International Journal of Audiology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iija20

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To cite this article: Yuzhong Zhang, Qiong Wu, Libo Liu, Yu Zhao, Qingqing Dai, Jose A. Lopez-Escamez & Qing Zhang (13 Jan 2025): Hearing loss rather than vestibular loss identifies patient subgroups with different outcomes in Meniere's disease, International Journal of Audiology, DOI: 10.1080/14992027.2025.2450657

To link to this article: https://doi.org/10.1080/14992027.2025.2450657

Published online: 13 Jan 2025.

INTERNATIONAL JOURNAL OF AUDIOLOGY
https://doi.org/10.1080/14992027.2025.2450657

ORIGINAL ARTICLE

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Hearing loss rather than vestibular loss identifies patient subgroups with different outcomes in Meniere's disease

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ABSTRACT

Objective: This study investigates the relationship between Meniere's disease (MD) duration and both hearing thresholds and vestibular dysfunction.

Design: Retrospective cohort study. First, the relationships between MD duration and pure-tone audiometry thresholds for each frequency, the canal paresis (CP) ratio, and the vestibulo-ocular reflex (VOR) gain were analysed. Second, clinical characteristics, CP values, and VOR gains were compared between patient groups with low and high hearing thresholds to determine whether they exhibited different clinical presentations.

Study sample: The study included 69 patients diagnosed with unilateral MD within a duration of 10 years. A hearing dataset from 306 MD Spanish patients was used to cluster patients according to the hearing profile overtime.

Results: The thresholds at 250–2000 Hz frequencies increased with the duration of the disease. Conversely, vestibular function tests were not related to the duration of MD. Additionally, no statistically significant differences were observed in clinical characteristics, CP values, or VOR gain between patient groups with low and high hearing thresholds.

Conclusions: Hearing loss involves all frequencies in most patients and hearing outcome, rather than vestibular loss, may define patient subgroups in MD. Moreover, not all patients with MD experience hearing loss progression as the duration of the disease increases.

ARTICLE HISTORY
Received 15 August 2024
Revised 22 December 2024
Accepted 3 January 2025

KEYWORDS
Meniere's disease; hearing; vestibular function; duration; clinical characteristics

Introduction

Meniere's disease (MD) is characterised by recurrent episodes of spontaneous vertigo typically accompanied by fluctuating sensorineural hearing loss (SNHL), tinnitus, and/or aural fullness (Lopez-Escamez et al. 2015). The histopathological finding associated with MD, endolymphatic hydrops, results from different mechanisms including genetic and immunological factors that damage the inner ear (Frejo and Lopez-Escamez 2023; Gallego-Martinez and Lopez-Escamez 2020; Sajjadi and Paparella 2008). The diagnosis primarily depends on the clinical symptoms reported by the patient, including confirmed SNHL during the vertigo attack (Lopez-Escamez et al. 2015). Frejo et al. (2017) categorised unilateral MD into five clinical types, according to the presence of familial history and other co-morbidities: (1) classic MD without migraine and autoimmune disorder, (2) delayed MD, (3) familial MD, (4) MD with migraine, and (5) MD with autoimmune features. As a result, the MD phenotype exhibits a large heterogeneity, with partial syndromes such as cochlear-type MD with only cochlear symptoms, or vestibular-type MD with only vestibular symptoms (Iwasaki et al. 2021). Regarding hearing phenotypes, distinct patterns have been observed, including (1) "peaked" curves, (2) downward-sloping curves, (3) upward-sloping curves, (4) bell curves, and (5) flat configurations (Mancini et al. 2002). However, limited research exists on the changes in hearing across all frequencies over time and on the differences in clinical characteristics among patients with MD and different hearing phenotypes.

Currently, there are no specific vestibular tests for MD diagnosis. The two predominant techniques employed to assess the vestibulo-ocular reflex (VOR) are the caloric test and video head impulse test (vHIT). The caloric test is a classic method used to evaluate the low-frequency function of the lateral semicircular canal (LSC) on each side, whereas vHIT can detect the high-

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frequency function of all six semicircular canals (SCs) (Halmagyi et al. 2017; Shepard and Jacobson 2016; Starkov et al. 2021). Numerous studies have revealed a dissociation between the caloric test and vHIT results in patients with MD, wherein most patients exhibiting abnormal caloric responses display normal vHIT gains (Fukushima et al. 2019; McCaslin et al. 2015; Yilmaz et al. 2021). However, few researchers have focused on the relationship between vestibular function and disease duration in patients with MD.

