Cross-cultural Adaption and Validation of the Zurich Chronic Middle Ear Inventory Translated into Italian (ZCMEI-21-It) - A Prospective Multicenter Study

Cross-cultural adaption and validation of the Zurich chronic middle ear inventory translated into Italian (ZCMEI-21-It) – a prospective multicenter study

Abstract

Objective: There are no instruments available to comprehensively assess health-related quality of life (HRQoL) in chronic otitis media (COM) in Italian-speaking countries. The Zurich chronic middle ear inventory (ZCMEI-21) is a well-established instrument for the assessment of HRQoL in COM. The objective of this study was to translate and cross-culturally adapt the ZCMEI-21 into Italian and validate this questionnaire for measuring HRQoL in patients with COM.

Study Design: Prospective multicenter study.

Setting: Three University hospitals (northern Italy, central Italy, southern Italy).

Patients: Adult patients suffering from COM (n = 128).

Intervention: Following international guidelines, the ZCMEI-21 was translated into Italian (ZCMEI-21-It). Validation was performed by psychometric test statistics. Moreover, ZCMEI-21-It total and subscale scores were compared and correlated to (i) the scores of the original validation study, (ii) to a question that directly addresses HRQoL and (iii) to the scores of the EQ-5D-5L, a generic questionnaire assessing HRQoL.

Results: From three study centers, a total of 128 patients with COM were included. Cronbach's α was 0.86 indicating a high reliability. Between the ZCMEI-21-It total score and the question that directly addresses HRQoL, we found a strong correlation ($r = 0.62$, $p < 0.0001$). Between the ZCMEI-21-It total score and the EQ-5D-5L scores, we expectedly found moderate correlations (descriptive system score: $r = 0.39$, $p < 0.0001$; VAS: $r = 0.30$, $p = 0.008$).

Conclusion: We translated the ZCMEI-21 questionnaire into Italian and validated the ZCMEI-21-It in a prospective multicenter study. The ZCMEI-21-It is the first instrument that comprehensively assesses relevant dimensions of HRQoL in Italian-speaking patients affected by COM.

Key words: Chronic otitis media, cholesteatoma patient-reported outcome measure, health-related quality of life, ZCMEI-21, Italian

Introduction

Chronic (suppurative) otitis media (COM) is a chronic inflammation of the middle ear and mastoid mucosa characterized by a tympanic perforation lasting > 6-12 weeks which usually leads to a persistent or recurrent discharge from the middle ear [1]. Chronic otitis media is a leading cause of health care visits, antibiotic prescriptions, and surgery [2 3]; it causes preventable conductive hearing loss and increases the risk for permanent sensorineural hearing loss [4-6]. The global incidence rate of COM is estimated at 4.8 new episodes per 1,000 people, with a total annual number of cases of 31 million [3 5]. A World Health Organization (WHO) report suggests that 65 to 350 million individuals are suffering from COM globally [7].

In the assessment of COM and its treatment, patient-reported outcomes (PROs) are gaining increasing importance and are often used in addition to objective outcome measures, such as audiometric results [8]. In contrast to objective outcomes, PROs represent a subjective assessment of the patient's perspective, which may be not reflected by objective outcomes. One of the most important PROs is health-related quality of life (HRQoL) [9], which is assessed by patient-reported outcomes measures (PROMs), usually in the form of questionnaires completed by the patient. Comparing PROM scores before and after an intervention can be used in the outcome analysis of an intervention, to evaluate its possible effectiveness [10]. As specific symptoms and their consequences impair HRQoL in COM, generic questionnaires generally are not well suited for COM due to their lack of sensitivity to reliably detect relevant aspects of HRQoL [6 11 12]. Nonetheless, several generic questionnaires, especially questionnaires including a hearing loss domain, have been applied to specific otologic conditions, e.g. the Hearing Handicap Inventory or the Health Utilities Index Mark 3 [13 14].

