



Tuberculosis impacts multiple aspects in quality of life in a Romanian cohort of drug-susceptible and drug resistant patients: A patient-reported outcome measures study

Ioana Margineanu¹ | Teodora Butnaru² | Marjolein Lam³ | Dragos Baiceanu² |
Raluca Dragomir² | Adriana Sorete Arbore⁴ | Beatrice Mahler² | Ioana Munteanu² |
Florin Mihaltan² | Onno Akkerman^{5,6} | Jan-Willem Alffenaar^{1,7,8,9}  |
Ymkje Stienstra^{3,10} 

¹Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centrum Groningen, Groningen, the Netherlands

²Department of Respiratory Medicine, Marius Nasta Tb Institute, Bucharest, Romania

³Department of Internal Medicine/Infectious Diseases, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

⁴Clinic of Pulmonary Diseases, Iasi, Romania

⁵Department of Pulmonary diseases and Tuberculosis, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

⁶Tuberculosis Center Beatrixoord, University of Groningen, University Medical Center Groningen, Haren, the Netherlands

⁷School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia

⁸Westmead Hospital, Westmead, New South Wales, Australia

⁹Sydney Institute for Infectious Diseases, University of Sydney, Sydney, New South Wales, Australia

¹⁰Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

Correspondence

Ioana Margineanu, Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centrum Groningen, Groningen, the Netherlands.
Email: ismargineanu@gmail.com

Funding information

European Union Horizon 2020 Research and Innovation Programme, Grant/Award Number: 713660

Abstract

Background: Tuberculosis (TB), and especially its drug resistant forms, is responsible for not only significant mortality, but also considerable morbidity, still under-quantified. This study used four Patient-Reported Outcome Measures (PROMS) to assess the status of persons affected by drug-susceptible and drug-resistant TB during their TB treatment or after treatment completion, in Romania, the highest TB burden country in the EU.

Methods: People affected by TB in two different regions in Romania were included during and after treatment, following a cross-sectional design. PROMs used were SF-36, EQ-5D-5L, WPAI and the app-based audiometry screening tool 'uHear.' Descriptive statistics and relevant statistical tests were used to compare groups between themselves and with the general Romanian population.

Results: Both patients with drug-susceptible and drug-resistant TB experience, with drug-resistant patients experiencing statistically significantly more pain and hearing loss. PROMs show some improvement in the after-treatment group; however, compared with the general Romanian population for which data were available, all groups scored lower on all outcome measures.

Conclusion: PROMs offer the possibility of obtaining a more comprehensive view of patients' status, by involving them directly in the medical process and could guide a rehabilitation strategy.

Ioana Margineanu and Teodora Butnaru are joint first authors.

Sustainable Development Goal: Good Health and Well-being; Decent Work and Economic Growth

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Author(s) Tropical Medicine & International Health Published by John Wiley & Sons Ltd.

KEYWORDS

clinical management, public health, quality of life, tuberculosis

INTRODUCTION

Patients' perspectives have become increasingly recognised as important to medical management, as they can offer information about the burden of a disease beyond indicators such as incidence and mortality. The expanding use of patient-reported outcome measures (PROMs) has been a part of this shift. Initially developed for clinical trials, they have now been embedded in routine clinical settings for several domains, especially mental health [1]. PROMs consist of surveys collecting data regarding general well-being, symptoms, health-related quality of life and functional status and are one of the possible patient follow-up tools.

Tuberculosis (TB), a primarily respiratory infectious disease caused by *Mycobacterium tuberculosis*, was not only responsible for 1.6 million deaths in 2021, but also has a significant impact on patients' lives [2]. The effects of the bacteria itself, combined with the complex, lengthy treatment and post-treatment sequelae, contribute to a decrease in TB patients' quality of life, including effects on physical and emotional health, disability and patients' financial well-being [3–5]. A recent systematic review found that after a TB diagnosis, nearly a quarter of patients had or developed mental health disorders. This percentage was higher than the percentage of patients reporting well-known disease effects such as respiratory impairment or treatment side effects, such as hearing loss [3]. On the economic plane, a study from India reported that nearly one third of patients on TB treatment had incurred catastrophic costs [4] and another study of Malawi TB patients showed that more patients were living in poverty 1 year after TB treatment completion [5].

Furthermore, there is evidence to indicate that the burden of TB is worse for drug-resistant TB (DR-TB), a form of TB with increasing incidence worldwide, where treatment can last 2 years which is much longer compared with drug-susceptible TB (DS-TB). Several studies showed that patients with resistant TB scored lower on quality-of-life indicators than those with DS-TB [6, 7].

Within the European Union/European Economic Area (EU/EEA), considered a low-incidence TB region, Romania accounts for 23.4% of total EU cases [8]. The 2019 European Commission report on Romania concluded that despite certain economic growth, inequality is increasing and poverty remains high, with deepening regional disparities being amongst the highest in the EU. In this context, the healthcare system has important challenges in offering medical accessibility and patient support [9]. PROMs are the outcomes of both the diseases and these challenges combined and can inform health care workers and policy makers on interventions potentially reducing disease impact.

Therefore, we studied differences in patient-reported outcomes between drug-susceptible and drug-resistant TB patients in Romania. The secondary aim was to observe

differences in PROMs between patients during TB treatment and patients after TB treatment completion.

METHODS**Study participants**

This is an observational, cross-sectional, multicentric study. Study participants were chosen from two main regions of Romania: the north-eastern region and the capital region, in south-Romania. The economic disparity between these two regions is the largest within Romania, 3.6 times the GDP. The study took place in TB centres and in field dispensaries, located in villages surrounding urban TB centres. Study sites were the Bisericani TB Expertise Centre (Piatra Neamt, Romania), the Iasi Regional Lung Hospital and TB Ambulatory (Iasi, Romania) and the Marius Nasta TB Institute and TB Ambulatory (Bucharest, Romania). Eligible participants were adults (≥ 18 years of age), capable and willing to provide consent, diagnosed with pulmonary TB, either in treatment or after a maximum of 5 years post-treatment. Treatment end was defined as the last medication intake, as noted in the clinical chart. All eligible patients were approached either in person or via telephone (a maximum of two times) and invited to participate in the study, either in the hospital or in the rural ambulatory clinics. Participation in this study was voluntary.

