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# Determinants of Hearing Recovery in Multidrug-Resistant Tuberculosis Patients with Ototoxic Hearing Loss: A Prospective Observational Cohort Study in Kinshasa, Democratic Republic of the Congo.

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## Abstract

**Purpose.** The ototoxic hearing loss (HL) during the treatment of multidrug-resistant tuberculosis (MDR-TB) remains a public health challenge, especially in resource-limited settings such as the Democratic Republic of the Congo (DRC). This study seeks to identify the risk factors associated with the hearing recovery (HR) in MDR-TB patients in order to implement effective preventive strategies.

**Methodology**. This prospective observational and analytic study included patients with MDR-TB. It was carried out in Kinshasa (Democratic Republic of the Congo) between February 15, 2020 and February 14, 2021. Sociodemographic, clinical, biological, therapeutic, and audiometric data were obtained and analyzed using SPSS for Windows software version 21. The hearing recovery (HR) was considered good if the final hearing loss (HL) was < 45 dB and poor if it was ≥ 45 dB. Pearson's Chi-square or Fisher's exact tests, as appropriate, were used to compare proportions. A multivariate logistic regression model was used to identify independent determinants of the HR. Odds ratios were provided with their 95% confidence intervals (Cis). Statistical significance was set at $p < 0.05$.

**Findings.** Of the 310 patients were examined (mean age 34.5 ± 14 years, men 64.8%), 245 patients (79%) received only an aminoglycosides-based regimen, 31 (10%) received only bedaquiline (BDQ), and 34 (11%) received aminoglycosides (AG) followed by BDQ. Twenty-eight patients (9%) had a positive HIV serology, two-thirds were anemic (67.4%) and one-third (32.9%) had hypoalbuminemia. According to the final HL at the three months of treatment, 89 patients (28.7%) had experienced a good HR. Age under 40 years ($p = 0.002$), the BDQ regimen ($p < 0.001$), normal hearing and mild HL ($p < 0.001$), and the type A and B audiometric curve ($p < 0.001$) were significantly associated with a favorable HR. Whereas, the presence of tinnitus ($p = 0.031$), hypoacusis ($p < 0.001$), hypoalbuminemia ($p = 0.046$), anemia ($p = 0.044$), and chronic renal failure ($p = 0.040$) were associated with a poor HR. In the multivariable logistic regression analysis, a moderate HL (OR 3.71; 95% CI [1.71 – 8.28]; $p = 0.001$) and a type B audiometric curve (OR 2.27; 95% CI [1.72 -7.8]; $p = 0.001$) emerged as the main determinants of a good HR.

**Unique contributor to theory, policy and practice:** The hearing recovery in MDR-TB patients is poor during the treatment. This requires a regular audiometric monitoring to detect the early hearing loss. To reduce the risk of an ototoxic hearing impairment, it is recommended to prioritize the use of bedaquiline and to address adverse prognostic factors such as anemia, hypoalbuminemia, and impaired renal function. Hence, the need for large prospective and interventional studies to confirm these results.

**Keywords**: *Multidrug-Resistant Tuberculosis, Determinants, Hearing Recovery*

## Introduction

The ototoxic hearing loss (HL) associated with the treatment of multidrug-resistant tuberculosis (MDR-TB) remains a significant public health challenge. Approximately one in three patients undergoing the treatment for MDR-TB experiences either a reversible or permanent ototoxic sensorineural hearing loss [1-4]. Various factors contribute to this increased risk, including advanced age, a genetic predisposition (such as mitochondrial DNA abnormalities), a prior history of HL, and a renal failure [5-7]. Notably, the Democratic Republic of the Congo (DRC), which faces a substantial burden of tuberculosis, is witnessing a rising incidence of the hearing impairment among MDR-TB patients [1, 3-5]. This ototoxic HL, often debilitating, is primarily a consequence of the side effects associated with several medications used in their treatment [1-4]. This study aims to assess the potential for hearing recovery (HR) in these patients who have developed an ototoxic HL, providing a foundation for the implementation of preventive measures in a population that currently lacks access to hearing aids [1].

