidence interval for the odds ratio.
The correlation was analyzed by multivariate logistic regression analysis adjusted by age, sex, and the onset of treatment.
According to Siegel's criteria, hearing recovery was defined as complete recovery (CR) and partial recovery (PR).

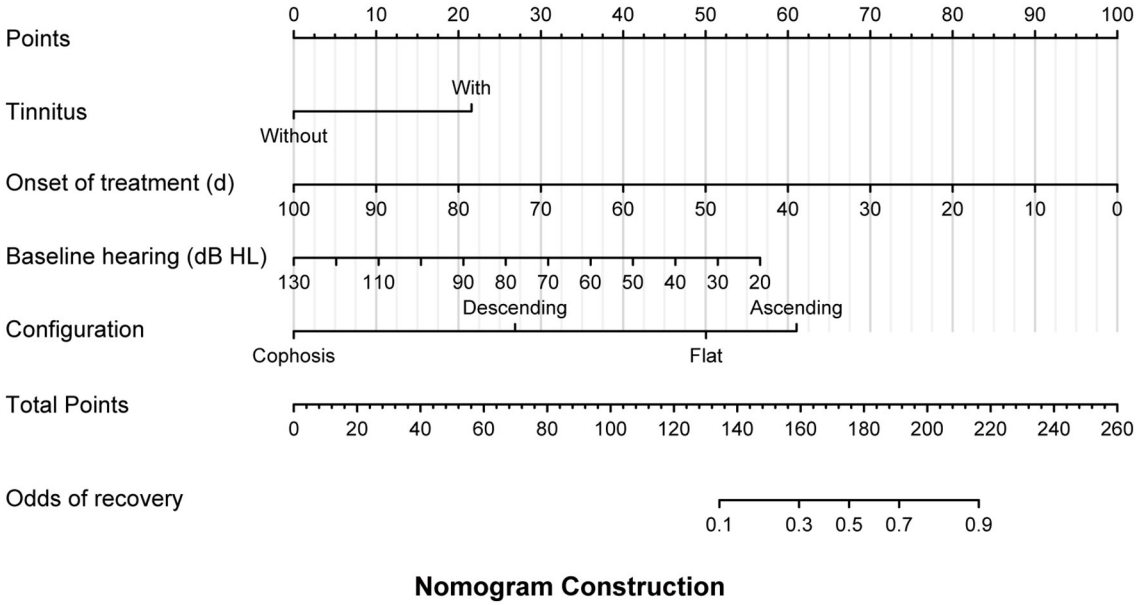

FIGURE 4
A multivariate logistic model was used to develop a prognostic nomogram for pediatric patients with sudden sensorineural hearing loss (SSNHL), which incorporated the odds of recovery as the response variable and independent variables including the presence of tinnitus, the onset of treatment, baseline hearing threshold, and audiogram configuration. To make a prediction regarding the probability of patient recovery in accordance with Siegel's criteria, the model identified the patient's values along each axis first. Subsequently, a vertical line was drawn upward from each value to the 'points' axis to determine the number of points generated by each variable. The points generated by all variables should then be summed to arrive at the total points line. Finally, a vertical line should be drawn down from this point, thereby providing the odds of recovery.

better hearing outcomes in pediatric patients with SSNHL; this finding is in line with earlier research in both children and adults (6, 22–25). Based on the multivariate analysis, pediatric patients with SSNHL and tinnitus generally have a 3.2-fold improvement in their recovery odds compared to those without. A recent study revealed an underlying mechanism for different cortical activity patterns in adult SSNHL patients with and without tinnitus (26), which may also be applicable to the child population. With regards to the presence of vertigo, some differences were observed. It was consistently reported to be detrimental to hearing recovery in adult patients (27). In contrast, it is still controversial in the studies on children and adolescent patients (6, 24, 25, 28–30). Our findings suggest that the baseline hearing severity but not the hearing outcome was independently related to the presence of vertigo. This finding is consistent with a previous study by Liu et al. (31), finding that patients with SSNHL with vertigo might suffer from a more severe cochlear and vestibular impairment, as indicated by vestibular function testing. It indicates that vertigo may indicate a more serious condition in pediatric patients with SSNHL, which could be a potential prognostic factor.

In terms of audiograms, we observed that patients with ascending and flat configurations had lower thresholds for the final hearing and greater recovery odds than patients with descending figures; these findings were consistent with the conclusions drawn by Qian et al. (30) and Chen et al. (6). However, Kim et al. (25) pointed out that although the decreasing figure was a good predictor, they had only found it in six individuals. According to the literature on adults, low-frequency hearing loss was confirmed to be the positive predictor, whereas the descending figure was the opposite indicator (19, 22, 32, 33). In addition, mid-frequency hearing loss, categorized under the flat figure in our analysis, was also referred to as a positive prognostic factor (34). Moreover, it appeared that for children, the association between configurations and hearing recovery was comparable with that for adults. Regarding the descending configuration, it was found that the hair cells at the base of the cochlea were delicate and that regaining high-frequency hearing function was more difficult (35–38). In addition, it has been reported that high-frequency hearing loss can go unnoticed in children, leading to delays in initiating therapy (39). This could explain why the descending configuration in pediatric patients with SSNHA is associated with poor recovery.

This study's results found that the lymphocyte count correlated with the initial hearing thresholds, with a marginally higher value in patients who recovered. Although a low lymphocyte count was identified as a risk factor and a poor prognostic factor in adults (13, 14), recent study reported inconsistent findings for children because of the small sample size (10–12). As an indicator of inflammation (40), low lymphocyte count in SSNHL was assumed to be caused by increased T lymphocyte extravasation from the blood vessel (13). Meanwhile, virus-induced immunosuppression might be another inflammation-related cause of decreased lymphocyte count (7, 8). According to our findings, PLR, another inflammatory biomarker (41), was significantly higher in the patients with profound initial hearing, and NLR had the same tendency but with a marginal significance. Several

inflammatory agents were also seen to cause cochlear damage (42, 43). These findings suggested that the extent of systemic inflammation might be associated with the severity of SSNHL in children.

In the current study, we observed that among the ears studied, 36.7% had profound initial hearing, and among these ears, 45.3% showed no improvement. The findings were similar to the conclusion drawn by a recent meta-analysis (21), with 36.7% of ears having profound hearing loss and 46.7% showing no improvement. However, substantial heterogeneity was present because of the relatively small sample, and the criteria in each research varied. Although previous studies indicated a higher complete recovery rate in children compared to adults, one of them defined adults as older than 15 years, and the other comprised a small sample of fewer than 40 children (6, 7). Conversely, age $<$ 15 years was regarded as a sign of poor prognosis in other literature (44, 45). Our study found no statistical significance in the correlation of age with severity and outcomes. The relationship between age and outcomes in the pediatric population would benefit from more precise examinations and analyses.

To the best of our knowledge, our study on SSNHL in children is one of the largest of its kind, with a sample size of 145 patients. Furthermore, we conducted a bi-center investigation, which increases the representativeness of the target population and reduces individual bias compared to single-center studies. Nonetheless, there are several drawbacks. First, because of the respective research design, it was impossible to confirm causal relationships between the investigated factors and the severity or outcomes. Second, the investigation was exploratory without a scientistic hypothesis or pivot statistical estimate—no sample size calculation to ensure a significant statistical power. Meanwhile, due to the low prevalence of SSNHL in children, only a portion of the patients had complete blood counts and coagulation tests available. Third, only the total lymphocyte count was determined; no subtype analysis was performed. Therefore, further research is warranted to focus on the potential biomarkers in children to demonstrate whether these biomarkers differ from those in adults.

In conclusion, it was an exploratory study on pediatric patients with SSNHL. Some factors, including accompanying tinnitus, the severity of the initial hearing loss, the onset of therapy, and the configuration of audiograms, might be related to the prognosis of pediatric patients with SSNHL. Meanwhile, the incidence of vertigo, lower lymphocytes, and higher PLR were associated with poor hearing severity. Further research is needed to establish a more accurate understanding of the relationship between pediatric SSNHL and its underlying mechanisms, given the diversity of clinical trials involving adults and children.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, PR China and Ethics Committee, The First People's Hospital of Foshan, Foshan, PR China. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

DB contributed to the study design, data analysis, and manuscript writing. YL and XZ contributed to the study design, data collection and analysis, and manuscript writing. ZD and DD contributed to the data analysis, collection, and holding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Lisheng Yu,
Peking University People's Hospital,
China

REVIEWED BY
Jun Wang,
Huazhong University of Science and Technology,
China
Mingming Wang,
Shandong Provincial ENT Hospital,
China
Yilai Shu,
Fudan University,
China

*CORRESPONDENCE
Xicheng Song
drxchsong@163.com
Yujuan Yang
yangyujuanyyj@163.com
Yan Sun
entsunyan@126.com

†These authors have contributed equally to this work and share first authorship

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Potential molecular mechanisms of Erlongjiaonang action in idiopathic sudden hearing loss: A network pharmacology and molecular docking analyses

He Zhao[1,2,3†], Yan Wang[1,2,3†], Cong Xu[1,2,3†], Guangjin Li[2,3,4], Yuwan Song[2,3], Jingjing Qiu[2,3], Limei Cui[2,3], Xicheng Song[2,3*], Yujuan Yang[2,3*] and Yan Sun[2,3*]

[1]The Second Medical College, Binzhou Medical University, Yantai, Shandong, China, [2]Department of Otolaryngology and Head and Neck Surgery, Yantai Yuhuangding Hospital, Qingdao University, Yantai, Shandong, China, [3]Shandong Provincial Clinical Research Center for Otorhinolaryngologic Diseases, Yantai, Shandong, China, [4]School of Clinical Medicine, Weifang Medical University, Weifang, China

Background: Idiopathic sudden hearing loss (ISHL) is characterized by sudden unexplainable and unilateral hearing loss as a clinically emergent symptom. The use of the herb Erlongjiaonang (ELJN) in traditional Chinese medicine is known to effectively control and cure ISHL. This study explored the underlying molecular mechanisms using network pharmacology and molecular docking analyses.

Method: The Traditional Chinese Medicine System Pharmacological database and the Swiss Target Prediction database were searched for the identification of ELJN constituents and potential gene targets, respectively, while ISHL-related gene abnormality was assessed using the Online Mendelian Inheritance in Man and Gene Card databases. The interaction of ELJN gene targets with ISHL genes was obtained after these databases were cross-screened, and a drug component–intersecting target network was constructed, and the gene ontology (GO) terms, Kyoto Encyclopedia of Genes and Genomes, and protein–protein interaction networks were analyzed. Cytoscape software tools were used to map the active components–crossover target–signaling pathway network and screened targets were then validated by establishing molecular docking with the corresponding components.

Result: Erlongjiaonang contains 85 components and 250 corresponding gene targets, while ISHL has 714 disease-related targets, resulting in 66 cross-targets. The bioinformatical analyses revealed these 66 cross-targets, including isorhamnetin and formononetin on NOS3 expression, baicalein on AKT1 activity, and kaempferol and quercetin on NOS3 and AKT1 activity, as potential ELJN-induced anti-ISHL targets.

Conclusion: This study uncovered potential ELJN gene targets and molecular signaling pathways in the control of ISHL, providing a molecular basis for further investigation of the anti-ISHL activity of ELJN.

KEYWORDS

ISHL, TCM, Erlongjiaonang, bioinformatics, gene targets

Introduction

Idiopathic sudden hearing loss (ISHL), a class of sudden sensorineural hearing loss (SSNHL), is characterized by sudden unexplainable and unilateral hearing loss. Clinically, ISHL can cause persistent tinnitus and/or hearing loss, leading to reduced quality of life. It affected an estimated 27 per 100,000 individuals in 2007 (1), with approximately 66,000 new cases identified annually in the USA (2). A Japanese study showed that the highest ISHL incidence rate occurred in patients aged 60 years or older, although the average age was 54 years old (3). To date, there are different approaches to SSNHL treatment, such as systemic and topical glucocorticoids, thrombolytic agents, antiviral agents, and drugs to improve microcirculation and nerve nourishment (4). Corticosteroids with or without combination with hyperbaric oxygen therapy (HBOT) may be used as initial therapy for the first 2 weeks, followed by combination therapy with HBOT as relief within the first month of disease (2). However, these treatments may not be able to cure all patients. For example, a recent study showed a cure rate of less than 30% after oral, intravenous, or tympanic administration of steroids in patients (5).

Traditional Chinese medicine, as one form of alternative medicine, utilizes botanical, mineral, or animal-derived agents to control or release human diseases and syndromes. According to Chinese Pharmacopoeia 2020, Erlongjiaonang (ELJN), as an oral capsule, is prescribed to treat dizziness, headache, deafness, tinnitus, and ear discharge as caused by the TCM theory of "damp heat" in the liver and gallbladder (6). A recent clinical trial of ELJN plus dexamethasone in the treatment of patients with SSNHL revealed that this regimen of treatment had better responses than the control group of dexamethasone alone (93.97% vs. 79.31%) (7). Another clinical trial data showed that ELJN plus gastrodin injection was more beneficial in SSHNL control than that of gastrodin injection alone (97.53% vs. 85.00%), and the adverse reactions were lower in the drug combination arm than in the control arm (6.17% vs. 20.00%) (8). However, to date, the underlying molecular mechanisms of ELJN in the treatment of ISHL remain unknown.

Network pharmacology refers to a combination of pharmacology with bioinformatics and systems biology to assess the multi-compound, multi-targets, and multi-pathway characteristics in TCM (9). Thus, in this study, we applied this novel analytic tool to construct the network of "effective components-action target" (drug–target network) and overlay the targets between ELJN and SSHNL (the drug–disease network), in order to discover the potential ELJN molecular targets on SSHNL. We analyzed different nodes after establishing networks to better understand the ELJN anti-SSHNL activity, which could provide us with a novel strategy for future SSHNL prevention and treatment and better understand SSHNL pathogenesis clinically (Figure 1).

Materials and methods

Screening of ELJN active components and therapeutic targets

Erlongjiaonang contains 10 different TCM herbs: Gardeniae Fructus, Alisma, Caulis Akebiae, Gentianae Radix Et Rhozima, Anemone Altaica Fisch, Rehmanniae Radix Praeparata, Angelicae Sinensis Radix, Licorice, Scutellariae Radix, and Antelope Horn. These herbs were used to search the 2020 Chinese Pharmacopoeia and the Traditional Chinese Medicine System Pharmacological (TCMSP) databases[1] (10) to identify their constituents. The screening criteria used were: >30% oral bioavailability (OB) and > 0.18 drug-likeness (DL) (11), according to the TCMSP database. The chemical structure of each component was obtained from the chemical source network database, and the corresponding components were then mapped according to their chemical structures using the Swiss Target Prediction database[2] for the species "Homo sapiens" (12) and the targets of each component were further screened. Subsequently, the validated human targets were then screened using the Uniprot database[3] (13), and the targets from these two databases were combined, while the target names (symbols) were corrected to match the official names in this database.

Screening of ISHL therapeutic targets

The terms "idiopathic sudden deafness" and "idiopathic sudden hearing loss" were used as the keywords when searching the Online Mendelian Inheritance in Man (OMIM) database[4] (14, 15), Gene Cards database[5] (16), and the Therapeutic Target Database (TTD)[6] (17). The resulting data were collected from each database and summarized in an *Excel* file.

Construction of the component–network–pathway network

We mapped the potential ELJN gene targets and ISHL targets with a Venn diagram using the Venny2.1 tool[7] and Cytoscape software (version 3.9.1) to create an ELJN active components–intersection target–signaling pathway network map using the data from the active components–target network and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. The "Degree" of each component in the network was then derived, and the top 20% of targets were selected for further analyses.

Bioinformatical gene ontology and Kyoto encyclopedia of genes and genomes pathway enrichment analysis

We next performed the GO and KEGG analyses of the intersecting genes. The GO terms included biological processes (BPs), cellular components (CCs), and molecular functions (MFs). The GO and KEGG analyses were performed using Metascape software[8]

1 https://tcmspw.com/
2 http://www.swisstargetprediction.ch/
3 https://www.uniprot.org/
4 https://omim.org/
5 https://www.genecards.org/
6 http://db.idrblab.net/ttd/
7 https://bioinfogp.cnb.csic.es/tools/venny/
8 https://metascape.org/gp/index.html#/main/step1

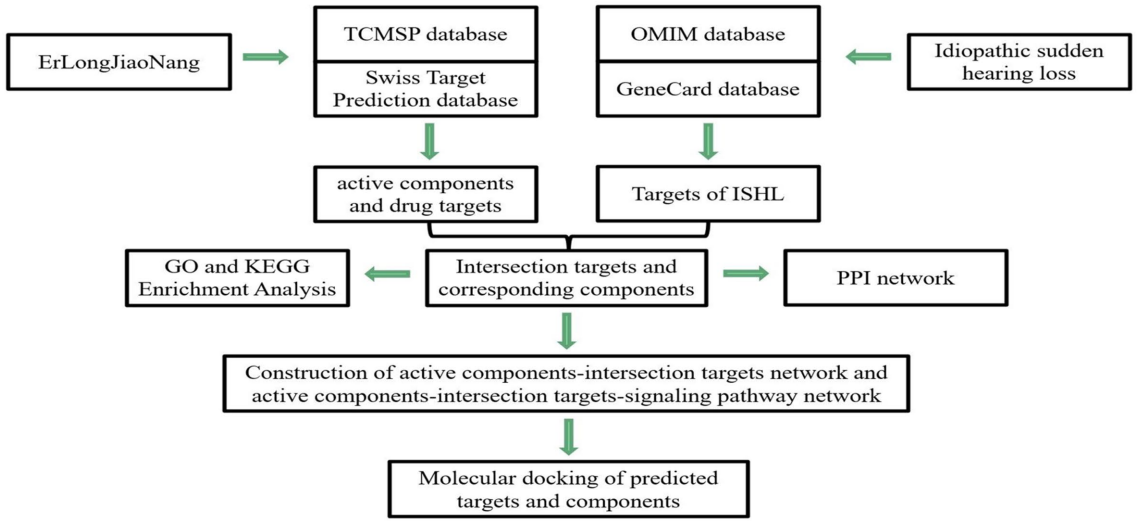

FIGURE 1
Illustration of study flow and data analysis. In this study, we first identified the possible active components in ELJN and then searched for their molecular targets. Meanwhile, we also identified ISHL-related genes. Subsequently, we constructed different networks to analyze the interaction of these two types of genes molecularly and then molecular docking analysis of the genes targeted by the active components of ELJN.

with the feature-rich tool. A p-value of <0.05 was considered statistically significant.

Construction of the target protein–protein interaction (PPI) network

The data on the common targets of ELJN and ISHL were imported into the STRING V11.5 database[9] (18), and the species "Homo sapiens" was selected to create the PPI network. Next, we derived these common targets using a Venn diagram, matched the drug components with the common targets, and then imported the matching results into Cytoscape (version 3.9.1) to construct the drug component and common target networks (19).

Molecular docking analysis

We performed molecular docking analysis of the target and corresponding active components from the above procedures using the retrieved InChlKey components from the TCMSP and PubChem databases (20), in order to retrieve the corresponding ligand data as a file. After converting it using the Chem3D software (version 20.0.0), the receptor files for the corresponding targets were retrieved from the RCSB PDB database[10] (21). The water and residue ligands of the receptors were removed using Pymol (version 2.5.0), while the receptor and ligand were converted to their secondary structures using the Autodock Tools (version 1.5.7) (22) and docked in the Autodock Vina software (version 1.1.2) (23). The molecular docking data were transferred into Pymol (version 2.5.0) for visualization.

9 https://cn.string-db.org/
10 https://www.rcsb.org/

Results

Identification of ELJN active components and targets

Erlongjiaonang, as in a powder form, contains 10 different TCM herbs, i.e., Gardeniae Fructus, Alisma, Caulis Akebiae, Gentianae Radix Et Rhozima, Anemone altaica Fisch, Rehmanniae Radix Praeparata, Angelicae Sinensis Radix, Licorice, Scutellariae Radix, and Antelope Horn. We then searched the constituent herbs of ELJN in the TCMSP database and reviewed the relevant PubMed literature, as well as considered Lipinski's rules (24) and found a total of 147 active components, including 10 active components of Gentianae Radix Et Rhozima, 36 active components of Scutellariae Radix, seven active components of Alisma, 10 active components of Zedoary, eight active components of Caulis Akebiae, 15 active components of Gardeniae Fructus, two active components of Angelicae Sinensis Radix, five active components in Anemone Altaica Fisch, and 92 active components in Licorice, but there were no active components of Antelope Horn.

Subsequently, we utilized the 85 active components in ELJN, using the cutoff values of >30% OB, and >0.18 DL, and obtained 250 gene targets accordingly (Supplementary Table S1); thus, we then constructed the component–target network using Cytoscape (version 3.9.1; Figure 2). Among them, we ranked these components according to the "degree" value for the top nine components (Supplementary Table S2), while based on the "Closeness Centrality" value, we identified the top 20 gene targets of the active components in ELJN (Supplementary Table S3).

Common targets of ELJN and ISHL and bioinformatical data

Similarly, we obtained a total of 714 ISHL-related gene targets after searching the OMIM, Genecards, and TTD databases. We then

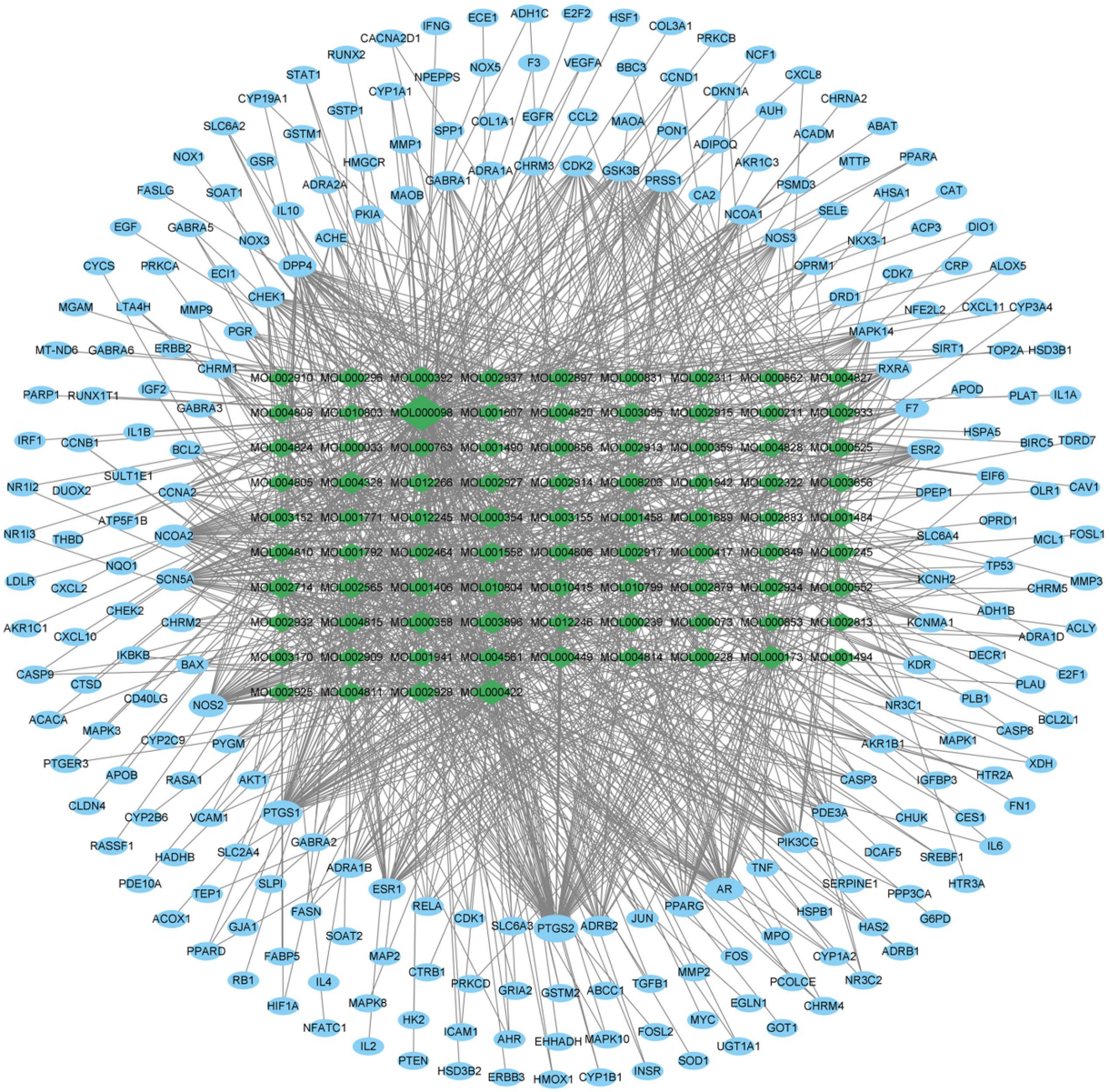

FIGURE 2
Drug components–target network. The green ovals correspond to the compositions, while the blue ovals refer to the targets. The more lines connected, the stronger the correlation.

constructed a Venn diagram using Venn 2.1 to illustrate the connection between ELJN and ISHL with 66 drug–disease intersection targets (Figure 3A). After combining the 66 gene targets, we built the drug components–intersecting target network (Figure 3B).

The results of the GO analysis show that mainly enriched biological processes, such as the responses to stimuli, regulation of biological processes, multicellular organismal processes, negative regulation of biological processes, positive regulation of biological processes, metabolic processes, biological processes involved in interspecies interaction between organisms, signaling pathways, biological regulation, growth, immune system processes, and many others. Furthermore, the enriched cellular components included cytokine activity, protease binding, protein domain-specific binding, phosphatase binding, metalloendopeptidase activity, scaffold protein binding, inorganic molecular entity transmembrane transporter activity, lipid binding, neurotransmitter receptor activity, kinase regulator activity, oxidoreductase activity, protein homodimerization activity, and protein kinase activity (Figure 4).

Furthermore, there were 157 relevant metabolic pathways after the KEGG analysis. The key KEGG enrichment pathways of ELJN anti-ISHL were the AGE-RAGE signaling pathway in diabetic complications, along with pathways in cancer, lipid and atherosclerosis, fluid shear stress and atherosclerosis, endocrine resistance, measles, allograft rejection, transcriptional misregulation in cancer, sphingolipid signaling pathway, gap junction, the p53 signaling pathway, the longevity regulating pathway, serotonergic synapses, Parkinson's disease, hypertrophic cardiomyopathy, tryptophan metabolism, dopaminergic synapse, epithelial cell signaling in *Helicobacter pylori* infection, and retrograde endocannabinoid signaling (Figures 5, 6).

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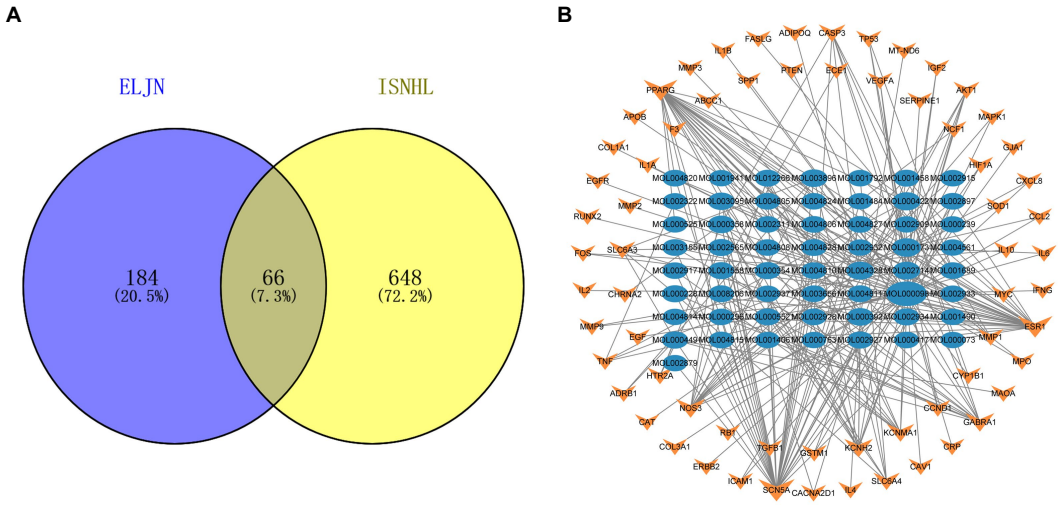

FIGURE 3
Intersection target Venn diagram and the drug components–intersection target network. **(A)** The purple corresponds to the ELJN targets, while the yellow refers to the ISHL gene targets and the gray is their intersection component. **(B)** The blue oval corresponds to the drug component, while the orange color refers to the intersection target of the drug and disease. The more lines connected, the stronger the correlation.

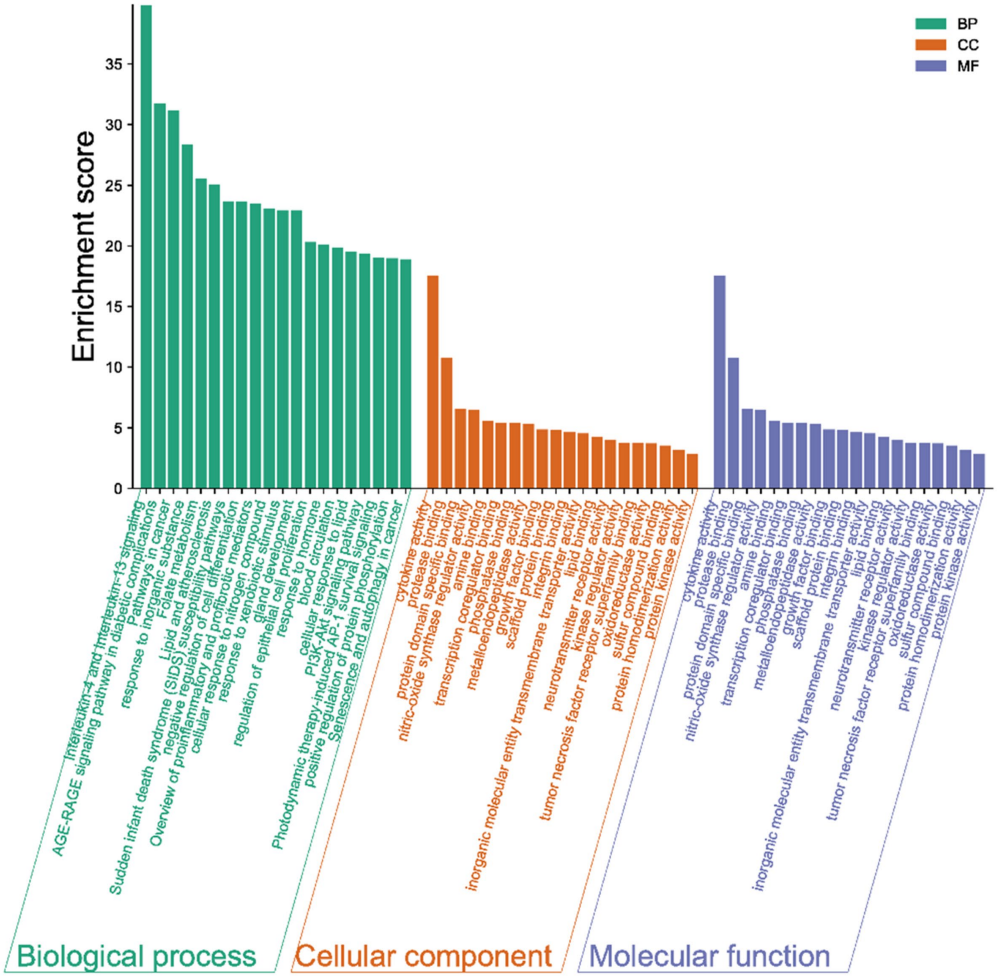

FIGURE 4
Gene ontology (GO) terms. The green bars represent the biological processes (BPs), while the orange refers to the cellular components (CCs), and the blue shows the molecular functions (MFs) of the genes. The vertical axis is the enrichment fractions.

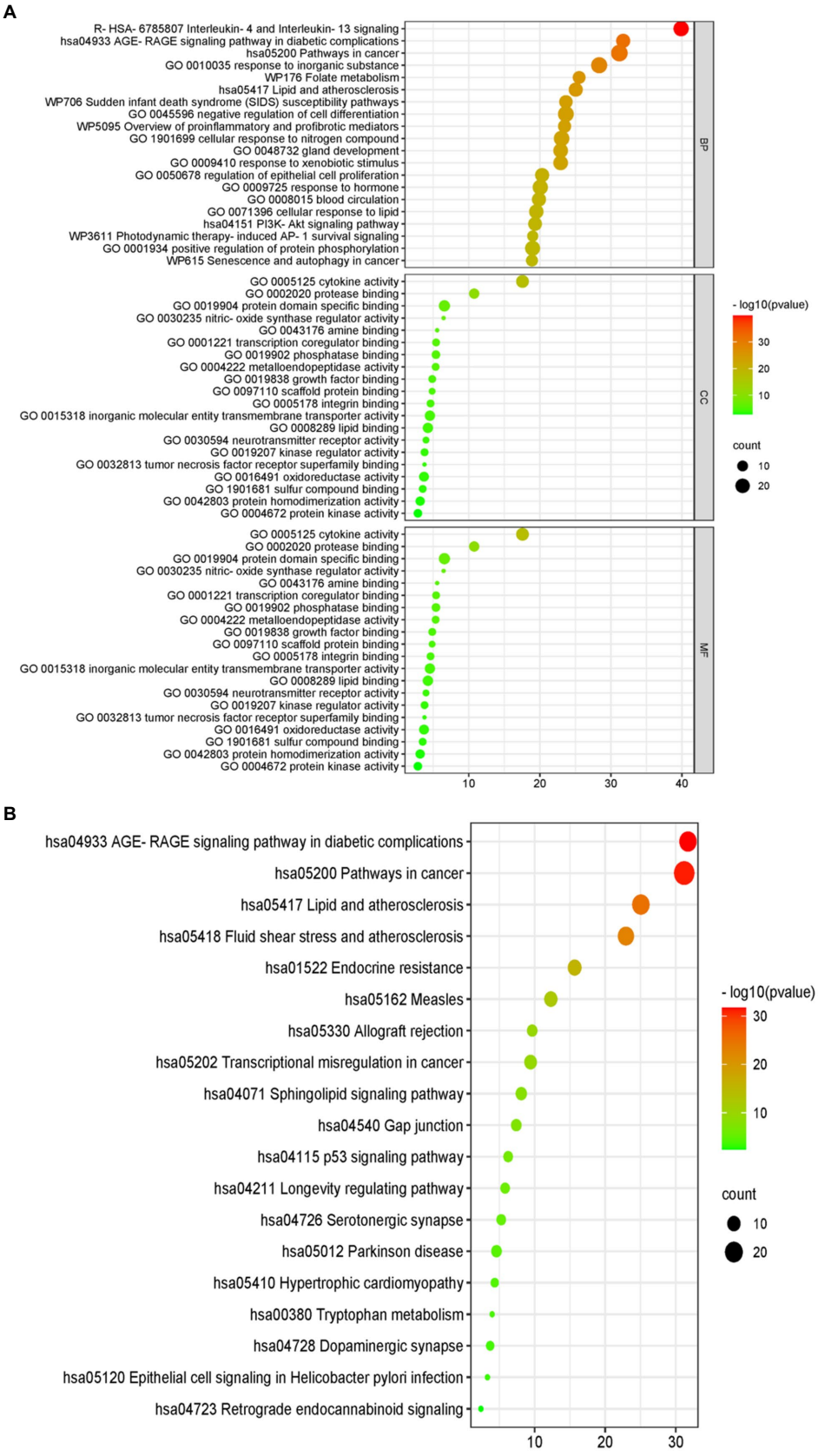

FIGURE 5
Gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses. **(A)** The GO analytic bubble diagram. **(B)** The KEGG analytic bubble diagram. The size of the circle represents the number of genes enriched in the pathway. The larger the circle, the greater the number of enriched proteins, and the color represents different *p*-values.

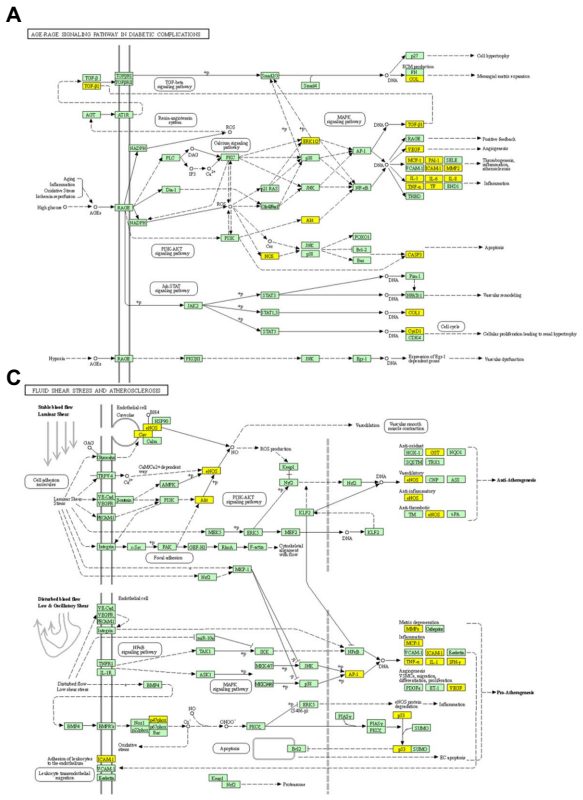

FIGURE 6
KEGG enrichment analysis pathway diagram. **(A)** The pathway map of AGE-RAGE signaling pathway in diabetic complications. **(B)** The pathway map of lipid and atherosclerosis. **(C)** The pathway map of fluid shear stress and atherosclerosis. The non-white targets in the pathway map are the intersection targets of ELJN and ISHL, while the yellow color is the possible targets present in the pathway as a result of KEGG enrichment analysis.

Identification of the protein–protein interaction (PPI) and active components–drug–disease intersection target–pathway networks

Next, we performed a PPI network analysis (Figure 7), and SCN5A, ESR1, PPARG, NOS3, GABRA1, and KCNH2 were the six gene targets with the most connected genes. However, according to the "combined_score" value, we obtained 20 targets (Supplementary Table S4).

We then mapped the ELJN active components–intersection target–pathway network using Cytoscape (version 3.9.1). We ranked the intersection targets according to the "degree" value for the top 10 intersection gene targets (Supplementary Tables S5, S6). Next, we compared the top 20 targets of each from the component–target network and the PPI network analysis, and the top 10 targets of the components–target–signaling pathway network and found that nitric oxide synthase 3 (NOS3) and AKT1 were visible in all three data sets, suggesting a strong association of NOS3 and AKT1 with ISHL during ELJN treatment.

In addition, we searched for components that are associated with these two genes and identified isorhamnetin, formononetin, kaempferol, quercetin, naringenin, oroxylin A, 7-methoxy-2-methyl isoflavone, Glepidotin A, Salvigenin, Skullcapflavone II, 5,2′-dihydroxy-6,7,8, trimethoxyflavone, coptisine, epiberberine, rivularin, sesamin, 5-hydroxy-7-methoxy-2-(3,4,5, trimethoxyphenyl) chromone, beta-sitosterol, acacetin, wogonin, and baicalein. After narrowing these down, we concluded that isorhamnetin, formononetin, kaempferol, quercetin, and baicalein were somehow associated with ISHL (Figure 8).

Molecular docking identification of ELJN components binding to NOS3 and AKT1

We then molecularly docked NOS3 and AKT1 with five ligands (isorhamnetin, formononetin, kaempferol, quercetin, and baicalein) and identified nine sets of docking results (Figure 9). The binding energies of isorhamnetin, formononetin, kaempferol, and quercetin to NOS3 were-9.8, −10.2, −9.7, and −9.9 kcal/mol, respectively, while the binding energies of kaempferol, quercetin, and baicalein to AKT1 were-6.1, −6.0, and −6.1 kcal/mol, respectively. It is generally a rule that a binding affinity below −4.5 kcal/mol indicates a weak binding capacity, while an affinity below-6 kcal/mol indicates a strong binding capacity. In our current data, this indicates that the binding between isorhamnetin, formononetin, or kaempferol vs. NOS3 or AKT1, quercetin vs. NOS3, and baicalein vs. AKT1 is stable and strong.

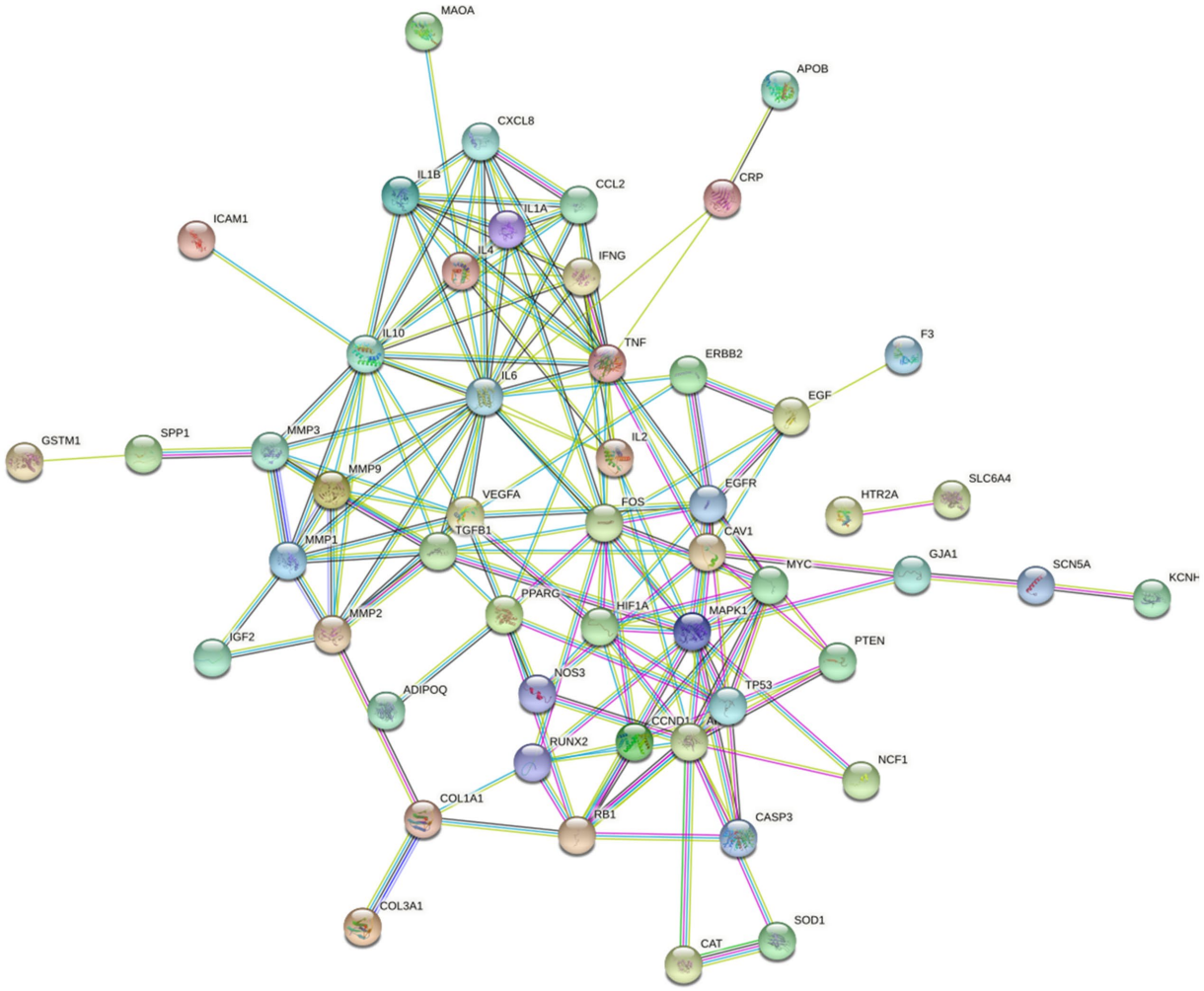

FIGURE 7
Protein–protein interaction (PPI) network. The more lines connected, the stronger the correlation.

Discussion

The precise etiology of ISHL remains to be defined, but multiple causes have been hypothesized, including vascular obstruction in the ear, viral infection, and/or labyrinthine membrane ruptures (25). Clinically, corticosteroids are the standard treatment course for patients with ISHL, although such a practice still has opposition as the effectiveness is relatively low (2). In China, ELJN is frequently prescribed to treat patients with ISHL by eliminating "the heat" from the liver to clear the dampness from orifices, in accordance with TCM theory (26). Indeed, the previous studies showed that ELJN had better anti-ISHL activity, especially in combination with dexamethasone than with dexamethasone alone (5), although the underlying molecular mechanism of ELJN action is unclear. Thus, our current study performed network pharmacology and molecular docking analyses to reveal the potential mechanism of ELJN in the treatment of ISHL. Our data showed that the ELJN components isorhamnetin and formononetin could target nitric oxide synthase 3 (NOS3), while the ELJN component baicalein could target AKT1, and the ELJN components kaempferol and quercetin could target both NOS3 and AKT1, as the party of the therapeutic effect of ELJN on ISHL.

Isorhamnetin, a component of ELJN, is also one of the most important active components in sea buckthorn fruit and ginkgo biloba (27). It is able to inhibit renal angiotensin-II-induced cardiac hypertrophy and fibrosis by manipulating transforming growth factor beta (TGF-β) signaling (28) or by altering the activity of the renal angiotensin system. Isorhamnetin also protected against concanavalin A-induced acute fulminant hepatitis (AFH) in a mouse model by inhibiting p38 phosphorylation and promoting PPAR-α expression, which in turn prevented the inflammatory responses and blocked cell apoptosis and autophagy in the mouse liver (29). In the current study, we identified that isorhamnetin could target NOS3, an enzyme localized in the endothelium that functions to synthesize nitric oxide (NO) for different biological activities (30), such as the promotion of vascular relaxation (31) and blood pressure control (32). Previous studies have shown that NOS3 deficiency could lead to the impairment of blood microcirculation (33). In contrast, an increase in NOS3 expression in brain ischemia–reperfusion injury improved and released neuronal injury but inhibited tissue inflammation, oxidative stress,

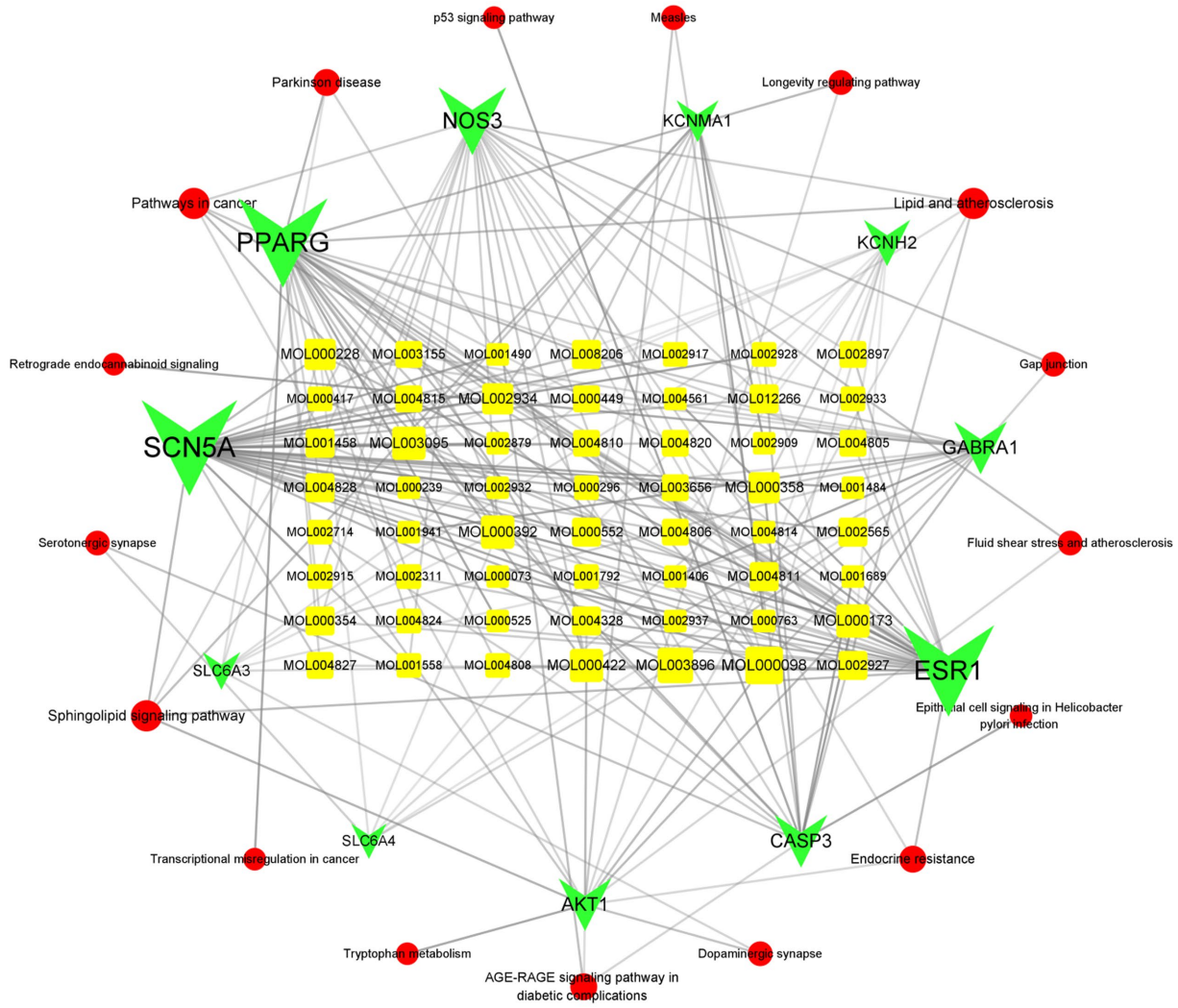

FIGURE 8
Active components–intersection target–signaling pathway network. The circular red color refers to the signal pathways, while the green color corresponds to the targets and the yellow color is the active component. The more lines connected, the stronger the correlation.

and apoptosis (34). Thus, we speculate that isorhamnetin in ELJN could target NOS3, thereby improving blood circulation in the cochlea and improving ISHL. However, such speculation requires further experimental validation.

The ELJN component formononetin is an isoflavone derived from the legume family. It is a member of the phytoestrogen class of compounds and clinically possesses antioxidative, anti-inflammatory, neuroprotective, and blood pressure-lowering activities (35). For example, formononetin has been shown to induce Kruppel-like factor 4 expression and nuclear translocation to inhibit inflammatory responses during atherosclerosis (36). In the current study, we found that formononetin could also target NOS3 in the treatment of ISHL.

In addition, the ELJN component baicalein is the most abundant active component in Scutellaria baicalensis with neuroprotective effects (37). Baicalein can attenuate neuroinflammatory responses by inhibiting the TLR4/NF-κB pathway (38, 39). Baicalein was able to modulate FOXO3a expression to inhibit reactive oxygen species (ROS) production in cardiac hypertrophy while also activating autophagy (40). Baicalein has the ability to scavenge oxygen-free radicals to protect DNA deoxyribose residues and repair double-stranded breaks (41), as well as inhibit inflammatory responses (42). Our current data showed that baicalein could bind to AKT1 in the treatment of ISHL. The Akt family of serine–threonine protein kinases consists of three isoforms, i.e., Akt1/PKB-α, Akt2/PKB-β, and Akt3/PKB-γ, to form the PI3K/Akt signaling to play an important role in the regulation of cell biology (43, 44). For example, AKT1 had a protective role in oxygen–glucose deprivation (OGD)-induced cochlear cell injury (45). High-density lipoprotein-induced increases in AKT phosphorylation protected against OGD-induced cell death (46). Therefore, we believe that baicalein exerts its role in reducing the inflammatory response by manipulating AKT1 activity, thereby protecting the auditory nerve.

Kaempferol, another active component in ELJN, is from a class of flavonoids found in a variety of vegetables and fruits, such as cauliflower, beans, tomatoes, strawberries, and grapes (47). Kaempferol possessed an inhibitory effect on the expression of oxidized low-density lipoprotein (oxLDL) and the development of

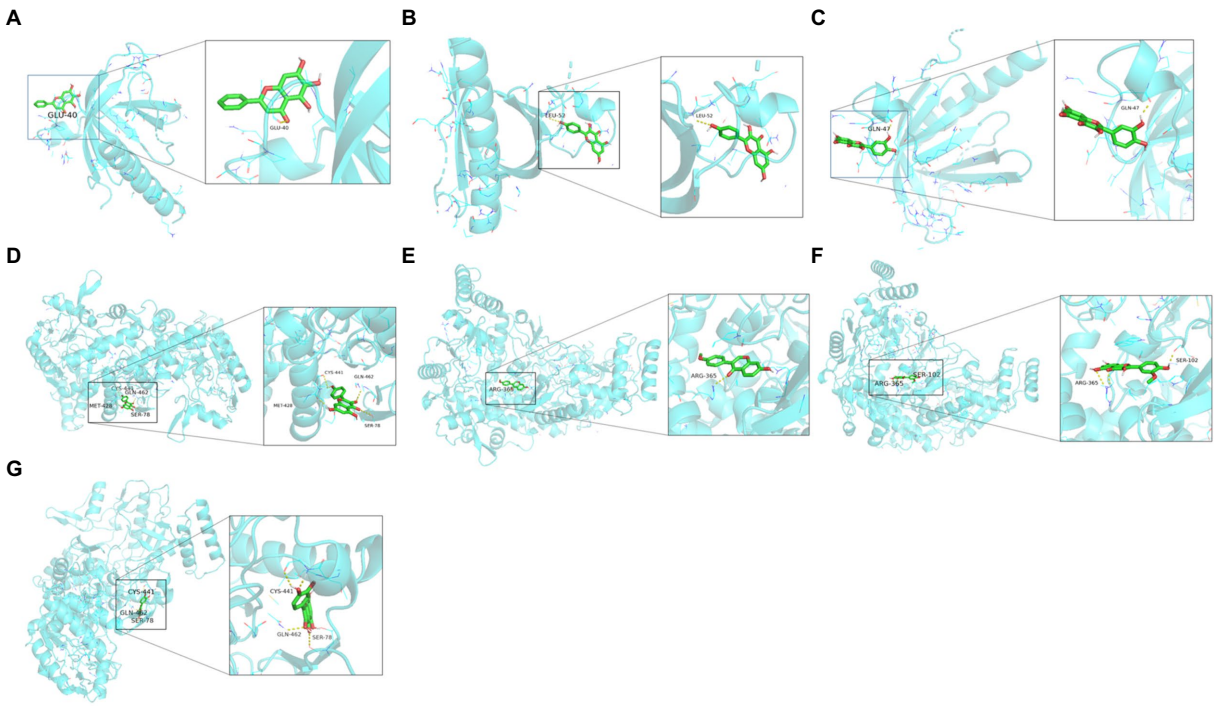

FIGURE 9
Molecular docking analytic data. **(A)** AKT1 docks with baicalein. **(B)** AKT1 docks with kaempferol. **(C)** AKT1 docks with quercetin. **(D)** NOS3 docks with kaempferol. **(E)** NOS3 docks with formononetin. **(F)** NOS3 docks with isorhamnetin. **(G)** NOS3 docks with quercetin. The blue molecular structure shows the target site, while the green molecular structure is the active component.

atherosclerosis, as well as an inhibitory effect on macrophage activation *via* CD36 inhibition (48). Kaempferol could prevent lipid peroxidation, protect hippocampal cells from oxidative damage (49), and inhibit ROS production to protect cells against oxidative stress (50). Kaempferol exerted its anti-inflammatory effects *via* the inhibition of NF-κB, MAPK, and Akt signaling (51). Our current data indicate that kaempferol binds to NOS3 and AKT1 in the context of ELJN-induced treatment of ISHL. Another active component of ELJN, quercetin, is a flavonoid found in various plants, including onions, apples, grapes, nuts, tea, and the bark of plants (52). Quercetin possesses anti-inflammatory and neuroprotective effects and activity in treating cardiovascular disease (53–55). Our current data speculated that the ELJN anti-ISHL activity could be a result of quercetin binding to NOS3 and AKT1.

Again, we found that naringenin, oroxylin A, 7-methoxy-2-methyl isoflavone, Glepidotin A, Salvigenin, Skullcapflavone II, 5,2′-dihydroxy-6,7,8, trimethoxyflavone, coptisine, epiberberine, rivularin, sesamin, 5-hydroxy-7-methoxy-2-(3,4,5, trimethoxyphenyl) chromone, beta-sitosterol, acacetin, and wogonin might have similar effects in the therapeutic process, but we excluded them after our screening, perhaps more evidence for their effects will be available later.

In conclusion, our network pharmacology and molecular docking analyses revealed the potential gene targets of both ELJN and ISHL. The effect of ELJN treatment on ISHL could be due to the ELJN components isorhamnetin, formononetin, baicalein, kaempferol, and quercetin binding to AKT1 and NOS3 to reduce inflammatory responses and damage to inner ear hair cells. Further studies are needed to experimentally confirm these data.

Data availbility statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

XS, YY, and YaS: conceptualization of the study. HZ and YW: data acquisition. CX and JQ: data analysis and processing. HZ, YW, and CX: software research. GL, YuS, JQ, LC, XS, YY, and YaS: supervision and design of this study. HZ, YW, and CX: preparation of the original draft of this manuscript. XS, YY, and YaS: manuscript revision, critical review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that this research was conducted in the absence of any commercial or financial support that could be considered a conflict of interest.

Publisher's note

Supplementary material

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Kathrine Jauregui-Renaud,
Mexican Social Security Institute (IMSS), Mexico

REVIEWED BY
Haibo Shi,
Shanghai Jiao Tong University, China
Norma De Oliveira Penido,
Federal University of São Paulo, Brazil
Daogong Zhang,
Shandong Provincial ENT Hospital, China

*CORRESPONDENCE
Yuehui Liu
✉ liuyuehuiclark@21cn.com
Maoli Duan
✉ maoli.duan@ki.se

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Efficacy of intratympanic or postauricular subperiosteal corticosteroid injection combined with systemic corticosteroid in the treatment of sudden sensorineural hearing loss: A prospective randomized study

Wen Xie[1], Niki Karpeta[2,3], Jiali Liu[1], Haisen Peng[1], Chunhua Li[1], Zhiling Zhang[1], Yuehui Liu[1]* and Maoli Duan[2,3]*

[1]Department of Otolaryngology Head and Neck Surgery, The Second Affiliated Hospital of Nanchang University, Nanchang, China, [2]Division of Ear, Nose and Throat Section, Department of Clinical Science, Intervention and Technology, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Department of Otolaryngology Head and Neck & Audiology and Neurotology, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

Objectives: This study aimed to investigate the efficacy and safety of intratympanic or postauricular subperiosteal glucocorticoid injection combined with systemic glucocorticoid in the treatment of sudden sensorineural hearing loss (SSNHL).

Methods: This study is a prospective randomized controlled study. This study included unilateral SSNHL patients who were hospitalized in our department between January 2020 and June 2021. Patients were randomly divided into three groups (groups A, B, and C). Patients in group A were treated with an intratympanic corticosteroid injection combined with systemic corticosteroid treatment, and patients in group B received a postauricular corticosteroid injection combined with systemic corticosteroid treatment. Patients in group C (control group) were treated with systemic corticosteroid alone. The case number of groups A, B, and C was 311, 375, and 369, respectively.

Results: There was no significant difference in gender distribution, the proportion of left and right affected ears, and the average interval from onset to treatment among the three groups ($P > 0.05$). However, there were significant differences in their average age, distribution of audiogram type, and hearing loss levels among them ($P < 0.01$). Our study shows that there was no significant difference in average hearing threshold improvement before and after treatment in the three groups ($P > 0.05$). Regarding the complications, in group A, 33 patients (10.6%) had a transient vertigo attack during tympanic injection, which lasted for ~1–3 min. In group B, 20 patients (6.43%) complained of pain at the injection site, which disappeared after 1–3 days. No other complications occurred in all the other patients.

Conclusion: The addition of intratympanic or postauricular corticosteroid to systemic steroids did not result in a significant effect on hearing recovery in SSNHL. No obvious complications occur in SSNHL patients treated with intratympanic injection or postauricular injection of corticosteroid.

Clinical trial registration: [chictr.org.cn], registration number: ChiCTR2100048762.

KEYWORDS

sudden sensorineural hearing loss, intratympanic injection, postauricular injection, corticosteroid, treatment

Introduction

Sudden sensorineural hearing loss (SSNHL) is an idiopathic emergency disease. The recommended treatments for SSNHL do not target the etiology of SSNHL specifically. As a result, a large number of patients cannot be cured completely despite comprehensive treatments. Therefore, it is an urgent challenge for clinicians to improve the treatment efficacy of SSNHL.

The adopted treatments of SSNHL by clinicians include systemic and local application of corticosteroids, vasodilators, defibrinogenating agents, thrombolytics, neurotrophic drugs, antioxidants, antivirals, and hyperbaric oxygen therapy. Currently, the widely accepted effective treatments are systemic and local use of corticosteroids, which are recommended by the latest Chinese and American SSNHL diagnosis and treatment guidelines (1, 2). The pharmacological mechanism of corticosteroids in the treatment of SSNHL has not been fully clarified, including systemic and local effects. The systemic effect is a systemic immunosuppressive response. Regarding local effects, the glucocorticoid exerts effects by combining receptors in the inner ear. These local effects of glucocorticoid include maintaining ion homeostasis in the inner ear, antioxidation, inhibiting apoptosis, downregulating local pro-inflammatory cytokines, and increasing cochlear blood flow (3).

Intratympanic corticosteroid injection for treating SSNHL was used for the first time in 1996 by Silverstein et al. (4). Since then, many clinicians have used this technology. The corticosteroids of the tympanic cavity can penetrate into the inner ear through the round window membrane. This mechanism has been confirmed in many animal experiments which showed that this technology can produce higher drug concentration in the perilymph than intravenous or oral administration (5, 6). After intratympanic injection, the corticosteroids are mainly distributed in the spiral ligament, basement membrane, Organ of Corti, and spiral ganglion (7). A prospective randomized controlled study conducted by Rauch et al. revealed that the effect of tympanic injection of corticosteroid and systemic medication is equivalent (8). Moreover, narrative and systematic reviews showed that there was a lack of a high-quality study to confirm the effectiveness of intratympanic corticosteroid injection for treating SSNHL (9, 10).

Although the effects of corticosteroid tympanic injection alone for treating SSNHL are controversial, there is some evidence that this technology could be used as a salvage treatment for SSNHL patients whose hearing do not restore after 14-day systematic treatment (11, 12). Therefore, intratympanic corticosteroid therapy is recommended by the SSNHL guidelines both in China and the United States as the salvage treatment for SSNHL. In addition to intratympanic corticosteroid treatment, postauricular subperiosteal corticosteroid injection is recommended by the latest Chinese guideline as a salvage procedure. At present, the mechanism of the drug entering the inner ear using this technology is not entirely clear and the speculated routes include circulation and local penetration routes (13). It is presumed that corticosteroids could be absorbed into the circulation *via* postauricular capillaries and lymphatic capillaries and transported to the inner ear *via* its arterial supply, and may also be transported to the inner ear through the bone suture of the auditory vesicle. The drug enters the outer lymph and consequently forms the osmotic gradient between the endolymph and perilymph to exert effects. Currently, the postauricular subperiosteal corticosteroid injection procedure is not mentioned in the American guideline. Therefore, further studies with large sample sizes are needed to evaluate the efficacy of this treatment regimen.

Currently, few reports focus on the treatment effect of local combined with systemic corticosteroid therapy for SSNHL, and most studies have focused on the efficacy of local corticosteroid administration as a salvage treatment for treating SSNHL. However, it is difficult for many patients to return to the hospital several times to receive salvage treatment, and they expect to achieve the best curative effect in the shortest time during hospitalization. In order to evaluate the efficacy of this combined treatment regimen as an initial treatment for SSNHL, we conducted this prospective randomized study. All enrolled SSNHL patients were divided into three groups: intratympanic corticosteroid injection combined with a systemic corticosteroid, postauricular subperiosteal corticosteroid injection combined with a systemic corticosteroid, and systemic corticosteroid treatment alone (control group). Since the prognostic factors of SSNHL include age, the interval from onset to treatment, type of audiometric curve, and degree of hearing loss, we first compared the baseline of clinical characteristics and pre-treatment hearing results of the patients. Then, we compared the hearing efficacy between the patients of the three groups with different audiometric-type SSNHL.

Materials and methods

Patients

In this randomized controlled study, we enrolled SSNHL patients hospitalized in the Second Affiliated Hospital of Nanchang University from January 2020 to June 2021. All patients underwent routine physical examination, general otorhinolaryngological examination, nervous system physical examination, pure tone

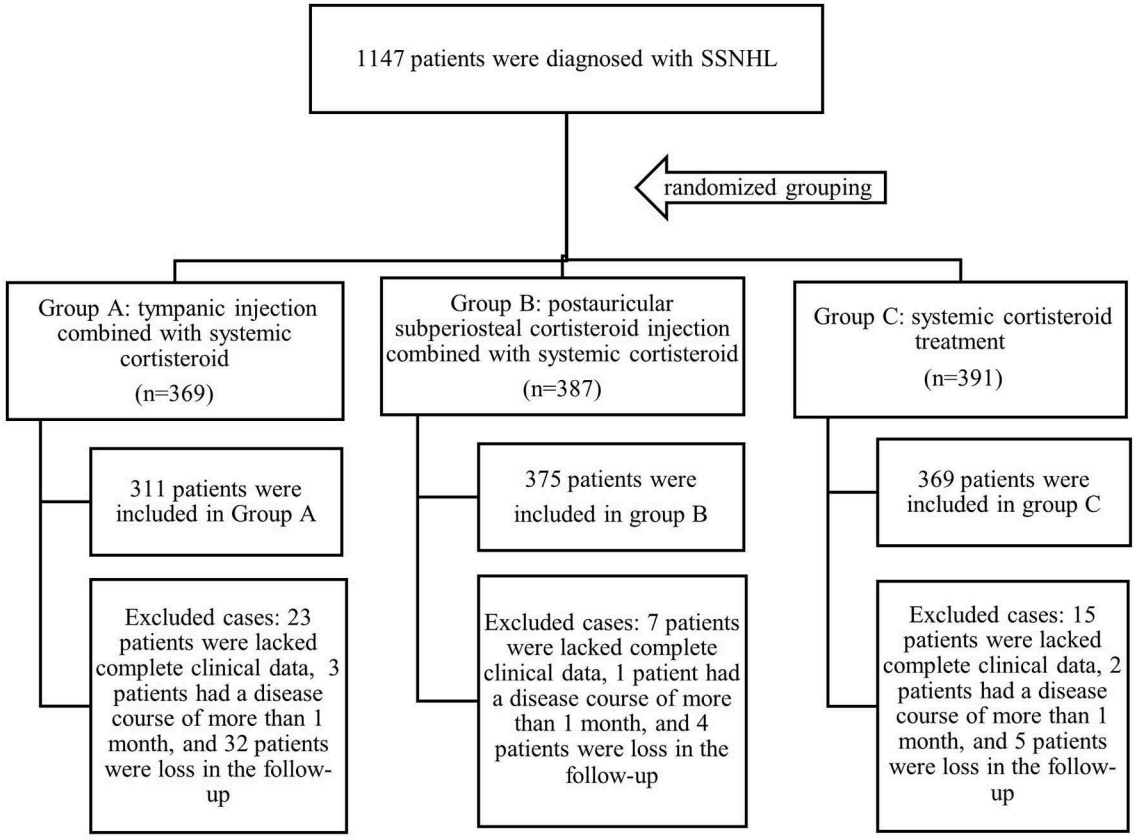

FIGURE 1
Flow gram of the study.

audiogram and tympanometry, laboratory examination, and brain magnetic resonance imaging (MRI) examination.

The study was performed in accordance with the ethical principles and approved by the Second Affiliated Hospital of Nanchang University Institutional Review Board. Written informed consent was obtained from all patients and/or their guardians.

Inclusion and exclusion criteria

Inclusion criteria

Inclusion criteria were as follows: (1) A diagnosis of unilateral SSNH. The diagnostic criteria were based on the latest guidelines revised by the American Academy of Otolaryngology-Head and Neck Surgery in 2019 (2). (2) The interval from onset to treatment was <1 month.

Exclusion criteria

Exclusion criteria were as follows: (1) patients with hearing loss due to other causes such as otitis media, Meniere's disease, otosclerosis, congenital deafness, presbycusis, vestibular schwannoma, and inner ear malformation. (2) The interval from onset to treatment was more than 1 month. (3) Patients who did not undergo standard treatment for 14 days and were discharged without restoring to normal hearing. (4) Patients who had previously received other treatment. (5) Patients with bilateral SSNHL. (6) Patients with contraindications of systemic corticosteroids, such as diabetes, gastrointestinal ulcers, mental disorders, and epilepsy. (7) Patients who dropped out of the study or were lost in follow-up. (8) Patients with insufficient medical record data were also excluded.

Patients who met the inclusion criteria were randomly divided into three groups. The patients of group A underwent intratympanic corticosteroid injection combined with systemic corticosteroid treatment; patients of Group B received postauricular subperiosteal corticosteroid injection combined with systemic corticosteroid treatment; and patients of group C were treated only with systemic corticosteroid. Due to the loss of follow-up or lack of complete clinical data, 311, 375, and 369 patients were included in groups A, B, and C, respectively (Figure 1).

Test procedure

All patients underwent a detailed clinical interview. Clinical data, demographic information, past medical history, and personal history were obtained. Routine physical examination,

TABLE 1 Protocol of SSNHL treatment.

Drugs	Treatment procedure
Prednisone	1 mg per kilogram of body weight (maximum dose 60 mg), orally/3 days. If it was effective, prednisone was continued to be taken for 2 days; if not effective, prednisone was stopped to be taken in the 4th day. Is this treatment according to American and Chinese guidelines? (yes)
Ginkgo biloba extract	105 mg, intravenously/14 days
Vitamin B1	10 mg, orally/14 days
Mecobalamin tablets	500 ug, orally/14 days
Mannitol	Only for patients with ascending-type hearing loss, 50 g, intravenously/14 days
Batroxobin	Only for patients with flat-type and profound hearing loss, 10 BU intravenously for the 1st day, when serum fibrinogen rises to over 1 g/L, intravenous infusion of 5 BU batroxobin again

otolaryngology examination, and audiological and laboratory tests were conducted in all subjects. MRI scanning of the ear and the brain was performed in all patients.

Treatment procedure

All patients received standard 14-day systemic treatment, which was based on the treatment recommended by the Chinese guidelines for SSNHL diagnosis and treatment revised in 2015 (1). All patients were prescribed 1 mg/kg of prednisone orally per day (maximum dose = 60 mg) for 3 days and were retested audiologically after that. If the treatment was effective, the patients continued to take prednisone for 2 more days; if no effect was seen on the audiogram, the treatment was discontinued on the fourth day. This treatment scheme was in accordance with the latest Chinese guidelines (1), which are revised on the basis of the 2010 German guidelines (14). This guideline recommended that SSNHL patients take prednisone for 3 days, with a total dose of 250 mg. Other medications included antioxidants, neurotrophic, and defibrinogenating agents. The treatment procedure is presented in Table 1.

Patients of group A underwent intratympanic dexamethasone injection under otoendoscopy. The procedure was as follows: the patient lay in the lateral position with the ear to be injected upward. After local anesthesia with 1% tetracaine, 0.5 ml of physiological saline and 5 mg of dexamethasone were injected into the middle ear after puncture of the anteroinferior or posteroinferior part of the tympanic membrane (Figure 2). Then, the patient remained still for ~30 min after injection. This procedure was conducted on the first day of treatment and then once every 2 days, a total of four times.

In group B, postauricular subperiosteal methylprednisolone injection was performed in all patients. The procedure was as follows: the patient sat on the chair. After the postauricular skin was disinfected, 40 mg (1 ml) of methylprednisolone was injected at the postauricular site. The injection site was located 0.5 cm behind the posterior sulcus of the affected ear and was level with the posterosuperior part of the external auditory meatus (Figure 3).