Ethics

After being informed by an investigator about the contents of the study and having time to consider participation and ask questions, willing participants signed the informed consent form in their native language. The study was approved by each medical centre (METC 21064/Iasi Regional Lung Hospital and TB Ambulatory) (Iasi, Romania), 210/Bisericani TB Expertise Centre (Piatra Neamt, Romania), 10593/Marius Nasta TB Institute and TB Ambulatory (Bucharest, Romania), 201800981/University Medical Centrum Groningen (Groningen, the Netherlands).

Data collection

Patient data collection was performed using standardised forms. Data collection included general demographics, clinical data, two questionnaires regarding quality of life, a questionnaire regarding work and general financial status, and a self-administered hearing test.

The SF-36, consisting of a set of 36 plain-language scale questions, is one of the most widely used questionnaires to

measure quality of life. Interpretation is based on grouping answers in eight domains: physical functioning, energy/fatigue, emotional well-being, physical and emotional limitations to work and daily life, bodily pain, energy/fatigue and general health. The instrument has been used to measure the quality of life of patient populations with a specific disease, including TB [10, 11], and has been validated and used previously to estimate quality of life of the general Romanian population [12]. The EQ-5D-5L, assesses quality of life through levels of impairment on different dimensions: mobility, self-care, daily activity, pain/discomfort, anxiety/depression and grouping results in health states (the best possible health state being 11,111 and worse 55,555). Additionally, this questionnaire contains a visual analogue scale for self-rated health. It has been used for TB outcomes [13] and it has been validated for the Romanian population [14, 15].

The WPAI-GH is the most frequently used tool in health-related economic evaluations [16], and it has been used for several respiratory diseases [17]. It assesses work productivity and the impact of health on work and daily life with a recall period of one week [10] by asking questions regarding absenteeism (work lost) and the impact of health on work and daily life productivity. The WPAI referred to patients of employment age (under 65 for male and 61 for female for the Romanian population). Instrument scoring was performed using the official user manuals.

Audiometry was performed using the uHear app v.2.0.2, a validated software screening tool for loss of hearing [18]. Hardware equipment was maintained constant for all testing centres and it consisted in Marshall over ear headphones and an Iphone 4 SE. The app shows results for left and right ear, for 0.5 kHz, 1 kHz, 2 kHz, 4 kHz, 6 kHz with 1 being 'normal' and 5 being 'profound hearing loss'. Additionally, patients were asked pretest if they perceived any subjective hearing loss.

Self-administered measures took 15–20 mins to complete and the hearing test approximately 10 min.

For laboratory values, 48 IU/L for alanine transaminase (ALAT), 42 IU/L for aspartate transaminase (ASAT) and 1.35 mg/dL for men and 1.04 mg/dL for women for creatinine were considered normal upper limits.

Data analysis

Sample size was calculated based on the assumption that drug-susceptibility (DS-TB) decreases overall quality of life by 10% measured by SF-36 results and drug-resistant (DR-TB) by 30%, with an enrolment ratio of 3:1, a power of 80% and a margin of error of 5%.

Comparisons of groups were performed through Chi-squared test, independent sample T tests or Mann-Whitney tests, as appropriate. Data analysis was performed using SPSS version 17.

TB drug sensitivity data obtained either through classical antibiogram or GeneXpert was used to classify patients as having either DS-TB or DR-TB. The latter category was defined as any first line drug resistance or intolerance or a

combination thereof and it included mono resistance to rifampicin or isoniazid, multidrug resistance (MDR-TB) and (pre) extensive drug-resistant TB (XDR-TB).

For the secondary research question, participants were grouped in during treatment (i.e., before the last medication intake) and after treatment (i.e., after the last medication intake) categories.

General participant characteristics are reported as such. Official registers were used for the income category and for cut-off points for the number of rooms per person [19].

SF-36 domain scores were obtained, with higher scores representing better outcomes (e.g., a participant experiences less pain at a score of 80 than at a score of 60). Median scores for each domain were compared between groups. Domain median and mean scores were further compared with their counterparts for the general Romanian population.

EQ-5D-5L results were dichotomised as participants with 'no problems' and 'problems' on each of the five dimensions and results were compared. The visual analogue scale results were compared as medians. Mean visual analogue scale results were used in the comparison with the general Romanian population as data on medians are not available.

The WPAI questionnaire was analysed for participants of employment age (under 65 for men and 63 for women). Results to question 1, referring to employment status, were compared as percentages of employed participants. Questions 2–4 refer to the amount of work hours lost due to health or other issues, with a recall period of 1 week. Results are reported in percentage of time lost from a maximum of 40-hour work week, the standard in Romania. Questions 5 and 6 are scales from 1 to 10 indicating the impact of healthcare status on work and other activities, respectively. Medians of results of questions 2–6 were compared.

Analysis of audiometry app results used the uHear manual interpretation [19, 20], of averaging results for the 0.5 kHz, 1 kHz, 2 kHz, 4 kHz and considering anything over 40 dB ('moderate loss') as abnormal. Hearing grades are presented as medians and abnormal hearing and subjective perception of abnormal hearing as percentages.

For categorical values, Chi-squared and or Fisher's exact test were used and for continuous values T-test and Mann-Whitney U test were used to compare groups, as appropriate, with significance set at $p < 0.05$. Software used was IBM SPSS® v.27.