## Methods

### Study design and participant sampling

This prospective observational analytical study was conducted between February 15, 2020 and February 14, 2021 at 42 centers for the screening and the treatment of MDR-TB in Kinshasa (DRC). The study population consisted of the MDR-TB patients receiving aminoglycoside (AG) and/or the BDQ-based regimens. Patients, diagnosed as MDR-TB by molecular methods such as MTB/RIF® or Genotype MTBR-plus sl ®, aged ≥14 years with a normal otoscopy examination, and who signed an informed consent form were included. Participants with a pathological eardrum, history of otological surgery, an exposure to noise less than 48 hours, and a current pregnancy were excluded from this study. Ethics approval for the study was obtained from the Ethics committee of Kinshasa School of Public Health at the University of Kinshasa.

### Data collection

Data were collected using a structured, standardized, and coded questionnaire, which included all the variables of interest in the study. Sociodemographic (age, sex, education) and clinical information (complaints at the first month of MDR-TB treatment, hypertension, diabetes, tobacco and alcohol use, HIV status, previous medications and therapeutic regimen for MDR-TB) were obtained. Anthropometric variables (height, weight, body mass index [BMI] calculated) and the blood pressure were measured during the physical examination. Laboratory variables (serum creatinine, serum albumin, glucose, and hemoglobin) were measured with a Cobas C 111 analyzer using an enzymatic colorimetric method.

The Liminal-tone audiometry was used to determine the degree of the HL. This was performed using a shoebox brand audiometer. It is an audiometry software incorporated in an iPad, which does not require a soundproof cabin. The examiner sends sounds of different frequencies (from 250 Hz to 8000 Hz) and intensities (from fies −5 dB to 90 dB). At the end of the examination, the automatic tracing and the average values indicating the degree of the hearing appears on

the electronic tablet. The monitoring considered audiometric data performed at 1 (M1), 2 (M2) and 3 (M3) months after the start of the MRD-TB treatment. Deafness was defined as HL ≥ 21 dB (5). The degree of the HL was classified according to the Pujol and Dubreuil scale [8]: mild (21–40 dB), moderate (41–60 dB), severe (61–80 dB), or profound (≥ 81 dB). The hearing recovery was considered good if the final hearing loss is < 45 dB and poor if it is ≥ 45 dB.

**Operational definitions**

The hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg or the use of the antihypertensive drugs treatment (9). Diabetes mellitus was diagnosed by a fasting serum glucose ≥ 126 mg/dL or the use of an antidiabetic medication (10). Underweight was identified by a BMI < 18.5 kg/m² (10). An excessive alcohol use was defined as more than two standards drink for men and one for women (11). Smoking was considered for anyone who smoked at least one cigarette/day for a year or more or weaned for less than 5 years (12). Anemia was defined as the hemoglobin (Hb) level < 12.0 g/dL in women and < 13.0 g/dL in men (13). Hypoalbuminemia was established by a serum albumin level < 35 g/L (14). Chronic kidney disease (CKD) was defined as an eGFR < 60 mL/min/1.73 $m^2$ (15). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

**Statistical analysis**

Data analysis was performed using SPSS for Windows software version 21 (SPSS Inc. Chicago, IL, USA, 2013). Descriptive statistical data are presented in tables and figures with the percentages for the qualitative variables. Quantitative variables are expressed as mean ± standard deviation (SD) when the distribution was normal. Pearson's Chi-square or Fisher's exact tests, as appropriate, were used to compare proportions. A multivariate logistic regression model was used to identify independent determinants of the hearing recovery. Odds ratios were provided with their 95% confidence intervals (Cis). Statistical significance was set at $p < 0.05$.

