**„CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST**

**DOCTORAL SCHOOL**

**MEDICAL FIELD**

# QUALITY OF LIFE OF ROMANIAN PATIENTS WITH SENSITIVE AND DRUG-RESISTANT TUBERCULOSIS DURING AND AFTER TREATMENT

## PhD THESIS SUMMARY

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**CONTENT**

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LIST OF ABBREVIATIONS AND SYMBOLS

ABG = antibiogram

BAAR = acid-alcohol-resistant bacilli

BPaL = regimen of bedaquiline, pretomanide, and linezolid

BPaLM = regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin

DOT = Directly Observed Treatment

DR = drug resistance

DPF = pneumophthisiology dispensary

EQ5D5L = EuroQol Group five dimensions quality of life questionnaire

HIV = human immunodeficiency virus

QFT = Quantiferon TB

QOL = quality of life

LPA MDR TB DR plus = line probe assay, genetic test of gene amplification for identification the MTB complex and the resistances to HIN and/or RMP

LPA MTB DRsl= line probe assay, genetic test of gene amplification for identification MTB complex and resistances to HIN and/or RMP and/or AGL and/or Q

WHO = World Health Organization

MTB = Mycobacterium tuberculosis

PNPSCT = National Tuberculosis Prevention, Surveillance and Control Program

PROM = a person's perception of their own health through questionnaires (patient-reported outcome measures)

SF-36 = Short Form 36 Health Survey

TB = tuberculosis

DR TB = drug resistant TB

TB DS = drug-susceptible TB

TBEP = extrapulmonary TB

TB Hr = TB susceptible to rifampicin and resistant to isoniazid

RR TB= Rifampicin-resistant TB

MDR TB = multidrug-resistant TB;

MDR/RR TB= multidrug or rifampicin-resistant TB

Pre-XDR TB = pre-extensively drug-resistant TB

XDR TB = extensively drug-resistant TB

WPAI = Work Productivity and Activity Impairment Questionnaire

Xpert MTB/Rif/ULTRA = rapid, standardized, complex identification genetic test

M.tuberculosis and mutations associated with resistance to RMP

Xpert MTB/XDR = rapid, standardized genetic test for the identification of the M.tuberculosis complex

and mutations associated with resistance to H, Q, to second-line injectable drugs (Ak, Km,

Cpm) and Etm

6 MWT = 6 Minute Walk Test

Antituberculosis drugs

Ak = amikacin

Amx/clv=clavulanic acid (amoxicillin/clavulanate)

B, Bdq = bedaquiline

Cfz = clofazimine

Cpm = capreomycin

Cs = cycloserine

Dlm = delamanid

E, ETB = ethambutol

Etm = ethionamide

H, HIN = Isoniazid

Ipm-Cln = imipenem - cilastatin

Km = kanamycin

Lfx = levofloxacin

L, Lnz = linezolid

Ofl = ofloxacin

Mfx = moxifloxacin

Mpn = meropenem

Pa= Pretomanid

PAS = para-aminosalicylic acid

Ptm = prothionamide

Q = Fluoroquinolones

RMP, RIF, R = Rifampicin

S = streptomycin

Tzd = terizidone

Z, PZM = pyrazinamide

# Introduction

Pulmonary tuberculosis, both the treatment-sensitive (S-TB) and the drug-resistant (DR-TB) forms, is an infectious-contagious disease that presented and is of interest as a public health problem, endemic in many regions of the globe, ranking among the top 10 causes of death worldwide; untreated or treated incorrectly, can lead to significant fatality. Combating this condition requires substantial financial resources. According to the World Health Organization (WHO), 13 billion dollars are needed annually for the prevention, diagnosis and treatment of tuberculosis.

The impact of tuberculosis is not limited only to clinical indicators, but also to the quality of life, directly reduced by the disease and treatment (weight loss, asthenia, side effects of medication, comorbidities), but also indirectly by the nature of the disease (social inclusion, job loss). The impairment of the quality of life associated with this pathology was not sufficiently included in the research nor covered by the existing guidelines.

Patients with drug-resistant tuberculosis (DR-TB) frequently have associated comorbidities and prior treatments, leading to additional social, family, and financial challenges. DR TB treatment takes a long time, is more complex, frequently associated with significant adverse effects and less favorable outcomes. Social rejection, stigmatization and side effects of treatment are examples of indicators of a reduced quality of life, affecting the social and professional integration of patients. Consequently, it is reasonable to assume that components of the quality of life of patients diagnosed with DR TB are significantly compromised.