RESULTS

Participant characteristics

A total of 201 patients with DS-TB and 80 with DR-TB were enrolled (Table 1), out of which 146 participants were receiving TB treatment. The median age was 45 years and 71% of the participants were male. Considering living conditions, including poverty indicators, the majority of patients lived in rural areas, and more than a third had their

TABLE 1 Patient characteristics.

	<u>DS-TB</u> N = 201	<u>DR-TB</u> N = 80	<u>Total</u> N = 281
Patient characteristics			
Male	139 (69%)	61 (76%)	199 (71%)
Age (years, median [IQR])	44 (31–55)	49 (40–57)	45 (33–57)
BMI (kg/m ² , median [IQR])	21 (20–24)	20 (18–24)	21 (19–24)
TB treatment phase			
During TB treatment	100 (50%)	46 (58%)	146
After TB treatment	101 (50%)	34 (42%)	135
Living conditions			
Urban	90 (45%)	36 (45%)	126 (45%)
Rural	109 (54%)	44 (55%)	153 (55%)
Homeless	2 (1%)	0	2 (0.7%)
Outdoor bathroom	83 (41%)	29 (35%)	112 (40%)
Education			
No education	2 (1%)	1 (1.3%)	3 (1%)
Under bachelor level	129 (64%)	57 (71%)	186 (66%)
Bachelor and above	70 (35%)	22 (28%)	92 (33%)
Lifestyle			
Current smokers	86 (43%)	41 (51%)	127 (45%)
Moderate or more alcohol intake ^a	28 (14%)	6 (8%)	34 (12%)

^aDefined as more than more than eight drinks per week for women and 15 for men, National Institute for Health, National Institute on Alcohol Abuse and Alcoholism, US 2023.

bathroom outdoors. The mean number of rooms per person in our study, 1.3 rooms per person was lower than the EU average of 1.6, but comparable with the Romanian mean of 1.1 [21]. A minority of patients presented with comorbidities: 3 (1%) with HIV, 12 (4%) with diabetes mellitus type 2 and 5 (2%) with cancer.

TB was diagnosed following the standard diagnostic routine. Almost all, 269 (96%), had a chest X-ray indicating TB, 208 (74%) had a positive sputum smear result, 222 (81%) had a positive culture result, with the rest of the patients being treated as TB based on clinical context. A majority, 222 (79%) were newly diagnosed with TB (177/201 (88%) of DS-TB and 45/80 (56%) of DR-TB), with the rest being retreatment cases.

Among the 80 patients with resistant TB, 4 (5%) had rifampicin mono-resistant TB, 5 (6%) had isoniazid mono-resistant TB, 50 (63%) had multidrug-resistant TB and 21 (26%) had extensively drug-resistant TB (2019 definition). An injectable drug (amikacin or kanamycin) was used for 42 (15%) patients. Forty-three (15%) patients had elevated liver enzymes (either ALAT, ASAT, or both) and eight (3%) had an elevated creatinine value in the course of their treatment.

SF-36

Seven of the eight SF-36 domains scores had no statistically significant differences between DS-TB and DR-TB groups. The only domain where groups' scores were statistically

different was the 'bodily pain' ($p = 0.029$, Mann–Whitney U test, Table 3). Compared with data available for the general Romanian population, DR-TB and during treatment groups scored lower on all domains, with the largest differences being noted in the 'role of limitations' domains, both for physical health and emotional problems. These two domains included questions such as 'during the past four weeks, have you had difficulty performing work or daily activities' and 'during the past four weeks, have you accomplished less than you would have liked'. DS-TB and after-treatment groups scored either similarly or slightly better median scores for several domains, including 'emotional well-being' and 'social functioning'. For the 'general health' domain, all groups scored lower medians and means (Table 2, Figure 1).

Domains with statistically significant differences depending on treatment stage were 'role of limitations due to physical health' (25 (0–100) for patients during treatment and 75 (0–100) after treatment, $p < 0.001$), 'role of limitations due to emotional problems' (33 (–100) for patients during treatment and 100 (0–100) after treatment, $p = 0.001$) and 'social functioning' (75 (50–100) in patients during treatment and 88 (63–88) after treatment, $p = 0.001$).

EQ-5D-5L

There were several domains with differences in proportions of patients experiencing problems; however, the 'pain'

TABLE 2 SF-36 domains scores comparisons between drug-susceptible and drug-resistant TB patients and between patients during and after treatment completion.

Domain	Median (IQR)				RO Pop ^a
	DS-TB	DR-TB	During	After	
	N = 201	N = 80	N = 146	N = 135	
Physical functioning	85 (55–95)	75 (55–93)	75 (49–90)	90 (65–100)	95
Role of limitations due to physical health	50 (0–100)	50 (0–100)	25 (0–100) ^b	75 (0–100) ^b	100
Role of limitations due to emotional problems	100 (0–100)	67 (0–100)	33 (0–100) ^b	100 (0–100) ^b	100
Energy/fatigue	60 (40–80)	60 (40–70)	55 (40–76)	60 (45–80)	65
Emotional well-being	72 (52–80)	68 (52–76)	68 (52–80)	72 (56–80)	68
Social functioning	88 (62–100)	75 (50–100)	75 (50–100)	88 (63–88)	86
Bodily Pain	80 (56–100) ^c	68 (45–100) ^c	78 (45–100)	88 (55–88)	78
General health	60 (45–75)	55 (45–70)	60 (45–70)	60 (45–75)	65

Note: Higher scores represent better outcomes. Final column represents general Romanian population.

^aGeneral Romanian Population; rows in grey represent statistically significant differences between groups.

^b Statistically significant differences between during and after treatment.

^c Statistically significant differences between DS-TB and DR-TB;

TABLE 3 EQ-5D-5L domains comparisons between drug-susceptible and drug-resistant TB patients and between patients during and after-treatment completion.