There have been several attempts to assess QoL in adult COM. To date, five questionnaires have been developed to assesses relevant symptoms and dimensions of HRQoL in COM: the Chronic Ear

Survey (CES; available in English, Chinese, Korean, and Italian) [15], the English Chronic Otitis Media 5 (COM-5) [16], the German Chronic Otitis Media Outcome Test 15 (COMOT-15) [17], the Chronic Otitis Media Questionnaire 12 (COMQ-12; available in English, Dutch, and Russian) [18] and the Zurich Chronic Middle Ear Inventory 21 (ZCMEI-21; available in German and Japanese) [19].

In order to provide a comparable and consistent assessment of HRQoL in different countries, questionnaires should be available in multiple languages. Only one of five available questionnaires for COM was developed and validated in the Italian-speaking countries, the CES-I questionnaire [20]. The CES-I appears to be a reliable and valid instrument for the investigation of health status among Italian speaking patients with COM. However, the CES has several shortcomings as it does not include vertigo/balance problems and tinnitus. Moreover, there is no comprehensive assessment of psychosocial problems as there is only one question, which is exclusively focused on restrictions due to hearing impairment. Similar shortcomings have also been pointed out for the COMOT-15 and the COMQ-12 previously [19]: the COMOT-15 is strongly focused on restriction of activities due to hearing impairment while the impact of other symptoms is not evaluated. The COMQ-12 does not assess activity restriction due to COM, which is also part of the CES, and does not provide a comprehensive assessment of psychosocial problems.

The ZCMEI-21 is a German-language questionnaire published in 2016, which provides a comprehensive assessment of HRQoL in COM patients, especially concerning psychological and social aspects [19]. The ZCMEI-21 questionnaire consists of 21 items grouped in four subscales: I. ear signs and symptoms; II. hearing; III. psychosocial impact; and IV. medical resources. Answers are presented using a 5-point Likert scale that ranges from 0 (no emotional or physical impact) to 4 (severe emotional or physical impact). The ZCMEI-21 has been recently validated in the Japanese language [21] and is currently being translated in other languages.

The aim of this multicenter study was to translate and cross-culturally adapt the ZCMEI-21 into Italian and validate this new Italian-language questionnaire for measuring HRQoL in patients with

COM.

Materials and methods

This multicenter study included patients recruited in three large Italian university hospitals. The involved centers were the Sapienza University of Rome, Policlinico Umberto I (central Italy), the University of Turin, Ospedale Molinette (northern Italy) and the Aldo Moro University of Bari (southern Italy). The inclusion criteria were the diagnosis of COM with or without cholesteatoma, age ≥ 18 years and sufficient Italian language skills. Further details on the study design are provided in Figure 1. The study was approved by the local Ethics Committees and was performed in accordance with the Helsinki declaration and its amendments. Informed consent was obtained from all the participants.

Translation of the ZCMEI-21 into Italian and cross-cultural adaptation

The translation and cross-cultural adaptation of ZCMEI-21 was performed following the Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes Measures according to the International Society for Pharmacoeconomics and Outcomes Research Task Force [22].

First, two forward translations were performed by two translation agencies specialized in medical translations. Then, the two translations were merged into a single translation by Italian speaking clinicians (ZCMEI-21-It, v1). This version of ZCMEI-21-It was reviewed by the involved physicians and was used for a first pilot test (cognitive debriefing 1) in five patients to detect difficulties in understanding of the questions and identify items that may not be well suited. The feedback received by the patients and the clinicians led to several minor modifications of the initial version. No items were excluded. The modified questionnaire constituted the second version of the ZCMEI-21-It (ZCMEI-21-It, v2). Lastly, a third translation agency specialized in medical translations carried out a back translation of the ZCMEI-21-It, v2, into German. After reviewing the back translation against