Beyond the clinical and technical aspects presented, this doctoral thesis emphasizes the need to adopt a patient-centered therapeutic approach that increases adherence to treatment and improves quality of life, as well as additional attention from the medical professionals involved in treating these patients and the implementation of some additional support measures to help patients.

Quality of life indicators could be more commonly associated with routine indicators used to assess treatment response and could be included in future guidelines. This integration would

allow healthcare professionals to identify specific aspects of mental and physical health adversely affected by the disease or its treatment.

The complex bibliography and vast interdisciplinary documentation, as well as access to numerous online scientific databases, constitute the foundation of this doctoral thesis. It consists of two parts: a theoretical section, which presents the current data from the specialized literature in a clear and concise way, specifically addressing the evaluated problems, and a practical, original section, represented by a prospective, observational, non-interventional study, based on two groups of patients.

The general part presents relevant data from the current guidelines in force, regarding the epidemiology, prevention, diagnostic algorithm, treatment and support services of sensitive and drug-resistant tuberculosis, as well as current data from the specialized literature regarding the impact of quality of life on patients with tuberculosis. This part is structured into three sub-chapters, each sub-chapter presenting data on susceptible, drug-resistant tuberculosis and the impairment of quality of life associated with tuberculosis.

The practical, original part is based on the study carried out and includes the objectives of the doctoral thesis, the methods and materials used in its elaboration, personal contributions, conclusions, bibliography and related appendices.

The main and secondary aims and objectives of this doctoral thesis, achieved through a prospective, observational, non-interventional study that took place in the period 2019 – 2021, in the "Marius Nasta" Institute of Pneumoftisiology, Bucharest, Romania, were the following:

→ To determine if there are differences between indicators on the quality of life of S-TB vs MDR-TB patients.

→ To determine if there are differences between indicators on the quality of life at the initiation and completion of treatment, as well as 12 months post-treatment.

- collecting data on the quality of life of patients in treatment as well as 12 months after its completion and comparing the results;

- collecting data on functional side effects during and after treatment;

- evaluation of differences between groups.

→ Stratification of results based on detailed clinical diagnoses (susceptible TB vs MDR-TB), major comorbidities (HIV, diabetes, liver or kidney disease, cancer), lifestyle (housing, social status, income) and major risk factors (alcohol, tobacco, drugs) to analyze changes in quality of life between subgroups.

- the collection of clinical data that allows an additional analysis of the subgroups;

- evaluation of differences between subgroups and main groups of patients.

The obtained results can be useful in order to increase the awareness of this disease and the implementation in tuberculosis control programs of indicators on quality of life. This integration would allow healthcare professionals to identify specific aspects of mental and physical health adversely affected by the disease or its treatment. The implementation of psychological support programs at the family or community level can bring significant benefits to improve the quality of life.

The present study aimed to complete the existing data in the literature, not only by comparing the degree of impact of the two forms of tuberculosis, but also by analyzing the impact of these types of disease on the quality of life of patients and at the same time raises an alarm signal about the need a radical change in the way patients diagnosed with tuberculosis are perceived and approached, moving from a perspective centered on traditional markers of disease severity and response to treatment, to an approach that captures overall health status, placing greater emphasis on the perspective the patient than from the clinician's point of view, with the main aim being the benefit of the patients.

## 1. General considerations regarding susceptible and drug-resistant tuberculosis and the implied impairment of quality of life

Every year, millions of people are infected with sensitive and drug-resistant tuberculosis, a public health problem, endemic in many regions of the globe and one of the top 10 causes of death worldwide. From data presented in the World Health Organization's Global Report on Tuberculosis (2023), 10.6 million people (respectively 5.8 million men, 3.5 million women and 1.3 million children) were diagnosed with tuberculosis in 2022 and 1.3 million died from this disease [1].

