UNIVERSITY “OVIDIUS” OF CONSTANTA
DOCTORAL SCHOOL OF MEDICINE
FIELD OF MEDICINE
ACADEMIC YEAR 2023 – 2024

PHD THESIS

SUMMARY

PhD supervisor: **Prof. Univ. Dr. Sorin Rugină**

PhD student : **Dr. Ciprian Constantin Popoiag**

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EVALUATION OF FUNCTIONAL, PSYCHOLOGICAL, AND QUALITY OF LIFE IMPACT IN PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS

DOCTORAL THESIS ABSTRACT

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Keywords

ADN – Deoxyribonucleic Acid (DNA)
ARN – Ribonucleic Acid (RNA)
BAAR – Acid-fast Bacilli (AFB)
BPOC – Chronic Obstructive Pulmonary Disease (COPD)
Bdq – Bedaquiline
BRICS – Brazil, Russia, India, China, and South Africa
CO2 – Carbon Dioxide
DASS-21R – Depression Anxiety Stress Scales
DST – Drug Susceptibility Testing
E – Ethambutol
Gyr A – DNA Gyrase A
Gyr B – DNA Gyrase B
H – Isoniazid
HIV – Human Immunodeficiency Virus
IMC – Body Mass Index (BMI)
InhA – Acyl-Carrier-Protein Reductase
KatG – Catalase-Peroxidase
Km – Kanamycin
LPA – Line Probe Assays
Lzn – Linezolid
M – Mycobacterium
mARN – Messenger RNA (mRNA)
MDR – Multidrug Resistance
MGIT – Mycobacterial Growth Indicator Tube
MIC – Minimum Inhibitory Concentration
M. TB – Mycobacterium Tuberculosis
Nipro NTM + MDRTB 2 – Nipro NTM + MDRTB 2 Detection Kit
OMS – World Health Organization (WHO)
PAS – Para-aminosalicylic Acid
PCR – Polymerase Chain Reaction (PCR)
PNPSCT – National Program for Tuberculosis Prevention, Surveillance, and Control
Pre TB XDR – Pre-Extensively Drug-Resistant Tuberculosis
rpoB – RNA Polymerase Beta
R – Rifampicin
RR – Rifampicin Resistance
SGRQ – Saint George Respiratory Questionnaire
SL-LPA – Second-Line Line Probe Assays
SLIDs – Second-Line Drug Resistance-Associated Intergenic Regions
TB – Tuberculosis
DR TB – Drug-Resistant Tuberculosis
DS TB – Drug-Sensitive Tuberculosis
MDR TB – Multidrug-Resistant Tuberculosis

RR TB – Rifampicin-Resistant Tuberculosis
XDR TB – Extensively Drug-Resistant Tuberculosis
UE – European Union (EU)
VSH – Erythrocyte Sedimentation Rate (ESR)
WHO – World Health Organization
Xpert MTB/RIF – Xpert MTB/RIF Test (Cepheid)
Z – Pyrazinamide
ZEE – European Economic Area (EEA)

I.CURRENT STATE OF KNOWLEDGE

Introduction

Tuberculosis (TB) represents one of the most serious threats to global public health, responsible for millions of deaths annually. Although it is a preventable and treatable disease, TB remains a major issue in many parts of the world, particularly in resource-limited regions and among vulnerable populations.

Approximately one-quarter of the global population is latently infected with *Mycobacterium tuberculosis*, with the risk of developing active disease during their lifetime. The prolonged duration of treatment, the difficulty in managing it, and the associated socio-economic conditions make Multidrug-Resistant Tuberculosis (MDR-TB) one of the most challenging pathologies of the 20th and 21st centuries.

I have chosen to investigate the symptomatology, functional impact, psychological effects, and quality of life of patients with Multidrug-Resistant Tuberculosis to highlight a human and social dimension of this condition. While existing studies have often explored the clinical, paraclinical, and epidemiological aspects of MDR-TB, a more in-depth examination is warranted to analyze the effects on mental health and quality of life of patients.

