www.nature.com/scientificreports

scientific reports

Check for updates

OPEN

Classification of ossicular fixation based on a computational simulation of ossicular mobility

Sinyoung Lee[1]✉, Hyeonsik You[2], Yoji Morita[2], Sho Kanzaki[3,4], Fei Zhao[5] & Takuji Koike[2]

Ossicular fixation disturbs the mobility of the ossicular chain and causes conductive hearing loss. To diagnose the lesion area, otologists typically assess ossicular mobility through intraoperative palpation. Quantification of ossicular mobility and evidence-based diagnostic criteria are necessary for accurate assessment of each pathology, because diagnosis via palpation can rely on the surgeons' experiences and skills. In this study, ossicular mobilities were simulated in 92 pathological cases of ossicular fixation as compliances using a finite-element (FE) model of the human middle ear. The validity of the ossicular mobilities obtained from the FE model was verified by comparison with measurements of ossicular mobilities in cadavers using our newly developed intraoperative ossicular mobility measurement system. The fixation-induced changes in hearing were validated by comparison with changes in the stapedial velocities obtained from the FE model with measurements reported in patients and in temporal bones. The 92 cases were classified into four groups by conducting a cluster analysis based on the simulated ossicular compliances. Most importantly, the cases of combined fixation of the malleus and/or the incus with otosclerosis were classified into two different surgical procedure groups by degree of fixation, i.e., malleo-stapedotomy and stapedotomy. These results suggest that pathological characteristics can be detected using quantitatively measured ossicular compliances followed by cluster analysis, and therefore, an effective diagnosis of ossicular fixation is achievable.

Keywords Ossiculoplasty, Finite-element model, Cluster analysis, Palpation, Middle ear transfer function, Otosclerosis

Ossicular fixation, which accompanies several pathological conditions, e.g., tympanosclerosis[1], epitympanic fixation of the malleus or the incus[2], and otosclerosis, disturbs the mobility of the ossicular chain, consequently causing conductive hearing loss. Otologists determine whether surgical treatments is necessary based on preoperative non-invasive audiological tests, such as, Carhart's notch on pure tone audiometry, low compliance on tympanometry, and/or absence of middle ear reflex. Recently, several studies have suggested that the use of measurement of wideband absorbance to diagnose patients with otosclerosis is effective[3,4]. However, wideband absorbance or tympanometry measures impedance at the tympanic membrane, therefore identification of the precise fixation area and degree of the fixation in the tympanic cavity is challenging, especially in patients with combined ossicular fixation, e.g., epitympanic fixation of the malleus with otosclerotic ankylosis of the stapes[2]. Otologists typically detect the lesion area by assessing ossicular mobility using palpation during the ossiculoplastical operation that is used to alleviate the ossicular fixation status by restoring or rebuilding the ossicular chain. Furthermore, Huber et al.[5] suggested that a postoperative air–bone gap could be expected in patients with otosclerosis and anterior malleal ligament (AML) fixation after stapedioplasty without treatment of malleal fixation. Therefore, precise assessment of the lesion areas in patients, particularly in those with combined ossicular fixation, is important because the mobility of the ossicular chain is associated with the postoperative hearing level[3,6]. However, palpation methods vary among otologic surgeons, and the diagnosis may rely on their

[1]Department of Mechanical Engineering, Faculty of Engineering, Graduate Faculty of Interdisciplinary Research, University of Yamanashi, Yamanashi, Japan. [2]Department of Mechanical and Intelligent Systems Engineering, Graduate School of Informatics and Engineering, The University of Electro-Communications, Tokyo, Japan. [3]Laboratory of auditory disorders, National Institute of Sensory Organs, National Hospital Organization Tokyo Medical Center, Tokyo, Japan. [4]Department of Otorhinolaryngology, Head and Neck Surgery, Keio University School of Medicine, Tokyo, Japan. [5]Centre for Speech and Language Therapy and Hearing Science, Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, UK. ✉email: leesinyoung@yamanashi.ac.jp

individual experiences and skills. Therefore, it is essential to develop an objective method for the assessment of ossicular mobility that can support identification of the fixation and the classification of the degree of fixation.

Several studies have investigated the characteristics of ossicular mobility in patients[5] and cadavers[7–9] with various degrees and types of ossicular fixation pathologies, to develop effective diagnostic methods. Artificial fixation pathologies in cadaveric temporal bones simulated various types of singular fixation and extensive combined ossicular fixation. Changes in the umbo and the stapes velocity in each ossicular fixation were measured using laser Doppler vibrometry (LDV), and then compared with clinical results. Additionally, some studies[5,9] compared the experimental results with mathematical results obtained using a computational model, i.e., the finite-element (FE) model, of the middle ear. However, it is difficult to measure ossicular velocities using LDV in a clinical setting. Schmelts et al., suggested three-dimensional visualization and quantification of middle ear movement using dynamic synchrotron-based X-ray imaging[10] instead of using LDV. Although three-dimensional ossicular chain movement could be measured, its application to diagnosis of middle ear dysfunction has not yet been investigated. Therefore, several intraoperative assessment systems that can provide an objective and quantitative measurement of the mobility of each ossicle during middle ear surgery have been developed[11–16]. Peacock et al.[14] developed a new measurement method that can assess ossicular motion using a magnet and a coil. They reported that, although the degree of stapedial fixation could be assessed, distinguishing an isolated AML fixation was challenging using this new measurement method in the temporal bone. Koike and his colleagues have been developing an intraoperative system to quantitatively assess the ossicular mobility in terms of compliance[13,16]. Their follow-up study[16] verified the system by measuring various spring coils that represent artificial ossicular mobility. However, it is necessary to confirm whether ossicular fixation can be diagnosed by ossicular compliances.

A database consisting of ossicular mobilities in various pathologies, such as the fixation site and the degree of ossicular fixation, is essential for evaluating the reliability of diagnoses established using quantitative measurement systems of ossicular mobility. However, it is difficult to build such a database based on substantial measurement data from patients or temporal bone, because of not only the individual differences in pathology, but also differences in the diagnosis criteria among clinics. In contrast, various ossicular mobilities can be quantitatively calculated using the FE model. This approach overcomes the limitation of the surgical view and the individual differences in pathology. Moreover, the FE model also offers advantages in monitoring the dynamic movement of the ossicles via palpation. Furthermore, machine learning has been developed to predict and classify unknown data via learning from datasets. Herrera et al.[17] reported that data mining using a cluster analysis (which is an unsupervised classification method) could correlate perioperative procedures with several non-evident relevant facts. Those authors also suggested that the analytical results could be adapted to evidence-based medicine, not only for enhancing the efficiency of the treatment, but also for improving its quality. A cluster analysis is a useful method for classifying data into various clustered groups based on similarities in terms of common features among data. Therefore, a cluster analysis of the dataset obtained from the computational model can suggest an effective diagnostic method for ossicular fixation based on the various features of ossicular mobility data, such as measurement points, the measurement angle, or the absolute value of the quantified ossicular mobilities.