Tuberculosis (TB) is an infectious disease produced by Mycobacterium tuberculosis widespread globally, with mainly airborne transmission and chronic evolution, which untreated or incorrectly treated can have a significant fatality. This condition mainly affects the adult population in the most productive years of life, causing both directly and indirectly significant social consequences [2]. Also, substantial financial resources are consumed to combat it. According to data reported by WHO, $13 billion are assigned annually for tuberculosis prevention, diagnosis and treatment to reach the global goal agreed by the UN in 2018 [3]. Although it is a preventable and curable disease, tuberculosis is currently the cause of 1.3 million deaths annually, being the most common cause of death caused by a single pathogen.

The impact of tuberculosis is not limited only to clinical indicators, but also to the quality of life, directly reduced by the disease and treatment (weight loss, asthenia, side effects of medication, comorbidities), but also indirectly by the nature of the disease (social inclusion, job loss). According to data from the specialized literature, multiple studies have highlighted the problem of affecting the quality of life of patients with drug-resistant tuberculosis [4].

Quality of life is a broad and complex multidimensional concept that includes the physical, social, psychological, economic and spiritual domains [5]. It is therefore difficult to define and measure, but it can be described as individuals' perception of their position in life in a cultural context, as well as in terms of the value systems in which they live and in relation to their goals, expectations, standards and concerns [5,6]. Therefore, QOL is an expression of the patient's preferences and values, rather than the clinician's assessment.

Patients with drug-resistant tuberculosis (DR-TB) frequently have associated comorbidities and previous treatments, leading to additional social, family and financial challenges. DR-TB treatment is long-lasting, more complex, frequently associated with significant adverse effects and less favorable outcomes. Consequently, it is reasonable to assume that components of the quality of life of patients diagnosed with DR-TB are significantly compromised [7].

Despite the positive impact of DR-TB treatment on physical health, a large part of the burden of tuberculosis is associated with deficiencies in quality of life, which is highly relevant given that tuberculosis is the number one cause of mortality from a single infectious disease worldwide [8].

Social exclusion, stigma and side effects of the treatment are examples of indicators of poor quality of life affecting social and professional life of the patients [9].

# 2. Personal contributions

## 2.1 Working hypothesis and general objectives

This study is non-interventional, observational, non-randomized. It involves clinical analysis (medical records), functional (walking test 6 minutes, portable audiometry) and quality of life (standardization questionnaires) of patients with sensitive and drug-resistant tuberculosis hospitalized in the Marius Nasta Institute of Pneumology Bucharest during 2019-2021 and at maximum 12 month post-treatment. The study participants were divided into 2 main groups, as follows: group 1 – 50 patients with treatment-sensitive tuberculosis evaluated at initiation, completion, and 12 month post-treatment, respectively group 2 – 50 patients with drug-resistant tuberculosis evaluated at initiation, completion, and 1 year post-treatment.

**The main purpose and objectives** involve determining the existence of differences between indicators on the quality of life of patients with pulmonary tuberculosis undergoing treatment compared to those who have completed treatment; collecting data on quality of life at initiation of treatment, at completion and after 1 year post-treatment and comparing results; collecting data on functional side effects during and after treatment, and assessing differences between groups.

**Secondary goals and objectives** are to stratify results based on detailed clinical diagnoses (S-TB vs DR-TB), major comorbidities (HIV, diabetes, liver or kidney disease, cancer), lifestyle (housing, social status, income) and major risk factors (alcohol, tobacco, drugs) to analyze changes in quality of life between subgroups.

## 2.2 The general methodology of the research

**Study protocol**

• The study of specialized literature, respectively original articles, reports, national and international guides, specialized books (by accessing the medical databases PubMed®, GoogleScholar, Embase, Ebsco, Cochrane);

• Elaboration of the patient's informed consent;

• Establishing the follow-up period of patients (initiation of treatment, completion of treatment, respectively 12 months post-treatment) and study directions;

• Obtaining the approval of the Ethics Commission (within the "Marius Nasta" Institute of Pneumoftisiology, Bucharest);

• Selection of patients with sensitive or drug-resistant tuberculosis from the "Marius Nasta" Institute of Pneumoftisiology, Bucharest, Romania, in the period 2019 - 2021;

• Evaluation of inclusion and exclusion criteria;

• Follow-up of patients according to the study protocol;

• Centralization and statistical processing of quality-of-life questionnaires, functional tests (audiometry, 6-minute walking test) and patient files with the establishment of conclusions;

• Elaboration and publication of scientific papers, as well as the elaboration of the doctoral thesis.

