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COMPARATIVE MULTIVARIATE ANALYSES OF TRANSIENT OTOACOUSTIC EMISSIONS AND DISTORSION PRODUCTS IN NORMAL AND IMPAIRED HEARING

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Abstract

Background and aim. *The clinical utility of otoacoustic emissions as a noninvasive objective test of cochlear function has been long studied. Both transient otoacoustic emissions and distorsion products can be used to identify hearing loss, but to what extent they can be used as predictors for hearing loss is still debated. Most studies agree that multivariate analyses have better test performances than univariate analyses. The aim of the study was to determine transient otoacoustic emissions and distorsion products performance in identifying normal and impaired hearing loss, using the pure tone audiogram as a gold standard procedure and different multivariate statistical approaches.*

Methods. *The study included 105 adult subjects with normal hearing and hearing loss who underwent the same test battery: pure-tone audiometry, tympanometry, otoacoustic emission tests. We chose to use the logistic regression as a multivariate statistical technique. Three logistic regression models were developed to characterize the relations between different risk factors (age, sex, tinnitus, demographic features, cochlear status defined by otoacoustic emissions) and hearing status defined by pure-tone audiometry. The multivariate analyses allow the calculation of the logistic score, which is a combination of the inputs, weighted by coefficients, calculated within the analyses. The accuracy of each model was assessed using receiver operating characteristics curve analysis. We used the logistic score to generate receivers operating curves and to estimate the areas under the curves in order to compare different multivariate analyses.*

Results. *We compared the performance of each otoacoustic emission (transient, distorsion product) using three different multivariate analyses for each ear, when multi-frequency gold standards were used. We demonstrated that all multivariate analyses provided high values of the area under the curve proving the performance of the otoacoustic emissions. Each otoacoustic emission test presented high values of area under the curve, suggesting that implementing a multivariate approach to evaluate the performances of each otoacoustic emission test would serve to increase the accuracy in identifying the normal and impaired ears. We encountered the highest area under the curve value for the combined multivariate analysis suggesting that both otoacoustic emission tests should be used in assessing hearing status. Our multivariate analyses revealed that age is a constant predictor factor of the auditory status for both ears, but the presence of tinnitus was the most important predictor for the hearing level, only for the left ear. Age presented similar coefficients, but tinnitus coefficients, by their high value, produced the highest variations of the logistic scores, only for the left ear group, thus increasing the risk of hearing loss. We did not find gender differences between ears for any otoacoustic emission tests, but studies still debate this question as the results are contradictory. Neither gender, nor environment origin had any predictive* *value for the hearing status, according to the results of our study.*

Conclusion. *Like any other audiological test, using otoacoustic emissions to identify hearing loss is not without error. Even when applying multivariate analysis, perfect test performance is never achieved. Although most studies demonstrated the benefit of using the multivariate analysis, it has not been incorporated into clinical decisions maybe because of the idiosyncratic nature of multivariate solutions or because of the lack of the validation studies.*

Keywords: otoacoustic emissions, multivariate analyses, logistic regression, hearing loss, receiver operating curves

Background and aims

The discovery of otoacoustic emissions (OAE) has provided a unique window into the physiology of the inner ear. Otoacoustic emissions are normal by-products of the active mechanical force generated by the outer hair cells [1] and transmitted from the cochlea through the ossicular chain and tympanum into the ear canal.

OAEs can appear spontaneously or can be induced by an acoustic stimulation. Spontaneous OAEs (SOAE) are produced without acoustic stimulation and appear in about 25-70% of normal hearing ears [2-7]. Transient evoked OAEs (TEOAE) are delayed responses with respect to the onset of brief acoustic stimulation [8,9]. Distortion-product OAEs (DPOAE) are produced by simultaneous stimulation with two primary tones at frequencies of f1 and f2 ($f1<f2$), and occur as a cubic distortion product [10]. The 2f1-f2 DPOAE emission is measured to predict auditory status, as it is typically the highest level distortion product in humans [11].

Since Kemp discovered OAEs in 1978, it has been confirmed that the presence of measurable otoacoustic emissions is influenced by both middle ear [12,13] and cochlear status [11,14-17]. As the otoacoustic emissions are invariably associated with the functioning of the outer hair cells (OHC), their presence is a reliable indicator of cochlear structural integrity and their absence may indicate a cochlear lesion. In general, when sensorineural hearing loss reaches approximately 40 dB to 50 dB HL, all types of OAEs are absent [15,18-20].

The clinical utility of otoacoustic emissions as a noninvasive objective test of cochlear function has been long studied. Both TEOAE and DPOAE can be used to identify hearing loss due to outer hair cell dysfunction at the frequency range where they would be normally expected. Generally speaking, DPOAE are more sensitive and frequency specific than TEOAE. Most of the studies stated that the measuring of TEOAE seems more effective than the measuring of DPOAE. Therefore, the measuring of TEOAEs is a good method for hearing screening [21,22] and the measuring of DPOAEs is a good method for a detailed research on cochlear disorders.

Many studies tried to use otoacoustic emissions as a predictive measure of the hearing threshold. Some authors agree that OAE can separate subjects with normal hearing from subjects with elevated hearing thresholds [11,16,23-26].

Using the univariate and multivariate analyses, Hussain evaluated the ability of the TEOAE to predict cochlear hearing loss [16]. He demonstrated that the multivariate technique improved the accuracy of TEOAE in predicting auditory status. Gorga also demonstrated that the multivariable analysis provided an improvement in DPOAE test performance [27]. Dorn also stated that multivariate solutions could be more accurate than univariate DPOAE methods for identifying hearing loss [28]. Other studies have been ambiguous in their recommendation of the use of multivariate analysis [24].

Assuming that the pure tone audiogram accurately represents cochlear status, prediction errors exist because test scores for normal and impaired ears overlap to some degree [11,15,29-31]. No stimulus condition or response criteria can be selected, for which all normal ears produce a response and all impaired ears do not [15,29].

The aim of this study was to determine to what extent the OAE (both the TEOAE and the DPOAE) can predict auditory status using the pure tone audiogram as a gold standard procedure, which defines hearing to be within normal limits or impaired. The main focus of this study was to determine if information about cochlear status using OAE could be improved with the use of multiple predictor variables.