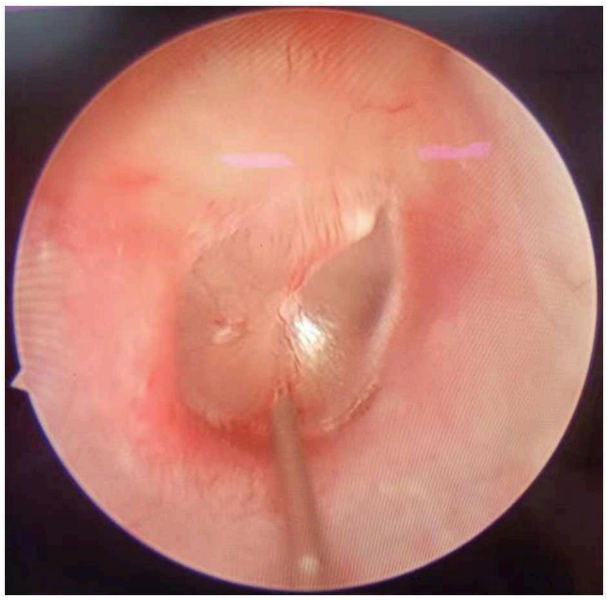

FIGURE 2
Intratympanic dexamethasone injection for SSNHL patient.

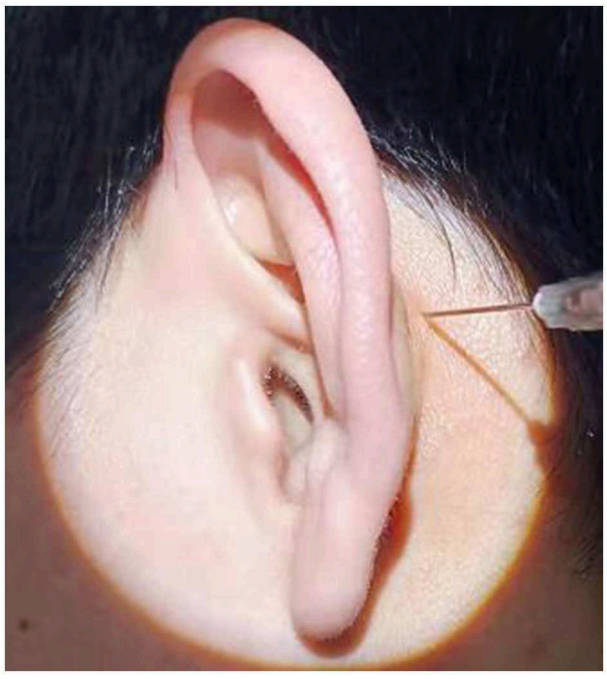

FIGURE 3
Postauricular subperiosteal methylprednisolone injection for SSNHL patient.

After the injection, the injection point was compressed for 5 min. This procedure was performed on the first day of treatment and then once every 2 days, a total of four times.

All patients' hearing was evaluated with pure tone audiogram and tympanometry. All hearing tests were carried out by the same

TABLE 2 Classification and standard of hearing efficacy.

Classification	Standard
Complete recovery	The hearing threshold at hearing impairment frequency is within normal limits, or reached to the hearing level of unaffected ear, or reached to the hearing level of affected ear's initial hearing
Significantly effective	>30 dB HL improvement at hearing impairment frequency
Effective	15- to 30 dB HL improvement at hearing impairment frequency
Ineffective	<15 dB HL improvement at hearing impairment frequency

audiologist. Air and bone conduction was assessed at frequencies of 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz, and 8 kHz.

Pure tone audiogram (PTA) was calculated by averaging air conduction thresholds at 0.5, 1, 2, and 4 kHz (15). The hearing loss levels were categorized into four grades: mild (26–40 dB HL), moderate (41–55 dB HL), moderate to severe (56–70 dB HL), severe (71–90 dB HL), and profound (>90 dB HL) (15). Audiogram patterns were classified into five types: ascending (the average threshold of 0.25–0.50 kHz was 20 dB higher than that of 4–8 kHz), descending (the average threshold of 4–8 kHz was 20 dB higher than that of 0.25–0.50 kHz), flat (all frequencies present similar thresholds and the hearing threshold was below 80 dB HL), profound (all frequencies show similar threshold and the hearing threshold was over 80 dB HL), and concave or convex type (average hearing degree of the mid-tone frequency was 20 dB higher than low and high frequencies) (1).

In addition to calculating patients' PTA, we evaluated patients' hearing by calculating the average air conduction hearing threshold at hearing impairment frequency. The patients' hearing of the affected ear was assessed by referring to the unaffected ears' hearing or their affected ears' initial hearing. Referring to the 2015 Chinese guidelines (1), the average air conduction hearing threshold at hearing impairment frequency was calculated as follows: among patients with flat-type or profound hearing loss, the hearing threshold at hearing impairment frequency was equivalent to the average hearing threshold of all frequencies. For the patients with low-frequency or high-frequency hearing loss, it was calculated as the average hearing threshold at hearing impairment low or high frequencies.

With reference to the Chinese guidelines for the diagnosis and treatment of SSNHL revised in 2015 (1), by comparing the hearing results before and 6 months after treatment, the hearing recovery of all patients was categorized into four grades: complete recovery, effective, significantly effective, and ineffective, as shown in Table 2.

Follow-up procedure

We tested the patients' hearing on the seventh day and 1 day before discharge after treatment, and retest their hearing immediately as long as they reported hearing improvement during hospitalization. If their hearing recovered, the treatment was terminated. If their hearing did not recover to normal, they would be instructed to continue taking 7.5 mg of *Ginkgo biloba* extract, 10 mg of vitamin B1, and 0.5 mg of Mecobalamin orally three times a day for 30 days. The second time of hearing examination was 30 days after discharge. If their hearing completely reached normal, drugs would be discontinued. If their hearing did not recover completely, the same cure would be given for 2 months. Three months after discharge, all treatments were terminated and patients revisited our hospital. The last follow-up time was 6 months after treatment, and their hearing was reevaluated and was taken as the final hearing result to evaluate the hearing effect. During the follow-up period, in addition to evaluating the patient's hearing, the general otorhinolaryngological examination and otoendoscopy were performed at each follow-up visit.

Statistical analysis

Quantitative data were presented as mean ± standard deviation for comparison, while frequency data were presented as cases and the ratio for comparison. An analysis of variance (ANOVA) was performed for the data conforming to normal distribution and homogeneity, while a Kruskal–Wallis test was conducted for those not conforming to normal distribution or homogeneity. Categorical data were shown as percentages and compared using the chi-square test. The Fisher exact test was used when expected counts in the chi-square test were insufficient. All analyses were conducted using SPSS version 25 for Windows. All statistical tests were two-sided, and statistically significant levels were set at a P-value of 0.05.

Result

Clinical characteristics and pre- and post-treatment hearing results of the patients in the three groups

Table 3 shows the clinical characteristics and post-treatment hearing results of the patients in the three groups. The case number of groups A, B, and C was 311, 375, and 369, respectively. The mean age of the patients in the three groups was 46.35 ± 15.104, 44.79 ± 13.893, and 41.85 ± 16.185 years. The number of male patients in the three groups was 151, 211, and 272, and the number of female patients in the three groups was 160, 164, and 197, respectively. There was a significant difference in the average ages of the three groups ($P < 0.01$). However, no significant difference existed in patients' gender distribution, the proportion of affected left or right ears, and the average interval from onset to treatment between the three groups ($P > 0.05$).

In terms of hearing results, a significant difference existed in the distribution of pre-treatment auditory curve type and degree of hearing loss among the three groups ($P < 0.01$). The pre- and post-treatment PTA and the PTA gap of the patients in the three groups were also significantly different ($P < 0.05$). The biggest pre- and post-treatment PTA gap existed in group B, followed by group A and group C. In addition, the pre- and post-treatment average hearing thresholds at the impairment frequency in patients of the three groups were significantly different ($P < 0.05$). As for

TABLE 3 Clinical characteristics and pre- and post-treatment hearing of patients of the three groups.

Characteristics	Group A ($n = 311$)	Group B ($n = 375$)	Group C ($n = 369$)	Statistical values	*P*-values
Age (years), mean ± standard deviation	46.35 ± 15.104	44.79 ± 13.893	41.85 ± 16.185	−4.915	0.000※
Gender					
Male [cases (%)]	151 (48.6)	211 (56.3)	172 (46.6)	7.686	0.021&
Female [cases (%)]	160 (51.4)	164 (43.7)	197 (53.4)		
Side of affected ear					
Left [cases (%)]	149 (47.9)	194 (51.7)	189 (51.2)	1.137	0.566&
Right [cases (%)]	162 (52.1)	181 (48.3)	180 (48.8)		
Interval from onset to treatment (days), mean ± standard deviation	7.59 ± 7.104	5.076 ± 5.139	7.07 ± 7.014	−0.577	0.564※
Type of auditory curve before treatment					
Ascending type [cases (%)]	18 (5.8)	53 (14.1)	135 (36.6)	172.677	0.000&
Descending type [cases (%)]	14 (4.5)	16 (4.3)	21 (5.7)		
Flat type [cases (%)]	175 (56.3)	117 (31.2)	144 (39)		
Profound type [cases (%)]	104 (33.4)	189 (50.4)	69 (18.7)		
Degree of hearing loss before treatment					
Mild [cases (%)]	17 (5.5)	20 (5.3)	107 (29)	164.308	0.000&
Moderate [cases (%)]	57 (18.3)	53 (14.1)	99 (26.8)		
Moderate to severe [cases (%)]	65 (20.9)	63 (16.8)	52 (14.1)		
Severe [cases (%)]	69 (22.2)	98 (26.1)	50 (13.6)		
Profound [cases (%)]	103 (33.1)	141 (37.6)	61 (16.5)		
Pre- and post-treatment hearing results					
Pre-treatment PTA (dB, HL)	76.998 ± 28.708	79.194 ± 30.428	53.677 ± 33.309	134.486	0.000※
Post-treatment PTA (dB, HL)	57.727 ± 31.177	56.689 ± 34.151	38.692 ± 31.134	92.206	0.000※
PTA gap (dB, HL)	19.272 ± 21.420	22.505 ± 22.893	14.985 ± 17.334	17.715	0.000※
Pre-treatment average hearing threshold at hearing impairment frequency (dB, HL)	78.302 ± 25.706	81.885 ± 25.983	61.132 ± 27.403	64.503	0.000#
Post-treatment average hearing threshold at hearing impairment frequency (dB, HL)	59.097 ± 29.614	58.405 ± 32.576	42.625 ± 29.490	74.846	0.000※
Hearing gap (dB, HL)	19.205 ± 20.115	23.479 ± 21.740	18.507 ± 16.681	10.207	0.006※
Hearing efficacy					
Complete recovery [cases (%)]	46 (14.8)	85 (22.7)	165 (44.6)	94.127	0.000&
Significant effective [cases (%)]	53 (17)	85 (22.7)	40 (10.8)		
Effective [cases (%)]	65 (20.9)	62 (16.5)	42 (11.4)		
Ineffective [cases (%)]	147 (47.3)	143 (38.1)	123 (33.2)		

#Variance Analysis.
&Chi-square test.
※Kruskal–Wallis test.

the pre- and post-treatment gap of hearing thresholds at hearing impairment frequency, the largest one existed in group B (23.479 ± 21.740 dB HL), followed by group A (19.205 ± 20.115 dB, HL) and group C (18.507 ± 16.681 dB, HL). This gap was statistically significant ($P < 0.05$). In terms of grading of hearing efficacy, the highest one was in patients of group C (66.8%), followed by group B (61.9%) and group A (52.7%) (Figure 4).

Efficacy of different topical corticosteroid administration methods in patients with different auditory types

The baseline of patients in the three groups including the average age, gender distribution, and the distribution of auditory types and hearing degrees was inequivalent, which may affect the

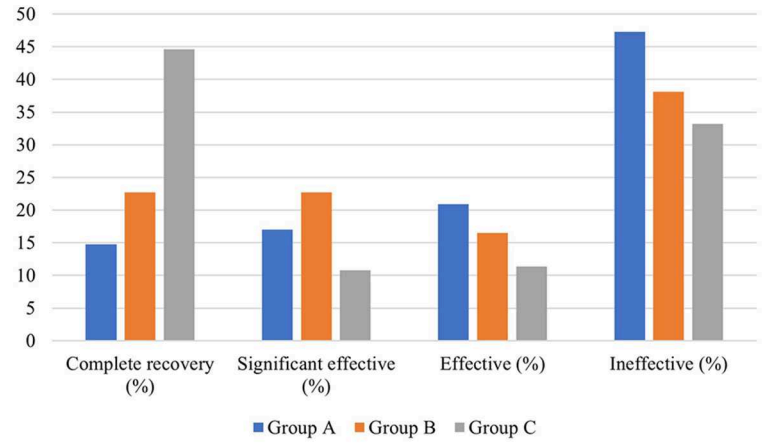

FIGURE 4
Hearing efficacy of SSNHL patients in the three groups.

post-treatment hearing effect. Therefore, we analyzed the efficacy of SSNHL patients with different audiogram-type SSNHL.

Efficacy of different local corticosteroids combined with systemic corticosteroid administration in patients with ascending-type SSNHL

There was no significant difference in average age, gender distribution, and average interval from onset to treatment among patients in the three groups ($P > 0.05$). In terms of hearing results, a significant difference existed in the pre- and post-treatment average hearing threshold at the hearing impairment frequency among the patients in the three groups ($P < 0.05$), but no significant difference was observed in the gap between pre- and post-treatment average hearing threshold at the hearing impairment frequency ($P > 0.05$), which were 17.454 ± 15.166 dB, 22.296 ± 14.959 dB, and 18.91 ± 13.142 dB, respectively. However, there was a significant difference in the proportion of patients with different hearing efficacy grading in the three groups ($P < 0.05$). Furthermore, the hearing recovery rate of patients in group C was higher than those in the other two groups (Table 4, Figure 5).

Efficacy of different local glucocorticoids combined with systemic glucocorticoid administration in patients with descending-type SSNHL

There was no significant difference in the average age, gender distribution, average interval from onset to treatment, and distribution of pre-treatment hearing loss degree among patients in the three groups ($P > 0.05$). In addition, no significant difference existed in the pre- and post-treatment average hearing threshold at the hearing impairment frequency among patients of the three groups ($P > 0.05$), as well as in the gap of the pre- and post-treatment average hearing threshold at the hearing impairment frequency between them ($P > 0.05$). Similarly, there was no significant difference in the proportion of patients with different hearing efficacy grading among patients in the three groups ($P > 0.05$) (Table 5, Figure 6).

Efficacy of different local corticosteroids combined with systemic corticosteroid administration in patients with flat-type SSNHL

There was no significant difference in average age, gender distribution, and average interval from onset to treatment among patients in the three groups ($P > 0.05$), but there was a significant difference in the degree of hearing loss before treatment and pre- and post-treatment average hearing threshold at the hearing impairment frequency among patients in the three groups ($P < 0.05$). However, no significant difference was observed in the gap between the pre- and post-treatment average hearing threshold at the hearing impairment frequency ($P > 0.05$). Moreover, there was no significant difference in the proportion of patients with different hearing efficacy grading among patients in the three groups ($P > 0.05$) (Table 6, Figure 7).

Efficacy of different local corticosteroids combined with systemic corticosteroid administration in patients with profound SSNHL

There was no significant difference in average age, gender distribution, and average interval from onset to treatment among patients in the three groups ($P > 0.05$). Regarding the hearing result, there was a significant difference in the pre-treatment average hearing threshold at the hearing impairment

TABLE 4 Clinical characteristics and hearing efficacy of patients with ascending-type SSNHL in the three groups.

Characteristics	Group A ($n = 18$)	Group B ($n = 53$)	Group C ($n = 135$)	Statistical values	*P*-values
Age (years), mean ± standard deviation	41.39 ± 12.363	39.45 ± 11.533	38.23 ± 12.090	4.041	0.07[#]
Male [cases (%)]	6 (33.3)	28 (52.8)	46 (57.5)	5.888	0.053[&]
Female [cases (%)]	12 (66.7)	25 (47.2)	89 (70.6)		
Interval from onset to treatment (days), mean ± standard deviation	10.833 ± 8.932	8.953 ± 4.081	8.222 ± 6.180	9.159	0.1[※]
Degree of hearing loss before treatment					
Mild [cases (%)]	3 (16.7)	12 (22.6)	69 (51.1)	27.687	0.000[@]
Moderate [cases (%)]	12 (66.7)	28 (52.8)	59 (43.7)		
Moderate to severe [cases (%)]	3 (16.7)	10 (18.9)	7 (5.2)		
Severe [cases (%)]	0 (0)	3 (5.7)	0 (0)		
Profound [cases (%)]	0 (0)	0 (0)	0 (0)		
Pre- and post-treatment hearing results					
Pre-treatment average hearing threshold at hearing impairment frequency (dB, HL)	49.097 ± 7.983	49.048 ± 10.270	41.744 ± 8.122	16.407	0.000[#]
Post-treatment average hearing threshold at hearing impairment frequency (dB, HL)	31.643 ± 14.759	26.753 ± 14.114	22.834 ± 12.596	4.481	0.012[#]
Hearing gap (dB, HL)	17.454 ± 15.166	22.296 ± 14.959	18.91 ± 13.142	1.395	0.25[#]
Hearing efficacy					
Completely recovery [cases (%)]	7 (38.9)	37 (69.8)	116 (85.9)	26.365	0.000[@]
Significantly effective [cases (%)]	0 (0)	1 (1.9)	0 (0)		
Effective [cases (%)]	3 (16.7)	6 (11.3)	3 (2.2)		
Ineffective [cases (%)]	8 (44.4)	9 (17)	16 (11.9)		

[#]Variance Analysis.
[&]Chi-square test.
[※]Kruskal–Wallis test.
[@]Fisher exact test.

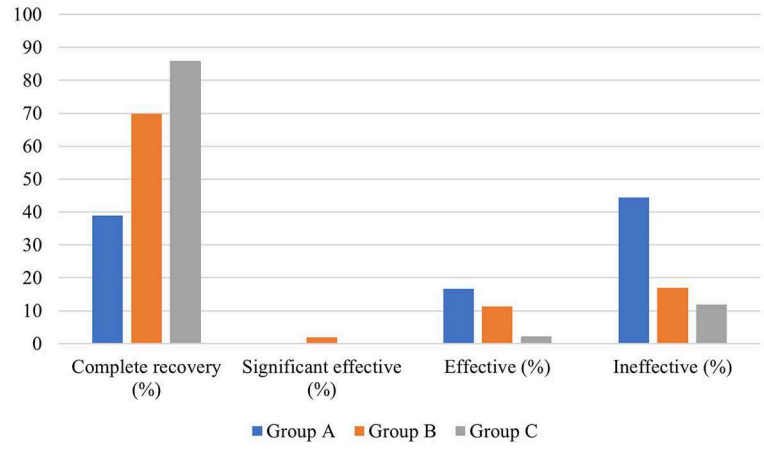

FIGURE 5
Hearing efficacy of patients with ascending-type SSNHL in the three groups.

frequency ($P < 0.05$), but no significant difference in the post-treatment average hearing threshold at the hearing impairment frequency, as well as the pre- and post-treatment gap at the hearing impairment frequency between the three groups ($P > 0.05$). Moreover, there was no significant difference in the proportion of patients with different hearing efficacy grading among patients in the three groups ($P > 0.05$) (Table 7, Figure 8).

TABLE 5 Clinical characteristics and hearing efficacy of patients with descending-type SSNHL in the three groups.

Characteristics	Group A ($n = 14$)	Group B ($n = 16$)	Group C ($n = 21$)	Statistical values	*P*-values
Age (years), mean ± standard deviation	43.5 ± 13.794	36.44 ± 3.306	34.24 ± 15.109	1.845	0.169[#]
Male [cases (%)]	9 (64.3)	9 (56.3)	13 (60.8)	0.221	0.895[&]
Female [cases (%)]	5 (35.7)	7 (43.8)	8 (38.1)		
Interval from onset to treatment (days), mean ± standard deviation	9.93 ± 10.011	6.19 ± 7.185	8.71 ± 8.684	0.75	0.478[#]
Degree of hearing loss before treatment					
Mild [cases (%)]	0 (0)	1 (6.3)	1 (4.8)	6.57	0.6[@]
Moderate [cases (%)]	5 (35.7)	3 (18.8)	7 (33.3)		
Moderate to severe [cases (%)]	4 (28.6)	3 (18.8)	6 (28.6)		
Severe [cases (%)]	1 (7.1)	5 (31.3)	5 (23.8)		
Profound [cases (%)]	4 (28.6)	4 (25)	2 (9.5)		
Pre- and post-treatment hearing results					
Pre-treatment average hearing threshold at hearing impairment frequency (dB, HL)	68.095 ± 19.575	74.792 ± 22.679	66.111 ± 20.817	0.804	0.453[#]
Post-treatment average hearing threshold at hearing impairment frequency (dB, HL)	53.452 ± 27.563	55.547 ± 21.703	52.738 ± 27.846	0.55	0.947[#]
Hearing gap (dB, HL)	14.642 ± 19.814	19.244 ± 20.249	13.373 ± 11.348	0.396	0.82[※]
Hearing efficacy					
Completely recovery [cases (%)]	2 (14.3)	4 (25)	11 (52.4)	9.504	0.098[@]
Significantly effective [cases (%)]	1 (7.1)	3 (18.8)	0 (0)		
Effective [cases (%)]	2 (14.3)	2 (12.5)	1 (4.8)		
Ineffective [cases (%)]	9 (64.3)	7 (43.8)	9 (42.9)		

[#]Variance Analysis.
[&]Chi-square test.
[※]Kruskal–Wallis test.
[@]Fisher exact test.

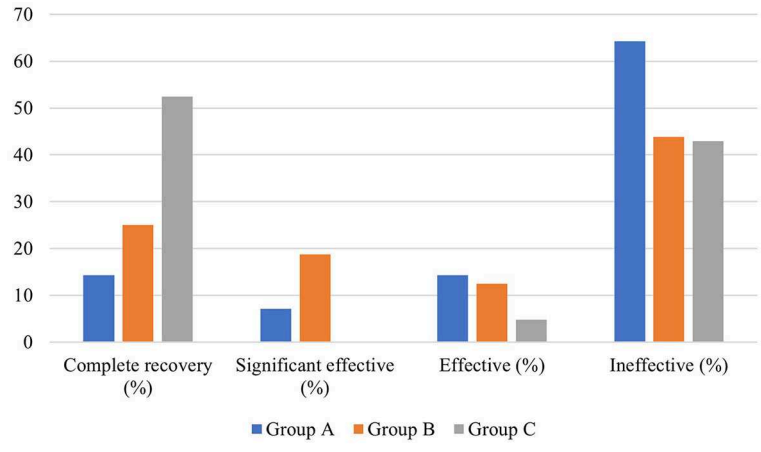

FIGURE 6
Hearing efficacy of patients with descending-type SSNHL in the three groups.

Complications and follow-up results

In group A, 33 patients (10.6%) had a transient vertigo attack during tympanic injection, which lasted for ~1–3 min; 20 patients felt earache, lasting for 1–3 days. In group B, 18 patients (4.8%) complained of swelling and pain at the injection site, which disappeared within 2 days. No obvious complications such as tympanic membrane perforation or acute and chronic

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TABLE 6 Clinical characteristics and hearing efficacy of patients with flat-type SSNHL in the three groups.

Characteristics	Group A ($n = 175$)	Group B ($n = 117$)	Group C ($n = 144$)	Statistical values	*P*-values
Age (years), mean ± standard deviation	47.99 ± 14.637	46.32 ± 13.927	45.76 ± 15.854	0.976	0.378[#]
Gender					
Male [cases (%)]	85 (48.6)	68 (58.1)	82 (56.9)	3.375	0.185[&]
Female [cases (%)]	90 (51.4)	49 (41.9)	62 (43.1)		
Interval from onset to treatment (days), mean ± standard deviation	7.897 ± 6.8	5.56 ± 5.000	7.167 ± 7.318	4.697	0.095[※]
Degree of hearing loss before treatment					
Mild [cases (%)]	14 (8)	7 (6.0)	37 (25.7)	32.261	0.000[@]
Moderate [cases (%)]	40 (22.9)	23 (19.7)	33 (22.9)		
Moderate to severe [cases (%)]	58 (33.1)	49 (141.9)	39 (27.1)		
Severe [cases (%)]	61 (34.9)	38 (32.5)	35 (24.3)		
Profound [cases (%)]	2 (1.1)	0 (0)	0 (0)		
Pre- and post-treatment hearing results					
Pre-treatment average hearing threshold at hearing impairment frequency (dB, HL)	64.237 ± 15.242	63.511 ± 13.458	56.266 ± 17.128	18.492	0.000[※]
Post-treatment average hearing threshold at hearing impairment frequency (dB, HL)	46.559 ± 20.059	42.652 ± 20.367	39.683 ± 18.676	4.884	0.008[#]
Hearing gap (dB, HL)	17.679 ± 19.517	20.859 ± 19.253	16.583 ± 16.410	4.097	0.129[※]
Hearing efficacy					
Completely recovery [cases (%)]	34 (19.4)	34 (29.1)	36 (25)	5.274	0.509[&]
Significantly effective [cases (%)]	22 (12.6)	13 (11.1)	18 (12.5)		
Effective [cases (%)]	34 (19.4)	21 (17.9)	20 (13.9)		
Ineffective [cases (%)]	85 (48.6)	49 (41.9)	70 (48.6)		

[#]Variance Analysis.
[&]Chi-square test.
[※]Kruskal–Wallis test.
[@]Fisher exact test.

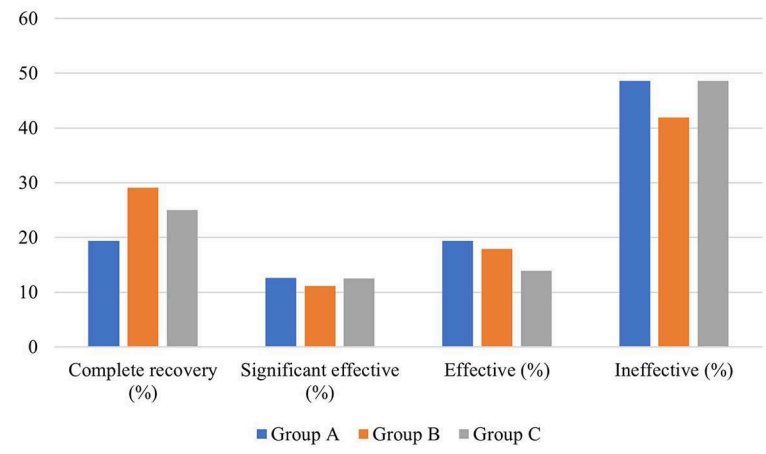

FIGURE 7
Hearing efficacy of patients with flat-type SSNHL in the three groups.

TABLE 7 Clinical characteristics and hearing efficacy of patients with profound SSNHL in the three groups.

Characteristics	Group A ($n = 104$)	Group B ($n = 189$)	Group C ($n = 69$)	Statistical values	*P*-values
Age (years), mean ± standard deviation	47.36 ± 16.327	46.71 ± 13.618	51.86 ± 15.855	6.413	0.052※
Gender					
Male [cases (%)]	52 (50)	106 (56.1)	31 (44.9)	2.807	0.246&
Female [cases (%)]	52 (50)	83 (43.9)	38 (55.1)		
Interval from onset to treatment (days), mean ± standard deviation	6.365 ± 6.614	7.719 ± 5.292	8.014 ± 7.279	10.593	0.061※
Pre- and post-treatment hearing results					
Pre-treatment average hearing threshold at hearing impairment frequency (dB, HL)	108.397 ± 11.119	102.979 ± 14.181	107.705 ± 13.579	12.434	0.002※
Post-treatment average hearing threshold at hearing impairment frequency (dB, HL)	85.705 ± 26.645	77.302 ± 31.060	84.408 ± 28.868	5.727	0.057※
Hearing gap (dB, HL)	22.692 ± 21.616	25.676 ± 24.680	23.366 ± 23.468	0.629	0.534#
Hearing efficacy					
Completely recovery [cases (%)]	3 (2.9)	10 (5.3)	2 (2.9)	4.773	0.573&
Significantly effective [cases (%)]	30 (28.8)	68 (36)	22 (31.9)		
Effective [cases (%)]	26 (25)	33 (17.5)	17 (24.6)		
Ineffective [cases (%)]	45 (43.3)	78 (41.3)	28 (40.6)		

#Variance Analysis.
&Chi-square test.
※Kruskal–Wallis test.
@Fisher exact test.

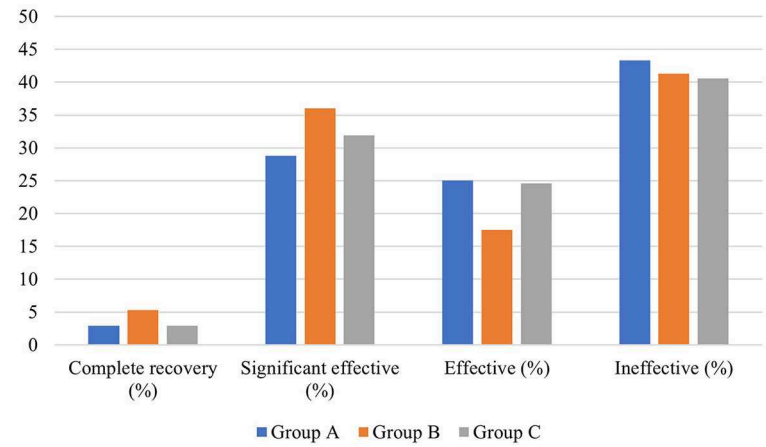

FIGURE 8
Hearing efficacy of patients with profound SSNHL in the three groups.

otitis media occurred in patients of group A during follow-up. In addition, there were no complications in all other patients during follow-up.

Discussion

The possible prognostic factors of SSNHL include the patient's age, the audiogram type, the degree of hearing loss, and the interval from onset to treatment (1, 16). The cofactors including the average age, gender distribution, and the distribution of auditory types and hearing degrees in the three groups were inequivalent, so we analyzed the efficacy of SSNHL patients with different audiogram-type SSNHL. It is reported that comparing patients with other types of audiometric curves, patients with low-frequency hearing loss may have a better prognosis (1, 17). In 2015, a Chinese multicenter study showed that the curative rate of patients with low-frequency hearing loss could be as high as 90.73%, whereas, in patients with high-frequency hearing loss, the number was only 65.96% (18).

The pathogenesis of SSNHL with various audiogram types may be different, which may explain this discrepancy. For example, the proposed pathogenesis of low-frequency hearing loss may be inner ear hydrops; the high-frequency hearing loss may be due to hair cell injury; the flat-type hearing loss is mostly caused by stria vascularis dysfunction or inner ear vasospasm; and the etiology of profound hearing loss is inner ear vascular embolism or thrombosis (14).

The effectiveness of intratympanic injection combined with systemic corticosteroids for treating SSNHL is still controversial. Several researchers showed that the effect of intratympanic combined with systemic corticosteroid therapy was better than that of systemic corticosteroid administration alone (19, 20). For example, a recent meta-analysis study result showed that the treatment effects ranked from high to low were as follows: intravenous, intratympanic corticosteroid, intravenous combined with an oral corticosteroid, intratympanic corticosteroid, intravenous corticosteroid, oral corticosteroid, and placebo (19). The results of animal experiments demonstrated that through intratympanic corticosteroid route, more drugs could be delivered into the inner ear, longer therapeutic window and more effective result could be achieved than by intravenous or intratympanic injection route alone in the pharmacokinetics (21). Therefore, researchers concluded that the curative effect of the combination of corticosteroid might be better than that of intravenous or intratympanic corticosteroid therapy alone. Indeed, theoretically, a blood–labyrinth barrier may limit the therapeutic agents permeating into the inner ear, and combined corticosteroid administration may reach higher drug concentrations and better effects. However, a prospective randomized study showed that the recovery rates in the patients with combined treatment and intratympanic injection treatment were 70 and 73%, respectively, and no significant difference existed between the patients of the two groups (3). In addition, another systematic meta-analysis also confirmed that the effect of combined therapy was equivalent to that of systemic or intratympanic injection of corticosteroid alone, and the hearing effect of intratympanic injection was similar to systemic corticosteroid among patients with moderate and severe SSNHL (22). Furthermore, our study results demonstrated that there was no significant difference between the efficacy of intratympanic injection combined with systemic corticosteroid treatment and the control group, suggesting that systemic corticosteroid treatment can achieve a similar efficacy as combined treatment as an initial treatment. We speculate that the reason for this phenomenon is that inner ear hormone receptors are saturated after patients receive a sufficient dose of systemic corticosteroid treatment, so the additional local medication has no additional effect.

Intratympanic corticosteroid injection has its own advantages. The first one is that it can avoid the side effects of systemic corticosteroid administration, which is contraindicated in patients with diabetes, hypertension, tumor, infection, and acute stage of peptic ulcer. Second, intratympanic injection is easy to operate. However, this technology is an invasive operation and may result in some local complications, such as pain, dizziness, and secondary acute or chronic otitis media. Therefore, it is necessary to select treatment strategies according to the patient's own circumstances. For example, for patients with contraindications of systemic administration of corticosteroids, local administration of corticosteroids can be taken as a priority.

Regarding the type of corticosteroid selected for intratympanic injection, dexamethasone, methylprednisolone, and prednisone are most used by medical institutions. Animal experiment results demonstrated that methylprednisolone has the highest permeability after intratympanic injection compared with dexamethasone and prednisone (5). However, the degree and incidence of pain response in patients after intratympanic methylprednisolone injection were significantly higher than those of patients who underwent intratympanic dexamethasone injection (23). Before we carried out this study, we also initially applied intratympanic methylprednisolone injection for SSNHL patients and found that many patients complained of unbearable earache. Some patients even suffered from tympanic perforation and ear pus. In contrast, a recent meta-analysis study demonstrated that as a salvage treatment for SSNHL, intratympanic injection of dexamethasone was more effective than methylprednisolone (24). Therefore, we chose dexamethasone as the intratympanic injection agent for treating SSNHL. Referring to the therapeutic schedule reported in the previous literature and recommended by the guidelines, we performed an intratympanic injection of 5 mg dexamethasone once a day, four times in total for SSNHL patients.

As a new treatment scheme for SSNHL, postauricular corticosteroid injection has been more and more valued by otologists. This scheme is recommended by the 2015 Chinese guideline for the diagnosis and treatment of SSNHL (1) but is not widely applied worldwide. Both animal and clinical studies have verified the effectiveness of the postauricular injection route. Wang et al. (25) explored the cochlear concentration and distribution of dexamethasone after administration by intratympanic, post-aural, and intraperitoneal methods. They found that intratympanic and post-aural administration could result in higher dexamethasone concentrations in the Organ of Corti than systemic administration, but systemic administration could produce higher dexamethasone concentrations in the stria vascularis than the other administration methods. Li et al. (13) conducted an animal study by using 7.0 Testa magnetic resonance imaging for guinea pigs after postauricular and intravenous injection of gadopentetate dimeglumine (Gd). They measured the relative signal intensity in the scala tympani of the basal turn to evaluate indirectly the dynamic Gd uptake in the perilymph. They found a delayed time to peak enhancement, prolonged elimination half-life, extended mean residence time, and a greater area under the signal–time curve among postauricularly treated guinea pigs. This study's results indicate that the bioavailability of drugs may increase to a certain extent and achieve a better effect through the postauricular injection route than systemic administration. In clinical studies, a retrospective study that enrolled 63 refractory SSNHL patients has revealed that the patients who underwent postauricular corticosteroid administration as a salvage treatment demonstrated better results than untreated patients. The most frequent adverse event was injection pain; other major adverse events included sleep change, increase in blood glucose, and headache (26). Moreover, another

multicenter clinical study that enrolled 173 SSNHL patients showed that the clinical efficacy of intratympanic steroid perfusion and postauricular steroid injection was similar for refractory severe and profound SSNHL patients (27). In contrast, compared with intratympanic injection, the postauricular injection has its own advantages. It is simple to operate and less likely to generate complications. However, due to the small number of literature reporting the effect of this technology currently, its effectiveness is uncertain. In future, more studies are needed to further investigate the efficacy and safety of this technology in SSNHL treatment. Although complications might be more likely to occur by applying the intratympanic injection route, our clinical practice shows that this technology is a safe procedure, since no patient suffered from severe complications during the follow-up period. In order to ensure the effectiveness of the medication, for patients with contraindications to systemic medication, intratympanic injection route is still a top priority currently.

The limitation of this study is that after stratification, the sample size of subjects in each subgroup is limited, although our study has a large sample size. Therefore, it is difficult to ensure the equivalence of the baseline such as age or pre-treatment hearing level between each group, which may generate methodological bias and affect the accuracy of the results. Nevertheless, since the baselines of most subgroups are equivalent, our results are convincing. In contrast, in order to ensure the treatment effect, patients received a combination of multiple therapies such as antioxidants, neurotrophic agents, and defibrinogen, which may also result in heterogeneity. In addition, a randomized blind placebo control multicenter study is necessary before we make a clear conclusion.

Conclusion

The exact role of intratympanic and postauricular corticosteroids requires additional trials. The addition of intratympanic or postauricular corticosteroid to systemic steroids did not result in a significant effect on hearing recovery in SSNHL. However, for patients with contraindications to systemic corticosteroid administration, intratympanic corticosteroid or postauricular corticosteroid may be safe and efficacious alternatives.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Second Affiliated Hospital of Nanchang University Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MD and YL conceived and designed the study. WX, NK, JL, and HP performed the experiments. CL and ZZ collected data. WX, NK, and MD wrote the manuscript. All authors contributed to the writing and final approval of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Arianna Di Stadio,
University of Catania, Italy

REVIEWED BY
Atsushi Matsubara,
Hirosaki University, Japan
Yilai Shu,
Fudan University, China

*CORRESPONDENCE
Maoli Duan
maoli.duan@ki.se

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Comorbidities and laboratory changes of sudden sensorineural hearing loss: a review

Wen Xie[1], Niki Karpeta[2,3], Busheng Tong[4], Yuehui Liu[1], Zhilin Zhang[1] and Maoli Duan[2,3]*

[1]Department of Otolaryngology, Head and Neck Surgery, The Second Affiliated Hospital of Nanchang University, Nanchang, China, [2]Division of Ear, Nose and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden, [3]Department of Otolaryngology-Head and Neck Surgery, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [4]Department of Otolaryngology, Head and Neck Surgery, The First Affiliated Hospital of Anhui Medical University, Anhui, Hefei, China

Sudden sensorineural hearing loss (SSNHL) is defined as an abrupt hearing loss of more than 30 dB in three contiguous frequencies within 72 h. It is an emergency disease requiring immediate diagnosis and treatment. The incidence of SSNHL in Western countries' population is estimated between 5 and 20 per 1,00,000 inhabitants. The etiology of SSNHL remains unknown. Due to the uncertainty of the cause of SSNHL, at present, no specific treatment targets the cause of SSNHL, resulting in poor efficacy. Previous studies have reported that some comorbidities are risk factors for SSNHL, and some laboratory results may provide some clues for the etiology of SSNHL. Atherosclerosis, microthrombosis, inflammation, and the immune system may be the main etiological factors for SSNHL. This study confirms that SSNHL is a multifactorial disease. Some comorbidities, such as virus infections, are suggested to be the causes of SSNHL. In summary, by analyzing the etiology of SSNHL, more targeting treatments should be used to achieve a better effect.

KEYWORDS

sudden sensorineural hearing loss, hearing loss, etiology, laboratory results, comorbidities

1. Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as an abrupt hearing loss of more than 30 dB in three contiguous frequencies within 72 h (1). Associated symptoms, including tinnitus, aural fullness, sound distortion, dizziness, vertigo, and benign paroxysmal positional vertigo (BPPV), may present in some cases (2). Moreover, SSNHL patients with vertigo tend to suffer from more severe hearing loss and worse hearing recovery (3, 4) due to a higher risk of vestibular organ lesions (5).

The incidence of SSNHL in developed countries' populations is an estimated 5–20 per 1,00,000 persons per year (6). There is an overall slight male preponderance, with a male-to-female ratio of 1.07:1 (7). Regarding age distribution, Rauch demonstrated that SSNHL most frequently occurred in 43–53-year-old patients (8). On the contrary, a Japanese survey showed that SSNHL was most prevalent among patients aged 60–69 years old (9). In addition, our study showed that the peak age prevalence was in the group of patients aged 41–50 years (3).

The etiology of SSNHL remains unknown, multiple factors are suggested to be the causes of SSNHL. Some pathophysiological mechanisms, including vascular disease, viral infection, metabolic disease, autoimmunity, and combinations of multiple factors are suggested to be the causes of ISSNHL. Due to the uncertainty of the cause of SSNHL, at present, there is no specific treatment targeting the cause of SSNHL, thus resulting in poor efficacy. This brief review focuses primarily on the etiological comorbidities and laboratory changes of SSNHL. We searched the U.S. National Library of Medicine's PubMed database using the terms "sudden sensorineural hearing loss," "sudden hearing loss," "idiopathic sudden sensory neural hearing loss," and "sudden deafness" as well as the keywords such as "etiology," "risk factors," "comorbidity," and "laboratory results."

2. Etiological comorbidities

Abundant evidence has proved that several diseases were associated with an increased risk of SSNHL; all these etiological diseases are listed in Table 1.

2.1. Cardiovascular disease

2.1.1. Hypertension

As shown in Table 1, hypertension is considered as one of the most common comorbidities of SSNHL. Animal experiments also showed that the blood flow in different parts of the cochlea was reduced by nearly 80% in hypertensive rats exposed to noise and 50–60% in hypertensive rats fed with an atherogenic diet (27). The cochlea is supplied by the cochlear artery, a terminal artery without any collateral vessels to compensate for any occlusion of the blood vessel. Thrombosis or vasospasm of the internal auditory artery is one of the main hypotheses to explain SSNHL. Hypertension may induce atherosclerotic changes and result in cochlear microcirculation disturbance.

2.1.2. Dysrhythmia

A study elucidated that patients with dysrhythmia showed a significantly higher risk of SSNHL (28). Even after the adjustment of confounders, the incidence of SSNHL in the dysrhythmia group was higher than that in the comparison group. This finding suggests that hemodynamic instability due to dysrhythmia resulting in impaired blood perfusion to the inner ear can lead to SSNHL.

2.2. Metabolic disease

2.2.1. Diabetes

A retrospective cohort study showed that the prevalence of SSNHL was 1.29 per 1,000 person-years among diabetic patients, which was 1.54-fold higher compared with non-diabetic subjects (20). In addition, earlier studies revealed that hearing impairment also occurred in the opposite ear, especially in high frequencies (29). Compared with diabetic patients without SSNHL, the glycated hemoglobin value was significantly higher in diabetes patients with SSNHL, and SSNHL patients with type-2 diabetes had more severe hearing loss (30). Moreover, a cohort study demonstrated that during 14 years of follow-up, a significantly lower percentage of diabetes patients with metformin use developed SSNHL compared with those without metformin intake, indicating that metformin use appeared to reduce the risk of developing SSNHL among diabetes patients (31).

Researchers found that the animal model of type-2 diabetes and obesity exhibited significantly elevated auditory brainstem response (ABR) thresholds. Regarding histological findings, outer hair cell degeneration and spiral ganglion cell loss were present in the middle and basal turns of the cochlear. This study indicates that diabetes and obesity may lead to early sensorineural hearing loss (32).

Microangiopathy may be one of the mechanisms underlying the association between diabetes and SSNHL. Other mechanisms, including upregulation of vascular endothelial growth factor, inducible nitric oxide synthase, and endothelial nitric oxide synthase, may be involved in the pathogenesis of cochlea functional loss (33).

2.2.2. Hyperlipidemia

Previous studies have demonstrated that patients with SSNHL had significantly higher plasma concentrations of cholesterol, triglyceride, lipoprotein A, and low-density lipoprotein cholesterol compared with controls (34, 35).

Animal experiments revealed that after a high-fat diet for 4 months, guinea pigs' inner ears showed impaired hearing sensitivity and pathologic alterations of the cochlear, especially in the basal turn and stria vascularis (36). It has also been reported that cholesterol had different distributions among outer hair cell membranes. Furthermore, after being incubated with water-soluble cholesterol, the outer cell's lateral wall stiffness parameter increased, which impaired the activity of the outer hair cells (37). In addition, Sikora et al. found that after being fed a high-fat diet, chinchillas exposed to noise exhibited more severe hearing loss at high frequency and significantly greater hair cell loss than those in chinchillas fed with a normal diet (38).

Overall, the pathophysiological mechanism of SSNHL caused by hyperlipidemia is through the modification of the microstructure of the stria vascularis and the composition and the electromotility of the outer hair cells by elevated cholesterol, thereby increasing the cochlea's vulnerability to noise. Moreover, hyperlipidemia promotes hyperviscosity, contributes to endothelial function damage, and decreases nitric oxide release. Consequently, it promotes the formation of atheromatous plaque, which might cause occlusion of the cochlear artery, therefore resulting in SSNHL (39, 40).

2.3. Autoimmune diseases

According to a review written by Ralli et al. (41), sensorineural hearing loss was the most common audiovestibular symptom

TABLE 1 Previous studies about the etiological comorbidities of SSNHL.

Study design	Patient group (n)	Control group (n)	Etiological comorbidities [incidence (%)][#]	Negative prognostic factors	References
Case-control study	109	109	Hypertension (21.1)	No mention	(10)
Case-control study	141	271	Diabetes (15.6), hyperlipidemia: hypercholesterolemia (40.0), Hypertriglyceridemia (64.9)	No mention	(11)
Case-control study	30	30	Diabetes (20), hyperlipidemia (20)	No mention	(12)
Case-control study	23	23	Hyperlipidemia (not described)	No mention	(13)
Case-control study	81	23	Metabolic syndrome: hypertension and hyperlipidemia (14.8)	No mention	(14)
Case-control study	181	181	Hypertension (39.2), hyperlipidemia (23.8)	Vertigo, hearing loss pattern	(15)
Case-control study	118	415	Hypertension (24), hyperlipidemia (14)	Hypertension, hyperlipidemia, diabetes, smoking	(16)
Cohort study	27,547 with depressive disorders	27,547 with anxiety disorders	Diabetes (18.45), hyperlipidemia (15.56), kidney disease (14.22)[&]	No mention	(17)
Case-control study	514	2,570	Hypertension (35.6), diabetes (19.6), hyperlipidemia (23.2)	No mention	(18)
Case-control study	3,331	13,324	Hypothyroidism (1.0): only for patients aged over 50 years; Hyperthyroidism (2.2): only for female patients	No mention	(19)
Retrospective cohort study	26,556	26,556	Diabetes (1.29)[&]	No mention	(20)
Prospective cohort study	73,957	73,957	Hypercholesterolemia (10.67)[&]	No mention	(21)
Retrospective cohort study	37,421 with kidney disease	37,421 without kidney disease	Diabetes (not described), kidney disease (10.24)[&]	No mention	(22)
Cohort Study	13,250 with autoimmune-disease	66,250 without autoimmune-disease	Autoimmune disease (1.09)	No mention	(23)
Cohort Study	7,619 with RA	30,476 without RA	RA (0.8)	No mention	(24)
Retrospective cohort study	464 with IDA	19,649 without IDA	IDA (1.72)	No mention	(25)
Case-control study	4,004	12,012	IDA (4.3)	No mention	(26)

RA, iron-deficient; IDA, iron deficiency anemia. [#]For the case-control study, the incidence rate refers to the incidence rate of comorbidity in the case group; for the cohort study, the incidence rate refers to the incidence rate of SSNHL among patients with pre-existing disease. [&]Rate: per 10,000 person-years.

related to systemic autoimmune diseases. Hearing loss may be present in a sudden, slowly, rapidly progressive, or fluctuating form, and is mostly bilateral and asymmetric. SSNHL has been reported as a symptom of some systemic autoimmune diseases, such as autoimmune hepatitis, sympathetic neural hyperalgesia edema syndrome, Cogan's syndrome, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis (RA), nodular polyarteritis, and Crohn's disease (42).

Previous studies showed that the risk of SSNHL was significantly higher in patients with antiphospholipid syndrome, multiple sclerosis, RA, and connective-tissue diseases than in patients without autoimmune diseases, and RA was in particular closely related to SSNHL (23, 24). Another retrospective study demonstrated that comorbid systemic lupus erythematosus or RA might negatively affect the prognosis of SSNHL (43). Furthermore, a systematic review reported that SSNHL could be an early manifestation of multiple sclerosis, especially in women. The pathophysiology of SSNHL caused by multiple sclerosis can be explained by the involvement of microglia attacking the central and/or peripheral auditory pathways (44).

Recently, O'Malley et al. (45) reported that the inflammatory cells are distributed in the inner ear. They found the presence of resident cochlear macrophages and the recruitment of inflammatory macrophages to the cochlea in animal models. This result indicates that the innate immune defense system

of the human inner ear may involve in many otologic diseases (45).

The pathophysiology of inner ear involvement in systemic autoimmune diseases remains uncertain. The possible pathophysiology may include activated circulating antibodies against inner ear antigens, leading to antibody-dependent cell-mediated cytotoxicity; the activation of the complement system, which directly triggers cytotoxic T cells; or immune complex-mediated damage, which results in vasculitis of the inner ear and causes atrophy of the stria vascularis (46–52).

2.4. Hematological disorders

Hematological disorders such as aplastic anemia, sickle cell anemia, and hyperviscosity syndrome have been described as being associated with inner ear deficits. These hematological diseases may cause inner ear hemorrhage or vasculopathy (53).

2.4.1. Iron deficiency anemia

A retrospective cohort study showed that children with iron deficiency anemia (IDA) demonstrated an increased likelihood of SSNHL (25). Another study also confirmed the link of SSNHL with IDA. In this study, absolute latencies for all ABR waves and interpeak latencies (except I-III interval) were significantly longer in children with IDA than in non-anemic infants (54). A population-based study also showed a significantly higher prevalence of prior IDA among participants with SSNHL compared with the controls, especially in those less than 60 years old. The researchers suggested that patients with IDA, especially those younger than 60 years, should be more aggressively surveyed to reduce hearing-related morbidities (26).

In the animal experiment, an electrophysiological study revealed that the incidence of an auditory threshold elevation of more than 15 dB was 31.85% in the iron-deficient (ID) rats, whereas it was unchanged in all the control animals. The main cochlear histopathological changes were strial atrophy and reduction of spiral ganglion cells in ID rats. So the authors concluded that the observed anomalies may be attributed solely to iron deficiency of the cochlear tissue (55).

The main cochlear pathological changes of SSNHL in ID rats were the synchronous abnormal activity of the iron-containing enzymatic, including succinic dehydrogenase and peroxidase, which in turn would disturb cell respiration and initiate peroxidative damage to the inner ear cells, resulting in a significant reduction of spiral ganglion cells and rapid damage of stereocilia of the outer and inner hair cells (56, 57).

2.4.2. Leukemia

It has been reported that 16–40% of leukemia patients had otolaryngological symptoms, such as SSNHL, vertigo, tinnitus, facial paralysis, and infection (58, 59). Among hematologic malignancies, SSNHL has often been described as the initial presentation in patients with acute lymphocytic leukemia. However, recent studies have indicated that both acute and chronic leukemia were associated with SSNHL (60, 61).

Lin et al. (53) reported that during the 20 years, they had identified 14 cases of SSNHL among patients with hematological disorders, i.e., leukemia or aplastic anemia. Most of these patients presented an abnormal mean hearing level, cervical vestibular-evoked myogenic potential test, ocular vestibular-evoked myogenic potential test, and caloric test results, exhibiting a significant sequential decline in inner ear function.

Chae et al. (62) documented a case of chronic myelogenous leukemia with the first manifestation being SSNHL, and the patient's hearing was restored after leukapheresis and chemotherapy without steroids. The authors presumed that cochlear vessel occlusion as a result of elevated blood viscosity may be responsible for this patient's hearing loss.

Numerous studies have demonstrated histopathological changes in the temporal bones of patients with leukemia. These histopathological changes include leukemic infiltration, inner ear hemorrhage, infection (58, 59, 63), and hyperviscosity syndrome (64, 65).

2.5. Chronic kidney disease

Chronic kidney disease (CKD) can significantly increase the risk of SSNHL (17). A cohort study showed that the incidence of SSNHL was 1.57 times higher in the CKD group compared to the non-CKD group (22).

Another study reported that two patients with kidney failure suffered from profound SSNHL during the course of hemodialysis (66). Moreover, a significant decrease in cochlear microphonic and cochlear nerve action potential has been demonstrated in guinea pigs in a uremic state (67).

One possible explanation of the association between CKD and SSNHL is that the cochlea and kidney have numerous anatomic, physiological, pharmacological, and pathological similarities and have a shared antigenicity, so both are influenced by similar immunologic factors. In addition, many nephrotoxic drugs are also ototoxic. As a result, many patients with CKD may suffer from SSNHL (66, 68).

Dialysis may sometimes result in deteriorated auditory function. Rizviand and Holmes found that the endolymphatic system collapsed in patients on dialysis in a case series (69). They also found edema and atrophy in the majority of the cells of the auditory and vestibular sensory organs. A cohort study reported that hemodialysis patients with SSNHL had higher risks of hemorrhagic stroke, ischemic stroke, acute coronary syndrome, and peripheral arterial occlusive disease than hemodialysis patients without SSNHL (70).

2.6. Thyroid diseases

Some researchers have studied the relationship between thyroid disease and SSNHL. Nakashima et al. explored the SSNHL risk factors in a case–control study including 109 patients, reporting that patients with a history of thyroid disease had a higher

odds ratio for SSNHL than those without such history (10). A case–control study with large samples showed that the correlation between hypothyroidism and increased SSNHL risk was significant only for patients aged over 50 years old and that the correlation between hyperthyroidism and SSNHL was remarkable only for female patients (19).

Thyroid autoantibodies can result in peripheral or central hearing organ dysfunction, increasing patients' susceptibility to SSNHL (71). In addition, thyroid dysfunction may lead to hypercoagulability and venous thrombosis, which may impair cochlear circulation, thus causing SSNHL (72, 73).

Overall, all these comorbidities which may affect the blood supply to the inner ear or alter the metabolism of the inner ear can cause SSNHL. Another evidence of circulatory disorder may be the main pathophysiology of SSNHL is that hyperbaric oxygen is effective for treating SSNHL. This treatment contributes to supply the oxygen needs to the peripheral neuronal structures of the inner ear (74).

3. Laboratory test results

In addition to hyperglycemia and hyperlipidemia, several laboratory abnormalities were reported in SSNHL patients (Table 2). The alterations of several major hematological parameters are reviewed and listed as follows.

3.1. Blood coagulation systems

Table 2 shows that laboratory abnormalities, such as hyperfibrinogenemia, antithrombin, protein C or protein S deficiency, and high factor VIII plasma levels, were associated with SSNHL. All these changes contribute to hypercoagulability and microthrombosis, which may cause cochlear ischemia and result in SSNHL.

Animal models showed increased levels of fibrinogen, accompanied by decreased cochlear blood flow as well as increased hearing thresholds. Moreover, hearing thresholds correlated negatively with cochlear blood flow (102).

Additional evidence for the role of hyperfibrinogenemia as one etiological factor of SSNHL is that acute and drastic removal of plasma fibrinogen and low-density lipoproteins can be used to effectively treat SSNHL. This treatment approach had a rapidly beneficial effect on endothelial dysfunction in SSNHL patients (103, 104).

3.2. Hemorheology

The changes in hemorheology observed in SSNHL patients included increased blood and plasma viscosity, erythrocyte aggregation index, and erythrocyte filtration index (Table 2). These changes can lead to impaired blood perfusion in the inner ear either by thrombosis or impaired regional blood flow.

3.3. Endothelial function

The biomarkers of endothelial function include flow-mediated dilation (FMD) of the brachial artery, endothelial progenitor cells (EPCs), and the expression of circulating adhesion molecules, such as soluble intercellular adhesion molecule 1 (ICAM-1) and soluble vascular cell adhesion molecule 1 (VCAM-1). Other factors, including oxidative stress, homocysteine, and folate also take part in the endothelial function.

3.3.1. FMD

FMD is a simple, non-invasive, and highly repeatable method to assess endothelial function. The mechanism of FMD is that after compression of the brachial artery for some minutes, the increased blood flow can induce shear stress, which can activate the endothelium to release nitric oxide with the consequence of vasodilation. This phenomenon can be monitored by ultrasonography. Diminished FMD is an early sign of subclinical atherosclerosis and is associated with coronary atherosclerosis (105–107). Recently, researchers also found reduced FMD among SSNHL patients (12, 77).

3.3.2. EPCs

EPCs are circulating cells, and their properties are similar to embryonal angioblasts. They can differentiate into mature endothelial cells. Increased EPCs have been found in case of acute vascular damage such as limb ischemia, acute myocardial infarction, or vascular trauma. By contrast, decreased EPCs were linked to a higher incidence of cardiovascular events (108, 109).

By analyzing peripheral blood $CD34^{+}KDR^{+}CD133^{+}$ cells, researchers found that the circulating levels of EPCs were much lower in SSNHL patients compared with controls (90). The results of this study confirm the existence of endothelial dysfunction in SSNHL patients.

3.3.3. Circulating adhesion molecules

Increased expression of some molecules is the early evidence of endothelial dysfunction. The activated endothelial cells can increase the expression of soluble ICAM-1 and soluble VCAM-1, and these molecules can mediate leukocyte adhesion to the endothelium and activate atherosclerosis formation (89, 110).

One prospective case–control study showed higher ICAM-1 and VCAM-1 in SSNHL patients (89). However, inconsistent results have been documented by another study, indicating that there was no difference between ICAM-1 and VCAM-1 between SSNHL patients and the controls. The authors considered that the role of soluble adhesion molecules in the pathogenesis of SSNHL remained unclear and needed further investigation (88).

3.3.4. Oxidative stress

The balanced reactive oxygen species (ROS) and antioxidant system can maintain the normal physiological oxidative status in living organisms. On the contrary, the imbalance between ROS and total antioxidant capacity is thought to be a potential pathogenetic

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TABLE 2 Previous studies about the laboratory findings of SSNHL.

Study design	Patient group (n)	Control group (n)	Changes of laboratory outcomes in patient group	The meaning of the indicator	Negative prognostic factors	Reference
Case-control study	250	250	TC, LDL, apolipoprotein B↑	Hyperlipidemia	No mention	(75)
Case-control study	30	60	TC↑, Coenzyme Q↓	Hyperlipidemia	No mention	(76)
Case-control study	29	29	TC, LDL↑, FMD↓	Hyperlipidemia and endothelial dysfunction.	No mention	(77)
Case-control study	54	55	TC, LDL↑	Hyperlipidemia	No mention	(78)
Systematic review and meta-analysis	6 articles		TC, LDL: no difference	Hyperlipidemia	No mention	(79)
Case-control study	324	972	TC, TG↑, LDL: no difference	Hyperlipidemia	No mention	(35)
Case-control study	324	972	Non-high-density lipoprotein↑	Hyperlipidemia	No mention	(80)
Case-control study	23	23	Fibrinogen, TC↑	Hypercoagulable state and hyperlipidemia	No mention	(13)
Case-control study	131	77	Blood glucose, HbA1C, lipoprotein (a), factor VIII ↑	Hyperlipidemia, diabetes and hypercoagulable state	No mention	(81)
Case-control study	118	415	Factor VIII, homocysteine↑, antithrombin, protein C↓, fibrinogen:no difference	Thrombophilia and cardiovascular risk factors	No mention	(16)
Case-control study	100	200	TC, fibrinogen, homocysteine↑, folate↓	Hyperlipidemia and cardiovascular risk factors	No mention	(82)
Case-control study	53	53	fibrinogen, erythrocyte aggregation, blood and plasma viscosity↑	Hypercoagulable state	No mention	(83)
Case-control study	142	84	Fibrinogen↑, TC, LDL, HDL: no difference	Hypercoagulable state	No mention	(84)
Case-control study	86	30	TC, TG, lipoprotein A, fibrinogen, erythrocyte aggregation, blood and plasma viscosity↑	Hyperlipidemia and hypercoagulable state	No mention	(34)
Case-control study	51	70	Blood and plasma viscosity↑	Thromboembolic factors	No mention	(85)
Case-control study	155	155	TC, homocysteine, plasminogen activator inhibitor-1, anticardiolipin↑	Cardiovascular risk factors	No mention	(86)
Case-control study	16	32	Erythrocyte filtration index↑	Microcirculation disturbance	No mention	(87)
Case-control study	30	30	FMD↓	Endothelial disfunction	No mention	(12)
Case-control study	35	35	ICAM-1, VCAM-1, E-selectin, IL-6, IL-8, and MCP-1: no different	Endothelial dysfunction	No mention	(88)
Prospective case-controlled study	37	47	VCAM-1↑	Endothelial dysfunction	No mention	(89)
Case-control study	21	21	Endothelial progenitor cells↓	Endothelial dysfunction	No mention	(90)
Case-control study	39	70	ROS, TAC, Oxidative-INDEX↑	High oxidative stress	No mention	(91)
Case-control study	43	24	Homocysteine↑, folate↓	Cardiovascular and thromboembolic risk factor	No mention	(92)
Systematic review and meta-analysis	22 articles		Folate↓	Cardiovascular and thromboembolic risk factor	No mention	(93)
Retrospective case review	203		WBC, ESR, blood glucose, HbA1C↑	Inflammation	High fibrinogen levels, WBC counts, ESR, and low FDP	(94)
Case-control study	348	537	NLR, PLR↑	Inflammation	High NLR	(95)

(Continued)

TABLE 2 (Continued)

Study design	Patient group (n)	Control group (n)	Changes of laboratory outcomes in patient group	The meaning of the indicator	Negative prognostic factors	Reference
Case-control study	47	50	NLR, PLR, SII↑	Inflammation	High SII scores	(96)
Case-control study	60	60	NLR, PLR↑	Inflammation	High NLRs and PLRs	(97)
Case-control study	43	10	Neutrophils↑, NKCA ↓ serum levels of IL-6 ↑	Inflammation	High neutrophil counts	(98)
Prospective case-controlled study	56	56	ESR, ANA, C3, C4, and monocytes ESR↑	Immune reaction	No mention	(99)
Case-control study	64	50	HSP70, the Hsp70 bound to CIC↑	Immune reaction	No mention	(100)
Case-control study	24	24	Monocyte population, TNF-α↑	Immune reaction	No mention	(101)

TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; FMD, flow-mediated dilation; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule; WBC, white blood cell counts; HbA1C, glycated hemoglobin; ESR, erythrocyte sedimentation rate; FDP, fibrinogen degradation products; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; ANA, antinuclear antibody; Hsp70, shock protein 70; ROS, serum reactive oxygen species capacity; NKCA, natural killer cell activity; CIC; circulating immune complex; TNF-α, tumor necrosis factor-α.

mechanism leading to endothelial dysfunction. If excessive ROS are not buffered by the cellular antioxidants, they can react with cellular macromolecules and promote lipid peroxidation, which may cause DNA damage and induce protein and nucleic acid modifications (111).

Recent studies have reported a significantly higher ROS in SSNHL patients, as well as oxidative stress status, supporting the vascular impairment involvement in ISSNHL etiopathogenesis (91, 112). The microcirculation disturbance due to an ischemic event may relate to increased oxidative stress, which may synergistically account for endothelial damage, especially in terminal microvascular systems (91, 113).

Other findings also reflect the involvement of oxidative stress in SSNHL. In a successive pioneering study, Cadoni et al. described an association between SSNHL and low serum levels of the antioxidant Co-enzyme Q (CoQ) (76).

3.3.5. Homocysteine and folate

Hyperhomocysteinemia is considered to be a cardiovascular and thromboembolic risk factor for atheromatous and vascular events (114). Homocysteine can promote platelet aggregation, hypercoagulability, oxidative stress response, endothelial impairment, and smooth muscle cell proliferation (115).

As an important regulator of homocysteine, folate is a coenzyme necessary for one-carbon metabolism. Low levels of folate may contribute to increased plasma levels of homocysteine (92). Lower serum folate and higher homocysteine levels have been found among SSNHL patients than among controls (92).

In general, it is known that endothelial dysfunction has a primary role in regulating vascular tone by modifying lipoproteins, thrombogenesis, and transformation of circulating monocytes into foam cells (82). Moreover, it can counterbalance pro-aggregation and anti-aggregation properties or even regulate coagulation conditions by mediums such as heparin. If endothelial dysfunction exists, the blood supply to the inner ear will be disturbed because of the sudden and transient thrombotic event, which could explain the nature of SSNHL (77, 92).

4. Inflammation

Chronic inflammation may lead to microvascular damage and atherogenesis, which increases ischemic risk in a direct way (116). Several studies revealed that some biomarkers of inflammation, including white blood cell (WBC) counts, neutrophil count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII) values, tumor necrosis factor-α level, and monocyte population were higher in SSNHL patients compared to the control groups. By contrast, lymphocyte count was significantly higher in the control group (Table 2). The lower NLR level might be taken into account as a novel potential marker to predict a better prognosis. A meta-analysis including 12 retrospective cohort studies also confirmed that NLR might be a useful biomarker to determine the onset and prognosis of SSNHL (95).

The high WBC counts among SSNHL may reflect an immune response to inner ear damage induced by ischemic changes or infections (94). In addition, the interrelation between neutrophils and endothelium may contribute to increased damage to the endothelium and was reported to explain platelet adhesion in patients with unstable angina (117). An elevated platelet count leading to an increased PLR might therefore lead to an increase in vascular endpoints. The SII, which is defined as platelets × neutrophils/lymphocytes, can serve as a prognostic marker for malignancies and inflammatory conditions. According to Ulu et al., as a novel index, the SII can be an indicator of SSNHL and it can predict the prognosis of SSNHL (96).

Masuda et al. (98) recruited 43 patients with SSNHL and found that, in SSNHL patients, neutrophils were above the reference range, natural killer cell activity (NKCA) was low and serum levels of interleukin-6 (IL-6) were higher compared to controls. Moreover, neutrophil count level was correlated with more severe

hearing loss and a worse prognosis. The authors hypothesized that high neutrophils together with low NKCA and high IL-6 may activate nuclear factor-κB in the cochlea and lead to SSNHL (98).

5. Immune system

As shown previously, immune factors are involved in the onset of SSNHL. Studies have found elevated levels of Circulating Immune Complexes and Heat Shock Proteins 70 in SSNHL patients, as well as IgG antibodies against the inner ear-specific proteins cochlin and β-tectorin (100, 118). These findings have provided compelling evidence that antibody-mediated tissue damage and Type III immunocomplex-mediated immune reaction in the inner ear are the pathogenetic mechanisms of the development of SSNHL. In addition, Baradaranfar M. reported that mean erythrocyte sedimentation rate, antinuclear antibody, C3, C4, and monocytes were higher in the case group (99).

In addition, no matter what kind of administration method, the use of steroids greatly improved the recovery of hearing in patients with SSNHL (119). The beneficial effect of corticosteroids in SSNHL could be due to an immunosuppressive and anti-inflammatory effect.

6. Conclusion

SSNHL is a multifactorial disease and its underlying mechanism remains uncertain. Some etiological comorbidities involving multiple systems may play a role in its pathogenesis. Atherosclerosis, microthrombosis, inflammation, and immune system may be the main etiological factors of SSNHL. In summary, by analyzing the etiology of SSNHL, more targeting treatments should be directed at the underlying cause to achieve a better effect.

Author contributions

Based on discussions with all authors, WX drafted the manuscript, which all authors revised. All authors contributed to the study design. All authors approved the final version submitted for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Jun Yang,
Xinhua Hospital, Shanghai Jiaotong University School of Medicine, China

REVIEWED BY
Hans Thomeer,
University Medical Center Utrecht, Netherlands
Daogong Zhang,
Shandong Provincial ENT Hospital, China

*CORRESPONDENCE
Takaomi Kurioka
✉ takaomi@xj9.so-net.ne.jp

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Is repetitive systemic corticosteroid therapy effective for idiopathic sudden sensorineural hearing loss? a retrospective study

Kengo Yamamoto[1,2], Takaomi Kurioka[3]*, Motofumi Ohki[1], Hajime Sano[4] and Taku Yamashita[2]

[1]Department of Otorhinolaryngology, Kitasato University Medical Center, Kitamoto, Japan, [2]Department of Otorhinolaryngology-Head and Neck Surgery, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan, [3]Department of Otorhinolaryngology, National Defense Medical College, Tokorozawa, Japan, [4]School of Allied Health Science, Kitasato University, Sagamihara, Kanagawa, Japan

Introduction: Some idiopathic sudden sensorineural hearing loss (ISSHL) cases experience repetitive systemic corticosteroid treatment, but studies focusing on repetitive systemic corticosteroid administration have not been reported. Thus, we investigated the clinical characteristics and usefulness of repetitive systemic corticosteroid treatment in ISSHL cases.

Methods: We reviewed the medical records of 103 patients who received corticosteroids only in our hospital (single-treatment group), and 46 patients who presented at our hospital after receiving corticosteroids in a nearby clinic and were subsequently treated with corticosteroids again in our hospital (repetitive-treatment group). Clinical backgrounds, hearing thresholds, and hearing prognosis were assessed.

Results: The final hearing outcomes were not different between the two groups. Further, in the repetitive-treatment group, statistical differences were found between the good and poor prognosis groups in the number of days to start corticosteroid administration (p =0.03), the dose of corticosteroid (p =0.02), and the duration of corticosteroid administration (p =0.02) at the previous facility. Multivariate analysis revealed a significant difference in the dose of corticosteroids administered by the previous clinic (p =0.004).

Conclusion: The repetitive systemic corticosteroid administration might play a supplementary role in hearing improvement, and initial sufficient corticosteroid administration would lead to good hearing outcomes in an early phase of ISSHL.

KEYWORDS

idiopathic sudden sensorineural hearing loss, hearing prognosis, prognostic factor, corticosteroid therapy, sudden deafness

Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) is usually defined as an acute unilateral sensorineural hearing loss (1). The etiology of ISSHL remains unknown, and various hypotheses have been proposed, including microcirculation disorders, viral infection, and autoimmunity (2, 3). Systemic corticosteroid administration is the

mainstream of standard treatment (4), but with only 30–60% of patient responses (5). Additionally, systemic corticosteroid therapy sometimes carries the risk of serious side effects (3) and systemic management would be required. In some cases, the intensity of systemic corticosteroid treatment is needed to be weakened or even suspended depending on general health conditions of the ISSHL patient. However, systemic corticosteroid treatment has no standardized protocol among institutions regarding doses, administration route, and duration. Therefore, some patients with ISSHL may have been treated with inadequate protocol of corticosteroid administration, which resulted in poor recovery. Thus, we hypothesize that these inadequately treated cases showing poor hearing recovery could be improved by readministrating adequate dose of corticosteroid repetitively, but to the best of our knowledge, no study has reported repetitive corticosteroid treatment for initial-treatment failure patients yet.

The primary goal of medical treatment for ISSHL is to restore hearing thresholds, and better prognostic factors of ISSHL have been reported as young age, short days between onset and the start of treatment, absence of vertigo (4, 6, 7), and better hearing thresholds at onset (8). Additionally, a recent report revealed that early response to systemic corticosteroid treatment correlates with final prognosis (7). Therefore, we hypothesized that we could improve the final hearing outcome for patients with ISSHL who do not achieve early hearing recovery under primary systemic corticosteroids by intensifying the conventional treatments. However, the efficacy of repeated systemic corticosteroid administration for patients with ISSHL as an additional consolidated treatment is unclear. This study investigated the hearing outcomes of affected ear and prognostic factors in patients with ISSHL who were treated with repetitive systemic corticosteroids.

Materials and methods

Study design

This retrospective study was approved by the Institutional Review Board of Kitasato University Medical center (2021004). The need for informed consent was omitted owing to the retrospective nature of the study.