**Results**

**General characteristics of the patients**

A total of 310 MDR-TB patients were enrolled during the study period. As shown in Table 1, the mean patient age was 34.5 ± 14 years, with male to female ratio of 1.8 to 1, 245 patients (79%) received only an AG-based regimen, 31 (10%) received only BDQ, and 34 (11%) received AG followed by BDQ. The majority (81%) had obtained their high school diploma. Almost a third of the patients (30.6%) complained of tinnitus, just over the quarter of the participants used tobacco products (26.8%), 39% consumed alcohol, and 9% had a TB-HIV coinfection. Two-thirds were anemic (67.4%) and one-third (32.9%) had hypoalbuminemia.

**Table 1. Clinical and paraclinical characteristics of the patients**

| Variable n (%) | n=310 | % |
|---|---|---|
| **Age (mean ± SD) years** | 34.5 ± 14 | |
| **Sex** | | |
| Male | 201 | 64.8 |
| Female | 109 | 35.2 |
| **Therapeutic regimen** | | |
| Aminoglycosides (AG) | 245 | 79 |
| Bedaquiline (BDQ) | 31 | 10 |
| AG followed by BDQ | 34 | 11 |
| **Education** | | |
| None/Primary | 14 | 4.5 |
| high school diploma | 251 | 81 |
| University | 45 | 14.5 |
| **Symptoms** | | |
| Tinnitus | 95 | 30.6 |
| Hypoacusis | 84 | 27.1 |
| Dizziness | 33 | 10.6 |
| **Medical history** | | |
| Diabetes | 12 | 3.9 |
| Smoking | 83 | 26.8 |
| HIV/AIDS | 28 | 9 |
| Hypertension | 8 | 2.6 |
| Alcohol intake | 121 | 39 |
| **Paraclinical** | | |
| Anemia | 209 | 67.4 |
| Hypoalbuminemia | 102 | 32.9 |

## Audiometric data

Figure 1 & 2 show the evolution of the hearing loss (HL) frequency and the severity in liminal audiometry performed at 1, 2 and 3 months. At the first month of the treatment, nearly four out of ten patients (36.6%) had a normal hearing. The HL frequency increased from six to nine out of ten patients within three months regardless of the regimen, and severe (30%) and profound (24.6%) deafness were the most predominant.

According to the final HL at the three months of the treatment, 89 patients (28.7%) had a good hearing recovery.

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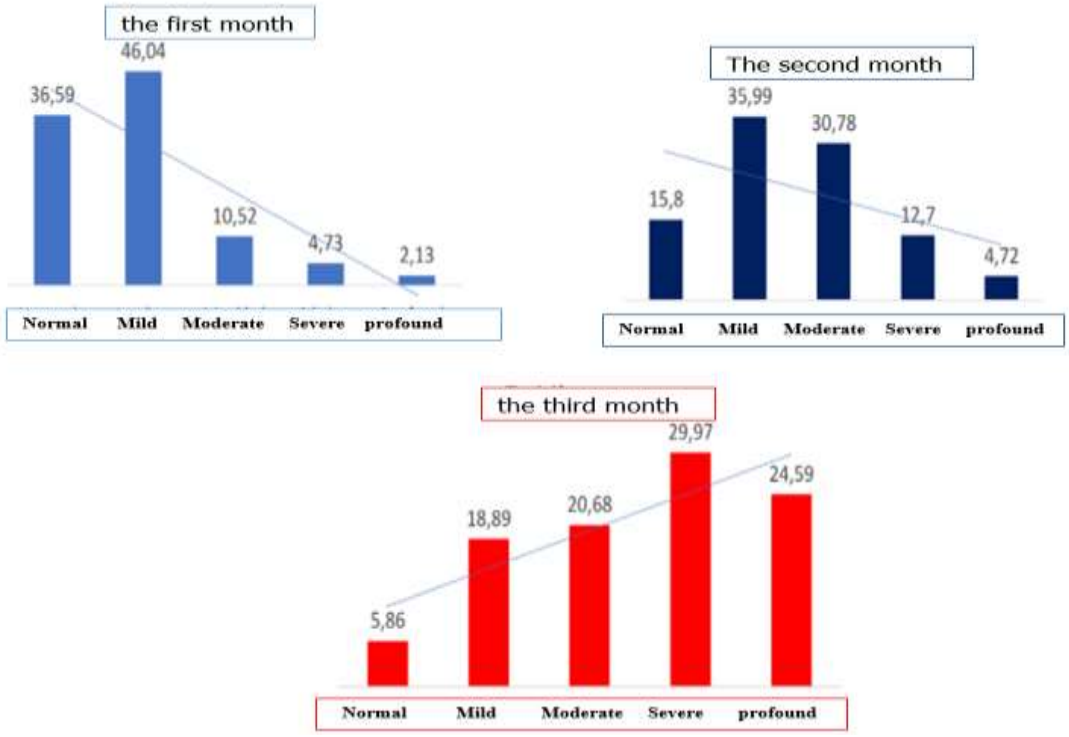