Patients and methods

The study was performed in the ENT Clinic of Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, between October 2013 and February 2014. All the patients were informed about the participation in this study and their written informed consent was obtained

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before the study was initiated. The study had the approval of the Ethics Committee of the University of Medicine and Pharmacy ”Iuliu Hatieganu” Cluj-Napoca and had been conducted according to the principles in the Declaration of Helsinki, revised in 2013.

Patients

105 adult subjects were recruited from the ENT Clinic. The subjects did not receive any payment for their participation. All the participants were tested in similar conditions and using the same personnel, the same methods and equipments and the data were collected from both ears. The inclusion criteria involved the patient’s agreement to participate in this study, normal or sensorineural hearing loss, either unilateral or bilateral. Patients with a history of outer, middle ear pathology or any other cause of a conductive hearing loss were excluded from the study group. Sudden hearing loss, Meniere syndrome and retrocochlear diseases were also excluded from the evaluation analysis. All the audiological tests were performed in the Audiology Compartment of the ENT Clinic of the Emergency County Hospital Cluj-Napoca.

Procedure

All subjects underwent the following test battery: anamnesis, otoscopic examination and, if necessary, cleaning the external ear canal, pure-tone audiometry, tympanometry, acoustic reflex and reflex decay test, otoacoustic emission tests (TEOAE and DPOAE).

Pure-tone Audiometry

Pure tone audiometry was conducted in a sound-treated booth using an Interacoustic Clinical Audiometer AC 40 DK-5610, Assens, Denmark audiometer calibrated annually according to ISO standards, with the patient sitting comfortably on a chair spatially separated from the PC and examiner. The tests of each ear included the standard frequencies 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz. For each test frequency, the signal was automatically increased by steps of 5 dB hearing level (HL), until the tested person responded. Afterwards the signal was decreased by 10 dB and, again, increased by 5 dB until response. The actual threshold was set after 2 out of 3 responses were consistent. The hearing threshold was calculated as the mathematical average for all the frequencies measured from 0.5 to 4 kHz, as recommended by the World Health Organization. Normal hearing was defined as thresholds ≤20 dB HL. For the purposes of counting the number of ears, subjects were considered hearing impaired if one or more pure-tone behavioral thresholds were >20 dB HL for the same frequency range. Only subjects with sensorineural hearing loss (defined as air-bone gaps <15 dB at the frequency range of 0.5-4 kHz) were included in the study. The degree of hearing loss ranged from mild to profound. For the subjects with hearing loss, the site of lesion was assumed to be the cochlea, based on clinical history and special audiological tests, including acoustic reflex threshold and reflex decay test.

The hearing loss was classified as mild (hearing thresholds between 21-40 dB HL), moderate (hearing thresholds between 41-70 dB HL), severe (hearing thresholds between 71-90 dB HL) and profound (hearing thresholds between 91-120 dB HL). While subjects presented audiometric thresholds ranging from normal hearing to profound hearing loss, efforts were made to increase the representation of subjects with normal hearing and mild or moderate hearing losses on the assumption that these subjects would be more likely to produce OAEs, compared to subjects with greater degrees of hearing loss.

Tympanometry

All the subjects had middle ear function assessed using an Interacoustics Titan Suite, Wideband Tympamometry, Assens, Denmark tympanometer with a 226-Hz probe tone. The test had been performed with the patient seated comfortably in a sound-treated booth. In order to correspond to the inclusion criteria, the following tympanometric criteria had to be observed: curve type A according to Jerger’s classification, acoustic reflex present both ipsilateral and contralateral, reflex decay test at the frequency of 1 kHz positive.

OAE tests

After audiometric and middle ear assessments, OAE data were collected from both ears. The participants sat comfortably upright, and were given instructions to remain as quiet as possible for the duration of the tests. An appropriate sized ear probe tip was placed and securely positioned into the ear canal with a good seal. We have chosen TEOAE and DPOAE because they are the most commonly used in clinical practice and have more standardized methodology.

TEOAE testing was always performed first. The equipment used was the Intelligent Hearing System SMART-EP. TEOAEs were performed with a nonlinear, click stimulus at the intensity of 85 dB sound pressure level (SPL) with a presentation rate of 19.3/msec. 1024 sweeps were performed on each test. The response was collected for the frequencies range of 1 to 4 kHz and regarded as pass if the signal noise ratio (SNR) was greater or equal to 6 dB SPL for all frequencies. An artifact rejection noise limit was automatically set. The measuring stopped when all the sweeps were performed.

DPOAEs were measured using a commercial equipment from Interacoustics Titan Suite, Assens, Denmark. The stimuli consisted of two pures tones (f1 and f2; f2/f1=1.22) presented simultaneously, with L1 and L2 set to 65, respectively 55 dB SPL. These stimulus levels were chosen because previous data had shown that they provided the greatest accuracy in classifying ears as normal or impaired, based on an audiometric criterion for normal hearing of 20 dB HL [14,31,32]. DPOAEs were estimated as the amplitude for the cubic distortion product 2f1-f2 and were collected and displayed in the form of a distortion product frequency profile (DP-gram) as a function of f2 for 1, 1.5, 2, 3, 4 and 6 kHz. The recording stopped automatically after it ran through the recording frequencies for 30 seconds for each ear. DPOAE responses were considered ’pass’ when signal/noise ratio was greater or equal to 6 dB SPL for all f2 frequencies and the reliability was greater than 98%.

We used the value of SNR for both tests, although there are studies which determined that neither the amplitude of the OAE nor the SNR can correctly identify normal and impaired hearing with 100% accuracy [11,15,29,31].

Statistical analysis

The data were collected using Microsoft Excel 2003, but for statistical analysis Microsoft Excel 2010 and Medcalc v12.1.2 had been used. Student t test, Kaplan-Meyer survival analysis, logistic regression and receivers operating curves were used as statistical methods. A p value <0.05 was considered statistically significant.

We used the Kaplan Meyer survival curves to determine the critical age associated with hearing loss defined by the pure-tone audiometry. We also wanted to demonstrate if other variables, like gender, environment origin and presence of tinnitus are important in predicting the age associated with hearing loss.

We also chose to use the logistic regression as a multivariate statistical technique and receivers operating curves (ROC curves). In the application of logistic regression to OAE data, pure-tone thresholds served as the gold standard to which OAE data were compared.