Patients

This study included 149 patients hospitalized and treated for ISSHL in our hospital from 2016 to 2020 who were divided into the single-treatment group (103 patients who received corticosteroids only in our hospital) and the repetitive-treatment group (46 patients who presented to our hospital after receiving corticosteroids in a nearby clinic and were subsequently treated with corticosteroids again in our hospital). We defined ISSHL as a sudden sensorineural hearing loss of 30 dB or greater in at least three consecutive frequencies and pathogen was unidentified. Patients with acute low-tone sensorineural hearing loss, fluctuating hearing loss, any history of otologic surgery, and acoustic neuroma were excluded. We primarily judged the need for hospitalization based on symptoms, such as dizziness and severity, or a history of diabetes mellitus.

Hearing test

Pure-tone audiometry was performed in a soundproof room. The hearing thresholds were measured through air conduction at frequencies of 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz and bone conduction at frequencies of 0.25–4 kHz for both ears. The arithmetic average air conduction thresholds were obtained from the thresholds at 0.25, 0.5, 1, 2, and 4 kHz. The severity of hearing loss grade was determined by the Japanese Ministry of Health and Welfare guidelines, using the initial audiogram data (Table 1). Hearing recovery was calculated as the difference between the average hearing thresholds at different time points. The evaluation of hearing recovery was based on the hearing outcome criteria proposed by the Acute Severe Hearing Loss Study Group of the Ministry of Health, Labor, and Welfare of Japan (Table 2). The severity of hearing loss and the evaluation of hearing recovery were obtained from the average thresholds of 0.25–4 kHz.

Audiometry was completed in our department in the single-treatment group, and the tests were performed three times: before the systemic corticosteroid administration, during corticosteroid titration, and more than 3 months following treatment, or the ISSHL is judged as fully recovered. Additionally, patients in the repetitive-treatment group underwent audiometry three times, but the first tests were measured by previous clinics. The other two tests were measured in our department before the repetitive-treatment and more than 3 months after treatment or the ISSHL is judged as fully recovered.

Patients in the repetitive-treatment group were accordingly classified into the following two groups: the good (i.e., complete and marked recovery) and the poor prognosis groups (i.e., slight and no recovery). Additionally, we investigated the prognostic factors in repetitive corticosteroid treatment.

Treatment

We administered a 10 day course of systemic corticosteroids as a standard treatment in our institution (8 mg of betamethasone via intramuscular injection for the first day followed by 4 mg of betamethasone via oral administration for the first 3 days, tapered to 2 mg for the second 3 days and 1 mg for the last 3 days). To enhance the efficacy of ISSHL treatment, we also prescribed prostaglandin E1 (60 μg daily), vitamin B12 (1.5 mg daily) and adenosine triphosphate (300 mg daily). The corticosteroid administration started by a previous physician was terminated in the repetitive-treatment group, and then the same protocol as in the single-treatment group was started at our department. Details of corticosteroid treatment attempted by a previous physician were shown in Supplementary Table.

TABLE 1 The severity of hearing loss grade by the guidelines of the Japanese ministry of health and welfare.

Severity	
Grade1	Averaged PTA thresholds of <40 dB
Grade2	Averaged PTA thresholds of 40–60 dB
Grade3	Averaged PTA thresholds of 60–90 dB
Grade4	Averaged PTA thresholds of ≥90 dB

Averaged PTA thresholds were obtained from the average air conduction thresholds of 0.25–4 kHz. PTA, pure-tone audiometry.

TABLE 2 Final treatment outcomes according to the guideline of the Acute Severe Hearing Loss Study Group of the Ministry of Health, Labor, and Welfare of Japan.

Description	
Complete recovery	All five frequencies at 0.25, 0.5, 1, 2, and 4 kHz of final audiograms are ≤20 dB, or improvement to the same degree of hearing in the unaffected ear
Marked recovery	Averaged PTA improvement of ≥30 dB
Slight recovery	Averaged PTA improvement of 10–30 dB
No recovery	Averaged PTA improvement of <10 dB

Averaged PTA improvement was calculated as the difference between average hearing thresholds of 0.25–4 kHz at different time points, including pre-and post-treatment. PTA, pure-tone audiometry.

TABLE 3 Patient backgrounds of the two groups.

	Single-treatment group (N =103)	Repetitive-treatment group (N =46)	p
Age (years)	63.5	54.5	**0.002**
Gender (male/ female)	59/44	23/23	*0.41*
Severity (Grade 1/2/3/4)	12/27/38/26	7/11/20/8	*0.66*
Presence of vertigo (+/−)	28/75	15/31	*0.50*
Days to start primary treatment	5.0	3.6	**0.01**
Days to start treatment in our department	5.0	8.6	**<0.0001**
Duration from onset to final hearing evaluation (weeks)	19.03	18.61	0.658

Bold indicates significant differences (<0.05).

Assessment

Individual clinical features and examination results, including age at onset, gender, the severity of hearing loss, presence of vertigo, time from the onset to the start of initial treatment, and time from the onset to the start of treatment in our hospital, were investigated. Additionally, we investigated the protocol of corticosteroid therapy performed by a nearby clinic in the repetitive-treatment group.

Statistical analyses

Statistical analysis was conducted using GraphPad Prism 8 (GraphPad Software Inc., La Jolla, CA, United States) or JMP 14.2 (SAS Institute Japan Inc., Tokyo, Japan). We used the chi-squared test to evaluate the clinical characteristics and possible prognostic factors. The *t*-test or nonparametric Mann–Whitney *U* test was applied to investigate continuous variable prognostic factors. The difference in hearing thresholds was analyzed using a two-way analysis of variance followed by Šidák's multiple comparison tests. After univariate analysis, we included various parameters that were statistically significant in the univariate analysis into a binary logistic regression model for multivariate analysis. A *value of p* of <0.05 was considered statistically significant.

Result

Backgrounds

First, no cases interrupted the repetitive corticosteroid treatment due to the serious side effects in the repetitive-treatment group. Additionally, patients in the repetitive-treatment group were significantly younger (63.5 years vs. 54.5 years, $p = 0.002$), but with no statistically significant differences in gender, the severity of hearing loss, or the presence of vertigo. The start of treatment in our department was significantly delayed (5.0 days vs. 8.6 days, $p < 0.0001$) because of the pre-treatment period at a nearby clinic although the time to start treatment was shorter in the repetitive-treatment group (5.0 days vs. 3.6 days, $p = 0.01$). No statistical difference was detected in the duration from onset to post-treatment hearing examination between the groups (Table 3).

The hearing thresholds of the two groups at pre-treatment, during treatment, and post-treatment are shown at every measured frequency (Figure 1). No statistical difference was found between the two groups in the hearing thresholds at the measurement of pre-treatment and post-treatment, indicating poor early response to initial corticosteroid treatment and slower hearing recovery in the repetitive-treatment groups than those of the single-treatment group although the repetitive-treatment group revealed significantly worse hearing thresholds during treatment.

Prognostic factors in the repetitive-treatment group

Prognostic factors in the repetitive-treatment group were further investigated by dividing 46 patients into two groups: good (24 patients) and poor prognosis groups (22 patients). Statistical differences were found in the number of days to start corticosteroid administration at a previous facility (2.5 days vs. 4.8 days, $p = 0.03$), the dose of corticosteroid in methylprednisolone (mPSL) equivalent (0.44 mg vs. 0.33 mg, $p = 0.02$) and the duration of corticosteroid administration (2.8 days vs. 4.0 days, $p = 0.02$), indicating patients in the poor prognosis group were treated later and received a smaller dose of corticosteroids at a previous clinic. Additionally, the start of corticosteroid administration in our department was significantly delayed in the poor prognosis group due to the previous facility treatment periods (6.1 days vs. 11.1 days, $p = 0.003$). In particular, the dose of corticosteroids administered by a previous clinic was significantly different on multivariate analysis ($p = 0.004$) (Table 4).

These results revealed that the timing and dose of corticosteroid administration at the previous clinic affected the prognosis of ISSHL. Therefore, we further calculated the cut-off value from the ROC curve to elucidate the effect of primary corticosteroid administration at the previous clinic. Cut-off values of the corticosteroid dose were 0.36 mg per kg of body weight (sensitivity: 0.74, specificity: 0.66, area under the curve [AUC]: 0.69), the duration of administration at the previous doctor was 2 days (sensitivity: 0.39, specificity: 0.95, AUC: 0.71), and the start date of re-initiation at our department was 6 days from the onset (sensitivity: 0.73, specificity: 0.77, AUC: 0.77) (Figure 2).

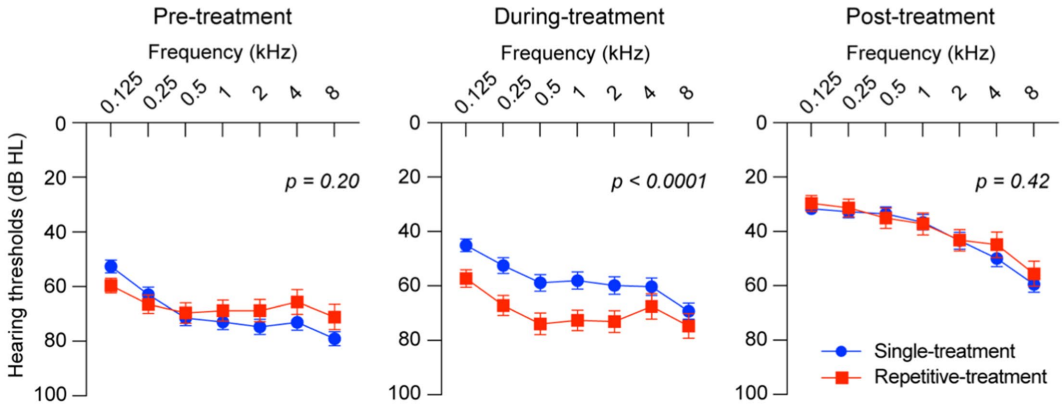

FIGURE 1
Hearing thresholds of the single-and repetitive-treatment groups. Hearing thresholds were significantly different between groups at during-treatment but not pre- and post-treatment. Bars represent standard error of the mean.

TABLE 4 Prognostic factors in the repetitive-treatment group.

	Good prognosis group	Poor prognosis group	*p*	
	(*N* =24)	(*N* =22)	Univariate	Multivariate
Age	52.5	56.8	*0.39*	
Gender(male/female)	10/14	13/9	*0.24*	
Severity (grade 1/2/3/4)	2/4/12/6	5/7/8/2	*0.19*	
Days to start treatment in the previous facility	2.5	4.8	**0.03**	*0.37*
Days to start treatment in our department	6.1	11.1	**0.003**	*0.25*
Dose of corticosteroid in the previous facility (equivalent to mPSL; mg/kg)	0.44	0.33	**0.02**	**0.004**
Duration of corticosteroid treatment in the previous clinic (days)	2.8	4.0	**0.02**	*0.06*

Bold indicates significant differences (< 0.05).

Discussion

Various therapeutic strategies for ISSHL are proposed in addition to systemic corticosteroid administration, which is considered one of the standard treatments worldwide. Intratympanic corticosteroid injection (9, 10) could deliver high concentration of corticosteroid to inner ear (11) without serious systemic side effects, and are recognized as one of the effective salvage treatments (12). Moreover, hyperbaric oxygen therapy (HBOT), which improves microcirculation by increasing oxygen concentration in inner ear (13), is also a therapeutic option for salvage in severe ISSHL (14). However, similar to systemic corticosteroid administration that has the risk of general side effects (15), intratympanic corticosteroid injections and HBOT also rarely, but occasionally have some risk of dizziness (16), persistent tympanic membrane perforation (17), inner ear injury occurred in 17.3% patients (18) and resultant hearing improvement was limited (19). Therefore, physicians may hesitate to prescribe large doses of corticosteroids systemically to all ISSHL cases without adequate medical care equipment, such as clinics, even to try intratympanic injection for salvage. Conversely, we often diagnosed patients with ISSHL who were initially treated with systemic corticosteroids at a nearby clinic and consulted our hospital for seeking additional treatment and examination because of poor hearing improvement. This consulting situation in Japan was considered for some reasons; some ISSHL cases recover slowly, and the policy of the national insurance system promotes segregation between hospitals and clinics. At present, there has been no established and standardized salvage treatment for ISSHL and proposed salvage therapies have some disadvantages, as mentioned above. To the best of our knowledge, no study has been reported focusing on the hearing outcome of repetitive systemic corticosteroid administration in patients with ISSHL. This is the first study to investigate the hearing outcomes of affected ear and its therapeutic characteristics in patients with ISSHL treated with repeated systemic corticosteroid therapy.

In our study, although no significant difference was observed in the hearing thresholds before and after treatment between the single-and repetitive-treatment groups, the hearing thresholds during the treatment was statistically different. The two groups tracked different recovery processes of hearing recovery, considering the difference in the number of days between the two groups until the start of treatment. It may be because of the difference in ISSHL pathogenesis between the two groups. However, patients in the repetitive-treatment group first visited other clinics and consulted our hospital for further detailed inspection and additional treatment. We hypothesized that patients with ISSHL with relatively slow hearing recovery accumulated in the repetitive-treatment group due to a selection bias because approximately 10% of patients with ISSHL recover their hearing even after >3 months (20) from ISSHL onset. Concluding the effects of repetitive corticosteroids treatment is difficult based on our study

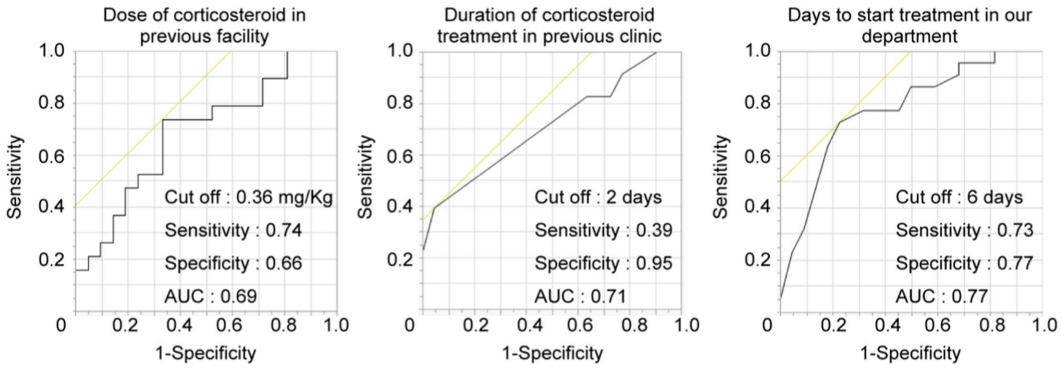

FIGURE 2
Cut-off value of prognostic factors in the repetitive-treatment group. ROC curve to predict the hearing prognosis according to corticosteroid dose, duration, and days to start treatment. The AUCs were 0.69, 0.71, and 0.77, respectively. AUC, area under the curve.

alone, but repetitive systemic administration of steroids did not hinder hearing recovery, thereby suggesting systemic repetitive corticosteroids treatment might be recommended as a choice of salvage therapy for ISSHL under certain conditions, such as in patients who are hesitant to receive intratympanic steroid injection, or in facilities where HBOT is not equipped. Then, we investigated therapeutic characteristics in the repetitive-treatment group and revealed significant differences in the number of days from the onset to the start of treatment and the initial dose of corticosteroid administered at nearby clinic between poor and good prognosis groups. Large doses of corticosteroids are considered necessary to elicit the efficacy of corticosteroids for inner ear pathology because the more systemic corticosteroids are prescribed, the more corticosteroids reach the inner ear (21). Initial treatment, especially sufficient corticosteroid administration in the early stage of onset, would make a significant contribution to hearing recovery, considering starting treatment within 7 days of onset is associated with a good prognosis (2) and the effectiveness of treatment is less likely to be obtained after 2 weeks of onset as consistent with previous reports (22). The comparable final hearing outcome in the repetitive-treatment group and the single-treatment group may be the result of the initial corticosteroid administration with a time lag. Therefore, we considered the repetitive systemic corticosteroid administration to play only a supplementary role in hearing improvement.

Our results indicated that an initial dose of corticosteroids should be sufficient and should be administered as early as possible after the onset of hearing loss. Moreover, repetitive systemic corticosteroid administration might be promising strategies as additional salvage treatment for ISSHL. The results of this study may serve as a guide to identifying patients with ISSHL who can be managed as an outpatient, while inpatient treatment may be restricted due to the COVID-19 pandemic. Additionally, the accumulation of ISSHL cases with different recovery time course is expected to lead to the subdivision of ISSHL as a syndrome and identify new pathogenesis or prognostic factors of ISSHL.

Finally, our study has several limitations. First, this was a retrospective study conducted in a single hospital, and the sample size was relatively small because we only chose hospitalized cases. Second, the repetitive-treatment group was younger and the time until the start of corticosteroid administration was shorter; thus, these factors may have modified the treatment outcome. Third, the dose and type of corticosteroid administrated by a previous physician are varied.

Conclusion

This retrospective study was conducted to determine whether repetitive systemic corticosteroid administration contributes to better hearing outcomes in patients with ISSHL, and investigate prognostic factors in the repetitive-treatment group. We concluded that sufficient and early corticosteroid administration would lead to good hearing outcomes in ISSHL although the effectiveness of repetitive systemic corticosteroid treatment remained unclear.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Kitasato University Medical center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

KY and TK designed this study, analyzed the results, and prepared the manuscript. TK performed the analysis. KY and MO included and treat the patients. HS and TY improved the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1167128/full#supplementary-material

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EDITED BY
Lisheng Yu,
Peking University People's Hospital, China

REVIEWED BY
Takaomi Kurioka,
National Defense Medical College (Japan), Japan
Wandong She,
Nanjing University of Chinese Medicine, China

*CORRESPONDENCE
Mingming Wang
✉ wmmship@126.com

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Characteristics and prognostic analysis of simultaneous bilateral sudden sensorineural hearing loss

Yingjun Wang[1,2], Wenping Xiong[1,2], Xiao Sun[1], Fujia Duan[1], Kunpeng Lu[1], Haibo Wang[3] and Mingming Wang[1,2]*

[1]Department of Otology Medicine, Shandong Provincial ENT Hospital, Shandong University, Jinan, China, [2]Shandong Institution of Otolaryngology, Jinan, China, [3]Department of Otology Center, Shandong Provincial ENT Hospital, Shandong University, Jinan, China

Objective: To evaluate the clinical characteristics of simultaneous bilateral sudden sensorineural hearing loss (Si-BSSNHL) as well as its prognostic factors.

Methods: Patients with Si-BSSNHL who were admitted to the Department of Otology Medicine between December 2018 and December 2021 were enrolled in the case group. Propensity score matching (PSM) for sex and age was used to select the control group, which included people who had unilateral sudden sensorineural hearing loss (USSNHL) during the same time period. Hearing recovery, audiological examinations, vestibular function assessments, laboratory tests, and demographic and clinical manifestations were analyzed for intergroup comparisons. Binary logistic regressions were used for both univariate and multivariate analyses of Si-BSSNHL prognostic factors.

Results: Before PSM, the Si-BSSNHL and USSNHL groups differed significantly ($p<0.05$) in terms of time from onset to treatment, initial pure-tone average (PTA), final PTA, hearing gain, audiogram curve type, proportion of tinnitus, high-density lipoprotein level, homocysteine level, and effective rate. After PSM, significant differences were also observed in time from onset to treatment, initial PTA, final PTA, hearing gain, total and indirect bilirubin levels, homocysteine level, and effective rate between the two groups ($p<0.05$). There was a significant difference in the classification of therapeutic effects between the two groups ($p<0.001$). For prognostic analysis, the audiogram curve type was significantly different between the effective group and the ineffective groups of Si-BSSNHL ($p=0.01$), in which the sloping type was an independent risk factor for the prognosis of the right ear in Si-SSNHL (95% confidence interval, 0.006–0.549, $p=0.013$).

Conclusion: Patients with Si-BSSNHL had mild deafness, elevated total and indirect bilirubin and homocysteine levels, and poorer prognosis than those with USSNHL. Audiogram curve type was linked to the therapeutic effect of Si-BSSNHL, and the sloping type was an independent risk factor for a poor prognosis in the right ear of Si-SSNHL.

KEYWORDS

sudden sensorineural hearing loss, bilateral, simultaneous, propensity score, prognosis

1. Introduction

Sudden sensorineural hearing loss (SSNHL) is a sudden, unexplained sensorineural hearing loss of ≥20 dB HL in at least two adjacent frequencies that occurs within 72 h (1). The incidence of SSNHL is approximately 5–30 per 100,000 people per year, and 95% of SSNHL cases are unilateral (2). Although the incidence of bilateral SSNHL (BSSNHL) is much lower than that of unilateral SSNHL (USSNHL), the incidence of BSSNHL has been increasing annually, accounting for 4.9–8.6% (3, 4). BSSNHL can be divided into simultaneous BSSNHL (Si-BSSNHL) depending on how the disease is progressing: sudden hearing loss in both ears simultaneously or within 3 days, and sequential BSSNHL (Se-BSSNHL): sudden hearing loss in both ears at an interval of more than 3 days (5). The rapid onset of Si-BSSNHL has a significant negative impact on patients' quality of life and social functions, and should be taken more seriously by physicians. In previous studies, there were few cases of Si-BSSNHL, confounding factors were rarely considered, fewer indicators were analyzed, and the results were controversial (5, 6). In this study, we set up a sex-and age-matched control group for USSBHL while conducting an exhaustive analysis of the relevant factors affecting the prognosis of Si-BSSNHL.

2. Materials and methods

2.1. Participants

Patients with Si-BSSNHL who were admitted to the Department of Otology between December 2018 and December 2021 were included in the case group, and patients with USSNHL during the same time period were selected as the control group. The inclusion criteria of case group were as follows: bilateral sudden deafness of ≥20 dB HL in at least two adjacent frequencies that occurs simultaneously or sequentially involving both ears within 72 h; age > 18 years; and first onset and duration ≤30 days. The inclusion criteria of control group were as follows: unilateral idiopathic sudden deafness (1); age > 18 years; and first onset and duration ≤30 days. Exclusion criteria of both groups were middle ear lesions, Meniere's disease, drug poisoning, noise-induced deafness, trauma, post-cochlear lesions, autoimmune diseases, and neurological, infectious, or hematologic diseases.

2.2. Ethics statement

This study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of our hospital (XYK20180605). Because this was a retrospective study, the need for informed consent was waived.

2.3. Research method

2.3.1. Data collection

Data on patient sex, age, time from onset to treatment, combined diseases (hypertension, diabetes mellitus, and coronary heart disease), accompanying symptoms (vertigo, tinnitus, aural fullness, and counted by person), audiological examinations, vestibular function assessments, and laboratory tests (including metabolic factors, inflammatory factors, and coagulation indexes) were collected.

2.3.2. Audiological examinations and efficacy assessments

Pure tone audiometry (GSI-61, United States), acoustic immittance (GSI Tympstar, United States), distortion product otoacoustic emission (IHS Smart EP, United States), and auditory brainstem response (IHS Smart EP, United States) were all used to rule out middle ear and retro-cochlear lesions. Audiogram curve type was classified as ascending, sloping, flat, or total deafness. The mean hearing threshold at 500 Hz, 1 kHz, 2 kHz, and 4 kHz was used to calculate pure tone average (PTA), and the degree of deafness was categorized according to the severity of the hearing loss: 25–40 dB HL as mild, 41–60 dB HL as moderate, 61–80 dB HL as severe, and > 80 dB HL as profound. The initial PTA was the pure-tone hearing threshold audiometric result examined before treatment in our hospital after the onset of the disease, and the final PTA was the hearing threshold result at 30 days post treatment.

The efficacy evaluations were divided into complete recovery: the hearing frequency returned either to the healthy side or normal level, or to the level before the disease started; partial recovery: the hearing frequencies improved by more than 30 dB on average; slight recovery: the hearing frequencies improved by 15–30 dB on average; and no recovery: the hearing frequencies improved by less than 15 dB on average. Complete, partial, and slight recovery were all included in the effective group. Patients with Si-BSSNHL were categorized as ineffective if both ears were ineffective and as effective if one or both ears were effective.

2.3.3. Vestibular function assessments

Vestibular function assessments included the caloric test (Ulmer VNG, v. 1.4; SYNAPSYS, Marseille, France), video head impulse test (Ulmer, Synapsys, Marseille, France), vestibular evoked myogenic potential (o/cVEMP) test (Neurosoft LTD, Ivanov, Russia), and vestibular autorotation test (Western Systems Research, Pasadena, United States). Any abnormality in vestibular function assessments is considered as positive.

2.3.4. Laboratory tests and imaging assessments

Routine peripheral blood samples were collected on the morning of the second day after admission. The metabolic indices included total bilirubin (TBIL), indirect bilirubin (IBIL), superoxide dismutase (SOD), glucose (GLU), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and homocysteine (Hcy). Inflammatory factors and coagulation parameters include C-reactive protein (CRP), neutrophil count, lymphocyte count, monocyte count, platelet count, and fibrinogen. The ratios of neutrophils to lymphocytes (NLR), monocytes-lymphocytes (MLR), and platelets-lymphocytes (PLR), respectively, are defined as the ratios of neutrophils, monocytes, and platelets to lymphocytes, respectively.

Contrast-enhanced MRI (PHILIPS, Intera, Holland) were performed to exclude occupying lesions.

2.3.5. Treatment

During hospitalization, all patients received the following treatment: improvement of microcirculation (*Ginkgo biloba* extract),

glucocorticoids (methylprednisolone sodium succinate), reduction of fibrinogen (batroxobin), and neurotrophic (methylcobalamin or mouse nerve growth factor) drugs. Patients with hypertension or diabetes mellitus were treated symptomatically and administered methylprednisolone sodium succinate systemically or locally behind the ear (in case of poor glycemic or blood pressure control), depending on the patient's glucose or blood pressure level.

2.4. Statistical analysis

A 1: 1 nearest neighbor matching was performed for sex and age between the case and control groups using propensity score matching (PSM), and the caliper was set at 0.05. For normally distributed variables, continuous variables are shown as mean ± standard deviation, and comparisons between groups were performed using an independent sample *t*-test. For non-normally distributed variables, the median (interquartile range) was used for continuous data, and the non-parametric Mann–Whitney *U* test was used to compare groups. The categorical variables were compared using the Chi-square and Fisher's exact tests. Binary logistic regression analysis was applied for univariate and multivariate analysis, and differences were significant at $p < 0.05$. The statistical software package SPSS 23.0 (IBM Corp., Armonk, NY, United States) was used for all analyses.

3. Results

3.1. Clinical data before PSM

A total of 50 cases of Si-BSSNHL were included in the case group, with a median age of 55.5 years (26 males and 24 females). Before PSM, the control group included 189 USSNHL cases with a median age of 47 years (100 males and 89 females). The differences in age, hearing gain, time from onset to treatment, initial PTA, final PTA, audiogram curve type, proportion of tinnitus, HDL and Hcy levels, and the effective rate were significant ($p < 0.05$) between the case group and control group, as shown in Table 1.

3.2. Clinical data after PSM

There were 50 patients with USSNHL in the control group after sex and age PSM matching with Si-BSSNHL, with a median age of 48.5 years (26 males and 24 females). There were significant differences in the hearing gain, time from onset to treatment, initial PTA, final PTA, TBIL and IBIL levels, Hcy level, and the effective rate between the two groups ($p < 0.05$), as shown in Table 2. There was a significant difference in the classification of efficacy between the two groups ($p < 0.001$), as shown in Figure 1. No significant difference was found in the audiogram curve type between the two groups ($p = 0.23$), as shown in Table 2.

3.3. Univariate prognostic analysis of Si-BSSNHL

The initial PTA, final PTA in the left ear of Si-BSSNHL was significantly higher than that in the right ear ($Z = -3.65$ and -2.43, respectively; both $p < 0.05$). Hearing gain in the left ear of Si-BSSNHL was significantly lower than that in the right ear ($Z = -4.14$, $p < 0.001$). No significant difference was found in the audiogram curve type between both ears of Si-BSSNHL ($\chi^2 = 2.92$, $p = 0.40$), as shown in Table 3. The effective rate after Si-BSSNHL treatment was 44%. Patients with Si-BSSNHL were divided into effective and ineffective groups according to their efficacy. Univariate binomial logistic regression was conducted to analyze the clinical characteristics, concomitant symptoms, combined underlying diseases (hypertension, diabetes mellitus, or coronary heart disease), audiological characteristics, vestibular function tests, and various blood index tests between the two groups. The audiogram curve type was significantly different between the different efficacy groups of patients with Si-BSSNHL ($p = 0.01$), as shown in Table 4.

3.4. Multivariate prognostic analysis

Parameters that yielded a value of $p < 0.1$ in the univariate logistic regression analysis were included in the multivariate analysis for prognosis of Si-BSSNHL, such as vertigo, TBIL, IBIL, TG, SOD, and audiogram curve type. Collinearity diagnosis was made for independent variables at $p < 0.1$ prior to inclusion, and collinearity was found for TBIL and IBIL; therefore, the final variables included in the multivariable logistic regression analysis included vertigo, TBIL, TG, SOD, and audiogram curve type. Due to the differences in the audiogram curve type of the right and left ears of patients with Si-BSSNHL, multivariate analysis was performed separately for the left and right ears, as shown in Figure 2. Multivariate logistic regression analysis revealed that the sloping type (95% confidence interval, 0.006–0.549, $p = 0.013$) was linked to the efficacy of the right ear in Si-BSSNHL.

4. Discussion

Simultaneous bilateral sudden sensorineural hearing loss has an acute onset and unclear etiological mechanisms; it is currently a diagnosis of exclusion having poor treatment efficiency, seriously impairing quality of life, and endangering patients' lives. Due to limitations in prevalence and data completeness, previous studies on BSSNHL have only reported a small number of cases, and most studies have analyzed clinical features and treatment efficacy; however, only a few distinctions have been made between Si-BSSNHL and Se-BSSNHL, or have been made in the post-PSM analysis for age and sex (5–8). Only Bing et al. analyzed Si-BSSNHL and Se-BSSNHL for classification and matching but did not conduct an analysis of prognostic risk factors (4). Although previous studies have analyzed the correlation between SSNHL and various blood parameters, such as prothrombotic states, metabolic parameters, inflammatory states, immunological factors, and oxidative stress, few analyses have been performed on Si-BSSNHL (9–11). The etiopathogenesis of Si-BSSNHL remains unclear due to the lack of research on the condition.

Hypertension, diabetes mellitus, and hyperlipidemia are risk factors for SSNHL's poor prognosis (10, 12), and abnormal thyroid function has been correlated with the development of SSNHL (13). Meanwhile, the onset of hypertension and diabetes is closely associated with age, and blood indices such as bilirubin and

TABLE 1 Demographics and clinical characteristics of patients (Before PSM).

Variable	Si-BSSNHL (n=50)	USSNHL (n=189)	Statistics	Value of p
Age of onset	55.5 (39, 62.5)	47 (34.5, 56)	−2.5	0.01[a,*]
Males: females	26:24	100:89	0.01	0.9[b]
Time from onset to treatment	10 (5, 20)	7 (4, 11.5)	−2.73	0.01[b,*]
Underlying diseases (Yes: No)	18:32	51:138	1.57	0.21[b]
Initial PTA (dB HL)	54.4 (41.3, 71.3)	68.8 (41.3, 88.8)	−2.53	0.01[a,*]
Final PTA (dB HL)	45.6 (35, 61.3)	32.5 (18.8, 66.9)	−3.3	0.00 [a,*]
Hearing gain (dB HL)	3.8 (0, 11.3)	21.3 (8.8, 43.8)	−8.0	0.00[a,*]
Audiogram curve type			9.6	0.02[b,*]
Ascending	14 (14.0%)	28 (14.8%)		
Sloping	31 (31.0%)	41 (21.8%)		
Flat	36 (36.0%)	53 (28.0%)		
Total deafness	19 (19.0%)	67 (35.4%)		
Vertigo	21 (42.0%)	75 (39.7%)	0.08	0.76[b]
Tinnitus	43 (86%)	181 (95.8%)	6.4	0.01[b,*]
Aural fulness	35 (70.0%)	153 (81.0%)	2.8	0.09[b]
Blood index				
NLR	1.7 (1.2, 2.2)	1.7 (1.3, 2.1)	−0.08	0.94[a]
MLR	0.17 (0.14, 0.24)	0.17 (0.14, 0.23)	−0.4	0.69[a]
PLR	107.3 (92.5, 141.2)	112.9 (92.5, 140.6)	−0.6	0.54[a]
CRP (mg/L)	0.3 (0.06, 1.5)	0.6 (0.1, 2.0)	−0.8	0.39[a]
Fibrinogen (g/L)	2.4 (2.1, 2.7)	2.4 (2.1, 2.8)	−0.1	0.89[a]
TBIL (μmol/L)	14.8 ± 6.0	14.3 ± 5.7	0.5	0.62[c]
IBIL (μmol/L)	10.7 ± 4.3	10.4 ± 4.1	0.5	0.60[c]
SOD (U/mL)	157.8 ± 32.1	165.3 ± 32.4	−1.5	0.15[c]
Glu (mmol/L)	4.9 (4.5, 5.6)	4.9 (4.5, 5.5)	−0.2	0.84[a]
TG (mmol/L)	1.2 (0.8, 1.8)	1.4 (1.0, 2.0)	−1.93	0.05[a]
TC (mmol/L)	4.5 (3.7, 5.3)	4.6 (4.1, 5.3)	−1.1	0.29[a]
HDL (mmol/L)	1.3 ± 0.3	1.4 ± 0.3	−2.6	0.01[c,*]
LDL (mmol/L)	2.7 (2.1, 3.3)	2.6 (2.1, 3.1)	−0.4	0.71[a]
Hcy (μmol/L)	9.8 (7.6, 13.5)	4.0 (2.7, 5.8)	−7.2	0.00[a,*]
Vestibular test (+)	44 (91.7%)	175 (92.6%)	0.05	0.83[b]
The effective rate (%)	22 (44.0%)	121 (64.0%)	6.6	0.01[b,*]

Si-BSSNHL, simultaneous sudden sensorineural hearing loss; USSNHL, unilateral sudden sensorineural hearing loss; NLR, neutrophil lymphocyte ratio; MLR, monocyte lymphocyte ratio; PLR, platelet lymphocyte ratio; CRP, C-reactive protein; TBIL, total bilirubin levels; IBIL, indirect bilirubin; SOD, superoxide dismutase; Glu, glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and Hcy, homocysteine. *$p < 0.05$.
[a]Mann-Whitney U test.
[b]Chi-square test.
[c]Independent sample t-test.

high-density lipoprotein are also correlated with sex and age (14, 15). Abnormalities in thyroid function are most common in women (16). Therefore, the effects of age, sex, and associated confounding factors in this study can be excluded using PSM for the case and control groups. The prevalence of vertigo and aural fullness between the two groups prior to and following PSM matching was not significantly different. The prevalence of tinnitus in the case group (86%) was significantly lower than that in the control group (95.8%) before PSM, while this disparity vanished after PSM. Vestibular function abnormality was a poor prognostic factor for Si-BSSNHL. Previous studies have reported a higher rate of vestibular function abnormality in patients with BSSNHL than those with USSNHL (7), but no significant difference was found in the prevalence of vertigo between the Si-BSSNHL and USSNHL groups (4). In the present study, there was no significant difference in the prevalence of vertigo or vestibular function abnormality between the Si-BSSNHL and USSNHL groups before and after PSM. This may be since the BSSNHL in previous studies included

TABLE 2 Demographics and clinical characteristics of patients (After PSM).

variable	Si-BSSNHL (n=50)	USSNHL (n=50)	Statistics	Value of p
Time from onset to treatment	10 (5, 20)	6 (4, 10.8)	−2.6	0.01[a,*]
Underlying diseases (Yes: No)	18:32	10:40	3.2	0.07[b]
Initial PTA (dB HL)	54.4 (41.3, 71.3)	69.4 (45.9, 85.3)	−2.2	0.03[a,*]
Final PTA (dB HL)	45.6 (35, 61.3)	24.4 (17.5, 66.3)	−3.2	0.00[a,*]
Hearing gain (dB HL)	3.8 (0, 11.3)	22.5 (10.9, 49.4)	−6.2	0.00[a,*]
Audiogram curve type			4.4	0.23[b]
Ascending	14 (14.0%)	9 (18.0%)		
Sloping	31 (31.0%)	12 (24.0%)		
Flat	36 (36.0%)	13 (26.0%)		
Total deafness	19 (19.0%)	16 (32.0%)		
Vertigo	21 (42.0%)	20 (40.0%)	0.04	0.84[b]
Tinnitus	43 (86%)	48 (96.0%)	3.0	0.08[b]
Aural fulness	35 (70.0%)	37 (74.0%)	0.2	0.66[b]
Blood index				
NLR	1.7 (1.2, 2.2)	1.7 (1.3, 2.2)	−0.6	0.58[a]
MLR	0.17 (0.14, 0.24)	0.18 (0.15, 0.24)	−1.2	0.24[a]
PLR	107.3 (92.5, 141.2)	111.9 (94.5, 141.3)	−0.02	0.98[a]
CRP (mg/L)	0.3 (0.06, 1.5)	0.8 (0.3, 2.1)	−1.3	0.19[a]
Fibrinogen (g/L)	2.4 (2.1, 2.7)	2.4 (2.1, 2.8)	−0.8	0.44[a]
TBIL (μmol/L)	14.8 ± 6.0	13.5 (10.3, 16.9)	−2.3	0.02[a,*]
IBIL (μmol/L)	10.7 ± 4.3	9.6 (7.5, 12.7)	−2.4	0.02[a,*]
SOD(U/mL)	157.8 ± 32.1	147.0 (135.0, 168.3)	−1.9	0.06[a]
Glu (mmol/L)	4.9 (4.5, 5.6)	4.9 (4.5, 5.5)	−0.4	0.66[a]
TG (mmol/L)	1.2 (0.8, 1.8)	1.6 (1.1, 2.1)	−1.0	0.31[a]
TC (mmol/L)	4.5 (3.7, 5.3)	4.6 (4.3, 5.2)	−0.4	0.73[a]
HDL (mmol/L)	1.3 ± 0.3	1.4 (1.1, 1.7)	−1.5	0.13[a]
LDL (mmol/L)	2.7 (2.1, 3.3)	2.6 (2.3, 3.0)	−0.6	0.13[a]
Hcy (μmol/L)	9.8 (7.6, 13.5)	4.2 (2.5, 5.1)	−5.9	0.00[a,*]
Vestibular test (+)	44 (91.7%)	46 (92.0%)	0.00	0.95[b]
The effective rate (%)	22 (44.0%)	33 (66.0%)	4.9	0.03[b,*]

Si-BSSNHL, simultaneous sudden sensorineural hearing loss; USSNHL, unilateral sudden sensorineural hearing loss; NLR, neutrophil lymphocyte ratio; MLR, monocyte lymphocyte ratio; PLR, platelet lymphocyte ratio; CRP, C-reactive protein; TBIL, total bilirubin levels; IBIL, indirect bilirubin; SOD, superoxide dismutase; Glu, glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and Hcy, homocysteine. *$p < 0.05$.
[a]Mann-Whitney U test.
[b]Chi-square test.

both Si-BSSNHL and Se-BSSNHL, and different study participants may have caused differences in the results. In addition, the lower rate of vestibular function abnormality was also supported by the significantly lower initial PTA in the Si-BSSNHL group before and after PSM along with mild deafness compared to the USSNHL group. However, the present results demonstrated that patients with Si-BSSNHL had a lower hearing gain, treatment effective rate, and poorer prognosis than those with USSNHL, which is consistent with previous results (5, 6). Although there was no statistical difference in the distribution of audiogram curve type between the two groups after PSM, Si-BSSNHL was more common, with flat (36%) and sloping types (31%). While the prognosis of mid-high-frequency hearing loss is worse than that of other audiogram curve types, the prognosis of Si-BSSNHL is worse than that of USSNHL. This also suggests that Si-BSSNHL and USSNHL may have different pathogeneses; hence, despite receiving the same treatment regimens, their prognoses differ. In addition, the fact that Si-BSSNHL patients had significantly longer time from onset to treatment than USSNHL patients in this study may also influence prognosis.

The pathological mechanism underlying Si-BSSNHL is unclear, but a systemic chronic inflammatory state, prethrombotic state, and metabolic factors may be involved. CRP, NLR, MLR, and PLR can be used as reliable and convenient indicators to

detect systemic chronic inflammation and coagulation status, which are associated with the prognosis of SSNHL (11, 17). Herein, we observed no significant differences in NLR, MLR, PLR, and CRP between Si-BSSNHL and USSNHL. Further univariate and multivariable analysis of Si-BSSNHL did not find any correlation between these indicators and the prognosis of Si-BSSNHL. This suggests that the systemic chronic inflammatory response and coagulation status may not be specific to the pathogenesis of Si-BSSNHL. Dyslipidemia, such as abnormalities in TG, TC, HDL, LDL, and other indicators, can be associated with the degree of hearing loss and prognosis of SSNHL by causing blood stagnation, blood flow deceleration, and lipid deposition, resulting in impaired microcirculation in the inner ear (18). In the present study, there were no significant differences between the Si-BSSNHL and USSNHL groups in any lipid metabolic indices, although the HDL levels in the Si-BSSNHL group were significantly lower than those in the USSNHL group before matching. HDL differs by sex, age, and race (14), therefore, the differences between the groups disappeared after PSM was performed. Hcy is a risk factor for vascular injury. An abnormal increase in Hcy level causes vascular endothelial dysfunction, decreased vascular flexibility, microcirculatory dysfunction, and ultimately leads to ischemic and hypoxic damage to the cochlea (19). Additionally, high Hcy level may be a high-risk factor for the development of SSNHL (9). Our results showed that Si-BSSNHL patients had significantly higher Hcy levels before and after PSM than the USSNHL group. It has been hypothesized that Hcy plays a role in the onset of inner ear microcirculatory dysfunction in Si-BSSNHL. Bilirubin is an important vascular protective factor with anti-inflammatory, antioxidant, and vasodilatory effects (20), and its level is correlated with age, sex, and oxidative stress (15). This study also showed that TBIL and IBIL levels were significantly higher in Si-BSSNHL patients than in matched USSNHL patients, although both were within the normal ranges. This suggests that Si-BSSNHL causes more severe oxidative stress damage than USSNHL does. This provides a theoretical basis for the rational clinical application of antioxidative stress drugs.

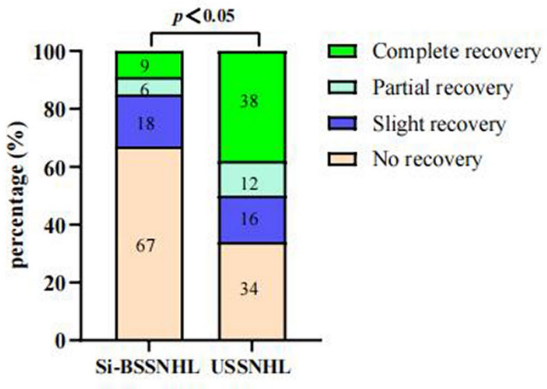

FIGURE 1
Comparisons of the efficacy between Si-BSSNHL and USSNHL after PSM. After PSM, there was a significant difference in efficacy between the Si-BSSNHL and USSNHL groups (χ^2=28.5, p<0.05). Si-BSSNHL, simultaneous bilateral sudden sensorineural hearing loss; USSNHL, unilateral sudden sensorineural hearing loss; PSM, propensity score matching.

Simultaneous bilateral sudden sensorineural hearing loss has a worse prognosis than USSNHL, as reported in previous studies (5, 8). This may be due to the fact that Si-BSSNHL has distinct pathophysiologic mechanisms, possibly accounted for by an underlying systemic disease (8). Given that Si-BSSNHL has a worse prognosis, this study further analyzed the relevant factors affecting the prognosis of Si-BSSNHL. In the univariate logistic analysis, the audiogram curve type between the effective and ineffective Si-BSSNHL groups was significantly different. Multivariable logistic regression analysis of Si-BSSNHL revealed that only the sloping type had a significant effect on right ear efficacy, which was an independent risk factor for poor prognosis in the right ear of Si-BSSNHL, and the prevalence of vertigo, TBIL, TG, and SOD levels were not associated with prognosis. The pathogenesis of various audiogram types varies, and sloping-type hearing loss is often associated with cochlear base transmural cell damage, which usually has a poor prognosis (1). However, further sample size expansion and analysis of related mechanisms are required to account for the disparity in effectiveness between the right and left ears. The time from onset to treatment, the degree of deafness, and audiogram curve type are usually considered to be associated with the treatment outcome of patients with USSNHL. In this study,

TABLE 3 The PTA and audiogram curve type of both ear in the Si-BSSNHL.

Variable	Left ear (n=50)	Right ear (n=50)	Statistics	Value of p
Initial PTA (dB HL)	66.3 (50.0, 83.8)	60 (48.8, 91.3)	−3.65	0.00[a].*
Final PTA (dB HL)	60 (41.3, 81.3)	56.3 (41.3, 86.3)	−2.43	0.02[a].*
Hearing gain (dB HL)	3.8 (0.0, 11.3)	5(−1.3, 8.8)	−4.14	0.00[a].*
Audiogram curve type			2.92	0.40[b]
Ascending	6 (12.0%)	8 (16.0%)		
Sloping	13 (26.0%)	18 (36.0%)		
Flat	22 (44.0%)	14 (28.0%)		
Total deafness	9 (18.0%)	10 (20.0%)		

Si-BSSNHL, simultaneous sudden sensorineural hearing loss. *p < 0.05.
[a]Mann-Whitney U test.
[b]Chi-square test.

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TABLE 4 Univariate logistic analysis of possible prognostic factors in Si-BSSNHL.

Variable	Effective group (n=22)	Ineffective group (n=28)	Statistics	Value of p
Age of onset	53.5 (36.7, 58.3)	56 (41, 65.8)	−1.3	0.19[a]
Time from onset to treatment	7 (5, 14.3)	16 (5.3, 28.3)	−1.4	0.16[a]
Males: Females	13 (59.1%)	13 (46.4%)	0.8	0.37[b]
Underlying diseases (Yes: No)	5: 17	7:21	0.04	0.85[b]
Vertigo	6 (27.3%)	15 (53.6%)	3.5	0.06[b]
Tinnitus	19 (86.4%)	24 (85.7%)	0.004	1.0[c]
Ear fullness	16 (72.7%)	19 (67.9%)	0.14	0.71[b]
Vestibular test (+)	19 (95%)	25 (89.2%)	0.49	0.63[c]
Audiogram curve type			11.2	0.01[b,*]
Ascending	10 (22.7%)	4 (7.1%)		
Sloping	7 (15.9%)	24 (42.9%)		
Flat	19 (43.2%)	17 (30.4%)		
Total deafness	8 (18.2%)	11 (19.6%)		
Deafness degree			0.8	0.86[b]
Mild	6 (13.6%)	8 (14.3%)		
Moderate	19 (43.2%)	24 (42.9%)		
Severe	12 (27.3%)	12 (21.4%)		
Profound	7 (15.9%)	12 (21.4%)		
Blood index				
NLR	1.6 (1.2,2.1)	1.9 (1.2,2.3)	−0.6	0.58[a]
MLR	0.17 (0.14,0.23)	0.18 (0.15,0.25)	−0.6	0.55[a]
PLR	103 (93.2, 130.0)	111 (90.9, 148.5)	−0.5	0.59[a]
CRP (mg/L)	0.2 (0.05, 0.7)	0.4 (0.06, 2.1)	−0.8	0.43[a]
Fibrinogen (g/L)	2.4 (2.2, 2.7)	2.3 (2.0, 2.9)	−0.7	0.48[a]
TBIL (μmol/L)	16.6 ± 7.0	13.4 ± 4.8	1.9	0.06[d]
IBIL (μmol/L)	11.9 ± 4.9	9.8 ± 3.6	1.8	0.07[d]
SOD (U/mL)	165.5 (141.8, 183.3)	155.5 (122.5, 172.8)	−1.7	0.09[a]
Glu (mmol/L)	5.0 (4.4, 5.8)	5.0 (4.5, 5.3)	−0.2	0.88[a]
TG (mmol/L)	1.0 (0.7, 1.5)	1.4 (0.9, 1.9)	−1.8	0.06[a]
TC (mmol/L)	4.4 (3.4, 5.2)	4.6 (4.0, 5.4)	−0.9	0.33[a]
HDL (mmol/L)	1.3 ± 0.3	1.3 ± 0.3	0.4	0.66[d]
LDL (mmol/L)	2.2 (1.9, 3.4)	2.9 (2.2, 3.3)	−1.3	0.18[a]
Hcy (μmol/L)	9.9 (4.0, 13.3)	10.1 (8.4, 14.7)	−0.7	0.52[a]

Si-BSSNHL, simultaneous sudden sensorineural hearing loss; CRP, C-reactive protein; TBIL, total bilirubin levels; IBIL, indirect bilirubin; SOD, superoxide dismutase; Glu, glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and Hcy, homocysteine. *$p < 0.05$.
[a]Mann-Whitney U test.
[b]Chi-square test.
[c]Fisher's test.
[d]Independent sample t-test.

however, only the audiogram curve type was associated with the prognosis of Si-BSSNHL. This may be due to the various number of cases, inclusion and exclusion criteria, or efficacy evaluation criteria of different studies.

In summary, to better analyze the differences in clinical characteristics between Si-BSSNHL and USSNHL, this study applied PSM to exclude the effects of sex, age and possible confounding factors associated with sex and age. After PSM, Si-BSSNHL had mild deafness, but the degree of oxidative stress damage and inner ear microcirculation involvement was more severe than that in USSNHL, with worse prognosis. The audiogram curve type was closely related to the prognosis of Si-BSSNHL, with the sloping type being an independent risk factor for prognosis in the right ear.

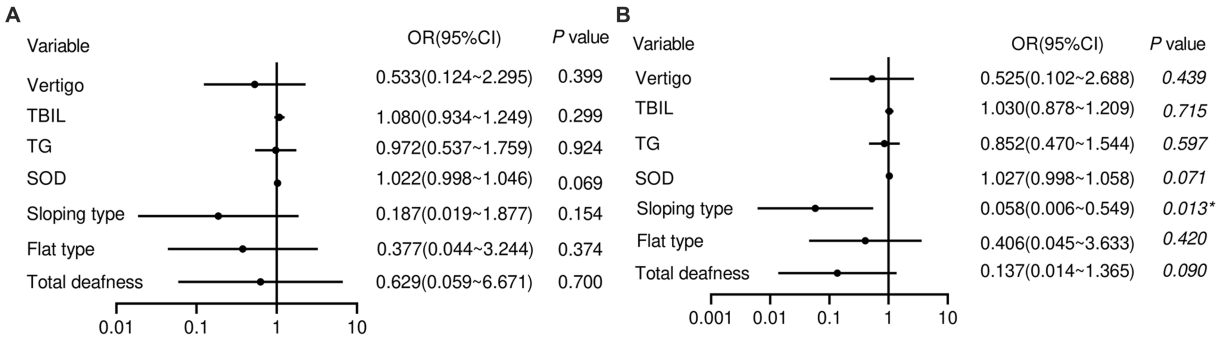

FIGURE 2
Multivariate logistic regression analysis for Si-BSSNHL. **(A)** Left ear; **(B)** Right ear; TBIL, Total bilirubin level; TG, Triglyceride; SOD, superoxide dismutase; and Si-BSSNHL, simultaneous bilateral sudden sensorineural hearing loss. *$p<0.05$.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Shandong Provincial ENT Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YW and MW designed the study and wrote the manuscript. WX, XS, KL, and FD performed the research and analyzed the data. HW funded the research. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Lisheng Yu,
Peking University People's Hospital, China

REVIEWED BY
Eduardo Martin-Sanz,
Hospital de Getafe, Spain
Benyu Nan,
Wenzhou Medical University, China

*CORRESPONDENCE
Chang Lin
✉ linc301@sina.com
Junying Chen
✉ junyingchen01@163.com

†These authors have contributed equally to this work and share first authorship

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Development and validation for multifactor prediction model of sudden sensorineural hearing loss

Chaojun Zeng[1,2,3†], Yunhua Yang[4†], Shuna Huang[2,5†], Wenjuan He[6†], Zhang Cai[3], Dongdong Huang[3], Chang Lin[1,2*] and Junying Chen[2,7*]

[1]Department of Otorhinolaryngology Head and Neck Surgery, Fujian Institute of Otorhinolaryngology, The First Affiliated Hospital, Fujian Medical University, Fuzhou, China, [2]National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou, China, [3]Department of Otorhinolaryngology Head and Neck Surgery, First Hospital of Putian City, Putian, Fujian, China, [4]Department of Otolaryngology, Fujian Provincial Geriatric Hospital, Fuzhou, China, [5]Department of Clinical Research and Translation Center, The First Affiliated Hospital, Fujian Medical University, Fuzhou, China, [6]Clinical Laboratory, Fujian Provincial Hospital South Branch, Fuzhou, China, [7]Central Laboratory, Key Laboratory of Radiation Biology of Fujian Higher Education Institutions, The First Affiliated Hospital, Fujian Medical University, Fuzhou, China

Background: Sudden sensorineural hearing loss (SSNHL) is a global problem threatening human health. Early and rapid diagnosis contributes to effective treatment. However, there is a lack of effective SSNHL prediction models.

Methods: A retrospective study of SSNHL patients from Fujian Geriatric Hospital (the development cohort with 77 participants) was conducted and data from First Hospital of Putian City (the validation cohort with 57 participants) from January 2018 to December 2021 were validated. Basic characteristics and the results of the conventional coagulation test (CCT) and the blood routine test (BRT) were then evaluated. Binary logistic regression was used to develop a prediction model to identify variables significantly associated with SSNHL, which were then included in the nomogram. The discrimination and calibration ability of the nomogram was evaluated by receiver operating characteristic (ROC), calibration plot, and decision curve analysis both in the development and validation cohorts. Delong's test was used to calculate the difference in ROC curves between the two cohorts.

Results: Thrombin time (TT), red blood cell (RBC), and granulocyte–lymphocyte ratio (GLR) were found to be associated with the diagnosis of SSNHL. A prediction nomogram was constructed using these three predictors. The AUC in the development and validation cohorts was 0.871 (95% CI: 0.789–0.953) and 0.759 (95% CI: 0.635–0.883), respectively. Delong's test showed no significant difference in the ROC curves between the two groups (D=1.482, p=0.141).

Conclusion: In this study, a multifactor prediction model for SSNHL was established and validated. The factors included in the model could be easily and quickly accessed, which could help physicians make early diagnosis and clinical treatment decisions.

KEYWORDS

sudden sensorineural hearing loss, prediction, nomogram, thrombin time, red blood cell, granulocyte lymphocyte ratio

Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as a rapid hearing loss of at least 30 dB at three consecutive frequencies within 72 h (1). As an otological emergency, SSNHL has an annual incidence of 5–30/100,000 cases, with an increasing trend worldwide (1). Only 4.47–15% of cases of SSNHL can be identified with a final diagnosis in the acute stage (2), such as labyrinthine hemorrhage (3) or vascular events (4). The prognosis of SSNHL is poor due to unclear pathophysiology, delayed diagnosis, and treatment. If the disease can be predicted in advance, it will help to give timely treatment and improve the therapeutic effect of SSNHL. Therefore, such prediction models are very important to SSNHL.

Ischemia and hypoxia caused by the alteration of blood flow are important causes of SSNHL (5). Several routine hematological parameters have been identified as prognostic factors, including platelet-to-lymphocyte ratio (PLR), neutrophil–lymphocyte ratio (NLR), and fibrinogen–albumin ratio (FAR) (6–9). However, the relationship between thrombin time (TT), red blood cell (RBC), granulocyte lymphocyte ratio (GLR), and SSNHL is not fully understood. It is worth noting that most of these studies have only predicted the prognosis of SSNHL, and these prognosis models were developed using data from single-center data with different clinical outcome settings leading to different conclusions. Even if several studies previously investigated diagnostic markers (10–12), few studies focused on prediction models for SSNHL.

Therefore, the purpose of this study was to develop a prediction model in the development cohort and verify its reliability in the validation cohort, thus establishing a promising prediction model for SSNHL.

Methods

Study participants

SSNHL refers to a sudden occurrence of sensorineural hearing loss of unknown etiology within 72 h with at least three consecutive frequency losses of 30 dB (1). In the development cohort, Fujian Provincial Geriatric Hospital recruited 39 patients diagnosed with SSNHL and 38 adults who were free of any ear disease, cancer, or any other blood disease in the physical examination as healthy controls from January 2018 to December 2021. All participants ranged in age from 18 to 79 years and underwent conventional coagulation test (CCT) and blood routine test (BRT). We excluded pregnant women and patients who are taking anticoagulant drugs, as well as patients with blood diseases, Meniere's disease, herpes zoster oticus, or any other disease with a known cause of hearing loss. Because low-frequency hearing loss is one of the symptoms of Meniere's disease, patients with low-frequency hearing loss were also excluded. At the same time, 57 adults (29 SSNHL patients and 28 healthy controls) from First Hospital of Putian City were incorporated into the validation cohort. The exclusion criteria were the same as the development cohort as depicted in Figure 1.

This study was reviewed and approved by the institutional review board and ethics committee of Fujian Geriatric Hospital (Ethics Committee No.2020-03-01). All the methods were carried out in accordance with the relevant guidelines and regulations. Informed consent was obtained from all participants.

Data collection

Detailed medical history, which includes details of baseline characteristics (including age, gender, hypertension, diabetes, hypertriglyceridemia, hypercholesterolemia, and autoimmune disease), clinical characteristics (including affected side), accompanying symptoms (such as tinnitus, vertigo, headache, and dizziness), was obtained from all participants.

Clinical and other measurements

Hearing loss was determined by pure-tone audiometry (Conera, Denmark) before and after treatment. Pure-tone average (PTA) was calculated as the average of thresholds (dB HL) at seven frequencies of 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz. The coagulation function parameters were measured by an automatic coagulation analyzer (Sysmex CS5100 or CS2000i, Japan), and the blood routine parameters were measured by a fully automatic hematology analyzer (Sysmex XN 1000 or CN3000, Japan).

Statistical analysis

Post hoc assessments of sample size were performed. In the development cohort, 39 samples in the positive group and 38 samples in the negative group were tested using a two-sided z-test between the area under the receiver operating characteristic (ROC) curve (AUC) under the null hypothesis of 0.500 and an AUC at the alternative hypothesis of 0.871, achieving>99% power at a significance level of 0.050 and a difference of 0.371 was detected. In the validation cohort, 29 samples in the positive group and 28 samples in the negative group achieved 95% power and the detected difference was 0.259.

Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages (%). To compare the difference between groups, the Chi-square test or the Fisher exact test was used for categorical variables and the *t*-test was used for continuous variables.

The prediction model for the risk of SSNHL was established based on the existing information. The steps are as follows:

First, the baseline characteristics of the control group and SSNHL group in the development cohort were balanced, and the 12 items of CCT and BRT parameters were initially selected for candidate predictors. Second, the potential predictors with $p < 0.05$ in the univariate analyses were selected to be included in a multivariate logistic model. Third, a backward step-down selection process was performed by a threshold of $p < 0.05$ to establish a parsimonious model, and a nomogram was formulated in the training cohort. Fourth, the discriminative ability, predictive accuracy, and clinical application value of the model in the training cohort were assessed using a ROC curve, calibration plot, and decision curve analysis (DCA). Finally, the external validity of model performance was

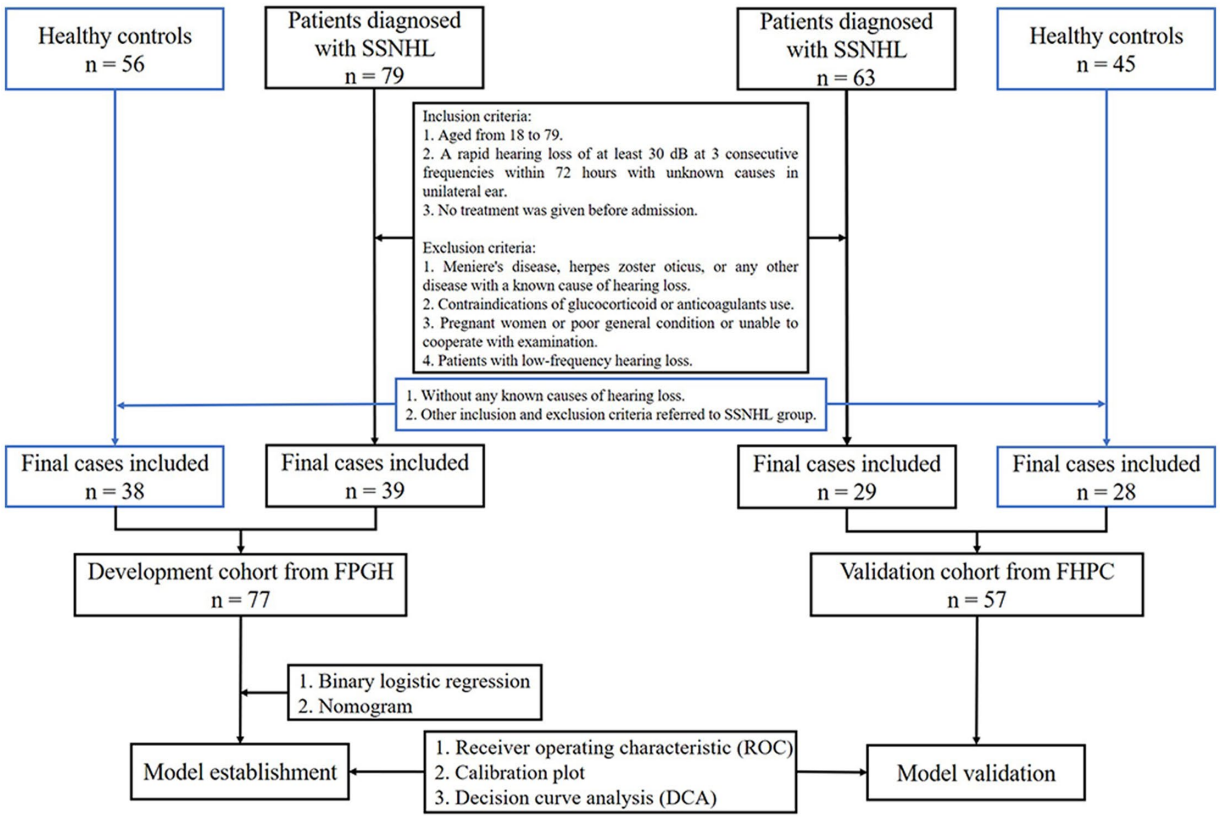

FIGURE 1
Flow chart (FPGH, Fujian Provincial Geriatric Hospital; FHPC, First Hospital of Putian City).

assessed in the validation cohort, and Delong's test was conducted to compare the ROC curves of the development cohort and the validation cohort.

The statistical software used in this study includes SPSS software version 17.0 (IBM) and R software (version 4.2.1). The *p*-values less than 0.05 were considered statistically significant in each statistical analysis.

Results

Baseline characteristics, blood CCT, and BRT parameters in the development and validation cohort

In total, 134 participants were enrolled, 77 in the development cohort and 57 in the validation cohort. The baseline characteristics, CCT, and BRT parameters are detailed in Table 1. Simply, the participants comprised the development cohort (28 women and 49 men) with a median age of 49.57 years and the validation cohort (27 women and 28 men) with a median age of 47.75 years. Both cohorts were comparable not only in terms of age, gender, hypertension, diabetes, hypertriglyceridemia, hypercholesterolemia, and autoimmune disease but also hearing loss, tinnitus, vertigo, dizziness, and headache. The probability of all the basic characteristics in the development cohort was similar to the validation cohort except for hypertension ($p = 0.027$).

Five coagulation function parameters and seven blood routine test parameters were within the normal range in both cohorts. The development cohort exhibited a significantly prolonged PT, INR, TT, and APTT compared with the validation cohort (all $p < 0.001$). Fibrinogen (FIB) in the development cohort was lower but had no statistical difference ($p = 0.130$) than in the validation cohort. The seven blood routine test parameters showed no statistical difference in both cohorts (all $p > 0.05$).

Factors selection for SSNHL prediction model construction in the development cohort

In the development cohort, all baseline characteristics were similar ($p > 0.05$) except for the SSNHL-specific characteristics, including hearing loss ($p < 0.001$), tinnitus ($p < 0.001$), vertigo ($p = 0.002$), in control and SSNHL group (Table 2). The parameters in CCT and BRT, including PT, INR, TT, RBC, granulocyte, lymphocyte, monocyte, and granulocyte to Lymphocyte ratio (GLR), were significantly different (all $p < 0.05$) between the control and the SSNHL group (Table 2).

The factors ($p < 0.05$) were incorporated for the predicted model using logistic regression analysis among the abovementioned CCT and BRT factors. TT (OR = 1.515, 95% CI: 1.031–2.225, $p = 0.034$), RBC (OR = 0.141, 95% CI: 0.039–0.507, $p = 0.003$), and GLR (OR = 3.142, 95% CI: 1.587–6.220, $p = 0.001$) in model 2 can be used for SSNHL prediction model construction (Table 3).

TABLE 1 Baseline characteristics, CCT, and BRT parameters in development and validation cohorts.

Variables	Development cohort (n=77)	Validation cohort (n=57)	χ^2 or t value	p
Age	49.57 ± 12.105	47.75 ± 11.350	0.882	0.379
Male	49(63.6%)	28(49.1%)	2.823	0.093
Hypertension	18(23.4%)	5(8.8%)	4.914	**0.027**
Diabetes	4(5.2%)	3(5.3%)	–	1.000#
Hypertriglyceridemia	18(23.4%)	20(35.1%)	2.211	0.137
Hypercholesterolemia	39(50.6%)	28(49.1%)	0.031	0.861
Autoimmune disease	2(2.6%)	0(0%)	–	0.507#
Headache	1(1.3%)	0(0%)	–	1.000#
Dizziness	4(5.2%)	0(0%)	–	0.136#
Vertigo	9(11.7%)	10(17.5%)	0.923	0.337
Hearing loss	39(50.6%)	29(50.9%)	0.001	0.979
Tinnitus	37(48.1%)	27(47.4%)	0.006	0.938
PT	10.90 ± 0.697	10.42 ± 0.555	4.302	**<0.001**
INR	0.95 ± 0.064	0.91 ± 0.049	4.026	**<0.001**
APTT	27.72 ± 3.216	25.03 ± 2.601	5.178	**<0.001**
TT	18.39 ± 1.873	17.39 ± 0.787	4.212	**<0.001**
FIB	2.68 ± 0.526	2.83 ± 0.574	−1.522	0.130
WBC	6.69 ± 2.279	6.77 ± 2.111	−0.205	0.838
RBC	4.82 ± 0.549	4.72 ± 0.517	1.038	0.301
Platelet	241.32 ± 58.294	246.18 ± 59.918	−0.471	0.639
Granulocyte	4.20 ± 2.013	4.26 ± 1.969	−0.153	0.878
Lymphocyte	1.94 ± 0.661	2.00 ± 0.700	−0.557	0.578
Monocyte	0.41 ± 0.160	0.53 ± 1.178	−0.850	0.397
GLR	2.40 ± 1.516	2.59 ± 2.173	−0.603	0.548

CCT, Conventional Coagulation Test; BRT, Blood Routine Test; PT, Prothrombin Time; INR, International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; TT, Thrombin Time; FIB, Fibrinogen; WBC, White Blood Cell; RBC, Red Blood Cell; GLR, Granulocyte Lymphocyte Ratio. Clinical characteristics were analyzed as a classified variable; all CCT, BRT parameters, and age were analyzed as continuous variables. Data were exhibited with Mean ± SD or n (%).
#Fisher's exact test.
The bold values means $p < 0.05$.

Construction of the prediction risk model

The three candidate factors (TT, RBC, and GLR) were chosen to construct the prediction risk model. According to the logistic regression derived β coefficients, an individual's risk of SSNHL might be calculated as follows:

$$P(\text{SSNHL}) = 1 / \left[1 + e^{(0.731 - \text{TT} \times 0.415 + \text{RBC} \times 1.958 - \text{Granulocyte/Lymphocyte} \times 1.145)}\right]$$

To evaluate the prediction model more readable and convenient, a nomogram was constructed, as shown in Figure 2.

Validation of the risk model

Based on the development cohort, the ROC analysis was significantly different between the control group and the SSNHL group ($p < 0.001$) (Figure 3A). The AUC value of the prediction model was 0.871 (95% CI: 0.789–0.953). The calibration plot is shown in Figure 3B, and DCA is shown in Figure 3C.

The SSNHL prediction model was evaluated in the validation cohort. The ROC analysis was significantly different between the two groups ($p < 0.001$) (Figure 3D). The AUC value of the prediction model was 0.759 (95% CI: 0.635–0.883).

Delong's test for two ROC curves did not find a significant difference between the AUC in the development cohort and the validation cohort ($D = 1.482$, $p = 0.141$). The calibration plot is shown in Figure 3E, and DCA is shown in Figure 3F.

Discussion

The diagnosis of SSNHL is mainly based on the audiogram; however, a subjective audiogram alone cannot accurately diagnose SSNHL, and may also misdiagnose prognosis. In this study, a prediction model of SSNHL was established via binary logistic regression and verified externally. TT, RBC, and GLR were identified

TABLE 2 Baseline characteristics, CCT and BRT parameters of control and SSNHL group in the development cohort.

Variables	Control (*n*=38)	SSNHL (*n*=39)	χ^2 or *t* value	*p*
Age	47.84 ± 11.173	51.26 ± 12.869	−1.242	0.218
Male	26 (68.4)	23 (59.0)	0.742	0.389
Hypertension	9 (23.7)	9 (23.1)	0.004	0.950
Diabetes	2 (5.3)	2 (5.1)	–	1.000
Hypertriglyceridemia	10 (26.3)	8 (20.5)	0.362	0.547
Hypercholesterolemia	18 (47.4)	21(53.8)	0.323	0.570
Autoimmune disease	0 (0.0)	2 (5.1)	–	0.494#
Headache	1 (2.6)	0 (0.0)	–	0.494#
Dizziness	1 (2.6)	3 (7.7)	–	0.615#
Vertigo	0 (0.0)	9 (23.1)	–	**0.002**
Hearing loss	0 (0.0)	39 (100.0)	77.000	**<0.001**
Tinnitus	1 (2.6)	36 (92.3)	62.006	**<0.001**
PT	10.72 ± 0.549	11.08 ± 0.782	−2.356	**0.021**
INR	0.93 ± 0.051	0.96 ± 0.070	−2.581	**0.012**
APTT	27.82 ± 1.934	27.62 ± 4.126	0.274	0.785
TT	17.71 ± 2.248	19.05 ± 1.091	−3.039	**0.002**
FIB	2.69 ± 0.500	2.67 ± 0.557	0.155	0.877
WBC	6.22 ± 1.804	7.16 ± 2.602	−1.851	0.069
RBC	4.99 ± 0.453	4.65 ± 0.588	2.840	**0.006**
Platelet	248.68 ± 56.497	234.15 ± 59.846	1.095	0.277
Granulocyte	3.58 ± 1.582	4.81 ± 2.212	−2.816	**0.006**
Lymphocyte	2.10 ± 0.531	1.78 ± 0.738	2.226	**0.029**
Monocyte	0.37 ± 0.092	0.46 ± 1.199	−2.336	**0.023**
GLR	1.76 ± 0.979	3.02 ± 1.782	−4.020	**<0.001**

CCT, Conventional Coagulation Test; BRT, Blood Routine Test; PT, Prothrombin Time; INR, International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; TT, Thrombin Time; FIB, Fibrinogen; WBC, White Blood Cell; RBC, Red Blood Cell; GLR, Granulocyte Lymphocyte Ratio. Clinical characteristics were analyzed as a classified variable; all CCT, BRT parameters, and age were analyzed as continuous variables. Data were exhibited with Mean ± SD or n (%).
#Fisher's exact test.
The bold values means $p < 0.05$.

as the diagnostic factors for SSNHL and used to build a reliable nomogram. Nomogram has been shown to predict SSNHL in both the development and the validation cohorts and is strongly recommended for clinical use.