Domain	Number of participants experiencing problems, n (%)			
	DS-TB	DR-TB	During	After
	N = 201	N = 80	N = 146	N = 135
Mobility	142 (71%)	49 (61%)	90 (62%)	101 (75%)
Self-care	180 (90%)	72 (90%)	132 (90%)	120 (89%)
Daily activity	147 (73%)	50 (63%)	101 (70%)	96 (71%)
Pain	114 (57%)	31 (39%)	75 (51%)	70 (52%)
Anxiety	110 (55%)	35 (44%)	70 (48%)	76 (56%)
EQ VAS (means, SD)	74 (SD 22)	73 (SD 21)	69 (SD 24)	80 (SD 18)

Note: Rows in grey represent statistically significant differences between groups; statistically significant differences between DS-TB and DR-TB; statistically significant differences between during and after treatment.

domain was the only one with statistically significant differences between DS-TB and DR-TB: 57% DS-TB reported not having any pain vs 39% DR-TB, $p = 0.007$ (Chi-squared test, Table 3). Furthermore, the only statistically significant difference between patients during and after treatment is in the ‘mobility’ domain.

Concerning the overall visual analogue scale, TB patients scored a mean of 74/100 (SD 22) and a median of 80 (60–90), with 35 (13%) reporting full health (100/100). The general Romanian population has a mean of 82.5 (SD 15.5) on the same scale and 52% reported full health.

Employment and WPAI

Of the total of 281 participants, 32 (11%) were of retirement age (65 for men and 63 for women) and were not included in the analysis. Approximately half of all patients earn less than the minimum wage in Romania. There were no statistically significant differences in the WPAI questionnaire between DS-TB and DR-TB, but there were differences between patients during and after treatment, with the latter

category scoring better on all questions regarding work and daily activities. Patients during treatment lost all work hours as they were either hospitalised or on medical leave. For the same question, after treatment, patients reported missing no work hours (work hours missed during treatment 100 (0–100) vs. after treatment 0 (0–0), $p < 0.001$). At the same time, the after-treatment group scored statistically significantly better on the domains pertaining to the impairment of TB on their work (impairment while working during treatment 50 (25–80) vs. after treatment 10 (0–45) $p < 0.001$, overall work impairment during treatment 100 (100–100) vs. after treatment 10 (0–80) $p < 0.001$) and daily activities (during treatment 50 (10–70) vs. after treatment 20 (0–70) $p = 0.003$), but they still reported certain degrees of impairment (Table 4).

uHear audiometry app results

Nine patients (7 DS-TB and 2 DR-TB) did not understand how to perform this test and were excluded from the analysis.

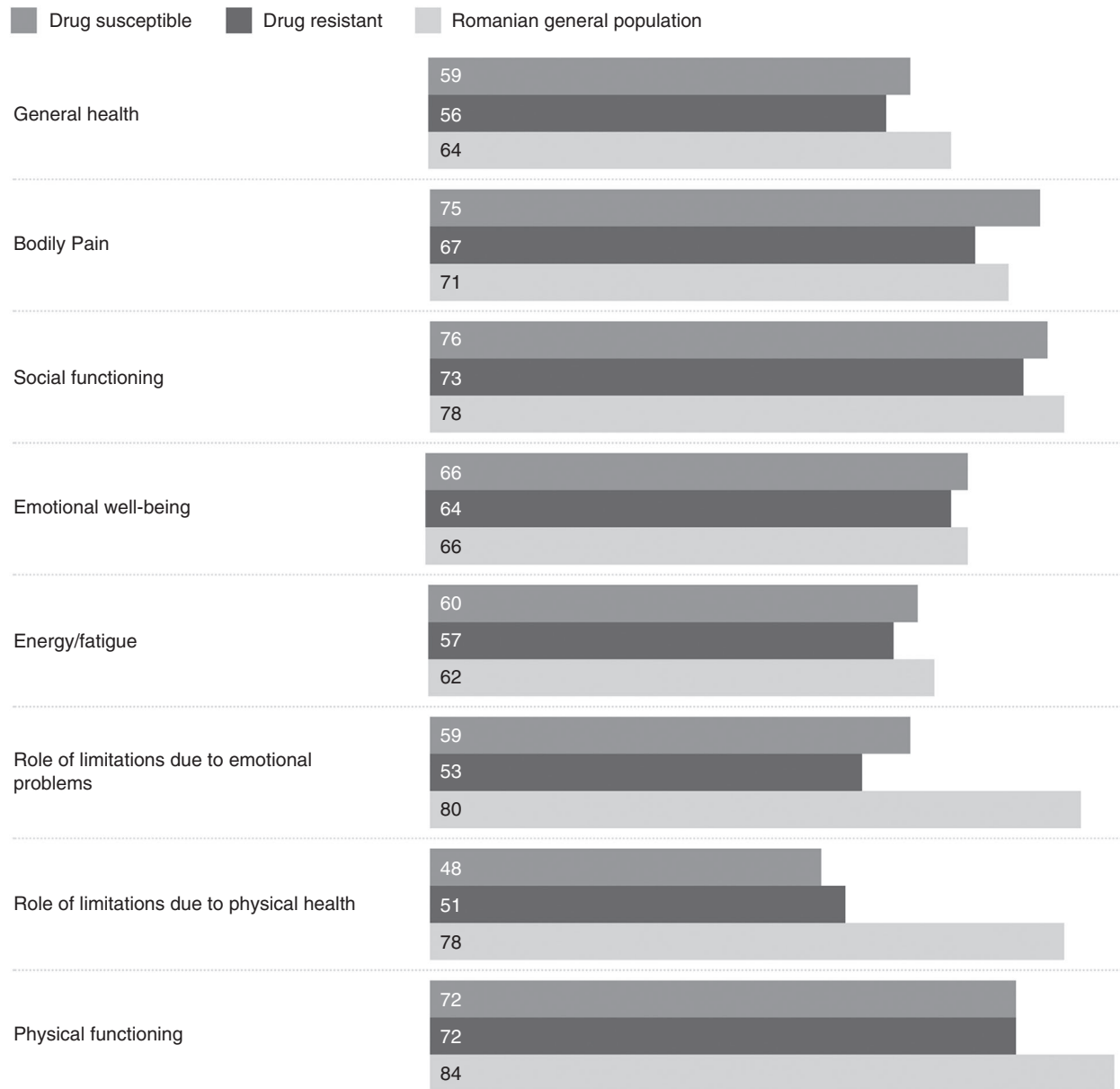


FIGURE 1 Mean of SF-36 domains for drug-susceptible TB patients, drug-resistant TB patients and the general Romanian population. Higher scores represent better outcomes.