Multivariate analyses use multiple input variables to calculate a univariate output variable, the logistic score, which is a combination of the inputs, weighted by coefficients calculated within the analysis. The logistic regression model assumes a transformation of variables in a dichotomous categorical variable (with values of 0 or 1) with an associated probability of impairment.

Logistic regression models were developed to characterize the relations between different variables (age, sex, tinnitus, environment origin, cochlear status defined by OAE tests) and hearing status (dependent factor), defined by pure-tone audiometry as normal or impaired. The logistic regression fitted the variables with a logistic model using a maximum likelihood method to calculate the coefficients associated with each variable. Models were developed for each OAE test and for each ear.

The first multivariate statistical analysis was performed for each otoacoustic emission test for each ear group. The goal was to group objective attributes, such as SNR for each OAE test, into either of two categories, normal or impaired hearing. We had assigned that the dependable factor was hearing classified as normal or impaired and the variables used were the values of SNR for each OAE test. On the basis of data derived from 105 ears, three, respectively four logistic regressions were computed for TEOAE, respectively DPOAE for each ear. After applying the logistic regression for each OAE test, the model was reduced in a backward fashion by eliminating gradually the SNRs that presented the highest p values, remaining only two SNR for each ear and for each test, which were considered to be the most important ones in predicting normal or impaired hearing.

Using the same dependent factor (hearing status), we added more variables in order to proceed to the second multivariate statistical analysis, such as age, gender, environment origin (urban or rural), tinnitus (present or absent) and the values of SNR for each OAE test. The age and gender variables were selected a priori on the basis of a belief that they would likely be important in predicting hearing. This model was reduced by a backward elimination for the variables with the highest p value, until we had left only variables with significant p value.

We performed the third multivariate analysis, by combining variables from both OAE tests. We kept the same dependent factor, the hearing level, normal or impaired. The chosen variables were: age, gender, environment origin, tinnitus and only SNR of OAE tests proven to be the best hearing predictors in the first multivariate analysis. The SNRs used for the right ear group were 1 and 4 kHz for TEOAE and 2 and 6 kHz for DPOAE. For the left ear group, we used SNRs at 1.5 and 3 kHz for TEOAE and SNRs at 1 and 6 kHz for DPOAE.

The accuracy of each model was assessed by using receiver operating characteristics (ROC) curve analysis. A ROC curve is a plot of test sensitivity (hit rates), which is the proportion of ears with hearing loss that were correctly identified against 1-specificity (false-alarm rates), which is the proportion of normal-hearing ears incorrectly identified as hearing impaired. Areas under the ROC curves were calculated nonparametrically using a Wilcoxon sign test, in which each value from the impaired distribution is compared with every value in the normal distribution. AUC ranges in value from 0.5 where hit and false-alarm rates are equal (chance performance) to 1.0 (perfect test performance) where the hit rate is 100% for all false-alarm rates, including a false-alarm rate of 0%.

We calculated the derived output variable (the logistic score) by summing the constant and the result from multiplying each final variable with its own coefficient. Each of the three multivariate analysis presented different values of the logistic score for each ear group. We used the logistic score to generate receivers operating curves (ROC) curves and to estimate ROC curve areas and the associated standard errors for each statistical analysis.

Results

The study group comprised 105 patients (210 ears tested) with the demographic features explained in table I.

The patients complained of the presence of the tinnitus in 34 right ears (13 normal hearing ears, 38.2% and 21 impaired hearing ears, 61,2%) and in 39 left ears (8 normal hearing ears, 20.5% and 31 impaired hearing ears, 73.5%).

The tested ears were divided in two study groups: right ear group and left ear group. Applying student's t test for the right ear group, we have found statistically significant values of p for gender distribution (p=0.02) and for the presence of tinnitus (p=0.04). For the left ear group, we recorded significant values of p for the environment origin (p=0.04) and for the presence of tinnitus (p<0.01).

Pure-Tone Audiometry

According to the pure tone audiometry, each tested ear was classified as normal or impaired as seen in table II. 40 patients (87%) presented bilateral normal hearing, while 44 patients (74.6 %) presented bilateral impaired hearing loss.

Results of pure-tone audiometry in the impaired hearing subgroups are illustrated in table III.

Using the Kaplan Meyer survival curves to determine the critical age associated with hearing loss, we found that left ear presented hearing loss at a younger age (right ear group, 45.6 years; left ear group, 41.4 years). We also observed that the presence of the tinnitus was statistically associated with hearing loss at a younger age in the left ear group (right ear group - tinnitus present: 56.2 years, tinnitus absent: 55.3 years, p=0.67; group 2 - tinnitus present: 49.5 years, tinnitus absent: 57.8 years, p=0.02). Gender and environment origin did not prove to have statistically significance in determining the critical age associated with hearing loss (female 57.8 years, male 55.9 years, p=0.73; urban, 61 years; rural, 46.2 years; p=0.05) according to Kaplan-Mayer survival analysis.

Otoacoustic Emission Tests

TEOAE

Applying pass criteria (SNR≥6 dB SPL for all frequencies), we determined a false positive response rate of 37% in both groups. We recorded significant differences for TEOAE between the distribution of normal hearing and hearing impaired in each study group (p<0.01), as seen in table IV.

We recorded measurable TEOAE for normal and mild hearing loss as seen in table V.

DPOAE

For DPOAE the false positive of response rate was 24% for the right ear group and 26% for the left ear group). We recorded significant differences between normal and impaired hearing for both ear groups, for DPOAE (p<0.01) (see table VI).

Table VII describes the presence of measurable DPOAE in relation to hearing status.

OAE performance

The first multivariate analysis uses the hearing level as the dependent factor, and the value of SNR of each OAE test, for each ear group as variables.

After the first step of the logistic regression for TEOAE, we encountered the smallest p values at 1 kHz in the right ear group (p=0.05) and at 3 kHz in the left ear group (p=0.14). The area under the curve presented higher values for the right ear group (AUC=0.88 in the right ear group, respectively 0.84 in the left ear group), SE presented similar values (0.03 in the right ear group, respectively 0.04 in the left ear group) while the confidence interval was different in the two groups (95%CI=0.81-0.94 for the right ear group, respectively 0.57-0.9 for the left ear group). After the last stage of the logistic regression, the value of the area under the curve and the standard error presented similar values as in the first step of the analysis, but the confidence interval presented higher values for the left ear group (95%CI=0.74-0.89) and similar values for the right ear group. The frequencies that best predict the auditory status were represented by 1 and 4 kHz (p=0.001) for the right ear and 1.5 and 3 kHz (p=0.05, respectively 0.004) for the left ear.