In this study, fixation of the ossicular ligaments and ankylosis between the malleus head and the wall of the tympanic cavity were simulated using a FE model of the human middle ear. The validity of the model was verified by comparing ossicular mobilities and middle ear transfer function (METF) between measurements from temporal bones and computational simulation results. Changes in the volume velocity of the stapes caused by the fixation were calculated for examining the corresponding changes in degree of hearing loss. The changes in ossicular mobility caused by singular fixation cases and combined fixation cases were calculated in terms of compliance. A dataset composed of the simulated ossicular compliances were classified using the cluster analysis. The purpose of the present study was to evaluate whether fixed sites and degree of the fixation could be identified via the cluster analysis of the ossicular compliances obtained from the computational simulation.

Methods

Measurement of ossicular mobilities

This measurement was approved by KEIO UNIVERSITY SCHOOL OF MEDICINE AN ETHICAL COMMITTEE (#20170398; UMIN000035512). The measurements performed in this study were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all donors included in this study, as well as the understanding and approval of the next-of-kin of the donors.

Ossicular mobilities were measured in four ears obtained from four fresh cadavers using our newly developed intraoperative assessment system[16]. Due to a limited number of donors, four temporal bones were the available in the present study. The donors ranged in age from 81 to 96 years, consisting of two males and two females. Exposure of the middle-ear ossicular chain, which included a near-full view of the stapes footplate, was achieved by mastoidectomy with posterior tympanotomy. The intact TM was confirmed by microscopic examination, and all suspensory attachments to the middle-ear ossicles, which included ligaments and tendons, were left intact during the preparation. An expert surgeon evaluated the ossicular mobilities via palpation, and normal mobilities were confirmed. The hand-held probe of the system consisted of a piezoelectric force censor (custom-made, Mechano Transformer Corp.), a piezoelectric actuator (MTKK10S100F30-S1, Mechano Transformer Corp.), and an ear pick (Fig. 2 in Koike et al.[16]). The actuator vibrated the ear pick by 40 μm at 20 Hz, and the reaction force from the ossicle that was in contact with the tip of the ear pick was measured using the force sensor. The frequency of 20 Hz used for the measurements was determined, because using a low frequency stimulus, such as palpation, has advantage for sensitively detecting changes in the stiffness component considering mechanical impedance of the ossicular chain[13]. In addition, it was the lowest available frequency to measure ossicular mobility regardless of effect of hand trembling[16]. Ossicular mobilities were measured in terms of the compliances, which are the ratios of the applied displacement to the reaction force. Ossicular compliances were measured five times at each ossicle, to verify the reproducibility of the method. The measurement points are depicted in Fig. 1a. The palpation directions are also described in the legend of Fig. 1a.

Computational simulation of ossicular-fixation-induced changes

Finite-element (FE) model of the intact human middle ear

The FE model of the human middle ear[18] modified based on the Koike's model[19] was used. The model (Fig. 2a) comprised the TM, the ossicles, the ligaments, the tensor tympani tendon, and the stapedial muscle tendon. The malleo-incudal (M-I) joint was disregarded in this model because it is almost immovable under stimuli with low frequencies, such as palpation[20,21]. The effect of the cochlea was represented by applying additional damping force to the stapes footplate, which was proportional to the velocity of the stapes. The cochlear impedance was also expressed by the mass. The mechanical properties of Koike's model[19] were used. However, Young's modulus of the stapedial annular ligament (SAL) and incudo-stapedial (I-S) joint were modified because of additional viscous damping. The mechanical properties of the additional ligaments and modified parts are shown in Table 1.

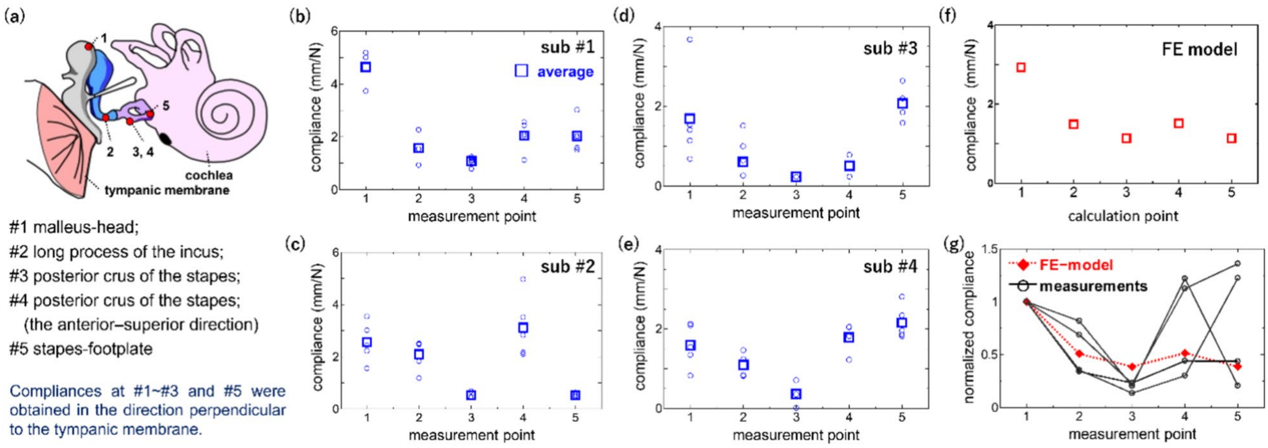

Fig. 1. Ossicular compliances obtained from fresh cadavers and the FE model. (**a**) Measurement points and direction. (**b**) Results of cadaver #1. (**c**) Results of cadaver #2. (**d**) Results of cadaver #3. (**e**) Results of cadaver #4. (**f**) Results obtained from the FE model. (**g**) Normalized compliances obtained from four donors and FE-model. The averaged compliance of the five measurements is indicated by an open square (□) in (**b**)–(**e**).