Hearing loss was statistically significantly worse for DR-TB across multiple hearing loss metrics, including patients' subjective perception, hearing test results through uHear and if taking in account only high frequency hearing loss (Table 5).

Subgroup analysis on different treatment schemes was performed. A total of 82 of 281 patients (28%) were on second-line medication, out of which 41 (50%) were on injectable therapy (amikacin or kanamycin). Of these, 26 (63%) had a result indicating on the uHear test compared with 83 (36%) of the participants without injectables in their treatment scheme ($p = 0.002$). Hearing loss for high frequencies (over 1 Hz) was recorded by 29 (71%) of the group on injectable therapy versus 106 (46%) in the non-injectables group ($p = 0.003$, Chi-squared test).

There were statistically significant differences in audiometry results between patients during and after treatment, with better scores noted in all parameters in the after-treatment group.

DISCUSSION

This cross-sectional study investigated Romanian TB patients' reported outcome measures concerning general health, physical, social and emotional wellbeing, and the impact the disease has had on their work and health through different instruments: three standardised questionnaires and app-based audiometry. The main statistically significant

TABLE 4 Employment and WPAI domains comparisons between drug-susceptible and drug-resistant TB patients and between patients during and after treatment completion.

	<u>DS-TB</u>	<u>DR-TB</u>	<u>During</u>	<u>After</u>
	<i>N</i> = 179	<i>N</i> = 70	<i>N</i> = 129	<i>N</i> = 120
Item	Number of participants, <i>n</i> (%)			
Employed	82 (46%)	28 (40%)	53 (41%)	67 (48%)
Earning less than minimum wage	89 (50%)	38 (54%)	70 (54%)	57 (48%)
Less income after TB diagnosis	64 (36%)	21 (30%)	64 (44%)	57 (42%)
Domain	Median (IQR)			
Percent work hours missed due to health	100 (0–100)	0 (0–100)	100 (100–100)	0 (0–0)
Percent impairment while working due to health	50 (0–80)	20 (5–50)	50 (25–80)	10 (0–45)
Percent overall work impairment due to health	100 (0–100)	60 (10–100)	100 (100–100)	10 (0–80)
Percent daily activity impairment due to health	30 (0–80)	25 (10–70)	50 (10–70)	20 (0–70)

Note: Rows in grey represent statistically significant differences between groups; statistically significant differences between during and after treatment.

TABLE 5 Audiometry with uHear test results comparisons between drug-susceptible and drug-resistant TB patients and between patients during and after treatment completion.

	<u>DS-TB</u>	<u>DR-TB</u>	<u>During</u>	<u>After</u>
Item	<i>N</i> = 194	<i>N</i> = 78	<i>N</i> = 129	<i>N</i> = 120
Number of participants, <i>n</i> (%)				
Abnormal hearing right or left ear	69 (36%)	42 (54%)	65 (47%)	42 (32%)
Severe or profound hearing loss right or left (>80 dB)	80 (41%)	49 (63%)	79 (60%)	46 (35%)
High frequency hearing loss right or left ear (for frequencies over 1 Hz)	93 (43%)	52 (67%)	80 (57%)	56 (42%)
Median (IQR)				
Hearing grades right ear	2.4 (1–6) (mild)	3.2 (1–6) (moderate)	3 (2.2–3.8) (moderate)	2.4 (2–3.3) (mild)
Hearing grades left ear	2.6 (1–6) (mild)	3 (1–5.4) (moderate)	3 (2.2–3.8) (moderate)	2.4 (2–3.3) (mild)

Note: Rows in grey represent statistically significant differences between groups; statistically significant differences between DS-TB and DR-TB; statistically significant differences between during and after treatment.

differences between DS-TB and DR-TB participants were in domains pertaining to bodily pain and in the audiometry. Patients in the after-treatment group scored better on a majority of outcome measures, however, scored lower than the general Romanian population on all outcomes with comparisons available.

Our study population is aligned with other research indicating that socioeconomic indicators and smoking are risk factors for TB [22, 23]. Compared with the general Romanian population, more study participants lived in rural areas (55% vs. 46%) [24], more earned less than minimum wage (51% vs. 13%) and there was a higher proportion of active smokers (55% vs. 37% Romanian general population). Unemployment rates in our study population were almost 10 times as high as the reported national unemployment rate for the same year (44% in our study vs. 5% Romania in 2019).

This research included two quality of life PROMs, the SF-36 and the EQ-5D-5L. Concerning both PROMs, there were no statistically significant differences between DS-TB

and DR-TB patients except in the ‘pain’ domains of both instruments. Joint pain is a reported side effect of second-line TB drugs, including bedaquiline [25]; however, other studies using the SF-36 found that pain was less significant in the MDR-TB group [26] than in the DS-TB group. At the same time, patients included in our study reported better quality of life outcomes than patients in other studies, especially concerning DR-TB [7, 26–29]. As in our study, other research showed improvement in quality of life after the completion of TB treatment, especially visible on the EQ-5D-5L general health visual analogue scale. It is worth mentioning that other studies included patients only after a maximum one-year post-treatment completion, and our inclusion criteria expanded this time frame to up to 5 years. The domains with the lowest scores (i.e., the largest impact on participants’ well-being) related to the limiting nature of the disease and emotional well-being. Concerning the latter, patients in the during and after-treatment groups scored very similarly, suggesting there is little mental health improvement post-treatment. This has been indicated by

other research, with experts calling for better mental support throughout and after TB [30].