From the first stage of the logistic regression for DPOAE, we recorded significant p values at 6 kHz for the right ear group and at 1 kHz for the left ear group. The AUC values were higher for the left ear group (AUC=0.85 for the right ear group, respectively 0.89 for the left ear group), with similar SE values for both groups (SE=0.04 for the right ear group and 0.03 for the left ear group) and the confidence interval is higher for the left ear group (95%CI=0.77-0.91 for the right ear group and 0.82-0.95 for the left ear group). After multiple stages of the statistical analyses, the AUC, SE and the CI presented similar values for both groups. For the right ear group, only the frequencies of 2 and 6 kHz (p=0.007, respectively p=0.005) remained as predictors for normal hearing and for the left ear group, the frequencies of 1 and 6 kHz (p=0.001, respectively p=0.04).

We calculated the logistic scores using the values of the constant and coefficients generated by the first multivariate analysis, as seen in table VIII. Then we recorded the distribution of the logistic scores for normal and impaired hearing, for each ear group and for each type of OAE in the figure 1.

For the second multivariate analysis, we added multiple variables (age, gender, environment origin, tinnitus) to the value of SNR for each frequency for each OAE test, to predict cochlear status (dependent factor, the hearing level, either normal or impaired).

In the first stage of the logistic regression for TEOAE, we encountered significant p values for age in both groups (right ear group, p=0.02; left ear group, p=0.002) and for tinnitus only for the left ear group (p=0.001). The first TEOAE SNR that proved a strong hearing prediction was recorded at the frequency of 3 kHz for the left ear group 2 (p=0.02). The value of area under the curve presented the same value in both groups (AUC=0.91), with similar SE (SE=0.02) and CI (right ear group, 95%CI=0.80-0.93; left ear group, 95%CI=0.83-0.94). After multiple stages of logistic regression, the area under the curve presented similar values in both groups (AUC=0.9 in the right ear group, 0.89 in the left ear group), standard error and confidence interval were similar in both groups (SE=0.03; 95%CI=0.83-0.95 in the right ear group and 0.82-0.94 in the left ear group). The variables that best predict hearing status were age for both groups (the right ear group, p=0.006; the left ear group, p=0.001), tinnitus only for the left ear group (p=0.0008). The TEOAE SNRs that presented the strongest predicting power were recorded at the same frequencies as revealed by the first multivariate analysis: the frequencies of 1 and 4 kHz for the right ear group (p=0.002, respectively 0.01) and of 1.5 and 3 kHz (p=0.04, respectively 0.01) for the left ear group. Neither gender nor environment origin had any predictive power in conjunction with TEOAE.

As seen in multivariate analysis for TEOAE, age presented a significant p for both groups, from the first stage of the logistic regression analysis for DPOAE (right ear group, p=0.004, respectively left ear group, p=0.01). We also recorded the SNR at frequency of 6 kHz as a good predictor for normal hearing (p=0.06) in the right ear group and 1 kHz in the left ear group (p=0.06). Tinnitus appeared to be a strong predictor for the left ear group from the first stage of the statistical analyses (p=0.001). After the first stage, we encountered an area under the curve similar for both groups (right ear group, AUC=0.89; left ear group, AUC=0.93), the same value for the standard error (SE=0.02) and different values for the confidence interval (right ear group, 95%CI=0.84-0.95; left ear group, 95%CI=0.73-0.97). In the final stage of the second multivariate analysis for DPOAE, the values of the area under the curve were higher for the left ear group (right ear group, AUC=0.89; left ear group, AUC=0.92) though similar to the value obtained after the first stage, the standard error and the interval of confidence presented similar values for both groups (right ear group, SE=0.03, 95%CI=0.82-0.94; left ear group, SE=0.02, 95%CI=0.85-0.96). Neither gender nor environment origin had any predictive power in conjunction with DPOAE. The second multivariate analyses demonstrated that the best predictors variables for normal hearing were: age for both groups (right ear group, p=0.0004; left ear group, p=0.005), the DPOAE SNR at frequencies of 2 and 6 kHz for the right ear group and 1.5 kHz for the left ear group (right ear group, p=0.006, respectively 0.02; left ear group, p<0.0001). Despite of the first analysis, the DPOAE SNR at frequency of 6 kHz for the left ear group lost its power of hearing prediction.

We calculated the logistic scores for each ear group, using the values of the constants and coefficients obtained by the second multivariate analysis (see table IX).

Then we generated the ROC curves for the logistic score of the second multivariate analysis for each ear group (see figure 2). The area under the curve presented similar values for both types of otoacoustic emissions (TEOAE AUC=0.91, DPOAE, AUC=0.90) for the right ear group. For the left ear group, we obtained an AUC slightly higher value for the DPOAE logistic score (TEOAE AUC=0.9, DPOAE AUC=0.92).

We performed the third multivariate analysis combining the OAE tests. We kept the same dependent factor (the hearing level, normal or impaired) and the same demographic variables (age, gender, environment origin, tinnitus), but we added as variables the value of SNR that proved to be the best hearing predictors in our first multivariate analysis. For TEOAE, we used for the right ear group the values of SNR at 1 and 4 kHz and for the left ear group, the values of SNR at 1.5 and 3 kHz. For DPOAE, we used the SNR at 2 and 6 kHz for the right ear group, respectively 1 and 6 kHz for the left ear group.