105 the original German version, the ZCMEI-21-It underwent some further minor modifications in order
106 to provide a conceptually equivalent Italian translation (ZCMEI-21-It, v3). Using the latter version,
107 a second cognitive debriefing was performed leading to no additional modifications. At the end of
108 the translation process, the final version of the questionnaire (ZCMEI-21-It) was obtained and used
109 for the validation process.
110
111 *Validation process*
112 The ZMCEI-21-It and the EuroQol five-dimensional questionnaire (EQ-5D) in its five-level version
113 (EQ-5D-5L) were administered to COM patients meeting the inclusion criteria during ambulatory
114 visits.
115 The EQ-5D-5L is a quickly administered and internationally recognized instrument aimed to obtain
116 a meaningful description and measurement of health-related quality of life. The EQ-5D-5L
117 questionnaire is composed of five questions that are converted to an index value (EQ-5D-5L
118 descriptive system score; it ranges from 0 to 1, where 1 corresponds to a perfect QoL) and a visual
119 analogue scale (EQ-5D-5L VAS, that ranges from 0 to 100, where 100 corresponds to the best health
120 state). The five questions in the EQ-5D-5L questionnaire investigate mobility, self-care, usual
121 activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L questionnaire has been validated
122 in the Italian language [23]; however, no specific value set has been developed for Italian. As a
123 replacement, the UK or the Spanish sets are conventionally used to conduct evaluations in the Italian
124 population [24-26]. In the present study, a value set for England was used [27].
125 As done in the original validation study [19], a general question was added to directly address HRQoL
126 (question 22, "My ear illness is worsening my quality of life . . . not at all/mildly/
127 moderately/severely/very severely") for assessment of the criterion validity.
128 The minimal sample size considered for this study was 84 patients, based on a subject to item ratio
129 of 4:1 (21 items) [28].
130

Statistical analysis

All statistical tests were selected before data collection. Values are reported as mean ± SD or as absolute number and percentage. Item total-correlation was calculated to assess if an item correlates with the total score. Internal consistency as an indicator of reliability was determined by calculation of Cronbach's α. Frequency distribution was analyzed by inspection of the histogram and statistical normality tests (D'Agostino and Pearson normality test, Shapiro-Wilk normality test; for both tests, $p > 0.05$ indicates normal distribution). Criterion validity was assessed using an additional general question (question 22) that directly addressed HRQoL. Concurrent validity was determined by comparing total scores of ZCMEI-21-It and sub-scores to the EQ-5D-5L descriptive system and VAS scores using Spearman's rank correlation and linear regression analysis including mean prediction intervals. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA) and Prism (version 7 for Apple Macintosh, GraphPad Software). The significance level was set to $p < 0.05$.

Results

One hundred twenty-eight patients were enrolled in the study and completed the ZCMEI-21-It and the EQ-5D-5L questionnaires in the three centers involved in this multicenter study: Sapienza University of Rome, Policlinico Umberto I (48 patients), the University of Turin, Ospedale Molinette (39 patients) and the Aldo Moro University of Bari (41 patients). Mean age was 54.1 ± 19.0 years. Chronic otitis media without cholesteatoma was found in 79 patients (61.7%); cholesteatoma was present in 49 (38.3%) patients. Chronic otitis media was unilateral in 105 patients (82%) and bilateral in 23 patients (18%). Detailed demographics and clinical characteristics are shown in Table 1. For all the items, we found well distributed answers with the full range of answers used in every question as well as item means close to 2, i.e. the middle value of possible answers (Table 2). Item-total-correlation of the single items were assessed as an indicator whether an item correlates well with the total score. An item-total-correlation of ≥ 0.3 is regarded as a good correlation with the total score

thus being a criterion for an important item. Of the ZMCEI-21-It, only three items had an item-total-correlation of < 0.3 (Table 2). Yet, all of these items were regarded as integral part of the questionnaire and moreover, the present study was not set up for an item reduction process. Therefore, no items were excluded because of statistical criteria. Internal consistency was determined as a measure of the questionnaire's reliability. We found a Cronbach's α of 0.86, which indicates a high internal consistency. Distribution of the answers showed a normal (Gaussian) distributed as evidenced by inspection of the histogram (Figure 2A) and normality tests (D'Agostino and Pearson normality test, $p = 0.12$; Shapiro-Wilk normality test, $p = 0.22$). Next, we assessed total scores in subgroups of the study population in order to identify any confounders affecting the ZCMEI-21-It total score and the subsequent subscale analysis. We found no significant differences in the mean total scores neither when patients were grouped according to having had surgery before nor according to the COM subtype (Figure 2B-C).