The sample Romanian population which was used to compare results had a comparable age (for SF-36 mean age of 40 years, for EQ-5D-5L mean age of 48), but included more female participants (for SF-36 and EQ-5D-5L there were 66% female participants). Compared with data available for the general Romanian population, TB patients scored lower especially in the domains pertaining to limitations due to physical health and emotional problems. This result matches other studies comparing quality of life with either control groups without TB or general populations [31].

Concerning employment, less than half of patients were employed, even after TB treatment completion. Another study performed in Malawi shows that employment was lowest at TB treatment completion, with 47% not being employed [5]. Furthermore, patients during treatment lost most of their working hours. For the patients in the intensive phase, this could be explained by the hospitalisation time. The Romanian TB guideline recommends hospitalisation for all pulmonary TB cases unless there is the possibility of direct observed therapy in isolation conditions [32]. A recent Global TB Network review notes that globally hospitalisation times range between 20 and 60 days [33] for DS-TB and 50–180 days for DR-TB. However, 40% of S-TB and 25% of DR-TB patients were included after the intensive phases, which could indicate that TB impairs work productivity beyond hospitalisation time, during the course of the illness. After treatment, results indicate that the participants who are employed lose less time off work because of the disease; however, unemployment rates were high in all study groups, including the after-treatment group. Audiometry through the uHear app was a convenient method for patients to self-evaluate their hearing, with only a minority of participants not understanding the procedure. uHear app results confirm previous known facts regarding second-line treatment ototoxicity [34, 35], with 30 out of the 41 (71%) patients who had aminoglycosides in their treatment scheme experiencing high-frequency hearing loss. Whilst international guidelines from 2018 have removed aminoglycosides from the DR-TB treatment schemes and they are being phased out, it is notable that 36% of participants without an injectable drug also experience hearing loss [36]. Hearing loss is the third cause of years lived with disability, after back pain and migraine. Hearing, therefore, may require extra attention in programmes supporting people affected by TB after treatment.

Considering TB follow-up, this study included several follow-up measures not included in current follow-up recommendations, but which would be useful for appraising patient status. International guidelines recommend follow-up post-treatment; however, the Romanian strategy does not include such a chapter [37, 38]. Clinicians demonstrated reluctance to implement PROMs in everyday practice as they feared, among other aspects, that it would add to the

workload [39]. However, with the advent of the COVID-19 pandemic, and the high penetration of mobile technologies, digital follow-up could be a feasible, cost-effective future direction to pursue [40, 41].

Strengths and limitations

This study is the first to investigate PROMs in the Romanian population, the highest TB burden country in the EU, accounting for a fourth of all TB cases in this region. Recruitment strategies aimed to ensure recruitment of a representative population sample of Romanian TB patients. Characteristics of the study population align with TB indicators for 2020 [7, 22]. Furthermore, this study consisted of several PROMs, offering a multi-dimensional view of patients' well-being and functional status. Employment and income may be underreported in our results as participants can be reluctant to report untaxed income. We did not follow people affected by TB longitudinally, which would have allowed us to look for factors influencing well-being over the course of treatment.

CONCLUSION

Both DS- and DR-TB patients experience limitations due to TB, with PROMs showing partial recovery in the people affected by TB even after finishing treatment. The main differences between participants affected by DS-TB and DR-TB were in the measures studying pain and hearing loss. Compared with the general Romanian population, all groups scored lower on all domains for which data were available. PROMs offer the possibility of obtaining a more comprehensive view of patients' status, by involving them directly in the medical process. The possibility of follow-up through PROMs might be appealing to both clinicians and patients in high burden settings as part of digital health strategies.

ACKNOWLEDGEMENTS

The authors would like to express gratitude for all the clinicians involved in this study who facilitated access to potential participants. A special thank you is extended to Marcela Brodner.

FUNDING INFORMATION

IM is funded from a doctoral project funded from the European Union Horizon 2020 Research and Innovation Programme, under the Marie-Skłodowska Curie grant agreement 713660. The funding source had no impact on any decision-making regarding this paper.