The goal of this study is to determine if hearing or vestibular loss progression can identify MD subgroups. For this, we first analysed the changes in hearing thresholds in MD patients throughout their disease. Subsequently, we performed clustering based on hearing thresholds to identify groups with the best and worst hearing, then compared their clinical characteristics. Finally, we validated our findings using data from a larger Spanish MD cohort.

Materials and methods

Participants

Patients meeting the diagnostic criteria for unilateral definite MD with a duration less than 10 years with audiological, imaging and vestibular tests, and normal A-type tympanogram curves were considered eligible for inclusion. All assessments were conducted during the interictal period following an episode. Of the 282 patients diagnosed with MD, 69 with unilateral MD met the inclusion criteria and were enrolled between August 2019 and December 2022. Patients were administered betahistine mesylate and sodium aescinate to control and reduce the frequency of vertigo episodes. The Institutional Review Board approved this retrospective study (Approval No.: XHEC-SHDC-2021-003), and each study participant provided informed consent at the institutional department. Hearing data were also retrieved from a series of 306 patients with MD previously published (Moleon et al. 2022).

Audiometry

A calibrated two-channel diagnostic audiometer (Otometrics Conera Audiometer, Otometrics, Denmark) was used to assess pure-tone audiometry (PTA) thresholds. Hearing levels were evaluated using the modified Hughson and Westlake procedures. When the PTA threshold at a specific frequency exceeded the upper-scale limit of the audiometer, the estimated threshold for each frequency was calculated by adding 10 dB to the maximum sound level set by the audiometer. Hearing analysis was performed according to MD clinical staging criteria, based on the worst hearing level recorded during the interval period following the most recent six-month.

Caloric test

The caloric test was recorded via video nystagmography using a Chart 200 VEG/ENG system (Otometrics, Denmark). The caloric test procedure has been described in detail previously (Hu et al. 2020). In summary, the participants assumed a supine position with their heads elevated at a 30° angle to the horizon. Bithermal air at temperatures of 24 °C and 50 °C was irrigated for 60 s in each ear, with a 5-min stimulus interval between irrigations. The absolute value of the maximum slow-phase velocity at the culmination phase (°/s) was measured to calculate canal paresis (CP= [(RW + RC) - (LW + LC)]/(RW + RC + LW + LC); CP, canal paresis; RW, right warm; RC, right cold; LW, left warm; LC, left cold), which was defined as abnormal for values >25 (Molina et al. 2006). The calculation of the CP value was unnecessary when the total reaction of the right and left ears to cold and warm air was <12°/s (Shepard and Jacobson 2016).

Video head impulse test (vHIT)

vHIT assessments were conducted using video goggles (ICS Impulse; Otometrics, Denmark) as described previously (Chen et al. 2021). Briefly, the participants were seated and wearing goggles equipped with a speed sensor and a laser. The examiner, seated behind the patients, secured their heads and initiated the test. Following the calibration, the participants were directed to fixate on a target positioned 1 m in front of them. The examiner administered passive, unpredictable, high-velocity, and low-amplitude (10–20°) head impulses in each canal plane. For the LSC, the peak velocity of the head impulses was >150°/s, whereas for the anterior SCs (ASC) and posterior SCs (PSC), it was >100°/s. A minimum of 20 appropriate head impulses were employed to calculate the VOR gain on each side, which was defined as the ratio of eye velocity to head velocity. The reference lower limits for VOR gain were 0.7 for LSCs and 0.6 for ASCs and PSCs, respectively (Halmagyi and Curthoys 2021; McGarvie et al. 2015). The results were considered abnormal if the VOR gain dropped below the specified lower limit or if catch-up saccades were recorded. Abnormal responses were quantified based on the number of individuals exhibiting abnormalities in any SC and the distribution of abnormalities in each SC, considering the MD stage and duration.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were obtained for all variables. Chi-squared or Fisher's exact tests were used to compare the rates of sex and side distribution (categorical variables). The correlations between each frequency PTA threshold and duration, CP value and duration, and each canal vHIT gain and duration of patients with MD were tested using Spearman's rho or Pearson correlation analysis. Linear regression curves were constructed using Prism 8.0 (GraphPad Software, La Jolla, CA, USA). Cluster analysis and heatmap generation were performed using R (R-4.3.1) and RStudio. The clustering method used the pheatmap function to first standardise the rows (for each hearing frequency), then perform hierarchical clustering on each patient (column) and different frequencies (rows) before generating the heatmap. For all comparisons, $\rho < 0.05$ was considered statistically significant.