After the first stage of the multivariate analysis for the right ear group, the following variables remained in equation as strong predictors for the hearing level: age (p=0.007), SNR for TEOAE at 1 kHz (p=0.15), sex, environment origin and SNR for DPOAE for 2 and 6 kHz (p=0.2-0.3). The value of the area under the ROC curve was 0.92, with a SE of 0.03 and 95% CI=0.85-0.96. Eliminating each variable that presented the highest p value in each stage of the multivariate analysis, we demonstrated that the best hearing predictors for the right ear remained: age (p=0.003), TEOAE for low frequencies (SNR at 1 kHz, p=0.002) and DPOAE for high frequencies (SNR at 6 kHz, p=0.01). The area under the ROC curves presented a slightly decreasing tendency (AUC=0.90), but with the same SE (SE=0.03) and CI (95%CI =0.84-0.96). Applying the first step of the multivariate analysis for the left ear group, we obtained significant p values for the following variables: age (p=0.03), tinnitus present in left ear (p=0.001) and for DPOAE at 1 kHz (p=0.004) and small p values for SNR for TEOAE at 3 kHz (p=0.09). We recorded high values for p for different variables, such as SNR for DPOAE at 6 kHz (p=0.94) and for TEOAE at 1.5 kHz (p=0.91), gender (p=0.58) and environment origin (p=0.13). The value of the area under the ROC curves presented a slightly higher value than the right ear group (AUC=0.93), with a SE of 0.02 and 95%CI of 0.87-0.97. We have eliminated step by step variables that presented the highest p values, and the best predictors for the hearing status remained: age (p=0.02), tinnitus (p=0.001), TEOAE SNR at 3 kHz (p=0.04) and DPOAE SNR at 1 kHz (p=0.0008). Analyzing the performance for combined multivariate analysis for the left ear group, using the value of the area under the ROC curves, we obtained similar results as in the first stage (AUC=0.93, SE=0.02, 95%CI=0.86-0.97).

Neither gender nor environment origin had any predictive power for hearing status.

We calculated the logistic scores for each ear group (see table X). Age presented similar coefficients for both ears, but tinnitus coefficient by its high value produced the biggest variations of the logistic scores.

Figure 3 illustrates the ROC curves for the logistic score of the combined multivariate analysis for each group.

The results of this analysis presented slightly higher values for the area under the ROC curves for the left ear group (right ear group, AUC=0.91; left ear group, AUC=0.93) with similar SE (SE=0.03) and CI (95%CI =0.86-0.97).

All the multivariate analyses provided high values of the area under the ROC curves. Each OAE tests presented different values of AUC, though there were small differences between the two groups. The highest AUC value was encountered for the combined multivariate analysis and for the left ear group, as seen in table XI.

Knowing the logistic score (LS) for each test performance, we can convert it into a risk function (RF), using the following equation:

$$RF=1/(1+e^{-LS}).$$

The higher the value of the logistic score, the higher the risk of hearing impairment, the smaller the logistic score, the lower the risk of hearing impairment. One of the characteristics of the risk function is represented by the fact that the midline of the risk function (RF=50%) can be used, independent of sensitivity and specificity. The risk function for the hearing impairment could be used in screening applications based on the compilation of data from several frequencies.

Table I. Demographic features of the participants.

Age	Average	44.78 years
	Standard deviation (SD)	15.7 years
	Age range	13-76 years
Gender	Female	63 (60%)
	Male	42 (40%)
Environment origin	Urban	84 (80%)
	Rural	21 (20%)

Table II. Distribution of the study groups according to pure-tone audiometry results.

	Right ear group	Left ear group
Normal hearing	55 (52.4%)	46 (43.8%)
Impaired hearing	50 (47.6%)	59 (56.2%)

Table III. The degree of hearing loss for each study group.

	Mild hearing loss	Moderate hearing loss	Severe hearing loss	Profound hearing loss
Right ear group	25 (23.8%)	17 (16.2%)	2 (1.9%)	6 (5.7%)
Left ear group	29 (27.6%)	26 (24.8%)	3 (2.8%)	1 (1%)

Table IV. The distribution of the TEOAE results (pass and refer) for each ear group according to the audiometric results.

	Right ear group		p	Left ear group		p
	Normal hearing	Impaired hearing		Normal hearing	Impaired hearing	
Pass	35 (92.1%)	3 (7.9%)	<0.01	29 (87.9%)	4 (12.1%)	<0.01
Refer	20 (29.9%)	47 (70.1%)		17 (23.6%)	55 (76.4%)	
Total	55 (52.4%)	50 (47.6%)		46 (43.8%)	59 (56.2%)	

Table V. TEOAE results according to the hearing status confirmed by the audiogram.

	TEOAE	Normal hearing	Impaired hearing			
			Mild	Moderate	Severe	Profound
Right ear group	Pass	35 (92.1%)	3 (7.9%)	0	0	0
	Refer	20 (29.9%)	23 (34.3%)	17 (25.4%)	2 (3%)	6
Left ear group	Pass	29 (87.9%)	3 (9.1%)	0	0	0
	Refer	17 (23.6%)	26 (36.1%)	26 (37.7%)	3 (4.2%	1 (1.4%)

Table VI. Distribution of the DPOAE results (pass and refer) for each ear group according to the audiometric results.

	Right ear group		p	Left ear group		p
	Normal hearing	Impaired hearing		Normal hearing	Impaired hearing	
Pass	42 (89.4%)	5 (10.6%)	<0.01	34 (81%)	8 (19%)	<0.01
Refer	13 (22.4%)	45 (77.6%)		12 (19%)	51 (81%)	
Total	55 (52.4%)	50 (47.6%)		46 (43.8%)	59 (56.2%)	

Table VII. DPOAE results according to the hearing status confirmed by the pure-tone audiometry.

	DPOAE	Normal hearing	Impaired hearing			
			Mild	Moderate	Severe	Profound
Right ear group	Pass	42 (89.4%)	4 (8.5%)	0	0	0
	Refer	13 (22.4%)	21 (36.2%)	17 (29.3%)	2 (3.4%)	6 (5.7%)
Left ear group	Pass	34 (81%)	6 (14.3%)	23 (36.5%)	0	0
	Refer	12 (19%)	23 (36.5%)	24 (38.1%)	3 (4.8%)	1 (1.6%)

Table VIII. Coefficients of the logistic regression for each group and each OAE test (for the first multivariate analysis performed).

		Variable	Coefficient	SE	p	Odds ratio	95%CI
TEOAE	Right ear group	1 kHz	-0.163	0.052	0.0017	0.848	0.776 to 0.94
		4 kHz	-0.225	0.071	0.0015	0.797	0.693 to 0.912
		Constant	2.382				
	Left ear group	1.5 kHz	-0.077	0.04	0.04	0.925	0.855 to 1
		3 kHz	-0.132	0.046	0.004	0.876	0.779 to 0.96
		Constant	2.245				
DPOAE	Right ear group	2 kHz	-0.083	0.031	0.0075	0.92	0.857 to 0.978
		6 kHz	-0.085	0.030	0.005	0.918	0.865 to 0.974
		Constant	1.536				
	Left ear group	1 kHz	-0.207	0.048	<0.0001	0.812	0.739 to 0.893
		6 kHz	-0.054	0.027	0.046	0.947	0.897 to 0.999
		Constant	2.674				

Table IX. Coefficients of the logistic regression for each group and each OAE test generated by the second multivariate analysis.