Figure 1. Evolution of the frequency and degree of the hearing loss.

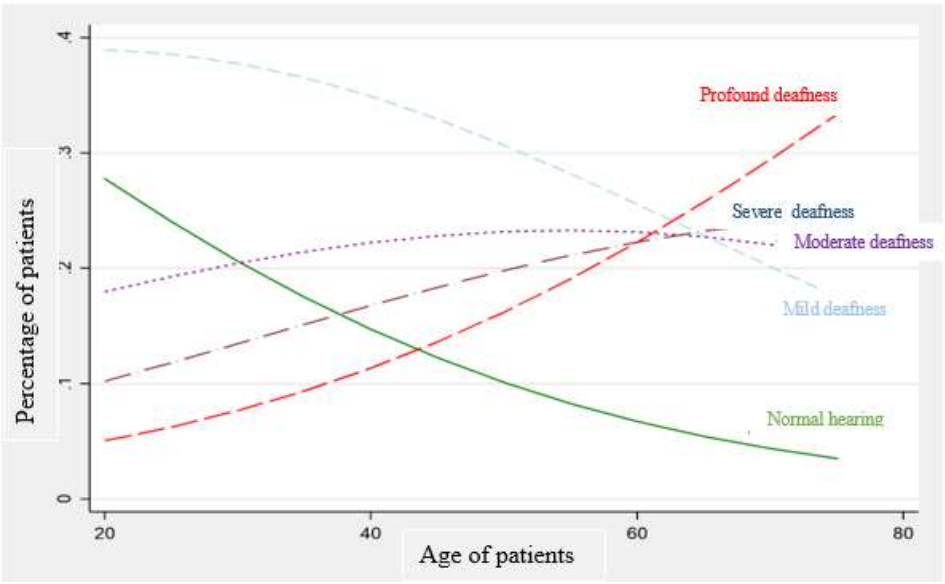


Figure 2. Evolution of hearing loss according to the age of patients

As for the evolution of the types of audiometric curves, in the first month of the treatment, a predominance of type B (45%) and C (32.9%) curves was observed, although 4 out of 10 patients had a normal hearing. The type C curve, considered to have a poor prognosis, seemed to increase proportionally with age and the worsening of the hearing loss, unlike the type B curve (figure 3 & 4).