Results

Participants

Overall, 69 unilateral patients with MD (33 males, 36 females) ranging in age from 20 to 78 years old (mean age: 52.86 ± 12.78 years) underwent investigation. Among them, 26 and 43 cases involved the right and left ears, respectively. For the Spanish cohort, 306 patients with unilateral MD were included in this study, comprising 183 males (59.80%) and 123 females (40.20%). The age range of the patients was 21 to 86 years, with a mean age of 56.09 years and a standard deviation

of 14.60. Among these patients, 144 (47.06%) and 162 (52.94%) cases involved the right and left ears, respectively.

Relationship between hearing threshold and duration of MD

To investigate the relationship between hearing thresholds at each frequency and the duration of MD, we conducted linear regression analyses for six frequencies: 250, 500, 1000, 2000, 4000, and 8000 Hz. The results showed that, except for 4000 and 8000 Hz (4000 Hz: $p = 0.086$; 8000 Hz: $p = 0.662$, $p > 0.05$), the thresholds at the other four frequencies increased with the duration of the disease (250 Hz: $p = 0.008$, 500 Hz: $p = 0.002$, 1000 Hz: $p = 0.003$, 2000 Hz: $p = 0.005$; $p < 0.05$) (Figure 1(A–F)). Furthermore, an analysis of the audiometric thresholds and disease duration in 306 Spanish patients with unilateral MD revealed a progressive increase in thresholds across all frequencies from 250 to 8000 Hz with the duration of the disease ($p < 0.05$) (Figure 2(A–F)). These results indicate that hearing at all frequencies worsens with the duration of MD disease.

Relationship between CP ratio/VOR gain and duration of MD

To explore whether vestibular function deteriorates with disease duration in patients with MD, we conducted regression analyses on the CP values from the caloric test and the VOR gain values of the three SCs from vHIT against the duration of the disease. The results showed no significant correlation between either the CP values or the VOR gain values and disease duration (CP: $p = 0.487$, LSC: $p = 0.799$, ASC: $p = 0.886$, PSC: $p = 0.806$; $p > 0.05$) (Figure 1(G,H)). Our findings indicate that vestibular function in patients with MD does not progressively worsen with disease duration.

Hearing features of patients with MD

To further investigate the hearing characteristics of patients with MD, we initially categorised all patients into three groups based on the disease duration: Group 1 included 29 patients (P1–P29, age from 31 to 78, mean age: 52.83) with a duration of ≤12 months; Group 2 included 28 patients (P30–P57, age from 20 to 78, mean age: 50.11) with a duration of >12 months and