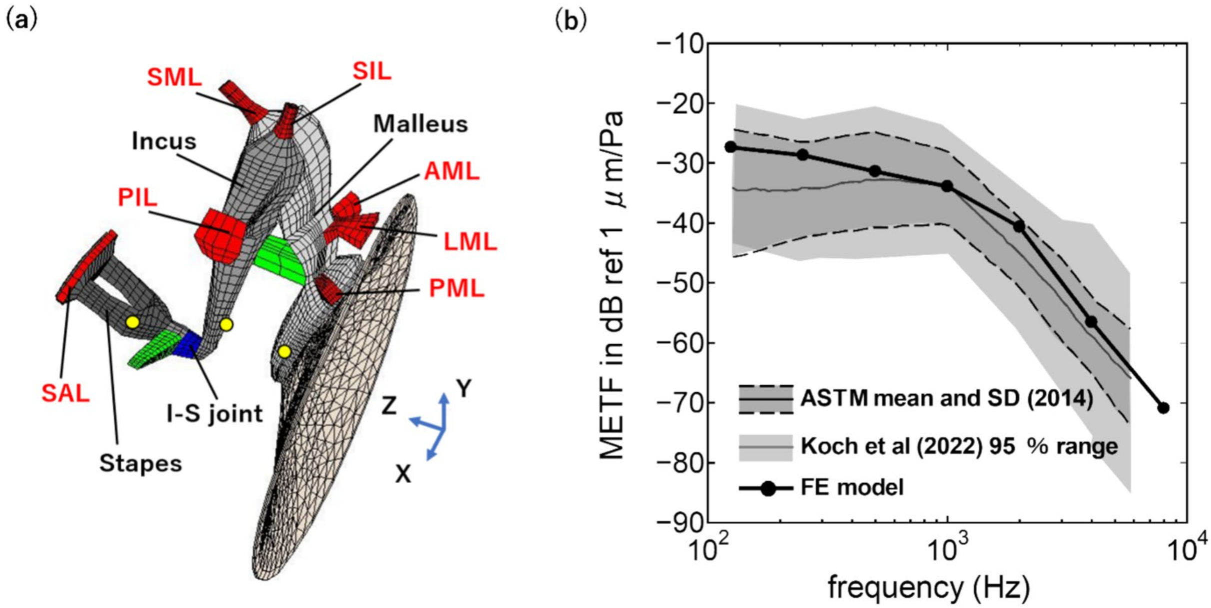

Fig. 2. Finite-element (FE) model of the human middle ear and Middle ear transfer function (METF). (**a**) FE model. (**b**) METF obtained from the temporal bone measurements and the FE model. The green areas in (**a**) are tendons. The blue part in (**a**) is incudo-stapedial (I-S) joint. The closed yellow circles in (**a**) are the calculation points of the ossicular compliances.

Young's modulus	**(Pa)**
SML	4.9×10^6
LML	6.7×10^6
SIL	4.9×10^6
PML	2.1×10^7
SAL	6.5×10^4
IS-joint	1.8×10^6
Viscous damping coefficient	**(Ns/m^3)**
cochlea	4.4×10^4
IS-joint	6.6×10^5

Table 1. Mechanical properties used in the FE model.

The nonlinearity of ligaments and tendons was not considered because the range of strain of the SAL in our pilot study[22] was less than 0.1 which is sufficiently small to be considered within the linear area of the shear stress–shear strain curve of the SALs obtained from cadaveric temporal bones[23]. A displacement of ossicle by palpation was assumed to be as under 40 µm in this study which was sufficiently small to be within the linear range of displacement of the cadaveric measurement[23]. Rayleigh damping was set to α parameter as 900 [s^{-1}], β parameter as 3.70×10^{-5} [s] and applied to the structural parts of the model. An additional damping force was applied to both faced interfaces between the I-S joint and the incus or the stapes, for representing the viscosity of the I-S joint in the directions that hinder the joint movement. The force was proportional to the difference in velocity between the surfaces, respectively. In terms of the boundary conditions, the ends of the ligaments and tendons, as well as the periphery of the TM, were fixed, because these are attached to the tympanic cavity wall. Time domain analyses were performed using the ACE + Suite software (APPLIED MATERIALS). The time accuracy was performed by using the 1st order of the backward Euler method.

The validity of the model was verified by comparing the METF obtained from the measurements[24,25] with those from the model (Fig. 2b). The American Society for Testing and Materials (ASTM) standard range and mean[24], the 95% range and mean of 366 METF measurements from four different research groups[25] were included. The METF was defined as the ratio of displacement of the stapes to the sound pressure at the TM. The displacement at the stapes footplate of the model was obtained when sound pressure was applied to the surface of the TM. Pure-tone frequencies of 125 Hz, 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz, and 8 kHz were used. Applied sound pressure was 80 dB SPL. The METF obtained from the model was compared with both ranges and the intact FE model represents the realistic behavior of the normal human middle ear.

In addition, the ossicular mobilities of the model was verified by comparing the ossicular compliances obtained from the intact model and the cadaveric measurement. Ossicular compliance was calculated by the ratio of the displacement to a point load, as shown in the following formula:

$$\text{Ossicular compliance} = \frac{\text{displacement(mm)}}{\text{point load(N)}},$$

the displacement was obtained when a point load of 20 Hz, which is the same frequency used in the cadaveric measurement, was applied. The point load was set to 0.01 N and applied to the same points and direction in Fig. 1a.

Simulation of ossicular fixation using the FE model

Several pathologies have been associated with ossicular fixation, such as ankylosis between the ossicles and the wall of the tympanic cavity caused by abnormal bony growth[26,27] or hyalinization of AML[28]. Various cases of abnormal ossicular mobility caused by ossicular fixation were simulated by increasing the stiffness of the ligaments (AML, lateral malleal ligament: LML, superior malleal ligament: SML, posterior malleal ligament: PML, posterior incudal ligament: PIL, superior incudal ligament: SIL, and SAL) or completely fixing the malleus-head. For example, otosclerosis which mainly affects mobility around the stapes footplate is simulated by stiffening SAL. Young's modulus of fixed ligament was set to three stiffness levels to simulate different degrees of fixation, i.e., 10 times (mild fixation), 100 times (moderate fixation), or 1000 times (severe fixation) to their stiffness in the intact model. The stiffening degrees were determined by comparing the changes in the stapedial velocity in frequency range of 125 Hz to 4 kHz caused by the artificial fixation of each ossicle in temporal bones[7,8] with the results obtained from the singular ligament fixation models in the three levels, as reported in our preliminary study[22]. Changes in stapes volume velocity, ΔV_s, caused by each fixation lead to the loss of transmission gain and consequently result in increase of the hearing thresholds. Ossicular fixation induced ΔV_s was calculated as follows:

$$\Delta V_s(\text{dB}) = -20 \times \log_{10}\left(V_{s(fixation)}/V_{s\ (intact)}\right).$$

The stapes volume velocity, V_s, was calculated when the application of a sound pressure of 80 dB SPL at 500 Hz to the TM. The stimulus frequency of 500 Hz was determined as several studies[7–9,15] have shown that ossicular velocities measured using temporal bones were significantly reduced by artificial fixation, particularly in the frequency range below 1 kHz. The ΔV_s values of the three levels of fixation were within the range of the ± 95% confidence interval obtained from the measurements.