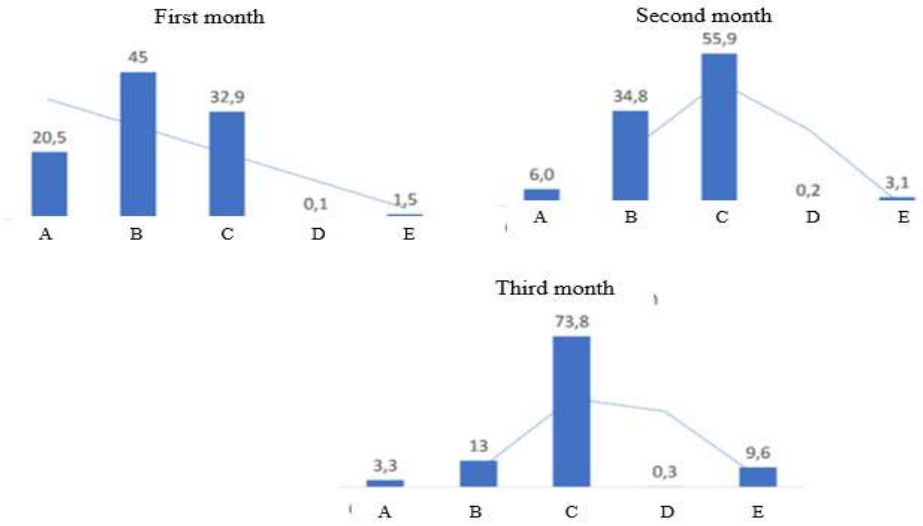


Figure 3. Evolution of audiometric curve types

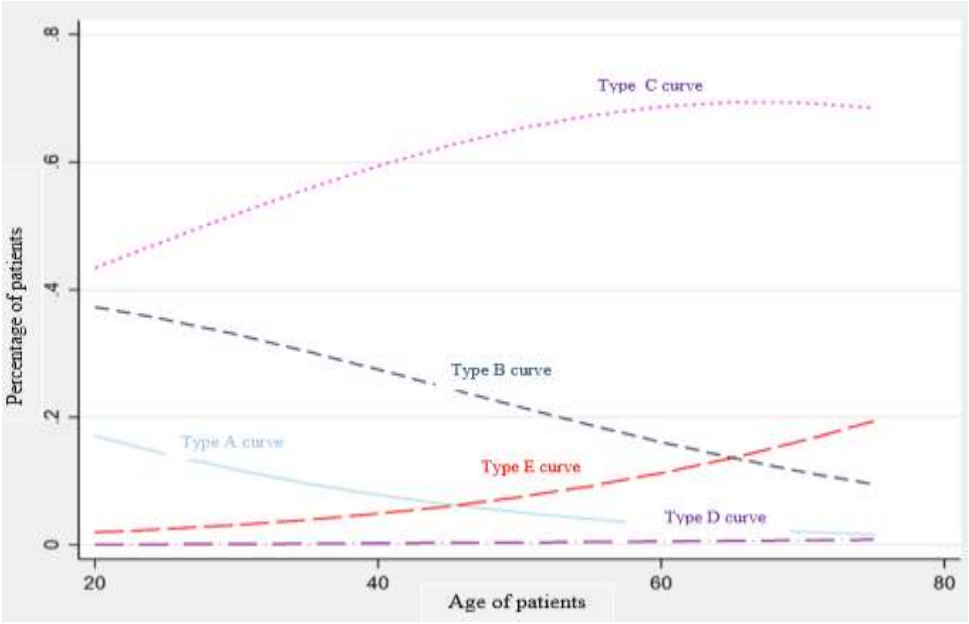


Figure 4. Types of audiometric curves according to the age of patients

**Determinants of the hearing recovery**

Table 2a and 2b summarize the results of a bivariate analysis used to determine the association between clinical and paraclinical variables, and the hearing recovery (HR) in the MDR-TB patients.

In the bivariate analysis, a good HR was observed more frequently in the patients aged less than 40 years (35% vs. 19%, p= 0.002) and those on a bedaquiline-based regimen (61% vs. 24.1%, p< 0.001). In contrast, the recovery was poor among patients aged 40 years or older (81%) and those receiving the AG-based regimen (75.9%). Mild HL exhibited a high recovery rate of 98.2%, whereas the recovery was significantly lower for the moderate (28.8%) and severe (0.6%) hearing loss (p < 0.001). Good HR rates were noted for type A and B audiometric curves at 100% and 87.5%, respectively; while the recovery was poor for type C (80.7%) and

E (93.8%) curves (p < 0.001). Additionally, the presence of tinnitus, hypoacusis, hypoalbuminemia, anemia, and a chronic renal failure (CRF) were associated with a poor hearing restoration in 78.9%, 89.3%, 75.5%, 71.8%, and 81.8% of cases, respectively.