Next, we compared ZCMEI-21 total and subscale scores as well as their correlation with the EQ-5D-5L descriptive system score between the original validation study [19] and our translated version, the ZCMEI-21-It. This comparison showed highly similar values for total scores, subscale scores and correlation coefficients (Table 3). The only exception was correlation of the ZCMEI-21-It total score and the EQ-5D-5L descriptive system score. The ZCMEI-21-It total score showed a strong correlation with the question that directly assesses HRQoL (question #22; $r = 0.62$, $p < 0.0001$; Figure 3A), indicating a high criterion validity. In contrast, there was only a low to moderate correlation between the ZCMEI-21-It total score and the EQ-5D-5L descriptive system score ($r = 0.39$, $p < 0.0001$) and the EQ-5D-5L VAS ($r = 0.30$, $p = 0.008$). Moreover, the ZCMEI-21-It subscale scores were correlated to the EQ-5D-5L descriptive system and VAS scores. The subscale score for "ear signs and symptoms" was weakly to moderately correlated to the EQ-5D-5L scores (Figure 4A-B; to EQ-5D-5L descriptive system score: $r = 0.43$, $p < 0.0001$; to EQ-5D-5L VAS: $r = 0.21$, $p = 0.02$). No significant correlation was found between the subscale score for "hearing" and the EQ-5D-5L scores (Figure 4C-D; to EQ-5D-5L descriptive system score: $p = 0.62$; to EQ-5D-5L VAS: $r = 0.57$). Lastly,

183 a significant but moderate correlation was found between the subscale score for "psychosocial
184 impact" and the EQ-5D-5L scores (Figure 4C-D; to EQ-5D-5L descriptive system score: r = 0.27, p
185 = 0.002; to EQ-5D-5L VAS: r = 0.25, p = 0.004).
186
187 **Discussion**
188 Here, we translated the ZCMEI-21 questionnaire into the Italian language, i.e. the ZCMEI-21-It, and
189 validated the ZCMEI-21-It in a prospective multicenter study. The ZCMEI-21-It is the first Italian
190 instrument that comprehensively assesses relevant symptoms and dimensions of HRQoL in Italian-
191 speaking patients affected by COM.
192 In current clinical practice, HRQoL in patients with COM in Italian-speaking countries is measured
193 using a generic questionnaire called the Short Form 36 Health Survey (SF-36), validated in the Italian
194 language in 1998 [29]. However, SF-36 has proven not to be sensitive enough for the COM condition
195 [15]. To compensate for this lack, a more specific questionnaire for COM, the CES questionnaire,
196 has been recently translated and validated in Italian (CES-I) [20]. The CES-I proved to be a valid,
197 disease-specific health measure that can be used to evaluate adult patients with COM among the
198 Italian speaking population [20]. However, the CES-I primarily focuses on disease-specific health
199 and lacks specific assessment of the impact of single symptoms on the QoL. Although the ZCMEI-
200 21 is partially based on the CES questionnaire, it differs in several relevant aspects and has multiple
201 advantages as it has been developed to overcome the above limitations of the CES and other
202 questionnaires [19]. Therefore, the use of the ZCMEI-21 questionnaire in Italian language patients
203 may be a useful tool to be applied and may also be used in conjunction with the CES-I questionnaire.
204 The translation of the ZCMEI-21 questionnaire in the Italian language followed a standardized
205 approach involving both patients and clinicians. In the validation process, we assessed the reliability
206 and validity of the ZCMEI-21-It. We found an excellent Cronbach's α, which provides evidence of
207 the questionnaire's reliability. As expected, only moderate correlation between the EQ-5D-5L and
208 the ZCMEI-21-It total score was found. In particular, weak to moderate correlations were found for