**Ethics.** After being informed by the investigator, willing participants signed the informed consent form in their native language. The study was approved by the Ethics Committee of "Marius Nasta" Institute of Pneumology.

**Materials and methods**

Data collection will be carried out from three main sources: questionnaires, patient summaries and functional tests.

Questionnaires are standardized tools for measuring quality of life indicators:

- The Short Form 36 Health Survey (SF-36) contains a set of generic, consistent and easily assessable questions about quality of life. This questionnaire is based on patient self-reporting and is widely used for routine monitoring and evaluation of patient care outcomes.

- EuroQol Group five dimensions quality of life questionnaire (EQ5D5L), The 5-dimensional Quality of Life Questionnaire is a quantitative measure of health assessment,

reflecting the patient's own judgment and underpinning the calculation of life years adjusted to their quality.

- Work Productivity and Activity Impairment Questionnaire (WPAI), the questionnaire on productivity and work activity, is validated to measure work capacity impairment caused by general or specific diseases.

Patient files will be used to collect clinical data, namely basic demographic data (age, sex, education, profession, income, living conditions), associated comorbidities (diabetes, HIV/AIDS, neoplasia, kidney or liver disease), lifestyle (smoking, alcohol consumption), respectively type of diagnosis (sensitive or drug-resistant TB) and treatment (new case/retreatment).

Functional tests will be performed by all patients, regardless of the stage of treatment, to establish the presence or absence of long-term treatment side effects and consists of using two simple and cost-effective methods:

- Audiometry (performed using a mobile application to assess hearing loss; this test is especially recommended for patients undergoing DR-TB treatment, to assess the ototoxicity of the medication);

- 6-minute walking test (provides information about the patient's physical capacity and assesses the degree of desaturation during sustained effort).

**Inclusion criteria**

- The participant is willing and able to give informed consent for participation in the study.

- Age over 18 years.

- Diagnosis of S-TB lung based on culture, Xpert or treated as such.

- DR-TB diagnosis based on cultures, Xpert or treated as such.

- Treatment in the last 5 years.

**Exclusion criteria**

- Mental disorders that make it impossible to fill out questionnaires (the patients must be able and willing to provide consent)

# 3. Results

**Statistical analysis**

Statistical analysis was performed using IBM SPSS Statistics 25 and Microsoft Office Excel/Word 2013. Quantitative variables were tested for normality using the Shapiro-Wilk test and were expressed using means and standard deviations or median with interpercentile intervals.

Independent quantitative variables with normal distribution were tested between groups using the Student T-Test/Welch T-Test (according to equality of variances between groups observed using the Leven test), while independent quantitative variables with nonparametric distribution were tested between groups using the Mann–Whitney U test.

Quantitative variables with repeated measurements and normal distribution were tested between intervals using the One-Way ANOVA test for repeated measurements (alongside post-hoc Bonferroni tests) while quantitative variables with repeated measurements and non-parametric distribution were tested between intervals using the Friedman test (alongside post-hoc DunnBonferroni tests).

Qualitative variables were expressed as absolute frequencies and percentages, and differences between groups were tested using Fisher's Exact test. The evolution of frequencies of qualitative variables between measurements was tested using Cochran's Q test (alongside post-hoc Dunn-Bonferroni tests).

The characteristics of the group analysed in the study, show the following:

- 50% of patients were in the treatment-sensitive tuberculosis group, 50% of patients were in the treatment-resistant tuberculosis group;
- The majority of patients were male (73%), from urban areas (68%), with a mean age of 47.24 ± 15.53 years, with a median of 45.5 years;
- Most patients had high school (45%) or gymnasium (22%), being employed (46%) or retired (26%);
- Most cases observed were new cases (65%) or relapses (23%);

- 40% of patients had adverse reactions to treatment;

- 76% of patients had comorbidities, the most common being bronchiectasis (45%), malnutrition (27%), COPD (24%);

- 65% of patients are smokers, 41% drink alcohol regularly and 7% use drugs.

When comparing the EQ-5D-5L score measured at baseline with the study group, the differences observed between groups were statistically significant for 3 of the 5 dimensions, namely Usual Activities, Pain/Discomfort, Restlessness/Depression according to the MannWhitney U test ($p=0.001$), so patients with drug-resistant tuberculosis had significantly higher score values compared to patients with sensitive tuberculosis.