This research aims to highlight the psycho-social impact of infection with a drug-resistant strain by identifying criteria for evaluating levels of depression, anxiety, and stress, correlated with data on the frequency and severity of respiratory symptoms, the patient's ability to engage in physical activities, and the effects of the disease on daily life.

1.General Information

1.1 Brief History

Tuberculosis has been contemporaneous with human evolution, with some studies suggesting that the disease emerged approximately 3 million years ago. The oldest evidence of tuberculosis in humans includes remains found in what is now Turkey, at Atlit Yam, an underwater site in the Mediterranean Sea, dating back approximately 9,000 years.

Research on Homo erectus skeletons suggests the presence of tuberculosis around 1.6 million years ago. Other evidence includes paleopathological analyses of skeletons from ancient Egypt, indicating the presence of tuberculosis around 3,000 years BCE [1, 2, 3, 4].

1.2 Epidemiology

Global

Approximately 3.7% of new TB cases globally are infected with multidrug-resistant strains (MDR-TB), while around 20% of patients who have been previously treated have MDR-TB. The estimated proportion of new MDR/RR-TB cases was 3.9% in 2015 and 3.6% in 2021, with the proportion of previously treated cases being 20% in 2015 and 18% in 2021 [5]. Additionally, about 9% of MDR-TB cases are extensively drug-resistant tuberculosis (XDR-TB). By March 2013, at least one case of XDR-TB had been reported in 84 countries.

In 2011, the global incidence of MDR-TB cases was approximately 500,000, with 60% of these cases recorded in BRICS countries [6]. People with HIV have a 20-fold higher risk of developing active TB compared to those without HIV [7].

Europe

The estimated incidence of multidrug-resistant tuberculosis (MDR-TB) patients in the European Region of the World Health Organization (WHO) varies considerably. In 2012, the incidence was reported at 1.6 cases per 100,000 people in the 29 countries of the European Union/European Economic Area (EU/EEA) [8].

Romania

Romania has the highest incidence of MDR-TB in the EU, with nearly a quarter (23.4%) of reported patients in 2017 and a TB notification rate six times higher than the EU average. Together with Lithuania, Romania accounts for more than 70% of the total number of XDR-TB cases in the EU, and Romania is responsible for 23.5% of all TB cases reported in the EU.

Although the incidence of TB has steadily decreased in the general population (71.7 in 2015, 64.8 in 2016, and 62.8 in 2017), it remains high among vulnerable populations, such as incarcerated individuals, the homeless, and those dependent on drugs [9].

2. Multidrug-Resistant Tuberculosis (MDR-TB)

2.1 Definition

Tuberculosis (TB) is a bacterial infection caused by *Mycobacterium tuberculosis*, primarily affecting the lungs but potentially involving other organs as well.

Multidrug-Resistant Tuberculosis (MDR-TB) is defined as resistance to at least Isoniazid (H) and Rifampicin (R), two of the most effective first-line anti-TB drugs, which are considered major drugs. This condition necessitates the use of second-line anti-TB medications, which are less potent, more toxic, more expensive, and require a longer treatment duration [10].

Extensively Drug-Resistant Tuberculosis (XDR-TB) is defined as MDR-TB associated with resistance to any Fluoroquinolone and any second-line injectable drug.