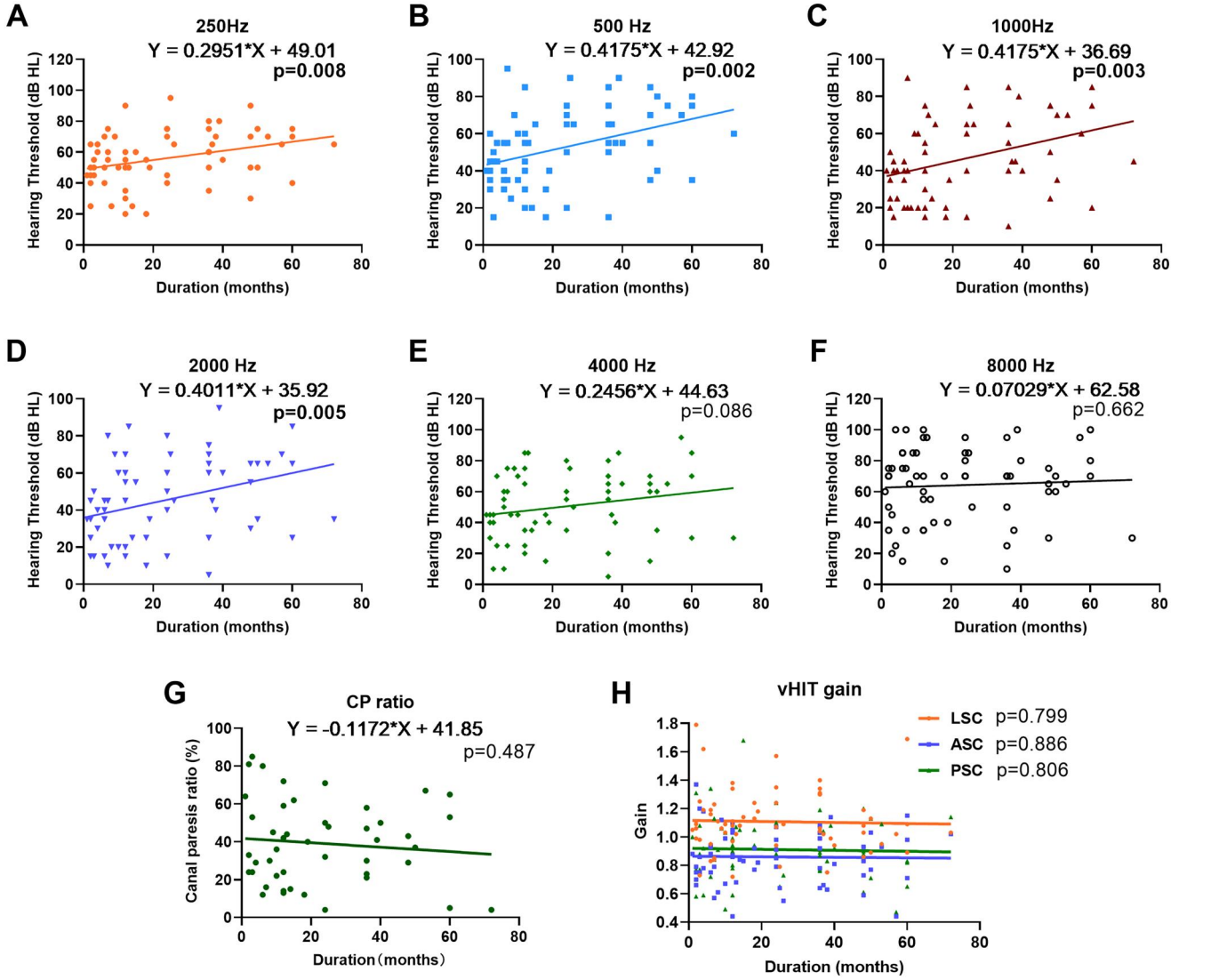

Figure 1. Relationship between hearing and vestibular results and disease duration. A–F. Hearing thresholds at 250, 500, 1000, and 2000 Hz increased with the disease duration, except at 4000 and 8000 Hz. G. No significant correlation was found between the CP value from the caloric test and the duration of MD. H. No significant correlation was observed between the VOR gain values of the three semicircular canals and the duration of MD. ASC: anterior semicircular canal; CP: canal paresis; LSC: lateral semicircular canal; PSC: posterior semicircular canal.