Some pathological conditions of ossicular fixation involved more than one ossicle. According to Sleeckx et al.[2], epitympanic fixation of the malleus, the incus or both can occur, and these fixation cases were more frequent in ears with otosclerosis[2]. Therefore, singular fixation of each ligament and combined fixation of several ligaments were simulated. In this study, 21 singular fixation cases were created, i.e., stiffening of each of the seven ligaments, respectively, in the three levels. Combined fixation of the AML, SIL, and PIL in the three levels were also simulated, i.e., three combined fixation cases around the malleus and incus. Furthermore, combined fixation cases with SAL fixation were simulated as combined fixation in otosclerosis, i.e., combined with one of the six ligaments attached to the malleus or the incus. The degree of fixation of each ligament in combined fixation cases was set to the three levels, i.e., 54 cases in total. Combined fixation cases of all ossicles were also simulated, i.e., additional SAL fixation values in the three levels to the combined malleal–incudal fixation (fixation of the AML, SIL, and PIL) in the three levels. As a result, 9 cases of whole ossicle combined fixation were simulated. Regarding the malleus-head fixation, the surface at which the SML attached to the malleus was set to be completely fixed, i.e., ossification occurred. Singular fixation of the malleus-head, and combined fixation of additional SAL fixation values in the three levels to the malleus-head were calculated (i.e., four cases in total). Therefore, a total of 91 fixation cases were simulated.

Cluster analysis using a dataset of ossicular compliances

The agglomerative hierarchical clustering method was used to classify the fixation sites and degree of the fixation by clustering the similarity of ossicular mobility among the various fixation cases. Ward's method[29] is a minimum variance approach that merges clusters by calculating the increment of the sum of squares and generates groups that minimize the between-group dispersion when merging the clusters[30]. The present cluster analysis was performed using a dataset composed of three features, i.e., the standardized compliances of three ossicles. The manubrium of the malleus, the long process of the incus, and the posterior crus of the stapes were selected as calculation points (closed yellow circles in Fig. 2a). The same point load used for validation of the model was used for calculating compliances and the direction of the load was set to a perpendicular direction to the TM (i.e., Z-axial direction) at each calculation point. The calculation points and the direction of the load were selected by considering the surgeon's field of view and the palpable angle, which could vary during the surgery because of individual operation conditions. The compliances at the points in each fixation case and in the intact case were obtained. The dataset consisted of the 92 data points obtained from the model (data from 91 fixation cases and one intact case). Statistical analysis among classified groups was performed to identify the clinical characteristics of each group, and determine the contributions of given features to classify the individual groups. Shapiro–Wilk test, Kruskal–Wallis rank-sum test, and Spearman's rank correlation tests were performed using software R (ver. 4.3.2).

Results

Comparison of ossicular compliances between the cadaver measurements and the FE model simulation

Ossicular compliances obtained from the four fresh cadavers are plotted in Fig. 1b–e. The absolute values of the ossicular compliances varied slightly among reproducibility measurements. The absolute values of the compliances might also include individual differences in the mobility of the ossicular chain. However, the relative difference in the average of compliances at measurement point #1–#4 showed similar tendencies between four cadavers with normal ossicular mobilities (Fig. 1b–e). The averaged compliances at each measurement point were normalized by that obtained at measurements point #1 individually (depicted in Fig. 1g). The mean and standard deviation of normalized compliances of four cadavers at each measurement point #2–#5 was 0.55 ± 0.24, 0.20 ± 0.044, 0.77 ± 0.47, and 0.81 ± 0.57 respectively. The ossicular compliances obtained from the intact model in the same way as that used for the measurements are shown in Fig. 1f. The relative difference among the compliances of each ossicle obtained from the model are compared with the compliances measured in four fresh cadavers. The absolute values of each compliance varied not only between cadavers (Fig. 1b–e), but also among the cadaveric measurements and simulation (Fig. 1g). However, a correlation coefficient between averaged normalized compliances obtained from the measurements and the normalized compliances obtained from simulation was 0.66 and exhibited similar tendencies at measurement point #1–#4.

Summary of dataset composed of the simulated ossicular compliances and the classification outcomes using cluster analysis

The ossicular compliances and ΔV_s obtained from 92 models are shown as box plots in Fig. 3a and b. The mean and standard deviation of compliance of malleus, incus and stapes was 0.40 ± 0.18, 0.27 ± 0.14, and 0.30 ± 0.39 mm/N, respectively. The normal compliance of each ossicle obtained from the normal model was 0.87, 0.63, 1.1 mm/N, respectively (displayed as thick line in Fig. 3a). Wide distribution of ossicular compliances in fixation models represents decreased ossicular mobilities by various graded fixation in pathological conditions. The mean and standard deviation of ΔV_s was 25 ± 19 dB. Range of ΔV_s in fixation models represents various degrees of hearing loss. Correlation coefficients between ΔV_s and each ossicular compliance were calculated using the Spearman method. Correlation tests were also performed between each ossicular compliance (Table 2). The ossicular compliances and ΔV_s obtained from SAL singular fixation in three fixation degrees are depicted in Fig. 3c. The harder fixation degree is, the lower ossicular compliance and the higher ΔV_s, i.e., increase of hearing threshold. There was a significantly negative correlation between the ossicular compliances and the ΔV_s, indicating a relationship between the ossicular fixation and hearing loss.