2.2 Types of Drug Resistance:

- Monoresistance: Defined as tuberculosis caused by a strain resistant to a single first-line anti-tuberculosis drug (Isoniazid, Rifampicin, Ethambutol, or Pyrazinamide).
- Polyresistance: Resistance to more than one first-line anti-tuberculosis drug other than Isoniazid and Rifampicin.
- Isoniazid-Resistant TB (HrTB): Resistance to Isoniazid with susceptibility to Rifampicin [11].
- Rifampicin-Resistant Tuberculosis (RR TB): Defined as resistance to Rifampicin detected using genotypic or phenotypic methods, with or without resistance to other first-line TB drugs [12].
- Multidrug-Resistant Tuberculosis (MDR TB): Defined as disease caused by *Mycobacterium tuberculosis* resistant to Isoniazid (H) and Rifampicin (R), but with susceptibility to Fluoroquinolones (Levofloxacin and Moxifloxacin) and Group A drugs (Bedaquiline or Linezolid) [11, 13, 14, 15, 16].
- Pre-XDR-TB: Resistance to Isoniazid, Rifampicin, and a Fluoroquinolone [17].
- Extensively Drug-Resistant Tuberculosis (XDR-TB): Defined as resistance to at least Isoniazid and Rifampicin, any Fluoroquinolone, and at least one other drug from "Group A" [11].

2.3 Mechanism of Occurrence

Primary resistance occurs when a patient is infected de novo with a strain of *Mycobacterium tuberculosis* that is already resistant to first-line drugs. This means that the tuberculosis bacilli have evolved to be resistant to the antibiotics used in standard treatment even before treatment begins [16].

Sequential drug resistance most commonly arises from fragmented or inadequate treatment due to socio-economic factors and administrative issues. However, there are situations where drug resistance occurs despite excellent adherence to treatment [17].

Predisposing Factors for the Development of Secondary Drug Resistance:

- Deficient Implementation of Guidelines
- Inadequate Training of Healthcare Personnel
- Insufficient Patient Education
- Lack of Treatment Supervision
- Inefficient Management of Adverse Drug Reactions
- Socio-economic Status
- Lack of Awareness About T
- Poor Adherence to Treatment
- Adverse Effects*
- Associated Conditions: HIV, Diabetes Mellitus, Malnutrition, Malabsorption, Mental Illness
- Drug Abuse [11]

2.4 Diagnostic Methods

Phenotypic Methods

Phenotypic culture methods are based on evaluating the ability of M. tuberculosis to grow in culture media containing a critical concentration of anti-TB agents (indicating resistance) or, conversely, its inability to grow in such media (indicating susceptibility). The critical concentration generally differs from the Minimum Inhibitory Concentration (MIC) [18].

Solid Cultures

To perform phenotypic drug susceptibility testing (DST) of M. tuberculosis, the bacteria are initially cultivated in various solid or liquid culture media. Löwenstein-Jensen is one of the most frequently used solid media worldwide. Solid culture is known for its relatively high sensitivity in identifying drug-resistant strains, particularly when high-quality specimens are used [19].

A significant drawback of solid culture is the long waiting time for results, which can range from 4 to 8 weeks, potentially delaying the initiation of treatment [20]. Additionally, solid culture requires strict laboratory conditions and rigorous contamination control, with improper handling potentially affecting results [21].

Liquid Cultures

Rapid culture techniques, such as BACTEC/MBBACT, represent an automated liquid culture system used for diagnosing tuberculosis, including multidrug-resistant TB (MDR-TB). BACTEC 960 monitors changes in the absorption of radiation by the incubation medium caused by CO2 production by bacteria during growth. These changes are detected and recorded automatically, signaling bacterial growth [22, 23, 24, 25].

Advantages of using the BACTEC 960 system include a shorter diagnostic time, which can be around 1-2 weeks compared to 4-8 weeks for solid cultures [26].

Molecular (Genotypic) Methods

Molecular (genotypic) methods detect specific DNA mutations in the *M. tuberculosis* genome associated with resistance to certain anti-TB drugs. These molecular methods offer significant advantages for programmatic TB management, particularly in terms of speed, standardized testing, capacity to process a large number of samples, and reduced laboratory requirements [27].

Molecular tests for detecting resistance to Rifampicin alone or in combination with Isoniazid have been recommended by WHO since 2008. These tests include: Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), commercial line probe assays (LPA), MTBDRplus (Hain Lifescience, Nehren, Germany), and the Nipro NTM+MDRTB 2 detection kit (Nipro Corporation, Tokyo, Japan).