ORCID

Jan-Willem Alffenaar  <https://orcid.org/0000-0001-6703-0288>

Ymkje Stienstra  <https://orcid.org/0000-0002-8844-8859>

REFERENCES

- Churruca K, Pomare C, Ellis LA, Long JC, Henderson SB, Murphy LED, et al. Patient-reported outcome measures (PROMs): a review of generic and condition-specific measures and a discussion of trends and issues. *Health Expect*. 2021;24(4):1015–24. <https://doi.org/10.1111/hex.13254>
- Bagcchi S. WHO's global tuberculosis report 2022. *Lancet Microbe*. 2023;4(1):e20. [https://doi.org/10.1016/S2666-5247\(22\)00359-7](https://doi.org/10.1016/S2666-5247(22)00359-7)
- Alene KA, Wangdi K, Colquhoun S, Chani K, Islam T, Rahevar K, et al. Tuberculosis related disability: a systematic review and meta-analysis. *BMC Med*. 2021;19(1):203. <https://doi.org/10.1186/s12916-021-02063-9>
- Prasanna T, Jeyashree K, Chinnakali P, Bahurupi Y, Vasudevan K, Das M. Catastrophic costs of tuberculosis care: a mixed methods study from Puducherry, India. *Glob Health Action*. 2018;11(1):1477493. <https://doi.org/10.1080/16549716.2018.1477493>
- Meghji J, Gregorius S, Madan J, Chitimbe F, Thomson R, Rylance J, et al. The long term effect of pulmonary tuberculosis on income and employment in a low income, urban setting. *Thorax*. 2021;76(4):387–95. <https://doi.org/10.1136/thoraxjnl-2020-215338>
- Araia ZZ, Mesfin AB, Mebrahtu AH, Tewelde AG, Tewelde AT, Ngusbrhan KS. Health-related quality of life in tuberculosis patients in Eritrea: comparison among drug-susceptible and rifampicin/multi-drug-resistant tuberculosis patients. *Patient Relat Outcome Meas*. 2021;12:205–12. <https://doi.org/10.2147/PROM.S316337>
- Jaber AAS, Ibrahim B. Health-related quality of life of patients with multidrug-resistant tuberculosis in Yemen: prospective study. *Health Qual Life Outcomes*. 2019;17(1):142. <https://doi.org/10.1186/s12955-019-1211-0>
- European Centre for Disease Prevention and Control. Tuberculosis surveillance and monitoring in Europe 2021–2019 data. 2021 [cited 2022 Feb 16]. Available from: <https://www.ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2021-2019-data>
- corporate-body.COM:European Commission, corporate-body.SG:Secretariat-General. SWD/2020/522 final. COMMISSION STAFF WORKING DOCUMENT Country Report Romania 2020 Accompanying the document COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE EUROPEAN COUNCIL, THE COUNCIL, THE EUROPEAN CENTRAL BANK AND THE EUROGROUP 2020 European Semester: Assessment of progress on structural reforms, prevention and correction of macro-economic imbalances, and results of in-depth reviews under Regulation (EU) No 1176/2011. 2020 [cited 2022 Feb 16]. Available from: <https://op.europa.eu/en/publication-detail/-/publication/8b39ae9a-5945-11ea-8b81-01aa75ed71a1/language-en/format-PDF>
- Chushkin M, Maliev B, Belevskiy A, Meshcheryakova N, Bukhareva S, Smerdin S. Using SF-36 in assessment of quality of life in patients cured of pulmonary tuberculosis. *Eur Respir J*. 2011;38(Suppl 55):2591. https://erj.ersjournals.com/content/38/Suppl_55/p2591
- Chamla D. The assessment of patients' health-related quality of life during tuberculosis treatment in Wuhan, China. *Int J Tuberc Lung Dis*. 2004 Sep;8(9):1100–6. <https://www.ncbi.nlm.nih.gov/pubmed/15455595>
- Mardare I, Furtunescu FL, Bratu EC, Anastasievici L. Measuring health related quality of life – methods and tools. [cited 2023 Jun 2]. Available from: <http://www.amtsibiu.ro/Arhiva/2019/Nr2-en/Mardare.pdf>
- Park HY, Cheon HB, Choi SH, Kwon JW. Health-related quality of life based on EQ-5D utility score in patients with tuberculosis: a systematic review. *Front Pharmacol*. 2021;12:659675. <https://doi.org/10.3389/fphar.2021.659675>
- Olariu E, Mohammed W, Oluboyede Y, Caplescu R, Niculescu-Aron IG, Paveliu MS, et al. EQ-5D-5L: a value set for Romania. *Eur J Health Econ*. 2022;24:399–412. <https://doi.org/10.1007/s10198-022-01481-7>
- Paveliu MS, Olariu E, Caplescu R, Oluboyede Y, Niculescu-Aron IG, Ernu S, et al. Estimating an EQ-5D-3L value set for Romania using time trade-off. *Int J Environ Res Public Health*. 2021;18(14):7415. <https://doi.org/10.3390/ijerph18147415>
- Hubens K, Krol M, Coast J, Drummond MF, Brouwer WBF, Uyl-de Groot CA, et al. Measurement instruments of productivity loss of paid and unpaid work: a systematic review and assessment of suitability for health economic evaluations from a societal perspective. *Value Health*. 2021;24:1686–99. <https://doi.org/10.1016/j.jval.2021.05.002>
- Chen H, Blanc PD, Hayden ML, Bleecker ER, Chawla A, Lee JH, et al. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. *Value Health*. 2008;11(2):231–9. <https://doi.org/10.1111/j.1524-4733.2007.00229.x>
- Ong Z-T, Lam B, Ooi K, Watcharasupat KN, Wong T, Gan W-S. Do uHear? Validation of uHear app for preliminary screening of hearing ability in soundscape studies. arXiv preprint arXiv. Available from: https://www.researchgate.net/profile/Bhan-Lam/publication/362121556_Do_uHear_Validation_of_uHear_App_for_Preliminary_Screening_of_Hearing_Ability_in_Soundscape_Studies/links/62d760f6593dae2f6a2a48c1/Do-uHear-Validation-of-uHear-App-for-Preliminary-Screening-of-Hearing-Ability-in-Soundscape-Studies.pdf
- Szudek J, Ostevik A, Dziegielewski P, Robinson-Anagor J, Goma N, Hodgetts B, et al. Can Uhear me now? Validation of an iPod-based hearing loss screening test. *J Otolaryngol Head Neck Surg*. 2012;41-(Suppl 1):S78–84. <https://www.ncbi.nlm.nih.gov/pubmed/22569055>
- Al-Abri R, Al-Balushi M, Kolethekkat A, Bhargava D, Al-Alwi A, Al-Bahlani H, et al. The accuracy of IOS device-based uHear as a screening tool for hearing loss: a preliminary study from the Middle East. *Oman Med J*. 2016;31(2):142–5. <https://doi.org/10.5001/omj.2016.27>
- Housing in Europe. Housing in Europe – size of housing. [cited 2023 Feb 14]. Available from: <https://ec.europa.eu/eurostat/cache/digpub/housing/bloc-1b.html?lang=en>
- Migliori GB, Garcia-Basteiro AL. Predicting the effect of improved socioeconomic health determinants on the tuberculosis epidemic. *Lancet Glob Health*. 2018;6(5):e475–6. [https://doi.org/10.1016/S2214-109X\(18\)30189-X](https://doi.org/10.1016/S2214-109X(18)30189-X)
- Amere GA, Nayak P, Salindri AD, Narayan KVM, Magee MJ. Contribution of smoking to tuberculosis incidence and mortality in high-tuberculosis-burden countries. *Am J Epidemiol*. 2018;187(9):1846–55. <https://doi.org/10.1093/aje/kwy081>
- Rural population (% of total population) – Romania [cited 2023 Feb 16]. Available from: <https://data.worldbank.org/indicator/SP.RUR.TOTL.ZS?locations=RO>
- Atif M, Ahmed W, Nouman Iqbal M, Ahmad N, Ahmad W, Malik I, et al. Frequency and factors associated with adverse events among multi-drug resistant tuberculosis patients in Pakistan: a retrospective study. *Front Med*. 2021;8:790718. <https://doi.org/10.3389/fmed.2021.790718>
- Roba AA, Dasa TT, Weldegebreal F, Asfaw A, Mitiku H, Teklemariam Z, et al. Tuberculosis patients are physically challenged and socially isolated: a mixed methods case-control study of health related quality of life in eastern Ethiopia. *PLoS One*. 2018;13(10):e0204697. <https://doi.org/10.1371/journal.pone.0204697>
- Ahmad N, Javaid A, Syed Sulaiman SA, Basit A, Afridi AK, Jaber AAS, et al. Effects of multidrug resistant tuberculosis treatment on Patients' health related quality of life: results from a follow up study. *PLoS One*. 2016;11(7):e0159560. <https://doi.org/10.1371/journal.pone.0159560>
- Dody Izhar M, Butar MB, Hidayati F, Ruwayda R. Predictors and health-related quality of life with short form-36 for multidrug-resistant tuberculosis patients in Jambi, Indonesia: a case-control study. *Clinic Epidemiol Global Health*. 2021;12:100872. <https://doi.org/10.1016/j.cegh.2021.100872>
- Ramkumar S, Vijayalakshmi S, Seetharaman N, Pajaniavel R, Lokeshmaran A. Health-related quality of life among tuberculosis patients under Revised National Tuberculosis Control Programme in rural and urban Puducherry. *Indian J Tuberc*. 2017;64(1):14–9. <https://doi.org/10.1016/j.ijtb.2016.11.004>
- BMJ. Tuberculosis patients need better mental health support, especially in the time of COVID-19. *The BMJ*. 2020 [cited 2023 Feb 16].