When comparing the SF-36 score measured at baseline versus the study group, the differences observed between groups were statistically significant across all 8 quality of life concepts assessed according to the Mann-Whitney U test ($p<0.001$), so patients with drug-resistant tuberculosis had significantly lower scores compared to patients with sensitive tuberculosis.

When comparing the baseline WPAI GH score with the study group, the differences observed between groups were statistically significant with deterioration of activity according to the Mann- Whitney U test ($p=0.001$), so that patients with drug-resistant tuberculosis had significantly higher scores (median = 70, IQR = 50-72.5) compared to patients with sensitive tuberculosis (median = 50, IQR = 27.4-70).

When comparing the level of fatigue in the baseline test versus the study group, the differences observed between groups were statistically significant, so patients with drug-resistant tuberculosis had significantly higher levels of fatigue compared to patients with sensitive tuberculosis. The patients with COPD and tuberculosis were significantly more frequently associated with desaturation on the 6 MWT test (50% vs. 15.6%) compared to patients without COPD (84.4% vs. 50%).

Post-hoc comparison in evolution of EQ-5D-5L score in patients with sensitive tuberculosis, applicable to all evaluated domains, shows significant differences between measurements according to the Friedman test ($p<0.001$) and post-hoc Dunn-Bonferroni tests showed that scores at baseline were significantly lower compared to those at treatment completion or compared to at

1 year ($p<0.001$). Also, values at 1 year were significantly higher compared to those at the end of the treatment ($p<0.001$).

Similarly, post-hoc comparison in evolution of SF-36 score in patients with sensitive tuberculosis across all 8 concepts evaluated showed significant differences between measurements according to the Friedman test ($p<0.001$) and post-hoc Dunn-Bonferroni tests showed that scores at baseline were significantly lower compared to those at treatment completion ($p<0.001$) or compared to those from 1 year ($p<0.001$). In the evolution of depression frequency observed by SF-36 score in patients with treatment-sensitive tuberculosis, Dunn-Bonferroni post-hoc tests showed that the frequency of depression decreased significantly from initiation of treatment (19.5%) to 1 year (2.4%) ($p=0.004$).

In the case of occupational impairment, the analysis in evolution of the WPAI:GH score, both in the absenteeism category and activity impairment, in the case of the patients with sensitive tuberculosis, significant differences were detected between measurements according to the Friedman test ($p<0.001$) and the Dunn-Bonferroni post-hoc tests showed that baseline score values were significantly higher compared to those at treatment completion ($p=0.003$) or compared to those at 1 year ($p<0.001$), demonstrating an improvement in post- treatment work capacity.

In the 6-minute walking test evaluated in patients with sensitive tuberculosis, the frequency of desaturation decreased significantly from initiation of treatment (17.9%) to completion (2.6%) ($p=0.016$) and to 1 year (0%) ($p=0.004$), and dyspnea and fatigue levels at baseline were significantly higher compared to those at the end of the treatment or compared to 1 year post-treatment ($p<0.001$).

In the case of patients with drug-resistant tuberculosis, post-hoc comparison in evolution of the EQ-5D-5L score, on 4 domains of quality of life assessed (except self-care), detected significant differences between measurements according to the Friedman test ($p<0.001$) and post- hoc Dunn-Bonferroni tests showed that baseline score values were significantly lower compared to those at the end of the treatment and compared to 1 year post-treatment ($p<0.001$).

Similarly, the evolving post-hoc comparison of SF-36 score in patients with drug-resistant tuberculosis, across all evaluated concepts, revealed significant differences between

measurements according to Friedman ($p<0.001$) and Repeated-Measures One-Way ANOVA tests with Greenhouse-Geisser correction ($p<0.001$) and Dunn-Bonferroni post-hoc tests showed that baseline score values were significantly lower compared to those at treatment completion ($p<0.001$) or compared to those at 1 year ($p<0.001$). In particular, the evolution of depression frequency observed by SF-36 score in patients with treatment-resistant tuberculosis detected significant interval differences according to Cochran's Q test ($p=0.014$), and Dunn-Bonferroni post-hoc tests showed that the frequency of depression decreased significantly from initiation of treatment (57.4%) to 1 year (42.6%) ($p=0.020$).