In this study, TT was considered to be a risk factor for SSNHL. Prolonged TT was seen in diseases with reduced plasma fibrinogen, such as disseminated intravascular coagulation (12) and dysfibrinogenemia (13). A previous study has shown that dysfunction of inner ear microcirculation plays an important role in SSNHL (14); however, due to the lack of effective evidence-based evidence, the use of anticoagulants has not reached an international consensus (11). Labyrinthine hemorrhage has also been reported as a potential factor for SSNHL (3); meanwhile, oral anticoagulants may interfere with microcirculation in the inner ear by influencing the viscosity of the plasma (15). Our data showed that TT was prolonged before treatment in the SSNHL group. Therefore, TT should be paid more attention to avoid bleeding events or aggravating the condition in older patients with SSNHL or patients who are taking anticoagulants.

RBC has been identified as a risk factor for myometrial invasion in endometrioid endometrial carcinoma patients with metabolic syndrome (16) and as a significant predictor of the risk of adverse cardiovascular events (17). Studies have indicated that the cochlea is more susceptible to hypoxia at high frequencies in rats (18), and hypoxia can impair hearing function in patients with chronic obstructive pulmonary disease (19). In this study, low RBC count is a risk factor for SSNHL and an indicator of blood viscosity. A low RBC count means reduced blood viscosity and the use of anticoagulants should be carefully considered in patients with SSNHL. Furthermore, the labyrinthian artery is the only small-diameter artery in the cochlea, and the decreased RBC count will lead to the reduction of oxygenation (20), which may aggravate cochlear ischemia and hypoxia, then causes SSNHL or exacerbate the condition.

GLR can be regarded as a reliable indicator to predict infectious complications after gastrectomy (21) or systemic spread of streptococcus pyogenes with acute skin infection (22), which is associated with inflammatory reactions. It suggested that increased GLR can be used as a predicted marker of SSNHL. The mechanism of SSNHL is associated with inflammation, which is well demonstrated by steroid therapy (23). Increased granulocyte and/or decreased lymphocyte (especially viral infection) will lead to increased GLR in

TABLE 3 Different logistic regression models for assessing the diagnostic factors of SSNHL.

Variables	Model 1			Model 2		
	B	OR (95% CI)	*p*	*B*	OR (95% CI)	*p*
PT	0.812	2.252(1.103–4.598)	**0.026**	–	–	–
INR$	0.975	2.650(1.198–5.863) $	**0.016**	–	–	–
TT	0.484	1.623(1.168–2.256)	**0.004**	0.415	1.515(1.031–2.225)	**0.034**
RBC	−1.244	0.288(0.114–0.730)	**0.009**	−1.958	0.141(0.039–0.507)	**0.003**
Granulocyte	0.373	1.452(1.088–1.938)	**0.011**	–		–
Lymphocyte	−0.856	0.425(0.189–0.953)	**0.038**	–	–	–
Monocyte$	0.037	1.458(1.031–2.062) $	**0.033**	–	–	–
GLR	0.979	2.662(1.475–4.807)	**0.001**	1.145	3.142(1.587–6.220)	**0.001**
Constant	–	–	–	−0.731	0.481	–

OR, Odds Ratio; CI, Confidence Interval; PT, Prothrombin Time; INR, International Normalized Ratio; TT, Thrombin Time; RBC, Red Blood Cell; GLR, Granulocyte Lymphocyte Ratio. Model 1, unadjusted; Method = Enter. Model 2, adjusted for all factors that $p < 0.05$ in development cohort at baseline; Method = Backward Stepwise (Wald).
$Data used for Logistic Regression was 10×.
The bold values means $p < 0.05$.

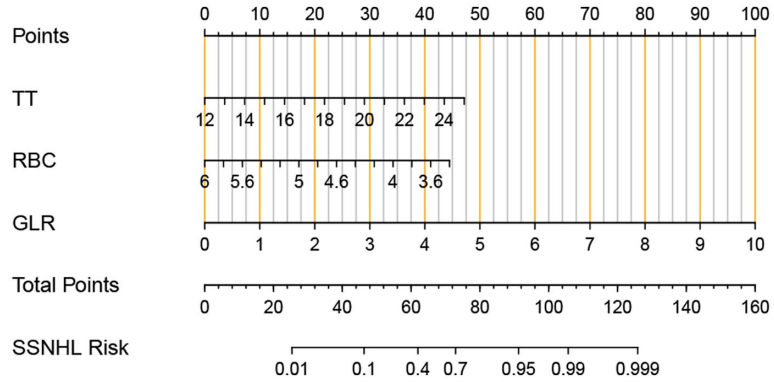

FIGURE 2
Nomogram for predicting the risk of an individual adult sudden sensorineural hearing loss (SSNHL). The values of thrombin time (TT), red blood cell (RBC), granulocyte lymphocyte Ratio (GLR), and points are acquired from each variable axis. The total points on the axis are the sum values of these three factors, which can predict the SSNHL risk.

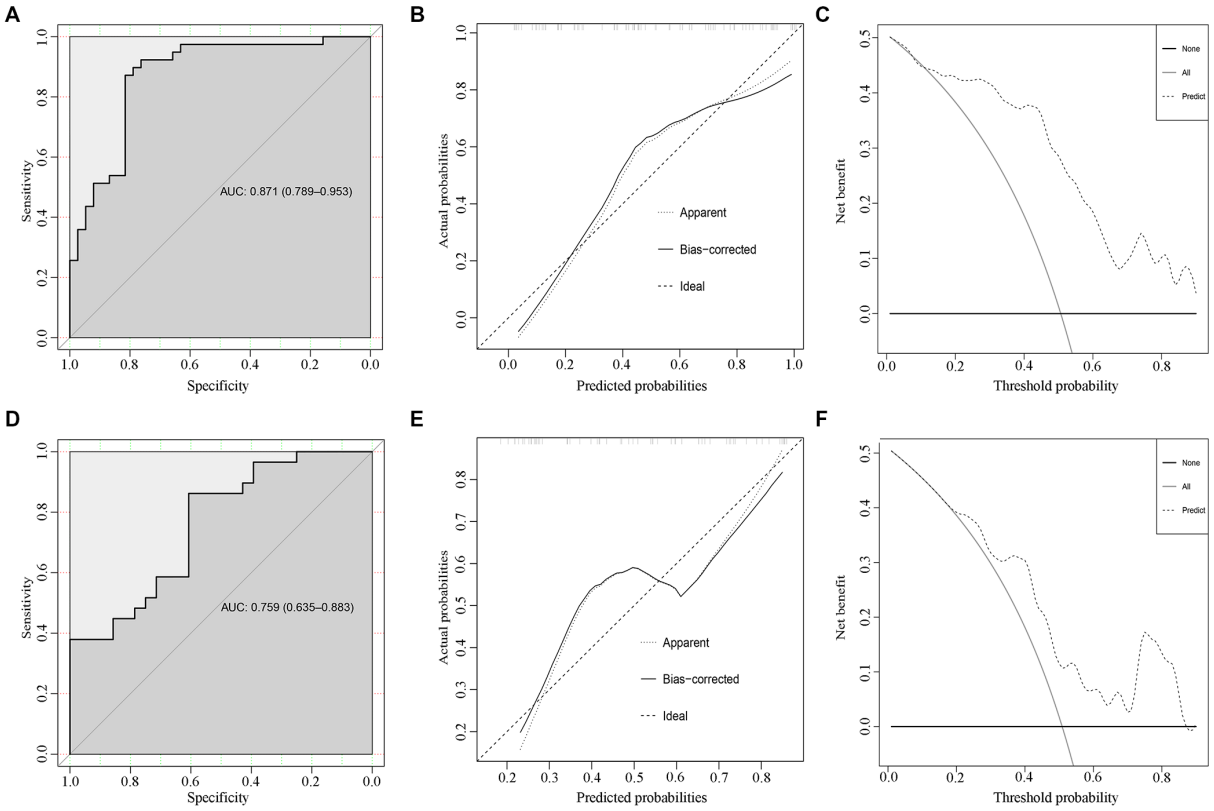

FIGURE 3
Internal and external validations for the SSNHL prediction model. The ROC, calibration plots, and decision curve analysis for the predicting model in the development cohort **(A–C)** and the validation cohort **(D–F)**.

the acute inflammation phase of patients with SSNHL. Therefore, GLR as a predictor of SSNHL is reliable and necessary.

In this study, after excluding not statistically significant variables, a prediction model of SSNHL was established by combining TT, RBC, and GLR, and visualized by nomogram. In the development and validation cohorts, the AUC values of the prediction model were 0.871 (95% CI: 0.789–0.953) and 0.759 (95% CI: 0.635–0.883), respectively, showing a certain predictive ability. Meanwhile, the calibration plot and DCA show good performance in the development and validation cohorts. However, it is difficult for all instruments in both centers to be the same. It has been found that the performance of the instruments is stable, and the measurement reference values are the same in both centers. In addition, the highly consistent results between the two centers further indicate the stability of our model. It is also limited by the retrospective design and small sample size, and a prospective cohort study with a larger sample size is needed to further refine this

study. Nevertheless, we believe that the prediction model and nomogram will play an important role in guiding the clinical diagnosis and management of SSNHL.

Conclusion

In this study, a prediction model and nomogram of SSNHL were established with good discrimination and calibration and were helpful for clinicians to diagnose SSNHL timely and to take reasonable treatment decisions.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding authors

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of Fujian Geriatric Hospital (Ethics Committee No. 2020-03-01). Written informed consent to participate in this study was provided by the patient/participants or patient/participants legal guardian/next of kin. Written informed consent was obtained from the individual(s) and/or minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

CZ and JC were involved in study conception and design, designed the experiment, analyzed the data, drafted the manuscript, discussed results, and revised and finalized the manuscript. YY performed the SSNHL diagnosis, collected the data, evaluated the treatment outcome, and discussed the results. SH analyzed the data and confirmed the statistical results. WH collected the data from physical examination persons. ZC and DH performed the SSNHL diagnosis, collected the data, and evaluated the treatment outcome. CL was involved in study conception and design, discussed the results, and revised and finalized the manuscript. All authors approved the final copy of this manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Jun Yang,
Shanghai Jiaotong University School of Medicine, China

REVIEWED BY
Yu Sun,
Huazhong University of Science and Technology, China
Shan Sun,
Fudan University, China
Jing Wang,
Fudan University, China

*CORRESPONDENCE
Mingming Wang
✉ wmmship@126.com

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Prognostic changes after sudden deafness in patients with inner ear malformations characterized by LSCC: a retrospective study

Lei Chen[1,2], Qinglei Dai[2], Xin Gao[1,2], Na Hu[3], Xiao Sun[2], Haibo Wang[1,2] and Mingming Wang[1,2]*

[1]Department of Otolaryngology Head and Neck Surgery, Shandong Provincial ENT Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China, [2]Department of Otology Medicine, Shandong Provincial ENT Hospital, Shandong University, Jinan, China, [3]Department of Radiology, Shandong Provincial ENT Hospital, Shandong University, Jinan, Shandong, China

Introduction: This study aimed to investigate the clinical features and prognosis of sudden sensorineural hearing loss in patients with lateral semicircular canal (LSCC) malformation.

Methods: This study enrolled patients with LSCC malformation and sudden sensorineural hearing loss (SSNHL) who were admitted to Shandong ENT Hospital between 2020 and 2022. We collected and analyzed data on examinations of audiology, vestibular function, and imaging records of patients and summarized the clinical characteristics and prognosis of these patients.

Results: Fourteen patients were enrolled. Patients with LSCC malformation was noted in 0.42% of all SSNHL cases during the same period. One patients had bilateral SSNHL and the rest had unilateral SSNHL. Of them, eight and six patients had unilateral and bilateral LSCC malformations, respectively. Flat hearing loss was noted in 12 ears (80.0%) and severe or profound hearing loss was noted in 10 ears (66.7%). After treatment, the total efficacy rate of SSNHL with LSCC malformation was 40.0%. Vestibular function was abnormal in all patients, but only five patients (35.7%) had dizziness. There were statistically significant differences in the vestibular functions between patients with LSCC malformation and matched patients without the malformation hospitalized during the same period ($p<0.05$).

Conclusion: Patients with SSNHL and LSCC malformation had flat-type and severe hearing loss and worse disease prognosis compared to those with SSNHL without LSCC malformation. Vestibular function is more likely to be abnormal; however, there was no significant difference in vestibular symptoms between patients with and without LSCC malformation. LSCC is a risk factor for the prognosis of SSNHL.

KEYWORDS

lateral semicircular canal malformation, semicircular canal, sudden sensorineural hearing loss, prognosis, vestibular function, dizziness

1. Introduction

Semicircular canal malformation is a rare type of inner ear malformation. In the fifth week of embryonic development, the superior semicircular canal develops, followed by the posterior semicircular canal and finally the lateral semicircular canal (LSCC), which is most prone to malformation. Therefore, malformations of the superior and posterior semicircular canals are always accompanied by LSCC abnormalities. Malformation of an isolated LSCC has been reported (1). LSCC malformation can occur with other inner ear malformations, including cochlear, vestibular, and vestibular aqueducts, depending on the stage of inner ear development (2). The malformed LSCC are usually short and wide but may be narrow. In extensive malformations, the vestibular is dilated and forms a common lumen with LSCC (3). The imaging diagnosis can be a temporal bone computed tomography (CT) finding in which the central bone island of the LSCC is shorter than 7 mm (4).

Sudden sensorineural hearing loss (SSNHL) is defined as a sudden, unexplained sensorineural hearing loss of ≥30 dB in at least three consecutive frequencies within 72 h (5). SSNHL can occur in patients of any age and does not vary with sex, side, season, or geographic area. Its clinical manifestations can be accompanied by vertigo or dizziness (6, 7). SSNHL can also occur in patients with LSCC malformation; however, few studies have examined the clinical characteristics of these patients. Thus, this study aimed to investigate the clinical features and prognosis of SSNHL in patients with LSCC malformation. To the best of our knowledge, no study has investigated this.

2. Materials and methods

2.1. Participants

A retrospective analysis was conducted on 14 patients with LSCC malformation who were hospitalized for SSNHL at Shandong ENT Hospital between 2020 and 2022. After admission, they underwent a detailed medical history inquiry, audiology examination, vestibular function examination, and imaging examination. We selected 165 matched patients admitted to the hospital during the same period as the control group. This study was conducted in accordance with the Declaration of Helsinki and was approved by committee ethics board of the hospital (No. 2023-006-01); informed consent was obtained from all the participants.

2.2. Inclusion and exclusion criteria

Patients presented with SSNHL, excluding retrocochlear diseases and middle ear lesions. Patients with LSCC malformation (with or without vestibular malformation) who underwent CT of their temporal bones, did not undergo treatment before admission, course of disease was less than 1 month, and had no contraindications with glucocorticoids. A total of 165 patients hospitalized during the same period and matched with clinical characteristics without LSCC deformity were selected as the control group.

2.3. Audiology examination

All patients underwent acoustic immittance (GSI TympStar, United States), pure-tone audiometric threshold tests (GSI-61, United States), distortion product optoacoustic emissions (IHS Smart EP, United States), auditory brainstem responses (IHS Smart EP, United States) before treatment to exclude other lesions. Pure-tone audiometric threshold tests were performed twice a week during treatment.

2.4. Vestibular function examination

All patients underwent video head impulse test (vHIT, Ulmer, SYNAPSIS, Marseille, France), caloric testing (Ulmer VNG, v. 1.4; SYNAPSYS, Marseille, France), vestibular autorotation test (VAT, Western Systems Research, Pasadena, United States) and vestibular-evoked myogenic potential testing (VEMP, Neurosoft Ltd., Ivanov, Russia). An abnormal test was considered to indicate abnormal vestibular function.

2.5. Imaging tests

Magnetic resonance imaging of the inner ear was performed in all patients to rule out abnormal development of the cochlea and inner auditory canals. Patients with abnormal vestibular and semicircular canals were diagnosed using high-resolution CT (HRCT) of the temporal bone.

2.6. Classification and treatment

According to German Guidelines (7), patients were classified into the following four groups. Total hearing loss group (affecting all frequencies with an average threshold ≥81 dB HL), flat-type group (affecting all frequencies with an average threshold ≤80 dB HL), high-frequency group (at least affecting frequencies of 4 and 8 kHz) and low-frequency SSNHL group (affecting frequencies of 250, 500, and 1,000 Hz). The degree of hearing loss was graded according to the pure-tone average (PTA) at the damaged frequencies: normal, ≤25 dB HL; mild, 26–40 dB HL; moderate, 41–60 dB HL; severe, 61–80 dB HL; and profound, ≥81 dB HL. According to the treatment protocol of the Chinese Guidelines for the Diagnosis and Treatment of Sudden Deafness (2015), all patients were treated after admission. We used glucocorticoids, neurotrophic drugs, and hemodynamic therapy to improve blood flow, blood thinning and viscosity reduction. Efficacy evaluation of treatment included complete recovery, the improvement of the affected ear within 10 dB HL of the hearing level of the unaffected ear or to normal; marked recovery, ≥30 dB HL improvement in PTA of the damaged frequencies; slight recovery, the PTA of damaged frequencies improved by15–30 dB HL improvement; and no recovery, the PTA of the damaged frequencies improved by <15 dB HL.

2.7. Statistical analysis

In this study, the chi-square test was used for all test methods, and Fisher's precision probability test was used when the chi-square test

could not be performed. SPSS 20.0 software was used for statistical analysis, and $p < 0.05$ indicated statistical significance.

3. Results

This study enrolled patients with SSNHL who were admitted to our hospital between January 2020 and December 2022. Of the 14 patients with LSCC malformation confirmed using HRCT of the temporal bone, 13 patients had unilateral SSNHL and one patient had bilateral SSNHL. The average age of the patients was 46.0 ± 12.3 years and 13 patients were male. Eight patients had unilateral LSCC malformation (Tables 1, 2), and six had bilateral LSCC malformation (Tables 3, 4). Four of the eight patients with unilateral LSCC malformation were associated with vestibular malformation, three of the six patients with bilateral malformation were associated with bilateral vestibular malformation, and none of these patients had cochlear malformation. Patients with LSCC malformation accounted for 0.42% of the patients with SSNHL during the same period.

In terms of hearing loss, of the eight patients with unilateral LSCC malformation, three (37.5%) cases were ipsilateral and five (62.5%) were contralateral. Among the six patients with bilateral LSCC malformation, one had bilateral SSNHL and the rest had unilateral SSNHL. Among the 15 ears with hearing loss, the hearing loss was mild in three ears (20.0%), moderate in two (13.3%), severe in eight (53.3%), and profound in two (13.3%); 12 ears (80.0%) were of the flat-type, one (6.7%) was of a high-frequency type, and two (13.3%) were of the total hearing loss type. We selected 165 patients as the control group. Among 165 matched patients admitted to the hospital during the same period, 88 (53.3%) had flat-type hearing loss and 77 (46.7%) non-flat-type, with a significant difference between these two groups ($p < 0.05$). Among these matched patients, 30 (18.2%) had mild hearing loss, 21 (12.7%) had moderate hearing loss, 91 (55.2%) had severe hearing loss and 23 (13.9%) had profound hearing loss, with no significant difference between these two groups ($p > 0.05$). After treatment, among the 15 treated ears, two (13.3%) showed complete recovery, three (20.0%) showed marked recovery, one (6.7%) showed a slight recovery, and nine (60.0%) had no recovery; the total effective rate was 40.0%. Among 88 controlled patients with SSNHL and without malformation who were hospitalized during the same period and had the flat type of hearing loss and less than 1 month of disease course, 10 (11.4%) showed complete recovery, 22 (25.0%) showed marked recovery, 28 (31.8%) showed a slight recovery, and 28 (31.8%) had no recovery. There was a statistically significant difference in the efficacy between these two groups ($p < 0.05$).

Typical CT images of the LSCC and vestibular malformations are shown in Figure 1. In terms of vestibular function, patients 4 and 7 experienced dizziness before the onset of SSNHL. Dizziness was present in three (37.5%) of eight patients with unilateral LSCC malformation and two (33.3%) of six patients with bilateral LSCC malformation. Abnormal vestibular function was observed in all (100%) patients with abnormal rates of 71.4% on the caloric test, 57.1% on cVEMP, 57.1% on oVEMP, and 42.9% on vHIT (25% in unilateral LSCC and 66.7% in bilateral LSCC). The VAT anomaly rate was 64.3% (unilateral LSCC anomaly rate, 37.5%; bilateral LSCC anomaly rate, 100%; $p < 0.05$). The caloric test results showed that among eight patients with unilateral LSCC malformations, three (37.5%) were normal, one (12.5%) had an abnormal contralateral side, and four (50.0%) had an abnormal ipsilateral side. Among the six patients with bilateral LSCC malformations, one was bilateral normal, one was bilateral abnormal, and four were unilateral

TABLE 1 Clinical characteristics of unilateral LSCC malformation patients with SSNHL.

Patient No.	Sex	Age	Side of LSCC malformation	Combined vestibular malformation	Side of SSNHL	Degree of hearing loss	Efficacy of treatment
1	M	57	L	No	L	L: Severe R: Normal	I
2	M	43	L	No	L	L: Profound R: Mild	III
3	M	33	R	No	L	L: Mild R: Normal	IV
4	M	38	L	No	R	L: Profound R: Moderate	IV
5	M	54	L	Yes	L	L: Severe R: Normal	IV
6	M	52	R	Yes	L	L: Severe R: Normal	I
7	M	52	R	Yes	L	L: Severe R: Profound	IV
8	F	58	R	Yes	L	L: Severe R: Normal	IV

M, male; F, female; L, left; R, right; I, complete recovery; II, marked recovery; III, slight recovery; IV, no recovery.

TABLE 2 Vestibular function tests of unilateral LSCC malformation patients with SSNHL.

Patient No.	Vertigo	Caloric test	cVEMP	oVEMP	vHIT	VAT
1	No	N	N	N	N	AN
2	No	N	RA	N	N	N
3	No	LA	BA	BA	N	N
4#	Yes	LA	LA	LA	LA	N
5	Yes	LA	N	BA	N	AN
6	No	RA	LA	N	N	N
7#	No	RA	BA	RA	RA	AN
8	Yes	N	LA	N	N	N

N, normal; AN, abnormal; LA, left abnormality; RA, right abnormality; BA, bilateral abnormality; #, there was dizziness before the onset of SSNHL.

TABLE 3 Clinical characteristics of bilateral LSCC malformation patients with SSNHL.

Patient No.	Sex	Age	Combined vestibular malformation	Side of SSNHL	Degree of hearing loss	Efficacy of treatment
9	M	64	L: No	L	L: Profound	II
			R: No		R: Mild	
10	M	56	L: No	R	L: Normal	IV
			R: No		R: Mild	
11	M	41	L: No	L	L: Moderate	IV
			R: No		R: Mild	
12	M	19	L: Yes	B	L: Severe	IV
			R: Yes		R: Mild	IV
13	M	35	L: Yes	L	L: Severe	II
			R: Yes		R: Normal	
14	M	42	L: Yes	R	L: Normal	II
			R: Yes		R: Severe	

M, male; F, female; L, left; R, right; B, bilateral side; I, complete recovery; II, marked recovery; III, slight recovery; IV, no recovery.

abnormal. Among 165 matched patients with SSNHL and without LSCC malformation during the same period, 121 (73.3%) had an abnormal vestibular function, and 44 (26.7%) had a normal vestibular function. There was a significant difference between these two groups ($p < 0.05$).

4. Discussion

To the best of our knowledge, this study is the first to report the clinical characteristics of SSNHL in patients with LSCC malformation.

Hearing loss or normal hearing may be associated with LSCC malformation, and the type of hearing loss may be conductive, sensorineural, or mixed (8). No correlation exists between hearing loss and isolated dysplasia in patients with LSCC (9). They may or may not have vestibular symptoms, and vestibular function tests can be normal or abnormal. Bilateral LSCC malformation with other inner ear malformations often present with profound bilateral hearing loss and vestibular diseases. Isolated unilateral LSCC malformation often presents as ipsilateral lateral semicircular canal paresis, and hearing function is usually impaired to varying degrees, but it can also be normal (10). There is also isolated LSCC malformation that may accompany sensorineural hearing loss without vestibular symptoms (11). Thus, the relationship between LSCC malformations, hearing loss, and vestibular dysfunction remains controversial.

The etiology and pathophysiological mechanisms of SSNHL have not been fully elucidated, and local and systemic factors may cause SSNHL. Thus, many factors are related to disease prognosis, which may include the characteristics of the disease, laboratory tests, and genetics (6, 12–14). Different types of SSNHL have different pathological mechanisms, curative effects, and prognostic factors (6, 15).

In this study, LSCC malformation was not accompanied by cochlear malformation, and hearing was good before onset. Patients with SSNHL mainly had flat-type hearing loss and the degree of hearing loss was severe or profound. The pathogenesis of the flat-type may be inner ear vasospasm or blood labyrinth barrier is broken, which may indicate that the inner ear vessels of patients with LSCC malformation are more likely to be abnormal (16–18). The specific mechanism needs to be further studied. It should be noted that patients with unilateral LSCC malformation may have ipsilateral and contralateral SSNHL. In this study, the ipsilateral and contralateral SSNHL incidence rates were 37.5 and 62.5%, respectively. After treatment, the disease prognosis of these patients was significantly

TABLE 4 Vestibular function tests of bilateral LSCC malformation patients with SSNHL.

Patient No.	Vertigo	Caloric test	cVEMP	oVEMP	vHIT	VAT
9	No	LA	N	LA	LA	AN
10	No	BA	BA	N	BA	AN
11	No	LA	N	N	N	AN
12	Yes	N	BA	LA	RA	AN
13	No	LA	N	LA	N	AN
14	Yes	RA	N	BA	RA	AN

N, normal; LA, left abnormality; RA, right abnormality; BA, bilateral abnormality; AN，abnormality.

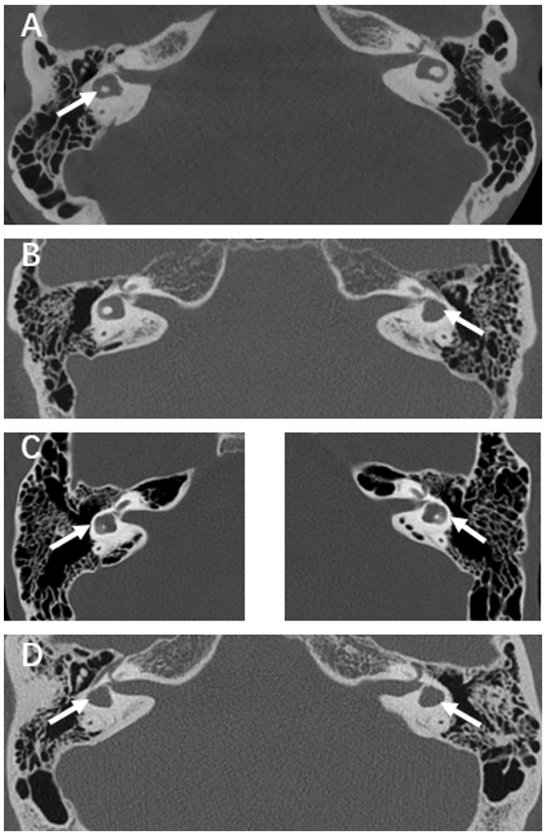

FIGURE 1
(A) HRCT scan of a patient with right LSCC malformation. **(B)** Example of a left LSCC malformation case with vestibular malformation. **(C)** Example of a bilateral LSCC malformations case, left and right side are placed separately. **(D)** Example of a bilateral LSCC malformations case with bilateral vestibular malformations.

different from that of patients with flat-type hearing loss and without LSCC malformation, indicating that LSCC malformation is a risk factor for disease prognosis.

Previous studies showed that dizziness is an uncommon symptom in patients with LSCC malformation, and even when abnormal findings are observed in vestibular function tests in patients with LSCC dysplasia, these patients may not be accompanied by dizziness (19, 20). Some studies have shown that although patients with LSCC deformity may not be accompanied by vertigo, atypical spontaneous nystagmus, such as downward pulsating nystagmus or spontaneous nystagmus changing direction, may be observed in patients with bilateral LSCC dysplasia (21). Only two patients in our study had a history of dizziness before the onset of SSNHL, and five patients experienced dizziness at SSNHL onset. This rate is similar to that of dizziness occurrence in patients without LSCC malformation (22), and patients with LSCC malformation are not more likely to have vestibular symptoms due to SSNHL. No vestibular symptoms were more likely to occur, even in patients with bilateral LSCC malformation. The absence of dizziness symptoms in patients with LSCC malformation is generally due to compensation of the central nervous system. Occurrence of dizziness may be due to incomplete compensation and insufficient residual balance function of the peripheral vestibular system. VAT examination has advantages in detecting bilateral LSCC deformities, and the abnormality rate of bilateral LSCC was significantly higher than that of unilateral LSCC. Previous studies have reported an important role of VAT in patients with vestibular migraine and decompensated Meniere's disease (23, 24). VAT inspection should receive sufficient attention (25).

A limitation of this study is the low incidence of LSCC malformation and the small number of patients. A study with a larger number of patients is needed to obtain more reliable results. We plan to continue to treat and monitor patients in this field to obtain more reliable results.

In summary, our findings revealed that patients with SSNHL and LSCC malformation usually have flat-type and severe hearing loss. There was significant difference in the efficacy of treatment between SSNHL patients with and without LSCC malformation. Patients with LSCC malformation often have abnormal vestibular function test results, but no significant difference was noted in the vestibular symptoms between SSNHL patients with and without LSCC malformation. The findings of this study might provide a basis for diagnosis, treatment, and prognosis in clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the Second People's Hospital of Shandong Province. Written informed consent for

participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

LC was responsible for collecting, analyzing data, and writing the article. QD, XG, NH, XS, and HW participated in the data collection and study design. MW conceived and designed the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Lisheng Yu,
Peking University People's Hospital, China

REVIEWED BY
Daogong Zhang,
Shandong Provincial ENT Hospital, China
Teru Kamogashira,
The University of Tokyo, Japan

*CORRESPONDENCE
Wei Yuan
✉ yuanwei@ucas.ac.cn

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Differentially expressed miRNA profiles of serum-derived exosomes in patients with sudden sensorineural hearing loss

Juhong Zhang[1,2], Haizhu Ma[1], Guijun Yang[1], Jing Ke[1,2], Wenfang Sun[1], Li Yang[1], Shaojing Kuang[1], Hai Li[3] and Wei Yuan[1,2]*

[1]Department of Otorhinolaryngology Head and Neck Surgery, Chongqing General Hospital, Chongqing, China, [2]School of Basic Medicine, Chongqing Medical University, Chongqing, China, [3]Department of Otorhinolaryngology Head and Neck Surgery, Xuanhan County People's Hospital, Dazhou, Sichuan, China

Objectives: This study aimed to compare the expressed microRNA (miRNA) profiles of serum-derived exosomes of patients with sudden sensorineural hearing loss (SSNHL) and normal hearing controls to identify exosomal miRNAs that may be associated with SSNHL or serve as biomarkers for SSNHL.

Methods: Peripheral venous blood of patients with SSNHL and healthy controls was collected to isolate exosomes. Nanoparticle tracking analysis, transmission electron microscopy, and Western blotting were used to identify the isolated exosomes, after which total RNA was extracted and used for miRNA transcriptome sequencing. Differentially expressed miRNAs (DE-miRNAs) were identified based on the thresholds of $P < 0.05$ and $|\log_2 \text{fold change}| > 1$ and subjected to functional analyses. Finally, four exosomal DE-miRNAs, including PC-5p-38556_39, PC-5p-29163_54, PC-5p-31742_49, and hsa-miR-93-3p_R+1, were chosen for validation using quantitative real-time polymerase chain reaction (RT-qPCR).

Results: Exosomes were isolated from serum and identified based on particle size, morphological examination, and expression of exosome-marker proteins. A total of 18 exosomal DE-miRNAs, including three upregulated and 15 downregulated miRNAs, were found in SSNHL cases. Gene ontology (GO) functional annotation analysis revealed that target genes in the top 20 terms were mainly related to "protein binding," "metal ion binding," "ATP binding," and "intracellular signal transduction." Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis revealed that these target genes were functionally enriched in the "Ras," "Hippo," "cGMP-PKG," and "AMPK signaling pathways." The expression levels of PC-5p-38556_39 and PC-5p-29163_54 were significantly downregulated and that of miR-93-3p_R+1 was highly upregulated in SSNHL. Consequently, the consistency rate between sequencing and RT-qPCR was 75% and sequencing results were highly reliable.

Conclusion: This study identified 18 exosomal DE-miRNAs, including PC-5p-38556_39, PC-5p-29163_54, and miR-93-3p, which may be closely related to SSNHL pathogenesis or serve as biomarkers for SSNHL.

KEYWORDS

sudden sensorineural hearing loss, exosomes, miRNA transcriptome sequencing, miRNA, biomarkers

1. Introduction

Sudden sensorineural hearing loss (SSNHL) has no identifiable cause and is characterized by a sudden hearing loss of ≥30 dB HL for at least three consecutive frequencies within 72 h (1). SSNHL is mostly unilateral but can occur bilaterally or successively. Its overall incidence rate is increasing globally (2), and treatment responses or effects vary greatly among individuals (3). A considerable number of patients with SSNHL have poor treatment responses (4), which can lead to varying degrees of hearing loss and even permanent severe deafness, thereby seriously affecting patients' quality of life and placing a burden on their families and society. Therefore, it is of great clinical significance to explore the underlying pathogenesis of SSNHL to formulate treatment plans and improve prognosis.

The etiology and pathogenesis of SSNHL have not been fully elucidated. A clear cause, such as certain drugs or tumors, was determined in only 10–15% of the patients with SSNHL, during the onset period (5). The onset of SSNHL may be related to infection, circulatory pathogenesis, or autoimmunity. Infections can be caused by bacteria, spirochetes, and other pathogens, of which viral infections are the most common. Vascular obstruction and changes in the biological activity of vascular endothelial cells can cause cochlear circulatory dysfunction, which is considered the main cause of SSNHL (6–8); however, the exact cause of SSNHL remains a controversial topic.

Exosomes are extracellular vesicles (with a diameter of 30–150 nm) wrapped in a lipid bilayer. They are released from most cell types and can mediate intercellular communication via receptor signaling or cargo delivery to recipient cells (9). In 2018, Wong et al. (10) discovered the existence of exosomes in the inner ear and found that exosomes exert a protective effect against cisplatin- and gentamicin-induced ototoxicity, thus suggesting their potential use as biomarkers. Breglio et al. (11) found that exosomes also protect against aminoglycoside-induced hair cell death, and hair-cell-derived exosomes were found in the perilymph of patients with Meniere's disease, conductive/mixed hearing loss, and genetic SNHL (12). Furthermore, mesenchymal stromal/stem cell-derived exosomes alleviate cisplatin-induced ototoxicity (13–15). However, there have been few studies regarding the relationship between exosomes and SSNHL.

MicroRNAs (miRNAs) are endogenous, short, and non-coding RNAs that regulate gene expression through sequence-specific base pairing with the 3′-untranslated regions (3′-UTRs) of target mRNAs. Circulatory miRNAs are secreted by exosomes, microparticles, vesicles, apoptotic bodies, and protein-miRNA complexes, which exist in saliva, blood, plasma, and other bodily fluids (16). Kamal and Shahidan (17) compared exosomal miRNAs to non-exosomal miRNAs and observed that exosomal miRNAs are more stable during the cell cycle and have a greater potential value as biomarkers. A small number of studies have identified differentially expressed miRNAs (DE-miRNAs) in the serum/plasma of patients with SSNHL, and these DE-miRNAs are functionally enriched (18–20). However, these DE-miRNAs are non-exosomal miRNAs, and exosomal DE-miRNAs have not been identified.

In this study, we compared the expression profiles of serum-derived exosomal miRNAs in patients with SSNHL and normal hearing controls to identify exosomal miRNAs that might be associated with SSNHL pathogenesis or serve as biomarkers for SSNHL.

Abbreviations: miRNA, microRNA; SSNHL, sudden sensorineural hearing loss; DE-miRNAs, differentially expressed miRNAs; RT-qPCR, quantitative real-time polymerase chain reaction; GO, Gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; 3′-UTR, 3′-untranslated region; NTA, nanoparticle tracking analysis; TEM, transmission electron microscopy; MDA, malondialdehyde; AMPK, Adenosine 5′-monophosphate activated protein kinase.

2. Materials and methods

2.1. Sample collection and ethics review

Based on clinical practice guidelines on sudden hearing loss (update) (1), we included hospitalized patients (18–65 years old), who met the following diagnostic criteria for unilateral SSNHL within 3 weeks of onset: no treatment, no previous trauma or surgery history, and no cranial nerve damage except for cranial nerve VIII. Normal hearing controls were recruited among hospital staff.

Exclusion criteria were as follows: Meniere's disease, herpes zoster infection, noise-induced deafness, exposure to toxic drugs, other internal diseases of known etiology, meningitis, metabolic diseases, vascular diseases, and autoimmune diseases.

According to the selection and exclusion criteria, six patients with SSNHL and six healthy volunteers were included in this study. Written informed consent was provided by each patient who volunteered before sampling. Clinical information concerning the recruited individuals is shown in Table 1 and Supplementary Figures 1, 2. This study was approved by the Medical Ethics Committee of Chongqing General Hospital (approval no. KYS2021-025-01).

Peripheral venous blood of the six patients with SSNHL and six controls was collected and centrifuged at 1,900 × *g* for 10 min and 13,000 × *g* for 2 min at 4°C. The obtained serum supernatants were stored at −80°C.

2.2. Isolation and identification of serum exosomes

Exosomes were isolated from the serum of patients with SSNHL and controls using high-speed centrifugation at 4°C (21). Briefly, the serum samples were thawed on ice and centrifuged at 500 × *g* for 10 min. The supernatant was transferred to a new sterile centrifuge tube and centrifuged initially at 2,000 × *g* for 30 min and then at 10,000 × *g* for 30 min. The supernatant was then filtered using a 0.22 μm sterile filter, added to an ultra-high-speed centrifuge tube, and centrifuged at 120,000 × *g* for 70 min. The sediments (i.e., exosomes) were resuspended in sterile phosphate buffer saline (PBS).

Concentrations of the isolated exosomes were determined using a bicinchoninic acid (BCA) assay kit (Beyotime Biotechnology, Shanghai, China) according to the manufacturer's

TABLE 1 Physiological and biochemical indices of sudden sensorineural hearing loss (SSNHL) patients and healthy individuals.

Type	Number	Sex	Age	Location	Complication	Pure tone hearing, dBHL						CPR (mg/dl)	SBP (mm Hg)	DBP (mm Hg)	blood glucose (mmol/L)	LDL (mmol/L)	TG (mmol/L)	ApoB (g/L)	Aim
						250 Hz	500 Hz	1,000 Hz	2,000 Hz	4,000 Hz	8,000 Hz								
SSNHL	1	Male	27	Right	Tinnitus, feeling of ear fullness	65	70	95	110	120	100↓	1.7	110	72	4.82	3.13	1.29	0.89	Sequencing
	2	Female	50	Left	Colitis with tinnitus, feeling of ear fullness, and dizziness	60	55	40	55	50	75	3.9	139	90	5.34	2.64	0.68	0.71	
	3	Female	57	Right	Tinnitus, feeling of ear fullness	95	90	95	95	90	80	11.7	120	72	4.19	2.96	0.86	0.72	
	4	Male	19	Left	Tinnitus, feeling of ear fullness	40	35	40	20	15	15	2.12	135	83	4.85	2.25	1.17	0.6	RT-qPCR
	5	Female	54	Right	Hepatitis B with Tinnitus, feeling of ear fullness	5	0	10	35	70	70	1.45	125	74	4.97	3.78	1.22	1.01	
	6	Male	68	Left	Tinnitus, feeling of ear fullness	55	65	70	55	70	85	0.41	109	77	4.99	1.17	1.41	0.46	
Healthy	1	Male	24	Right	/	−5	0	−5	0	5	5	/	/	/	/	/	/	/	Sequencing
				Left		0	0	−5	0	0	0								
	2	Male	24	Right	/	0	0	−5	0	0	0	/	/	/	/	/	/	/	
				Left		0	−5	0	0	−5	0								
	3	Male	26	Right	/	5	5	0	0	5	5	/	/	/	/	/	/	/	
				Left		0	0	5	0	5	0								
	4	Male	35	Right	/	5	5	0	5	5	10	/	/	/	/	/	/	/	RT-qPCR
				Left		5	0	5	5	10	5								
	5	Female	33	Right	/	0	0	−5	0	5	5	/	/	/	/	/	/	/	
				Left		0	0	5	0	−5	0								
	6	Female	33	Righ	/	−5	0	0	0	5	5	/	/	/	/	/	/	/	
				Left		0	0	0	−5	0	0								

CPR, cardiopulmonary resuscitation; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; TG, triglyceride; ApoB, Apolipoprotein B; RT-qPCR, quantitative real-time polymerase chain reaction.

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instructions, and exosomes were identified using nanoparticle tracking analysis (NTA) (22), transmission electron microscopy (TEM) (23), and Western blotting (24). NTA was performed using a ZetaView PMX 110 instrument (Particle Metrix, Meerbusch, Germany) and its corresponding software (ZetaView 8.02.28) to measure exosome mean, median, and mode sizes (indicated as diameters) as well as the sample concentration. TEM was performed using a JEM 1230 transmission electron microscope (JEOL USA Inc., Peabody, MA, USA) at 110 kV, and images were captured with an UltraScan 4000 CCD camera & First Light Digital Camera Controller (Gatan Inc., Pleasanton, CA, USA) to visualize the exosome morphology and ultrastructure. Anti-TSG101 (1:1,000 dilution), anti-CD9 (1:500 dilution), and anti-HSP70 (1:2,000 dilution) were used as primary antibodies and incubated overnight at 4°C. Goat anti-rabbit IgG (H + L)-HRP (1:5,000 dilution) was used as the secondary antibody and incubated at 37°C for 1 h. Then, 1 × PBST was used to wash the membrane for 5 min each time, and chemiluminescent development was monitored after washing the film three times.

2.3. Exosomal miRNA sequencing

RNAiso Plus (TAKARA, Japan) was used to extract total RNA from the isolated exosomes, which was sent to Lianchuan Biotechnology (Hangzhou, China) for miRNA sequencing ($n = 3$). TruSeq Small RNA Sample Prep Kits (Illumina, San Diego, USA) were employed for miRNA library preparation and sequencing. The constructed cDNA library products were sequenced using an Illumina Hiseq2500 platform, and the sequence reading was 1 × 50 bp at single ends.

Raw data incorporate sequence and sequencing quality information of Illumina reads in FASTQ format. ACGT101-miR software (v.4.2) was used to perform the following data quality control steps: the removal of 3′ connectors and N sequences to obtain clean data, retention of sequences with the base degree of 18–26 nt, mapping of sequences to Rfam/Repbase databases, and filtering of non-miRNA sequences. The data obtained after quality control, called valid data, were used for subsequent analyses.

2.4. Identification of DE-miRNAs and functional analyses

The expression amounts were first normalized to normal values (25), and then DE significance analysis was conducted based on the normal distribution difference algorithm. A differential expression analysis of miRNAs involving SSNHL and normal control groups was performed using DESeq software. DE-miRNAs were identified based on the thresholds of a p-value of <0.05 and $|\log_2$ fold change (FC)$| > 1$.

Next, TargetScan (v5.0) (26–28) and miRanda (v3.3a) (29–31) databases were used to predict target genes of the identified DE-miRNAs, and intersections of the two databases were established as the final target genes of the identified DE-miRNAs. The TargetScan algorithm removed target genes whose context score percentile was <50, and the miRanda algorithm removed target genes whose TargetScan score was ≥50 and miRanda Energy was <-10. Then, predicted genes of the identified DE-miRNAs were submitted for functional analyses, including gene ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses.

2.5. RT-qPCR

Expression levels of the selected DE-miRNAs were determined using a stem-loop method. Briefly, total exosomal RNA was extracted from the other three exosome samples using RNAiso Plus (TAKARA) according to the manufacturer's instructions. After total RNA extraction, miRNA reverse transcription was performed using the PrimeScript™ II 1st Strand cDNA Synthesis Kit (TAKARA) based on the manufacturer's protocols. Briefly, a 20 μl mixture was prepared using 3 μl RT-Primer (10 μM), 1 μl dNTP Mixture (10 mM each), 300 ng RNA, and RNase-free H_2O; this mixture was incubated at 65°C for 5 min and 10 μl of it was added to 4 μl 5 × PrimeScript II buffer, 0.5 μl RNase inhibitor (40 U/μl), 1 μl PrimeScript II RTase (200 U/μl), and 4.5μl RNase-free H_2O. The resulting mixture was first incubated at 42°C for 60 min and then at 95°C for 5 min. Subsequently, the Power SYBR Green PCR Master Mix (Thermo Fisher Scientific, USA) was used for PCR amplification. *U6* served as a reference gene, and the sequences of all primers used are listed in Table 2. The relative expression levels of the selected DE-miRNAs were calculated using the $2^{-\Delta\Delta Ct}$ method.

2.6. Statistical analysis

All experiments were performed with at least three biological replicates, and differences between the two groups of samples were analyzed using Student's t-test. Statistical significance was set at a P-value of <0.05.

3. Results

3.1. Identification of serum-derived exosomes

NTA revealed that most exosomes were ~30–150 nm in size, and peak sizes were 98.1 and 98.3 nm in healthy control and SSNHL groups, respectively (Figure 1A). TEM showed that the exosomes were spherical or saucer-shaped with a double-membrane structure (Figure 1B). Western blotting showed that exosomal marker proteins HSP70, TSG101, and CD9 were present (Figure 1C). These results indicated that exosomes were successfully isolated from the serum of healthy controls and SSNHL patients.

3.2. Quality control of sequence reads and identification of miRNAs

The number of total reads, total bases, and the proportions of each base are shown in Table 3. There were 9,350,833–22,323,603

TABLE 2 Details of PCR primers utilized in this investigation.

Name of primer	Primer sequence (5′-3′)
PC-5p-38556_39-Stem-loop	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACGCCGCC
PC-5p-38556_39-Forward	GGAGTTTGGCTGG
PC-5p-29163_54-Stem-loop	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACTCACAC
PC-5p-29163_54-Forward	GCCGGCCGGCGATTTTGATTTTCA
PC-5p-31742_49-Stem-loop	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAGGCTT
PC-5p-31742_49-Forward	GCGAGAGCGTTCTGT
miR-93-3p_R+1-Stem-loop	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACTCGGGA
miR-93-3p_R+1-Forward	GCGACTGCTGAGCTAGCACT
U6-human	CTCGCTTCGGCAGCACA
U6-h-Reverse	AACGCTTCACGAATTTGCGT
Downstream universal primer sequence	GTGCAGGGTCCGAGGT

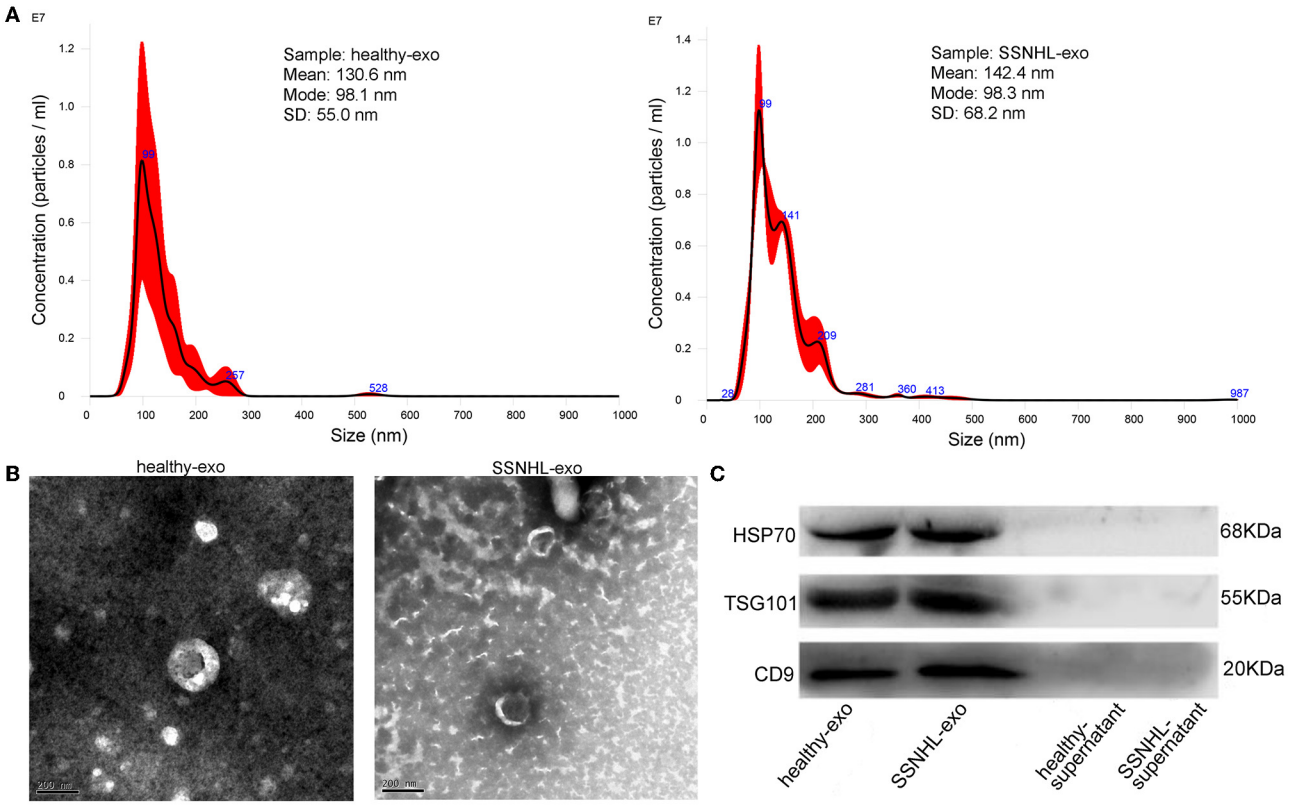

FIGURE 1
Identification of exosomes isolated from serum of healthy individuals and sudden sensorineural hearing loss (SSNHL) patients. **(A)** Particle size distribution and number of exosomes measured by Nanosight. **(B)** Transmission electron microscopy revealed spherical or saucer-shaped morphology of exosomes with a double-membrane structure. **(C)** Western blotting showed that exosomal surface markers (HSP70, TSG101, and CD9) were all expressed. Healthy-exo, exosomes isolated from healthy individuals; SSNHL-exo, exosomes isolated from SSNHL patients; healthy-supernatant, supernatant from healthy individuals; SSNHL-supernatant, supernatant from SSNHL patients.

total reads and 577,118,448–1,138,503,753 total bases. Meanwhile, >98% base call error probability was <1%, and >95% base error probability was <0.1%. The sequencing results were thus considered reliable.

Rfam and Repbase database alignment analyses were performed to remove non-miRNA and repetitive sequences in the clean data. Total reads and unique reads were counted and visualized as pie and stacked charts, respectively (Figures 2A–D).

TABLE 3 Quality control and error probability.

Sample ID	Total Reads	Total Bases	A%	T%	C%	G%	N%	Q20%	Q30%	GC%
C1	9,350,833	476,892,483	23.16	21.77	24.61	30.45	0.01	99.10	97.09	55.06
C2	11,316,048	577,118,448	24.01	21.52	26.17	28.29	0.01	98.82	96.40	54.46
C3	22,323,603	1,138,503,753	22.76	22.86	26.73	27.65	0.00	98.50	95.75	54.37
D1	10,720,432	546,742,032	23.50	21.84	26.50	28.16	0.01	98.68	95.87	54.66
D2	10,186,256	519,499,056	23.50	22.86	25.22	28.41	0.01	98.79	96.20	53.63
D3	11,008,900	561,453,900	22.63	22.36	25.26	29.75	0.01	98.38	95.00	55.01

The Venn diagram showed that 399 miRNAs were identified in the two groups, including 350 in the control group, 339 in the case group, and 290 that were co-expressed by the two cohorts (Figure 2E). Length distribution analysis indicated that the majority of reads were between 18 and 24 nucleotides (nt) long, with the most common length being 22 nt (Figure 2F).

3.3. Screening of DE-miRNAs

A total of 18 miRNAs were identified as DE-miRNAs in the SSNHL and healthy control samples based on the thresholds of $|\log_2 FC| > 1$ and $P < 0.05$ (Figure 3A), which included PC-5p-38556_39, PC-5p-29163_54, mmu-mir-6240-p5_1ss19GT, mmu-mir-6236-p5_1ss8CG, mmu-mir-6240-p3_1ss2GA, mmu-mir-6240-p5_1ss16GT, hsa-miR-2355-5p_R+1, PC-5p-31742_49, mmu-mir-6240-p5_3, mmu-mir-6240-p5_2, mmu-mir-6240-p5_1, PC-3p-53547_25, hsa-miR-93-3p_R+1, PC-5p-65002_19, mmu-mir-6236-p5_1ss4CG_1, mmu-mir-6236-p5_1ss4CG_2, hsa-let-7e-5p, and bta-miR-339b_R+2. The identified DE-miRNAs also significantly differentiated SSNHL from the healthy control samples according to a heat map (Figure 3B). To identify miRNAs with the most significant differences, we generated a volcano map to observe the overall distribution of DE-miRNAs (Figure 3C) and a scatter diagram to visually depict differences in miRNA expression (Figure 3D).

3.4. Functional analyses

GO functional annotation analysis revealed that target genes of the identified DE-miRNAs in the top 20 terms were mainly related to "protein binding," "metal ion binding," "ATP binding," and "intracellular signal transduction" (Figure 4). KEGG pathway enrichment analysis showed that the target genes of the identified DE-miRNAs were functionally enriched in the "Ras," "Hippo," "cGMP-PKG," and "AMPK signaling pathways" (Figure 5).

3.5. Verification of sequencing by RT-qPCR

Finally, four DE-miRNAs, including PC-5p-38556_39, PC-5p-29163_54, PC-5p-31742_49, and hsa-miR-93-3p_R+1, were chosen for RT-qPCR verification. It was found that compared with healthy controls, the expression levels of PC-5p-38556_39 and PC-5p-29163_54 were significantly downregulated ($P < 0.05$), whereas the expression level of miR-93-3p_R+1 was highly upregulated in exosomes from the SSNHL samples ($P < 0.05$, Figure 6). These results were consistent with the expression trends of the sequencing results. However, no significant difference was found in the level of PC-5p-31742_49 between exosomes from the SSNHL group and healthy samples ($P > 0.05$, Figure 6). All the results indicated that the consistency rate between sequencing and RT-qPCR was 75%, thereby indicating that the sequencing results were highly reliable.

4. Discussion

SSNHL is a common emergency in otolaryngology. Early recognition and treatment are crucial to improve hearing and alleviate tinnitus (32). Although pure tone audiometry results exhibit a variety of hearing curve types, systemic and intratympanic steroid therapy remains the main treatment for SSNHL (33). Owing to the lack of valuable early diagnostic markers, SSNHL can only be diagnosed after the onset of hearing loss through an audiological and medical history examination. Therefore, further studies surrounding potential SSNHL biomarkers are of great significance.

Scholars from various countries have studied SSNHL markers in plasma and serum, as well as from imaging perspectives. Elias et al. studied plasma malondialdehyde (MDA) activity in patients with SSNHL from the perspective of oxidative stress and studied the role of MDA in the prognosis of sudden deafness (34). Yao et al. studied inflammatory indexes in the peripheral blood of patients with SSNHL by using different audiogram shapes (35). Feng et al. investigated serum albumin and bone turnover biomarkers as potential prognostic markers for SSNHL (36, 37). Based on resting-state functional magnetic resonance imaging, Minosse et al. investigated the potential value of graph-theoretical measures as biomarkers for SSNHL (38). Liu et al. studied the potential value of regional homogeneity in the left cerebellum region as a neuroimaging biomarker for SSNHL (39). Fluctuations in exosome levels in the inner ear during disease states and their ability to carry and transmit intracellular signals have attracted increased interest (40). For instance, exosomes derived from inner ear stem cells increase the relative expression of miR-182-5p, alleviate gentamicin-induced ototoxicity, and improve the survival rate of HEI-OC1 cells (41), thus highlighting the potential use of exosomes as biomarkers for diseases of the inner ear. However,

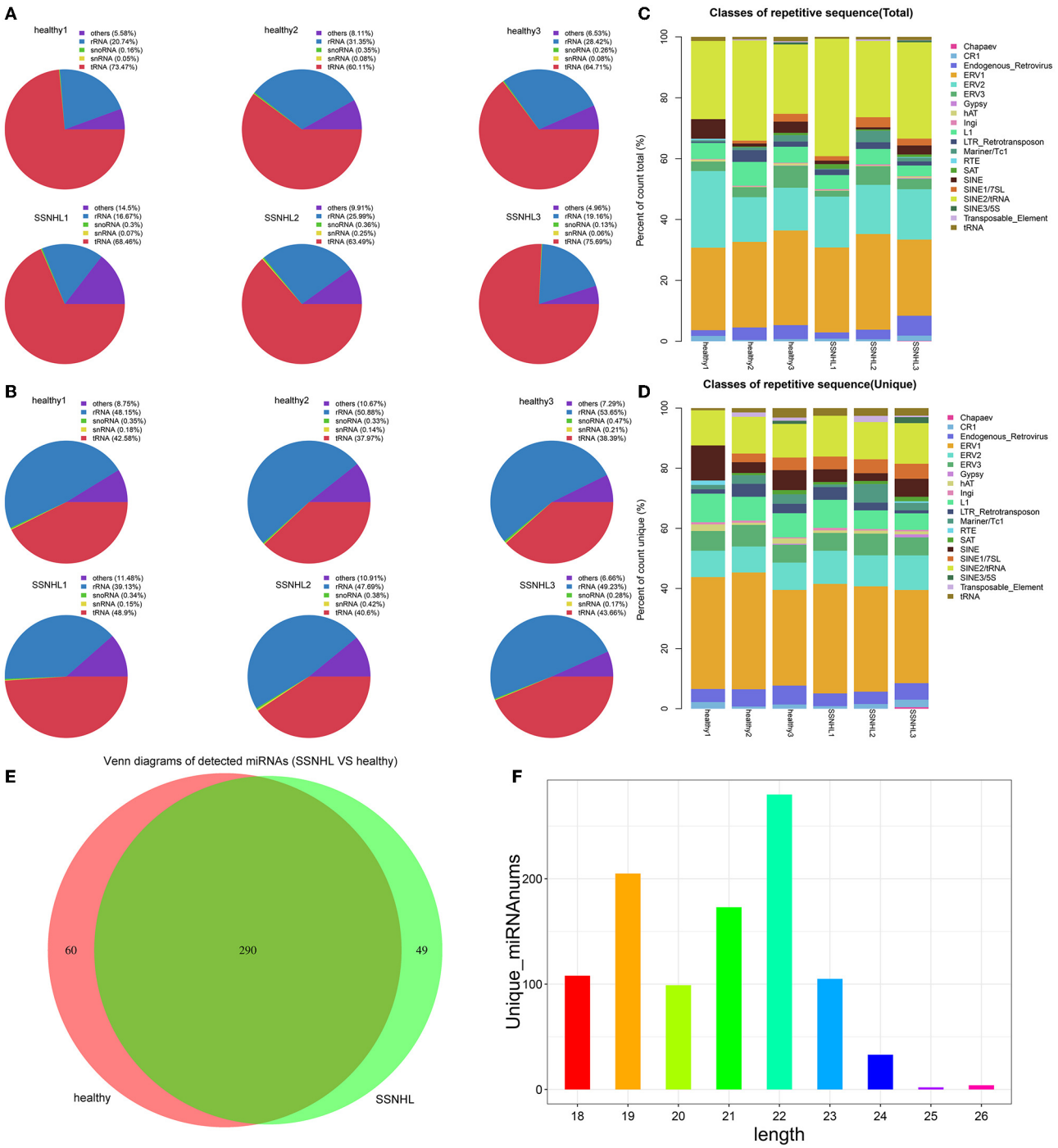

FIGURE 2
Database comparison and microRNA (miRNA) identification. **(A)** The ratio of rRNA, snoRNA, snRNA, tRNA, and other non-miRNA sequences in total reads to Rfam data. **(B)** The ratio of rRNA, snoRNA, snRNA, tRNA, and other non-miRNA sequences in unique reads to Rfam data. **(C)** The ratio of rRNA, snoRNA, snRNA, tRNA, and other non-miRNA sequences in total reads to Repbase data. **(D)** The ratio of rRNA, snoRNA, snRNA, tRNA, and other non-miRNA sequences in unique reads to Repbase data. **(E)** Venn diagram showing the number of miRNAs detected in the two groups of samples. **(F)** Length distribution of the detected miRNAs.

the inner ear is a complex structure located in the temporal bone, which makes it difficult to obtain cochlear specimens. Therefore, we collected peripheral venous blood for our study.

Cochlear ischemia-reperfusion injury is considered one of the crucial pathogeneses in SSNHL (42, 43). Hao et al. (44) found that exosomes derived from miR-21-transfected neural progenitor cells prevented hearing loss caused due to ischemia-reperfusion injury in mice by inhibiting inflammatory processes in the cochlea. Yang et al. (45) observed that cochlear spiral ganglion progenitor cell-derived exosomes reduced hearing

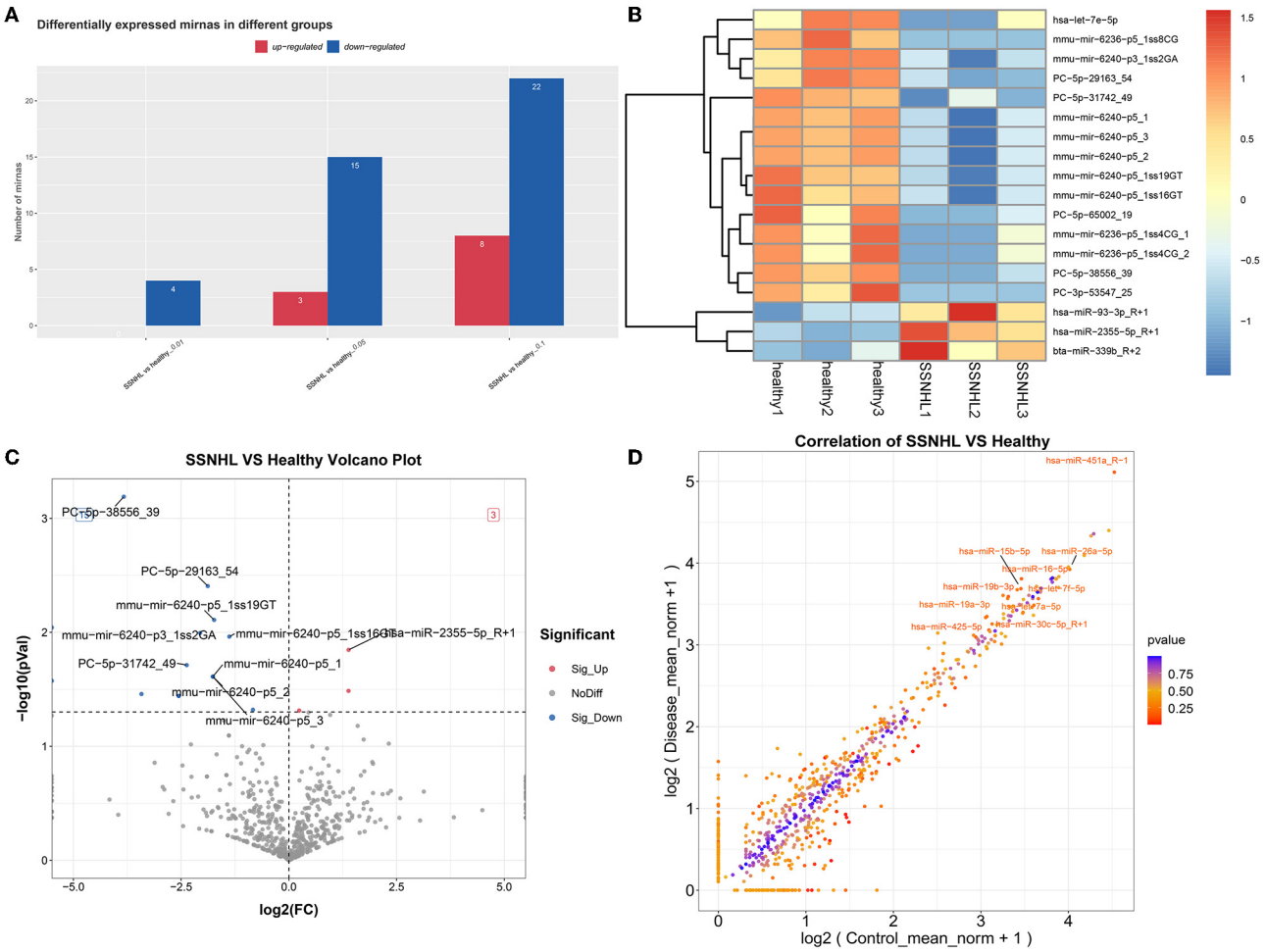

FIGURE 3
Screening of differentially expressed miRNAs (DE-miRNAs) in exosomes from SSNHL and healthy samples. Red: upregulated; blue: downregulated. **(A)** Statistical diagram of upregulated or downregulated miRNAs in the different groups. **(B)** Heat map of DE-miRNAs in exosomes from SSNHL and healthy samples. **(C)** Volcano map of DE-miRNAs from SSNHL and healthy samples. **(D)** Scatterplot of DE-miRNAs in SSNHL and healthy samples.

loss caused due to ischemia-reperfusion injury in the cochlea by upregulating the expression of anti-inflammatory miRNAs (miR-21-5p, miR-26a-5p, and miR-181a-5p). In this study, we identified a total of eight personally sourced exosomal DE-miRNAs in SSNHL and compared them with controls, including PC-5p-38556_39, PC-5p-29163_54, hsa-miR-2335-5p_R+1, PC-5p-31742_49, PC-3p-53547_25, hsa-miR-93-3p_R+1, PC-5p-65002_19, and hsa-let-7e-5p. Moreover, miR-93 is an important regulatory factor in ischemia-reperfusion injury. The miR-93/IRAK4 (46) signaling pathway inhibits inflammation and cell apoptosis following cerebral ischemia-reperfusion injury. miR-93/STAT3 (47) and miR-93/PTEN (48) play protective roles in the inhibition of ischemia-reperfusion-induced liver injury and myocardial cell injury, respectively. miR-93 also plays a protective role in renal ischemia-reperfusion injury (49). Let-7e (50) is significantly altered in myocardial ischemia-reperfusion injury; Xu et al. (51) revealed that let-7e expression is reduced in noise-exposed rat cochlea, suggesting that *let-7e* and *fas* gene interactions are involved in noise-induced hearing loss. However, there are only a small number of studies on the relationship between exosomal DE-miRNAs and SSNHL.

The Hippo signaling pathway has been highly conserved throughout evolution (52). It is one of the most important signaling pathways that regulate the growth, differentiation, and regeneration of cochlear sensory and supporting cells (53). The regulation of the Hippo pathway can not only promote cell proliferation, hair cell regeneration, and neuronal reconnection (54) but also prevent aminoglycoside-induced cochlear injury/sensorineural deafness (55). However, its specific role in SSNHL requires further investigation.

Adenosine 5′-monophosphate activated protein kinase (AMPK) is a core regulator of cellular decomposition and anabolic pathways, which help maintain intracellular ATP levels (56). A decrease in AMPK levels reduces apoptosis and oxidative stress through the ROS-AMPK-bcl2 pathway in the cochlea and delays age-related hearing loss (57). Knocking out AMPK kinase in the cochlea can protect it from cisplatin or noise damage (58). We speculate that the AMPK signaling pathway may also play an important role in SSNHL.

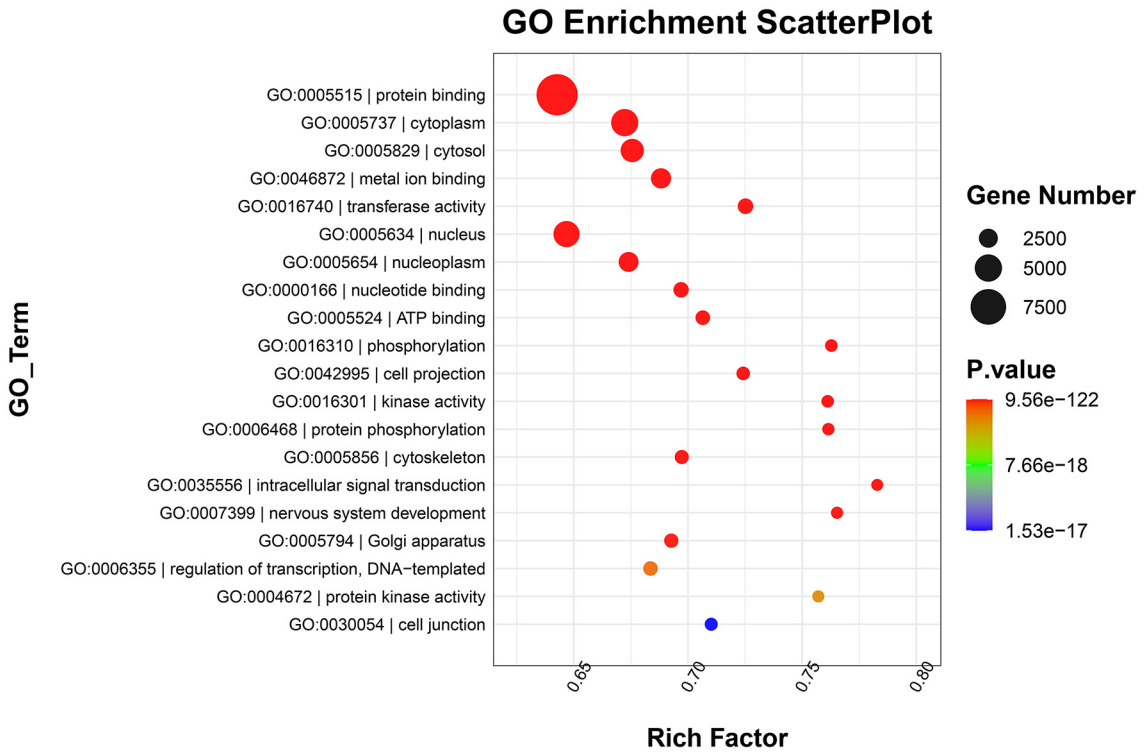

FIGURE 4
Gene Ontology (GO) enrichment scatterplot showing the top 20 terms with the lowest *p*-values. Rich factor: the proportion of the target gene number located in the GO to the total gene number located in the GO (rich factor = S gene number/B gene number).

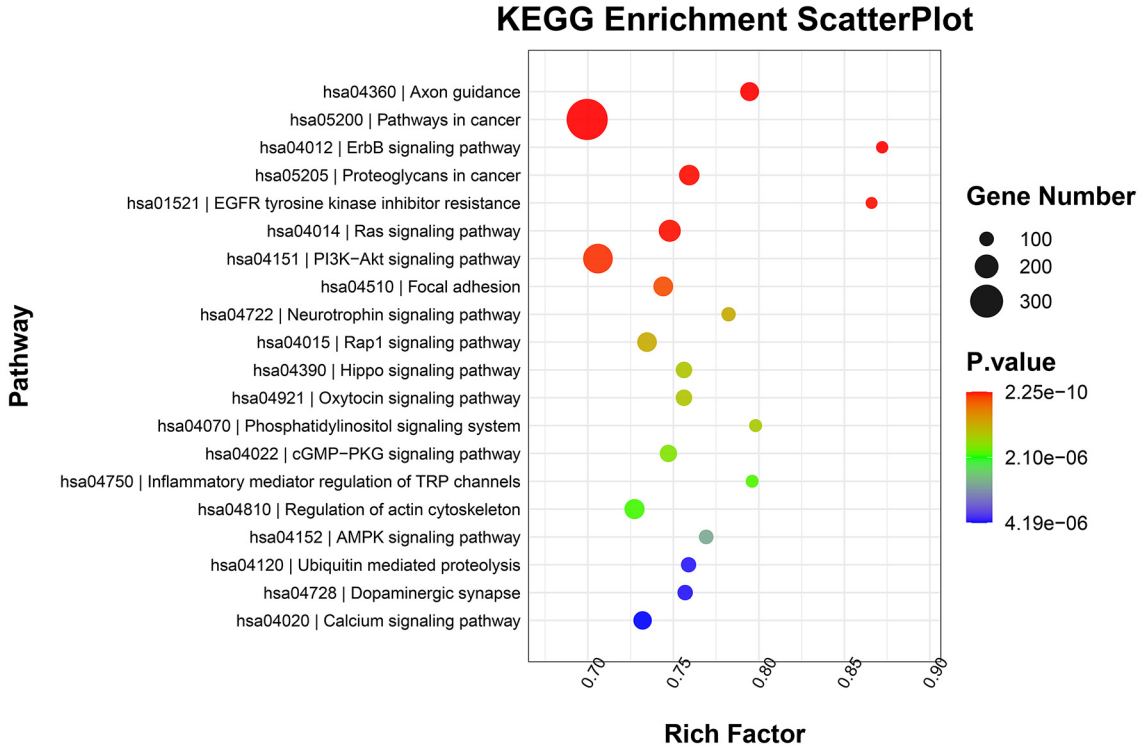

FIGURE 5
Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment scatterplot showing the top 20 terms with the lowest *p*-values.