209 the ear signs and symptoms subscale as well as the psychosocial impact subscale. This data provide
210 evidence that the ZCMEI-21-It in fact measures the complex construct of HRQoL; yet it also
211 underscores the fact that generic questionnaires generally are less reliable in assessing HRQoL in
212 specific conditions. The EQ-5D-5L constitutes a generic HRQoL questionnaire and does therefore
213 not meet the requirements of assessing detailed HRQoL in specific diseases, such as COM [30].
214 Interestingly, no correlation could be found between the ZCMEI-21-It subscale score of "hearing"
215 and the EQ-5D-5L, meaning that the patient's subjective hearing ability does not well correlate to the
216 perceived HRQoL in COM. Similar findings have also been demonstrated in other studies [30 31].
217 This may further corroborate the application of specific PROMs in COM which do not only account
218 for hearing impairment as the sole factor affecting HRQoL.
219 The cohort included in the present validation study included both patients that already underwent
220 surgery for COM and patients that did not undergo surgery. Furthermore, both types of COM, i.e.
221 COM with and without cholesteatoma, were included. This is similar to the cohort of the original
222 ZCMEI-21 study, as the questionnaire has been developed to evaluate both pre- and postoperative
223 HRQoL in patients with both COM with and without cholesteatoma. Thus, the ZCMEI-21 and its
224 translations are suited for research purposes as well as for application in the clinical routine for the
225 entire spectrum of COM and both pre- and postoperatively.
226 In the present study, a paper-based version of the ZCMEI-21-It has been used. In contrast, the original
227 ZCMEI-21 was developed as an electronic questionnaire delivered on a tablet computer. Yet, similar
228 results are expected in paper-based and electronic application of questionnaires [32]. Therefore, the
229 use of both paper-based and electronic versions of the ZCMEI-21-It is justified based on the present
230 validation data.
231
232 **Conclusion**
233 In the present paper, we undertook an Italian translation of the ZCMEI-21 questionnaire according to
234 standardized guidelines. In the subsequent validation study, we acquired ample evidence

demonstrating that the ZCMEI-21-It is a reliable and valid questionnaire. Hence, this new Italian-language questionnaire can be used to quantify HRQoL in COM in both patients with and without cholesteatoma, and regardless of whether they had undergone surgery for COM.