		Variable	Coefficient	SE	p	Odds ratio	95%CI
TEOAE	Right ear group	Age	0.057	0.02	0.006	1.058	1.016 to 1.103
		1 kHz	-0.170	0.056	0.002	0.843	0.754 to 0.941
		4 kHz	-0.172	0.072	0.018	0.841	0.729 to 0.971
		Constant	-0.297				
	Left ear group	Age	0.060	0.019	0.001	1.062	1.023 to 1.103
		Tinnitus	2.169	0.644	0.0008	8.758	2.475 to 30.984
		1.5 kHz	-0.091	0.045	0.04	0.912	0.834 to 0.997
		3 kHz	-0.133	0.053	0.012	0.874	0.788 to 0.971
		Constant	-1.011				
DPOAE	Right ear group	Age	0.054	0.019	0.004	1.055	1.016 to 1.096
		2 kHz	-0.093	0.034	0.006	0.91	0.85 to 0.974
		6 kHz	-0.068	0.03	0.02	0.933	0.879 to 0.991
		Constant	-0.960				
	Left ear group	Age	0.058	0.020	0.005	1.059	1.017 to 1.104
		Tinnitus	2.192	0.687	0.001	8.955	2.327 to 34.467
		1.5 kHz	-0.176	0.038	<0.0001	0.838	0.838 to 0.903
		Constant	-0.783				

Table X. Coefficients of the logistic regression for each group (for the third multivariate analysis).

	Variable	Coefficient	SE	p	Odds ratio	95%CI
Right ear group	Age	0.062	0.02	0.003	1.064	1.021 to 1.108
	TEOAE 1 kHz	-0.175	0.056	0.002	0.838	0.75 to 0.937
	DPOAE 6 kHz	-0.071	0.03	0.018	0.93	0.877 to 0.988
	Constant	-0.704				
Left ear group	Age	0.046	0.02	0.027	1.047	1.005 to 1.091
	Tinnitus	2.248	0.71	0.001	9.471	2.351 to 38.158
	TEOAE 3 kHz	-0.094	0.059	0.0008	0.909	0.828 to 0.998
	DPOAE 1 kHz	-0.199	0.047	0.047	0.818	0.728 to 0.92
	Constant	3.141				

Table XI. Differences in AUC for the three multivariate analyses.

AUC	Right ear group		Left ear group	
The first multivariate analysis	TEOAE DPOAE	0.87 0.84	TEOAE DPOAE	0.83 0.89
The second multivariate analysis	TEOAE DPOAE	0.9 0.89	TEOAE DPOAE	0.89 0.92
The third multivariate analysis		0.9		0.93

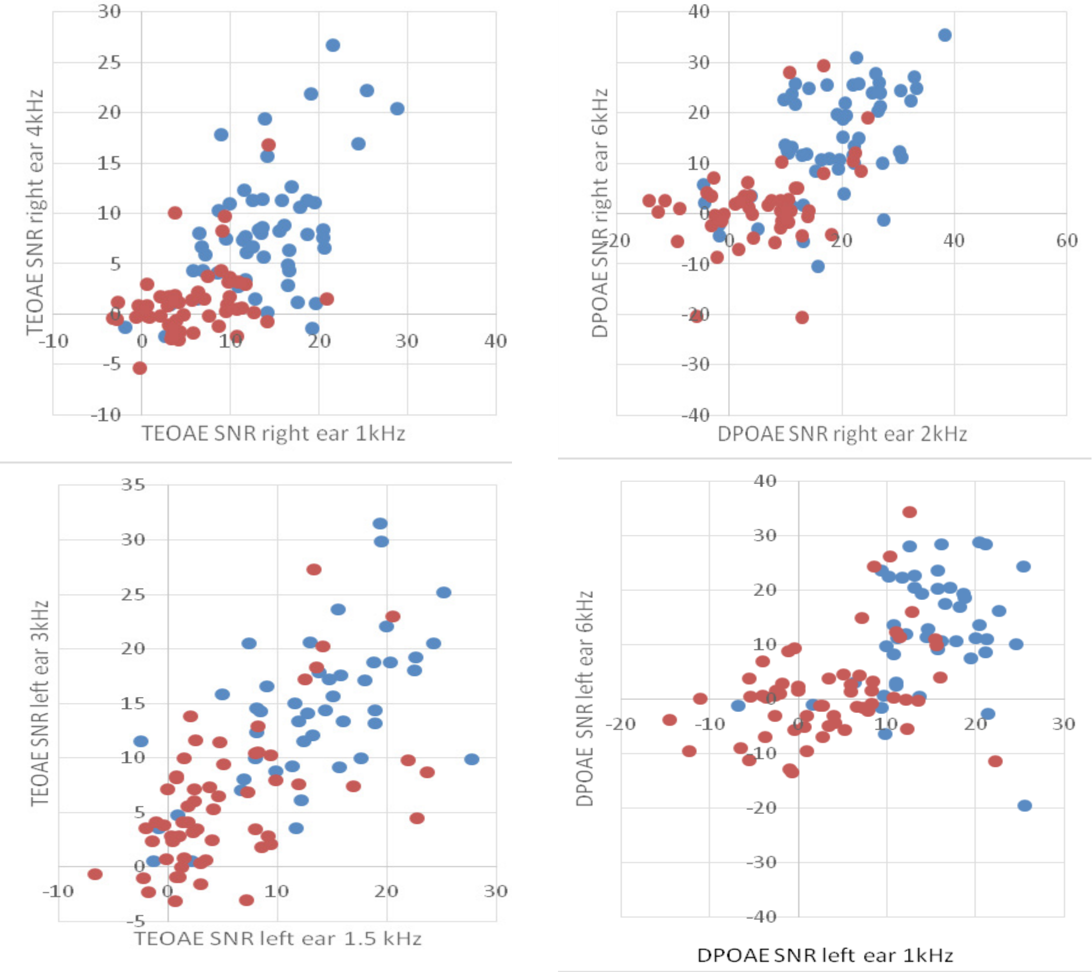


Figure 1. Distribution of the hearing status, according to the logistic scores for the first multivariate analysis performed for both TEOAE and DPOAE, for the right ear group and for the left ear group. The distribution of the normal hearing is represented by the blue color and impaired hearing by the red color.