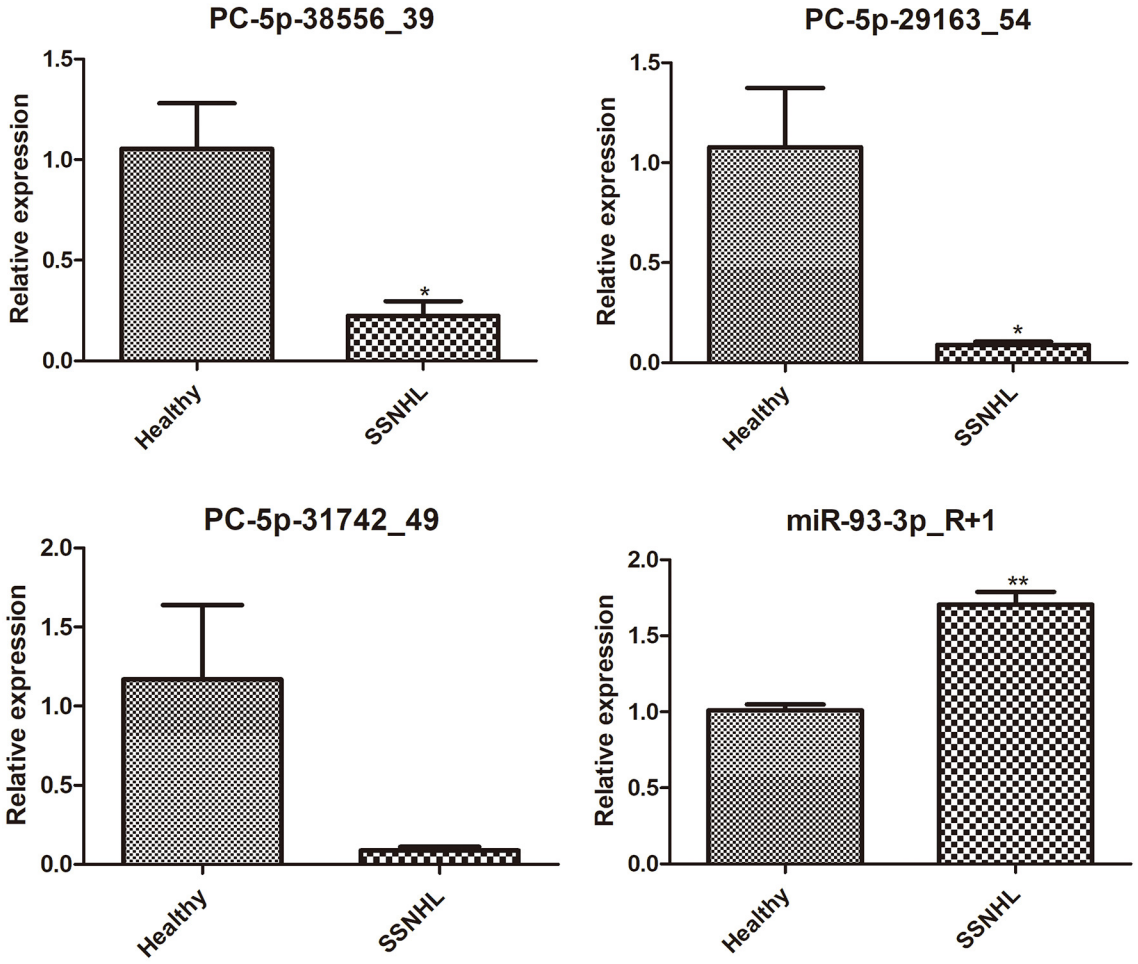

FIGURE 6
Expression Analysis of exosomal PC-5p-38556_39, PC-5p-29163_54, PC-5p-31742_49, and miR-93-3p_R+1 in exosomes isolated from healthy individuals and SSNHL patients ($n = 3$). *$P < 0.05$, **$P < 0.01$ vs. healthy controls.

Our study had certain limitations. First, we only verified the expression of some DE-miRNAs and did not verify the expression of all personally sourced DE-miRNAs. Second, the sample size was small. For instance, although PC-5p-31742_49 was identified as a DE-miRNA with downregulated expression, this result could not be confirmed using qRT-PCR in this study because of the large differences in the expression among samples; hence, further experiments with a larger sample size must be conducted to substantiate our findings. Finally, a machine learning model should be built to accurately verify whether the personally sourced DE-miRNAs can be used as SSNHL biomarkers; our future research will focus on the same.

5. Conclusion

To the best of our knowledge, this study is the first to establish DE-miRNA profiles of serum-derived exosomes in patients with SSNHL and conduct pathway analysis to determine the potential regulatory mechanisms involving exosomal miRNAs in SSNHL. The results of this study provide new ideas for further revealing the pathogenesis and potential biomarkers for SSNHL.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: National Center for Biotechnology Information (NCBI) BioProject, https://www.ncbi.nlm.nih.gov/bioproject/, PRJNA935061.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Chongqing General Hospital (approval no. KYS2021-025-01). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JZ and WY: conception and design of the study and obtaining funding. JZ, HM, GY, and JK: acquisition of data. JZ, WS,

LY, and SK: analysis and interpretation of data. HL: statistical analysis. JZ, HM, WS, and SK: drafting the manuscript. WY: revision of the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1177988/full#supplementary-material

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EDITED BY
Brian John McKinnon,
University of Texas Medical Branch at Galveston, United States

REVIEWED BY
Francesco Comacchio,
University Hospital Sant'Antonio, Italy
Takaomi Kurioka,
National Defense Medical College, Japan

*CORRESPONDENCE
Maoli Duan
✉ maoli.duan@ki.se
Yulian Jin
✉ jinyulian8548@xinhuamed.com.cn
Jun Yang
✉ yangjun@xinhuamed.com.cn

†These authors have contributed equally to this work

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The functional status of vestibular otolith and conductive pathway in patients with unilateral idiopathic sudden sensorineural hearing loss

Jiali Shen[1,2,3†], Xiaobao Ma[1,2,3†], Qing Zhang[1,2,3†], Jianyong Chen[1,2,3], Lu Wang[1,2,3], Wei Wang[1,2,3], Kuan He[1,2,3], Jin Sun[1,2,3], Qin Zhang[1,2,3], Xiangping Chen[1,2,3], Maoli Duan[4,5*], Yulian Jin[1,2,3*] and Jun Yang[1,2,3*]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]ENT Department, Shanghai Jiaotong University School of Medicine Ear Institute, Shanghai, China, [3]ENT Department, Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China, [4]Ear Nose and Throat Patient Area, Trauma and Reparative Medicine Theme, Karolinska University Hospital, Stockholm, Sweden, [5]Division of Ear, Nose, and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden

Background: The cause of idiopathic sudden sensorineural hearing loss (ISSNHL) remains unknown. It has been found that the functional status of the vestibular otolith is relevant to its prognosis; however, the evaluation of the vestibular otolith (intra-labyrinth) and superior and inferior vestibular nerve pathways (retro-labyrinth) in ISSNHL patients is not well-documented.

Objective: This study aimed to investigate the functional status of the vestibular otolith and conductive pathway in patients with unilateral ISSNHL and analyze the correlations between vestibular evoked myogenic potentials (VEMPs) and hearing improvement after treatment.

Methods: A total of 50 patients with unilateral ISSNHL underwent a battery of audio-vestibular evaluations, including pure tone audiometry, middle ear function, air-conducted sound-cervical VEMP (ACS-cVEMP), ACS-ocular VEMP (ACS-oVEMP), galvanic vestibular stimulation-cervical VEMP (GVS-cVEMP), and GVS-ocular VEMP (GVS-oVEMP). The results of auditory and VEMPs were retrospectively analyzed.

Results: The abnormal rates of ACS-cVEMP, ACS-oVEMP, GVS-cVEMP, and GVS-oVEMP in affected ears were 30, 52, 8, and 16%, respectively. In affected ears, the abnormal rate of ACS-oVEMP was significantly higher than that of ACS-cVEMP ($p = 0.025$), while it was similar between GVS-cVEMP and GVS-oVEMP ($p = 0.218$). Compared with GVS-cVEMP, affected ears presented with a significantly higher abnormal rate of ACS-cVEMP ($p = 0.005$), and the abnormal rate of ACS-oVEMP was significantly higher than that of GVS-oVEMP ($p < 0.001$). No significant difference existed in latency and amplitude between affected and unaffected ears in ACS-VEMPs or GVS-VEMPs ($p > 0.05$). The abnormal rate of VEMPs in the poor recovery group was significantly higher than that of the good recovery group ($p = 0.040$). The abnormality percentages of ACS-oVEMP and GVS-oVEMP in the poor recovery group were significantly higher than that of the good recovery group ($p = 0.004$ and 0.039, respectively). The good hearing recovery rates were 76.47% in the normal VEMPs group, 58.33% in the

intra-labyrinth lesion group, and 22.22% in the retro-labyrinth lesion group. Hearing recovery worsened as a greater number of abnormal VEMPs was presented.

Conclusion: Besides Corti's organ, the impairment of otolithic organs was prominent in patients with ISSNHL. The normal VEMPs group had the highest rate of good recovery, followed by the intra-labyrinth lesion group and the retro-labyrinth lesion group presented with the lowest recovery rate. Abnormalities in ACS-oVEMP and/or GVS-oVEMP were indicators of a poor prognosis.

KEYWORDS

idiopathic sudden sensorineural hearing loss, vestibular evoked myogenic potential, hearing improvement, vestibular otolith, vestibular conductive pathway

1. Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) was defined as a sudden hearing loss that occurs within 72 h, and pure tone audiometry results show a decline at least in the three adjacent frequencies (>30 dBHL) without any identifiable cause (1), which may lead to difficulty in speech recognition and sound localization, especially in noisy environments, and has a significant negative impact on the quality of life and mental status of patients (2–4).

Although several etiologies of ISSNHL, such as viral infection, inflammation, inner ear circulation disorders, cochlear membrane breaks, and vascular occlusion, have been suggested, the exact pathogenesis is still unclear (3, 5). Due to the anatomical proximity of the cochlea and vestibule, ISSNHL is frequently accompanied by vestibular dysfunction (6, 7). Multiple studies have shown that patients with ISSSNHL also have clinical symptoms of dizziness, indicating that the vestibular organ may get involved. It was reported that nearly 40–55% of patients with ISSNHL suffered from vestibular dysfunction and were more commonly associated with severe hearing loss rather than mild and moderate hearing loss (8–13).

Considering that a high proportion of patients with ISSNHL have vestibular dysfunction, it is of great importance to evaluate vestibular function in these populations. The most commonly used tests include the caloric test, cervical vestibular evoked myogenic potential (cVEMP), and ocular VEMP (oVEMP), as well as video head impulse test (vHIT) (14–16). The caloric test can be conducted to assess lateral semicircular canal (LSCC) and superior vestibular nerve function. cVEMP can be used for investigating the function of the saccule and the inferior vestibular nerve, while oVEMP can be applied for evaluating the function of the utricle and the superior vestibular nerve. Researchers found that vestibular function can predict the hearing outcomes of patients with ISSNHL to a certain extent (8–10, 17, 18). A correlation was found between poor prognosis and vestibular dysfunction. However, most of them mainly applied air-conducted sound VEMPs (ACS-VEMPs) to evaluate the functional status of the vestibular otolith. There are few studies on the evaluation of the vestibular otolith (intra-labyrinth) and the superior and inferior vestibular nerve pathways (retro-labyrinth). In fact, ACS-VEMPs can only evaluate the integrity of the vestibular otolith conductive pathway; they are unable to distinguish intra-labyrinth or retro-labyrinth lesions (15, 19). Damage to anywhere in the conductive pathway can result in an abnormal ACS-cVEMP or oVEMP. However, since galvanic vestibular stimulation (GVS) directly stimulates vestibular afferents, it could be evoked in patients with only labyrinthine deficits (14, 20). Therefore, the combined application of ACS-VEMPs and GVS-VEMPs could be more efficient in localization diagnosis and may contribute to the prediction of prognosis (18–20). The purpose of this study was to investigate the functional status of the vestibular otolith and conductive pathway in patients with unilateral ISSNHL and analyze the relationship between VEMPs and hearing prognosis.

2. Materials and methods

2.1. Subjects

A retrospective study was performed on 50 patients with ISSNHL who were hospitalized at the Department of Otolaryngology-Head and Neck Surgery, Xinhua Hospital, affiliated with Shanghai Jiao Tong University School of Medicine from October 2019 to March 2023, including 26 male participants and 24 female participants aged between 8 and 75 years (an average of 45.87 ± 20.91 years). There were 28 ears with severe hearing loss and 22 ears with profound hearing loss. For the entire cohort, 28 patients had hearing loss in the left ear and 22 in the right ear, and 25 patients had vertigo. Patients were included if the results of VEMPs were normal on the contralateral unaffected ear, which could eliminate the influence of advanced age.

The inclusion criteria were as follows: (1) unilateral sudden sensorineural hearing loss without apparent cause at least in the adjacent three-frequency hearing loss of ≥30 dB HL in 72 h; (2) initiation of treatment within 20 days after onset; (3) underwent all the required tests; (4) Type A tympanogram in both ears; and (5) the same comprehensive treatment plan was used during hospitalization. The exclusion criteria were as follows: (1) abnormal results of VEMPs on the contralateral healthy ear; (2) external and middle ear diseases; (3) space-occupying lesions of the internal auditory canal and central organic pathology; and (4) sensorineural hearing loss due to noise exposure or ototoxic drugs.

2.2. Methods

2.2.1. Audiological assessment

A tympanogram was obtained by the Interacoustics AT235H Middle Ear Analyzer (Interacoustics, Denmark). Type A at 226 Hz probe tone was considered a normal middle ear function.

Pure-tone audiometry was conducted in a soundproof room using an audiometer (Type Astera, Madsen, Denmark). The pure-tone average (PTA) is the average of the 0.5, 1, 2, and 4 kHz pure-tone thresholds. According to the latest standards of the World Health Organization, PTA <20 dB HL is defined as normal hearing. Repeated pure-tone audiometry was carried out before and after the 10-day treatment. The hearing outcome was classified as good recovery (referring to PTA gain ≥15 dB HL) and poor recovery (hearing improvement <15 dB HL). If no response was obtained for a certain frequency, which exceeded the maximum output of the audiometer (120 dB HL), 120 dB HL was used as the estimated hearing threshold.

2.2.2. ACS-VEMPs

ACS-VEMPs were recorded by the electrophysiological device (Neuropack MEB-9400, NIHON KOHDEN, Japan). A sound stimulus of Tone-Burst 500 Hz (the rise/fall time = 1 ms and the plateau time = 2 ms) at 132 dB peSPL was presented monaurally through a calibrated headphone TDH-39 at a rate of 5 Hz. A minimum of 100 sweeps were averaged and at least repeated twice to verify the waveform repeatability. The electromyogram (EMG) signals were amplified and bandpass filtered between 10 and 3,000 Hz.

For ACS-cVEMP, the two recording electrodes were placed on the upper third of the bilateral sternocleidomastoid muscles (SCMs). The two reference electrodes were placed on the sternal end of the SCM. Then the ground electrode was placed in the middle of the forehead. Patients were asked to rotate their heads toward the shoulder in a sitting position, keeping the SCMs activated and tense until the stimulus sound stopped.

ACS-oVEMP was also performed in a sitting position. The two recording electrodes were placed 1 cm below the middle of the contralateral lower eyelid, the reference electrodes were placed below the same side of the recording electrodes, and the ground electrode was placed in the middle of the forehead. Patients were required to maintain eye gaze upward for 25–30° when hearing a single acoustic stimulus and minimize blinking to maintain tension in the inferior oblique muscle until the stimulation stopped.

2.2.3. GVS-VEMPs

GVS-VEMPs were performed by the same device. The electrode placement of GVS-VEMPs was similar to that of ACS-VEMPs, but there was a set of cathode and anode electrodes for direct current stimulation. The cathode of direct current stimulation was placed at the mastoid, and the anode was placed over the forehead (21).

GVS-cVEMP: The initial stimulation intensity was 3.0 mA/1 ms (stimulation rate 5 Hz, bandpass filter 20–2,000 Hz, and 50 sweeps were averaged). The waveform of muscle relaxation was subtracted from the waveform of muscle contraction to eliminate the artifact of the mechanical wave and obtain the final waveform. The method of muscle contraction was the same as in ACS-cVEMP.

GVS-oVEMP: The initial stimulation intensity was 3.0 mA/1 ms (stimulation rate 5 Hz, bandpass filter 1–1,000 Hz, and 50 sweeps were averaged). The waveforms of the extraocular muscles were recorded during upward gaze (extraocular muscles contraction) and downward gaze (extraocular muscles relaxation), and the final GVS-oVEMPs waveform was obtained by subtracting the waveform of muscle relaxation from muscle contraction.

To verify the repeatability of the waveform, the process was repeated at least twice. If 3.0 mA cannot elicit repeatable waveforms, the stimulation intensity can be appropriately increased according to the patient's tolerance level but usually does not exceed 5.0 mA. Characteristics of latencies, amplitudes, and the interaural asymmetry ratio (IAR) were recorded. IAR = (AL-AS)/(AL+AS) × 100%, where AL is the larger corrected amplitude and AS is the smaller corrected amplitude (22, 24, 26). Absent response, latency exceeding the normal limit, or IAR >30% was considered abnormal in our laboratory.

2.3. Statistical analyses

All statistical analyses were performed using SPSS 26 (SPSS Inc., Chicago, IL, United States). A chi-square test was used to evaluate the demographics of the two groups of ISSNHL patients and the abnormal rates of various VEMPs. The pre-treatment and post-treatment PTAs were compared using the paired *t*-test. Latencies and amplitudes of various modes of VEMPs were determined by independent *t*-test for parametric variables and Mann-Whitney *U*-test for non-parametric variables. A chi-square test with Bonferroni correction was applied to evaluate the good hearing recovery rate among different groups. Significance was determined at $p < 0.05$.

3. Results

3.1. Subject characteristics

According to the inclusion criteria, 50 patients with severe to profound ISSNHL were enrolled in this study. Based on the hearing recovery, they were categorized into two groups, namely, the good recovery (GR) group and the poor recovery (PR) group, with 29 cases (58%) in the GR group and 21 cases (42%) in the PR group. Figure 1 displays audiograms and VEMPs of a patient with good hearing recovery. Figure 2 depicts the initial hearing, after-treatment hearing, and VEMPs of a patient with poor hearing recovery. Demographics and results of chi-square and Mann-Whitney *U*-tests in the two groups are shown in Table 1. Our results showed there was no significant difference in gender, affected side, age, or initial hearing loss between the two groups ($p > 0.05$). However, the number of patients accompanied by vestibular symptoms and the presence of abnormal VEMPs were significantly higher in the PR group ($p = 0.010$ and 0.040, respectively).

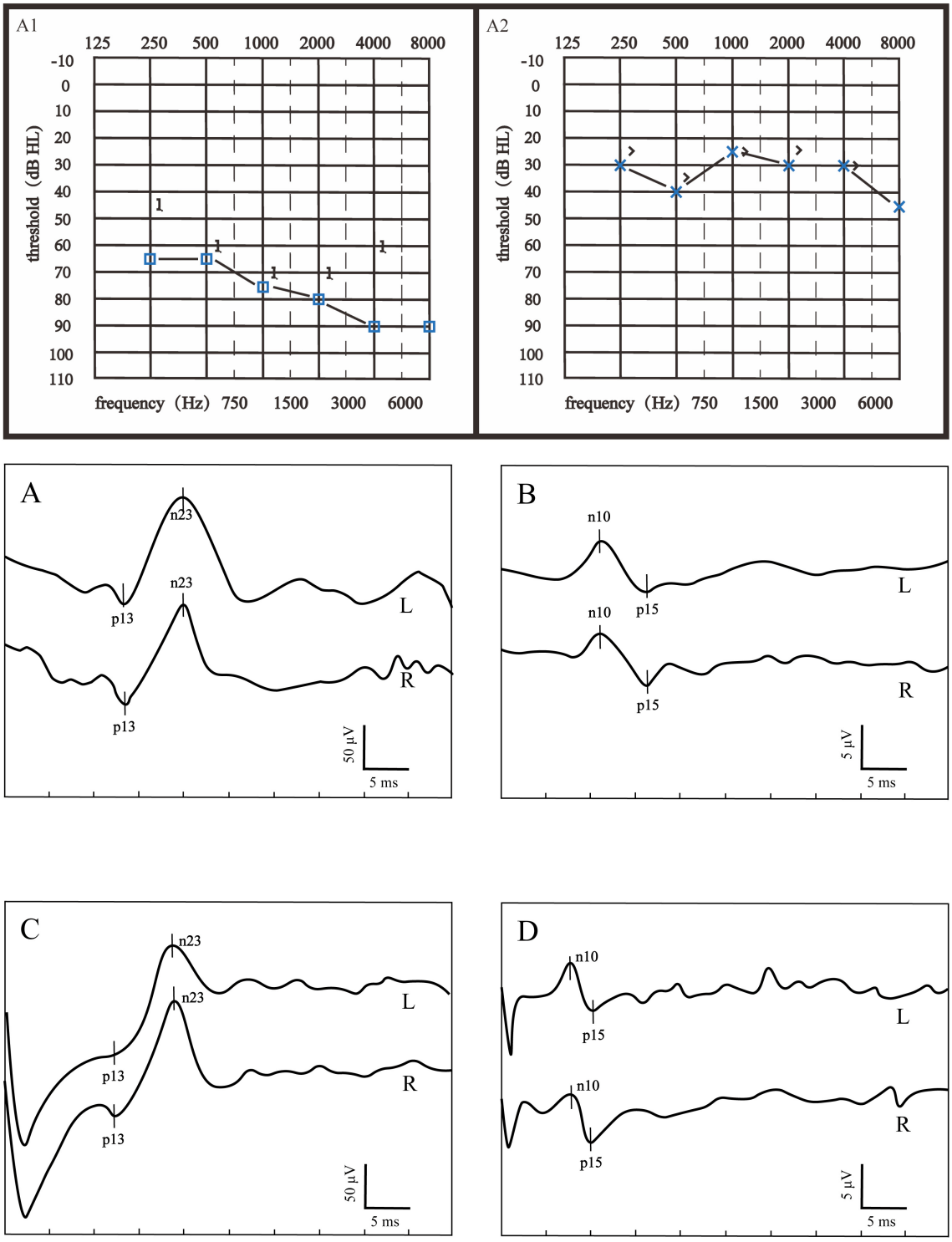

FIGURE 1
Audiograms and VEMPs of a patient with good hearing recovery. **(A1)** showed the initial hearing and **(A2)** showed the after-treatment hearing. **(A)** ACS-cVEMP; **(B)** ACS-oVEMP; **(C)** GVS-cVEMP; **(D)** GVS-oVEMP; L, left ear; R, Right ear. The left ear was the affected ear. There was no significant difference in waveform between the healthy and affected ears in **(A–D)**.

3.2. Abnormal rate of VEMPs in affected ears

As shown in Table 2, in the 50 affected ears, the abnormal rates of ACS-cVEMP, ACS-oVEMP, GVS-cVEMP, and GVS-oVEMP were 30, 52, 8, and 16%, respectively. Specifically, there were eight absent responses, three delayed responses, and four smaller amplitude responses in ACS-cVEMP. In total, 23 absent responses and 3 asymmetric responses were observed in ACS-oVEMP. For GVS-cVEMP, only one absent response and three asymmetric

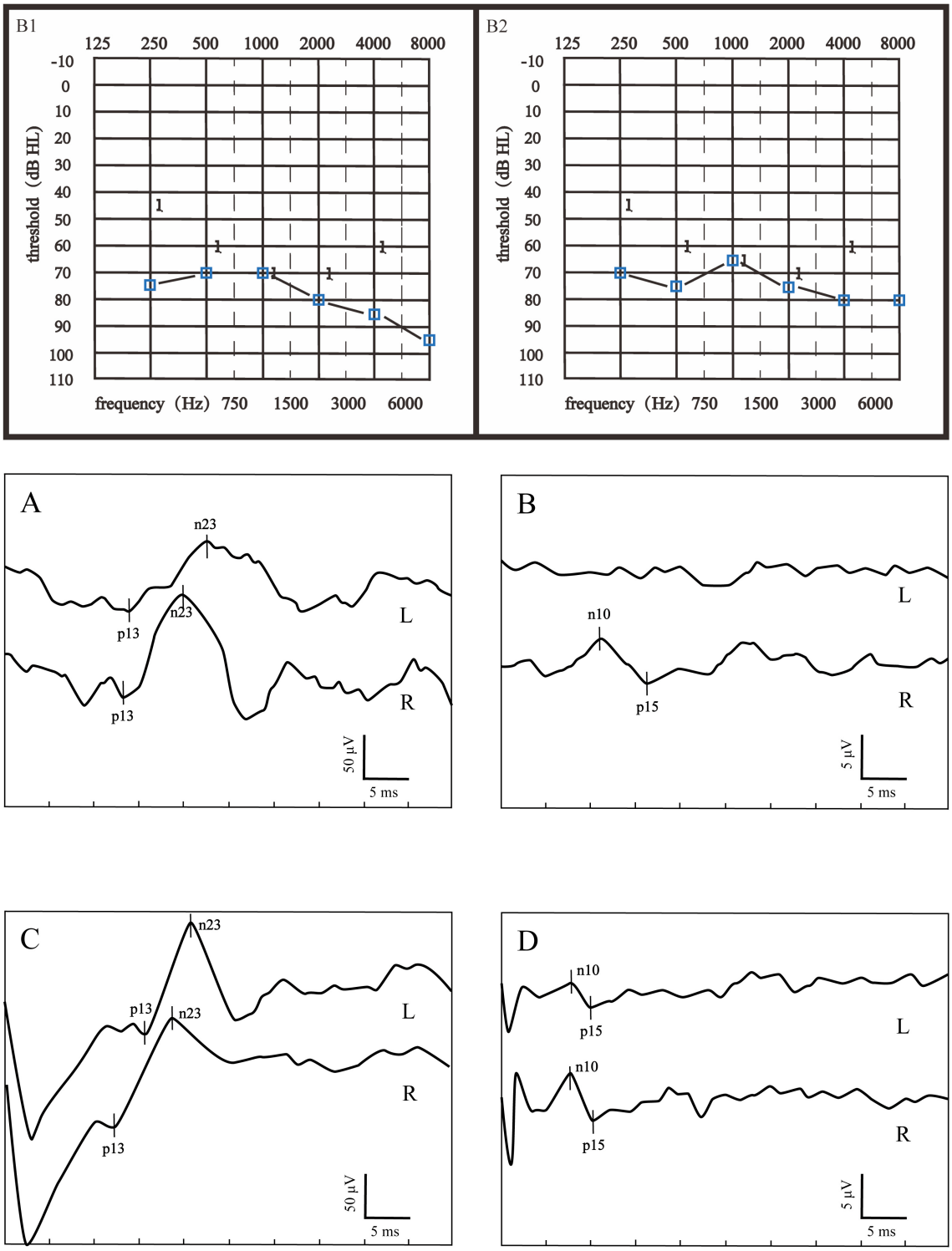

FIGURE 2
Audiograms and VEMPs of a patient with poor hearing recovery. **(B1)** showed the initial hearing and **(B2)** showed the audiogram after treatment. **(A)** ACS-cVEMP; **(B)** ACS-oVEMP; **(C)** GVS-cVEMP; **(D)** GVS-oVEMP; L, left ear; R, Right ear. The left ear was the affected ear. This patient presented with longer p13 and n23 latencies both in ACS-cVEMP and GVS-cVEMP, an absent waveform in ACS-oVEMP, and amplitude asymmetry in GVS-oVEMP.

responses were noted. Meanwhile, four absent responses, two delayed responses, and two amplitude reduction responses were discovered in GVS-oVEMP. The abnormal rate of ACS-cVEMP was significantly higher than that of GVS-cVEMP ($p = 0.005$). Similar to the results of cVEMP, the abnormal rate of ACS-oVEMP significantly exceeded that of GVS-oVEMP in affected ears

TABLE 1 Clinical characteristics of patients in good and poor recovery groups.

Variables	GR group ($n = 29$)	PR group ($n = 21$)	p-value
Gender (male:female)	14:15	12:9	0.536
Affected side (left:right)	16:13	12:9	0.890
VEMPs (normal:abnormal)	13:16	4:17	0.040*
Age (years)	34.59 ± 19.95	43.29 ± 23.32	0.215
Initial hearing loss (dB)	88.97 ± 22.70	82.38 ± 33.01	0.637
Vestibular symptoms, n (%)	10/29 (34.48%)	15/21 (71.42%)	0.010*

n, number of ears.
*$p < 0.05$.

TABLE 2 Comparison of abnormal rates of VEMPs in affected ears.

	ACS-oVEMP (26/50, 52%)	GVS-cVEMP (4/50, 8%)
ACS-cVEMP (15/50, 30%)	$p = 0.025$*	$p = 0.005$*
GVS-oVEMP (8/50, 16%)	$p < 0.001$*	$p = 0.218$

*$p < 0.05$.

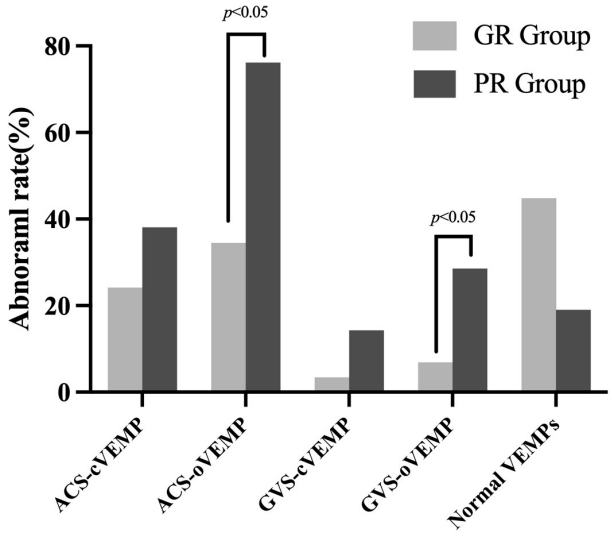

FIGURE 3
Abnormal rate of VEMPs in good and poor recovery groups. The light gray box plot represented a good recovery group ($n = 29$ ears); the dark gray box plot represented a poor recovery group ($n = 21$ ears). The abnormal rates of ACS-oVEMP and GVS-oVEMP were significantly higher in the PR group than in the GR group ($p = 0.004$, 0.039, respectively). No significant difference was found in ACS-cVEMP, GVS-cVEMP, or normal VEMPs ($p = 0.288$, 0.163, and 0.058, respectively).

($p < 0001$). No significant difference existed between the abnormal rates of GVS-cVEMP and GVS-oVEMP ($p = 0.218$). However, the abnormal rate of ACS-oVEMP was significantly higher than that of ACS-cVEMP ($p = 0.025$).

3.3. Comparison of latency and amplitude between the affected and unaffected ears

The descriptive data, including the mean and standard deviation (SD) of the latency and amplitude of VEMPs in affected and unaffected ears, were displayed in Tables 3, 4. The results indicated that there was no significant difference in these parameters between affected and unaffected ears in ACS-cVEMP, ACS-oVEMP, GVS-cVEMP, or GVS-oVEMP ($p > 0.05$).

3.4. Relationship between hearing outcomes and VEMP results

According to the VEMP results, vestibular dysfunction locations were categorized into intra-labyrinth and retro-labyrinth lesions. The normal VEMPs group refers to normal results in ACS-VEMPs and GVS-VEMPs. Intra-labyrinth lesion refers to abnormal ACS-cVEMP and/or ACS-oVEMP but normal GVS-cVEMP and GVS-oVEMP. Retro-labyrinth lesion refers to abnormal GVS-cVEMP and/or GVS-oVEMP. As shown in Figure 3, abnormal rates of ACS-oVEMP and GVS-oVEMP were significantly higher in the PR group than in the GR group ($p = 0.004$ and 0.039, respectively). However, no significant difference was observed in terms of abnormality percentage in ACS-cVEMP, GVS-cVEMP, or normal VEMPs between the GR and PR groups ($p = 0.288$, 0.163, and 0.058, respectively). Additionally, 24 affected ears suffered from intra-labyrinth lesion, including three with saccule dysfunction, 13 with utricle dysfunction, and eight with abnormal function both in the saccule and utricle; nine affected ears showed lesions in retro-labyrinth; and 17 affected ears had normal function in the vestibular otolith and conductive pathway. The good hearing recovery rates are shown in Table 5. The normal VEMPs group had the highest rate of good recovery, followed by the intra-labyrinth lesion group, and the retro-labyrinth lesion group presented with the lowest recovery rate. Table 6 displays the good recovery rate in patients with different numbers of abnormal VEMPs. The rates were 76.47% in patients with four normal VEMPs, 61.90% in patients with one abnormal VEMP, 33.33% in patients with two abnormal VEMPs, and 16.67% in patients with three or four abnormal VEMPs, suggesting that the hearing recovery worsened as a greater number of abnormal VEMPs presented.

4. Discussion

According to the results, the rate of abnormalities in ACS-VEMPs was greater than in GVS-cVEMPs, suggesting that the otolith organs may be involved more frequently than vestibular afferents, which was consistent with previous studies (18, 22–25). Chang et al. (25) reported that the abnormal rate of ACS-cVEMP in patients with ISSNHL was significantly higher than that of GVS-cVEMP (60 vs. 37%) in affected ears. The abnormal rate of bone conducted vibration oVEMP (BCV-oVEMP) significantly exceeded

TABLE 3 Comparison of latency and amplitude of ACS-VEMPs between the affected and unaffected ears.

Group	*n*	ACS-cVEMP			ACS-oVEMP		
		p13 latency (ms)	n23 latency (ms)	Amplitude (μV)	n10 latency (ms)	p15 latency (ms)	Amplitude (μV)
Affected ears	50	16.80 ± 2.22	24.61 ± 2.85	214.20 ± 143.90	11.17 ± 0.92	15.32 ± 1.32	3.57 ± 2.03
Unaffected ears	50	16.44 ± 1.91	23.89 ± 2.72	260.34 ± 156.85	11.2 ± 0.86	15.59 ± 1.32	4.62 ± 3.22
p-value		0.243	0.056	0.058	0.715	0.429	0.100

TABLE 4 Comparison of latency and amplitude of GVS-VEMPs between the affected and unaffected ears.

Group	*n*	GVS-cVEMP			GVS-oVEMP		
		p13 latency (ms)	n23 latency (ms)	Amplitude (μV)	n10 latency (ms)	p15 latency (ms)	Amplitude (μV)
Affected ears	50	12.03 ± 1.66	20.18 ± 2.09	157.43 ± 95.14	8.10 ± 0.83	11.45 ± 1.11	6.76 ± 5.02
Unaffected ears	50	12.26 ± 2.20	19.82 ± 2.22	150.16 ± 76.58	8.20 ± 0.77	11.58 ± 1.31	6.43 ± 4.43
p-value		0.404	0.172	0.800	0.385	0.691	0.627

n, number of ears.

that of GVS-oVEMP in affected ears (47 vs. 20%). Iwasaki et al. (18) found that all ISSNHL patients in their study presented with normal GVS-VEMPs, which implied that the lesion site of ISSNHL was within the labyrinth. Additionally, we found that the abnormal rate of ACS-oVEMP was significantly higher than that of ACS-cVEMP. Nevertheless, the abnormal rates of GVS-cVEMP and GVS-oVEMP were comparable. These findings suggested that the utricle was most susceptible to damage in patients with ISSNHL, followed by the saccule and vestibular nerve. Vestibular organs could be affected individually or simultaneously.

A recent meta-analysis reported that the utricle was the most easily affected organ in ISSNHL (7), which was in agreement with our results. Lim et al. (26) demonstrated the association between vestibular function and prognosis in 264 SSNHL patients and reported that the functions of vestibular organs, particularly the utricle and lateral semicircular canal, are associated with disease severity and hearing outcome. Wang et al. (27) conducted a retrospective study to evaluate the association between hearing characteristics/prognosis and the patterns of vestibular/cochlear lesions in SSNHL patients with vertigo and found that more cases of vestibular dysfunction appeared in the lateral semicircular canal and the utricle than in the saccule. Liu et al. (6) also reported that the abnormal rate of oVEMP was the highest, indicating that the utricle might be more prone to damage than the saccule. This could be explained by the differential effects of ischemia on the anterior and posterior vestibular arteries. It has been found that the pattern of vestibular organ dysfunction correlates with the blood supply pattern of the cochlea and vestibule (28, 29). cVEMP reflects saccular function, and perfusion to the saccule is mainly supplied by the posterior vestibular arteries, while oVEMP reflects the function of the utricle, and perfusion is mainly provided by the anterior vestibular artery. Considering that the vestibulocochlear and posterior vestibular arteries have more intraosseous collaterals than the anterior vestibular arteries, the saccule may be more resistant to ischemic damage due to the better collateral blood supply (26, 29). In addition, although the cochlea and saccule are primarily supplied by branches of the common cochlea artery, the deterioration of saccular function may be less severe than that of the cochlea in common cochlea artery infarction (26).

However, some researchers have reported inconsistent results. It has been found that vestibular dysfunction in patients with ISSNHL affects the vestibular organs close to the cochlea first (30). Atrophic changes in the saccule were observed in patients with SSNHL (16). Fujimoto et al. (30) classified SSNHL patients with vertigo based on vestibular dysfunction patterns and discovered that the cochlea was most susceptible to damage, followed by the cochlea and saccule and the cochlea-saccule-utricle-semicircular canal type. They attributed this phenomenon to the anatomy of the saccule and its proximity to the cochlea. Meanwhile, Chang et al. (31) reported that there was no statistically significant difference between the rates of abnormal cVEMP and oVEMP, no matter what kind of stimulus modes were used. The inconsistency might be related to the following reasons: first, the different characteristics of participants. Due to the close relationship between the cochlea and vestibule, the degree of hearing loss had an effect on the percentage of abnormalities. In addition, the response rate of VEMP was strongly correlated with age. When the age exceeds 60 years, the response rate may decrease (23). All unaffected ears in our study presented with normal VEMPs, which could exclude the influence of age on the results. Second, test conditions are different. The stimulus modality (air conducted, bone vibration, or galvanic stimulation), intensity, and test position (supine or sitting) are all related to the VEMP results. Furthermore, unequal diagnostic criteria in different institutions also lead to various interpretations.

It has been documented that VEMP test results have predictive value for hearing outcomes in SSNHL patients. Several recent reports have included the VEMP test in the evaluation of patients with ISSNHL, for whom abnormal results of vestibular examinations were associated with poor hearing recovery (3, 10, 24, 32, 33). Wang et al. (17) proposed that profound hearing loss with normal VEMP was associated with favorable hearing results. Liang et al. (12) found that patients with abnormal

TABLE 5 Comparison of a good recovery rate with different VEMP results.

	n	Good recovery rate	*p*-value
Intra-labyrinth	24	14/24 (58.33%)	0.029*
Retro-labyrinth	9	2/9 (22.22%)	
Normal VEMPs	17	13/17 (76.47%)	

n, number of ears.
*$p < 0.05$.

TABLE 6 Good recovery rate in patients with different numbers of abnormal VEMPs.

	n	Good recovery rate	*p*-value
Normal VEMPs	17	13/17 (76.47%)	<0.01*
One abnormal VEMP	21	13/21 (61.90%)	
Two abnormal VEMPs	6	2/6 (33.33%)	
Three or four abnormal VEMPs	6	1/6 (16.67%)	

n, number of ears.
*$p < 0.05$.

oVEMP or/and cVEMP had poor hearing outcomes, suggesting that oVEMP and cVEMP may be effective indicators for predicting the prognosis.

The improvement of the pure tone threshold is currently a common and international outcome index (34, 35). We classified all patients into good recovery or poor recovery groups according to the hearing improvement of the affected ear. Our results showed that the abnormal rate of VEMP in the PR group was significantly higher than that in the GR group. The abnormality percentage of ACS-oVEMP and GVS-oVEMP in the poor recovery group was significantly higher than that in the good recovery group (Figure 3), while no significant difference was observed in terms of ACS-cVEMP, GVS-cVEMP, or normal VEMPs, indicating that the oVEMP pathway was more commonly affected, which agreed with previous findings (8, 16, 36, 37). It has been noted that the superior division of the vestibular nerve was preferentially affected. The lateral bony channel of the superior vestibular nerve is seven times longer than the inferior vestibular and more than three times longer than the singular channel. Additionally, the superior vestibular nerve and arteriole travel through a relatively narrower passage compared with the inferior or singular nerves. From an anatomical perspective, this makes the superior vestibular nerve more susceptible to entrapment and possible ischemic labyrinthine changes (37, 38). In addition, we found ISSNHL patients with normal VEMPs had the highest good recovery rate, followed by the intra-labyrinth lesion group and the retro-labyrinth lesion group presented with the lowest recovery rate, which was consistent with the results of previous research (5, 25). GVS-VEMP would stimulate the most distal portion of the vestibular nerve (20); an abnormal GVS-VEMP result indicates that the lesion area has extended to the nerve. It has been reported that the degree of inner ear lesions is negatively correlated with the possibility of hearing recovery; the involvement of otoliths and/or vestibular nerves implies a wider range of diseases, indicating a poorer prognosis (17, 18, 39). In other words, vestibular nerve injury may be a discriminant indicator of severe disease and negatively correlated with hearing recovery. Furthermore, it was reported that abnormalities in GVS-cVEMP and/or GVS-oVEMP may indicate degenerative changes in the vestibular nerve; patients with a longer onset of disease are more likely to experience auditory and vestibular nerve dysfunction. The functional recovery of nerves may take a long time, thus affecting hearing recovery (31). However, Iwasaki et al. (18) found that all ISSNHL patients in their study presented with normal GVS-VEMPs and concluded that GVS-VEMPs were not related to recovery.

The cause of this discrepancy may possibly relate to the following factors. First, the degree of hearing loss, accompanying symptoms (vertigo and tinnitus), delays after the onset of hearing loss, and etiology can lead to a significant risk of selection bias and unmatched groups. The extent of vestibular abnormalities correlated well with the degree of hearing loss (24, 32). Nearly 50% of ISSNHL patients in the study by Iwasaki et al. (18) had mild to moderate initial hearing loss, while our study focused on severe to profound hearing loss. Although several etiologies have been suggested, the exact pathogen is still unclear. Vascular dysfunction and viral infection are considered to be the most common causes of ISSNHL. It was reported that vascular damage could increase blood viscosity, make the blood in a hypercoagulable state, cause microcirculation disorders in the inner ear, and lead to damage to cochlear hair cells, and ultrastructural changes (5). Viruses, such as the herpes simplex virus, varicella-zoster virus, mumps, cytomegalovirus, and rubella, have been considered to correlate with the pathogenesis of ISSNHL. The role of viral infection is unknown, but it may cause endolymphatic biochemical changes or intravascular coagulation, affecting hair cell function and further leading to neurodegenerative changes (18, 40, 41). Additionally, the criteria for hearing recovery, PTA calculation, hearing loss classifications, and vestibular function evaluation were different.

4.1. Limitations and future direction

Although some valuable results were achieved, there were still some limitations in our study. First, we focused on a subgroup of ISSNHL patients with severe to profound hearing loss, so the effect of the degree of hearing loss was not mentioned in this study, which should be further studied on a large sample scale. Second, VEMPs do not reflect canal function; a comprehensive evaluation is required in combination with other vestibular tests. Due to the insufficient sample size of this study, it was not grouped according to etiology, medical diseases, etc. The effect of these potential factors on hearing prediction should be incorporated into statistical analysis in future studies with larger sample sizes. In addition, we could also follow up on hearing and vestibular

recovery at 1 and 3 months after treatment, making the study more comprehensive.

5. Conclusion

There were significant differences in the recovery of hearing loss in patients with ISSNHL. Patients with abnormal VEMPs have unfavorable hearing outcomes compared with those with normal VEMPs. Otolith organs are involved more frequently than afferents in patients with ISSNHL. Furthermore, the utricle was more susceptible compared to the saccule. The combination of ACS and GVS-VEMPs can better evaluate the lesion site and contribute to the clinical diagnosis, treatment, and prognosis evaluation of ISSNHL.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

This study was approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine (Approval No. XHEC-D-2022-259). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JSh was responsible for data interpretation and manuscript preparation. XM contributed to the data analysis. QingZ helped optimize the VEMP test procedure. JC contributed to the clinical consultation. LW, WW, KH, JSu, and QinZ were responsible for auditory tests and VEMP tests. XC contributed to the statistical consultation. MD and YJ reviewed and revised the manuscript and study design. JY was responsible for the research design and manuscript revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Jose Antonio Lopez-Escamez,
University of Sydney, Australia

REVIEWED BY
Takaomi Kurioka,
National Defense Medical College, Japan
Jean-Charles Ceccato,
Université de Montpellier, France

*CORRESPONDENCE
Jingchun He
✉ hejingchun@xinhuamed.com.cn
Maoli Duan
✉ maoli.duan@ki.se
Jun Yang
✉ yangjun@xinhuamed.com.cn

†These authors have contributed equally to this work

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Clinical characteristics and prognosis of sudden sensorineural hearing loss in single-sided deafness patients

Yupeng Liu[1,2,3†], Wenjin Wu[1,2,3†], Shuna Li[1,2,3], Qing Zhang[1,2,3], Jingchun He[1,2,3*], Maoli Duan[4,5*] and Jun Yang[1,2,3*]

[1]Department of Otorhinolaryngology-Head & Neck Surgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [2]Shanghai Jiaotong University School of Medicine Ear Institute, Shanghai, China, [3]Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, Shanghai, China, [4]Ear Nose and Throat Patient Area, Trauma and Reparative Medicine Theme, Karolinska University Hospital, Stockholm, Sweden, [5]Division of Ear, Nose and Throat Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

Background: Sudden sensorineural hearing loss (SSNHL) in patients with single-sided deafness (SSD) is rare. The prognosis of the sole serviceable hearing ear is very important for these patients. However, the clinical characteristics and prognosis of SSNHL in SSD patients are not well-documented.

Objective: This study aimed to investigate the clinical features and treatment outcomes of SSNHL in SSD patients.

Methods: Clinical data of 36 SSD patients and 116 non-SSD patients with unilateral SSNHL from January 2013 to December 2022 were retrospectively investigated. The clinical characteristics of the SSD patients were analyzed. All SSD patients were treated with intratympanic steroids plus intravenous steroids. Pure-tone average (PTA) and word recognition score (WRS) before and after treatment were recorded. The hearing recovery of SSNHL in SSD patients in comparison with non-SSD patients was explored. Auditory outcomes in SSD patients with different etiologies were also compared.

Results: Initial hearing threshold showed no significant differences between the SSD group and the non-SSD group (66.41 ± 24.64 dB HL vs. 69.21 ± 31.48 dB HL, $p = 0.625$). The SSD group had a higher post-treatment hearing threshold (median (interquartile range, IQR) 53.13(36.56) dB HL) than the non-SSD group (median 32.50(47.5) dB HL, $p < 0.01$). Hearing gains (median 8.75(13.00) dB) and the rate of significant recovery (13.89%) were lower in the SSD group than in the non-SSD group (median 23.75(34.69) dB, 45.69%). The etiology of SSD was classified as SSNHL, special types of infection, chronic otitis media, and unknown causes. SSNHL accounted for the maximum proportion (38.9%) of causes of SSD in the SSD group. Hearing gains were lower in the SSNHL-SSD group than in other causes of the SSD group. A binary logistic regression analysis demonstrated that SSD serves as an indicator of unfavorable hearing recovery outcomes (OR = 5.264, $p < 0.01$).

Conclusion: The prognosis of SSNHL in SSD patients is unsatisfactory. SSNHL accounts for the maximum proportion of causes of SSD in this group of patients. For SSD patients caused by SSNHL, less hearing improvement after treatment was expected when SSNHL occurred in the contralateral ear in comparison with SSD patients with other causes.

KEYWORDS

sudden sensorineural hearing loss, single sided deafness, clinical feature, prognosis, glucocorticoid

Introduction

Sudden sensorineural hearing loss (SSNHL) is characterized by an abrupt onset of sensorineural hearing impairment, involving a decrease of at least 30 dB in hearing across three consecutive frequencies within a span of 72 h. This condition affects an estimated 5 to 20 individuals out of every 100,000 people annually (1). The precise cause of SSNHL remains elusive, but it is widely believed to result from a complex interplay of factors. These factors include viral infections, autoimmune disorders, and vascular insufficiency. The prognosis of SSNHL is influenced by a variety of determinants, which encompass the severity of auditory impairment, the time interval between the onset of symptoms and treatment, and the coexistence of underlying comorbidities (2).

Single-sided deafness (SSD) is defined as a hearing loss of 70 dB or greater in the affected ear, with normal hearing in the other ear (3). In the United States, approximately 7.20% of adults are affected by SSD, with approximately 60,000 new cases emerging each year. Similarly, the United Kingdom reports an annual count of approximately 7,500 new SSD cases (4–6). The underlying etiology of congenital SSD remains elusive, though genetic factors are considered to be primary contributors. In cases of acquired SSD, SSNHL stands as the most frequent factor. Other etiologies encompass head injuries, Meniere's disease, labyrinthitis, unilateral acoustic neuroma, complications following middle ear surgery, exposure to ototoxic drugs, viral infections, noise-induced hearing loss, and presbycusis. Usami et al. revealed that SSNHL accounted for the majority (54.6%) of cases of post-lingual SSD, followed by various forms of chronic otitis media (7). A subgroup of individuals initially experiencing unilateral profound SSNHL eventually transition to SSD status due to inadequate treatment outcomes. SSD can have a significant impact on the quality of life of affected individuals, including difficulty in localizing sounds, understanding speech in noisy environments, and feeling socially isolated (8, 9).

SSNHL is a debilitating condition that can profoundly affect a patient's quality of life. In cases where it occurs in individuals with SSD, it presents a distinctive challenge. The prognosis of the remaining functional hearing ear becomes crucial, as any hearing impairment in that ear can significantly compromise their quality of life. Despite the absence of a standardized treatment protocol for SSNHL, glucocorticoids (GCs) have emerged as a foundational pharmacotherapy. GC delivery methods are categorized into systemic and local administration. Systemic administration includes intravenous and oral routes, while local administration commonly involves intratympanic (IT) injections and retroauricular injections. Treatment strategies involving GC encompass both single-agent therapy and combination therapy. However, studies prospectively comparing the effectiveness of different drug delivery methods are scarce. Combination therapy has shown promise in effectively treating severe to profound SSNHL (10, 11). While extensive research has explored the prognosis of SSNHL overall, there is a lack of comprehensive documentation regarding the clinical characteristics and treatment outcomes of SSD patients specifically. Therefore, the objective of this study is to investigate the clinical attributes and treatment responses of SSNHL in individuals with SSD. A comparative analysis will be conducted with non-SSD individuals affected by unilateral SSNHL. Gaining insight into the distinctive features and outcomes of SSNHL within these distinct populations is vital for optimizing management strategies and enhancing treatment outcomes.

Materials and methods

Patients

This was a retrospective study that included 36 SSD patients and 116 non-SSD patients with unilateral SSNHL treated at Xinhua Hospital from January 2013 to December 2022. The study was approved by the Institutional Review Board. The diagnostic criteria for SSNHL are defined as a rapid onset of hearing loss, occurring within 72 h, with a sensorineural hearing loss of at least 30 dB in three contiguous frequencies on pure-tone audiometry. These criteria were established by the American Academy of Otolaryngology-Head and Neck Surgery in 2012 (12). The diagnostic criteria for SSD are defined as pure-tone audiometry testing showing a pure-tone average (PTA) of 25 dB HL or greater in the better ear and a PTA of 70 dB HL or greater in the affected ear (3). Exclusion criteria applied in this study encompassed patients with a history of previous otologic surgery, ototoxic drug use, a history of genetic disorders associated with familial deafness, head trauma, retrocochlear disease, and abnormal findings in the central nervous system. Additionally, patients with incomplete medical records or those who did not complete the full course of treatment were excluded from the analysis. Clinical data of all patients were collected, including age, gender, etiology of SSD, hearing thresholds before and after treatment, and treatment methods. The etiology of SSD was determined based on the patients' medical history, physical examination, laboratory tests, and imaging studies.

Treatment methods

All patients received a combination treatment of intratympanic steroid (ITS) and intravenous steroid (IVS). The treatment protocol involved a regimen of 10 consecutive days during which patients received intravenous administration of 10 mg dexamethasone, along with IT injections of 2 mg dexamethasone. The successful completion of this 10-day protocol marked the conclusion of the entire treatment course.

Outcome assessment

The primary outcomes assessed in this study were the changes in pure-tone average (PTA) and word recognition score (WRS) before

and after the treatment. Mandarin speech test materials (MSTMs) were utilized for conducting the WRS evaluation. The MSTMs comprised 12 sets of lists, with each list containing 20 sentences. Each sentence consisted of 10 Chinese characters. The testing procedure was conducted using the bilateral implant test (BLIMP) system, maintaining a sound level set at 30 dB above the PTA threshold. A comprehensive test sheet was played, encompassing a total of 20 sentences, each comprising 10 words. WRS was calculated based on this test. The degree of hearing improvement was determined by assessing the alteration in the PTA following the treatment. Given the absence of an "unaffected ear" in the SSD group, a combined approach of the American and Chinese guidelines was employed for outcome assessment (13). Hearing gain ≥30 dB HL was considered indicative of significant recovery. Hearing gain ≥10 dB HL but less than 30 dB HL, or an enhancement in WRS by ≥10% (within the serviceable range, WRS ≥ 50%), was categorized as partial recovery. Hearing improvement of less than 10 dB HL was defined as no recovery. To facilitate the binary logistic regression during the statistical analysis, instances of significant and partial recovery were amalgamated into a "good recovery" category. Conversely, cases of no recovery were categorized as "poor recovery."

Statistical analysis

The statistical analysis was conducted using SPSS version 20.0 (IBM Corp., Armonk, NY, United States). Descriptive statistics were utilized to summarize the demographic and clinical characteristics of the study participants. For normally distributed values, the results were presented as mean ± standard deviation. Non-normally distributed values were expressed as median (interquartile range, IQR), while categorical variables were represented as frequency and percentage. To compare continuous variables between the SSD and non-SSD groups, an independent t-test was employed. Categorical variables were compared using the chi-square test. Non-parametric statistics were compared between the two groups using the Mann–Whitney test. Spearman's correlation analysis was utilized to establish relationships between non-parametric statistics in the two groups. For comparisons among multiple subgroups, non-parametric statistics were analyzed using the Kruskal–Wallis test. A binary logistic regression analysis was performed to calculate the odds ratio (OR) and its corresponding 95% confidence intervals (CIs). This analysis aimed to identify independent prognostic factors associated with SSNHL. The level of statistical significance was defined as a value of p of <0.05.

Results

Demographics

Table 1 displays the demographic and clinical characteristics of both the SSD and non-SSD groups. The SSD group comprised 20 men and 16 women, with a median age of 59.50 (14.75) years. The affected ear in the SSD group exhibited a median PTA of 97.50 (39.38) dB HL. The median duration of SSD was 8.50 (9.00) years. The non-SSD group consisted of 54 men and 62 women, with a median age of 57.50 (22.75) years. No significant differences were observed in age and gender distribution between the two groups ($p < 0.05$). Additionally, no statistically significant differences were noted in terms of the affected ear, the presence of tinnitus, vertigo, diabetes mellitus, or hypertension. However, there was a statistically significant difference in the interval between symptom onset and treatment initiation, with the SSD group having a median interval of 2.00 (2.00) days compared to 2.00 (5.00) days in the non-SSD group ($p < 0.05$). The initial hearing threshold did not significantly differ between the SSD group and the non-SSD group (66.41 ± 24.64 dB HL vs. 69.21 ± 31.48 dB HL, $p = 0.625$). Figure 1 illustrates the distribution of the etiology of hearing loss in the SSD group. Within the SSD group, the etiology of SSD was categorized as follows: SSNHL (14 cases), special types of infection (8 cases), chronic otitis media (4 cases), and unknown causes (10 cases). Notably, SSNHL accounted for the largest proportion (38.9%) of SSD cases. According to the World Report on Hearing by the World Health Organization in 2021, hearing loss was categorized from "mild" to "total." In the SSD group, five (13.9%) patients exhibited mild hearing loss, six (16.7%) had moderate hearing loss, eight (22.2%) displayed moderate–severe hearing loss, seven (19.4%) had severe hearing loss, six (16.7%) had profound hearing loss, and four (11.1%) had total hearing loss. In the non-SSD group, 24 (20.7%) patients had mild hearing loss, 8 (6.9%) had moderate hearing loss, 14 (12.1%) had moderate–severe hearing loss, 22 (19.0%) had severe hearing loss, 23 (19.8%) had profound hearing loss, and 25 (21.6%) had total hearing loss. These findings are presented in Figure 2. Notably, there were no significant differences in hearing loss across different frequencies (500 Hz, 1,000 Hz, 2000 Hz, and 4,000 Hz) within both the SSD group ($p = 0.95$) and the non-SSD group ($p = 0.99$).

Treatment outcomes

Table 2 provides an overview of the treatment outcomes observed in both the SSD and non-SSD groups. Among the patients in the SSD group, 5 individuals (13.89%) showed significant recovery, 13 patients (36.11%) showed partial recovery, and 18 patients (50.0%) showed no recovery. In contrast, within the non-SSD group, 53 patients (45.69%) achieved significant recovery, 38 patients (32.76%) displayed partial recovery, and 25 patients (21.56%) experienced no recovery. The post-treatment hearing threshold was significantly higher in the SSD group (median 53.12 (36.56) dB HL) compared to the non-SSD group (median 32.50 (47.50) dB HL, $p < 0.01$), as depicted in Figure 3. Furthermore, the SSD group exhibited lower hearing gains (median 8.75(13.00) dB) and a decreased rate of significant recovery in contrast to the non-SSD group (median 23.75(34.69) dB). Notably, there were no substantial differences in hearing gains across different frequencies (500 Hz, 1,000 Hz, 2000 Hz, and 4,000 Hz) within either the SSD group ($p = 0.921$) or the non-SSD group ($p = 0.319$). In the SSD group, WRS was 100% in 14 patients prior to treatment. WRS was improved (improvement ≥10%, in the serviceable range) in the remaining 8 of 22 patients. In the non-SSD group, WRS was 100% in 54 patients prior to treatment. WRS was improved (improvement ≥10%, in the serviceable range) in the remaining 43 of 62 patients. The non-SSD group showed a better improvement rate of WRS ($p = 0.006$). Spearman's correlation analysis was conducted to examine the correlations between pre-treatment PTA and hearing

TABLE 1 Comparison of clinical features of SSNHL patients between the SSD group and the non-SSD group.

	SSD group (n = 36)	Non-SSD group (n = 116)	p-value
Gender, men/women	20/16	56/60	0.445
Age (y)	59.50 (14.75)	57.50 (22.75)	0.201
Side, right/left	19/17	63/53	0.872
Symptom onset to treatment initiation interval, d	2.00 (2.00)	2.00 (5.00)	0.109
Initial hearing threshold (dB HL)	66.41 ± 24.64	69.21 ± 31.48	0.625
Hearing threshold of SSD side (dB HL)	97.50 (39.38)	/	
Duration of SSD (y)	8.50 (9.00)	/	
Tinnitus, n (%)	26 (72.2%)	85 (73.3%)	0.901
Vertigo, n (%)	9 (25%)	37 (31.9%)	0.431
Hypertension, n (%)	10 (27.8%)	19 (16.4%)	0.128
Diabetes, n (%)	8 (22.2%)	20 (17.2%)	0.501

SSNHL, sudden sensorineural hearing loss; SSD, single-sided deafness; normal distribution values are mean ± SD; non-normal distribution values are median (interquartile range, IQR).

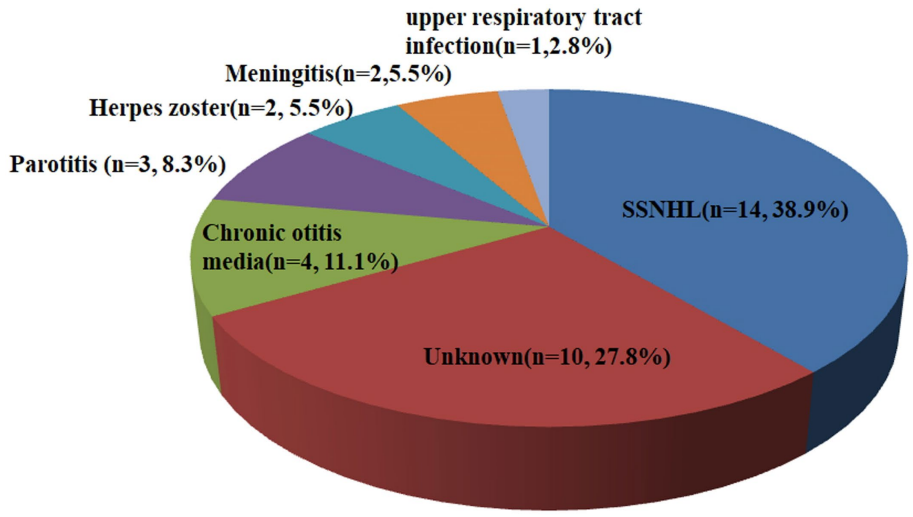

FIGURE 1
Etiology of hearing loss in the SSD group. Fourteen cases were attributed to SSNHL, eight cases were attributed to special types of infection (three cases of parotitis, two cases of herpes zoster, two cases of meningitis, and one case of upper respiratory tract infection), four cases were attributed to chronic otitis media, and ten cases were attributed to unknown causes. SSD, single-sided deafness; SSNHL, sudden sensorineural hearing loss.

gains in the SSD group, non-SSD group, and the whole population. In the whole SSD group and four subgroups, hearing gains were not significantly correlated with pre-treatment PTA (p = 0.563, 0.368, 0.866, 0.200, and 0.828, respectively). Hearing gains showed no significant correlation with PTA on the SSD side either (p = 0.432). In the non-SSD group, hearing gains were significantly correlated with pre-treatment PTA (r = 0.514, p < 0.01). Hearing gains were also significantly correlated with pre-treatment PTA in the whole population (r = 0.417, p < 0.01), as depicted in Figure 4.

Subgroup analysis of the SSD group

A subgroup analysis was conducted within the SSD group, categorized based on the cause of SSD. The treatment outcomes of these subgroups are presented in Table 3. In the "SSNHL" subgroup, 1 patient achieved significant recovery, 3 patients showed partial recovery, and 10 patients experienced no recovery. Within the "special infection" subgroup, one patient achieved significant recovery, five patients demonstrated partial recovery, and two patients displayed no recovery. In the "chronic otitis media" subgroup, two patients achieved significant recovery, one patient experienced partial recovery, and one patient had no recovery. In the "unknown cause" subgroup, one patient achieved significant recovery, five patients showed partial recovery, and four patients did not experience recovery. To compare the pre-treatment PTA and hearing gains among the four subgroups, the Kruskal–Wallis test was employed. The results indicated that there was no significant difference in pre-treatment PTA across the four groups (p = 0.12). However, a significant difference was observed in terms of hearing gains among the four subgroups (p = 0.03). Further analysis using the Steel–Dwass test indicated that the "SSNHL" subgroup had significantly lower hearing gains compared to the other three groups, as illustrated in Figure 5.

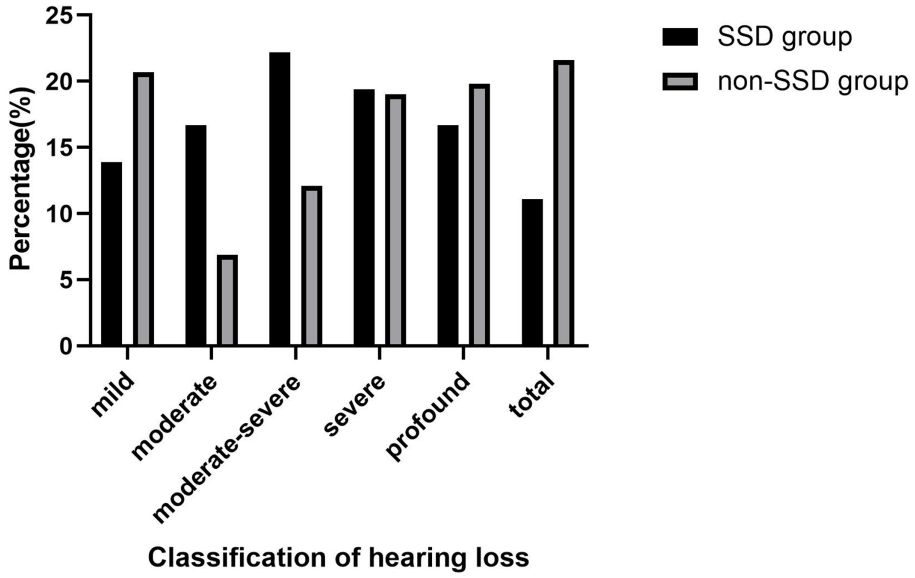

FIGURE 2
According to the "World Report On Hearing" of the World Health Organization in 2021, hearing loss was classified from "mild" to "total." In the SSD group, five (13.9%) patients were mild hearing loss, six (16.7%) patients were moderate hearing loss, eight (22.2%) patients were moderate–severe hearing loss, seven (19.4%) patients were severe hearing loss, six (16.7%) patients were profound hearing loss, and four (11.1%) patients were total hearing loss. In the non-SSD group, 24 (20.7%) patients were mild hearing loss, 8 (6.9%) patients were moderate hearing loss, 14 (12.1%) patients were moderate–severe hearing loss, 22 (19.0%) patients were severe hearing loss, 23 (19.8%) patients were profound hearing loss, and 25 (21.6%) patients were total hearing loss. SSD, single-sided deafness.

TABLE 2 Treatment outcomes of the SSD and non-SSD groups.

Outcome	SSD group	Non-SSD group	*p*-value
Significant recovery	5(13.9%)	53(45.7%)	<0.01
Partial recovery	13(36.1%)	38(32.8%)	0.710
No recovery	18(50.0%)	25(21.6%)	0.022
Hearing gains (dB)	8.75(13.00)	23.75(34.69)	<0.01
Posttreatment hearing threshold (dB HL)	53.12(36.56)	32.50(47.50)	<0.01

SSD, single-sided deafness.

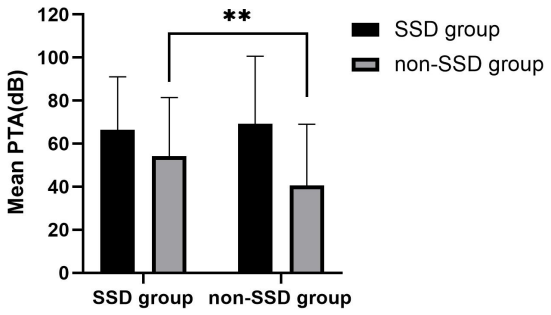

FIGURE 3
Initial hearing threshold showed no significant differences between the SSD group and the non-SSD group (66.41 ± 24.64 dB HL vs. 69.21 ± 31.48 dB HL, $p = 0.625$). SSD group had a higher post-treatment hearing threshold (median 53.12(36.56) dB HL) than the non-SSD group (32.50(47.50) dB HL, $p < 0.01$). SSD, single-sided deafness.

Prognostic factors of SSNHL

Based on their treatment outcomes, the patients were divided into two groups: good recovery and poor recovery. As a result, 108 patients exhibited good recovery, while 44 patients exhibited poor recovery. Variable comparisons were included in a binary logistic regression analysis. According to the analysis results, symptom onset to treatment initiation interval (OR = 1.125, $p = 0.016$), SSD (OR = 5.264, $p < 0.01$), and diabetes (OR = 2.113, $p = 0.012$) were significantly associated with poor hearing recovery, as outlined in Table 4.

Discussion

Sudden sensorineural hearing loss is a challenging condition that can significantly impact a patient's quality of life. Its impact becomes particularly intricate when it strikes individuals with SSD, as the prognosis of the remaining functional ear takes on paramount importance. In this retrospective study, we investigated the clinical features and treatment outcomes of SSNHL in SSD patients and compared them with those of non-SSD patients with unilateral SSNHL. Furthermore, we performed a subgroup analysis of the SSD group based on the cause of SSD. Our findings provide valuable insights into the unique characteristics of SSNHL in SSD patients and highlight the importance of optimizing management strategies for this population.

In our study, the results revealed that SSNHL accounted for the maximal proportion (38.9%) of causes of SSD in the SSD group, which is consistent with the previous report. Infectious disease constituted

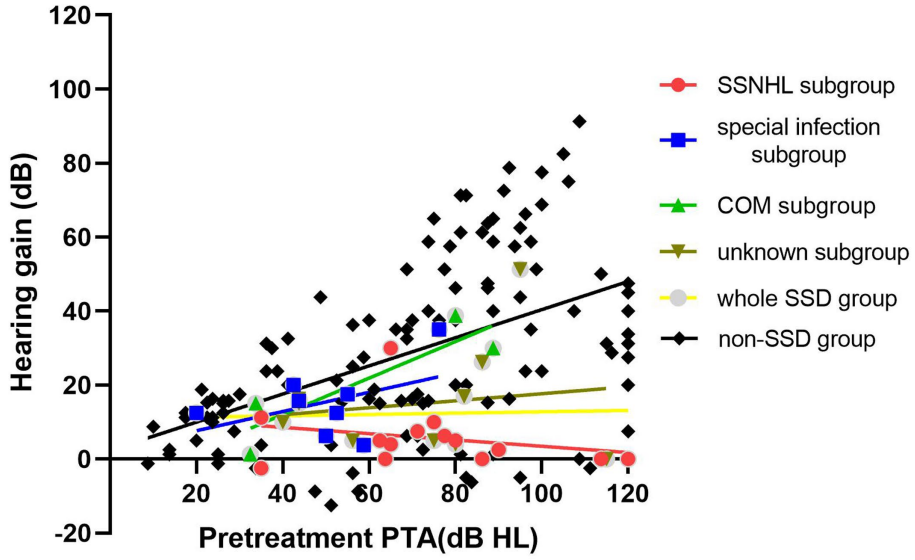

FIGURE 4
In the whole SSD group and four subgroups, hearing gains were not significantly correlated with pre-treatment PTA (p = 0.563, 0.368, 0.866, 0.200, and 0.828, respectively). In the non-SSD group, hearing gains were significantly correlated with pre-treatment PTA (r = 0.514, p < 0.01). SSD, single-sided deafness; SSNHL, sudden sensorineural hearing loss; COM, chronic otitis media.

TABLE 3 Treatment outcomes of the subgroups of different etiologies.