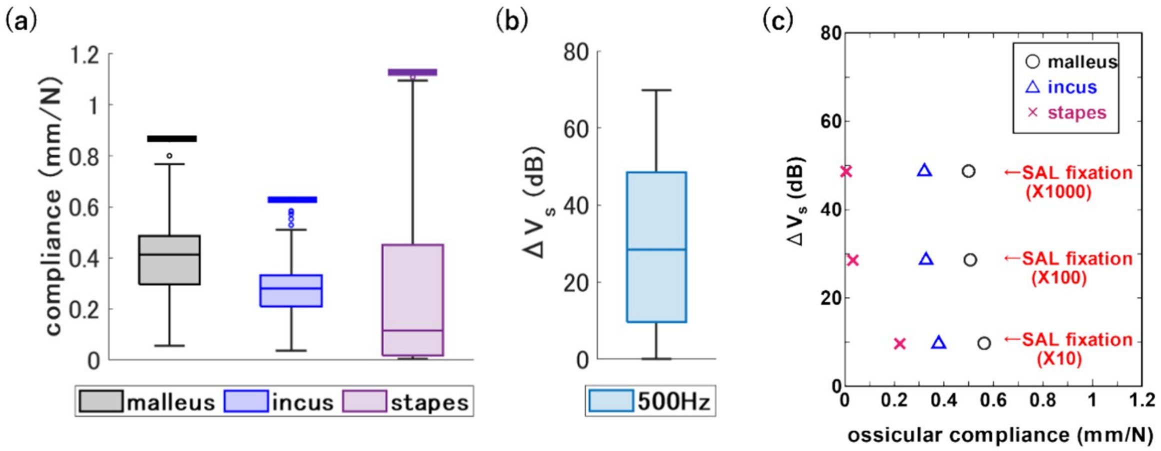

Fig. 3. The ossicular compliances and ΔV_s obtained from 92 models. (**a**) Boxplot of each ossicular compliance. (**b**) Boxplot of ΔV_s when 500 Hz of pure tone was applied to the surface of tympanic membrane. (**c**) The results obtained from SAL singular fixation cases (otosclerosis). Thick line in (**a**) shows each ossicular compliance obtained from the normal model.

	Malleal compliance	Incudal compliance	Stapedial compliance
Incudal compliance	0.97*	–	–
Stapedial compliance	0.56*	0.60*	–
ΔV_s	−0.61*	-0.64*	−0.97*

Table 2. Results of the correlation test using the Spearman method. *Statistically significant $p < 0.05$.

A dendrogram depicting the results of the cluster analysis of the dataset is provided in Fig. 4. The horizontal axis displays the list of the data. It displays the ossicle to which the stiffened ligaments were attached, and degree of the fixation is indicated under the dendrogram using colored labels. For example, the simulation data obtained from the intact model was classified into Group 1, which corresponds to the farthest data on the left side of the dendrogram, i.e., green labels of three ossicles. The farthest data on the right side of the dendrogram classified

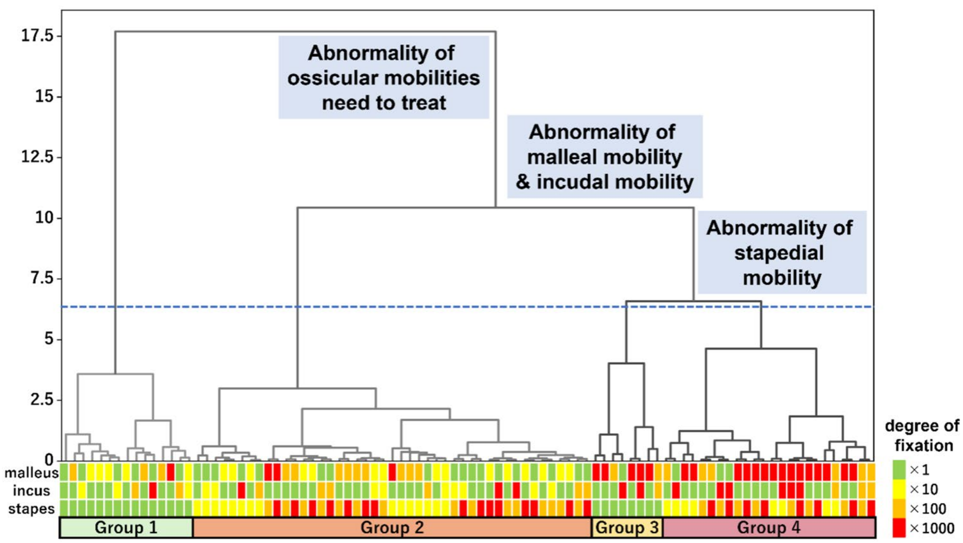

Fig. 4. Dendrogram of the dataset. The label under the dendrogram indicates the information of the data, i.e., ossicle to which the fixed ligaments were attached, and the color indicates degree of the fixation, as follows: normal in green, 10-times stiffened in yellow, 100-times stiffened in orange, and 1000-times stiffened in red. The blue dashed line indicates the threshold used for the classification into four groups. Features of classified data are indicated at the bifurcation. The features were determined based on the details of fixation degree and fixation location of the classified data, and significant difference of the ossicular compliances among the groups.

into Group 4 was obtained from three ossicles combined fixation model, i.e., severe fixation of SAL with mild fixation of AML, PIL and SIL. The height of the dendrogram indicates the merging order. In this study, four groups are demarcated by a horizontal threshold line, as indicated by the dash line. The height of the threshold line indicates the relative distance among the clustered groups. For example, a higher threshold line could be set when the groups were classified more distinctly. The threshold of the height of the dendrogram was set at approximately 6.

Ossicular compliances and ΔV_s obtained from each classified group are shown in Fig. 5. Those data non-normally distributed were confirmed by a Shapiro–Wilk test. The Kruskal–Wallis rank-sum test was performed to test the differences in ossicular compliances and ΔV_s at a significance level of 5% among the groups. As a result, significant difference was found ($p < 0.001$). Further pairwise comparisons were also conducted using the Wilcoxon rank-sum exact test. The p-values were corrected using the Bonferroni method. Significant difference was found ($p < 0.001$) except for few pairs of comparisons. The significant difference of the ossicular compliances between the groups and that of the degree of hearing loss as ΔV_s between the groups were summarized in Fig. 5a–c and d, respectively. For example, there are significant differences of malleal compliance and incudal compliance between Group 2 and 4. In contrast, there are no significant differences of stapedial compliance and the degree of hearing loss as ΔV_s between Group 2 and 4.

Fixation conditions of the models, i.e., stiffened ossicles and degree of the fixation, were summarized in Table 3, as the number of color labels in each individual group in the dendrogram (Fig. 4). For example, Group 1 consisted of 15 fixation models without stapedial fixation. Within this group, there were a total of 9 malleal fixation and 5 incudal fixation models with various degree of stiffness (i.e., slightly, mild and severe). The corresponding clinical pathological conditions may be considered as normal or a certain level of fixation around malleus or/and incus without certain degree of hearing loss (Group 1 in Fig. 5), suggesting that surgical intervention may not necessary.