Supplementary material

ZCMEI-21-It.pdf

References

1. Verhoeff M, van der Veen EL, Rovers MM, Sanders EA, Schilder AG. Chronic suppurative otitis media: a review. Int J Pediatr Otorhinolaryngol 2006;**70**(1):1-12 doi: 10.1016/j.ijporl.2005.08.021[published Online First: Epub Date]|.
2. Ahmed S, Shapiro NL, Bhattacharyya N. Incremental health care utilization and costs for acute otitis media in children. Laryngoscope 2014;**124**(1):301-5 doi: 10.1002/lary.24190[published Online First: Epub Date]|.
3. Monasta L, Ronfani L, Marchetti F, et al. Burden of disease caused by otitis media: systematic review and global estimates. PLoS One 2012;**7**(4):e36226 doi: 10.1371/journal.pone.0036226[published Online First: Epub Date]|.
4. Singer AEA, Abdel-Naby Awad OG, El-Kader RMA, Mohamed AR. Risk factors of sensorineural hearing loss in patients with unilateral safe chronic suppurative otitis media. Am J Otolaryngol 2018;**39**(2):88-93 doi: 10.1016/j.amjoto.2018.01.002[published Online First: Epub Date]|.
5. Schilder AG, Chonmaitree T, Cripps AW, et al. Otitis media. Nat Rev Dis Primers 2016;**2**:16063 doi: 10.1038/nrdp.2016.63[published Online First: Epub Date]|.
6. Wallis S, Atkinson H, Coatesworth AP. Chronic otitis media. Postgrad Med 2015;**127**(4):391-5 doi: 10.1080/00325481.2015.1027133[published Online First: Epub Date]|.
7. Organization WH. Chronic suppurative otitis media: burden of illness and management options. World Health Organization. 2004;**Geneve**(http://www.who.int/iris/handle/10665/42941)
8. Phillips JS, Yung MW. A systematic review of patient-reported outcome measures for chronic suppurative otitis media. Laryngoscope 2016;**126**(6):1458-63 doi: 10.1002/lary.25657[published Online First: Epub Date]|.
9. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? Pharmacoeconomics 2016;**34**(7):645-9 doi: 10.1007/s40273-016-0389-9[published Online First: Epub Date]|.
10. Murphy M, Hollinghurst S, Salisbury C. Identification, description and appraisal of generic PROMs for primary care: a systematic review. BMC Fam Pract 2018;**19**(1):41 doi: 10.1186/s12875-018-0722-9[published Online First: Epub Date]|.
11. Guyatt GH, Bombardier C, Tugwell PX. Measuring disease-specific quality of life in clinical trials. CMAJ 1986;**134**(8):889-95
12. Alakarppa A, Alho OP. Patient-recorded outcomes and quality of life in evidence-based medicine databases on most common ear, throat and nose procedures: a systematic review. Clin Otolaryngol 2012;**37**(6):436-45 doi: 10.1111/coa.12048[published Online First: Epub Date]|.
13. Newman CW, Weinstein BE, Jacobson GP, Hug GA. The Hearing Handicap Inventory for Adults: psychometric adequacy and audiometric correlates. Ear Hear 1990;**11**(6):430-3
14. Feeny D, Furlong W, Boyle M, Torrance GW. Multi-attribute health status classification systems. Health Utilities Index. Pharmacoeconomics 1995;**7**(6):490-502
15. Nadol JB, Jr., Staecker H, Gliklich RE. Outcomes assessment for chronic otitis media: the Chronic Ear Survey. Laryngoscope 2000;**110**(3 Pt 3):32-5 doi: 10.1097/00005537-200003002-00009[published Online First: Epub Date]|.
16. Vlastos IM, Kandiloros D, Manolopoulos L, Ferekidis E, Yiotakis I. Quality of life in children with chronic suppurative otitis media with or without cholesteatoma. Int J Pediatr Otorhinolaryngol 2009;**73**(3):363-9 doi: 10.1016/j.ijporl.2008.10.030[published Online First: Epub Date]|.
17. Baumann I, Kurpiers B, Plinkert PK, Praetorius M. [Development and validation of the Chronic Otitis Media Outcome Test 15 (COMOT-15). Measurement of health-related