Comparison in evolution of WPAI:GH score in patients with drug-resistant tuberculosis, both in terms of absenteeism and activity impairment, significant differences can be observed according to the Friedman test ($p<0.001$) and post-hoc Dunn-Bonferroni tests showed that scores at initiation were significantly higher compared to those at treatment completion ($p=0.001$) or compared to those from 1 year ($p<0.001$).

In the case of the 6-minute walking test in patients with drug-resistant tuberculosis, the frequency of desaturation decreased significantly from initiation of treatment (17.8%) to 1 year (4.4%) ($p=0.016$), and dyspnea and fatigue levels at initiation were significantly higher compared to those at the end of treatment or compared to those at 1 year ($p<0.001$). Also, fatigue levels at 1 year were significantly lower compared to those at the end of treatment ($p=0.006$).

Finally, comparing the difference from baseline to 1 year post-treatment in EQ5D-5L score relative to study groups in mobility, self-care, usual activities, and pain level demonstrates that patients with drug-resistant tuberculosis had significantly less improvement (with less decrease) from baseline to 1-year assessment, EQ-5D-5L score compared to sensitive tuberculosis patients. Also, comparing the difference from baseline to 1 year post-treatment in terms of emotional impairment relative to study groups found significant differences between groups, so that patients with drug-resistant tuberculosis had significantly better improvement (through greater increase) from initiation to 1-year assessment (median = -66.7, IQR = 66.7 - -33.3) compared to patients with sensitive tuberculosis (median = 0, IQR = -66.7 - 0). The frequency of depression evaluated by the Mental Health (MH) score between study groups showed statistically significant differences, according to the Fisher test ($p=0.048$), so that patients with drug- resistant

tuberculosis were significantly more associated with the disappearance of depression (67.6% vs. 44.4%) compared to patients with sensitive tuberculosis (55.6% vs. 32.4%).

When comparing the difference from baseline to 1 year post-treatment in WPAI:GH absenteeism score relative to study groups, the differences between groups were significant according to the Mann-Whitney U test ($p=0.048$) so that patients with drug-resistant tuberculosis had a significantly better improvement (by a greater decrease) from initiation of treatment to 1-year assessment.

And in terms of exercise tolerance, assessed by the 6-minute walking test, comparing the difference from initiation of treatment to 1 year post-treatment based of the degree of fatigue reported in the study groups, the differences between groups were significant according to the MannWhitney U test ($p=0.017$) so that patients with drug-resistant tuberculosis had a better improvement (through a greater decrease) from initiation of treatment to evaluation at 1 year compared to patients with sensitive tuberculosis.

In the case of the comparison in evolution of the auditory impairment through the uHear app in patients with tuberculosis sensitive to the treatment, the distribution of the variable was non-parametric in all measurements according to the Shapiro-Wilk test ($p<0.05$). The differences between the measurements were not significant according to the Friedman test ($p=0.368$), so the evolution of the degree of hearing impairment was not significantly different in patients with treatment-sensitive tuberculosis.

Also comparing the evolution of hearing impairment by the uHear app in patients with drug-resistant tuberculosis, the distribution of the variable was non-parametric in all measurements according to the Shapiro-Wilk test ($p<0.05$). The differences between the measurements were not significant according to the Friedman test ($p=0.111$), so the evolution of the degree of hearing impairment was not significantly different in patients with treatment-resistant tuberculosis.

However, the distribution of patients related to the evolution of the degree of hearing impairment from the initiation of treatment to 1 year by the uHear test at the frequency of 4 Hz between the study groups, statistically significant differences were observed according to the Fisher test ($p=0.003$) so that patients with tuberculosis resistant to treatment were significantly more

frequently associated with a decrease in the degree of hearing impairment (100% vs. 46.9%) compared to patients with treatment-sensitive tuberculosis (53.1% vs. 0%).

## 4. Discussion

This cross-sectional non-interventional non-interventional study investigated the quality of life of Romanian patients with sensitive and drug-resistant tuberculosis, hospitalized in the Marius Nasta Institute of Pneumology between 2019-2021, being evaluated both at the initiation and completion of treatment and at 1 year post-treatment, in terms of physical, social, emotional impairment and the impact that the disease had on their work and health through various instruments respectively three standardized questionnaires, walk tests and application-based audiometry.