The GeneXpert MTB/RIF system uses real-time PCR technology to amplify MTB-specific DNA and identify mutations in the rpoB gene associated with Rifampicin resistance. The sputum sample is pretreated with a reagent that lyses the bacteria and releases DNA. This sample is then placed into the GeneXpert cartridge, where amplification and detection of specific DNA occur [28, 29].

The sensitivity and specificity of the GeneXpert MTB/RIF test are key indicators of its reliability. Studies have shown that GeneXpert has a sensitivity of approximately 98% for detecting TB and a specificity of 99%. For Rifampicin resistance, sensitivity is approximately 95%, and specificity is nearly 98%. These high values make it an essential tool for rapid and accurate TB diagnosis [30, 31].

Line Probe Assay (LPA) is a molecular diagnostic method used for the rapid detection of *Mycobacterium tuberculosis* and drug resistance. For sputum-negative samples, accuracy is compromised, and thus, direct testing of sputum-negative samples is not recommended [27].

LPA works by extracting DNA from sputum or other clinical specimens, followed by amplification of target gene regions through PCR. PCR products are then hybridized on membranes containing specific probes for drug-resistance-associated genes. Hybridization signals are visualized as bands, allowing for the rapid identification of MTB and specific mutations [30, 32].

LPA targets several genes associated with drug resistance, including rpoB, katG, inhA, and gyrA. Detection of mutations in these genes allows for rapid diagnosis of drug resistance and appropriate treatment adjustments [33, 34].

LPA provides rapid results, usually within 1-2 days, compared to traditional culture methods, which can take several weeks. Another major advantage is its ability to simultaneously detect resistance to multiple drugs [35].

II. PERSONAL CONTRIBUTION

3. General Objectives

In our study, we aim to investigate the impact of Multidrug-Resistant Tuberculosis (MDR TB) on mental health and quality of life, compared to patients with Drug-Sensitive TB (DS TB), to provide a transparent perspective on the emotional impact of this severe form of tuberculosis on affected patients.

The primary goal of the research is to identify statistically significant factors by evaluating levels of depression, anxiety, and stress among patients with MDR TB using the DASS-21R self-assessment questionnaire. Additionally, we aim to determine how MDR TB affects quality of life by analyzing respiratory symptoms, limitations in daily activities, and the overall impact of the disease, using the SGRQ questionnaire, correlated with clinical evidence and demographic profiles, to develop predictive statistical models.

4. General Methodology

A retrospective study was conducted involving 224 patients from the Dobrogea region, divided into two groups: one with Drug-Sensitive TB (149 patients) and the other with Multidrug-Resistant TB (MDR TB) (75 patients), diagnosed between 2010 and 2020.

The necessary data were extracted from patient records, MDR TB registers, and the computerized system. The data provided included demographic details, smoking status, number of relapses, HIV status, time from new case to MDR TB diagnosis, drug resistance profile, diagnostic methods, treatment regimens, adverse reactions, radiological forms, and paraclinical investigations.

Patients diagnosed with DS TB and MDR TB were selected based on inclusion criteria. After obtaining informed consent, they were contacted by phone to participate in completing the DASS-21 and SGRQ questionnaires.

The DASS-21R (Depression, Anxiety, and Stress Scales - 21 items) is a brief psychometric instrument used to assess symptoms of depression, anxiety, and stress.

The SGRQ (St. George's Respiratory Questionnaire) is a standardized tool used to assess the impact of chronic respiratory diseases on patients' quality of life. It was developed to measure both symptoms and limitations in daily activities caused by conditions such as Chronic Obstructive Pulmonary Disease (COPD) and asthma. SGRQ contains 50 questions grouped into three main domains: symptoms, activity, and impact.

Descriptive statistical analysis was used to describe the variables studied. For continuous variables, the mean, standard deviation, median, range, minimum, and maximum values were calculated. Categorical variables were presented as counts and percentages.

To analyze associations between exposure and outcome, the Chi-square test was used for categorical variables. When the expected number of values below 5 exceeded 20%, the Odds Ratio was employed.