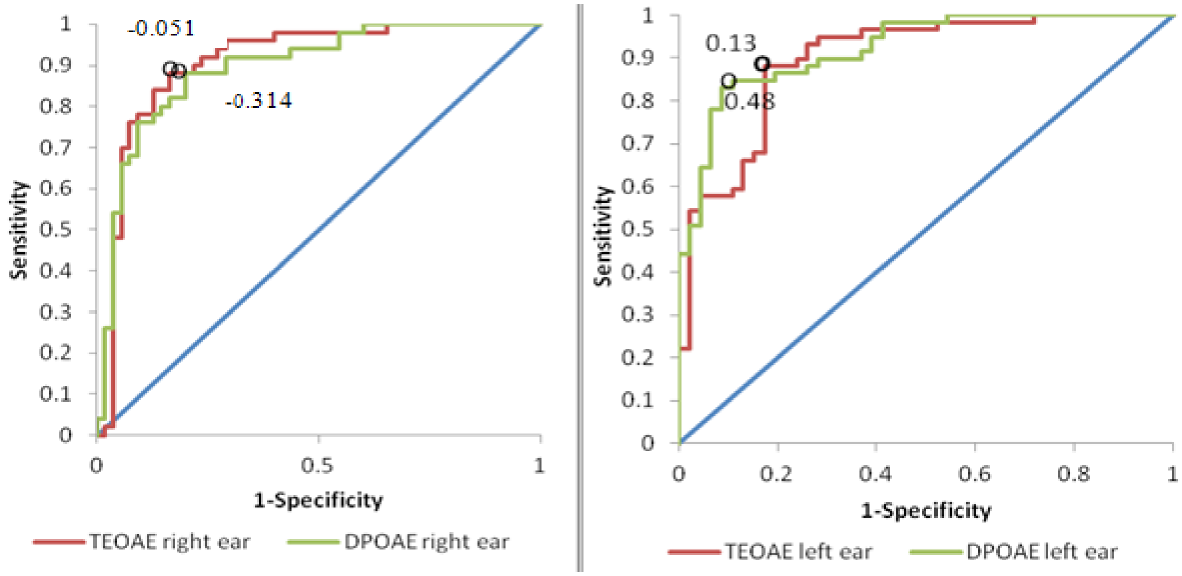
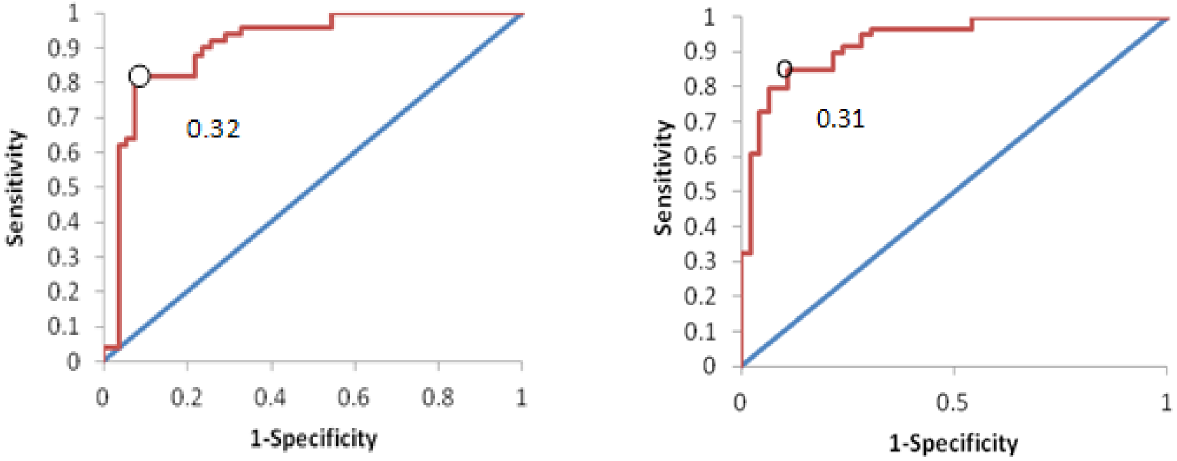


Figure 2. ROC curves for the second multivariate analysis for both OAE test, for both ear groups. For the right ear group, we encountered a negative cutoff value for the logistic score (TEOAE cutoff= -0.051, sensitivity= 88%, specificity=84%; DPOAE cutoff= -0.314, sensitivity=88%, specificity=80%). In the left ear group, we encountered positive cutoffs for both OAE tests (TEOAE cutoff=0.13, sensitivity=88%, specificity= 83%; DPOAE cutoff=0.48, sensitivity=85%, specificity= 89%).



A

B

Figure 3. ROC curves for the combined multivariate analysis; panel A for the right ear group, panel B for the left ear group. The cutoffs of the logistic score for the two groups were similar (right ear group, cutoff=0.32, sensitivity=82%, specificity=93%; left ear group, cutoff=0.31, sensitivity=85%, specificity=89%).

Discussion

We have compared the performance of each OAE test (TEOAE, DPOAE) using three different multivariate analyses for each ear, when multi-frequency gold standards were used. We chose to use multi-frequency gold standard because the diagnosis of the auditory status is made on the basis of a group of frequencies and not on the basis of each frequency individually. By using multi-frequency gold standard in multivariate analyses, the use of OAE measurements in screening applications of hearing impairments may be justified. Nevertheless there are studies reporting that statistical analyses for both OAE tests have better results when using single-frequency rather than multi-frequency [26].

The statistical method chosen was the logistic regression because it allowed the conversion of the measurements for each ear in terms of a probability of impairment rather than simply as a linear combination of decibel values. Dorn suggested that logistic regression had slightly better performance than other statistical techniques, such as discriminant function [28]. Kimberly studied predictor factors for DPOAE test performance using the value of SNR at six test frequencies [24]. His study did not support strong evidence that discriminant analyses can improve test performance in multivariate versus univariate analyses. On the other hand, Dorn applied multivariate techniques to DPOAE data, without including age or gender as variables and reported better test performance for single frequency [28]. Hussain evaluated TEOAE test performance using both univariate and multivariate techniques and found out that results for multivariate analysis were better than results of the univariate analysis for the overall test performance [16].