Tableau 2a. Clinical variables associated with hearing recovery

| variable | Good HR | | Poor HR | | Total | | p-value |
|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | |
| **Sex** | | | | | | | 0.317 |
| Female | 30 | 27.5 | 79 | 72.5 | 109 | 100 | |
| Male | 62 | 30.8 | 139 | 69.2 | 201 | 100 | |
| **Age groups** | | | | | | | 0.002 |
| < 40 years | 74 | 35.24 | 136 | 64.76 | 210 | 100 | |
| ≥ 40 years | 19 | 19 | 81 | 81 | 100 | 100 | |
| **Therapeutic regimen** | | | | | | | < 0.001 |
| Bédaquiline (BDQ) | 19 | 61.3 | 12 | 38.7 | 31 | 100 | |
| AG + BDQ | 15 | 44.12 | 19 | 55.88 | 34 | 100 | |
| Aminoglycosides (AG) | 59 | 24.08 | 186 | 75.92 | 245 | 100 | |
| **BMI categories** | | | | | | | 0.230 |
| underweight | 32 | 27.1 | 86 | 72.9 | 118 | 100 | |
| Normal | 61 | 31.77 | 131 | 68.23 | 192 | 100 | |
| **Hypoacusis** | | | | | | | < 0.001 |
| No | 84 | 37.2 | 142 | 62.8 | 226 | 100 | |
| Yes | 9 | 10.71 | 75 | 89.29 | 84 | 100 | |
| **Tinnitus** | | | | | | | 0.031 |
| No | 69 | 32.1 | 146 | 67.9 | 215 | 100 | |
| Yes | 20 | 21.1 | 73 | 78.9 | 95 | 100 | |
| **Smoking** | | | | | | | 0,277 |
| No | 70 | 30.8 | 157 | 69.2 | 227 | 100 | |
| Yes | 22 | 26.51 | 61 | 73.49 | 83 | 100 | |
| **HIV status** | | | | | | | 0.109 |
| No | 87 | 30.1 | 195 | 69.1 | 282 | 100 | |
| Yes | 5 | 17.86 | 23 | 82.14 | 28 | 100 | |

Tableau 2b. Paraclinical variables associated with hearing recovery

| variable | Good HR | | Poor HR | | Total | | p-value |
|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | |
| **Anemia** | | | | | | | 0.044 |
| No | 39 | 38.6 | 62 | 61.4 | 101 | 100 | |
| Yes | 59 | 28.23 | 150 | 71.77 | 209 | 100 | |
| **Hypoalbuminemia** | | | | | | | 0,046 |
| No | 72 | 34.6 | 136 | 65.4 | 208 | 100 | |
| Yes | 25 | 24.51 | 77 | 75.49 | 102 | 100 | |
| **Chronic renal failure** | | | | | | | 0.040 |
| No | 96 | 34.7 | 181 | 65.3 | 277 | 100 | |
| Yes | 6 | 18.18 | 27 | 81.82 | 33 | 100 | |
| **Severity of HL at third month of treatment** | | | | | | | < 0.001 |
| Normal | 19 | 100 | 0 | 0 | 19 | 100 | |
| Mild | 53 | 98.15 | 1 | 1.85 | 54 | 100 | |
| Moderate | 17 | 28.81 | 42 | 71.19 | 59 | 100 | |
| Severe + profound | 1 | 0.56 | 177 | 99.44 | 178 | 100 | |
| **Type of curve at third month of treatment** | | | | | | | < 0.001 |
| A | 10 | 100 | 0 | 0 | 10 | 100 | |
| B | 35 | 87.50 | 5 | 12.50 | 40 | 100 | |
| C | 47 | 19.26 | 197 | 80.74 | 244 | 100 | |
| E | 1 | 6.25 | 15 | 93.75 | 16 | 100 | |