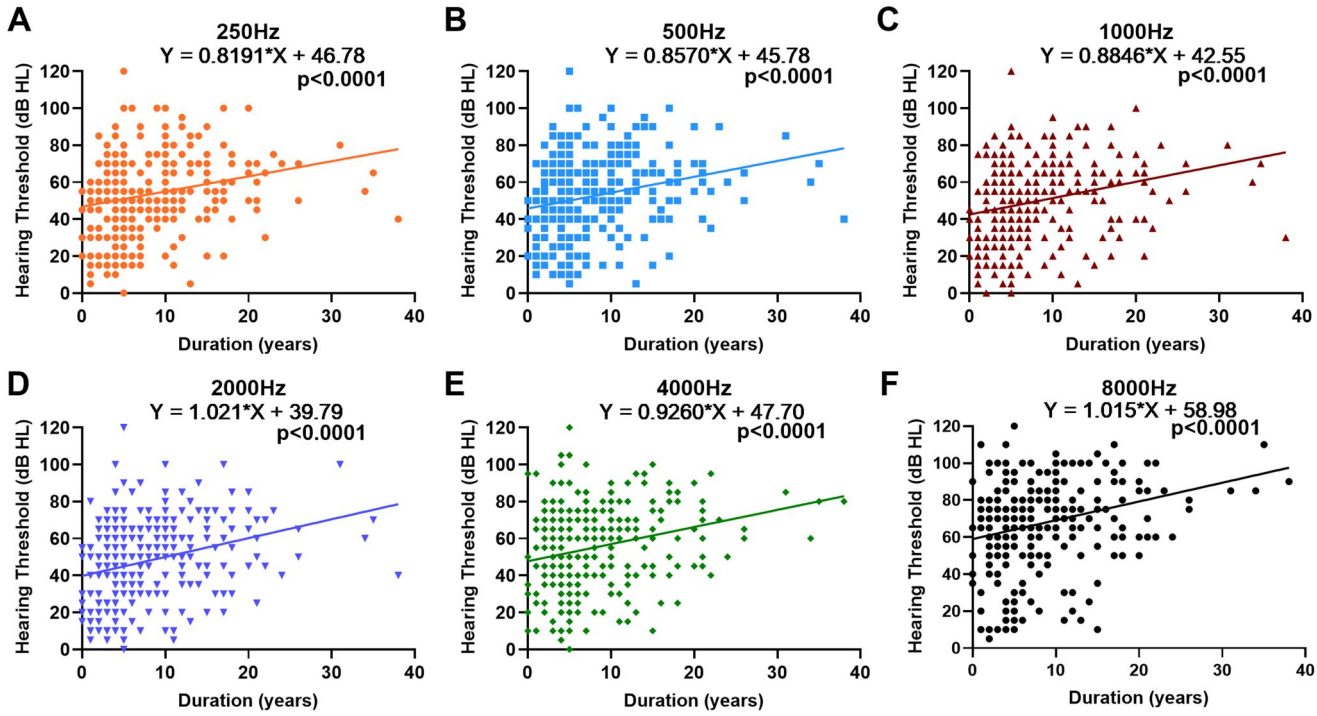

Figure 2. Relationship between hearing and disease duration in the Spanish cohort. A–F. Hearing thresholds at all frequencies (250–8000 Hz) increased with the disease duration.