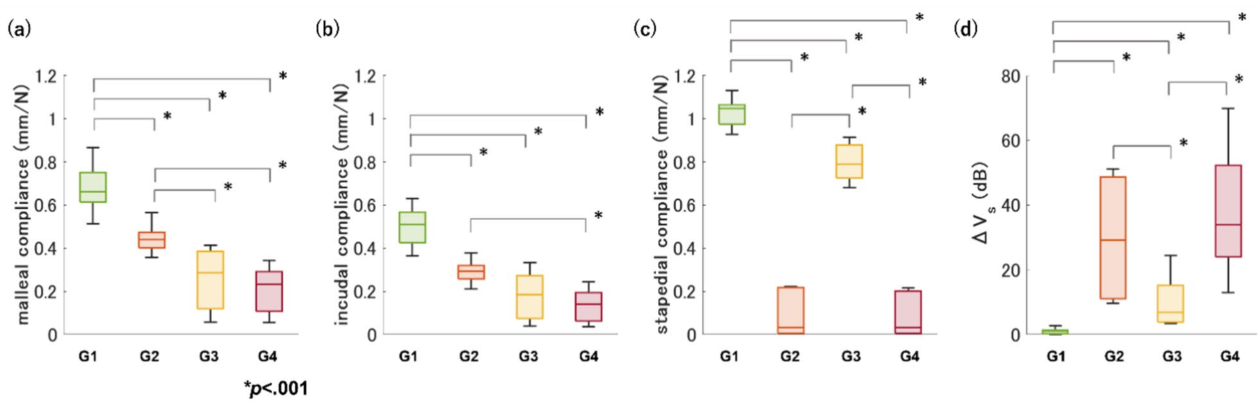

Fig. 5. Ossicular compliances and ΔV_s of each classified group. (**a**) Boxplot of malleal compliances. (**b**) Boxplot of incudal compliances. (**c**) Boxplot of stapedial compliance. (**d**) Boxplot of ΔV_s when 500 Hz of pure tone was applied.

	Number of fixation conditions in models (stiffened ossicles and degree of fixation)				Presumed pathological conditions in patients	Indication for surgical intervention procedure
Group 1 (N = 15)		M	I	S	Normal Slight fixation around malleus or/and incus	No necessary
	Slight	5	3	–		
	Mild	3	1	–		
	Severe	1	1	–		
Group 2 (N = 45)		M	I	S	Combined mild fixation around the malleus or/and incus with otosclerosis	Stapedotomy Stapedectomy
	Slight	15	9	15		
	Mild	9	6	15		
	Severe	3	3	15		
Group 3 (N = 8)		M	I	S	Normal stapes Severe fixation around the malleus or/and incus	Ossiculoplasty
	Slight	–	–	–		
	Mild	2	1	–		
	Severe	5	2	–		
Group 4 (N = 24)		M	I	S	Combined severe fixation around the malleus or/and incus with otosclerosis	Malleostapedotomy Malleostapedectomy
	Slight	–	–	8		
	Mild	6	3	8		
	Severe	15	6	8		

Table 3. Details of classified groups and related pathological conditions with suggestion of surgical procedure for each group. Fixation type abbreviation: *M* malleal fixation, *I* incudal fixation, *S* stapedial fixation. *N:* The total number of fixation models in each classified group.

Discussion

The relative difference between the compliances of each ossicle obtained from the intact model was similar to that obtained from the measurements (Fig. 1). These results suggest that the intact FE model accurately represents the ossicular mobility of normal ossicular chain, and that the compliances obtained from the model are reliable. The changes in stapedial velocities, ΔV_s obtained from the FE model in the case of whole singular fixation cases mostly matched those of the measurements performed by several groups researching cadaveric temporal bones. According to Nakajima et al.[7], the results of combined fixation cases were almost identical to the sum of the results of each singular fixation case. The ΔV_s obtained from the combined fixation cases in the model exhibited approximately the same range as the sum of the results of each singular fixation case. The similarities between the results of the experimental measurements and those of the numerical analysis suggest that our modeling of not only the singular fixation cases, but also of the combined fixation cases, represents realistic ossicular fixation. The maximum ΔV_s obtained from a fixation model was 70 dB (Fig. 3(b)) when the malleus-head was fixed in addition to otosclerosis by severe fixation of SAL. The ΔV_s correlated with increase in hearing level, because the stapedial velocities could be considered as output from the middle ear[7]. The American Speech-Language-Hearing Association suggests the common range of each degree of hearing loss to be: normal hearing as – 10 to 15 dB HL, slight hearing loss as 16–25 dB HL, mild hearing loss as 26–40 dB HL, moderate haring loss as 41–55 dB HL, and moderately severe as 56–70 dB HL. Therefore, the 92 models used in this study could represent a range of clinical hearing loss. Crompton et al.[31] reported preoperative and postoperative pure tone hearing levels in a cohort of otosclerosis patients (n = 154). Mean value of preoperative hearing level of 500 Hz was 61 dB and postoperative that was 28 dB. The ΔV_s caused by the otosclerosis could be estimated by the differences in preoperative and postoperative hearing levels. The ΔV_s of Crompton's report would be approximately 30 dB. In this study, Group 2 and Group 4 represented otosclerosis and the mean of ΔV_s in each group was 30 and 38 dB respectively. Therefore, hearing loss caused by otosclerosis was well represented the clinical pathology.

Fixation of the AML in cadaveric temporal bones was assessed by otologists via palpation of the ossicular mobility, as a blind test[8]. As a result of this palpation, no significant difference in mobility was detected. Fisch et al.[32] reported that 37.5% of the patients who needed additional surgery had untreated fixation of the AML and the anterior mallear process. A histopathological study performed by Nandapalan et al.[28] reported that 30% of 43 otosclerotic specimens had severe hyalinization of the AML. These reports suggest that fixation of the AML was often diagnosed insufficiently in patients suffering from combined fixation. Nakajima et al.[8] suggested diagnostic approaches to distinguish stapes fixation from malleus fixation using the umbo velocity and air–bone gap measurements. However, distinguishing some combined fixation cases was difficult because of the similarities among the features of ossicular velocities. On the other hand, fixation degree of malleal fixation was classified to Group 2 and Groups of 3 and 4, and severe malleal fixation in addition to stapedial fixation was classified to Group 3 and Group 4 except for few cases (Fig. 4) in this study. As shown in Fig. 5, statistical analysis results indicate that these groups were classified by significant differences of ossicular compliances. In Fig. 5d, the median of ΔV_s in Group 2 and Group 4 falls within a similar degree of hearing loss. This result implies that patients who have the same pure-tone hearing thresholds, but have different underlying pathological changes in terms of ossicular fixation could be classified. Therefore, the results of this study suggest that classifying the severity of fixation degree and fixation sites particularly among combined fixation pathologies is possible using quantitative ossicular mobilities.