Predictive statistical models for the association of depression scores among patients with MDR TB and DS TB were developed using multiple linear regression to predict patients' depression scores. This approach allowed us to quantify the impact of each independent variable on the final outcome. It enabled the analysis of the influence of multiple independent variables (Bacteriological Status, Age, and Gender) on a continuous dependent variable (scores for depression, anxiety, stress, and impact).

In the first stage, we described the study variables using appropriate statistical measures. For continuous variables, we calculated the mean, standard deviation, median, range, minimum, and maximum to obtain a general overview of data distribution.

For continuous variables, we compared different groups using parametric or non-parametric tests, depending on data distribution. Distribution was assessed using the Shapiro-Wilk test and visual inspection of histograms. If the data were normally distributed, we used the Independent Samples t-test (for comparing two groups) or ANOVA (for comparing more than two groups). If distribution significantly deviated from normality, non-parametric tests were employed (Mann-Whitney U for two groups and Kruskal-Wallis H for more than two groups).

For categorical variables, results were presented as counts and percentages. To identify relationships between categorical variables and depression scores, the Chi-square test was used.

Analyses were performed using IBM SPSS Statistics Edition 28, with charts created in the same program or in Microsoft Office Excel.[36]

5. Results

The study cohort included 224 tuberculosis patients. Of these, 66.5% were included in the group with drug-sensitive TB (DS TB), while patients with multidrug-resistant TB (MDR TB) represented 33.5% of the total cohort (Table 1).

Table 1 Distribution of Patients by Drug Sensitivity

BK status		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	DS TB	149	66.5	66.5	66.5

MDR TB	75	33.5	33.5	100.0
Total	224	100.0	100.0	

Regarding the depression score, the mean value was approximately twice as low for DS TB patients, being 11.83 ± 5.13 compared to 23.87 ± 6.18 for MDR TB patients. (table 2)

Table 2 Descriptive Analysis of Depression Score

BK status	N	Median	Deviation Standard	Median	Range Variation	of Minimum	Maximum
DS TB	149	11.83	5.130	12.00	30	0	30
MDR TB	75	23.87	6.180	24.00	32	6	38
Total	224	15.86	7.911	14.00	38	0	38

The Chi-square test applied to examine the association between the type of TB identified and the depression category indicated that there is a statistically significant association ($p<0.001$), with patients in the MDR TB group exhibiting a higher proportion of more severe depression categories. (Table 3)

3 Chi-square test association depression – bacteriological BK status

	Value	Df	Statistical Significance (p) (2-tails)
Chi-square	119.345[a]	4	<0.001
Likelihood Ratio	142.512	4	<0.001
Valid Cases Count	224		

a. 0 cells (0.0%) have expected values less than 5. The minimum expected value is 7.70.

Regarding the anxiety component, the mean score for patients in the MDR TB group was nearly twice as high at 20.37 ± 7.96 compared to the anxiety score for patients in the DS TB group, which was 12.85 ± 5.29. (4)

Table 4 Descriptive Analysis of the Anxiety Score

BK Status	N	Media	Deviation Standard	Mediana	Range Variation	of Minimum	Ma
DS TB	149	12.85	5.292	12.00	24	2	26
MDR TB	75	20.37	7.964	22.00	28	8	36
Total	224	15.37	7.233	14.00	34	2	36

The observed differences are statistically significant, with the p-value calculated using the Chi-square test being less than 0.001 (Table 5).

Tabel 5 Chi-square test for testing the association between anxiety category and bacteriological BK status

	Value	df	Statistical Significance (p) (2-tails)
Chi-square	63.751[a]	4	<0.001
Likelihood Ratio	68.752	4	<0.001
Mantel- Haenszel Test	43.905	1	<0.001
Valid cases number	224		

a. 0 cells (0.0%) have expected values less than 5. The minimum expected value is 6.70.