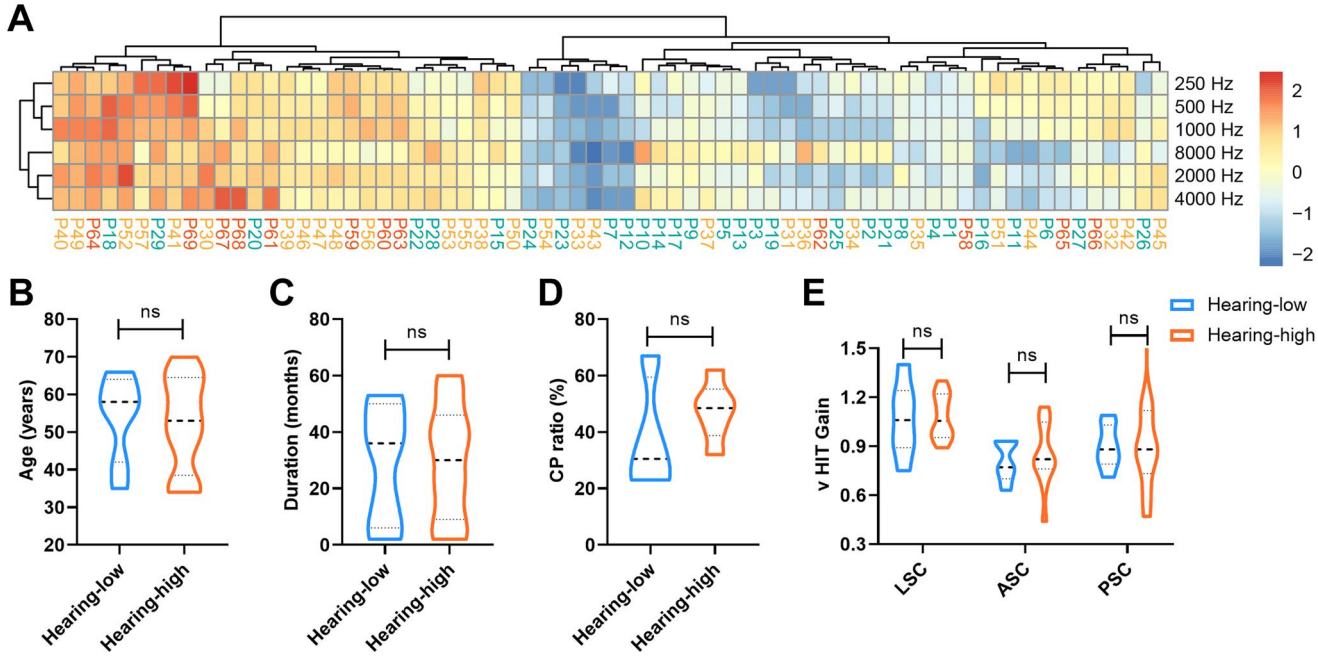

Figure 3. Distribution of Chinese patients with MD according to hearing threshold and disease duration. A. The heatmap displays clustered results based on hearing outcomes, with indigo representing patients P1–P29 with MD duration $\leq$ 12 months, orange representing patients P30–P57 with MD duration between 12 and 48 months, and red representing patients P58–P69 with MD duration $>$ 48 months. B–E. No significant differences were observed between patients with MD having the best and worst hearing in terms of age, disease duration, CP ratio, and VOR gain. ASC: anterior semicircular canal; CP: canal paresis; LSC: lateral semicircular canal; PSC: posterior semicircular canal.

$\leq$48 months; and Group 3 included 12 patients (P58–P69, age from 41 to 71, mean age: 59.33) with a duration of $>$48 months. Subsequently, we performed cluster analysis based on the hearing thresholds at six frequencies. The results showed that most patients with MD exhibited strong consistency in hearing thresholds across frequencies, with the best hearing patients showing low thresholds at all frequencies (patients P7, P12, P23, P24, P33, P43, and P54). Conversely, the poorest-hearing patients displayed high thresholds across all frequencies, such as patients P18, P29, P30, P40, P41, P49, P52, P57, P64, P67, P68, and P69 (Figure 3(A)). Only a few patients showed a separation between low and high frequencies, such as P6, P11, P16, P44, P51, and

P65, who were identified as having significant low-frequency hearing loss (Figure 3(A)). Therefore, based on cluster analysis, the results of this study indicate that most patients with MD exhibit consistent hearing loss across all frequencies, with relatively few patients experiencing predominantly low-frequency SNHL. Additionally, not all patients experience worsening hearing with the duration of the disease.

Clinical features of low and high hearing thresholds in patients with MD

Finally, we analysed the clinical characteristics of patients at the extremes of hearing ability, i.e., the groups with the best and worst hearing. The results showed no significant statistical differences between the two groups in terms of age, sex, affected side, and disease duration (age: $p = 0.413$, sex: $p = 0.821$, sides: $p = 0.361$, duration: $p = 0.602$; $p > 0.05$) (Figure 3(B, C)). Additionally, no significant differences were observed in CP values from the caloric test and gain values from vHIT across the three SCs between the two groups (CP: $p = 0.172$, LSC: $p = 0.850$, ASC: $p = 0.632$, PSC: $p = 0.770$, $p > 0.05$) (Figure 3(D, E)). Our findings suggest that no significant differences were observed in the clinical characteristics between the groups with good and poor hearing. Furthermore, vestibular function in patients with MD is not significantly correlated with the degree of hearing loss.