quality of life in patients with chronic otitis media]. HNO 2009;**57**(9):889-95 doi: 10.1007/s00106-008-1870-3[published Online First: Epub Date]|.
18. Phillips JS, Haggard M, Yung M. A new health-related quality of life measure for active chronic otitis media (COMQ-12): development and initial validation. Otol Neurotol 2014;**35**(3):454-8 doi: 10.1097/MAO.0000000000000205[published Online First: Epub Date]|.
19. Bachinger D, Roosli C, Ditzen B, Huber AM. Development and validation of the Zurich chronic middle ear inventory (ZCMEI-21): an electronic questionnaire for assessing quality of life in patients with chronic otitis media. Eur Arch Otorhinolaryngol 2016;**273**(10):3073-81 doi: 10.1007/s00405-016-3915-7[published Online First: Epub Date]|.
20. Ralli G, Milella C, Ralli M, Fusconi M, La Torre G. Quality of life measurements for patients with chronic suppurative otitis media: Italian adaptation of "Chronic Ear Survey". Acta Otorhinolaryngol Ital 2017;**37**(1):51-57 doi: 10.14639/0392-100X-1041[published Online First: Epub Date]|.
21. Bachinger D, Takagi D, Yamada H, et al. Japanese translation, cross-cultural adaption and multicentre validation of the Zurich chronic middle ear inventory (ZCMEI-21-Jap). Auris Nasus Larynx 2018 doi: 10.1016/j.anl.2018.05.008[published Online First: Epub Date]|.
22. Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health 2005;**8**(2):94-104 doi: 10.1111/j.1524-4733.2005.04054.x[published Online First: Epub Date]|.
23. Savoia E, Fantini MP, Pandolfi PP, Dallolio L, Collina N. Assessing the construct validity of the Italian version of the EQ-5D: preliminary results from a cross-sectional study in North Italy. Health Qual Life Outcomes 2006;**4**:47 doi: 10.1186/1477-7525-4-47[published Online First: Epub Date]|.
24. Scalone L, Cortesi PA, Ciampichini R, et al. Italian population-based values of EQ-5D health states. Value Health 2013;**16**(5):814-22 doi: 10.1016/j.jval.2013.04.008[published Online First: Epub Date]|.
25. Olivieri I, de Portu S, Salvarani C, et al. The psoriatic arthritis cost evaluation study: a cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy. Rheumatology (Oxford) 2008;**47**(11):1664-70 doi: 10.1093/rheumatology/ken320[published Online First: Epub Date]|.
26. Gringeri A, Mantovani LG, Scalone L, Mannucci PM, Group CS. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. Blood 2003;**102**(7):2358-63 doi: 10.1182/blood-2003-03-0941[published Online First: Epub Date]|.
27. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ 2018;**27**(1):7-22 doi: 10.1002/hec.3564[published Online First: Epub Date]|.
28. Anthoine E, Moret L, Regnault A, Sebille V, Hardouin JB. Sample size used to validate a scale: a review of publications on newly-developed patient reported outcomes measures. Health Qual Life Outcomes 2014;**12**:176 doi: 10.1186/s12955-014-0176-2[published Online First: Epub Date]|.
29. Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. J Clin Epidemiol 1998;**51**(11):1025-36
30. Hallberg LR, Hallberg U, Kramer SE. Self-reported hearing difficulties, communication strategies and psychological general well-being (quality of life) in patients with acquired

hearing impairment. Disabil Rehabil 2008;**30**(3):203-12 doi: 10.1080/09638280701228073[published Online First: Epub Date]|.
31. Bakir S, Kinis V, Bez Y, et al. Mental health and quality of life in patients with chronic otitis media. Eur Arch Otorhinolaryngol 2013;**270**(2):521-6 doi: 10.1007/s00405-012-2031-6[published Online First: Epub Date]|.
32. Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. Value Health 2008;**11**(2):322-33 doi: 10.1111/j.1524-4733.2007.00231.x[published Online First: Epub Date]|.

Figure legends

Figure 1. Study design for the translation of the ZCMEI-21 into the Italian language questionnaire (ZCMEI-21-It) and validation of the ZCMEI-21-It.

Figure 2. **A** Frequency distribution of the ZCMEI-21-It (bin width on x-axis: 4). **B-C** Comparison of ZCMEI-21-It total scores between pre-operative and post-operative patients with COM (B) and between patients suffering from COM with and without cholesteatoma (C). Unpaired t-test, whiskers indicates standard deviation range, bold horizontal line represents mean.

Figure 3. A Correlation for ZCMEI-21-It total scores and the question #22, which directly assessed HRQoL (0 on the x-axis: no impact on HRQoL in question #22; 4 on the x-axis: huge impact on HRQoL in question #22; Spearman's rank correlation). **B-C** Correlation between ZCMEI-21-It total score and EQ-5D-5L descriptive systems score (B) as well as the EQ-5D-5L VAS (C). Solid line indicates linear regression line, dashed lines indicates 95% prediction interval, r, Spearman's rank correlation coefficient.

Figure 4. Spearman's rank correlation between ZCMEI-21-It subscale scores and EQ-5D-5L scores (descriptive system score and VAS). Solid line represents linear regression line, dashed lines represent 95% prediction interval, r, Spearman's rank correlation coefficient.