	SSNHL	Special infection	Chronic otitis media	Unknown
Significant recovery	1 (7.1%)	1 (12.5%)	2 (50.0%)	1 (10.0%)
Partial recovery	3 (21.4%)	5 (61.2%)	1 (25.0%)	5 (50.0%)
No recovery	10 (71.4%)	2 (25.0%)	1 (25.0%)	4 (40.0%)
Hearing gains (dB)	4.50 (8.13)	14.13 (11.57)	22.50 (31.87)	12.50 (14.56)
Posttreatment hearing threshold (dB HL)	64.38 (34.06)	38.75 (19.25)	36.25 (32.50)	55.62 (41.82)

SSNHL, sudden sensorineural hearing loss.

the second largest proportion of the SSD identified in our study. Mumps virus, bacterial meningitis, and herpesvirus are common causes that can lead to unilateral hearing loss (14, 15). Mumps is transmitted through infected respiratory secretions and is highly contagious. The mumps virus directly affects the endolymphatic system of the cochlea, thereby affecting the cochlear spiral organ, the cochlear capsule, and the myelin sheath of the cochlea nerve, leading to hearing loss. Morita et al. reviewed 67 patients with hearing loss caused by a mumps virus infection in a Japanese hospital. Among them, 63 individuals grappled with unilateral hearing loss, with a substantial portion aligning with the criteria for SSD (16). In this study, three patients suffered from bacterial meningitis, which led to SSD in their childhood. Meningitis in infants and young children can cause various complications, with hearing loss being a prominent consequence. Approximately 25% of infants with purulent meningitis will experience long-term hearing loss (17). Among these children, the majority suffer from moderate to severe hearing loss, which can have a serious impact on their quality of life and social interaction abilities.

The importance of treatment efficacy in SSNHL for SSD patients lies in the potential to restore or improve their hearing in the affected ear. Despite several treatments being available, the optimal approach for the treatment of SSNHL remains controversial. Combined IT and systemic GC administration is a promising treatment for SSNHL. Gundogan et al. substantiated the superiority of combined therapy through a prospective, randomized controlled trial (10). In this study, the fourth-week improvements in PTA for the combined therapy group and oral therapy group were 44.05 ± 21.53 dB and 25.72 ± 19.77 dB, respectively. Similarly, Battaglia et al. conducted a multicenter trial to compare hearing recovery outcomes between a combined therapy group and an IT therapy group (11). Their findings underscored that combination therapy provided SSNHL patients with the highest likelihood of achieving class A and B hearing. A recent meta-analysis of randomized controlled trials on the efficacy of combined IT and systemic GC therapies showed that they significantly improved hearing outcomes and increased the recovery rate compared to systemic therapy alone (18). Considering the great importance of hearing recovery for SSD patients, maximal delivery of corticosteroids to the inner ear using both systemic and IT options optimizes the potential for hearing recovery. Although there is still some controversy on the optimal treatment for SSNHL, especially about the efficacy of combination therapy, an aggressive treatment protocol of the combination therapy for SSD group of SSNHL patients is acceptable for both patients and clinicians.

TABLE 4 Clinical factors related to hearing recovery by binary logistic regression.

Variables	OR	95%CI	*p*-value
Age	0.979	0.953–1.006	0.135
Symptom onset to treatment initiation interval, d	1.125	1.022–1.237	0.016
Initial hearing threshold (dB HL)	0.996	0.983–1.010	0.609
SSD	5.264	2.178–12.723	<0.001
Tinnitus	1.342	0.846–2.128	0.219
Vertigo	1.275	0.778–2.076	0.349
Diabetes	2.113	1.182–3.785	0.012
Hypertension	1.464	0.872–2.436	0.150

CI, confidence interval; SSD, single-sided deafness; OR, odds ratio.

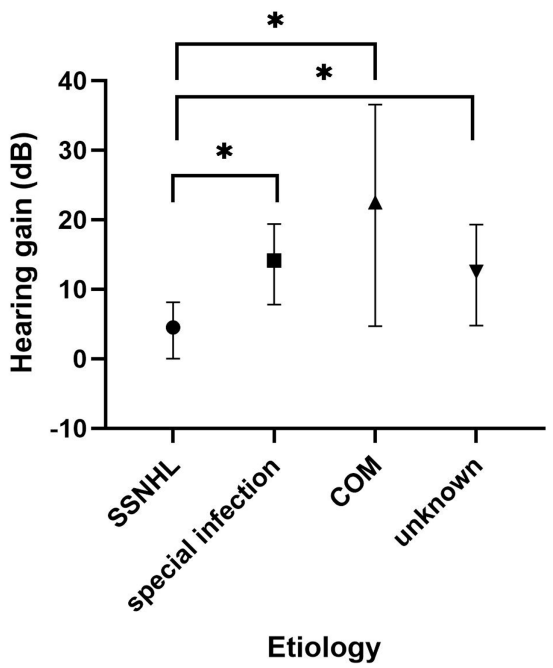

FIGURE 5
Subgroup analysis of the SSD group based on the cause of SSD. The Kruskal–Wallis test revealed a significant difference between the four groups (p = 0.03). The "SSNHL" group had lower hearing gains than the other three groups (p = 0.013, 0.034, and 0.048, respectively). SSD, single-sided deafness; SSNHL, sudden sensorineural hearing loss; COM, chronic otitis media.

In our study, the initial hearing loss across different frequencies (500 Hz, 1,000 Hz, 2000 Hz, and 4,000 Hz) exhibited no statistically significant differences, both within the SSD group and the non-SSD group. This observation might be attributed to the high prevalence of hearing loss categorized as "severe" or above in both groups (47.2% in the SSD group and 59.5% in the non-SSD group). Patients with hearing loss classified as "severe" to "total" typically display a flat audiogram pattern. Consequently, there is a lack of distinct variations across different frequencies, which could explain the absence of significant differences within these frequencies in our study. Our study also revealed that there was no significant frequency specificity in hearing gains, both within the SSD group and the non-SSD group. This observation contrasts with previous reports that suggest a more favorable hearing recovery for low frequencies compared to high frequencies in SSNHL patients. Suzuki et al. reported that hearing recovery at 500 Hz and 1,000 Hz was notably higher than at other frequencies, and recovery at 8000 Hz was comparatively lower (19). However, Zheng et al. drew a different conclusion in their research. They reported that hearing recovery was significantly greater in the all-frequency SSNHL and total deafness SSNHL subgroups and to a less extent in the low-frequency SSNHL subgroup (20). These disparities in findings could potentially stem from variations in patient characteristics and differences in treatment methodologies. The intricate interplay of these factors likely contributes to the divergence in conclusions observed across different studies.

In this study, the initial hearing thresholds did not exhibit significant differences between the SSD group and the non-SSD group. However, we observed that hearing gains and the rate of significant recovery were notably lower in the SSD group compared to the non-SSD group. To further explore the intricate relationship between SSD and the prognosis of SSNHL, we conducted a binary logistic regression analysis. The outcomes of this analysis revealed that SSD functions as a predictor of unfavorable hearing recovery outcomes (OR = 5.264, $p < 0.01$). This finding underscores the substantial impact of SSD on the potential for hearing improvement in SSNHL cases. The potential mechanism underlying this phenomenon could be associated with deafferentation and subsequent compensatory neural plastic changes occurring within the inferior colliculus. Lee et al. discovered a reduction in the expression of target genes linked to cAMP signaling pathways, metal ion binding, and calcium ion transport within the auditory pathway of SSD rats (21). Moreover, Kim et al. suggested that subcortical auditory neural activities, as observed through Manganum (Mn)-enhanced magnetic resonance imaging, were diminished in regions such as the superior olivary complex, lateral lemniscus, and inferior colliculus on the contralateral side of SSD mice (22). Morphological changes in the cytoskeleton of neurons within the contralateral inferior colliculus were also observed in SSD mice (23). These functional and morphological investigations collectively indicate that both the ipsilateral and contralateral inferior colliculi encounter disruptions within the auditory pathway of SSD patients. Consequently, when patients with healthy ears experience SSNHL, the central auditory system faces pronounced challenges in auditory conduction due to these intricate alterations.

Spearman's correlation analysis was conducted to examine the relationship between pre-treatment PTA and hearing gains within the SSD group, the non-SSD group, and the whole population. In the SSD

group, hearing gains displayed no significant correlation with pre-treatment PTA. In contrast, the non-SSD group showed a significant positive correlation between hearing gains and pre-treatment PTA. This finding seemed to contradict established beliefs that recovery rates decline in proportion to the severity of the initial hearing loss. Prior studies have indicated that the severity of initial hearing loss and audiometric configuration tend to impact prognosis (24–26). However, our results suggested a different perspective. We theorize that this phenomenon may result from the substantial hearing gain experienced by non-SSD patients with profound to total deafness after treatment. In this study, 41.4% of patients in the non-SSD group had profound hearing loss or total deafness. In other words, these individuals had more room for improvement in their hearing levels compared to those with mild to moderate hearing loss. Among the non-SSD group, 66.7% of patients with profound hearing loss or total deafness achieved significant recovery after treatment, while only 20% of patients in the SSD group exhibited significant recovery. This discrepancy suggests that the favorable therapeutic effect observed in severe hearing loss patients within the non-SSD group contributes to the positive correlation between hearing gains and pre-treatment hearing loss. In this study, the lack of a significant correlation between hearing gains and pre-treatment PTA in the SSD group might be linked to the relatively high proportion of "no recovery" patients (50.0%) regardless of their initial hearing loss level. It is noteworthy that the lack of correlation between the PTA on the SSD side and treatment outcomes on the SSNHL side is unexpected. The profound hearing loss already present in the SSD side (97.94 ± 18.49 dB HL) implies a significant level of hearing deprivation that has persisted for years. Given this long-standing condition, the difference between PTA values of 90 dB HL and 100 dB HL becomes essentially negligible, as there is no serviceable hearing. Even if SSD has some influence on the contralateral hearing recovery, this impact appears to be nearly consistent across these patients. Consequently, treatment outcomes show no significant correlations with the PTA on the SSD side.

In our subgroup analysis focusing on the SSD group, the "SSNHL" subgroup stood out by displaying significantly lower hearing gains compared to the other three subgroups. Recurrent cases of SSNHL have been reported to range from 1.4 to 17% in various studies (27). In our study, the patients belonging to the "SSNHL" subgroup could be interpreted as experiencing a second episode of SSNHL in the contralateral ear. The phenomenon of contralateral recurrence in SSNHL patients is relatively uncommon, and the characteristics of this subgroup of patients have not been extensively documented in previous research. The study by Kuo et al. delved into the comparison of two types of recurrence in SSNHL: ipsilateral recurrence and contralateral recurrence. In their investigation of 16 patients, 7 exhibited ipsilateral recurrence, while 9 experienced contralateral recurrence. Their findings revealed no statistically significant differences in the side of recurrence concerning age, inter-episode interval, gender, presence of vertigo, or abnormal caloric results (28). The prognosis for recurrent SSNHL can be quite heterogeneous among individuals. A study by Wu et al. illuminated an interesting relationship between hearing recovery following the first and recurrent episodes of SSNHL. They observed a strong positive association, indicating that a favorable hearing outcome after the initial episode was predictive of a superior outcome after the subsequent episode. Moreover, they identified a distinctive pattern in the distribution of hearing recovery between the first and second episodes. All patients who achieved complete recovery after the second episode also experienced complete recovery after the first episode (29). Obviously, the "SSNHL" group of SSD patients had an unsatisfactory treatment outcome after the first episode. The suboptimal treatment outcomes observed in the "SSNHL" subgroup of SSD patients, both in their first episode and contralateral second attack, may be attributed to the phenomenon of GC resistance. GC resistance in cases of sudden hearing loss refers to the lack of response to standard GC therapy, despite the absence of apparent underlying medical conditions that would hinder a positive response. Overcoming this resistance presents a significant clinical challenge in ensuring effective treatment for patients. Recent research has begun to shed light on potential factors underlying GC resistance in sudden hearing loss. One proposed mechanism involves genetic mutations that impact the expression or activity of GC receptors within the ear. While the exact genetic mechanisms contributing to GC resistance are not fully understood, several genes, including the NR3C1 gene responsible for encoding the GC receptor, have been implicated. Mutations in the NR3C1 gene can lead to altered GC receptor activity or expression, resulting in reduced responsiveness to GC therapy (30). Additionally, GC resistance could be related to decreased expression of histone deacetylase-2, increased levels of macrophage migration inhibitory factor, and P-glycoprotein, along with other factors such as chronic inflammation, oxidative stress, and immune system alterations (31, 32). It is important to recognize that these proposed mechanisms are not mutually exclusive, and it is likely that a combination of factors contributes to GC resistance in sudden hearing loss. Ongoing research aims to further uncover the underlying causes of this resistance and develop more effective treatment strategies for patients who do not respond well to GC therapy. Despite the challenges posed by GC resistance, there are alternative treatment options available for patients in this category. These may involve the use of different medications, such as vasodilators, antioxidants, or anti-inflammatory drugs, as part of a comprehensive approach to managing glucocorticoid-resistant sudden hearing loss. In addition, 21.6% of patients in the non-SSD group experienced "no recovery" following GC therapy. Some of these patients may meet the criteria for SSD based on their hearing levels after treatment. It is crucial for clinicians to fully inform these special patients that if SSNHL occurs again in the contralateral ear, the prognosis for the contralateral ear is generally unfavorable. Consequently, when managing these patients once more, clinicians should not confine themselves to using GC therapy exclusively. They should consider a broader spectrum of treatment options, including vasodilators, antioxidants, and anti-inflammatory drugs. This multifaceted approach ensures comprehensive care tailored to the patient's unique condition, increasing the likelihood of improved outcomes.

It is important to note that our study has several limitations. First, its retrospective nature and relatively small sample size may restrict the broader applicability of our results. The limited number of participants could potentially introduce bias and affect the robustness of our conclusions. Second, the duration of follow-up in our study was relatively short, which could impede a comprehensive assessment of the long-term outcomes. Extending the follow-up period would offer a more accurate understanding of the prognosis and treatment efficacy over time. Additionally, the treatment protocol employed in our study was based on practices specific to our institution, introducing the possibility of treatment variability across different settings. To address these limitations and enhance the credibility of our conclusions, future

research should strive for larger sample sizes, longer follow-up periods, and multi-center collaboration to provide a more comprehensive perspective on the clinical characteristics, treatment outcomes, and management options for SSNHL in SSD patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Xinhua hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JH, MD, and JY contributed to the study design. SL and QZ contributed to the statistical analysis and interpretation of the results. YL and WW drafted the manuscript. YL, WW, SL, QZ, JH, MD, and JY revised the manuscript with constructive discussions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Lisheng Yu,
Peking University People's Hospital, China

REVIEWED BY
Sulin Zhang,
Huazhong University of Science and Technology, China
Takaomi Kurioka,
National Defense Medical College, Japan
Jian-hua Zhuang,
Shanghai Changzheng Hospital, China
Jeremy Hornibrook,
University of Canterbury, New Zealand

*CORRESPONDENCE
Yi Ju
✉ juyi1226@vip.163.com

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Early detection of stroke at the sudden sensorineural hearing loss stage

Yao Zhong, Hongyan Li, Gaifen Liu, Jia Liu, Jia-Jie Mo, Xingquan Zhao and Yi Ju*

Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Background and purpose: Sudden sensorineural hearing loss (SSNHL) can be a prodromal symptom of ischemic stroke, especially posterior circulation strokes in the anterior inferior cerebellar artery (AICA) area. Early diagnosis and optimal treatment for vascular SSNHL provide an opportunity to prevent more extensive area infarction. The objective of our research was to find clues that suggest stroke at the stage of isolated sudden hearing loss.

Methods: We retrospectively investigated the medical records of patients who received an initial diagnosis of sudden sensorineural hearing loss upon admission from January 2017 to December 2022 at Capital Medical University Affiliated Beijing Tiantan Hospital. Among these patients, 30 individuals who developed acute ischemic stroke during their hospital stay were enrolled as the case group. To create a control group, we matched individuals from the nonstroke idiopathic SSNHL patients to the case group in terms of age (±3 years old) at a ratio of 1:4. We collected the clinical characteristics, pure tone hearing threshold test results, and imaging information for all patients included in the study.

Results: Three models were constructed to simulate different clinical situations and to identify vascular sudden sensorineural hearing loss (SSNHL). The results revealed that patients with SSNHL who had three or more stroke risk factors, bilateral hearing loss, moderately severe to total hearing loss, and any intracranial large artery stenosis and occlusion (≥50%) were at a higher risk of developing ischemic stroke during hospitalization. Consistent with previous studies, the presence of vertigo at onset also played a significant role in the early detection of upcoming stroke.

Conclusion: Clinicians should be alert to SSNHL patients with bilateral hearing loss, moderately severe to total hearing loss and other aforementioned features. Early pure tone audiometric hearing assessment and vascular assessment are necessary for high-risk patients with SSNHL.

KEYWORDS

sudden sensorineural hearing loss, stroke, hearing loss, clinical feature, magnetic resonance imaging

1. Introduction

Sudden sensorineural hearing loss (SSNHL), a subset of sensorineural hearing loss (SHL) (1), is widely regarded as one of the most common otolaryngological and potentially neurological emergencies (2). The incidence of SSNHL ranges from 5 per 100,000 to 150 per 100,000, primarily affecting individuals in the age group of 41–55 years, and the incidence has been rising in China in recent years (1, 3). Often, but not always, it is accompanied by vertigo and/or tinnitus. The pathogenesis and etiology of SSNHL remains unclear, and vascular mechanisms have gained more attention.

Previous studies indicated that 1.8%−4.2% of SSNHL patients were diagnosed with ischemic stroke, which was a higher percentage than that of people who were never diagnosed with SSNHL (4, 5). Several studies have demonstrated that sudden sensorineural hearing loss (SSNHL) is often a warning sign of an imminent stroke, particularly in the anterior inferior cerebellar artery (AICA) (4, 6–9). However, the diagnostic efficacy of HINTS (Head-Impulse-Nystagmus-Test-of-Skew) tests and HINTS-plus is compromised in these patients (10, 11). Clinical physicians currently do not possess efficient means to detect stroke during the SSNHL stage, specifically before the appearance of typical neurological symptoms and signs. This limitation can lead to a potential misdiagnosis.

Considering the time window for thrombolytic or interventional treatment, it is crucial to identify vascular SSNHL early before more devastating cerebral infarction. However, to our knowledge, there is still a lack of research on risk factors of stroke in isolated SSNHL patients. This case–control study aims to investigate the clinical characteristics, laboratory tests, auditory, and neuroimaging findings to facilitate the early identification of SSNHL related to stroke.

2. Methods

2.1. Study design and patients

Retrospectively, we investigated the medical records of patients who received an initial diagnosis of sudden sensorineural hearing loss upon admission from January 2017 to December 2022 at Capital Medical University Affiliated Beijing Tiantan Hospital. According to the Guidelines for Diagnosis and Treatment of Sudden Deafness 2015, China (3), the diagnostic standard of SSNHL in this study is rapidly evolving SHL with a minimum of 20 dB over at least two consecutive frequencies on tone audiometry that occurs within a period of 72 h. The inclusion criteria of the case group were as follows: ①age ≥18 years old; ②SSNHL as the first symptom (identified on pure tone audiometry on the day or second day of admission) and without neurological deficits at admission; ③development of focal neurological deficits (e.g., facial numbness and limb weakness, hemiataxia, dysarthria or Horner's syndrome) during hospitalization and diagnosis of acute ischemic stroke by magnetic resonance imaging (MRI) diffusion weighted imaging (DWI) or following computed tomography (CT, only for patients who are contraindicated for MRI); and ④complete medical records, laboratory test results and pure-tone audiometry records. The exclusion criteria included ①definite neurological deficits preceding SSNHL; ②no new focal neurological deficits during hospitalization but existing acute cerebral infarction on MRI-DWI; and ③hearing loss due to other specific diseases. Among all 1,882 patients with SSNHL on admission, 30 individuals (1.59%) met the above inclusion/exclusion criteria for the case group, which was checked and verified by two stroke specialists.

The controls were nonstroke idiopathic SSNHL inpatients in the same period (January 2017 to December 2022) as the case group. Patients with identifiable causes of hearing loss, such as noise-induced hearing loss, traumatic hearing loss, ototoxic drug poisoning, and Meniere's disease, were excluded. Given that atherosclerosis is commonly associated with advancing age (12), age-related hearing loss is the most prevalent type of auditory impairment (13). The control group was matched with each individual in the case group according to the patient's age (±3 years old) by random sampling. To optimize sample utilization and enhance the research efficiency to the maximum extent possible, each case had four age-matched controls. The control participants also underwent complete magnetic resonance imaging examinations and were examined by ENT specialists. Finally, a total of 150 patients were enrolled, with 30 patients in the case group and 120 patients in the control group. The standardized treatment plan for all of SSNHL patients in this study was based on the 2015 Guidelines for Sudden Deafness of China (10). Glucocorticoids and ginkgo leaf extract drop were the drugs mainly used in the treatment. Vasodilator prostaglandins, such as alprostadil, were not used.

2.2. Baseline characteristics and data collection

We edited a case report form (CRF) and digitized it using Epidata 3.1 software developed by EpiData Association in Copenhagen, Denmark. The study encompassed the collection of demographic and medical records from all 150 patients, including information on sex, age, hypertension, diabetes, hyperlipidaemia, history of stroke, and drinking and smoking history.

The detailed definitions of the six risk factors for stroke mentioned above are as follows: ① hypertension, indicated by a history of high blood pressure with a measurement of ≥140/90 mmHg as reported by the individual or diagnosed by a physician (14); ②diabetes, indicated by fasting plasma glucose levels of ≥7.0 mmol/L or taking glucose-lowering drugs (15); ③ dyslipidaemia, deemed either self-reported physician-diagnosed hyperlipidaemia or the use of lipid-lowering drugs (16); ④stroke history, characterized by the sudden onset of focal neurologic deficits and diagnosed as either ischemic or haemorrhagic stroke; and ⑤smoking history, defined as smoking at least 1 cigarette per day for >6 months before admission (17); and ⑥drinking history, defined as consuming more than 100 ml of spirit alcohol more than three times a week based on self-report (18). Furthermore, accompanying symptoms and laboratory test results were also recorded. The detailed descriptions of the accompanying symptoms are as follows: ①dizziness, defined as the feeling of disturbed or impaired spatial orientation without a distorted or false sense of motion (19); ②vertigo, referring to the sensation of self-motion of the head or body, even when there is no actual movement, or the false perception that the visual surroundings are flowing or spinning (19); ③headache, defined as pain located above the orbitomeatal line (20); and ④tinnitus, defined as the perception of sounds that are not actually present (21).

2.3. Audiometric and neuroimaging assessments

The auditory assessment was ascertained by measuring pure tone averages (PTAs) from 500 Hz to 4,000 Hz for both bone and air conduction (ISO/EC17025), and the auditory assessments were

performed by audiologists. According to the World Report on Hearing 2021, the degree of hearing loss was determined using the average hearing thresholds at 500 Hz, 1,000 Hz, 2,000 Hz, and 4,000 Hz. Hearing loss was classified as either mild to moderately severe (20–50 dB) or moderately severe to total hearing loss (≥50 dB) (22). Moreover, bilateral SSNHL was defined in this study as hearing loss in both ears that met the diagnostic criteria for SSNHL, and the grading of the audiometric assessment was based on the side with more severe hearing loss.

Brain MRI and magnetic resonance angiography (MRA) imaging were performed on all but one patient who had previously undergone coronary artery bypass graft surgery. However, one patient had typical focal neurological deficits (dysarthria and diplopia) after SSNHL, and subsequent CT (11 days later) showed hypodensity in the right brachium pontis. The interpretation of neuroimaging was independently achieved by a neurologist and a neuroradiologist to ensure accuracy and reliability. The vascular territories of infarct lesions in the case group were determined using MRI anatomical templates that have been previously validated for diagnosing arterial territories (23, 24). The distribution of lesions was classified into anterior circulation infarction (4/30), posterior circulation infarction (24/30) and border zone infarction (2/30). Furthermore, as per the New England Medical Center Posterior Circulation Registry, posterior circulation infarcts were classified into proximal (medulla and posterior inferior cerebellum), middle (pons and anterior inferior cerebellum), and distal territories (rostral brainstem, superior cerebellum, occipital and temporal lobes) (25).

In addition, we evaluated major intracranial large arteries in all 150 patients, including the internal carotid arteries (ICAs, intracranial segments), anterior cerebral arteries (ACAs, A1 segments), middle cerebral arteries (MCAs, M1–M3 segments), posterior cerebral arteries (PCAs, P1–P3 segments), vertebral arteries (VAs, intracranial segments), and basilar artery (BA). We used magnetic resonance angiography (MRA) with the WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) criteria to measure the degree of intracranial artery stenosis (ICAS). This was graded as normal to mild stenosis (<50%) and moderate stenosis to occlusion (≥50%) (26).

2.4. Statistical analysis

SPSS version 26.0 (IBM, Armonk, NY, USA) was used for statistical analysis. We expressed dichotomous data as the numbers (percentages) and expressed continuous data as the median (Q1–Q3; interquartile range) or mean standard deviation. For continuous data, the Mann–Whitney U test or Student's t test was applied to compare data between the groups. The chi-square test was applied to analyse comparisons for dichotomous data; $p < 0.05$ was regarded as statistically significant. Three multivariate logistic regression models were constructed based on the different situations in clinical practice. Due to the limited sample size, we combined stroke risk factors such as "smoking history" from Table 1 into the variable of "Three or more stroke risk factors" to ensure the robustness of the fitted logistic model. Statistically significant variables in the clinical characteristics and laboratory tests were then included in the multifactor logistic regression analyses as model-1, simulating a scenario where patients did not receive a hearing test and head MRI scan in outpatient, emergency, or primary care settings. Model-2 was built upon model-1 and incorporated audiometry findings, simulating a situation where patients had undergone pure tone audiometry in the ENT clinic or ward but did not receive an MRI scan. Exploratory Model-3 added any large artery moderate stenosis to occlusion (≥50%) to Model-2. The 95% confidence intervals (95% CIs) and adjusted odds ratios (ORs) were calculated, and bilateral p values ($p < 0.05$) were assumed to be statistically significant. A receiver operating characteristic curve (ROC) was plotted, and the area under the ROC curve (AUC) was calculated.

3. Results

3.1. Baseline information

The case group consisted of twenty five males and five females, with an average age of 57.13 ± 10.64 years. The nonstroke control group consisted of 120 patients, comprised of 58 females and 62 males, with an average age of 56.67 ± 10.82 years. Table 1 presents a comparison of the baseline information. There were statistically significant differences between the two groups ($p < 0.05$) in terms of sex, dyslipidaemia, hypertension, stroke history, smoking, and drinking history. In the case group, 14 patients (46.67%) had three or more stroke risk factors, while in the control group, there were 12 patients (10%) with the same condition ($p < 0.001$). The incidence of vertigo in the case group was significantly higher ($p = 0.011$) than that in the control group among the accompanying symptoms. No significant differences were found between the two groups in terms of dizziness, headache, tinnitus, or other accompanying symptoms.

3.2. Audiometric findings and laboratory test findings

As depicted in Table 2, a comparison was conducted between the two groups regarding the hearing loss features. Concerning the side of hearing loss, there was a notable disparity in the proportion of bilateral SSNHL patients between the case group and the control group, with the former exhibiting a significantly higher proportion ($p = 0.003$). With respect to the degree of SSNHL, a significant distinction was observed in the range of moderately severe to total hearing loss ($p = 0.017$). Therefore, individuals with SSNHL displaying a degree of moderately severe to total HL have an increased likelihood of developing ischemic stroke. For lab tests, statistically significant differences ($p < 0.001$) were observed in serum creatinine (Scr). No significant difference was observed in the other indicators ($p > 0.05$).

3.3. Neuroimaging findings

Among the individuals in the case group, the infarcts involved the cerebellum in seventeen cases, pons in nine cases, corona radiata in five cases, occipital lobe in four cases, frontotemporal

TABLE 1 Demographics and clinical features.

Variables	Control Group ($n = 120$)	Case Group ($n = 30$)	Total ($n = 150$)	*P* value
Demographic				
Age (Mean ± SD)	56.67 ± 10.82	57.13 ± 10.64	56.76 ± 10.71	0.835
Male *n* (%)	62 (51.67)	25 (83.33)	87 (58.00)	**0.002**
Medical history				
Smoking History *n* (%)	25 (20.83)	19 (63.33)	44 (29.33)	<0.001
Drinking History *n* (%)	22 (18.33)	17 (56.67)	39 (26.00)	<0.001
Hypertension *n* (%)	39 (32.50)	20 (66.67)	59 (39.33)	<0.001
Diabetes mellitus *n* (%)	18 (15.00)	7 (23.33)	25 (16.67)	0.273
Dyslipidaemia *n* (%)	11 (9.17)	9 (30.00)	20 (13.33)	0.003
Stroke history *n* (%)	3 (2.50)	4 (13.33)	7 (4.67)	0.012
Three or more stroke risk factors *n* (%)	12 (10.00)	14 (46.67)	26 (17.33)	**<0.001**
Dizziness history *n* (%)	1 (0.83)	1 (3.33)	2 (1.33)	0.286
Tinnitus history *n* (%)	5 (4.17)	2 (6.67)	7 (4.67)	0.561
Accompanying symptoms				
Dizziness *n* (%)	55 (45.83)	17 (56.67)	72 (48.00)	0.288
Vertigo *n* (%)	25 (20.83)	13 (43.33)	38 (25.33)	**0.011**
Headache *n* (%)	3 (2.50)	3 (10.00)	6 (4.00)	0.061
Tinnitus *n* (%)	5 (4.17)	2 (6.67)	7 (4.67)	0.561

The variables marked in bold are clinically important and meaningful variables in univariate analysis.

lobe in three cases, corpus callosum in three cases, medulla oblongata in two cases, midbrain in one case, and thalamus in two cases. Table 3 shows the vascular territory of the infarct lesions in the case group. There were 24 cases (80%) of posterior circulation infarction (PCI), with significantly higher rates than anterior circulation (4, 13.3%) and border zone infarction (2, 6.6%). Specifically, the middle territory of PCI was most often involved, either as an isolated infarct or in combination with other territory infarcts. Regarding to hearing loss features in different arterial territories of case group, there was no significant difference between the PCI and anterior circulation or border zone, as illustrated in Supplementary material.

For the assessment of intracranial arteries, 22 of 30 (73.3%) patients in the case group had intracranial large artery stenosis or occlusion, among whom 20 (66.6%) patients had ≥50% stenosis or occlusion, including 18 (60.0%) cases presenting with ≥50% stenosis or occlusion in the vertebral arteries and/or basilar artery. Additionally, out of the 120 patients in the nonstroke control group, 24 individuals (20%) were found to have moderate to severe stenosis or occlusion in their large arteries, with a statistically significant difference (p<0.001).

3.4. Multivariate logistic regression analysis

To improve clinical applicability, three distinct multivariate logistic regression models were designed to determine the risk factors associated with ischemic stroke in patients with sudden sensorineural hearing loss (SSNHL).

Model 1: clinical presentation

For this primary model, the hypothesized scenarios were that patients did not undergo pure tone audiometry and MRI during their clinic visits. Patients with three or more stroke risk factors showed a markedly higher risk of ischemic stroke (adjusted OR 4.974; 95% CI 1.659–14.918; $p = 0.004$). Vertigo, when present at onset, was a significant risk factor of stroke-related SSNHL (adjusted OR 2.846; 95% CI 1.031–7.857; $p = 0.044$). Similarly, patients with higher serum creatinine levels on admission were at a greater risk of stroke (adjusted OR 4.974; 95% CI 1.659–14.918; $p = 0.004$), as shown in Table 4.

Model 2: audiometric findings

For cases where complete audiometry was carried out, findings related to the side and degree of hearing loss were integrated into Model-1. Audiometric data indicated that both bilateral hearing loss (adjusted OR 8.040; 95% CI 1.694–38.153; $p = 0.009$) and moderate to severe hearing loss (adjusted OR 5.219; 95% CI 1.214–22.431; $p = 0.026$) were associated with an increased risk of stroke.

Model 3: MRI findings

Building on Model-2, the presence of intracranial artery stenosis or occlusion (≥50%) was introduced to develop Model-3. Factoring in intracranial artery issues became a strong risk factor for evolving into cerebral infarction during hospitalization (adjusted OR 7.264; 95% CI 2.403–21.961; $p < 0.001$).

TABLE 2 Audiometric, laboratory tests and neuroimaging findings.

Variable		Control group ($n = 120$)	Case group ($n = 30$)	Total ($n = 150$)	p value
Pure tone audiometry *n* (%)					
Side of hearing loss	Unilateral	115 (95.83)	24 (80.00)	139 (92.67)	**0.003**
	Bilateral	5 (4.17)	6 (20.00)	11 (7.33)	
Moderately severe to total hearing loss	No	43 (35.83)	4 (13.33)	47 (31.33)	**0.017**
	Yes	77 (64.17)	26 (86.67)	103 (68.67)	
Laboratory data M (Q1, Q3)					
HGB(g/L)		141.50 (131.0, 151.0)	147.00 (134.5, 155.3)	—-	0.147
LDL-C(mmol/L)		2.93 (2.5, 3.6)	2.95 (1.8, 3.8)	—-	0.618
AST (U/L)		17.15 (13.2, 21.6)	20.20 (14.6, 23.7)	—-	0.179
ALT (U/L)		20.05 (14.1, 30.0)	22.35 (16.8, 30.8)	—-	0.250
GFR (ml/min)		113.30 (103.9, 121.9)	107.73 (91.2, 121.5)	—-	0.310
Scr(μmol/L)		58.60 (49.5, 66.8)	70.45 (61.7, 82.5)	—-	**<0.001**
Intracranial large arteries stenosis or occlusion(≥50%)*n* (%)					
Any intracranial large arteries		24 (20.00)	20 (66.67)	44 (29.33)	**<0.001**
Vertebrobasilar arteries		15 (45.50)	18 (60.00)	33 (22.00)	
Posterior cerebral arteries		8 (6.67)	4 (13.33)	12 (8.00)	
Middle cerebral arteries		2 (1.67)	4 (13.33)	6 (4.00)	

HGB, hemoglobin; LDL-C, low-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; Scr, serum creatinine; vertebrobasilar artery, vertebral arteries and/or basilar artery.

TABLE 3 Distribution of infarcts in the case group.

Arterial territories of ischemic lesions	$n = 30$
Posterior circulation territories	24 (80.0%)
Distal territory alone	2 (6.6%)
Middle territory alone	8 (26.6)
Proximal territory alone	3 (10%)
Middle territory + proximal and/or distal territory	11 (36.7%)
Border zone and anterior circulation territories	6 (20.0%)
Border zone	2 (6.6%)
Middle cerebral arteries supply area	4 (13.3%)

The effectiveness of each model was gauged through receiver operating characteristic curves (Figure 1). Of all the models, Model-3 showed the highest predictive precision with an area under the curve (AUC) value of 0.908, followed by Model-2 (0.876) and Model-1 (0.830).

3.5. Illustrative cases

Patient 1: a 42-year-old male, who had a medical history significant for essential hypertension and type II diabetes mellitus, presented with acute unilateral right-sided sensorineural hearing loss, concomitant vertigo, and tinnitus. The initial cranial CT performed in the emergency department demonstrated no acute intracranial pathology, as visualized in Figure 2A. On the fifth day of hospitalization, he developed clinical signs of right-sided central facial nerve palsy and hypoesthesia to thermal and nociceptive stimuli over the facial region. A subsequent MRI of the brain revealed an acute ischemic infarct localized on the right dorsolateral pontine region, as evidenced in Figure 2B. Magnetic resonance angiography (MRA) corroborated significant vascular pathology, with pronounced stenosis of the right intracranial vertebral artery and a moderate stenotic lesion in the mid-segment of the basilar artery, as detailed in Figure 2C. Audiometric evaluation using pure tone audiometry documented profound sensorineural hearing impairment on the right, registering at 108.75 dB.

Patient 2: A 63-year-old male presented with intermittent dizziness for seven days and bilateral hearing loss for 3 days prior to admission. Two days after being admitted, the patient developed weakness in his left lower extremity (grade 4/5). MRI of the brain revealed acute infarction in the bilateral cerebellum, pons, and left occipital lobe (Figure 3A). Magnetic resonance angiography showed multiple stenoses in the bilateral vertebral arteries and basal artery (Figure 3B), indicating that the condition was likely caused by an artery-to-artery embolism. Figure 3C illustrates severe hearing loss (71.25 dB) in the patient's left ear and moderately severe hearing loss (52.5 dB) in the right ear.

TABLE 4 Multivariate regression logistic models in different practical situations.

Variables	Crude OR (95% CIs)	Model-1	Model-2	Model-3
		Adjusted OR (95%CIs)	Adjusted OR (95%CIs)	Adjusted OR (95%CIs)
Male	0.214 (0.077, 0.596)**	0.753 (0.227, 2.499)	0.816 (0.232, 2.869)	0.631 (0.157, 2.542)
With three or more stroke risk factors	7.875 (3.098, 20.016)***	4.974 (1.659, 14.918)**	4.967 (1.563, 15.784)**	3.913 (1.101, 13.905)*
Accompanying Vertigo	2.906 (1.247, 6.771)**	2.846 (1.031, 7.857)*	3.754 (1.250, 11.275)*	3.393 (1.022, 11.262)*
SCr(μmol/L)	1.065 (1.031, 1.100)***	1.053 (1.016, 1.092)**	1.061 (1.021, 1.103)**	1.057 (1.020, 1.096)**
Binaural hearing loss	5.750 (1.622, 20.387)**	—	8.040 (1.694, 38.153)**	6.823 (1.301, 35.783)*
Moderately severe to total HL	3.630 (1.188, 11.090)*	—	5.219 (1.214, 22.431)*	5.613 (1.192, 26.425)*
Any large arteries stenosis or occlusion(≥50%)	8.000(3.315, 19.308)***	—	–	7.264 (2.403, 21.961)***

OR, odds ratio; CI, confidence interval; Scr, serum creatinine; HL, hearing loss.
Model-1: Clinical presentation and laboratory data (simulating a scenario without audiometry and neuroimaging).
Model-2: Model-1+ pure tone audiometric (simulating a scenario without neuroimaging).
Model-3: Model-2+ any intracranial large artery stenosis or occlusion (≥50%).
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

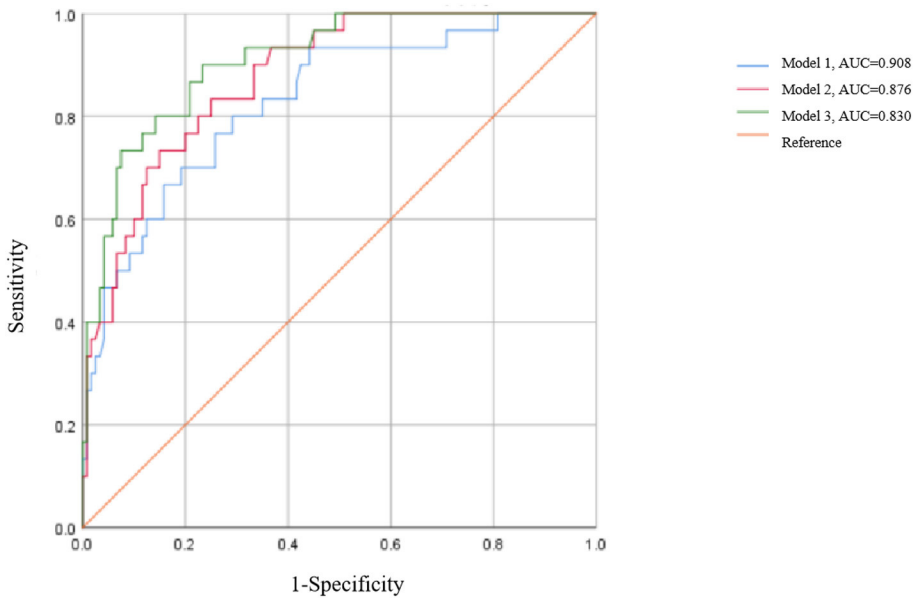

FIGURE 1
Receiver operating characteristic curves (ROC) of the three models.

4. Discussion

4.1. Association of accompanying vertigo with stroke

Regardless of the inclusion or exclusion of audiometric and neuroimaging variables in model-1 to model-3, the presence of accompanying vertigo consistently serves as a dependable risk factor for stroke. Similarly, Tzu-Pu Chang et al. found that individuals who presented with both sudden hearing loss and vertigo had a higher likelihood of stroke than those with either vertigo or sudden hearing loss alone. Furthermore, there seemed to be an increasing risk of stroke as the interval between episodes of these two symptoms diminished (27). This may be relevant to the inner ear anatomical structure and its associated blood supply. Fundamentally, internal auditory arteries (IAAs), which supply the inner ear, originating from the AICA (45.4%), superior cerebellar artery (24.4%), posterior inferior cerebellar arteries (5.4%) and even basilar artery (16%), as well as other anastomotic branches (6.7%), are extremely sensitive to ischaemia and hypoxia (28–30). The common cochlear artery and anterior vestibular artery are branches of the IAA, and simple ischaemia of the common cochlear artery or anterior vestibular artery may cause isolated hearing loss or vertigo. Compared with the common cochlear artery, the IAA is closer to the larger branch of the vertebrobasilar artery. Therefore, ischaemia of the IAA is more likely to indicate local stenosis or occlusion of the large vessels rather than impairment of the inner ear microcirculation. Furthermore, an animal study (31) demonstrated

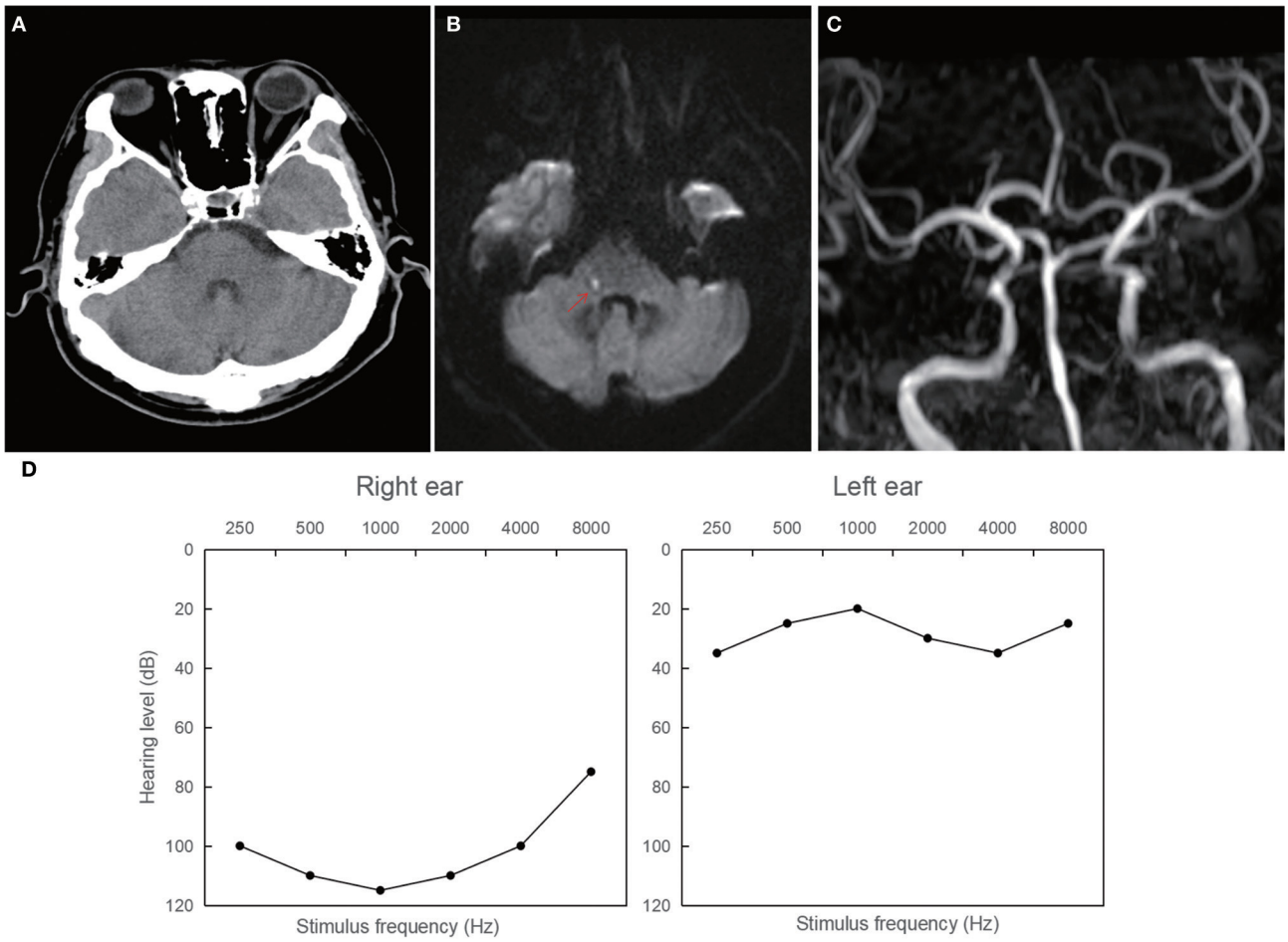

FIGURE 2
Neuroimaging and audiological findings in patient 1. **(A)** The initial normal CT. **(B)** Magnetic resonance imaging of the brain showing an acute ischemic lesion localized on the right dorsolateral pontine region. **(C)** Magnetic resonance angiography showings stenosis of the right intracranial vertebral artery and a moderate stenotic lesion in the mid-segment of the basilar artery. **(D)** Pure tone audiometry documenting profound sensorineural hearing impairment on the right ear (108.75 dB).

that the medial vestibular nucleus is more susceptible to ischaemia than other structures in the brainstem and cerebellum. Therefore, accompanying vertigo may also be attributed to dorsolateral medulla damage caused by vertebrobasilar system ischaemia.

4.2. Hearing loss features and stroke

Bilateral SSNHL is rare, accounting for approximately 5% of all SSNHL cases, and is often associated with poor prognosis (32). Our study demonstrates that there is a significant correlation between bilateral SSNHL and potential ischemic stroke. Hence, it highlights the importance of standardized hearing assessments in clinical practice, especially in a scenario when MRI has not yet been applied (Model-2). Case reports and case series suggest that bilateral SSNHL is associated with posterior circulation infarction (33–35). However, due to the lack of a control group and the relatively small sample size, those results have been considered less convincing. A previous study analyzed the characteristics of patients who had bilateral SHL with occlusion of the vertebrobasilar artery and showed that the patients often suffered early vertigo and delayed neurological deficits (36). The findings are similar to those of our study, but the relation between bilateral hearing loss and stroke-related SSNHL has not been explored in the past. The mechanism may be bilateral inner ear ischaemia caused by local stenosis or occlusion of the inferior 1/3 of the BA where bilateral AICA or IAA emanates or, rarely, bilateral vertebral artery stenosis (37), resulting in damage to inner ear hair cells that are hypersensitive to hypoxia and ischaemia. Further advancements in vascular examination techniques are required to accurately detect stenoses or occlusions from the AICA or PICA to the IAA to ascertain the hypothesis.

Apart from which side hearing loss occurs, the multivariate logistic model-2 and model-3 showed that the severity of hearingloss was a risk indicator for stroke. A previous study showed that individuals with more severe hearing loss tend to have a higher CHADS2 score, suggesting that the severity of hearing loss was positively related to the degree of atherosclerosis (38). Another study showed that individuals with moderate to severe hearing loss were more likely to have a history of stroke; but there is no statistically significant correlation between moderate to severe hearing loss and occurrence of stroke 5 years later (39). There may be a potential link between the degree of hearing loss and

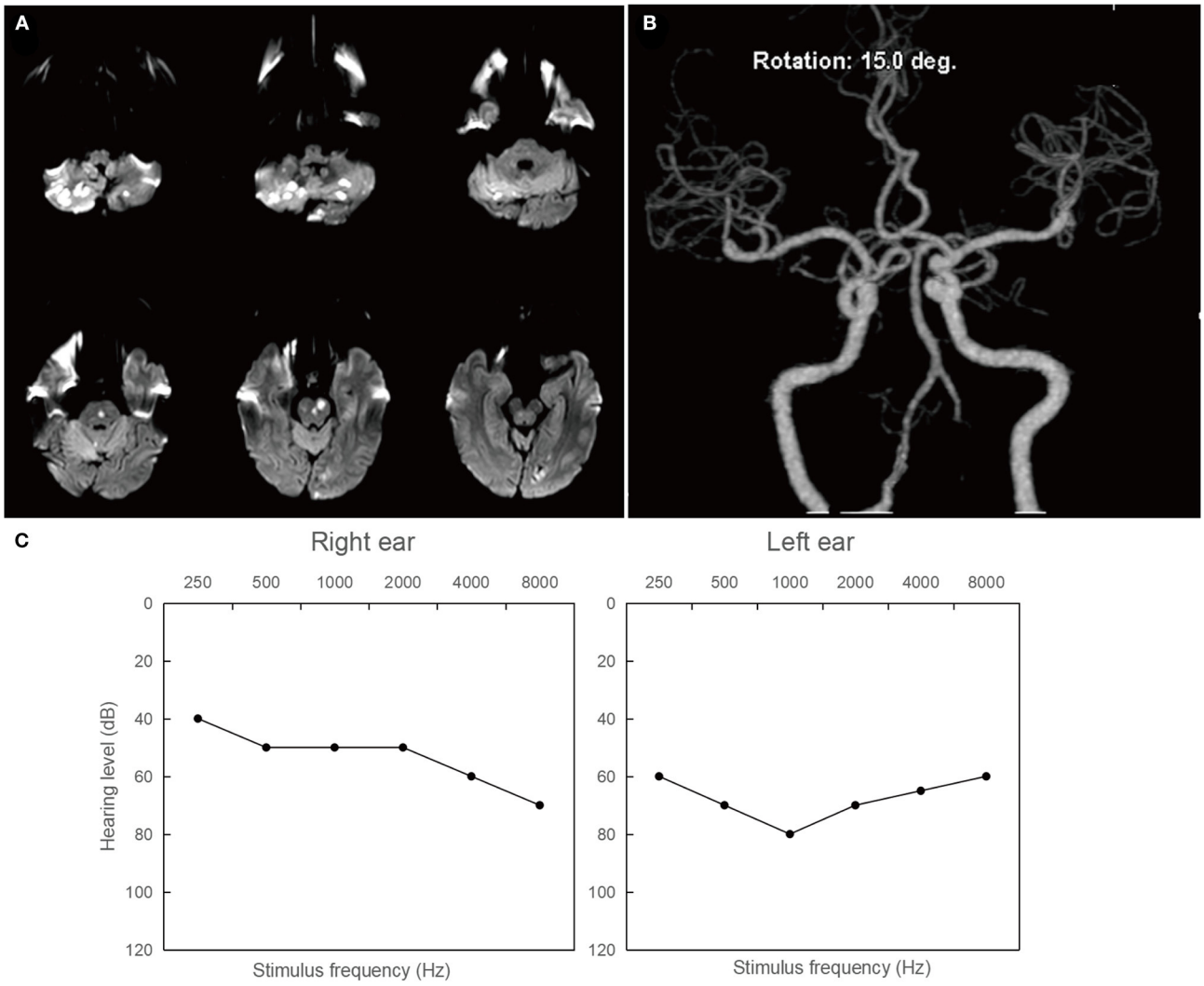

FIGURE 3
Neuroimaging and audiological findings in patient 2. **(A)** Diffusion weighted imaging of the brain showing hyperintense lesions involving in the bilateral cerebellum, pons, and left occipital lobe. **(B)** Magnetic resonance angiography showings multiple stenoses in the bilateral vertebral arteries and basal artery. **(C)** Pure tone air conduction audiograms illustrating severe hearing loss (71.25 dB) in the left ear and moderately severe hearing loss (52.5 dB) in the right ear.

the occurrence of stroke. However, the ability to predict long-term stroke occurrence based on this association is currently insufficient. To our knowledge, our study is the first to explore the link between the degree and side of hearing loss and the incidence of short-term stroke in SSNHL patients. For patients presenting with moderate to severe bilateral hearing loss, it is necessary to conduct brain magnetic resonance imaging (MRI) and assess the cranial large vessels (Model-3). Further research with a larger sample size is required to further study the correlation between the type of hearing loss and the likelihood of stroke.

4.3. Intracranial large artery stenosis and ischemic stroke in SSNHL patients

In contrast to previous studies that exclusively examined patients with anterior inferior cerebellar artery infarction (40–42), our study concentrates on patients with SSNHL, especially those who developed ischemic stroke in the hospital. Among the case group, the middle territory (19/30, 63.33%) of posterior circulation vascular territories (24/30, 80%) was the most common position of infarcts. There were significantly more people with moderate to severe intracranial artery stenosis in the case group (20/30, 66.67%) than in the control group (24/120, 20%). First, this result demonstrates the significance of vertebrobasilar artery ischaemia, specifically the basilar artery and its branches in the middle territory, as a major concern for patients with suspected vascular SSNHL. It is crucial for clinicians to pay more attention to large artery conditions, as shown in model-3, particularly in arteries such as the vertebral arteries or basilar artery, even in the absence of typical neurological symptoms and signs. In addition, anterior circulation (4/30, 13.33%) and border zone (2/30, 6.66%) stroke can also be upcoming events in SSNHL patients, whose pathogenesis remains unknown. Previous studies

have demonstrated that hypoperfusion of the anterior inferior cerebellar artery (AICA) can potentially cause episodic sudden sensorineural hearing loss (SSNHL), not only as a prodrome of AICA or PICA territory infarcts but also in other infarct cases (43). In this study, 50% of patients (3 out of 6) with anterior circulation or border zone infarction also had posterior circulation vascular stenosis or occlusion. The first symptom of hearing loss may be attributed to inadequate blood supply in the labyrinthine as a warning signal of global cerebral hypoperfusion at the same time. However, there are currently no effective methods to confirm inner ear ischaemia or infarction. Future studies with larger sample sizes and with more comprehensive examinations of the inner ear are needed. Moreover, among the few patients (2/30, 6.67%) who did not exhibit major intracranial artery stenosis, it is worth considering and investigating the possibility of cardiogenic or extracranial vascular embolism.

This study represents the initial endeavor to explore the risk of stroke among patients with sudden sensorineural hearing loss (SSNHL) during their hospitalization. In cases where there is no noticeable neurological deficit or it appears too late, thrombolytic or antithrombotic treatment may not be feasible. This study provides clues to this apparent conundrum. We conducted an exploration to build three models simulating different clinical situations, incorporating clinical characteristics, laboratory tests, pure tone audiometry, and neuroimaging. These models aim to assist clinicians and serve as a reference for future research. The innovative findings reveal that bilateral sudden sensorineural hearing loss and moderately severe to total hearing loss are independent risk factors for subsequent stroke. Additionally, our study supports earlier findings indicating that individuals with SSNHL accompanied by vertigo at onset are at an elevated risk of stroke (27, 44).

4.4. Limitations

Despite our study's implications, we acknowledge its limitations. First, this study is a retrospective case–control study with a limited sample size and thus is at risk of information bias. Second, pure tone audiometry was measured as the average of 500, 1,000, 2,000, and 4,000 Hz. Quartering is a common method of hearing calculation and may not be sufficient to assess hearing loss at low or high frequencies alone; therefore, additional studies in patients with high-tone or low-tone hearing loss are needed. Third, due to the retrospective nature of this study, detailed time information between SSNHL and neurological deficits was not fully collected. As a result, the study was unable to determine the ideal time point for magnetic resonance imaging. There is still a need for further sample size expansion and multicentre validation in the future.

5. Conclusion

We cautiously consider that SSNHL may not be the direct cause of stroke but rather a potential indicator or warning sign, particularly for posterior circulation stroke in the middle territory, during the progression of the disease. According to our research, clinicians should be alert to patients with three or more stroke risk factors, bilateral SSNHL, and moderately severe to total hearing loss, effectively screen high-risk vascular SSNHL groups and complete brain structure and vascular imaging evaluations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

YZ: Investigation, Writing—original draft, Data curation, Methodology. HL: Writing—review & editing, Investigation. GL: Data curation, Writing—review & editing. JL: Formal analysis, Writing—review & editing. J-JM: Methodology, Writing—review & editing. XZ: Conceptualization, Funding acquisition, Writing—review & editing. YJ: Conceptualization, Funding acquisition, Methodology, Supervision, Writing—review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1293102/full#supplementary-material

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EDITED BY
Maoli Duan,
Karolinska Institutet (KI), Sweden

REVIEWED BY
Zhengnong Chen,
Shanghai Jiao Tong University, China
Norma De Oliveira Penido,
Federal University of São Paulo, Brazil

*CORRESPONDENCE
Shixun Zhong
✉ 313997490@qq.com
Jing Luo
✉ luojing668yeah@163.com

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Causal associations of thyroid function and sudden sensorineural hearing loss: a bidirectional and multivariable Mendelian randomization study

Jialei Chen[1,2,3], Chao Wu[4], Jing He[1], Linsui Wu[1], Yongkang Yang[5], Shixun Zhong[1]* and Jing Luo[6,7]*

[1]Department of Otolaryngology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2]Department of Pathology and Pathophysiology, Chongqing Medical University, Chongqing, China, [3]Molecular Medicine and Cancer Research Center, College of Basic Medical Sciences, Chongqing Medical University, Chongqing, China, [4]Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [5]Department of Clinical Medicine, Clinical Medical College of Chengdu University, Chengdu, China, [6]Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [7]Department of Pathology, Chongqing Medical University, Chongqing, China

Background: Observational studies have indicated a potential association between thyroid dysfunction and the risk of sudden sensorineural hearing loss (SSNHL). However, the precise causal relationship between the two remains uncertain. The objective of our study was to assess the causal influence of thyroid function on SSNHL by employing a bidirectional and multivariable Mendelian randomization (MR) approach.

Methods: Single-nucleotide polymorphisms (SNPs) associated with free thyroid (FT4) and thyroid stimulating hormone (TSH) were selected from the summary data of a large genome-wide association study (GWAS) conducted on European individuals. The summary-level data of SSNHL were also obtained from a GWAS, which included 196,592 participants (1,491 cases and 195,101 controls). The MR analysis primarily utilized the inverse variance weighted (IVW) method, with sensitivity analyses performed using the weighted median, MR-Egger, and MR-PRESSO approaches.

Results: In the IVW method, an elevated genetically predicted FT4 level was found to effectively reduce the risk of SSNHL (OR = 0.747, 95% CI = 0.565–0.987, P = 0.04). These findings were consistent when conducting multivariate MR analysis, which adjusted for TSH levels (OR = 0.929, 95% CI = 0.867–0.995, P = 0.036). However, genetically predicted TSH levels did not emerge as a risk factor for SSNHL (OR = 1.409, 95% CI = 0.895–1.230, P = 0.547). Furthermore, even after adjusting for FT4 levels in the multivariate MR analysis, no evidence of a direct causal relationship between TSH levels and the risk of SSNHL was observed (OR = 1.011, 95% CI = 0.880–1.161, P = 0.867). The reverse MR analysis showed that there was no evidence of a direct causal relationship between SSNHL and the risk of FT4 level (OR = 1.026, 95% CI = 0.999–1.054, P = 0.056) or TSH level (OR = 1.002, 95% CI = 0.989–1.015, P = 0.702).

Conclusion: Within the normal range, genetic variants associated with higher FT4 levels demonstrate a potential protective effect against SSNHL, whereas there is no direct causal relationship between TSH levels and the risk of SSNHL.

KEYWORDS

sudden sensorineural hearing loss, free thyroxine, thyroid-stimulating 2 hormone, risk factor, Mendelian randomization

1 Introduction

Sudden sensorineural hearing loss (SSNHL) is a common and alarming otolaryngological emergency with unknown etiology. It was defined as a sudden occurrence of unexplained sensorineural hearing loss occurring within 72 h, including hearing loss greater than 30 dB affecting at least in three consecutive frequencies (1). The incidence of SSNHL in Western countries ranges from 5 of 100,000 to 400 of 100,000 (2–4). The latest research reported that autoimmune diseases (5), infectious diseases (6), vascular diseases (7), and viral infections (8) are the most common causes of SSNHL, which indicates that SSNHL is caused by many factors (systemic and local).

The incidence rate of SSNHL in the worldwide is gradually rising. The World Health Assembly estimated that more than 2.5 billion people worldwide will be living with hearing loss to varying degrees by 2050 (9). Hearing loss not only leads to numerous neurological and psychological ailments but also significantly diminishes the quality of life for affected individuals, resulting in reduced productivity and an escalating social burden (10). Therefore, the swift and effective establishment of practical prevention and treatment strategies holds the utmost importance for otologists.

Thyroid hormone plays a vital role in the developmental maturation of hair cells spiral and ganglion cells as well as in the metabolism of the vascular cortex and stria vascularis (11–14). Thyroid dysfunction (hypothyroidism and hyperthyroidism) has been associated with increased hearing thresholds, abnormal V wave, and TOAE in auditory brainstem responses (15, 16). Additionally, there is evidence that SSNHL patients suffered from a higher prevalence of thyroid disease in comparison to the general population (17). However, it is important to note that these studies are based on clinical observations, which may introduce potential selection biases, confounding factors, and the possibility of reverse causality. Consequently, the causal relationship between thyroid function and SSNHL remains an unresolved question. By elucidating the causal connection between thyroid function and SSNHL, effective prevention and treatment strategies can be developed for the benefit of SSNHL.

The Mendelian randomization (MR) investigates causal relationships between risk factors associated with diseases using genetic variants as instrumental variables (IVs) (18). This emerging epidemiological technique effectively mitigates potential confounding factors and interferences, enabling more robust causal conclusions compared to traditional observational studies (19). Previous research utilizing MR analysis has successfully demonstrated causal relationships between FT4 and TSH levels with C-reactive protein (20), age-related macular degeneration (AMD) (21), and atrial fibrillation (22). Building upon this foundation, our study utilizes a large-scale genome-wide association study (GWAS) to examine the causal relationship and risk between thyroid function and SSNHL by using a bidirectional and multivariable MR analysis. By doing so, we aspire to contribute fresh perspectives and insights into the etiology of SSNHL.

2 Method

2.1 Study design

Utilizing a bidirectional and multivariable Mendelian randomization analysis, we aimed to explore the potential causal relationship between genetically predicted TSH levels and FT4 levels and their association with SSNHL. A robust MR design relies on three fundamental assumptions: (1) The correlation hypothesis, which assumes a strong correlation between genetic variation and the exposure factors (thyroid function). (2) The independence hypothesis, which posits that genetic variation is independent of confounding factors that may influence both the exposure and outcome. (3) The exclusivity hypothesis, which suggests that genetic variation only impacts the outcome (SSNHL) through exposure and not through alternative pathways (23). Figure 1 provides an overview of the design employed in this thyroid function-SSNHL two-sample bidirectional MR study. As this study involves a reanalysis of previously published data, no additional ethical approval is required.

2.2 GWAS data of thyroid function

The genetic association of TSH within the reference range was obtained from the GWAS meta-analysis conducted by Zhou et al., encompassing a total of 119,715 subjects from the Nord-Trøndelag Health Study, Michigan Genomics Initiative, and the ThyroidOmics consortium, with over 22.4 million genetic markers. These data are available for download from the GWAS database (https://www.ebi.ac.uk/gwas) (24). The summary data of FT4 within the reference range was derived from the GWAS meta-analysis carried out by Teumer et al. that involved 49,269 individuals and more than 8 million genetic markers. These data can be accessed for download from the dbGaP website with the accession number phs000930 (25).

2.3 GWAS data of SSNHL

Genetic data pertaining to SSNHL was obtained from the publicly accessible GWAS database, specifically identified with the entry number "finn-b-H8_HL_IDIOP." The study encompassed a total of 196,592 participants, consisting of 1,491 cases and 195,101 controls.

2.4 Instrumental variable selection

Based on the GWAS results for TSH and FT4, we conducted a rigorous screening of single nucleotide polymorphisms (SNPs) that exhibited close associations with TSH and FT4, achieving genome-wide significance ($P < 5 \times 10^{-8}$). SNPs closely associated with SSNHL were defined by the criterion of a P-value of $<10^{-6}$. These

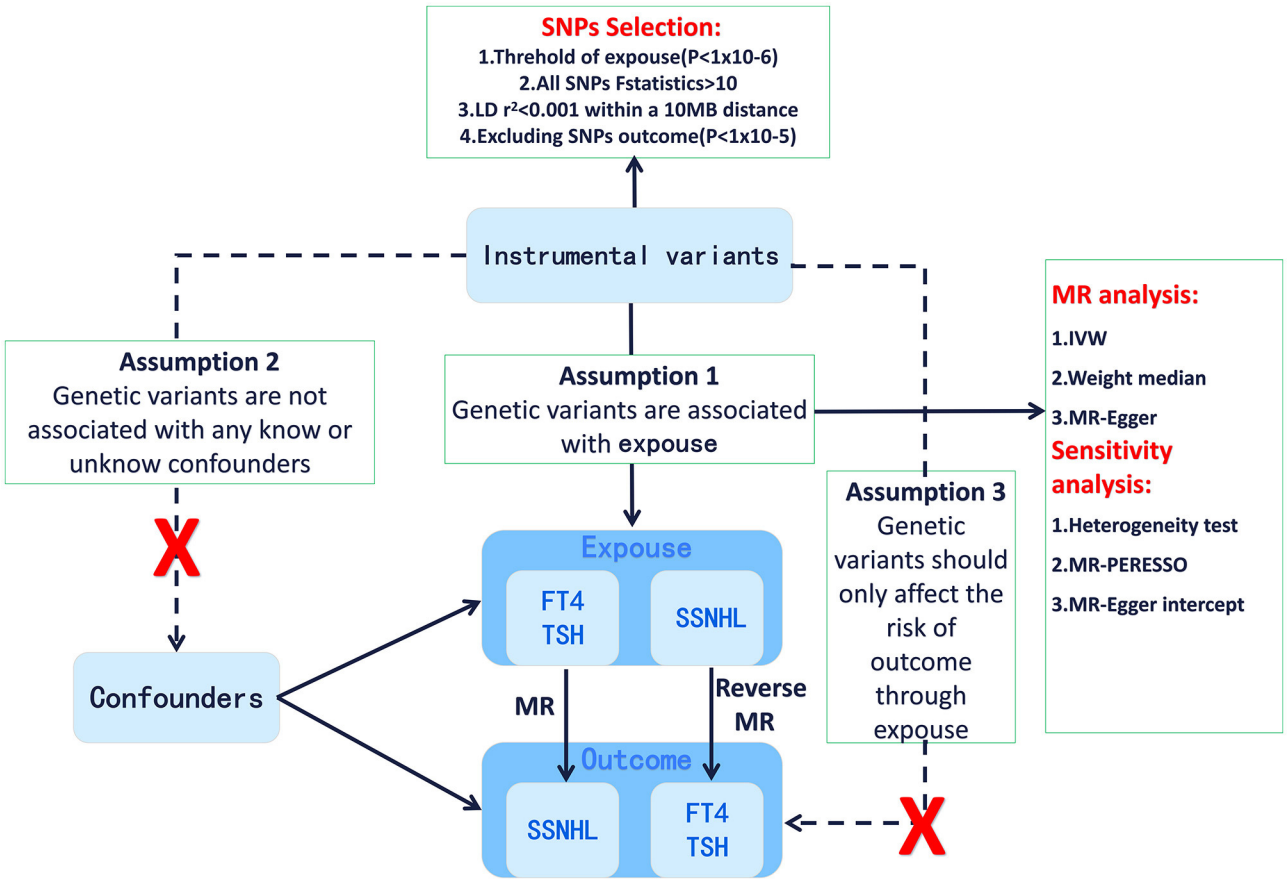

FIGURE 1
Framework design for the thyroid function-SSNHL two-sample bidirectional MR analyses. SSNHL, sudden sensorineural hearing loss; MR, Mendelian randomization; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

selected SNPs were then utilized as instrumental variables (IVs) in the Mendelian randomization (MR) analysis. The IVs for MR analysis were chosen based on the following criteria: (1) To mitigate estimation bias resulting from weak IVs, we employed the equation $F = (R^2 \times (n - 2))/(1 - R^2)$ to assess the correlation between instrument strength and exposure. A significant correlation was considered when $F \geq 10$. The estimated R^2 of IVs was calculated using the equation $2EAF\ (1 - EAF)^*\beta^2$, where EAF denotes the frequency of the effect allele and β represents the estimated genetic impact on FT4 (or TSH) (26). (2) To account for the influence of linkage disequilibrium, we ensured that the r^2-value was less than 0.001 within a distance of 10MB (27). (3) In order to satisfy the exclusive hypothesis (that IV variants solely affect SSNHL through thyroid function), any hearing loss-related SNP outcomes ($P < 1 \times 10^{-5}$) were excluded from each analysis as well. Phenoscanner search was used to eliminate all known phenotypes associated with any genetic instruments considered in our analysis (28). In Supplementary Table 1, we summarized the association between exposure and SNPs and their relationship to outcome.

2.5 Univariate Mendelian randomization analysis

The primary analysis employed to assess the causal relationship between the exposure and outcomes is the inverse variance weighting (IVW) method. This method involves regressing the genetic variance (exposure) of TSH and FT4 against the genetic variance (outcome) of SSNHL, with each data point representing a conflict (29). However, it is important to note that the estimated effect obtained through IVW may be subject to bias. To address this, we conducted additional sensitivity analyses using MR-Egger and weighted medians as supplementary approaches to IVW (30). The intercept derived from the MR-Egger regression model serves as an indicator of directional pleiotropy, whereby a p-value below 0.05 suggests the presence of horizontal pleiotropy (31). Weighted median estimates generally provide robust estimates that are nearly as accurate as those obtained through IVW even in situations where more than half of the genetic variants violate assumptions (32). The MR-PRESSO method detects and eliminates outliers to yield relatively unbiased estimates while also identifying potential

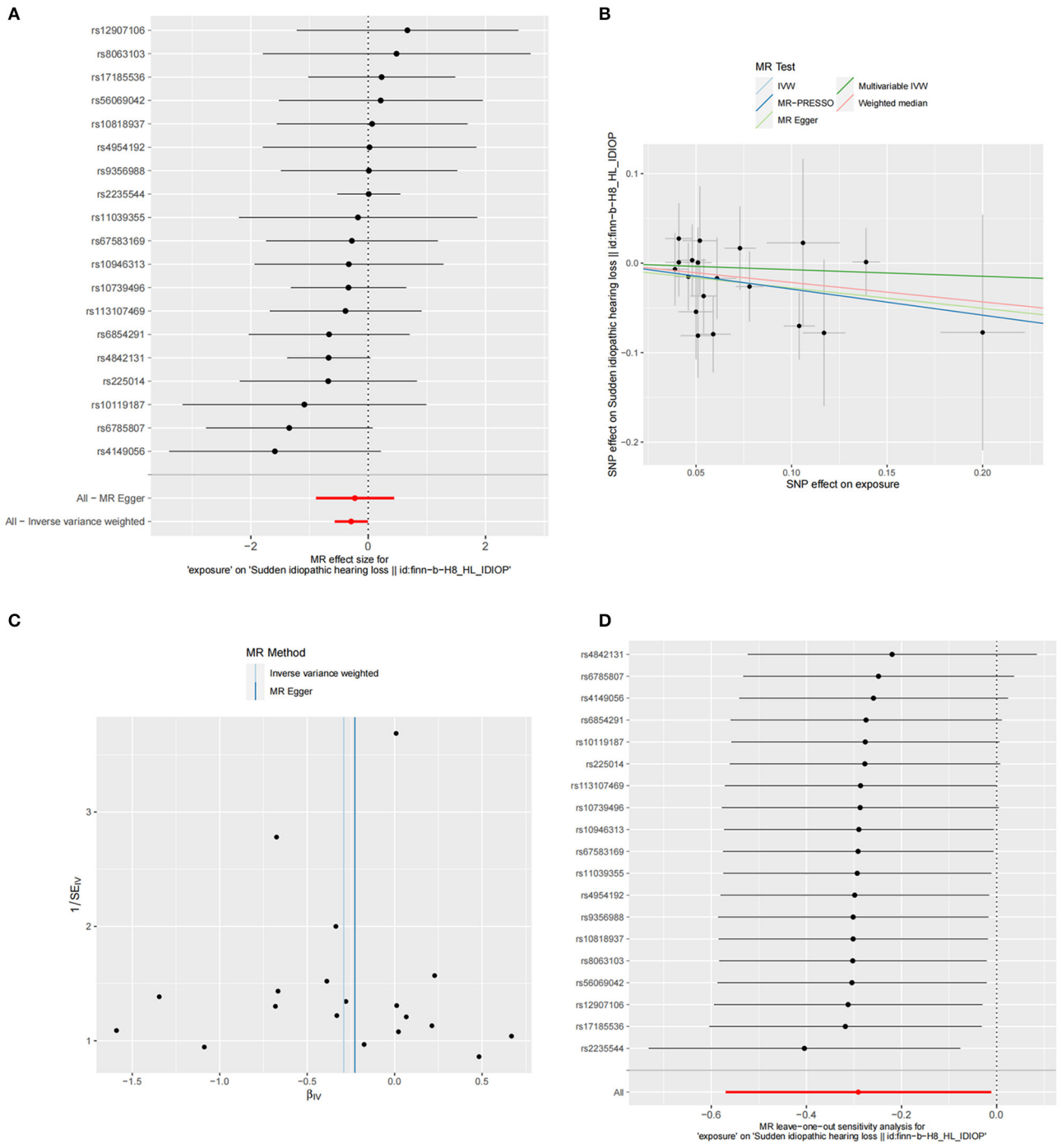

FIGURE 2
(A) Forest plot of the potential effects of FT4-associated SNPs on SSNHL. **(B)** Scatter plot demonstrates the effect of each FT4-associated genetic variant on SSNHL on the log-odds scale. **(C)** Funnel plot of the causal effect of FT4-related SNPs on SSNHL. **(D)** Leave-one-out plots for the MR analyses of SSNHL on FT4.

horizontal pleiotropic effects of SNPs through global testing (33). We utilized Cochran's *Q*-test to assess the heterogeneity of all SNPs. Additionally, employing the leave-one-out method, we systematically removed each SNP one at a time to evaluate whether bias in MR estimation is driven by a single SNP by calculating the causal effect of gene-predicted exposure on the outcomes using the remaining SNPs (33).The reverse MR analysis was conducted with the objective of exploring whether SSNHL might be a risk factor for FT4 levels or TSH levels. Given that genotypes are established at conception in accordance with Mendelian segregation laws, the potential for reverse causality is greatly reduced (34).