To ensure the robustness of our findings, we performed cluster analysis by using the hearing data from 306 Spanish patients diagnosed with unilateral MD. In patients with a disease history of less than 10 years, 31 cases were clustered into a group with low-threshold hearing (males: 19 cases; females: 12 cases, mean age ± standard deviation: 48.58 ± 14.41; disease duration: 3.84 ± 2.66), while 20 patients were clustered into a group with high-threshold hearing (males: 12 cases; females: 8 cases, age: 69.00 ± 13.17, disease duration: 6.25 ± 2.67). Subsequently, we contrasted the clinical characteristics of individuals with low and high hearing thresholds. Our analysis revealed that most patients showed consistent alterations in hearing thresholds across all frequencies, with a minority experiencing either low or high-frequency hearing loss (Figure 4(A)). Furthermore, no statistically significant differences were observed in age, sex, affected side, or disease duration between patients with differing hearing capabilities (age: $p = 0.058$, sex: $p = 0.397$, sides: $p = 0.779$, duration: $p = 0.674$; $p > 0.05$) (Figure 4(B,C)). These findings align with those observed in the cohort of Chinese patients, further validating our results.

Discussion

It is currently accepted that genetic and environmental factors contribute to MD (Flook et al. 2024; Lopez-Escamez and Liu 2024; Paparella 1985; Song et al. 2024). The clinical heterogeneity of MD presents challenges for diagnosis. Patients with MD exhibit diverse hearing patterns, including low-frequency hearing loss, mid-to-high-frequency hearing loss, and loss across all frequencies (Frejo et al. 2017; Moleon et al. 2022). Additionally, the severity and type of vertigo experienced by patients with MD vary widely, with episodes lasting from minutes to days and

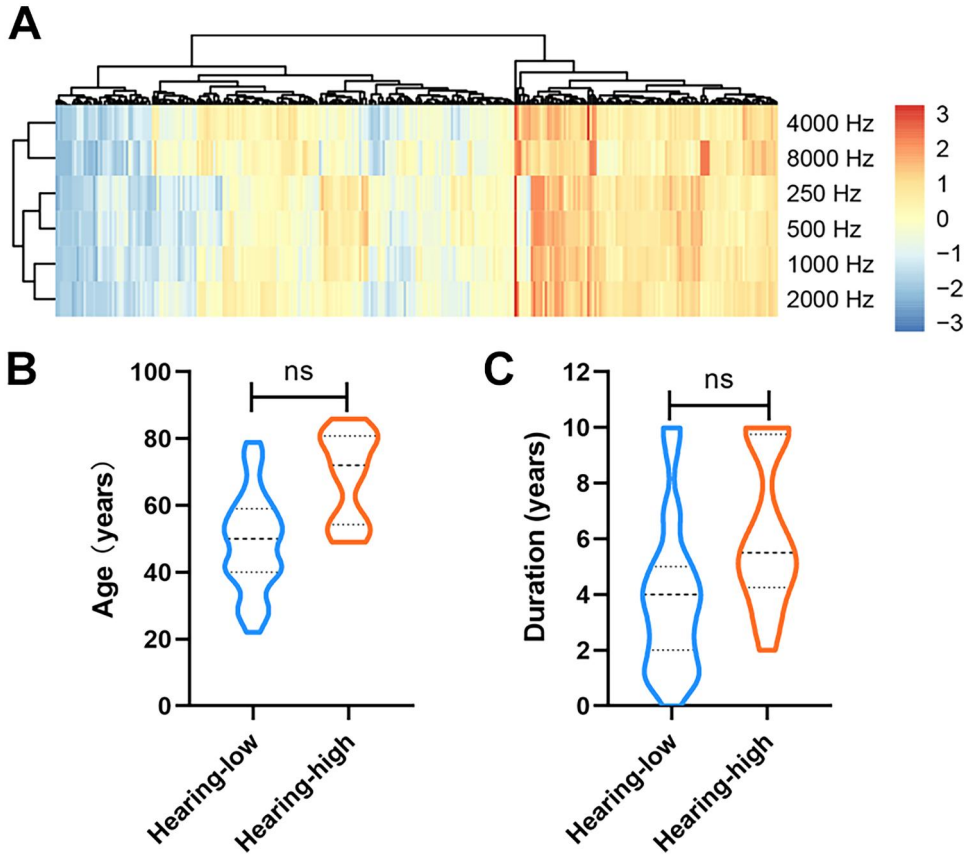

Figure 4. Distribution of patients with MD according to hearing threshold and disease duration in Spanish cohort. A. The heatmap illustrates clustered outcomes from hearing tests. B, C. No significant statistical differences were found between patients with MD having the best and worst hearing regarding age and disease duration.