A Multivariate logistic regression analysis, revealed that the moderate HL and the type B audiometric curve have emerged as significant determinants of a successful hearing recovery. In fact, the patients with a mild HL and a type B curve had a four- and two-fold increased likelihood, respectively, of a good HR.

Tableau 3. Determinants of a good hearing recovery

| variable | ORa | IC 95% | p-value |
|---|---|---|---|
| Age (< 40 years = ref) | | | |
| ≥ 40 years | 0.73 | 0.33–1.59 | 0.426 |
| Therapeutic regimen (Bedaquiline = ref) | | | |
| AG + BDQ | 1.06 | 0.22–4.98 | 0.945 |
| Aminoglycosides | 0.30 | 0.08–1.05 | 0.060 |
| Severity of HL at third month of treatment (Mild=ref) | | | |
| Moderate | 3.71 | 1.71 – 8.28 | 0.001 |
| Severe + profound | 0.13 | 0.01 – 1.06 | 0.057 |
| Type of curve at third month of treatment (A=ref) | | | |
| B | 2.27 | 1.72 –7.80 | 0.001 |
| C +D +E | 0.48 | 0.16 –1.46 | 0.202 |

## DISCUSSION

The objective of this study was to identify the independent risk factors associated with the hearing recovery during the treatment of MDR-TB in order to implement a preventive approach.

### Clinical and audiometric data

This study found that MDR-TB predominantly affects younger male individuals in their thirties (mean age of 34.5 years) and tinnitus identified as the primary symptom. This finding aligns with previous reports [3,4,16-21]. Several socioeconomic and behavioral factors contribute to this male predominance, including men's professional mobility and the higher rates of alcohol, tobacco, and drug abuse, which elevate the risk of contracting and developing tuberculosis. Additionally, socioeconomic inequalities and cultural barriers in sub-Saharan Africa significantly hinder women's access to healthcare, primarily due to a lack of financial resources. Our data also revealed a progressive deterioration of the HL that correlated with the patients' age, observed within three months after the treatment, regardless of the regimen. These results are consistent with existing literature [4-6]. After one month of the treatment, nearly four out of ten patients (36.6%) achieved a normal hearing. However, a predominant type C curve was observed, which increased with both age and the progression of the HL. This pattern suggests alterations in high-frequency sounds, which are typically associated with a poor prognosis. Furthermore, research has demonstrated that the HL often stems from the degeneration of cochlear hair cells, beginning at the base and extending toward the apex [22-24]. Initially, these lesions primarily impact higher frequencies and typically do not affect those essential for the conversational hearing [21]. This observation may explain the tinnitus experienced by our patients, which can occur independently of hypoacusis [21]. This hearing impairment is more accurately represented by the shape of the audiometric curves rather than solely by the degree of the HL. [22-24].

### Determinants of hearing recovery

This study revealed that one in three patients had a good recovery, the participants aged < 40 years and receiving the BDQ-based treatment exhibited a better HR compared to those aged ≥ 40 years and receiving the AG-based regimen. The ototoxicity associated with AG is well-documented, especially concerning the cochlear damage they can inflict [6,18]. Moreover, this ototoxicity worsens with age due to a fragile vascularization and the reduced recovery capacity in elderly patients [25-27]. It results from a series of intricate reactions that lead to excessive production of reactive oxygen species (ROS) [28]. The penetration of AG into the inner ear does not only depend on the serum or the perilymphatic level, but is also mainly influenced by the total dose administered [29] and the duration for which serum concentrations remain elevated [30]. AG are able to penetrate all cell types within the cochlea, and their binding to the membrane is probably mediated by a receptor that has yet to be identified [31,32]. Subsequent endocytosis appears to be dependent on myosin VIIA, a protein crucial for membrane trafficking [32-34]. Additionally, AG enter the hair cells through mechanically sensitive ion channels of stereocilia [35]. Once inside, they accumulate in lysosomal vesicles before being released into the cytoplasm [36]. At this stage, they can become highly toxic by