TABLE 1 MR results of FT4 and TSH on risk of SSNHL.

Exposure	Method	No. of SNPs	OR	(95% CI)	*P*-value
FT4	IVW	19	0.747	(0.565–0.987)	0.040
	Weighted median	19	0.805	(0.553–1.171)	0.257
	MR-Egger	19	0.796	(0.411–1.542)	0.509
	MR-PRESSO	19	/	/	0.886
	Multivariable IVW	19	0.929	(0.867–0.995)	0.036
TSH	IVW	88	1.409	(0.895–1.230)	0.547
	Weighted median	88	1.108	(0.860–1.427)	0.402
	MR-Egger	88	0.900	(0.647–1.252)	0.536
	MR-PRESSO	88	/	/	0.905
	Multivariable IVW	87	1.011	(0.880–1.161)	0.867

SSNHL, sudden sensorineural hearing loss; MR, Mendelian randomization; FT4, free thyroxine; TSH, thyroid-stimulating hormone; IVW, inverse variance weighted; SNPs, single-nucleotide polymorphisms; MR-PRESSO, Mendelian randomization-pleiotropy residual sum outlier; OR, odds ratio; multivariable MR using IVW of FT4 and TSH on SSNHL risks.

2.6 Multivariable Mendelian randomization analysis

The function of multivariate MR is similar to the independent evaluation of the effect of several intervention modalities in a randomized controlled trial. For this approach, genetic tools may be associated with multiple risk factors, but they must meet the equivalent instrumental variable assumption (35, 36). To investigate the independent influence of FT4 and TSH on the risk of SSNHL, given their close correlation, we employed multivariate MR analysis. When MR analysis showed a causal relationship between FT4 (TSH) and SSNHL, multivariate MR analysis was performed to evaluate the role of TSH (FT4) as a risk factor for SSNHL. The SNPs used in the multivariate MR analysis were derived from the combination of instrumental variables (IVs) identified in the univariate MR analysis for each exposure (35). To ensure data quality, we limited our analysis to SNPs with a clumping threshold of $r^2 < 0.001$ within a 10 MB region and removed any duplicates. A *p*-value less than 0.05 was considered statistically significant when estimating the causal effect of exposure. All statistical analyses were performed using the R package "TwoSampleMR2 (version 0.5.6)" in R (version 4.2.1). For further details, please refer to the following link: https://mrcieu.github.io/TwoSampleMR/ (37).

3 Result

3.1 Causal association of FT4 with SSHNL

The summary statistics of SSNHL include all 19 SNPs associated with FT4 levels. The F-statistic for each of the SNPs included in the analysis exceeded 10 (FT4 F statistics ranged from 32.66 to 479.82). Phenoscanner analysis showed that there was no association between SNPs and any other traits that could confound the exposure-outcome relationship. The MR analysis using the IVW method revealed a significant causal relationship between FT4 levels and the risk of SSNHL (OR = 0.747, 95% CI = 0.565–0.987, $P = 0.04$). The forest plot illustrates that genetically predicted FT4 levels are significantly associated with SSNHL (Figure 2A). Similarly, risk estimation results in MR-Egger regression and weighted median methods demonstrate a similar trend although the associations did not reach statistical significance (Figure 2B; Table 1). The *P*-values obtained from the Cochran *Q*-test for MR-Egger (Cochrane's $Q = 10.54$, $P = 0.88$) and IVW (Cochrane's $Q = 10.50$, $P = 0.91$) were both greater than 0.05, indicating no heterogeneity in the results (Figure 2C). No abnormal instrumental variables were found to contribute to pleiotropic effects in the overall MR estimation, as indicated by the global test for MR-PRESSO (*P* Global Test = 0.88). The leave-one-out sensitivity analysis suggests that the overall impact of FT4 on SSNHL is not driven by a single SNP (Figure 2D). We conducted a reverse MR analysis to assess the causal impact of SSNHL on FT4 levels. Following the application of the aforementioned criteria, we identified 14 SNPs significantly associated with SSNHL (Supplementary Table 1). In our reverse MR analysis employing the IVW method, we found no significant evidence supporting a causal relationship between SSNHL and the risk of FT4 levels (OR = 1.026, 95% CI = 0.999–1.054, $P = 0.056$; Supplementary Table 2). Finally, the results of the multivariate MR analysis, with adjustments made for TSH levels using the IVW method, demonstrated a direct causal effect of FT4 levels on the risk of SSNHL (OR = 0.929, 95% CI = 0.867–0.995, $P = 0.036$).

3.2 Causal association of TSH with SSHNL

The summary statistics of SSNHL include all 88 SNPs associated with TSH levels, each with an F-statistic greater than 10 (TSH F statistics ranged from 37.00 to 1541.78). However, we did not find significant evidence indicating a potential causal effect of TSH on the risk of SSNHL (IVW, OR = 1.409, 95% CI = 0.895–1.230, $P = 0.547$; Figure 3A). Similar risk estimation results were observed in the MR-Egger regression and weighted median methods. The Cochran *Q*-test results for MR-Egger (Cochrane's $Q = 69.39$, $P = 0.90$) and IVW (Cochrane's $Q = 70.47$, $P = 0.90$) yielded *p*-values greater than 0.05, indicating no heterogeneity in the results (Figure 3B; Table 1). No abnormal instrumental variables were identified that could lead to pleiotropic effects in

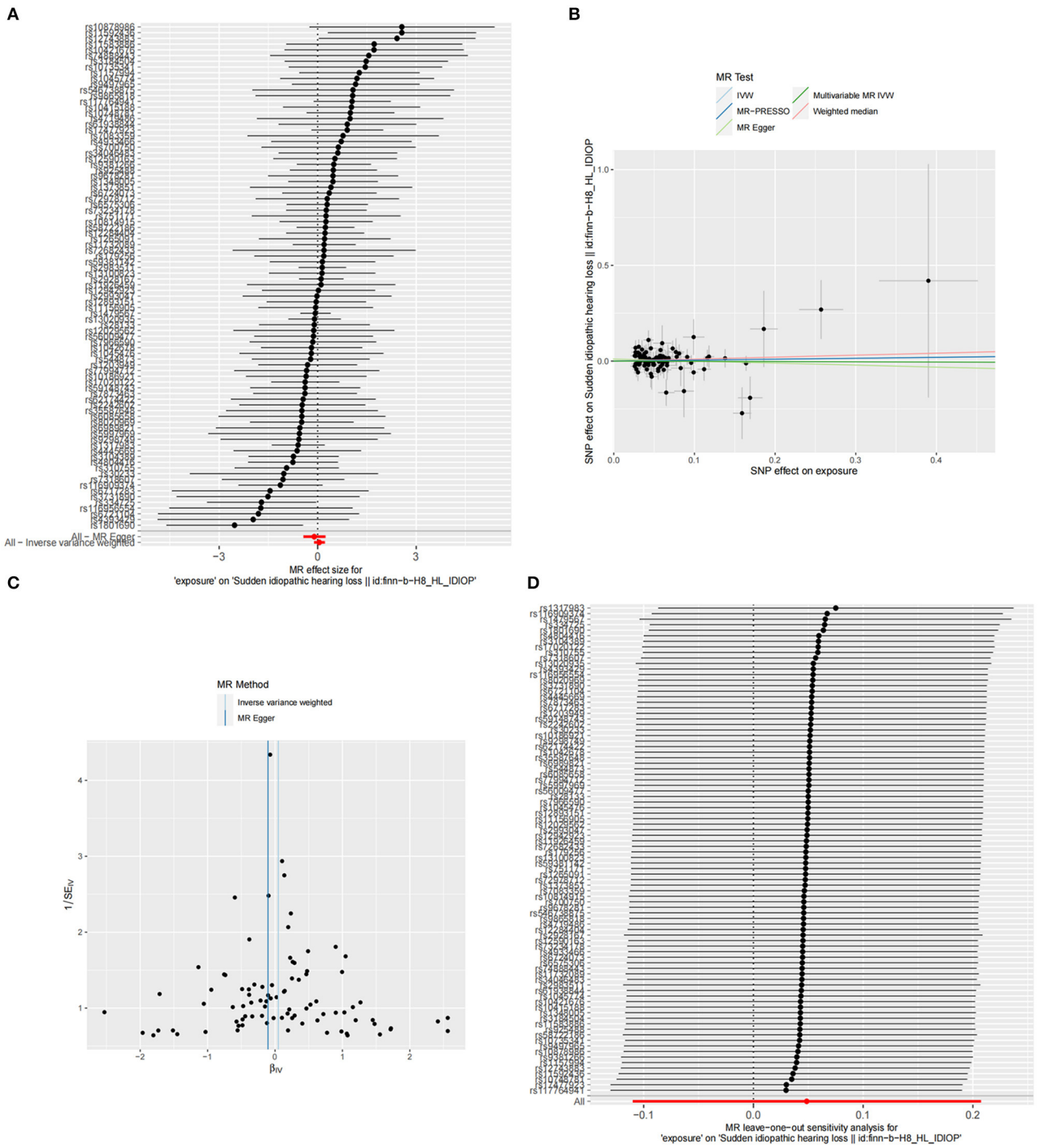

FIGURE 3
(A) Forest plot of the potential effects of TSH-associated SNPs on SSNHL. **(B)** Scatter plot demonstrates the effect of each TSH-associated genetic variant on SSNHL on the log-odds scale. **(C)** Funnel plot of the causal effect of TSH-related SNPs on SSNHL. **(D)** Leave-one-out plots for the MR analyses of SSNHL on TSH.

the overall MR estimation, as indicated by the global test for MR-PRESSO (*P* Global Test = 0.88; Figure 3C). In the leave-one-out sensitivity analysis, it was determined that the association between TSH and SSNHL was not driven by a single SNP (Figure 3D). We conducted a reverse MR analysis using the IVW method, and the results did not yield significant evidence indicating a potential causal effect of SSNHL on TSH levels (OR = 1.002, 95% CI = 0.989–1.015, $P = 0.702$; Supplementary Table 2). Furthermore, even in the multivariate MR analysis, where adjustments were made for FT4 levels, we found no evidence supporting a direct causal relationship between TSH levels and the risk of SSNHL (IVW, OR = 1.011, 95% CI = 0.880–1.161, $P = 0.867$).

4 Discussion

Based on the comprehensive large-scale GWAS summary statistics, our bidirectional and multivariable MR study revealed a negative correlation between FT4 levels and the risk of SSNHL. However, there is insufficient evidence to support a significant association between TSH levels and the risk of SSNHL. To investigate the independent influence of FT4, we conducted a multivariate MR analysis to account for any potential interaction between FT4 and TSH, and the results remained consistent.

Thyroid hormone is an essential endocrine substance that plays a critical role in the development of the auditory system (38). The middle and inner ears are highly sensitive to fluctuations in thyroid hormone serum levels (39). Thyroid hormone plays a vital role in the development and maturation of spiral ganglion cells and hair cells as well as in the metabolism of the vascular cortex and stria vascularis (11–14). Both hypothyroidism and hyperthyroidism have the potential to cause sensorineural hearing loss, that may be manifested as intracochlear, posterior cochlear, or central hearing impairments (40). Moreover, the blood supply to the cochlea primarily depends on a single labyrinthine artery with no collateral circulation. Individuals with hypothyroidism may experience hypercoagulability, thereby increasing the risk of thromboembolism (41). Hair cells, which consume a significant amount of oxygen, are highly susceptible to hypoxia, which can result in hair cell damage. While reports on the correlation between TSH and SSNHL are limited, a recent study underscores the significance of early TSH testing in the diagnosis of SSNHL (42). This study identified early lower or abnormal TSH levels as independent predictive factors for moderate-to-severe SSNHL, while FT4 level abnormalities were not a risk factor for SSNHL. Conversely, another study conducted a retrospective analysis of 676 SSNHL patients, and the results indicated that FT4 level disturbances were a risk factor for SSNHL, while TSH level abnormalities were not associated with an increased risk of SSNHL (43). This discovery is consistent with our findings. Potential reasons for this discrepancy may include those as follows: (1) gender-specificity in the correlation between SSNHL (44) and thyroid hormones as well as TSH levels (45). (2) SSNHL may be categorized into a minimum of four distinct subtypes, each characterized by unique pathogenic mechanisms (4). To the best of our knowledge, there is currently no study that has employed both gender-specific and subgroup-specific data to discuss the correlation between thyroid hormones, TSH, and the risk of SSNHL occurrence. Although a meta-analysis of the association between FT4 and SSNHL is currently lacking, several independent studies have suggested an association between hypothyroidism and susceptibility to SSNHL. These studies have demonstrated that hypothyroidism and hyperthyroidism are associated with SSNHL susceptibility (39). Additionally, research has shown positive correlations between hypothyroidism and risk of SSNHL in both young and elderly subgroups of patients (46). Furthermore, retrospective analysis of a large cohort of SSNHL patients revealed abnormal thyroid function test results in a substantial proportion of cases (43). Notably, the incidence of thyroid dysfunction in SSNHL patients was found to be more than twice that of the general population (17). Overall, these studies collectively support the pivotal role of FT4 in the occurrence and development of SSNHL.

The research design offers distinct advantages. First, it leverages freely accessible GWAS data, thereby significantly reducing research costs. Second, employing genetic variation as instrumental variables in MR analysis effectively mitigates confounding biases and reverse causal effects. Finally, our findings indicate that genetically predicted elevated levels of FT4 are associated with a reduced risk of SSNHL, offering potential clinical prevention strategies for otologists. Nonetheless, it is essential to acknowledge several potential limitations in our study. First, the study population primarily comprises individuals of European ancestry, prompting cautious interpretation of the generalizability of our findings to other populations. Second, thyroid function exhibits gender specificity, and unfortunately, due to limitations in available TSH and FT4 summary data, we were unable to conduct sex-specific MR analysis. Finally, there are at least four subgroups of SSNHL with different pathogenic mechanisms. However, we were also unable to perform subgroup-specific MR analyses due to the limitations of the available SSNHL summary data. Future research endeavors encompassing diverse populations and accounting for gender-specific and subgroup-specific effects would enhance our understanding of the causal relationship between thyroid function and SSNHL.

In summary, our bidirectional and multivariable MR analysis revealed that higher FT4 levels are associated with a decreased risk of SSNHL. However, we did not find evidence of an independent causal relationship between TSH and SSNHL risk. These findings contribute to our understanding of the relationship between thyroid function and SSNHL, offering new insights. We anticipate that our results will inform otologists of clinical prevention and treatment strategies for SSNHL.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

JC: Conceptualization, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing, Data curation, Investigation, Methodology. CW: Data curation, Resources, Validation, Visualization, Writing—original draft. JH: Resources, Validation, Visualization, Writing—original draft. LW: Resources, Validation, Visualization, Writing—original draft. YY: Resources, Visualization, Writing—original draft, Data

curation. SZ: Conceptualization, Project administration, Writing—review & editing, Funding acquisition. JL: Conceptualization, Project administration, Writing—review & editing, Resources, Supervision, Validation, Visualization, Writing—original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1269545/full#supplementary-material

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EDITED BY
Lisheng Yu,
Peking University People's Hospital, China

REVIEWED BY
Norma De Oliveira Penido,
Federal University of São Paulo, Brazil
Santosh Kumar Swain,
All India Institute of Medical Sciences Bhubaneswar, India

*CORRESPONDENCE
Wei Liu
liuwei007@csu.edu.cn

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Clinical characteristics of patients diagnosed with bilateral sudden sensorineural hearing loss

Jun He[1], Li Jin[1], Jacqueline Yao[2], Ahmad Mahmoudi[2], Zhen Pan[3], Jinfeng Fu[1], Qiulin Yuan[1] and Wei Liu[1]*

[1]Department of Otolaryngology-Head and Neck Surgery, The Second Xiangya Hospital, Central South University, Changsha, China, [2]Department of Otolaryngology-Head and Neck Surgery, Stanford University School of Medicine, Stanford, CA, United States, [3]Department of Otolaryngology-Head and Neck Surgery, Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City), Changde, China

This study investigated the etiology, clinical features, and prognosis of patients diagnosed with bilateral sudden sensorineural hearing loss (BSSNHL). The clinical data of 100 patients with bilateral sudden hearing loss as a chief complaint treated at Xiangya Second Hospital of Central South University between January 2010 and August 2022, including clinical characteristics, audiometric data, and prognosis, were retrospectively analyzed. These 100 cases accounted for 8.09% (100/1235) of all patients admitted for sudden sensorineural hearing loss (SSNHL) during the same period. Of these, 71 were simultaneous cases and 29 were sequential cases of BSSNHL. Among the 200 ears analyzed in this study, 13, 36, 57, and 94 had mild, moderate, severe, and profound sensorineural hearing loss, respectively. The overall effective rate after comprehensive treatment was 32%, with significant differences in efficacy and prognosis among different degrees of hearing loss ($p < 0.05$). Comorbidities of hypertension (24 cases), diabetes (14 cases), and coronary heart disease (9 cases) significantly impacted therapeutic efficacy and prognosis in patients with BSSNHL ($p < 0.05$). Compared to unilateral SSNHL, BSSNHL exhibits distinctive characteristics.

KEYWORDS

bilateral sudden sensorineural hearing loss (BSSNHL), sudden hearing loss, etiology, risk factor, prognosis

1 Introduction

Sudden sensorineural hearing loss (SSNHL) is an acute, unexplained hearing loss occurring within 72 h. Criteria for a SSNHL diagnosis varies; the latest Chinese guidelines define SSNHL as ≥20 dB of hearing loss in two consecutive frequencies (1) and the American Academy of Otolaryngology-Head and Neck Surgery defines SSNHL as hearing loss ≥30 dB at three consecutive frequencies (2). Clinically, SSNHL is categorized into unilateral SSNHL (USSNHL) and bilateral SSNHL (BSSNHL). The incidence of BSSNHL is considerably lower than that of USSNHL (3, 4). Based on the time interval between the onset of hearing loss in both ears, BSSNHL is further divided into simultaneous BSSNHL (Si-BSSNHL, onset in both ears within ≤3 days) and sequential BSSNHL (Se-BSSNHL, onset in both ears with an interval of >3 days) (4). Existing evidence suggests that BSSNHL differs from USSNHL in etiology, treatment, and prognosis (5). USSNHL is often idiopathic and has higher recovery rates (6). In contrast, BSSNHL is frequently associated with underlying systemic diseases, leading to more profound hearing loss and less favorable treatment outcomes (5–7). Given the heterogeneity of BSSNHL etiologies and

its low incidence, BSSNHL remains relatively poorly understood (2). This study aims to retrospectively analyze the clinical data of patients diagnosed with BSSNHL and summarize the clinical characteristics, etiologies, treatment outcomes, and factors influencing prognosis.

2 Materials and methods

2.1 Retrospective study design and patient selection

Clinical data were gathered from 100 patients diagnosed with BSSNHL who were treated at the Department of Otolaryngology, Head, and Neck Surgery, the Second Xiangya Hospital of Central South University, between January 2010 and August 2022. The inclusion criteria were as follows: (1) confirmed SSNHL with audiometry; (2) sudden onset of ≥20 dB HL within 72 h, affecting at least two consecutive frequencies (1); (3) simultaneous or sequential involvement of both ears. Patients previously diagnosed with Meniere's Disease were excluded from the study. A retrospective analysis encompassed patients' general information, physical exam findings, audiometric examinations, laboratory tests, imaging evaluations, and details regarding treatment and prognosis. We excluded patients who were lost to follow-up.

Pre- and post-treatment, all patients underwent standard audiometric assessments, including pure-tone audiometry, impedance audiometry, auditory brainstem response, and otoacoustic emissions. High-resolution computed tomography of the temporal bone was conducted to rule out middle and inner ear diseases. A brain magnetic resonance imaging (MRI) examination was performed to rule out intracranial diseases. Serological tests included C-reactive protein, neutrophil count, lymphocyte count, monocyte count, platelet count, and fibrinogen level. Antibody tests included immunoglobulin G, immunoglobulin M, immunoglobulin A, complement 3 and complement 4, antinuclear antibody, antineutrophil cytoplasmic antibodies (ANCA), and rheumatoid factor. Biochemical tests included total bilirubin, indirect bilirubin, blood glucose, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein. Patients were also administered tests for human immunodeficiency virus (HIV), syphilis, hepatitis B, hepatitis C, and herpes virus.

This study was conducted by the principles of the Declaration of Helsinki and approved by the Ethics Committee of Second Xiangya Hospital.

2.2 Audiologic evaluation

Based on pure-tone audiometry results, the pure-tone average of air-conduction hearing thresholds was calculated at four frequencies (500 Hz, 1,000 Hz, 2000 Hz, and 4,000 Hz). Subsequently, hearing loss was classified according to the WHO proposed hearing-impairment grading system (2008) (8) as follows: mild: 26–40 dB HL; moderate: 41–60 dB HL; severe: 61–80 dB HL; and profound: ≥81 dB HL.

2.3 Treatment methods

Adhering to the 2015 Chinese Medical Association guidelines for SSNHL (1), the patients' treatment protocol involved intravenous administration of dexamethasone at 10 mg/day for adults, with pediatric dosage calculated based on their body weight. This treatment was administered continuously for 3 days; if deemed effective, an additional 2-day course was administered before discontinuation. For patients with contraindications to systemic corticosteroid use or insufficient systemic corticosteroid efficacy, intratympanic dexamethasone perfusion at 5 mg/session was administered once every other day for a total of four to five sessions. Additionally, depending on the patient's condition, treatment was complemented with neurotrophic agents (such as methylcobalamin), drugs enhancing inner ear microcirculation (such as *Ginkgo biloba* leaf extract), antioxidants, fibrinolysis inhibitors, or hyperbaric oxygen therapy. For patients with identified SSNHL etiologies, specific treatments were integrated alongside the aforementioned therapies.

Treatment efficacy was evaluated by pure-tone audiometry results 3 months after standard treatment (1). When evaluating the efficacy of Si-BSSNHL, it is considered effective if one of the two ears shows improvement; if both ears are ineffective, it is considered ineffective. When evaluating the efficacy of Se-BSSHL, the effectiveness is based on the second ear. Further sub-categories include (1) curative: average hearing thresholds normalizing or reverting to pre-illness levels; (2) significantly effective: average hearing improvement of >30 dB at the specified frequencies; (3) effective: average hearing improvement of 15–30 dB at the specified frequencies; and (4) ineffective: average hearing improvement of <15 dB at the specified frequencies.

2.4 Statistical analysis

Statistical analysis was conducted using SPSS 26.0 software (IBM Corp., Armonk, NY, United States). Kruskal–Wallis test was applied for continuous data analysis, while categorical data were analyzed using chi-square, or Fisher's exact probability tests, depending on the circumstances. The level of significance was set at values of $p < 0.05$.

3 Results

3.1 General information and clinical characteristics

Among the 100 patients diagnosed with BSSNHL, 52 patients were male and 48 were female. Patients' ages ranged from 2 to 86 years, with an average age of 46.28 ± 19.77 years. Eighty-nine patients were adults, and 11 patients were children. Triggers, such as respiratory infections, exposure to cold, and physical exertion, were reported by 20% of the patients before the BSSNHL onset. Of the 100 patients, 71 and 29 patients had Si-BSSNHL and Se-BSSNHL, respectively. In the Si-BSSNHL group, 44 patients reported tinnitus, 5 reported ear fullness, 31 reported dizziness/vertigo, and 17 reported nausea/vomiting. Sixteen Si-BSSNHL patients had hypertension (22.5%), 12 had diabetes (16.9%), and 7 had coronary heart disease (9.9%). In the Se-BSSNHL group, 21 patients reported tinnitus, 2 reported ear fullness, 10 reported dizziness/vertigo, and 6 reported nausea/vomiting. Eight Se-BSSNHL patients had hypertension (27.6%), two had diabetes (6.9%), and two had coronary heart disease (6.9%). Some patients have also reported ear pain, headache, unsteady gait, speech

impairment, photophobia, rhinorrhea, nasal congestion, and depression.

When comparing clinical characteristics between the two groups of BSSNHL patients, no statistically significant differences were observed in sex, age, presence of tinnitus, ear fullness, dizziness/vertigo, nausea/vomiting symptoms, concurrent hypertension, diabetes, and coronary heart disease ($p > 0.05$) (Table 1).

3.2 Etiological distribution

Possible SSNHL etiologies were identified in 38 of all patients evaluated in this study (38%) (Table 2). Vascular, autoimmune, and infectious diseases were identified in 15, 6, and 5 patients, respectively. Neoplasms, large vestibular aqueduct syndrome (LVAS), and uremia was diagnosed in 2, 7, and 3 patients, respectively. The etiologies for the remaining 62 patients were classified as idiopathic. Five of the 11 pediatric patients had LVAS, which was preceded by falls and head trauma in all 5 patients.

3.3 Audiometric examination results

In the total cohort of 100 patients and 200 ears tested, mild sensorineural hearing loss was observed in 13 ears (6.5%), moderate sensorineural hearing loss in 36 ears (18.0%), severe sensorineural hearing loss in 57 ears (28.5%); and profound sensorineural hearing loss in 94 ears (47.0%) (Figure 1).

TABLE 1 Clinical characteristics of patients diagnosed with BSSNHL.

Variables	Si-BSSNHL (n = 71)	Se-BSSNHL (n = 29)	p-value
Sex			
Male	38 (53.5%)	14 (48.3%)	0.634[C2]
Female	33 (46.5%)	15 (51.7%)	
Age	44.85 ± 19.37	49.79 ± 20.64	0.372[H]
Triggers	13 (65%)	7 (35%)	0.634[C2]
Accompanying symptoms			
Tinnitus	44 (62.0%)	21 (72.4%)	0.321[C2]
Ear fullness	5 (7.0%)	2 (6.9%)	>0.9[F]
Dizziness/vertigo	31 (43.7%)	10 (34.5%)	0.397[C2]
Nausea/vomiting	17 (23.9%)	6 (20.7%)	0.726[C2]
Comorbidities			
Hypertension	16 (22.5%)	8 (27.6%)	0.592[C2]
Diabetes mellitus	12 (16.9%)	2 (6.9%)	0.340[F]
Coronary heart disease	7 (9.9%)	2 (6.9%)	>0.9[F]

[C2]Chi-square test; [H]Kruskal–Wallis test; [F]Fisher's exact tests. BSSNHL, bilateral sudden sensorineural hearing loss; Si-BSSNHL, simultaneous BSSNHL; Se-BSSNHL, sequential BSSNHL.

3.4 Treatment outcomes

Treatment outcomes of etiological therapy, steroid administration (systemic or intratympanic dexamethasone), and interventions to enhance microcirculation and neurotrophic support, were as follows: of the 200 ears, treatment was curative for 4 ears, significantly effective for 2 ears, effective for 58 ears, and ineffective for 136 ears, resulting in an overall efficacy rate of 32%. Significant differences in treatment efficacy were observed among patients with different degrees of hearing loss ($p = 0.004$). The treatment effect deteriorates as the severity of hearing loss increases (Figure 2A). The treatment efficacy in patients with mild, moderate, severe, and profound hearing loss was 61.6, 47.2, 31.6, and 22.3%, respectively. Patients with mild ($p < 0.05$) and moderate ($p < 0.05$) hearing loss demonstrated higher treatment efficacy than that of patients with profound hearing loss (Figure 2B).

The overall treatment efficacy rate in male patients was significantly higher than that in female patients ($p < 0.05$). Additionally, comorbidities of hypertension, diabetes, and coronary heart disease significantly decreased BSSNHL treatment efficacy ($p < 0.05$). Tinnitus, ear fullness, dizziness/vertigo, nausea/vomiting did not significantly affect treatment efficacy ($p > 0.05$) (Table 3). Moreover, we observed that some patients with BSSNHL were more likely to have progressive hearing loss, even during treatment. In one patient affected by HIV, the hearing threshold showed progressive decline (Figure 3).

4 Discussion

BSSNHL is a rare otologic condition that can occur simultaneously or sequentially, presenting in only 0.57–14.5% of all patients with SSNHL (4–6, 9). In this study, the 100 patients diagnosed with BSSNHL without prior diagnosis of Meniere's Disease constituted 8.09% (100/1235) of all patients admitted for SSNHL during the selected period. Clinical data from in-patients with BSSNHL was analyzed for the condition's etiology and clinical characteristics, thereby offering insights into the diagnosis and treatment of BSSNHL.

Underlying etiologies were identified in 38/100 patients; of these, 7 patients (18.4%) were diagnosed with LVAS, the only otologic etiology in this patient group. Thirty-one patients were diagnosed with systemic conditions, including vascular diseases, autoimmune diseases, infectious diseases, neoplastic diseases, and uremia. Co-morbidities were not present in this study's pediatric group.

Vascular diseases were the most common possible etiologies of BSSNHL in this study and were more prevalent in older patients with BSSNHL. The inner ear is supplied by blood from the labyrinthine artery, which branches into the cochlea-vestibular artery, cochlear artery, and the anterior vestibular artery (10). Existing literature indicates that cases of SSNHL with concurrent cerebral infarction are predominately caused by infarction in the anterior inferior cerebellar artery—from which the labyrinthine artery most commonly arises (11) with only a minority associated with infarctions in the posterior inferior cerebellar artery or vertebral-basilar artery (9). Evidently, thrombosis, vasospasm, bleeding, and other vascular diseases can disturb otovestibular microcirculation, causing auditory and vestibular functional impairment. Brain MRI and magnetic resonance angiography examinations often reveal corresponding ischemic lesions in the affected areas (9, 12). However, in the early stages of the disease, MRI examinations may indicate negative results and multiple

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TABLE 2 Etiologies of patients with diagnosed with BSSNHL.

Pathogenesis	Si-BSSNHL	Se-BSSNHL	Total
Vascular disease	8	7	15
Stroke	7	4	11
Sigmoid sinus thrombosis	1	—	1
Craniofacial vascular malformation	—	1	1
Bilateral lower limb venous thrombosis	—	2	2
Autoimmune disease	3	3	6
Antiphospholipid syndrome	1	—	1
Relapsing polychondritis	1	1	2
Sjögren's syndrome	—	1	1
Vogt–Koyanagi–Harada disease	1	—	1
Cogan syndrome	—	1	1
Infectious disease	4	1	5
HIV	2	—	2
HIV coexisting with syphilis	—	1	1
Bacterial meningitis	2	—	2
Neoplastic disease	2	—	2
Neurofibromatosis type 2	1	—	1
Acute myeloblastic leukemia with maturation (AML-M2)	1	—	1
Large vestibular aqueduct syndrome	7	—	7
Uremia	3	—	3
Idiopathic	44	18	62
Total	71	29	100

BSSNHL, bilateral sudden sensorineural hearing loss; Si-BSSNHL, simultaneous BSSNHL; Se-BSSNHL, sequential BSSNHL; HIV, human immunodeficiency virus.

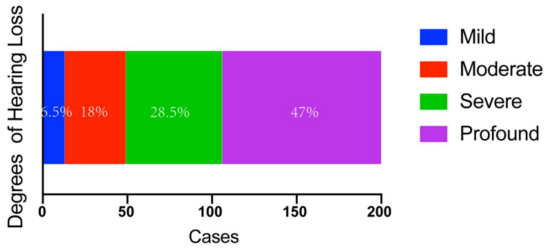

FIGURE 1
Audiometric examination results with BSSNHL. The main hearing loss type is severe (28.5%) and profound (47%) HL. BSSNHL, bilateral sudden sensorineural hearing loss.

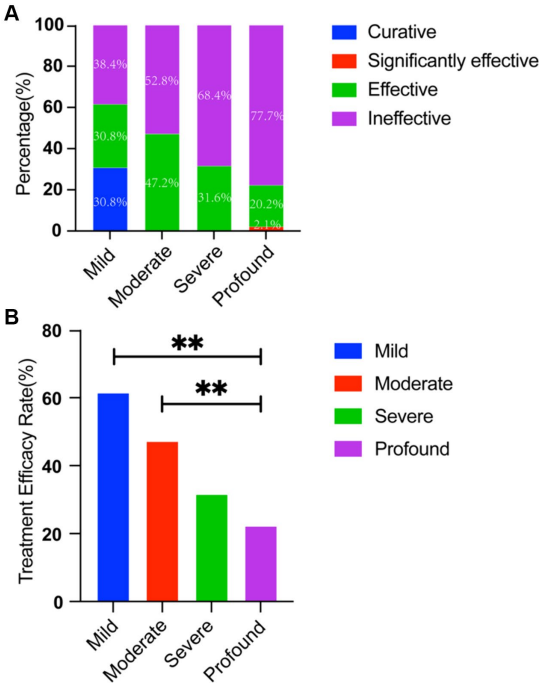

FIGURE 2
(A) Comparison of efficacy in patients with BSSNHL at different degrees of hearing loss. Treatment outcomes deteriorates as the severity of hearing loss increases. **(B)** The treatment efficacy for profound sensorineural hearing loss was significantly lower than that of mild sensorineural hearing loss ($p < 0.01$) and moderate sensorineural hearing loss ($p < 0.01$). **$p < 001$. BSSNHL, bilateral sudden sensorineural hearing loss.

TABLE 3 Analysis of clinical characteristics and treatment efficacy in patients diagnosed with BSSNHL.

Variables	Cases (n = 100)	Efficacy	p-value
Sex			
Male	52	24 (46.1%)	0.004[C2]
Female	48	9 (18.9%)	
Classification			
Si-BSSNHL	71	23 (32.4%)	0.84[C2]
Se-BSSNHL	29	10 (34.5%)	
Tinnitus	65	18 (27.7%)	0.124[C2]
Ear fullness	7	3 (42.9%)	0.681[C2]
Dizziness/vertigo	41	15 (36.6%)	0.525[C2]
Nausea/vomiting	23	7 (30.4%)	0.766[C2]
Hypertension	24	4 (16.7%)	0.032[C2]
Diabetes mellitus	14	2 (14.3%)	0.044[F]
Coronary heart disease	9	1 (11.1%)	0.026[F]

[C2]Chi-square test; [F]Fisher's exact tests. BSSNHL, bilateral sudden sensorineural hearing loss; Si-BSSNHL, simultaneous BSSNHL; Se-BSSNHL, sequential BSSNHL.

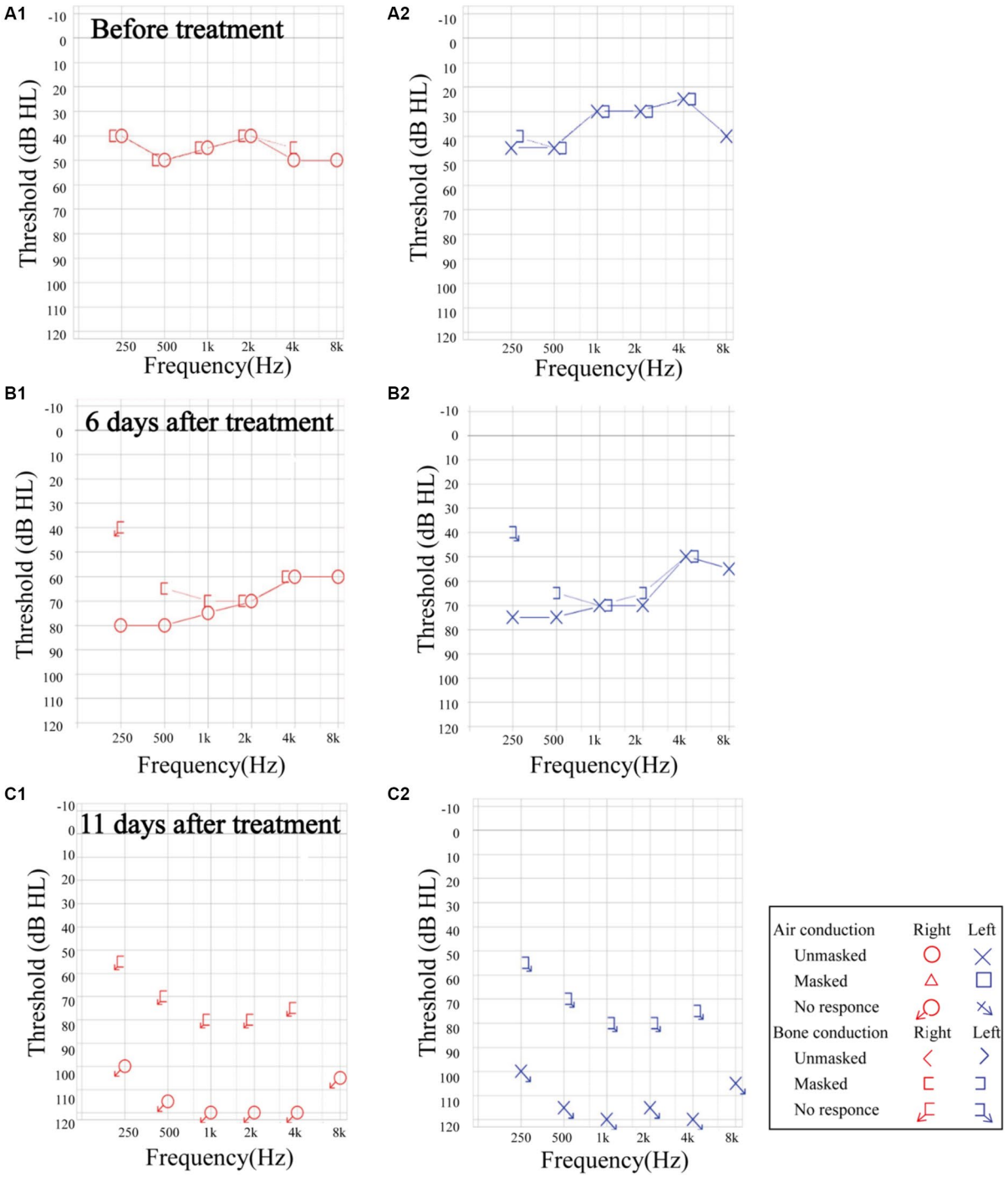

FIGURE 3
The progression of sensorineural hearing loss in a patient with HIV. **(A1,A2)** Before treatment, the pure tone audiometry threshold was 45.83 dB HL in the right ear. and 35.83 dB HL in the left ear. **(B1,B2)** At 6 days post-treatment, the unmasked hearing threshold increased across all frequencies. The average auditory threshold was 70.83 dB HL in the right ear, and 65.83 dB HL in the left ear. **(C1,C2)** At 11 days after treatment, the hearing threshold presented profound sensorineural hearing loss. The auditory threshold could not be tested bilaterally. HIV: human immunodeficiency virus.

evaluations may be necessary to identify the cause. Therefore, some patients with SSNHL and concurrent ischemia present with BSSNHL as the only symptom, whereas others experience symptoms more consistent with cerebral infarctions such as dizziness, nystagmus, ataxia, falls, and speech challenges. Clinical manifestations and prognosis are related to the location and severity of vascular lesions, with severe cases posing a potential threat to life (13). Therefore, in patients with BSSNHL, accompanying focal neurological symptoms or signs such as ataxia and speech challenges warrant a high level of vigilance for cerebral infarction (14).

Autoimmune diseases are a major cause of BSSNHL, with reported cases of bilateral sensorineural hearing loss associated with systemic

lupus erythematosus, granulomatosis with polyangiitis, relapsing polychondritis, antiphospholipid syndrome, Behçet's disease, and Sweet syndrome, among others (9, 15–18). In this study, the occurrence of BSSNHL in five patients may be attributed to autoimmune diseases, including one case of antiphospholipid syndrome, two cases of relapsing polychondritis, one case of Sjögren's syndrome, one case of Vogt–Koyanagi–Harada disease, and one case of Cogan syndrome. A prospective cohort study found that the risk for SSNHL is significantly higher in patients with autoimmune diseases (i.e., multiple sclerosis, Behçet's disease, antiphospholipid syndrome), which supports this study's findings (19). The pathophysiology mechanism may involve vascular endothelial inflammation in the cochlea, leading to impaired blood supply (20).

LVAS is the most common cause of sensorineural hearing loss in children (21). Five (45%) pediatric patients in this study underwent high-resolution temporal bone computed tomography scans and were diagnosed with LVAS. Recurrence is possible, often with precipitating factors leading to inner ear pressure imbalance and disturbances in the internal environment before onset (21). Given the prevalence of LVAS, for pediatric patients presenting with BSSNHL, a detailed medical history examination and a high-resolution temporal bone CT examination are necessary to identify inner ear abnormalities.

The suspected BSSNHL etiology in two patients in this study is meningitis, a finding previously reported (22). Other identified infectious causes in the literature include COVID-19 (23) and Lyme disease (24). Three patients were diagnosed with HIV, a risk factor not previously extensively investigated as a risk factor for BSSNHL. Notably, the patient with an HIV presented with increased hearing loss after treatment. Clinicians should consider SSNHL as an additional potential complication in HIV patients.

Vestibular schwannomas, which are present in most patients with neurofibromatosis type 2, are highly prevalent in patients with SSNHL (1.12–4.0%) (25–27) compared to the general population. One patient (1%) in this study has been diagnosed with neurofibromatosis type 2, which is consistent with previous findings. To our knowledge, acute myeloblastic leukemia with maturation (AML-M2) has not been associated with SSNHL in previous studies. Given that one patient in our study is diagnosed with AML-M2 alongside BSSNHL, future research should investigate the role of non-vestibular neoplasms, such as AML-M2, in SSNHL pathophysiological and progression.

BSSNHL causes more significant hearing impairment and poorer treatment outcomes and prognosis compared to USSNHL, consistent with the findings of the present study (4, 5). The overall treatment efficacy in this study was 32%, which aligns with previous studies reporting a treatment efficacy for BSSNHL of 12.5–37.5% (7, 22, 28). Though consistent with previous studies, the relatively low efficacy and poorer prognosis in this study may also be associated with a higher proportion of patients with severe or profound sensorineural hearing loss. Among the 100 patients (200 ears), 75.5% (151/200) exhibited severe or profound sensorineural hearing loss, while only 24.5% (49/200) had mild or moderate sensorineural hearing loss. This indicates that patients with BSSNHL are more likely to experience a more severe degree of hearing loss. The study findings revealed significant differences in treatment efficacy and prognosis among different degrees of hearing loss ($p = 0.004$). The treatment efficacy for profound sensorineural hearing loss was lower than that of mild sensorineural hearing loss ($p < 0.01$) and moderate sensorineural hearing loss ($p < 0.01$), suggesting that the degree of hearing loss is a crucial factor influencing the efficacy and prognosis of BSSNHL. Most patients with effective treatment had idiopathic etiology (70%). Moreover, hearing loss usually presents with full-frequency descent, and patients with BSSNHL may have progressive hearing loss. It emphasizes the importance of paying attention to unexpected outcomes and poor prognosis during treatment to avoid further sequelae.

The most common accompanying symptom in BSSNHL patients is tinnitus, present in 65/100 of the BSSNHL patients in this study. The effect of tinnitus on BSSNHL prognosis varies in previous studies (28). In our study, tinnitus showed no statistically significant relevance to efficacy evaluation.

In this study, patients with BSSNHL and comorbidities such as hypertension, diabetes, and coronary heart disease accounted for 24, 14, and 9% of all participants, respectively. Furthermore, patients with these comorbidities had a poorer prognosis ($p < 0.05$). Aimoni et al. (29) indicated that cardiovascular diseases, diabetes, and metabolic disorders were risk factors for the onset of SSNHL and demonstrated an unfavorable impact on the prognosis, aligning with our study's findings. It is important to note that other patient characteristics variables (i.e., age, gender) can confound the association between these chronic conditions and BSSNHL. Nonetheless, clinicians should be aware of hypertension, diabetes, and coronary heart disease as risk factors for poor treatment outcomes in BSSNHL patients.

5 Conclusion

In summary, BSSNHL exhibits distinctive clinical characteristics compared to USSNHL. BSSNHL usually manifests with severe sensorineural hearing loss which may progressively worsen. Vascular, autoimmune, infectious, neoplastic, and uremic were considered as potential pathogenesis in our study. BSSNHL is closely associated with underlying chronic conditions such as diabetes, hypertension, and coronary heart disease, all of which predict poor prognosis. Clinical diagnosis and treatment should involve a detailed medical history and early comprehensive systemic examinations to achieve a precise diagnosis and timely targeted treatment, preventing misdiagnosis or delayed treatment. Based on our findings, accounting for patient sex and other comorbidities can guide us toward the proper diagnostic tests to unravel the underlying cause of BSSNHL. Although early examination, diagnosis, and treatment are crucial, long-term and close follow-up visits are necessary for patients with an unclear etiology.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the local ethics committee at the Second Xiangya Hospital of Central South University (protocol code: LYF20230181, November 2023). Written informed consent for participation in this study was provided by the participants or their legal guardians/next of kin.

Author contributions

JH: Investigation, Writing – original draft. LJ: Investigation, Writing – review & editing. JY: Formal Analysis, Writing – review & editing. AM: Formal Analysis, Writing – review & editing. ZP: Data curation, Writing – review & editing, Investigation. JF: Data curation, Writing – review & editing, Investigation. QY: Data curation, Writing – review & editing, Investigation. WL: Writing – review & editing, Supervision, Methodology, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Lisheng Yu,
Peking University People's Hospital, China

REVIEWED BY
Sasa R. Vasilijic,
Stanford University, United States
Arwa Kurabi,
University of California San Diego,
United States

*CORRESPONDENCE
Jônatas Bussador do Amaral
✉ jbamaral@unifesp.br

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The inflammatory and metabolic status of patients with sudden-onset sensorineural hearing loss

Jônatas Bussador do Amaral[1]*, Kelly Abdo Peron[1], Tracy Lima Tavares Soeiro[1], Marina Cançado Passarelli Scott[1], Flávia Tatiana Pedrolo Hortense[1], Michelly Damasceno da Silva[2], Carolina Nunes França[2], Luiz Henrique da Silva Nali[2], André Luis Lacerda Bachi[2] and Norma de Oliveira Penido[1]

[1]ENT Research Lab, Department of Otorhinolaryngology—Head and Neck Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil, [2]Post-Graduation Program in Health Sciences, Santo Amaro University (UNISA), São Paulo, Brazil

Introduction: Sudden sensorineural hearing loss (SSNHL) is a common emergency symptom in otolaryngology that requires immediate diagnosis and treatment. SSNHL has a multifactorial etiology, and its pathophysiologic mechanisms may be associated with inflammatory and metabolic changes that may affect the cochlear microenvironment or its nervous component, thus triggering the process or hindering hearing recovery. Therefore, the aim of this study was to assess metabolic and inflammatory changes to identify systemic parameters that could serve as prognostic factors for hearing recovery in patients with SSNHL.

Materials and methods: Thirty patients with a sudden hearing loss of at least 30 dB in three contiguous frequencies were enrolled in this study. Patients were followed up for 4 months and peripheral blood samples were collected at 7 days (V1), 30 days (V2) and 120 days (V3). Interleukins (IL)-1F7, IL-2, IL-4, IL-5, IL-6, IL-10, interferon γ (IFN-γ), tumor necrosis factor α (TNF-α) and adiponectin were quantified in serum. In addition, lipid and glycemic profiles as well as concentration of creatinine, uric acid, fructosamine, peroxide, total proteins and albumin were analyzed. Patients underwent weekly ear-specific hearing tests with standard pure tone thresholds for frequencies of 250–8,000 Hz, speech recognition threshold and word recognition score.

Results: Patients with SSNHL were divided into a group of patients who did not achieve hearing recovery ($n = 14$) and another group who achieved complete and significant recovery ($n = 16$). Most serologic parameters showed no significant changes or values indicating clinical changes. However, IFN-γ levels decreased by 36.3% between V1 and V2. The cytokine TNF-α showed a statistically significant decrease from V1 to V3 (from 22.91 to 10.34 pg./mL). Adiponectin showed a decrease from 553.7 ng/mL in V1 to 454.4 ng/mL in V3.

Discussion: Our results show that serologic cytokine levels change in the acute phase of manifestation of SSNHL and establish a parallel between systemic changes and improvements in hearing, especially TNF-α, which showed differences in hearing recovery. The use of IFN-γ, TNF-α and adiponectin may elucidate the clinical improvement in these patients.

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KEYWORDS

sudden sensorineural hearing loss, cytokines, inflammation, metabolism, adiponectin, IFNγ, TNF-α

1 Introduction

Sudden Sensorineural Hearing Loss (SSNHL) is a common emergency symptom in otolaryngology that requires immediate diagnosis and treatment. It is clinically characterized by a rapid onset of sensorineural hearing loss of more than 30 dB in at least 3 contiguous audiometric frequencies within 72 h (1). SSNHL can usually manifest unilaterally, while in rare cases it can occur in both ears (simultaneously or sequentially) (2). The resulting deterioration in the quality of life of individuals affected by SSNHL may be exacerbated by other associated symptoms such as aural fullness, sound distortion, tinnitus, dizziness, and vertigo (3–5). Although a few cases are mild or resolve spontaneously, a minority of patients may develop permanent profound hearing loss associated with severe tinnitus and even vestibular symptoms (6). In some cases, SSNHL is diagnosed only by describing the symptoms of hearing loss; regardless of the cause, treatment methods are necessarily different (7). The prognosis for hearing recovery depends largely on the severity of hearing loss, age, time between onset of symptoms and treatment, comorbidities, and specific effects on cochlear structures (8–10).

SSNHL has a multifactorial etiology whose pathophysiologic mechanism remains unclear. The cause may be associated with cochlear membrane injury (11), microarteriosclerosis (12), microthrombosis (13), viral infections (14), autoimmunity (15), metabolic diseases (16) and other risk factors. The effect of these processes, which can even occur simultaneously, leads to inflammatory and metabolic changes that can affect the cochlear microenvironment or its nervous component. In this perspective, cytokines play an important role in the balance between innate and adaptive immunity (17). Their pro-inflammatory and anti-inflammatory effects may act on inflammatory and immunological processes both in the inner ear (18) and systemically (19) in the context of hearing loss. These compounds include interleukins (ILs), tumor necrosis factors (TNFs), interferons (IFNs), and adipocytokines, and can provide values prognosis and diagnosis in a variety of diseases and disorders, including neurological diseases, metabolic syndrome, cancer, and infectious diseases (20, 21). Inflammation is considered one of the significant causative factors for the occurrence of SSNHL, especially when analyzed in the context of vascular injury (22), endococlear responses (23), and atherogenesis (24).

Compared to the cochlear microenvironment, peripheral blood has easier access, and this approach is also used in studies related to hearing loss. The change in cytokine levels in the peripheral blood of patients with SSNHL indicates a possible systemic effect that may lead to lesions in the inner ear (19). An example of this is the decrease in IFN-γ and IL-12 levels and the increase in TNF-α levels and monocyte counts in patients with SSNHL compared to controls (25). Another interesting fact is that SSNHL patients with better prognosis had mononuclear cells that produced higher levels of IL-1β after activation with LPS (26).

Extending this analysis to other metabolic parameters makes the interpretation of SSNHL more thorough, as it also takes into account the additive effect of factors such as dyslipidemia (27), oxidative stress (28), hyperglycemia (29), and plasma proteins (30). For instance, high cholesterol levels have been associated with a higher incidence of SSNHL and poorer hearing recovery outcomes (31, 32). Changes in levels related to oxidative stress may also be altered in patients with SSNHL too. This ranges from an impaired thiol-disulfide balance to the possible formation of reactive oxygen species (ROS), which can affect microcirculation in the inner ear (33, 34). Glycemic changes can also have an impact on the prognosis of SNHL, as patients with poor glucose regulation have a poorer hearing outcome (35). In summary, a thorough understanding of the multiple functions of cytokines, lipids, glycemic factors and oxidative stress is essential to elucidate their complex role in physiological and pathological processes in SSNHL and may also provide new perspectives for the development of better treatment approaches.

The aim of this study was therefore to investigate the possible changes in oxidative stress, pro- and anti-inflammatory cytokines, protein, lipid and glucose profiles as well as over 7, 30, and 120 days in SSNHL patients undergoing treatment. In addition to comparing these results at these time points, the data will also be linked to hearing recovery observed.

2 Materials and methods

2.1 Participants, clinical data, and sample collection

Patients with a sudden hearing loss of at least 30 dB in three contiguous frequencies were included in this study and designated as having Sudden Sensorineural Hearing Loss (SSNHL). Exclusion criteria included congenital hearing loss, incomplete treatment, a diagnosis other than SSNHL (conductive hearing loss, acoustic trauma, vestibular schwannoma, Meniere's disease) (36) and failure to follow-up. During a 4 month observation period, 30 patients with SSNHL were examined in the ENT emergency department and outpatient clinic of a tertiary hospital. During this period, audiometric examinations and blood samples were taken on three visit assessments: V1 took place after 7 days and allowed us to analyze the most acute phase of SSNHL involvement. V2 allowed us to follow the metabolic and inflammatory profile of the patients after 30 days of corticosteroid treatment, and finally V3, after 120 days, to obtain information on the recovery of hearing when no longer under corticosteroid treatment. Each patient underwent a thorough medical history, physical examination, audiometry and magnetic resonance imaging (MRI) of the inner ears (28). Only patients who were previously untreated were included in our case study. All participants provided written informed consent. The Ethics Committee for Research of the Escola Paulista de

Medicina/Universidade Federal de São Paulo (EPM/UNIFESP) accepted the current study under protocol number 4.507.315.

2.2 Audiometric testes

Patients underwent weekly ear-specific auditory assessment with standard pure tone thresholds (PTTs) for frequencies of 250–8,000 Hz, speech recognition threshold (SRT) and word recognition score (WRS). Four sessions were carried out during the first 30 days, and then auditory assessments were moved to a monthly frequency until the completing 120 days. Tympanometry and acoustic reflex measurements were only performed at the first examination to exclude middle ear pathologies. The degree of HL was classified according to WHO 2020 using the four-frequency pure tone average (4fPTA) by taking the mean of the thresholds at 500, 1,000, 2,000, and 4,000 Hz (28). Hearing outcomes were analyzed in comparison between the first (7 days) and last (120 days) visit, with pure-tone and speech audiometer assessment based on the "Clinical Practice Guideline: Sudden Hearing Loss (Update)" (1). This particular guideline divides patients into three groups: Complete, partial or no recovery. To better allocate and for statistical analysis, the hearing recovery was subclassified in two groups: one comprising patients with complete and significant recovery and the other including patients with partial and no recovery. The first was defined as a hearing level difference of <10 dB between the affected and the unaffected ear and recovery of Word Recognition Scores (WRS) within 5 to 10% compared to the unaffected ear. Partial recovery was defined as 4fPTA < 50 dB or WRS > 50%, or an improvement of >10 dB in pure tone thresholds or an improvement in WRS ≥ 10%. Any hearing level improvement of <10 dB was classified as no recovery.

2.3 Corticosteroid treatment

Prednisolone 1 mg/kg/day (highest dose: 60 mg/day) was administered to all patients once daily for at least 14 days. Prednisolone was then reduced weekly until complete discontinuation within 15 days. In the following three weeks, the prednisolone dose was reduced until complete discontinuation. Patients who could not take prednisone and suffered from arterial hypertension or diabetes received equivalent doses of deflazacort (maximum dose 90 mg/day). Corticosteroid treatment was carried out throughout the first two samples (V1 and V2) (37). In the third collection (V3), all patients were no longer receiving corticosteroid treatment after 120 days.

2.4 Cytokines quantification

The serum was separated from the blood samples by centrifugation (800G, 8 min at 4°C) and stored at −80°C until analysis. The concentrations of interleukin (IL)-2, IL-4, IL-5, IL-6, IL-10, interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α) were measured using ELISA kits (enzyme-linked immunosorbent assay) from Thermo Fisher Scientific (Vienna, Austria). IL-1F7 and adiponectin were determined using ELISA kits from RD Systems (Minneapolis, United States). The procedures were performed strictly according to the manufacturer's protocols. Absorbance at 450 nm was measured with a Multiskan Sky Spectrophotometer microplate reader (Thermo Fisher Scientific—Vienna, Austria).

2.5 Metabolic parameters

Circulating serum levels of total cholesterol and fractions (LDL and HDL), triglycerides, albumin, total protein, creatinine, uric acid, fructosamine, glucose (LabTest diagnostica, Lagoa Santa, Brazil) and peroxide (Bioassay Systems-Hayward, United States) were determined with commercially available kits. The results were analysed using a Multiskan Sky Spectrophotometer microplate reader (Thermo Fisher Scientific—Vienna, Austria). LDL values were estimated according to the Friedewald formula (38).

2.6 Statistical analysis

Statistical analyses were calculated with SPSS v26.0 (IBM Corp). Graphs were created using GraphPad Prism v8.01 (GraphPad Software Inc.). The normality of the data was tested for normality using the Kolmogorov–Smirnov test. The comparison was analysed using the Wilcoxon test (for skewed continuous variables) or the Student *t*-test and the Anova one-way test (for normally distributed continuous variables). The correlation was calculated using Pearson's rank correlation test. A p value < of 0.05 was considered statistically significant.

3 Results

3.1 Demographic data and clinical characteristics

The average age of the subjects was 50.26 years, the gender ratio was equal: 15 men and 15 women. The medical history revealed a variety of symptoms and diseases that had both local and systemic effects. Of particular note were systemic arterial hypertension (13 subjects), diabetes mellitus (7 subjects), chronic kidney disease (4 subjects) and hypothyroidism (3 subjects). Trigeminal neuralgia, herpes zoster, Raynaud's disease and multiple myeloma each occurred once. In addition, the body mass index (BMI) was 27.37 kg/m^2, a value indicative of overweight adults (39) (Table 1).

Four-frequency pure tone average (4fPTA) and the word recognition scores were carried out on all patients who took part in the study (Figure 1). Of the 30 study participants, 25 had unilateral SSNHL and 5 had bilateral SNHL (Table 1). For this reason, we analyzed all affected ears, totaling $n = 35$. The 4fPTA assessment showed that patients' hearing deficits decreased over time between visits, with median values of 51.25 dB in V1, 45.00 dB in V2, and 41.25 dB in V3. On closer inspection, 6 subjects showed an increase in hearing threshold, with the worst case being a 67.5 dB increase in tone threshold. In four subjects, the hearing threshold remained the same, and in the remaining 25 subjects, the hearing threshold

10.3389/fneur.2024.1382096

decreased in a range from 1.25 dB (which would be considered clinically unchanged) to patients who showed a decrease of 51.25 dB (63.75 to 12.5 dB) (Figure 1A).

Figure 1B shows the word recognition scores for the 3 visits analyzed. The median values of this test were: 72% in V1, 80% in V2 and 92% in V3. Regarding the other symptoms associated with hearing loss, all subjects in the study had tinnitus and 70% of them also had vestibular symptoms (Table 1).

3.2 Metabolic evaluation

Mean albumin levels were similar, showing mean values of 4.232 g/dL in V1, 3.930 g/dL in V2, and 4.174 g/dL in V3. The only statistical difference was the increase between V2 and V3. There were no statistically significant differences in total protein, and the mean values were very close throughout the period. The mean values were 6.456 g/dL in V1, 6.535 g/dL in V2, and 6.671 g/dL in V3 (Figure 2B).

Glycemic parameters were determined by quantification of glucose and fructosamine (Figures 2C,D). Median glucose levels were 126.7 mg/dL in V1, 117.2 mg/dL in V2, and 108.4 mg/dL in V3, with only the decrease between V2 and V3 being statistically significant. Fructosamine results showed the following mean values: 227.4 µM/L in V1, 220.3 µM/L in V2, and 183.1 µM/L in V3, with no significant differences between visits.

Concentration of uric acid, peroxide, and creatinine showed no statistically significant differences (Figures 2E–G). The medians found for uric acid and creatinine were closest between time points, with uric acid values of 4.83 mg/dL in V1, 5.27 mg/dL in V2, and 5.30 mg/dL in V3, and creatinine of 1.359 mg/dL in V1, 0.991 mg/dL in V2, and 1.444 mg/dL in V3. Quantification of peroxide in serum showed results ranging from 0.400 to 388.1 ng/mL. Because of this wide range of values, the peroxide medians found were 7.90 ng/mL in V1, 43.05 ng/mL in V2, and 19.20 ng/mL in V3. Figure 2H shows the mean adiponectin values: 553.7 ng/mL in V1, 612.5 ng/mL in V2, and 454.4 ng/mL in V3. The decrease at V3 is statistically significant compared with the other visits.

Regarding the lipid profile analysis, total cholesterol, triglycerides, LDL, and HDL were quantified. HDL was the only analyte that showed statistically significant differences at each visit (Figure 3). Median total cholesterol levels were 216.7 mg/dL in V1, 223.1 mg/dL in V2, and 216.4 mg/mL in V3. The medians of triglycerides were 122.9 mg/mL in V1, 119.4 mg/mL in V2, and 132.3 mg/mL in V3. The LDL averages were 148.7, 149.3, and 144 mg/mL in V1, V2, and V3, respectively. Finally, mean HDL levels were 48.40 mg/mL in V1, 47.73 mg/mL in V2, and 46.07 mg/mL in V3. The only statistically significant difference was the reduction in values in V3 compared to V1.

TABLE 1 Demographic data and clinical characteristics of the 30 subjects.

Variables	Value*
Female	15 (50%)
Age	50.26 ± 14.10 years (±SD)
BMI	27.37 ± 4.48 kg/m² (±SD)
Tinnitus	30 (100%)
Vestibular symptoms	21 (70%)
Unilaterally affected ears	25 (83.33%)
Bilaterally affected ears	5 (16.67%)
Complete and significant hearing recovery**	16 (53.33%)
Partial and no hearing recovery**	14 (46.67%)
Systemic arterial hypertension	13 (43.33%)
Diabetes mellitus	7 (23.33%)
Chronic kidney disease	4 (13.33%)
Hypothyroidism	3 (10%)
Trigeminal neuralgia	1 (3.33%)
Herpes zoster	1 (3.33%)
Raynaud's disease	1 (3.33%)
Multiple myeloma	1 (3.33%)

*Mean ± S.D. or *n* (%). **Classification based described by the American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) (1). SD, standard deviation.

3.3 Inflammatory cytokines

Interleukins IL-1F7 (Figure 4A) and IL-4 (Figure 4C) showed no statistically significant differences. Their medians were: IL-1F7: 94.33 pg./mL in V1, 92.75 pg./mL in V2, and 93.96 pg./mL in V3. For IL-4 quantification: 10.73 pg./mL in V1, 10.74 pg./mL in V2, and 10.87 pg./mL in V3.

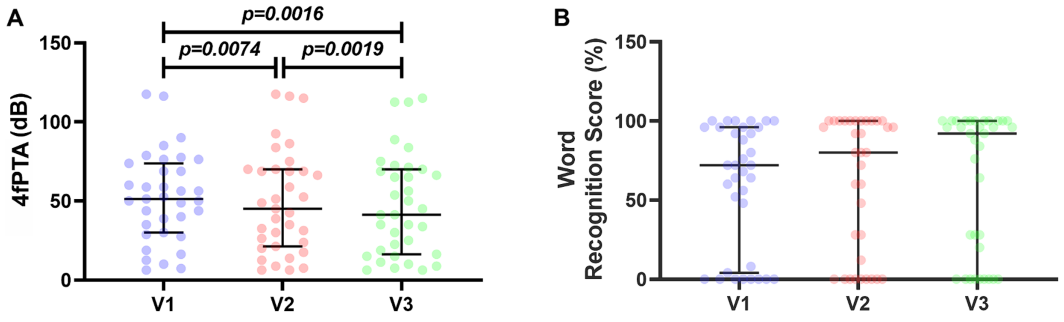

FIGURE 1
Audiometric evaluations of 30 patients followed up for 120 days. **(A)** Four-frequency pure tone average (4fPTA) in decibels (dB). **(B)** Word recognition score (WRS) in percentages (%). For statistical analysis, Wilcoxon test was used and *p*-values <0.05 were considered significant.

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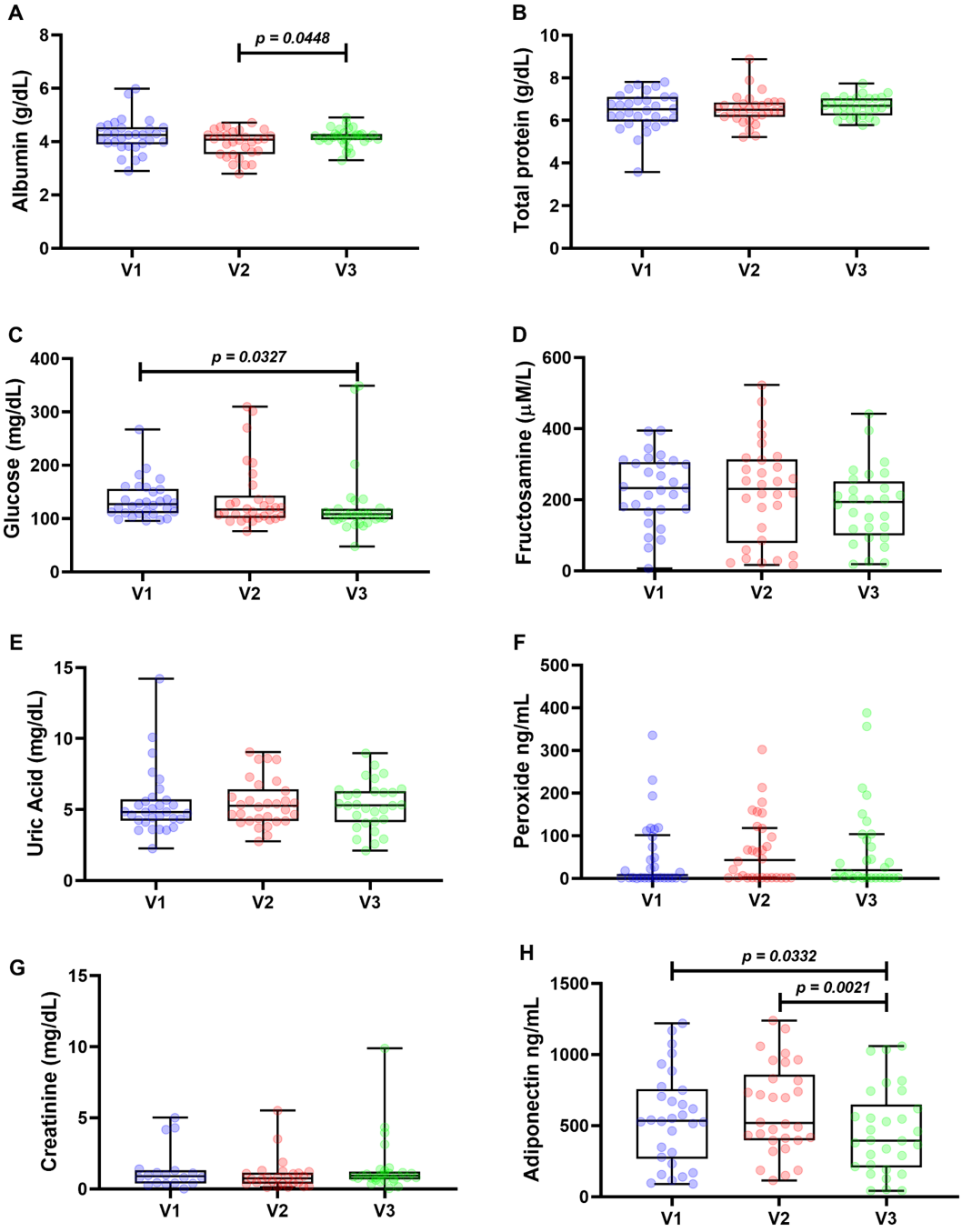

FIGURE 2
Metabolic assessments of 30 patients followed up for 120 days. Protein profile: albumin **(A)** and total proteins **(B)**. Glycemic profile: glucose **(C)** and fructosamine **(D)**. Uric acid **(E)**, peroxide **(F)**, creatinine **(G)**, and adiponectin **(H)** Wilcoxon test was used for statistical analysis in **(C)**, **(E–G)**, Anova one way **(A,B,H)**, and paired *t* test in **(D)**. Values of $p < 0.05$ were considered significant.

IL-2 dosages had the following medians: 3.75 pg./mL in V1, 1.75 pg./mL in V2, and 3.30 in V3. It is noteworthy that the levels of this interleukin decreased at visit 2, a statistically significant difference (Figure 4B). This decrease in V2 was also observed for IL-5, with medians of 42.25, 36.92, and 39.81 pg./mL in V1, V2, and V3, respectively (Figure 4D).

Interleukin 6 had the following medians: 26.66 pg./mL in V1, 26.43 pg./mL in V2, and 27.29 pg./mL in V3. Although the values were very close, there was a statistical difference at points V1 and V3 (Figure 4E).

Interleukin 10 showed a statistically significant decrease between V2 and V3, with median values of 29.93 pg./mL in V1, 28.52 pg./mL in V2, and 24.65 pg./mL in V3 (Figure 4F).

The Interferon γ decreased between V1 and V2, with median values of 20.94, 13.33, and 14.36 pg./mL in V1, V2, and V3, respectively (Figure 4G).

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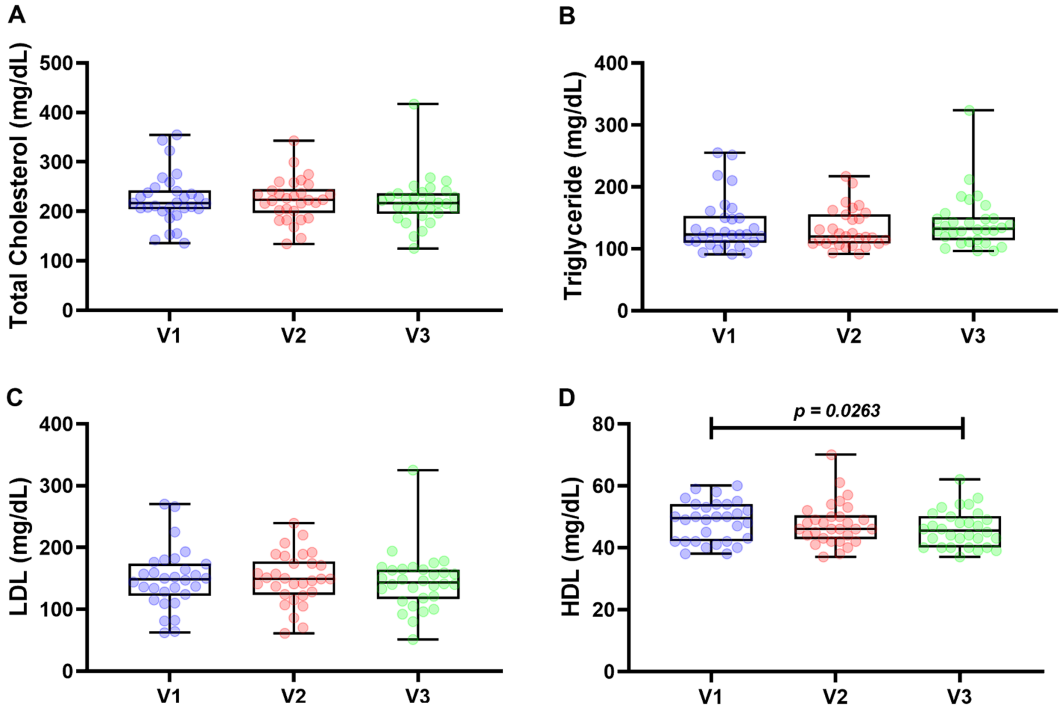

FIGURE 3
Lipid profile of 30 patients followed up for 120 days. Total cholesterol **(A)**, triglycerides **(B)**, LDL **(C)**, and HDL **(D)**. For statistical analysis, Wilcoxon test was used in **(A,B)**, and paired *t*-test was used in **(C,D)**. Values of $p < 0.05$ were considered significant.