According to the labels beneath the dendrogram in Fig. 4, a few data were either classified into Group 1 or Group 2, even though the cases had a severe degree of fixation around the malleus or incus. As shown in Table 3, although Group 1 includes a couple of models with severe fixation condition, surgical intervention may not be necessary, because ΔV_s was sufficiently small, indicating that such fixations are unlikely to cause hearing loss (Fig. 5d). In contrast, the mean ΔV_s in Group 2 suggests a clinical symptom of mild hearing loss. The malleus exhibited a translational motion, in addition to a rotational motion around an axis from the AML to the PIL when the point load in the Z-axial direction was applied to the manubrium of the malleus or the long process of the incus in a normal model (Fig. 7 in Lee et al.[21]). Conversely, the malleus only showed the rotational motion in the model with AML fixation. The absolute values of stapedial compliance were varied among the obtained point and direction (#3–#5 in Fig. 1a) both in the measurements and simulation, though the stapedial mobilities were normal. These results indicate that not only the ossicular compliances in fixation cases, but also those in the intact cases could be varied by measurement points and palpation angles. Therefore, various conditions of ossicular fixation could be diagnosed more significantly by measuring ossicular mobilities at specific palpation angle or the palpation point, which serve as indicators of pathological changes in the ossicular mobilities. The results also imply that the measuring points or the angle of ossicular compliances should be carefully determined. A range of changes in ossicular compliance by a palpation angle and point could be simulated quantitatively by our model and consequently investigate their influence on the accuracy of diagnosis. In addition, performing clustering using computational simulation results by modifying the direction of the load or calculation point could suggest different classified groups of the same pathologies and propose effective palpation angles or palpation points for the diagnosis of the fixation sites.

This novel study intended to classify ossicular fixation pathologies through cluster analysis, using ossicular compliance theoretically derived from the FE model. In our study, abnormalities in ossicular mobilities that need to be treated were initially classified (Fig. 4), followed by the cases of combined ossicular fixation that were categorized in sequence by severity of fixation and fixation sites. According to the previous studies, the decision-making process for ossiculoplasty presents challenges as preoperative tests often provide limited guidance, and thus ultimately the final determination typically relies on intraoperative palpation to assess the presence of ossicular fixation. In respect of clinical application, a more precise operative procedure could be determined, particularly in combined fixation pathology conditions, by cluster analysis of quantitatively measured ossicular mobilities using our measurement system[16]. In addition, the theoretical changes in ossicular mobilities and classification of them in this study could provide the surgeon with a guidance for effective palpating method at the preoperative planning stage. Such an approach could lead to better postoperative outcomes, particularly in improvement of hearing thresholds. Furthermore, the measurement system will be integrated with an expanded database in the future. The database would be composed with clinical information (e.g., pre/postoperative auditory tests and age), ossicular mobilities in various pathological conditions both obtained from measurements and simulation. The system will suggest pathological condition and suggest an effective surgical procedure to the surgeon based on the measurements results and analysis based on the database. This can lead to development of a new computer assisted operative technique for effective surgery.

The relative ossicular compliances in the intact ossicular chain, applying a point load of 20 Hz, and the changes in the stapedial velocities when 500 Hz of sound stimulus was applied, observed in fixation cases matched between the cadaveric measurements and computational simulation results. These results suggest that the ossicular compliances obtained from our model replicate the changes in ossicular compliances occurring under pathological conditions in the low frequency range, which has advantage for sensitive detection of changes in the ossicular stiffness. However, changes in dynamics of ossicular motion due to fixation were not considered at the high frequency range. This is because factors such as the mass and viscosity (damping) components of mechanical impedance would be dominant at the high frequency range. In this study, the low frequency range was used which allows a focus on the stiffness component, because the aim is detection of stiffness changes induced by ossicular fixation. In addition, the degree of fixation was simply set to three levels in tenfold in this study, and it could influence ease of classification, i.e., height of threshold in dendrogram. Therefore, a new database representing degree of the fixation on a finer scale should be evaluated for the investigation of its influence on classification of fixation sites and degree of fixation. Simulating the fixation-induced changes in the compliances of ossicles using the FE model could provide a theoretical foundation for developing diagnostic criteria and guidelines for patients with ossicular fixation. To establish and improve these diagnostic criteria, quantitative measurements of the compliances in various pathologies are also necessary for validation. Our future work will focus on the quantitative measurement of the ossicular mobility and transfer function of the middle ear in patients with various pathologies, as well as the evaluation of the availability of classification using the measurement data.

Conclusions

In this study, 92 various pathological conditions associated with ossicular fixations were classified into four discrete groups via a cluster analysis using a dataset composed of ossicular compliances obtained from a FE-model. Most importantly, combined fixation cases of the malleus or/and the incus with otosclerosis, which could have similar hearing loss degree, were classified into two different surgical procedure groups, i.e., malleo-stapedotomy/stapedectomy and stapedotomy/stapedectomy. Particularly noteworthy that these cases are difficult to identify by existing clinical tests and palpation. In the context of clinical implementation, our results suggest that it is possible to categorize pathological conditions of combined ossicular fixation based on quantitatively measured ossicular mobilities, and achieve a quantitative and effective diagnosis. To achieve a more accurate classification and to identify effective measurement points or angles, it is essential to increase the features of the dataset by varying the calculation points and/or directions.

Data availability

The data that support the findings of this study are available from the corresponding author, S.L., upon reasonable request.