The majority of patients participating in the study were male (73%), predominantly from urban areas (68%), with a mean age of 47.24 years. Most patients had high school (45%) or gymnasium (22%), being employed (46%) or retired (26%). The study group is aligned with other research indicating that socioeconomic indices, smoking and alcohol consumption are risk factors for tuberculosis. 76% of patients had comorbidities, the most common being bronchiectasis (45%), malnutrition (27%), COPD (24%).

This research included two quality of life PROMs, SF-36 and EQ-5D-5L respectively. Regarding both questionnaires, there were statistically significant differences between patients with sensitive tuberculosis and treatment-resistant tuberculosis at the initiation of treatment, so that patients with resistant tuberculosis had a more significant impairment of all domains evaluated, the most important being the physical domain, of the degree of independence as well as the emotional one, most likely due to the severity of symptoms and the degree of pulmonary and systemic involvement due to drug-resistant tuberculosis, which demonstrates a greater impact on quality of life in patients with DR-TB.

Similar to this study, other research has shown improvements in quality of life after completion of treatment, particularly visible on the EQ-5D-5L General Visual Analogue Scale [13,14]. The evolution comparison of the two PROMs both in the case of patients with sensitive tuberculosis and in the case of those with treatment-resistant tuberculosis, showed that the values of the

scores from the initiation of the treatment were significantly lower compared to those from the completion of the treatment or compared to those from 1 year. Also, values at 1 year were significantly higher compared to those at completion of treatment, demonstrating improvements in quality of life after completion of treatment.

The domains with the lowest scores are those related to the limiting nature of the illness and emotional well-being. The significantly increased impairment of the physical domain during treatment in patients with drug-resistant tuberculosis may also be explained by the treatment administered, with joint pain being a reported side effect of second-line tuberculosis drugs, including bedaquiline [14,15].

In the case of affecting the emotional domain, depression was the most frequently reported, both in the case of patients with sensitive and resistant tuberculosis, but its frequency decreased significantly from the initiation of treatment, both in the case of patients with TB-S at the initiation of treatment (19.5%) vs 1 year post-treatment (2.4%), and in the case of DR-TB, 57.4% at the start of treatment vs 42.6% 1 year post-treatment. The frequency of depression was higher among DR-TB patients, which may be explained by the greater impact of DR-TB on quality of life. Thus, an improvement in mental health can be observed post-treatment. This has been indicated by other research, with experts calling for better mental support throughout treatment [13,14,17].

Regarding employment, from the study group a percentage of 46% of patients were salaried, 26% retired, and 28% unemployed or unemployed. From the point of view of affecting the professional field measured at the initiation of treatment, both from the point of view of absenteeism and the deterioration of activity in relation to the study group, patients with treatment-resistant tuberculosis had significantly higher score values compared to patients with treatment-sensitive tuberculosis. In addition, patients during treatment lost most of their working hours. For patients in the intensive phase, this could be explained by the hospitalization time. According to the recommendations in force, hospitalization is necessary for all cases of pulmonary tuberculosis, unless there is the possibility of direct therapy observed in isolation conditions [14,17]. Globally, the length of hospital stay varies between 20 and 60 days for S-TB and 50–180 days for DR-TB [14,18].

But in evolution, respectively at the end of treatment and 1 year after treatment, an improvement can be observed both in terms of the number of hours worked and the degree of productivity, both among patients with sensitive tuberculosis and those with tuberculosis resistant to treatment, which indicates an increase in the quality of life post-treatment and in the case of the professional field. Also, when comparing the difference from treatment initiation to 1 year post-treatment in the absenteeism category reported across study groups, patients with drug-resistant TB had significantly better improvement from treatment initiation to the 1-year assessment.

In the case of the 6-minute walk test, the degree of fatigue and desaturation upon exertion was significantly higher in patients with TB-DR, these results also being found in other specialized studies, this can be explained by the systemic impact that drug-resistant tuberculosis has on the body, through the severity of the disease, symptoms and associated comorbidities [16].

Audiometry via the uHear App is a convenient way for patients to self-assess their hearing. The results of the uHear application confirm the data from the specialized literature regarding the ototoxicity of the second-line treatment [14,16,19,20]. Thus, patients with treatment-resistant tuberculosis were significantly more frequently associated with an increase in the degree of auditory impairment, especially in the case of high-frequency sounds, respectively 4 Hz compared to patients with treatment-sensitive tuberculosis. According to the international guidelines in force, aminoglycosides have been eliminated from TB-DR treatment regimens. Hearing loss is the third cause of decreased quality of life. Therefore, hearing may require additional attention in programs to support people affected by tuberculosis after treatment.