The cytokine TNF-α showed a statistically significant decrease from V1 to V2 (with a median decrease from 22.91 to 14.36 pg./mL) and from V1 to V3 (from 22.91 to 10.34 pg./mL) (Figure 4H).

3.4 Pearson's correlation coefficient (ρ)

Supplementary material shows the different correlations between the results presented in Table 1 and Figures 1–4.

The 4fPTA showed a negative correlation coefficient with the Word Recognition Score. This correlation was very strong as it was present in the 3 analyzed periods with the following values: $r = -0.947$ in V1, $r = -0.939$ in V2, and $r = -0.935$ in V3. Both 4fPTA and the Word Recognition Score (WRS) also showed a relationship with peroxide in V2 ($r = -0.446$ for 4fPTA and 0.410 for WRS).

The correlation between total cholesterol X LDL was maintained across the 3 visits, with ρ values of $r = 0.947$ in V1, $r = 0.942$ in V2, and $r = 0.945$ in V3. The correlation between total cholesterol X HDL was observed only in V1 and V3, with values of $r = 0.665$ and 0.450, respectively. Total cholesterol also showed a correlation with adiponectin in V2 ($r = 0.435$) and had a negative correlation coefficient with some interleukins in V2, which values were: $r = -0.487$ for IL-2, $r = -0.456$ for IL-4, and $r = -0.366$ for IL-6.

The analysis of cholesterol fractions also allowed to establish correlations. The correlation HDL X LDL occurred only in V1 and showed ρ values of $r = 0.480$. HDL showed correlations with the interleukins IL-2 ($r = 0.439$ in V1) and IL-4, the latter with negative values ($r = -0.404$ in V3). This cholesterol fraction also correlated with Word Recognition Score ($r = 0.408$ in V2) and peroxide ($r = 0.395$ in V3). HDL levels correlated negatively with 4fPTA ($r = -0.389$ in V2). In contrast, the LDL fraction correlated negatively with IL-6 in V1 ($r = -0.395$) and V3 ($r = -0.413$). In the latter period, LDL also correlated with IL-2 ($r = -0.434$) and IL-4 ($r = -0.438$). Adiponectin and total proteins correlated with LDL only in V2, with values of $r = 0.470$ and 0.378, respectively.

The correlation with triglycerides that remained the same at all 3 time points was that produced by peroxide, with the coefficient values found being: $r = 0.451$ (V1), 0.504 (V2), and 0.362 (V3). The correlation with interleukins was IL-5 in V1 ($r = 0.442$) and IL-6 in V1 ($r = 0.668$) and V2 ($r = 0.446$). The correlation coefficient between triglycerides and age was $r = 0.397$ in V1, and in V2 the results showed a negative correlation coefficient in relation to fructosamine (−0.412) and 4fPTA ($r = -0.400$).

With the exception of IL-1F7, all other inflammatory cytokines showed correlations with each other, with interleukins 4 and 5 being more pronounced. It is noteworthy that these correlations are present eight times in V1, decrease to two correlations among cytokines in V2, and increase again to five correlations in V3. The only correlation that remained the same at all three time points was that of IL-4 X IL-2, which showed a decrease in the intensity of correlations between V1 and V2 ($r = 0.472$ and $r = 0.435$, respectively), with this coefficient increasing in V3 ($r = 0.682$). The correlation of TNF-α with IL-4 and IL-5 was present in V1 and V3, with values for IL-4 X TNF-α being very close at these two time points, $r = 0.599$ in V1 and $r = 0.605$ in V3. The correlation IL-5 X TNF-α gave values of 0.568 in V1 and 0.518 in V3. The interferon-γ correlation is also present in IL-4 and IL-5. However, these correlations occur only in V1. The value of IL-4 X interferon-γ was $r = 0.642$. The correlation between IL-5 and

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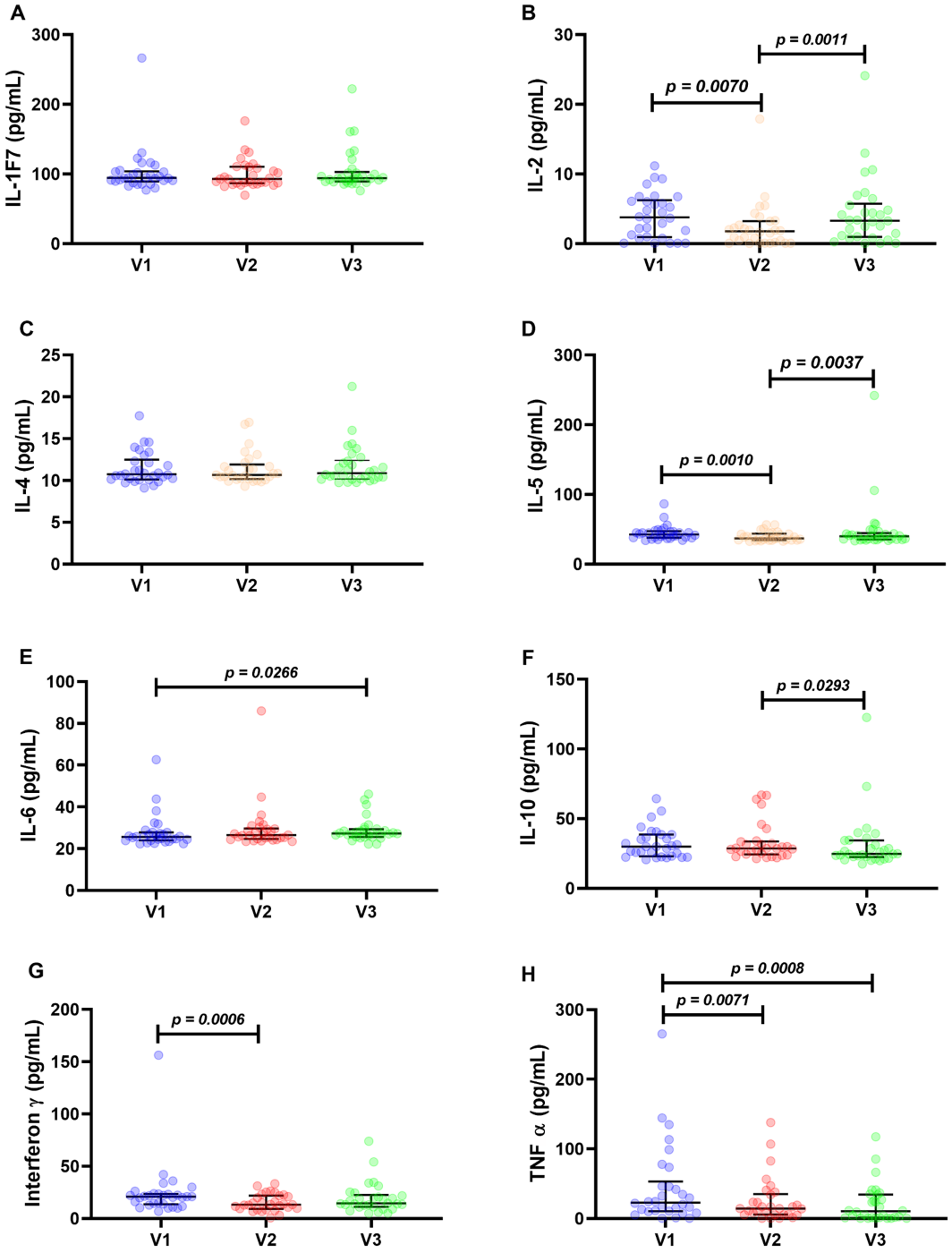

FIGURE 4
Inflammatory cytokines of 30 patients followed up for 120 days. Interleukin 1F7 **(A)**, interleukin 2 **(B)**, interleukin 4 **(C)**, interleukin 5 **(D)**, interleukin 6 **(E)**, interleukin 10 **(F)**, interferon γ **(G)**, and TNF-α **(H)**. The Wilcoxon test was used for statistical analysis, and *p* values <0.05 were considered significant.

interferon-γ was $r = 0.586$. Interleukins 4 and 5 yielded a correlation coefficient ($r = 0.374$) only in V3. Interleukin 4 also correlated with IL-10 in V1 ($r = 0.374$). Another cytokine that correlated with IL-10 was TNF-α ($r = 0.410$ in V1). TNF-α also correlated with the following cytokines: Interferon-γ ($r = 0.492$ in V1); and IL-2 in V3, where the correlation coefficient was negative ($r = -0.363$).

Albumin and total protein also correlated with other parameters analyzed. Albumin, for example, had a negative correlation coefficient with IL-4 in V1 ($r = -0.382$) and in V2 ($r = -0.371$). The correlations also extended to fructosamine in V1 ($r = 0.476$) and established a correlation with a negative coefficient with TNF-α ($r = -0.421$ in V1), IL-2 ($r = -0.373$ in V1), and finally with uric acid in V3 ($r = 0.555$). Total proteins also showed a negative personal correlation coefficient, correlating with IL-6 ($r = -0.361$), IL-4 ($r = -0.506$), and fructosamine ($r = -0.386$) in V2.

Adiponectin also correlated with other parameters: IL-10 in V2 ($r = 0.390$) and, with negative correlation coefficients, with uric acid ($r = -0.497$ in V1), peroxide ($r = -0.494$ in V3), and body mass index ($r = -0.405$ in V3).

Uric acid also correlated with other parameters such as IL-1F7 ($r = 0.404$ in V3) and showed negative correlation coefficients with TNF-α ($r = -0.364$ in V2) and IL-5, this cytokine showing a correlation in V1 and V2 ($r = -0.337$ and $r = -0.478$ respectively).

Glycemic responses were also correlated with other parameters. Fructosamide was correlated with age ($r = 0.565$ in V1) and INF-γ in V2. Glucose also showed a correlation with peroxide ($r = 0.457$ in V2).

Finally, a correlation was found between BMI and TNF-α, which was correlated with negative coefficients in V1 ($r = -0.377$) and V2 ($r = -0.412$).

3.5 Outcome analysis on hearing recovery

Due to the sudden onset of hearing loss, all patients had hearing characteristics that made them suitable for the study. Over time and as a result of the treatment, we observed statistically significant changes in hearing, metabolic and inflammatory parameters at the three proposed visits. This analysis was complemented by the results in terms of hearing recovery at the end of the study (120 days). After analyzing the results in Table and Figure 1, the patients were divided into a group of patients with partial and no hearing recovery ($n = 14$) and another group who achieved complete and significant hearing recovery ($n = 16$). Figure 5 shows all metabolic and inflammatory parameters when analyzed the hearing recovery. Significant variations between 4fPTA, WRS and peroxide can be observed when comparing the two groups. Tables 2, 3 show the variations between visits, which showed statistically significant differences. Table 2 shows the results of patients who had complete and significant hearing recovery. As expected, 4fPTA and WRS scores improved over time, with the median 4fPTA going from 46.87 db in V1 to 31.87 db in V3 and the WRS score increasing from 82 to 96% (V1 and V3, respectively). Compared to the results in patients who had not recovered their hearing, both 4fPTA and WRS scores showed no statistically significant differences between visits, with median 4fPTA of 71.25, 69.68 and 70.62 db and WRS of 28, 6 and 10% over V1, V2 and V3, respectively. One observation that stands out is the arrangement of the peroxide results in Figure 5. When all data were analyzed together (Figure 2F), no statistically significant differences were found between visits. However, when the patients were divided into 2 groups, the lowest values (in red in Figure 5) were concentrated in the patients for whom hearing did not recover. The medians for this group were 1.65 in V1, 1.7 in V2 and 20.25 ng/mL in V3 and were not statistically different. However, for the patients who showed complete and significant hearing recovery, the medians were 15.8, 66.55 and 19.2 ng/mL (V1, V2 and V3, respectively). In addition to the higher median values, the increase at 30 days was statistically significant in patients who showed some hearing improvement (Table 2).

Adiponectin, interferon γ, IL-2, and IL-5 showed differences between visits in terms of hearing recovery regardless of situation. The decrease in adiponectin in V3 compared to V2 was maintained in all scenarios of this study. After 120 days, the values in patients with complete and significant hearing recovery fell from 569.4 ng/mL to 394.95 ng/mL (Table 2). In patients partian and no hearing recovery, the median values also fell in V3, with a concentration of 517.5 ng/mL in V2 and 418.35 ng/mL in V3 (Table 3). Interferon γ maintained its pattern of decline after the acute phase of SSNHL in all situations. The median levels found decreased from V1 to V2 as follows: 18.71 to 13.63 pg./mL in patients with complete and significant hearing recovery (Table 2) and 20.94 to 12.5 pg./mL in patients who did not

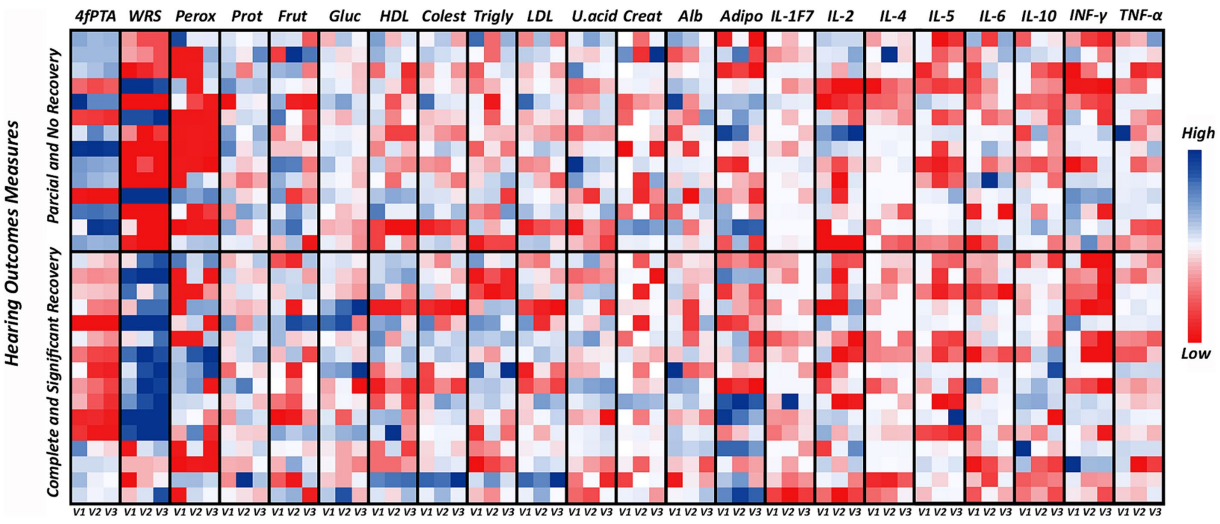

FIGURE 5
Heat map of metabolic and inflammatory parameters in patients with sudden sensorineural hearing loss. The values for each patient are shown in the small squares, with the color intensity representing the highest values in blue, the average values in white and the lowest values in red for each analyte tested after 7 days (V1), 30 days (V2) and 120 days (V3). The graph is divided according to hearing recovery, with 14 patients having partial and no recovery and 16 having complete and significant hearing recovery. V1 = 7 days, V2 = 30 days and V3 = 120 days. 4fPTA, four-frequency pure tone average; WRS, word recognition score; Perox, peroxide; Frut, frutosamine; Gluc, glucose; Colest, cholesterol; Trigly, triglycerides; U. acid, uric acid; Creat, creatinine; Alb, albumin; Adipo, adiponectin.

10.3389/fneur.2024.1382096

TABLE 2 Parameters with statistically significant differences between patients with hearing recovery (complete and significant).

4fPTA	Db	*p*-value*
V1 (7d)	46.87 (31.56; 58.125)	0.001 (V2-V1)
V2 (30d)	32.5 (15.31; 47.81)	0.001 (V3-V1)
V3 (120d)	31.87 (12.18; 44.06)	0.007 (V3-V2)
WRS	**%**	***p*-value***
V1 (7d)	82 (64;95)	0.012 (V2-V1)
V2 (30d)	94 (80;100)	0.002 (V3-V1)
V3 (120d)	96 (89;100)	0.013 (V3-V2)
Peroxide	**ng/mL**	***p*-value***
V1 (7d)	15.8 (1.625; 108.22)	0.035 (V2-V1)
V2 (30d)	66.55 (27.22; 159.22)	0.836 (V3-V1)
V3 (120d)	19.2 (1.55; 139.2)	0.501 (V3-V2)
Adiponectin	**ng/mL**	***p*-value***
V1 (7d)	556.8 (286.14; 926.77)	0.570 (V2-V1)
V2 (30d)	569.4 (352.35; 926.77)	0.079 (V3-V1)
V3 (120d)	394.95 (240.39; 745.87)	0.026 (V3-V2)
IFN-γ	**pg/mL**	***p*-value***
V1 (7d)	18.71 (13.02; 28.30)	0.010 (V2-V1)
V2 (30d)	13.63 (9.98; 21.47)	0.121 (V3-V1)
V3 (120d)	14.26 (12.73; 23.30)	0.301 (V3-V2)
IL-2	**pg/mL**	***p*-value***
V1 (7d)	3.61 (1.05; 6.56)	0.031 (V2-V1)
V2 (30d)	1.57 (0.082; 2.975)	0.326 (V3-V1)
V3 (120d)	3.2 (0.8275; 6.04)	0.30 (V3-V2)
IL-5	**pg/mL**	***p*-value***
V1 (7d)	41.12 (38.36; 47.18)	0.015 (V2-V1)
V2 (30d)	38.83 (34.38; 44.25)	0.032 (V3-V1)
V3 (120d)	40.67 (35.21; 42.39)	0.127 (V3-V2)
TNF-α	**pg/mL**	***p*-value***
V1 (7d)	21.07 (11.31; 39.99)	0.026 (V2-V1)
V2 (30d)	12.4 (5.49; 36.9)	0.001 (V3-V1)
V3 (120d)	3.73 (0.41; 26.69)	0.016 (V3-V2)

$n = 16$. Data represent medians (interquartile interval 25; 75). *Wilcoxon test between visits. p-values < 0.05 were considered significant.

recover their hearing (Table 3). IL-2 showed a significant reduction at visit 2 in all situations tested (Figure 4B and Tables 2, 3). In the group that showed complete and significant hearing recovery, the median levels at the 3 visits were 3.61, 1.57, and 3.2 pg./mL, respectively. In the patients who did not recover, the values were 4.17, 1.93, and 3.75 pg./mL. Statistical significance between visits varied, with only the increase from V2 to V3 being statistically significant in the group without hearing improvement. In the group with some hearing improvement, both the reduction in V2 and the subsequent increase in median levels in V3 were statistically significant (just as in the no separation group, Figure 4B). IL-5 showed too a very similar median values before and after separation according to hearing recovery. However, the statistical significance changed between visits, and in patients with complete and significant hearing recovery (Table 2), the statistically significant values were found in V2 and V3 compared to V1. The IL-5 medians in this context were 41.12 (V1), 38.83 (V2) and 40.67 pg./mL in (V3). The patients who did not regain their hearing had values of 43.98, 36.24, and 38 pg./mL (V1, V2 and V3, respectively), although there was no statistical difference when the values of V3 were compared with V1 (Table 3).

TNF-α showed a significant reduction over 120 days in the patients who showed complete and significant hearing recovery, from 21.07 pg./mL in V1 to 3.73 pg./mL in V3 (Table 2). This result is close to that found in the analysis of all 30 patients. However, in this case the statistical difference between V2 and V3 was not significant. When looking at the TNF-α levels in the patients who did not regain their hearing, no statistical difference was found between the visits. The median values in this group were: 28.42 in V1, 16.86 in V2, and 17.35 in V3.

The group that did not recover (Table 3) had statistically significant differences in some metabolic and inflammatory parameters that differed from those of the patients who recovered. However, when we looked at the differences between the visits, many values showed very little variation and were within normal parameters. Let us start with the blood protein levels (albumin and total protein). Only the values obtained at visit 3 showed statistical differences, and these values are practically the same as the other points. The median albumin values were 4.16, 4.04, and 4.24 g/dL and the total protein values were 6.86, 6.51, and 6.77 g/dL (V1, V2 and V3, respectively). The cytokines IL-6 and IL-10 as well as HDL also showed results that did not differ significantly from the values found in the 30 patients. Furthermore, in the cases where the values are statistically different, the results are very close to each other and have no clinical relevance. The median IL-6 levels were 26.46, 26.74, and 28.23 pg./mL ($p = 0.035$ for the difference between V1 and V3). IL-10, on the other hand, showed a decrease in V3 and the median values were 29.93, 28.62, and 24.13 pg./mL ($p = 0.026$ between V1 and V3 and $p = 0.019$ between V2 and V3). Finally, HDL levels were 49 in V1 and 45.5 in V2 and V3, with this decrease being statistically significant from V1 to V3. Another component of the lipid profile, triglycerides, showed an increase in the blood of patients in V3 (compared to V2), with medians of 124.84, 117.44, and 133.56 mg/dL (Table 3). Finally, for two glycemic parameters (fructosamine and glucose), values decreased between V2 and V3 (V1-V3 and V2-V3 with a statistical difference), with values of 275.32, 246.98, and 122.48 µmol/L for fructosamine and 123.80, 116.70, and 108.99 mg/dL for glucose (Table 3).

4 Discussion

It is well known that SSNHL is a condition with a number of causes, including autoimmune diseases, infections, trauma, as well as vascular, hematologic, and other factors (40). There is no recognized pathogenesis for SSNHL and this symptom is probably due to a multifactorial etiology. The results found are related to this, as they show that inflammatory and metabolic factors change during the development of SSNHL, demonstrating a dynamic interaction between the patient's general condition, hearing recovery, treatment duration, and the effect of cytokines.

Identifying preventable or modifiable factors for hearing loss should be considered a top public health priority, given its potential impact on physical, mental and social well-being and quality of life in

10.3389/fneur.2024.1382096

TABLE 3 Parameters with statistically significant differences between patients with partial and no recovery hearing.

Adiponectin	ng/mL	*p*-value*
V1 (7d)	529.05 (215.74; 716.17)	0.245 (V2-V1)
V2 (30d)	517.5 (415.12; 849)	0.300 (V3-V1)
V3 (120d)	418.35 (150.11; 569.85)	0.048 (V3-V2)
IFN-γ	pg/mL	*p*-value*
V1 (7d)	20.94 (17.48; 23.13)	0.048 (V2-V1)
V2 (30d)	12.5 (8.11; 22.72)	0.397 (V3-V1)
V3 (120d)	15.39 (10.47; 24.71)	0.331 (V3-V2)
IL-2	pg/mL	*p*-value*
V1 (7d)	4.17 (0.58; 6)	0.116 (V2-V1)
V2 (30d)	1.93 (0.36; 4.59)	0.650 (V3-V1)
V3 (120d)	3.75 (1.07; 5.95)	0.019 (V3-V2)
IL-5	pg/mL	*p*-value*
V1 (7d)	43.98 (36.47; 47.06)	0.048 (V2-V1)
V2 (30d)	36.24 (34.37; 43.89)	0.638 (V3-V1)
V3 (120d)	38 (35.69; 49.29)	0.016 (V3-V2)
Albumin	g/dL	*p*-value*
V1 (7d)	4.16 (3.72; 4.64)	0.272 (V2-V1)
V2 (30d)	4.04 (3.52; 4.27)	0.510 (V3-V1)
V3 (120d)	4.24 (4.16; 4.35)	0.041 (V3-V2)
Total Protein	g/dL	*p*-value*
V1 (7d)	6.86 (6.16;7.44)	0.177 (V2-V1)
V2 (30d)	6.51 (6.077; 6.75)	0.638 (V3-V1)
V3 (120d)	6.77 (6.50; 7.05)	0.048 (V3-V2)
IL-6	pg/mL	*p*-value*
V1 (7d)	26.46 (23.76; 28.88)	0.363 (V2-V1)
V2 (30d)	26.74 (24.39; 31.14)	0.035 (V3-V1)
V3 (120d)	28.23 (26.31; 37.70)	0.638 (V3-V2)
IL-10	pg/mL	*p*-value*
V1 (7d)	29.93 (22.32; 35.73)	0.778 (V2-V1)
V2 (30d)	28.62 (23.51; 34.45)	0.026 (V3-V1)
V3 (120d)	24.13 (22.5; 29.19)	0.019 (V3-V2)
HDL	mg/dL	*p*-value*
V1 (7d)	49 (42.75; 52.5)	0.156 (V2-V1)
V2 (30d)	45.5 (41.75; 49)	0.014 (V3-V1)
V3 (120d)	45.5 (40; 48)	0.592 (V3-V2)
Triglycerides	mg/dL	*p*-value*
V1 (7d)	124.84 (110.51; 136.51)	0.551 (V2-V1)
V2 (30d)	117.44 (107.88; 126.37)	0.414(V3-V1)
V3 (120d)	133.56 (117.40; 164.08)	0.035 (V3-V2)
Fructosamine	µmol/L	*p*-value*
V1 (7d)	275.32 (178.15; 324.42)	0.975 (V2-V1)
V2 (30d)	246.98 (197.89; 364.40)	0.026 (V3-V1)
V3 (120d)	122.48 (86.54; 208.52)	0.004 (V3-V2)
Glucose	mg/dL	*p*-value*
V1 (7d)	123,80 (112,25; 140,62)	0.198 (V2-V1)
V2 (30d)	116,70 (105,31; 128,99)	0.019 (V3-V1)
V3 (120d)	108,99 (100,46; 113,64)	0.019 (V3-V2)

n = 14. Data represent medians (interquartile interval 25; 75). *Wilcoxon test between visits. *p*-values < 0.05 were considered significant.

general. This would be of crucial importance in efforts to prevent or at least delay the onset of this disease (41). Obesity is an important factor as it can affect sensory systems and other organs, either directly or as a result of associated comorbidities, so an unhealthy metabolic status poses an additional risk (42). In this context, a first layer of analysis focused on factors related to fat metabolism. The mean body mass index of participants affected by SSNHL was described as overweight ($27.37 \pm 4.48\,kg/m^2$). Studies show that high BMI levels may be associated with hearing loss (41), and obesity may be related to atherogenic processes that restrict blood flow in the cochlea, the release of proinflammatory cytokines by macrophage infiltrates, and hypoxia and oxidative stress which may negatively affect the innervation and hair cells in the cochlear microenvironment (42). In addition, adipose tissue plays an important endocrine function mediated by adipokines (43). Adiponectin is an adipokine that acts as a mediator of obesity-related metabolic and vascular diseases, and its imbalance can also affect hearing. The presence of the adiponectin receptor in the inner ear and the use of adiponectin-knockout mice have demonstrated its otoprotective role (44). Increased apoptosis of auditory sensory hair cells and endothelial cells has been associated with a decrease in adiponectin. Low adiponectin levels are also associated with reduced blood flow in the cochlea (45, 46). Our results show that after 120 days, the average adiponectin levels in all patients with SSNHL have decreased compared to visits 1 and 2. These visits (30 days) are the most acute period of manifestation of SSNHL. In our opinion, adiponectin could therefore act systemically and protect as an anti-inflammatory agent (47), as it showed a positive correlation with IL-10 at visit 2 ($r = 0.390$). The situation was similar with IL-10, which was also reduced in V3. The correlations with peroxide ($r = -0.494$) in V3 and with LDL ($r = 0.470$) in V2 and uric acid ($r = -0.497$) in V1 indicate a dynamic of protective relationships that changes during the course of SSNHL. It may act as a modulator of oxidative stress (48), as an LDL binder (49) or protection from uric acid-induced inflammation (50). No direct otoprotective effect can be derived from our results. However, the systemic effect of adiponectin could contribute to a clinical improvement and, consequently, better hearing recovery.

Analysis of the other metabolite parameters revealed an increase in albumin (V3) and a decrease in glucose and HDL (V3). Even when these differences are analyzed, the average values are very close to each other, which we do not consider to be a reduction in the relevant clinical value. Thus, we can assume that the average values of all metabolic parameters over the 120 days of the study showed no significant differences in their mean values. The interpretation of these results must be accompanied by a description of some pre-existing diseases in patients with SSNHL. Of the 30 patients analyzed, 13 had systemic arterial hypertension, 7 had diabetes mellitus and 4 had chronic kidney disease. So if we include BMI and age in this context,

even if serologic analysis shows no significant abnormalities, the clinical profile suggests that metabolic imbalances may be present and acting on SSNHL. Previous studies by our group have shown that microangiopathies are more common in patients with SSNHL when diabetes mellitus, arterial hypertension and dyslipidemia are also present (51). Other factors such as chronic kidney disease (52), history of myocardial infarction and a higher risk of stroke in SSNHL (compared to controls) (53) suggest a possible vascular involvement in the its pathogenesis. Changes in the microstructure of the stria vascularis, hyperviscosity, alterations in endothelial function and the formation of atherosclerotic plaques are processes that play an important role in hearing loss (3). From our results, we can conclude that hyperlipidemia may not be acutely involved in the pathogenesis of SSNHL, as the lipid profile did not change during the study. The effects of the lipid profile leading to lesions in the inner ear take longer to manifest and are likely to be progressive and may act synergistically with inflammatory processes that may culminate in SSNHL.

Inflammation is a critical component in the pathogenesis of SSNHL (54, 55). Understanding this process at local and systemic levels is fundamental to a better understanding of symptoms, prognosis and hearing recovery. Therefore, systemic inflammatory markers may be useful for monitoring the development and progression of SSNHL over time (56, 57). In this context, this study investigated cytokines with pro-inflammatory and anti-inflammatory effects during the course of SSNHL over 120 days. In an initial analysis, 2 cytokines showed no changes across the 3 visits, namely IL-1F7 and IL-4. Interleukin 6 did show a statistically significant increase between visit 1 and visit 3, but the mean values found were very close to each other (26.66 pg./mL in V1 and 27.29 pg./mL in V3), which led us to believe that there was no change over time. Interleukin (IL) 1F7, also known as IL-37, has an important anti-inflammatory and immunosuppressive effect. Systemic alterations of IL-1F7 have been described in cancer (58), central nervous system disorders (59) and other autoimmune and inflammatory diseases (60). Although IL-1F7 has an effective effect on pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (61), our results showed that IL-1F7 did not change at any of the time points analyzed and showed no correlation with other inflammatory cytokines. Only at visit 3 did it show a correlation with uric acid ($r = 0.404$), a result that was probably not related to SSNHL. In contrast to IL-1F7, the TH2 cytokines IL-4 and IL-6 have already been described as being involved in processes associated with SSNHL (26, 62). It is noteworthy that although our results showed no significant changes over the course of the visits, both cytokines showed a positive correlation at visit 2 ($r = 0.547$). The presence of these cytokines indicates pro-inflammatory processes, with IL-6 being associated with the response to infection and tissue damage (63) and IL-4 with the production of immunoglobulin E, regulation of cell proliferation and apoptosis (62). Our results suggest that IL-4 correlates not only with IL-6 but also with other pro- and anti-inflammatory cytokines across the 3 visits. The stimulation of IL-4 production in the context of SSNHL could therefore correlate with the general clinical condition of affected patients and interact with various inflammatory and metabolic aspects. For example, IL-4 shows a correlation with IFN-γ and TNF-α at visit 1 ($r = 0.642$ and 0.599, respectively), which would indicate a joint effect of proinflammatory cytokines in the acute phase of SSNHL. The results of the correlation with IL-2 at visit 1, 2 and 3 ($r = 0.472$, 0.435, and 0.682, respectively) suggest a common effect of different inflammatory showing a higher correlation in visit 3. However, the variability of interactions with other cytokines/metabolites also allows the interpretation that IL-4 is related to other processes not exclusively associated with SSNHL. This suggests that IL-4 may play a wide-ranging role in the maintenance of immune regulation and does not change between visits. Although the systemic presence of IL-4 has been described in patients with SSNHL (62), the function of this cytokine in the inner ear is still unknown. The effect of interleukin-6, on the other hand, has been described both in peripheral blood and in cochlear studies. For example, the relationship between IL-6 and the activation of the NF-kB signalling pathway has been described, as well as the relationship between the risk of vascular occlusion and the action of this cytokine (64), an increase in lesions in the human blood-labyrinth barrier model (65) or even an improvement in inflammatory parameters when this IL-6 cytokine is blocked in animal models (66). The quantification of this cytokine in peripheral blood still shows contradictory results, and although some studies have shown changes in this cytokine during the course of SSNHL (64), no direct correlation has yet been established between the levels found and disease progression (67). The possible correlation with IL-4 in V2 could indicate a synergistic effect within an immunoregulatory system. However, the fact that IL-6 shows no significant serologic changes over time could mean that its effect is limited to the inner ear in patients with SSNHL.

Interleukins 2 and 5 showed a decrease after 30 days with a subsequent increase in V3. These cytokines, which act through different pathways (IL-2 in TH1 and IL-5 in TH-2), are associated with hearing loss in a few articles. Interleukin 2 is secreted by activated T lymphocytes (both CD4+ and CD8+) and plays an important role in the proliferation of T and B lymphocytes by inducing effector T lymphocytes as well as generating Tregs that can prevent autoimmunity (68). In rats injected with IL-2 into the inner ear (round window), sensorineural hearing loss gradually developed within 5–7 days. Although it proved to be reversible, the inflammatory process impaired cochlear function (69). Interleukin-2 activates the endothelial cells of the modiolar spiral vein in the area of the cochlea so that they increasingly express ICAM-1 and take on the characteristics of high endothelial venules. These morphological changes allow the recruitment of leukocytes from the bloodstream, which in some situations trigger an inflammatory process that may be accompanied by the formation of fibrosis, which, if not absorbed, can form a fibro-osseous matrix that eventually leads to degeneration of the inner ear (70, 71). The association between IL-2 levels and progression of SSNHL has been described in patients treated with corticosteroids for 8 days (64), but it was not possible to discern a pattern between fluctuations in IL-2 levels during SSNHL treatment and disease progression. Our results are based on a longer analysis period (120 days), with corticosteroid treatment lasting 30 days. It is possible that this reduction in IL-2 levels in V2 is related to a systemic regulatory effect that may have been influenced by the corticosteroid treatment rather than an effect in the cochlea. IL-5 is produced by TH2 lymphocytes, mast cells and innate lymphoid cells. When activated by various environmental stimuli, these cells release this interleukin, which promotes eosinophil activation, maturation, survival and migration (72). The quantification of IL-5 in the patients in this study aimed to characterize a possible link between the worsening of inflammatory parameters (especially those related to allergens) and SSNHL. Interestingly, this cytokine maintained a significant positive correlation with IFN-γ and TNF-α in V1 ($r = 0.586$ and 0.568, respectively), which then disappeared in V2. The positive

correlation is resumed later, after 120 days, with TNF-α ($r = 0.586$). These results suggest that systemically IL-5 acts synergistically with other inflammatory pathways that may influence the progression of SSNHL. Locally, no patient had middle ear manifestations of eosinophilic otitis, a condition strongly associated with the action of eosinophils and IL-5 (73).

Interleukin-10 plays a key role in the modulation of inflammation and the maintenance of cellular homeostasis. Its anti-inflammatory effect protects the body from an uncontrolled immune response. Its immunomodulatory role leads to important effects in diseases caused by a hyperinflammatory state, such as infectious diseases or cancer (74). It is increasingly recognized that inflammation in the cochlea contributes to the pathophysiology of sensorineural hearing loss. The local effect of IL-10 is evidenced by the presence of labeled cells in different regions of the inner ear following the induction of inflammatory processes by lipopolysaccharides in animal models (75). The quantification of IL-10 in the peripheral blood of patients affected by SSNHL has already been described in some studies, but this cytokine did not play a relevant role (25, 76). In our context, it is noteworthy that IL-10 levels decrease after 120 days, i.e., after the acute inflammatory process. Its correlation with adiponectin in V2 and especially with TNF-α in V1 ($r = 0.410$) suggests that the anti-inflammatory effect might be present throughout the treatment/time and has a systemic immunomodulatory effect during this period.

TNF-α is a cytokine with important key functions in various cellular processes, such as the maintenance of cellular homeostasis and the regulation of pro-inflammatory responses (77) and which plays an important role in the inner ear in the context of hearing loss (78). This cytokine may act in signaling pathways related to cell death (79), the process of differentiation of monocytes into mature dendritic cells (25), blood flow in the cochlea (80), and also in noise-induced hearing loss (81). Our results suggest that serum TNF-α levels decrease significantly between the acute phase (median 22.91 pg./mL) and V3 (median 10.34 pg./mL). In addition, the correlations with other cytokines (IL-2, 4, 5, 10 and IFN-γ) suggest that in the context of SSNHL, systemic TNF-α may be a parameter that should be analyzed during treatment. Some results support our findings, such as the fact that patients with immune-mediated sensorineural hearing loss had TNF-α levels above 18.8 pg./mL, with a greater than 97% positive predictive value (82). The reduction of TNF-α over time/treatment has also been described in patients with SSNHL between days 1 and 8, with a strong correlation between positive therapeutic outcomes and TNF-α reduction (64). In our analysis, we categorized the patients according to the outcome in terms of hearing recovery (Tables 2, 3). Interestingly, TNF-α levels decreased over time in patients who showed some improvement in hearing. However, in patients who did not recover their hearing, the levels did not differ significantly between visits. These results suggest a possible effect of TNF-α in relation to hearing recovery. The heterogeneity of the levels found for TNF-α in the peripheral circulation of patients with SSNHL (57, 76, 83) makes it necessary to further investigate the role of this cytokine, from the nature of its action (systemic and local effect) to its role in SSNHL (main effect or as part of an inflammatory chain).

IFN-γ is produced by NK cells and CD4 and CD8 T cells. One of the main functions of IFN-γ is the activation of macrophages to enhance phagocytosis, tumoricidal activity and intracellular clearance of pathogens, especially bacteria and fungi. Reactive oxygen and nitrogen intermediates and other inflammatory mediators are produced by macrophages in response to IFN-γ (84). Similar to the levels found for TNF-α, IFN-γ also showed a significant decrease between V1 and V2 in all patients with SSNHL. It was noteworthy that these two cytokines showed a positive correlation ($r = 0.492$) in the most acute phase of the process (V1). These results are consistent with those previously described in animal models evaluating inner ear injury, where IFN-γ locally increases the susceptibility of cochlear sensory cells to TNF-α cytotoxicity via JAK1/2-STAT1 signaling and caspase-1 activation (85). Its positive correlation with IL-4 and IL5 in the most acute phase of SSNHL demonstrates its importance for systemic inflammatory processes.

The complexity of the factors and the possibly different etiopathogenesis, which are still classified as idiopathic, may play a role in the progression of SSNHL. This means that the investigative approach is becoming broader, suggesting that early clinical phenotyping is necessary to select the appropriate laboratory tests to be performed in the etiologic investigation of this symptom. Our aim was to assist such selection by describing several inflammatory and metabolic parameters and relating them to hearing improvement over 120 days in patients with SSNHL.

Our results show that there is a considerable change in serologic cytokine levels in the acute phase of manifestation of SSNHL and a parallel can be established between systemic changes and improvements in hearing, especially when analyzed over time and as a result of outcomes related to hearing improvement. The use of IFN-γ, TNF-α and adiponectin may shed light on the clinical improvement in these patients, as these cytokines play a role in both the onset and 120 days of the study. The effect of TNF-α stands out because its modulation is not only part of the context of SSNHL implantation, but also of a possible differential effect in hearing recovery. So far, it has not been possible to identify a single biomarker that covers the multi-etiology of SSNHL symptoms. Further research into the role of inflammatory cytokines could be useful to obtain information on the relationship between systemic parameters and the inner ear and consequently to understand hearing recovery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee for Research of the Escola Paulista de Medicina/Universidade Federal de São Paulo (EPM/UNIFESP) under protocol number 4.507.315. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration,

Writing – original draft. KP: Conceptualization, Investigation, Methodology, Writing – review & editing. TS: Conceptualization, Investigation, Methodology, Writing – review & editing. MaS: Conceptualization, Investigation, Methodology, Writing – review & editing. FH: Conceptualization, Investigation, Methodology, Writing – review & editing. MiS: Data curation, Formal analysis, Visualization, Writing – review & editing. CF: Data curation, Formal analysis, Visualization, Writing – review & editing. LN: Data curation, Formal analysis, Visualization, Writing – review & editing. AB: Conceptualization, Data curation, Formal analysis, Visualization, Writing – review & editing. NO: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1382096/full#supplementary-material

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EDITED BY
Lisheng Yu,
Peking University People's Hospital, China

REVIEWED BY
Hongyang Wang,
People's Liberation Army General Hospital, China
Manuel Oliva Domínguez,
Costa del Sol Hospital, Spain

*CORRESPONDENCE
Jing Luo
✉ luojing668yeah@163.com
Ping Tang
✉ 19923322139@163.com

†These authors share first authorship

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Causal associations of white blood cell count and sudden sensorineural hearing loss: a bidirectional and multivariable Mendelian randomization study

Ling Zhang[1†], Jialei Chen[2,3,4†], Shixun Zhong[2], Jing Luo[5,6*] and Ping Tang[1*]

[1]Department of Otorhinolaryngology, The People's Hospital of Yubei District of Chongqing, Chongqing, China, [2]Department of Otolaryngology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [3]Department of Pathology and Pathophysiology, Chongqing Medical University, Chongqing, China, [4]Molecular Medicine and Cancer Research Center, College of Basic Medical Sciences, Chongqing Medical University, Chongqing, China, [5]Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [6]Department of Pathology, Chongqing Medical University, Chongqing, China

Background: Numerous compelling observational studies have demonstrated a plausible correlation between the white blood cell count and the susceptibility to sudden sensorineural hearing loss (SSNHL). Nevertheless, the exact causal relationship between these two factors remains ambiguous. The objective of our study was to assess the causal impact of white blood cell count on sudden sensorineural hearing loss through the implementation of a bidirectional and multivariable Mendelian randomization (MR) methodology.

Methods: Genetic data pertaining to white blood cell count were acquired from the Blood Cell Consortium, encompassing a total of 563,946 subjects. Concurrently, summary data on sudden sensorineural hearing loss were sourced from a Genome-Wide Association Study (GWAS), involving 196,592 participants, comprising 1,491 cases and 195,101 controls. The primary method employed for MR analysis was the Inverse Variance Weighted method (IVW), while sensitivity analysis utilized the Weighted Median method, MR-Egger method, and MR-PRESSO method.

Results: In IVW method, genetically predicted elevated lymphocyte cell count demonstrates an effective reduction in the risk of sudden sensorineural hearing loss (odds ratio = 0.747, 95% CI = 0.565–0.987, $p = 0.04$). These findings remain consistent in multivariate MR analysis, even after adjusting for monocyte cell count and neutrophil cell count levels (odds ratio = 0.929, 95% CI = 0.867–0.995, $p = 0.036$). However, there is no discernible evidence supporting a direct causal relationship between monocyte cell count and neutrophil cell count levels and the occurrence of SSNHL.

Conclusion: Within the normal range, higher lymphocyte cell count levels exhibit a potential protective effect against SSNHL. Meanwhile, no direct causal relationship are identified between monocyte cell count and neutrophil cell count levels and the risk of SSNHL.

KEYWORDS

sudden sensorineural hearing loss, lymphocyte cell count, monocyte cell count, neutrophil cell count, Mendelian randomization

1 Introduction

Sudden sensorineural hearing loss (SSNHL) represents an otological emergency characterized by an unknown etiology influenced by diverse factors. It is defined as the abrupt onset of unexplained sensorineural hearing loss within a 72 h timeframe, involving a hearing loss exceeding 30 dB across a minimum of three consecutive frequencies (1). Epidemiological studies indicate that in industrialized nations, the annual incidence rate of SSNHL ranges from 5 to 400 cases per 100,000 individuals (2). SSNHL typically manifests as a unilateral, isolated condition, displaying distinct clinical characteristics in terms of hearing loss severity, accompanying symptoms, and prognosis. Numerous investigations suggest a close association between vascular dysfunction (3), infectious diseases (4), autoimmune conditions (5), and other factors with the onset and progression of SSNHL, signifying its likely multifactorial origin rather than a singular cause. The global incidence of SSNHL is escalating rapidly, and as of yet, no proven or universally recommended treatment exists (6). Consequently, otologists face an imperative need to identify biomarkers for predicting the occurrence and progression of SSNHL. This is essential for the development of more effective prevention and treatment strategies tailored to address this challenging condition.

In recent times, the etiological investigation of sudden sensorineural hearing loss has prominently centered around chronic inflammation (7). The cochlea's blood supply predominantly relies on a single cochlear artery, rendering it susceptible to damage from ischemia and hypoxia. Given this delicate anatomical condition, chronic inflammation induced by various factors may precipitate vascular dysfunction and an immune response in the cochlea, ultimately resulting in cochlear ischemia and injury (8). White blood cells and their constituents serve as cost-effective and valuable inflammatory markers in clinical practice. White blood cell count are widely employed as predictive markers for various diseases, such as diabetes (9), kidney disease (10), and cardiovascular conditions (11). Elevated white blood cell count are frequently observed in patients with SSNHL. However, it is essential to note that these findings are derived from clinical observations, introducing the potential for selection bias, confounding factors, and the risk of reverse causality. Consequently, the causal relationship between white blood cell count and SSNHL remains an open question. Unraveling this causal connection is pivotal in formulating effective prevention and treatment strategies for SSNHL.

Mendelian randomization employs genetic variants as instrumental variables to explore the causal relationships between disease-related risk factors (12). This emerging epidemiological methodology effectively mitigates potential confounding factors and interferences, enabling the derivation of more robust causal conclusions compared to traditional observational studies (13). Previous MR analyses have successfully elucidated the causal connections between thyroid hormones (2), blood lipids (14), and sudden sensorineural hearing loss. The present study employs Bidirectional and multivariate MR analysis to assess the association between genetically predicted white blood cell count and the corresponding SSNHL risk. Three specific white blood cell count of interest—lymphocyte cell count, neutrophil cell count, and monocyte cell count—have been identified, demonstrating associations with infection risk and detectable through genetic instruments. This endeavor aims to offer novel perspectives and insights into the etiology of SSNHL.

2 Method

2.1 Study design

We conducted a bidirectional and multivariate MR study utilizing Genome-Wide Association Study (GWAS) data for both white blood cell count and sudden sensorineural hearing loss. To minimize population stratification bias, both the exposure and outcome cohorts were confined to individuals of European ancestry. The robust MR design hinges on three fundamental assumptions: (1) The correlation hypothesis posits a strong correlation between genetic variation and exposure factors, in this case, white blood cell count. (2) The independence hypothesis assumes that gene variation is independent of confounding factors that might influence both exposure and outcome. (3) The exclusivity hypothesis suggests that genetic variation impacts the outcome solely through exposure and not through alternative pathways, specifically SSNHL (15). Figure 1 offers an overview of the design employed in the bidirectional and multivariate MR study of white blood cell count and SSNHL. Given that this study involved the reanalysis of previously published data, no additional ethical approval was deemed necessary.

2.2 GWAS data of white blood cell count

The genetic data for white blood cell count were sourced from the Blood Cell Consortium (16), encompassing a total of 563,946 subjects included in this study. These data are publicly accessible and downloadable from Genome-Wide Association Study websites. Their respective GWAS IDs are ieu-b-31 (monocyte cell count), ieu-b-32 (lymphocyte cell count), and ieu-b-34 (neutrophil cell count).

2.3 GWAS data of SSNHL

Genetic data related to sudden sensorineural hearing loss were acquired from the publicly accessible Genome-Wide Association Study (GWAS) database, specifically identified with the entry number "finn-b-H8_HL_IDIOP." The study involved a total of 196,592 participants, comprising 1,491 cases and 195,101 controls (17).

2.4 Instrumental variable selection

Based on the GWAS results for white blood count, a meticulous screening of single nucleotide polymorphisms (SNPs) closely associated with white blood count and achieving genome-wide significance ($p < 5 \times 10^{-8}$) was conducted (16). However, during the reverse MR analysis, considering the limited sample size and number of SNPs, we loosened the association threshold to select SNPs related to SSNHL, setting the significance level at $p < 5 \times 10^{-6}$ (17). These selected SNPs were subsequently utilized as IVs in MR analysis (18). The criteria for IVs selection in MR analysis were as follows: (1) To mitigate estimation bias stemming from weak IVs, the equation $F = (R^2$

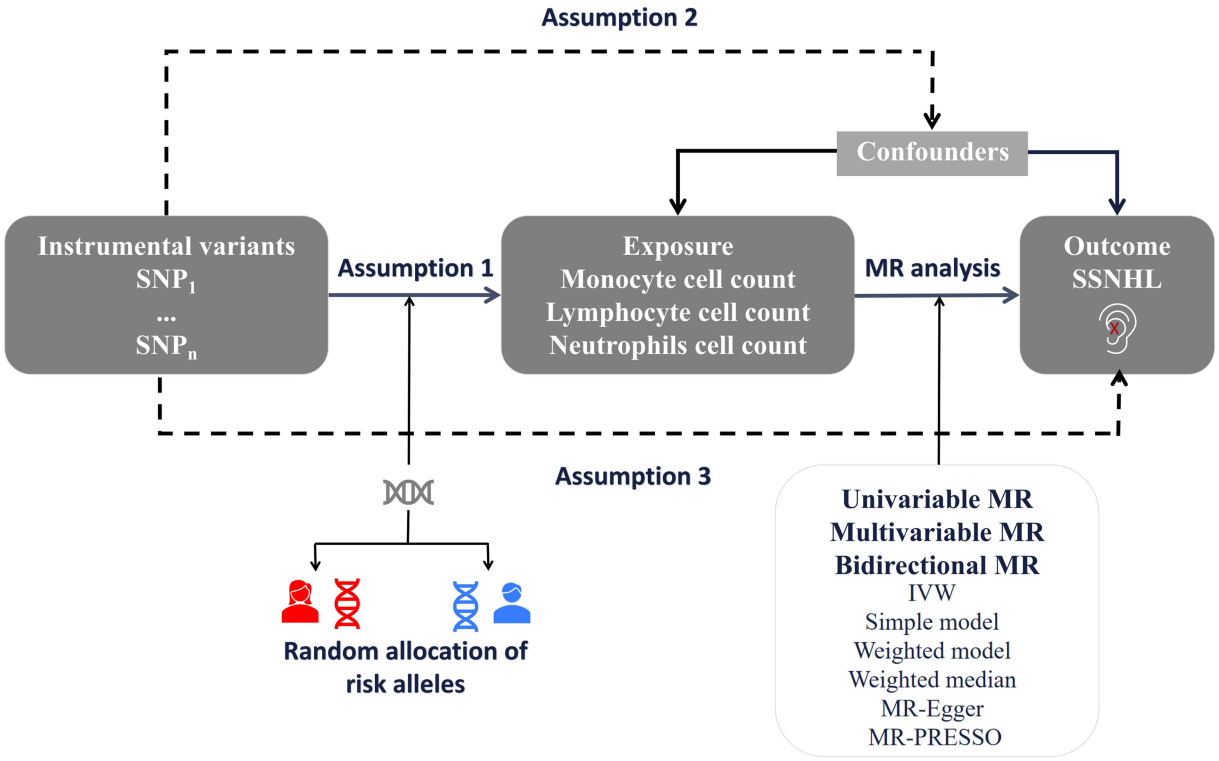

FIGURE 1
A framework design for bidirectional and multivariable MR analyses. Assumption 1: genetic variants are associated with exposure. Assumption 2: genetic variants are not associated with any know or unknown confounders. Assumption 3: Genetic variants should only affect the risk of outcome through exposure. SSNHL, sudden sensorineural hearing loss; MR, Mendelian randomization.

× (n−2))/(1−R2) was employed to evaluate the correlation between instrument strength and exposure. A significant correlation was considered when $F \geq 10$. The estimated R^2 for IVs was calculated using the equation 2EAF (1−EAF)*β^2, where EAF represents the frequency of the effector allele, and β represents the estimated genetic effect on exposure factors. (2) To address the impact of linkage disequilibrium, efforts were made to ensure that the r^2 value was less than 0.001 at a distance of 10 MB, and palindromic SNPs with moderate allele frequencies were excluded. (3) In adherence to the exclusivity hypothesis (IV variants only affecting SSNHL through white blood cell count), all SNPs associated with hearing loss ($p < 1 \times 10^{-5}$) were excluded from each analysis (19, 20). The PhenoScanner database[1] was utilized to eliminate all known phenotypes associated with any genetic tools considered in our analysis (21). In Supplementary Table S1, a comprehensive summary is provided, detailing the relationship between exposure, SNPs, and their associations with outcomes.

2.5 Univariate Mendelian randomization analysis

Utilizing the IVW method as the primary analysis, we employed a range of complementary Mendelian randomization tests to rigorously examine causal effects and correct for the impact of horizontal multiplicity (22). These included the weighted median method, the simple mode method, the MR-Egger regression method, and the MR-pleiosis residuals and outliers method (MR-PRESSO) (23–25). In essence, the IVW method effectively combines the causal effects of individual single SNPs. However, it is crucial to emphasize that this method yields unbiased estimates of causal effects only under the condition that all SNPs are devoid of invalid IVs and horizontal pleiotropy. In response to this concern, additional sensitivity analyses were performed using MR Egger and weighted median as complementary methods to IVW. The MR-Egger method serves to assess the presence of horizontal pleiotropic effects among all SNPs through the intercept, providing a reliable and unbiased evaluation of causality. A p-value below 0.05 indicates the existence of horizontal pleiotropy. The weighted median method, relying on the median effect of all available genetic tools, ensures consistency in potential causality if at least half of the genetic variation adheres to assumptions. The MR-PRESSO method, designed to identify and eliminate outliers, generates relatively unbiased estimates while detecting potential horizontal pleiotropic effects through global testing. Cochran's Q test was applied to assess SNP heterogeneity, with a p-value >0.05 for Cochran's Q test indicating no heterogeneity. Additionally, a leave-one-out analysis was conducted, systematically removing one SNP at a time to evaluate whether bias in MR estimates was driven by a single SNP. Reverse MR analysis explored the possibility of sudden sensorineural hearing loss acting as a risk factor for white blood count. To ensure the validity of bidirectional MR, genetic instruments

1 http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner

exposed in bidirectional analysis (white blood count or SSNHL) were scrutinized for independence, revealing no overlapping SNPs or SNPs in high linkage disequilibrium. Given that genotypes are determined at conception in accordance with Mendel's laws of segregation, the likelihood of reverse causation is significantly diminished (26).

2.6 Multivariable Mendelian randomization analysis

Multivariate Mendelian randomization operates analogously to independently assessing the effects of various intervention modalities in a randomized controlled trial. In this methodology, genetic instruments may exhibit associations with multiple risk factors, provided they meet the prerequisite of being equivalent instrumental variables (27). Given the close genetic correlation observed between monocyte cell count, lymphocyte cell count, and neutrophil cell count, coupled with their analogous associations with SSNHL in observational studies. In this analysis, we included all instrumental variables for monocyte cell count, lymphocyte cell count, and neutrophil cell count to assess their independent impacts on SSNHL. The SNPs employed in multivariate MR analysis were derived from combinations of instrumental variables identified in univariate MR analyses for each exposure (28). Statistical significance in estimating the causal effect of exposure was determined with p-values less than 0.05. All statistical analyses were carried out using the R package "TwoSampleMR2 (version 0.5.6)" and "Mendelian Randomization" (version 0.5.1) in R (version 4.2.1). For a more detailed description, please refer to the following link[2] (29).

3 Result

3.1 Univariate MR analysis of the causal relationship between white blood cell count and SSNHL

The F-statistics for each SNP included in the analysis exceeded 10 (Supplementary Table S1). The results of the univariate MR analysis, after assessing and removing SNPs associated with confounding, are depicted in Figure 2. The MR analysis utilizing the IVW method revealed a significant causal relationship between lymphocyte cell count and the risk of sudden sensorineural hearing loss (OR = 0.83, 95%CI = 0.70–0.99, $p = 0.04$). Similarly, risk estimates from MR-Egger regression and weighted median methods exhibited similar trends, although these associations did not reach statistical significance (Figure 3A). p-values obtained from the Cochran Q tests for MR-Egger (Cochrane's Q = 438.6, $p = 0.73$) and IVW (Cochrane's Q = 438.7, $p = 0.74$) were greater than 0.05, indicating no heterogeneity in the results. The global test for MR-PRESSO (P Global Test = 0.71) and Egger_intercept (−0.0013) and the p values derived from Egger intercepts (0.75) indicated that no anomalous instrumental variables contributed to the effect of multiplicity in the overall MR estimates. Leave-one-out sensitivity analyses affirmed the robustness of the conclusion (Figure 3B). However, no evidence supporting a causal relationship was found between monocyte cell count (IVW, OR = 0.89, 95% CI = 0.77–1.02, $p = 0.10$) and neutrophil cell count (IVW, OR = 1.11, 95% CI = 0.92–1.34, $p = 0.28$) and SSNHL. Finally, a reverse MR analysis was performed to evaluate the causal effect of SSNHL on white blood cell count. After applying the aforementioned criteria, 14 SNPs significantly associated with SSNHL were identified (Supplementary Table S1). In our reverse MR analysis using the IVW method, no significant evidence supporting a causal relationship between SSNHL and the risk of white blood count levels was found (Figure 3C).

3.2 Multivariate MR analysis of the causal relationship between white blood cell count and SSNHL

Building upon the robust correlation observed in observational studies between lymphocyte cell count, monocyte cell count, and neutrophil cell count, we conducted multivariate MR analyses to investigate their independent impacts on SSNHL. The findings of the multivariate MR analysis demonstrated that even after adjusting for monocyte cell count and/or neutrophil cell count, results consistent with the univariate MR analysis were attained (Figure 4). Lymphocyte cell count exhibited a negative association with the risk of developing sudden sensorineural hearing loss.

4 Discussion

Comprehending the pathogenesis of a disease is a fundamental prerequisite for the effective treatment of patients. Nevertheless, the precise pathophysiological mechanisms underlying sudden sensorineural hearing loss remain elusive. It is postulated that SSNHL may arise from a combination of local and systemic factors, with thrombosis and infection considered the most common causes. Notably, Chinese and German guidelines attribute thrombosis as the principal pathophysiological feature of SSNHL (30). However, Weng (31) and Qiao (32) contested the thrombosis hypothesis, pointing out the absence of a gender-based incidence difference. Recent compelling evidence has significantly shifted focus towards the role of chronic inflammation in SSNHL. Studies indicate that chronic inflammation induced by bacteria or viruses can lead to microvascular damage and atherosclerosis. Given the cochlea's unique blood supply, primarily reliant on a single labyrinthine artery without collateral circulation, these factors directly elevate the risk of cochlear ischemia. The cochlear hair cells, characterized by high oxygen consumption, render the cochlea particularly susceptible to hypoxia, heightening sensitivity to alterations in blood circulation (8).

Biomarkers associated with inflammation in sudden sensorineural hearing loss patients encompassed elevated neutrophil, monocyte, and lymphocyte cell count, while composite markers linked to inflammation in these patients included heightened Neutrophil-to-Lymphocyte Ratio (NLR) and Monocyte-to-Lymphocyte Ratio (MLR) (33). Despite recent meta-analyses consistently indicating significantly higher neutrophil cell counts in SSNHL patients compared to the normal group (34), Sun (35) and Cao's (36) study distinctly highlights that this elevation is confined to a specific subgroup of SSNHL

2 https://mrcieu.github.io/TwoSampleMR/37

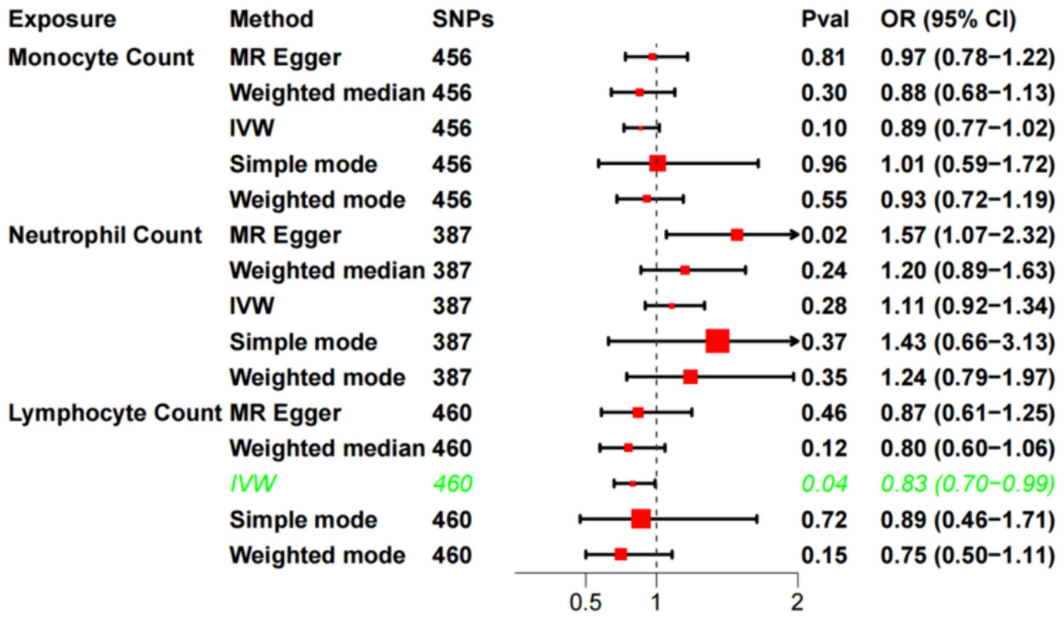

FIGURE 2
Univariate MR analysis of the causal relationship between white blood cell count and SSHNL.

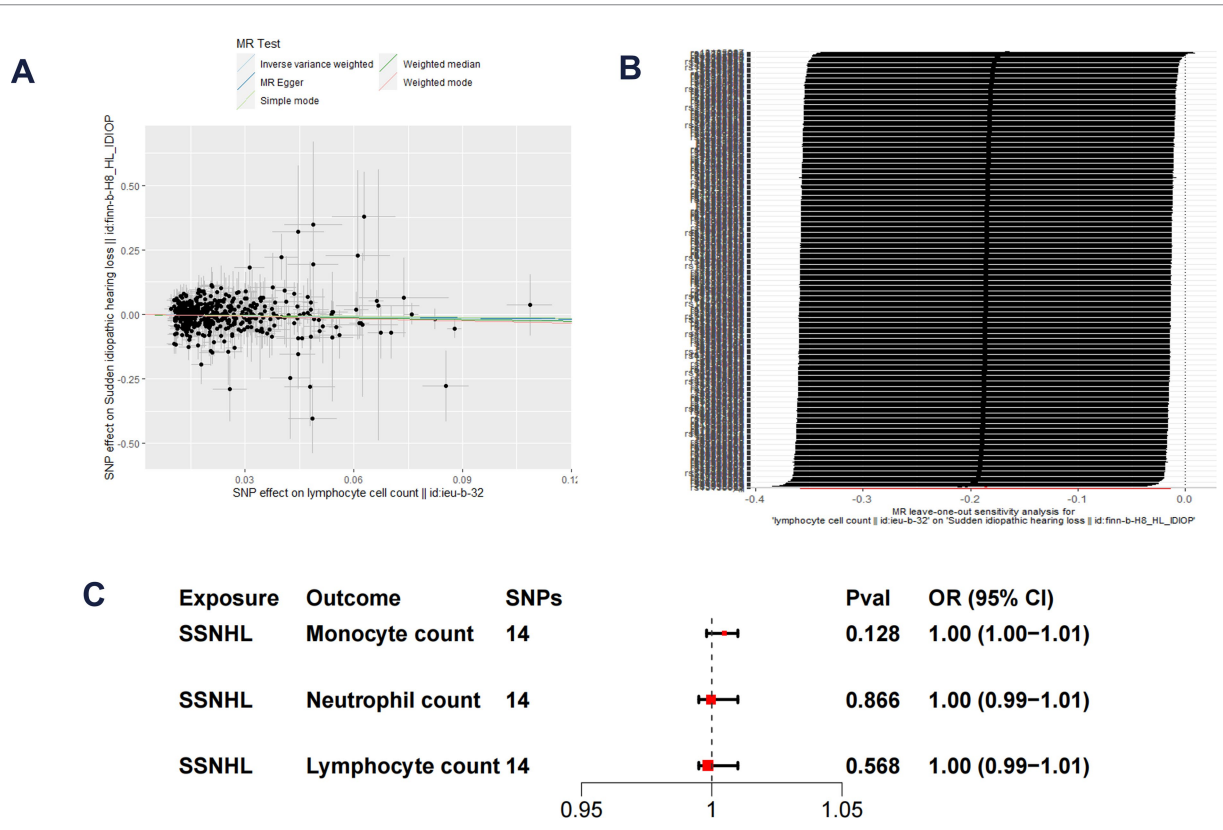

FIGURE 3
(A) Scatter plot demonstrate the effect of each lymphocyte cell count-associated genetic variant and SSNHL on the log-odds scale. **(B)** Leave-one-out plots for the MR analyses of lymphocyte cell count and SSNHL. **(C)** Reverse MR analysis of SSNHL and white blood cell count.

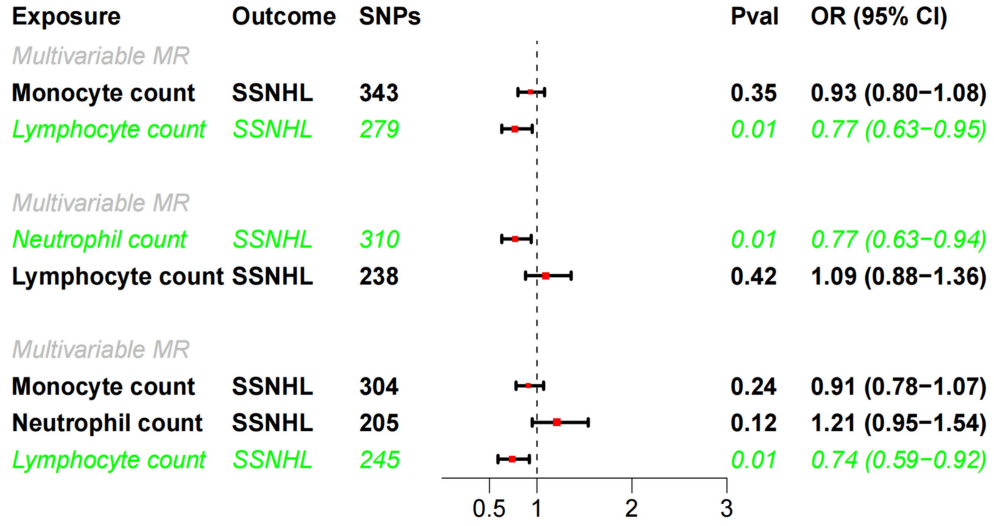

FIGURE 4
Multivariate MR analysis of the causal relationship between white blood cell count and SSHNL.

patients. In our study, we found that monocyte cell count was not a risk factor for SSNHL. Koçak's (37) study aligns with our findings, revealing no difference in monocyte cell count between the control and SSNHL groups. Interestingly, most studies demonstrate a significantly elevated monocyte-to-lymphocyte ratio in SSNHL patients compared to the control group (33, 34). Most studies have found a decrease in lymphocyte count in patients with SSNHL, with a high lymphocyte count being a protective factor against the risk of SSNHL, which aligns with our findings (35, 38, 39). To our knowledge, nearly all studies have reported a significantly higher NLR or (and) MLR in SSNHL patients than in the normal group. Except for lymphocyte cell count, no significant difference in any single inflammatory marker was identified in the prognosis of SSNHL (33). Current research on the etiology of SSNHL is predominantly focused on chronic inflammation (7). It is believed that chronic inflammation induced by bacteria or viruses can lead to microvascular damage, endothelial dysfunction, and atherosclerosis, thereby increasing the risk of cochlear ischemia (40–42). Lower lymphocyte counts are associated with an inflammatory response (43). Furthermore, an elevated NLR in the periphery indicates the occurrence of atherosclerosis and local microartery inflammation. In patients with SSNHL, a higher peripherally measured NLR suggests the presence of local microvascular inflammation, with the inflammation affecting the labyrinthine artery (44). These findings collectively indicate a profound association between the inflammatory response mediated by lymphocyte count and SSNHL (32). The varied conclusions across studies may arise from the categorization of SSNHL into at least four distinct subtypes, each with a unique pathogenic mechanism. Unfortunately, only a limited number of studies have conducted subgroup-specific analyses.

The design of this study offers notable advantages. Primarily, it leverages freely accessible GWAS data, thereby substantially reducing research costs. Nevertheless, it is essential to acknowledge several potential limitations in our study. Firstly, single blood inflammation markers are susceptible to various factors. In contrast, composite markers such as NLR and MLR are relatively stable, easily measurable, and cost-effective. Unfortunately, due to limitations in available pooled white blood cell count data, we were unable to conduct subgroup-specific Mendelian randomization analyses. Secondly, sudden sensorineural hearing loss comprises at least four subgroups with different pathogenic mechanisms. However, limitations in available SSNHL summary data hindered the performance of subgroup-specific MR analyses. Finally, the study population predominantly consisted of individuals of European descent, necessitating caution in interpreting the generalizability of our findings to other populations. Future research endeavors will encompass diverse populations and consider the impact of specific subgroups, thereby advancing our comprehension of the causal relationship between blood inflammatory indicators and SSNHL.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

LZ: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review

& editing. JC: Conceptualization, Data curation, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. SZ: Funding acquisition, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. JL: Data curation, Investigation, Project administration, Resources, Validation, Writing – original draft, Writing – review & editing. PT: Data curation, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1387244/full#supplementary-material

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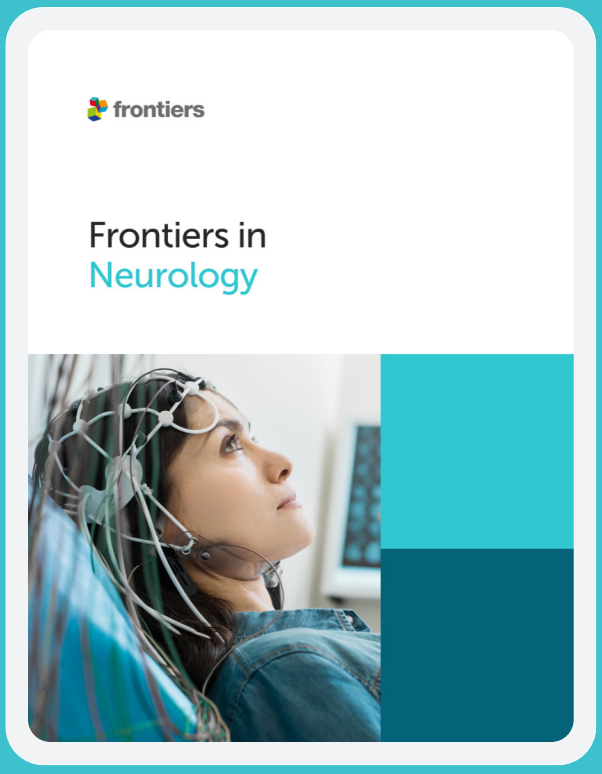

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