considerable variability in vestibular function test results (Bhandari 2024; Limviriyakul et al. 2020; Phillips et al. 2018). MD staging primarily relies on audiometric tests, while vestibular assessments serve only to evaluate vestibular function status.

Our study not only explored the relationship between hearing thresholds across various frequencies and MD duration, but also examined the correlation between vestibular function tests and disease duration. Our findings indicate that, except for 4000 and 8000 Hz, hearing thresholds at other frequencies increase with longer disease duration. The lack of significant correlation at 8000 Hz might be attributed to the mean age of our participants being 53 years, which suggests age-related high-frequency hearing loss. The lack of association at 8000 Hz may be due to the susceptibility of this frequency to noise exposure or age-related hearing loss, resulting in higher thresholds (supported by the high intercept of 61.48 on the Y-axis in the regression equation, Figure 1(F)). Additionally, neither the caloric test CP ratios nor the VOR gain values showed significant correlation with disease duration, suggesting that while hearing thresholds worsen over time, vestibular function does not exhibit a progressive decline.

Furthermore, we observed that most patients with MD demonstrate consistent hearing thresholds across all frequencies, either consistently good or consistently poor, supporting the hypothesis that the damage involves the entire cochlear duct from the base to the apex. Cluster analysis also revealed that some patients experience rapid hearing deterioration over a short period, while others maintain stable hearing thresholds over a prolonged disease course, highlighting the heterogeneity of auditory phenotypes in MD, possibly linked to different aetiologies (Frejo et al. 2017; Frejo and Lopez-Escamez 2023; Mancini et al. 2002).

We then compared the clinical characteristics of patients with the worst and best hearing. The results showed no significant differences in age, sex, affected side, disease duration, or vestibular function test results between these groups. Similar findings were observed in the Spanish MD cohort, where no significant differences in age, sex, or disease duration were found between patients with the worst and best hearing thresholds. These results suggest that clinical features and vestibular test results may not reliably predict hearing loss progression in patients with MD. However, other studies have supported that elevated CP values may be associated with poorer hearing outcomes in early-stage MD, but not in later stages (Sun et al. 2024). To address these discrepancies, further large-scale prospective cohort studies are needed to investigate the factors influencing long-term hearing changes in patients with MD.

A limitation of this study is the lack of an age-matched control group to estimate the contribution of age-related hearing loss to hearing loss progression in MD; however, the replication cohort showed consistent findings in hearing loss clustering between Spanish and Chinese patients with MD. Additionally, co-morbidities such as migraine or autoimmune diseases could influence hearing outcomes in MD. Finally, this study underscores the need for larger, more comprehensive collaborative studies (e.g.: detailed aetiological classification of the patients) that investigate both the natural history and aetiology of MD across different populations with divergent genetic and environmental factors.

Conclusions

Hearing loss involves all frequencies in most patients with MD and the hearing outcome rather than the vestibular loss may define patient subgroups in MD. Moreover, not all patients with MD experience hearing loss progression as the duration of the disease increases.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Qing Zhang has received funds to support the research from the National Natural Science Foundation of China (Grant No. 82471160, 82171137) and the Medicine-Science and Engineering Interdisciplinary Foundation of Shanghai Hospital Development Centre (Grant No. SHDC2022CRD013). Shanghai Jiao Tong University School of Medicine Affiliated Xinhua Hospital Project (Grant No. 23XHCR05A). Jose A Lopez-Escamez has received funds to support research on MD from The University of Sydney (K7013_B3413 Grant), Asociación Sindrome de Meniere España (ASMES) and Meniere's Society, UK.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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