Received: 28 March 2024; Accepted: 28 August 2024
Published online: 03 September 2024

References

1. Morgan, W. C. Tympanosclerosis. *Laryngoscope* **87**, 1821–1825 (1977).
2. Sleeckx, J. P., Shea, J. J. & Pitzer, F. J. Epitympanic ossicular fixation. *Arch. Otolaryngol.* **85**, 619–631 (1967).
3. Niemczyk, E., Lachowska, M., Tataj, E., Kurczak, K. & Niemczyk, K. Wideband tympanometry and absorbance measurements in otosclerotic ears. *Laryngoscope* **129**, 365–376 (2019).
4. Sliwa, L., Kochanek, K., Jedrzejczak, W. W., Mrugala, K. & Skarzynski, H. Measurement of wideband absorbance as a test for otosclerosis. *J. Clin. Med.* **9**, 1908 (2020).
5. Huber, A., Koike, T., Nandapalan, V., Wada, H. & Fisch, U. Fixation of the anterior mallear ligament: Diagnosis and consequences for hearing results in stapes surgery. *Ann. Otol. Rhinol. Laryngol.* **112**, 348–355 (2003).
6. Nguyen, D. D., Judd, R. T., Imbery, T. E. & Gluth, M. B. Frequency-specific analysis of hearing outcomes associated with ossiculoplasty versus stapedotomy. *Ann. Otol. Rhinol. Laryngol.* **130**, 1010–1015 (2021).
7. Nakajima, H. H., Ravicz, M. E., Merchant, S. N., Peake, W. T. & Rosowski, J. J. Experimental ossicular fixations and the middle ear's response to sound: Evidence for a flexible ossicular chain. *Hear. Res.* **204**, 60–77 (2005).
8. Nakajima, H. H., Ravicz, M. E., Rosowski, J. J., Peake, W. T. & Merchant, S. N. Experimental and clinical studies of malleus. *Laryngoscope* **115**, 147–154 (2005).
9. Dai, C., Cheng, T., Wood, M. W. & Gan, R. Z. Fixation and detachment of superior and anterior malleolar ligaments in human middle ear: Experiment and modeling. *Hear. Res.* **230**, 24–33 (2007).
10. Schmeltz, M. *et al.* The human middle ear in motion: 3D visualization and quantification using dynamic synchrotron-based X-ray imaging. *Commun. Biol.* **7**, 157 (2024).
11. Gyo, K., Yumoto, E., Sato, H. & Yanagihara, N. Assessment of stapes mobility by use of a newly developed piezoelectric ceramic device: A preliminary experiment in dogs. *Ann. Otol. Rhinol. Laryngol.* **109**, 473–477 (2000).
12. Hato, N. *et al.* A new tool for testing ossicular mobility during middle ear surgery: Preliminary report of four cases. *Otol. Neurotol.* **27**, 592–595 (2006).
13. Koike, T. *et al.* An apparatus for diagnosis of ossicular chain mobility in humans. *Int. J. Audiol.* **45**, 121–128 (2006).
14. Peacock, J., Dirckx, J. & von Unge, M. Intraoperative assessment of ossicular fixation. *Hear. Res.* **340**, 99–106 (2016).

15. Dobrev, I. *et al.* Effects of middle ear quasi-static stiffness on sound transmission quantified by a novel 3-axis optical force sensor. *Hear. Res.* **357**, 1–9 (2018).
16. Koike, T. *et al.* Development of intra-operative assessment system for ossicular mobility and middle ear transfer function. *Hear. Res.* **378**, 139–148 (2019).
17. Herrera, M., Izquierdo, J., Montalvo, I., Garcia-Armengol, J. & Roig, J. V. Identification of surgical practice patterns using evolutionary cluster analysis. *Math. Comput. Model.* **50**, 705–712 (2009).
18. Kita, S. *et al.* Diagnosing middle ear malformation by pure-tone audiometry using a three-dimensional finite element model: A case-control study. *J. Clin. Med.* **12**, 7493 (2023).
19. Koike, T., Wada, H. & Kobayashi, T. Modeling of the human middle ear using the finite-element method. *J. Acoust. Soc. Am.* **111**, 1306–1317 (2002).
20. Gerig, R. *et al.* Contribution of the incudo-malleolar joint to middle-ear sound transmission. *Hear. Res.* **327**, 218–226 (2015).
21. Gottlieb, P. K., Vaisbuvh, Y. & Puria, S. Human ossicular-joint flexibility transforms the peak amplitude and width of impulsive acoustic stimuli. *J. Acoust. Soc. Am.* **143**, 3418–3433 (2018).
22. Lee, S., Kanzaki, S. & Koike, T. Study of diagnostic criteria for ossicular fixation based on numerical analysis. *Otol. Jpn.* **29**, 154–161 (2019).
23. Gan, R. Z., Yang, F., Zhang, X. & Nakmali, D. Mechanical properties of stapedial annular ligament. *Med. Eng. Phys.* **33**, 330–339 (2011).
24. ASTM. *Standard Practice for Describing System Output of Implantable Middle Ear Hearing Devices* (ASTM International, 2014).
25. Koch, M. *et al.* Methods and reference data for middle ear transfer functions. *Sci. Rep.* **12**, 17241 (2022).
26. Merchant, S. & Rosowski, J. J. Syntax of referencing. In *Auditory Physiology and Middle-Ear Mechanics* (eds Gulya, A. J. & Glasscock, M. E., III.) 59–82 (BC Decker, 2003).
27. Nakajima, H. H., Ravicz, M. E., Rosowski, J. J., Peake, W. T. & Merchant, S. N. Syntax of referencing. In *Middle Ear Mechanics in Research and Otology* (eds Gyo, K. *et al.*) 189–196 (World Scientific, 2004).
28. Nandapalan, V., Pollak, A., Langner, A. & Fisch, U. The anterior and superior malleal ligaments in otosclerosis: A histopathologic observation. *Otol. Neurotol.* **23**, 854–861 (2002).
29. Ward, J. H. Hierarchical grouping to optimize an objective function. *J. Am. Stat. Assoc.* **58**, 236–244 (1963).
30. Murtagh, F. & Legendre, P. Ward's hierarchical agglomerative clustering method: Which algorithms implement ward's criterion?. *J. Classif.* **31**, 274–295 (2014).
31. Crompton, M. *et al.* The epidemiology of otosclerosis in a British Cohort. *Otol. Neurotol.* **40**, 22–30 (2019).
32. Fisch, U., Acar, G. O. & Huber, A. M. Malleostapedotomy in revision surgery for otosclerosis. *Otol. Neurotol.* **22**, 776–785 (2001).

Acknowledgements
This research was supported by Japan Agency for Medical Research and Development (AMED) under Grant Number (#20he0122007j0001) and Grant-in-Aid from Hirose Foundation. All figures in the manuscript were created by authors using commercially supplied software, with modifications made as needed.

Author contributions
S.L. and T.K. conceived and supervised the study; S.L. designed and performed the simulations and analyzed the data; H.Y. and Y.M. performed the simulations; F.Z. analyzed the data; K.S., T.K. and S.L. designed and performed the experiments; S.L. wrote the manuscript; S.L., F.Z., K.S. and T.K made the manuscript revision.

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to S.L.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2024