## 5. Conclusions and personal contributions

Both treatment-susceptible and drug-resistant TB patients experience limitations in all areas of quality of life due to TB, both at initiation and completion of treatment. The main differences between the two study groups were in the area of emotional and physical impairment, with drug-resistant TB patients having more significant impairment and slower recovery.

The particular aspect of the psychological impact of DR-TB patients requires additional attention from the medical staff involved in the treatment of these patients and the implementation of additional support measures to help the patients.

Adopting a patient-centered therapeutic approach is essential to increase adherence to treatment and improve quality of life. However, the quality of care for TB patients remains suboptimal, especially in endemic countries. Significant delays in the diagnosis of tuberculosis result in the loss of many patients before treatment is initiated. Also, many patients find current methods of treatment under direct observation to be rigid and intrusive, preferring unsupervised treatments that are less effective. In addition, there are significant concerns about the quality and guaranteed availability of drugs, especially in the case of drug-resistant tuberculosis. The non-medical aspects of TB are inadequately addressed by most TB programs, directly affecting patients' quality of life. These problems can negatively influence the rate of recovery and the results of treatment, indirectly contributing to the decrease in the quality of life.

A radical change is needed in the way we perceive and approach patients diagnosed with tuberculosis, moving from a perspective centered on traditional markers of disease severity and treatment response to an approach that captures overall health, placing a greater emphasis on on the patient's perspective rather than on the clinician's point of view. Tuberculosis control programs should expand their scope beyond the clinical and microbiological aspects to include the socio-economic, cultural and psychological dimensions that influence both the disease and its treatment, within assessment and monitoring tools.

Consequently, quality of life assessment indicators could be more commonly associated with routine indices used to assess treatment response and could be included in future guidelines. This integration would allow healthcare professionals to identify specific aspects of mental and physical health adversely affected by the disease or its treatment.

Another crucial goal is to raise awareness of this disease. Understanding the origins of misconceptions about tuberculosis and addressing the lack of knowledge about the disease are essential. Effective communication, particularly during diagnosis and initiation of treatment, is vital, and the integration of psychological counseling into TB management is imperative. Patients diagnosed with tuberculosis who receive social support from family, friends and community tend to experience a better quality of life.

Therefore, the implementation of psychological support programs at the family or community level can bring significant benefits for improving the quality of life. Culturally relevant psychosocial support interventions tailored to people undergoing TB treatment, especially during

the intensive phase, can play an important role in the rapid reintegration of patients into their communities.

The quality of life of patients with sensitive and especially drug-resistant tuberculosis is an area that requires additional research, having an extremely important role in the success of antituberculosis treatment. The present study aimed to complete the existing data in the literature, not only by comparing the degree of impact of the two forms of tuberculosis, but also by analyzing the impact of these types of disease on the patients' quality of life.

Quality of life indicators could shape a more complete picture of the impact of TB on patients' lives, both during and after treatment.

## 6. Limitations and solutions

This study aimed to investigate the impairment of the quality of life in the case of Romanian patients diagnosed with sensitive and drug-resistant tuberculosis, given that tuberculosis is a priority public health problem in Romania, the global incidence of tuberculosis being by far the highest in the EU and one of the highest in the WHO European Region. Moreover, this study consisted of several PROMs, thus providing a multidimensional view of multiple aspects of quality of life. Among the limitations is the possible underreporting of employee status and income, given patients' reluctance to report untaxed income. Among the inclusion criteria is the pulmonary location of tuberculosis, given the statistically insufficient number of patients with extrapulmonary tuberculosis. Another limitation was the relatively small number of patients enrolled in the study, given the particular situation of the SARS-COV2 pandemic, with the introduction of the state of emergency and the maintenance of the alert state, accessibility to patients eligible for the study decreased dramatically. And the number of patients hospitalized with tuberculosis has decreased significantly. In this context, patients presented late to the hospital, having severe forms of tuberculosis, as well as the reluctance of patients evaluated 1 year after the completion of treatment to go to the hospital.

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