We had used the ROC curves areas, a statistical parameter that provides strong evidence of the performance of each OAE test in order to differentiate normal hearing from impaired hearing based on audiometric results. This method has been widely used in many studies [15,29-31] because the area under the ROC curve is a good measure of prediction performance [32].

We had demonstrated that all multivariate analyses provided high values of the area under the curve, which prove the performance of the OAE, thus confirming the discovery of other studies [27,28] that regard the superiority of multivariate analysis of OAE data. Each OAE test presented high values of AUC, though small differences were recorded between the two groups, suggesting that the implementation of a multivariate approach to evaluate the performances of each OAE test would serve to increase the accuracy in identifying the normal and impaired ears. We encountered the highest AUC value for the combined multivariate analysis, especially for the left ear group. Our study proved that using variables from both OAE tests, the multivariate model had a better performance confirming other studies results [25,33] and suggesting that both OAE test should be used in assessing hearing status. Most studies have demonstrated that it is more advantageous to use the multivariable analysis than univariate approaches, but there are differences of stimulus and recording conditions between studies. In his study, Gorga [27] compared univariate and multivariate analyses for different pure-tone averages, while we used the same hearing threshold average to determine the differences from both ears.

The coefficients and constants for each multivariate analysis are applicable only when using the same stimulus and recording conditions used in our study, fact sustained by other studies [28,29]. Assuming that the cochlear status is accurately represented by the pure-tone audiogram, diagnostic errors can occur for every clinical audiological test even under the best of circumstances. The results of our first multivariate analysis had shown that the distribution of normal and impaired hearing is overlapping in some degree as a reminder that there is no perfect method to define normal hearing. Prediction errors always exist because test scores for normal and impaired ears overlap to some degree [11,15,29-31]. Applying pass criteria, we observed that not all ears declared normal hearing according to pure-tone audiometry present measurable OAEs (both TEOAE and DPOAE). We recorded measurable TEOAE only for normal hearing and for mild hearing loss. Also, we observed that as the hearing impairement increases, TEOAE are more likely to be absent. DPOAE present the advantage to be present even in moderate hearing loss in contrast to TEAOE which are measurable only for normal hearing and for mild hearing loss. This allows us to monitor the function of the outer hair cells even when damage lesions are advanced. The sources of diagnostic errors remain undetermined, but might result from the fact that OAEs only reflect OHC function (providing no information about the integrity of the IHCs or auditory nervous system), OAEs may be affected by reverse energy transmission from the damaged cochlear regions.

There are numerous studies that have analyzed sex and ear differences in OAE [14,34-40]. Neither gender nor environment origin had any predictive value for hearing status according to the results of our study. We had not found sex differences between ears for any OAE tests, but studies still debate this question as the results are contradictory. Bonfils also stated that there are no statistical differences in the OAE threshold when using gender as a variable [34]. In his thesis, Jun Cheng concluded that gender and the hearing thresholds are related to the presence of SOAE, and the response levels of TEOAE and DPOAE [41].

Age and hearing loss represent a controversial subject. The amplitude of the OAEs is decreasing with increasing age [42,43], but it is still unclear whether this fact is due to aging or to age-related hearing loss [44-46]. Our multivariate analyses revealed that age is a predictor factor of the auditory status for both ears. Our study also confirms the conclusion of Kimberley that the combination of age and DPOAE can better predict hearing level than DPOAE alone (the values of the areas under ROC curves were slightly higher in the second multivariate than in the first analysis) [24].

Tinnitus is frequently a sign of hearing loss, but not all hearing losses are accompanied by tinnitus. It is generally assumed that tinnitus may be the result of multiple physiological causes [47]. The results of our study showed that tinnitus was the most important predictor for hearing level, but only for the left ear. According to Gorga, the two ears of a subject are not independent on any measurement [27]. The presence of tinnitus is statistically significant for hearing loss at a younger age, but only for the left ear. Our results suggested a more sensitive left ear, contrary to other studies that found a more sensitive right ear [33,34]. Our second and third multivariate analysis demonstrated that age presented similar coefficients, but tinnitus coefficients by their high value produced the biggest variations of the logistic scores once again only for the left ear group. The higher the logistic score, the higher the risk of hearing loss. Other studies [48,49] showed that hearing loss is predictive of the tinnitus percept, in particular when including DPOAE as additional measure of peripheral processing. Xiang Zhou demonstrated that OAE measurements of cochlear function are more predictive of tinnitus than the conventional audiogram [50].

Limits of the study

Our study presents some limits. First of all, when defining normal or impaired hearing, we have chosen the pure-tone threshold for 0.5, 1, 2 and 4 kHz and thus we have eliminated higher frequencies, such as 8 kHz.

In order to assess test performance a study should include both normal hearing and impaired hearing ears. In our study groups, the distribution of different hearing impairment was not equal as the representations of severe or profound hearing loss was very low on the assumption that OAEs are not present if hearing thresholds are greater than 30-40 dB HL [19] for TEOAE and greater than 50-60 dB HL for DPOAE [5,11,15,30,31,51]. Emphasis on subjects with these degrees of hearing loss may have had the inadvertent effect of reducing the estimations of test performance relative to the performance one might observe in an unselected sample of subjects. This would occur because the overlap between ears with normal and impaired hearing is likely to be greater for mild and moderate degrees of hearing loss.

We used the SNR-based approach because it was conceptually simpler. Studies performed up to now are controversial when it comes to select the best OEA parameter. Gorga reported better results for DPOAE when using the SNR than DPOAE level al lowest frequency, while DPOAE level presented larger areas under the ROC curve at mid and high frequencies [11,15,29,31].

We have determined how the multivariate predictors derived from our analyses influenced our study group (training group), but we have not generalized the results to a validation group.

Conclusions

Like any other audiological test, using OAE test to identify hearing loss is not free of errors. Even when applying multivariate analysis, perfect test performance is never achieved. Most errors appear when identifying normal or mild hearing losses or mild and moderate hearing losses. It is very likely to confuse normal hearing with moderate or greater hearing losses. Test performance for TEOAE and DPOAE are different because of their intrinsic properties recording procedures.

Although most studies demonstrated the benefit of using the multivariate analysis, it has not been incorporated into clinical decisions maybe because of the idiosyncratic nature of multivariate solutions or because of the lack of validation studies.

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