- Available from: <https://blogs.bmj.com/bmj/2020/10/09/tuberculosis-patients-need-better-mental-health-support-especially-in-the-time-of-covid-19/>
31. Guo N, Marra F, Marra CA. Measuring health-related quality of life in tuberculosis: a systematic review. *Health Qual Life Outcomes*. 2009;7:14. <https://doi.org/10.1186/1477-7525-7-14>
 32. metodologic de implementare a Programului G. național de prevenire, supraveghere și control al tuberculozei. București, 2015. ISBN 978-973-139-325-4. Ordinul Ministerului Sănătății; 2015.
 33. Migliori GB, Visca D, van den Boom M, Tiberi S, Silva DR, Centis R, et al. Tuberculosis, COVID-19 and hospital admission: consensus on pros and cons based on a review of the evidence. *Pulmonology*. 2021; 27(3):248–56. <https://doi.org/10.1016/j.pulmoe.2020.12.016>
 34. Verma J, Syed MT. Evaluating hearing loss in patients undergoing second line anti tubercular treatment. *Indian J Otolaryngol Head Neck Surg*. 2019;71(Suppl 2):1202–6. <https://doi.org/10.1007/s12070-018-1266-y>
 35. Varaine F, Rich ML, Grouzard V. Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. *Med Sans Front Partners Health*.
 36. Médecins Sans Frontières (MSF) International [Internet]. Step up for TB report 2020 [cited 2023 Mar 9]. Available from: <https://www.msf.org/step-tb-report-2020>
 37. Ariadna Petronela F, Daniela H, Beatrice M, Ramona Elena N, Cristian George P, Gilda Georgeta P. TUBERCULOZA MANUAL PENTRU PROFESIONIȘTII DIN SĂNĂTATE [Internet]. 2022 Available from: https://marius-nasta.ro/wp-content/uploads/2022/07/Manual-TB-FINAL_A-1.pdf
 38. Popovici O, Șerban R, Janță D, Moisoiu A, Arbore AS, Dragoș M, et al. Strategia Națională pentru Controlul Tuberculozei în România – 2022-2030. Governmental General Secretariat.
 39. Nelson EC, Eftimovska E, Lind C, Hager A, Wasson JH, Lindblad S. Patient reported outcome measures in practice. *BMJ*. 2015;350:g7818. <https://doi.org/10.1136/bmj.g7818>
 40. Margineanu I, Louka C, Vincenti-Gonzalez M, Saktiawati AMI, Schierle J, Abass KM, et al. Patients and medical staff attitudes toward the future inclusion of ehealth in tuberculosis management: perspectives from six countries evaluated using a qualitative framework. *JMIR MHealth UHealth*. 2020;8(11):e18156. <https://doi.org/10.2196/18156>
 41. Margineanu I, Louka C, Akkerman O, Stienstra Y, Alffenaar JW. eHealth in TB clinical management. *Int J Tuberc Lung Dis*. 2022; 26(12):1151–61. <https://doi.org/10.5588/ijtld.21.0602>

How to cite this article: Margineanu I, Butnaru T, Lam M, Baiceanu D, Dragomir R, Arbore AS, et al. Tuberculosis impacts multiple aspects in quality of life in a Romanian cohort of drug-susceptible and drug resistant patients: A patient-reported outcome measures study. *Trop Med Int Health*. 2024. <https://doi.org/10.1111/tmi.13996>