forming complexes with iron [37,38], which catalyze the production of ROS [38-40]. In addition, AG inhibit catalase activity while activating inducible nitric oxide synthase and NADPH oxidase, resulting in an increased accumulation of ROS [38-40].

When considering the severity of the HL, mild and moderate cases had a more favorable prognosis compared to severe and profound deafness. Likewise, the prognosis appears to be more optimistic for type A and B audiometric curves, in contrast to types C, D, and E. These findings are in line with the views of other researchers, who suggest that the potential for the hearing recovery (HR) is influenced by factors such as age, the degree of the HL, the configuration of the audiometric curve, and the presence of vertigo or tinnitus, as well as the lack of the recovery after a two-week period [41-43]. In general, patients with higher hearing thresholds on the initial audiogram exhibit lower rates of the HR compared to those with a mild hearing loss. Research has indicated that the shape of the audiogram significantly impacts recovery outcomes, with more favorable rates reported for the HL in the low (63 to 88%) or a mid-frequency (36 to 71%)[41-43]. Many authors concur that ascending curves (type A) and cup-shaped curves (type D) are associated with a better prognosis, while horizontal curves (type B) (40 to 56%) and descending curves (type C) (19 to 38%) are associated to poor outcomes [41-43]. Our results suggested that hypoalbuminemia, anemia, and CRF are linked to poor hearing recovery. This finding is backed by several studies [20,44,45]. Specifically, CRF impairs the urinary excretion of medications, and when coupled with hypoalbuminemia, it may elevate the unbound fraction of these drugs, thereby increasing the risk of adverse effects [44,46]. Additionally, anemia can lead to rheological changes and tissue hypoxia, potentially exacerbating the dysfunction in the auditory system [47].

## Conclusion

The hearing recovery rate remains low in the treatment of MDR-TB with the ototoxic hearing loss. The moderate hearing loss, and the type B audiometric curve were the determinants of a successful HR. The prevention is essential for the early diagnosis of ototoxicity signs. It is advised to conduct the otoacoustic emissions testing alongside liminal-tone audiometry prior to the initiation of the treatment. Additionally, to establish an audiometric monitoring plan to assess the progression of the hearing loss, especially in elderly MDR-TB patients and those with an impaired renal function. Patients should report any signs of the hearing impairment promptly. Furthermore, healthcare professionals should prioritize a bedaquiline-based regimen and address adverse prognostic factors, such as anemia and hypoalbuminemia. Therefore, there is a pressing need for scientific and medical research to actively develop otoprotective agents that can preserve hearing in patients with MDR-TB.

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**Conflicts of interest**

The authors have no conflicts of interest to disclose.

**Contribution of the authors**

Study design: Mireille A. Mpwate, Gauthier K. Mesia, Jean Marie N. Kayembe, Zacharie M. Kashogwe, and Richard N. Matanda; data collection: Mireille A. Mpwate, Eddy Mampuya Mbambu, Gabriel Mabuaka Lema, Dominique M. Mupepe, Innocent M. Kashogwe, Luc L. Lukasu; Data analysis and interpretation: Mireille A. Mpwate, Marc M Bonsukie, Dominique M. Mupepe, Gauthier K. Mesia and Richard N. Matanda; Draft writing and manuscript revision : Mireille A. Mpwate, Zacharie M. Kashogwe, Marc M Bonsukie, Dominique M. Mupepe, Gauthier K. Mesia and Richard N. Matanda. All the authors have read and approved the final version of this manuscript.

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