Regarding the stress component score, patients in the MDR TB group had an average value more than twice as high (26.21 ± 7.03) compared to patients in the DS TB group (12.81 ± 4.86). (6)

Table 6 Descriptive Statistical Analysis of Stress Score

BK Status	N	Media	Standard deviation	Mediana	Range of Variation	Minimum	Maximum
DS TB	149	12.81	4.860	12.00	26	2	28
MDR TB	75	26.21	7.033	26.00	28	14	42
Total	224	17.29	8.503	16.00	40	2	42

The observed differences are statistically significant, with $p < 0.001$. (Table 7)

Tabel 7 Chi-square test for association between bacteriological BK status and stress category

	Value	df	Statistical Significance (p) (2-tails)
Chi-square	138.407[a]	4	<0.001
Likelihood ratio	163.409	4	<0.001
Mantel- Haenszel Test	134.570	1	<0.001
Valid cases number	224		

a. 0 cells (0.0%) have expected values less than 5. The minimum expected count is 5.02.

Comparing symptom scores (SGRQ) between patients with drug-susceptible TB (DS TB) and multidrug-resistant TB (MDR TB) reveals significant differences. Patients with MDR TB have a significantly higher mean symptom score (64.59 ± 9.45) compared to those with DS TB (42.08 ± 9.23). The median symptom scores also confirm this observation, with medians of 42.05 for the DS TB group and 64.44 for the MDR TB group. (Table 8)

Table 8 Descriptive Statistical Analysis of SGRQ – Symptom Score

BK Status	N	Media	Deviation Standard	Mediana	Range variation	Minimum	Maximum
DS TB	149	42.0863	9.22807	42.0528	48.47	23.70	72.17
MDR TB	75	64.5915	9.45486	64.4377	43.98	40.91	84.89
Total	224	49.6215	14.12409	46.7698	61.19	23.70	84.89

The t-test has a statistically significant result ($p<0.001$), with a mean difference of 22.5 points and a 95% Confidence Interval (CI) ranging from 19.9 to 24.1 points.

Table 9 T-test – Comparison of Symptom Scores on SGRQ by Bacteriological Status

			SGRQ – Symptom scores	
			Homogenous Variants	Heterogenous Variants
Levene's Test for Equality of Variances	F		0.603	
	P		0.438	
T-Test for Equality of Means	T		-17.084	-16.947
	Df		222	145.279
	Statistical semnification (p)	1 tail	**<0.001**	<0.001
		2 tails	0.000	0.000
	Mean difference		-22.50524	-22.50524
	Standard Error of the Difference		1.31730	1.32795
	Confidence Interval of the difference 95%	Inferior limit	-25.10124	-25.12983
		Superior limit	-19.90923	-19.88064

Activity Score falls into the same range, with higher values in patients with MDR TB. Thus, the average score for these patients was 70.26 ± 23.79, whereas for DS TB patients, the mean value was 41.52 ± 18.03 points. (Table 10)

Table 10 Descriptive Statistical Analysis of SGRQ – Activity Score

BK Status	N	Media	Standard deviation	Mediana	Range	Minimum	Maximum
DS TB	149	41.5233	18.02666	37.1516	74.41	6.21	80.62
MDR TB	75	70.2633	23.79958	80.4069	76.63	18.12	94.75
Total	224	51.1460	24.25726	43.9749	88.54	6.21	94.75

The Mann-Whitney U test result is statistically significant ($p<0.001$), with observed differences between the two groups being statistically significant, showing lower activity scores for DS TB patients. (Table 11)

Table 11 Mann-Whitney U Test – SGRQ – Activity Score

	SGRQ – Activity score
Mann-Whitney U	2073.500
Wilcoxon W	13248.500
Z	-7.684
p (2-tails)	<0.001

a. Grouping Variable: Bacteriological Status BK

In the case of the impact score, we observed that the average values are relatively close, with DS TB patients having an average of 33.09 ± 15.88, and MDR TB patients having

an average impact score of 39.14 ± 17.61. In both cases, there is a noticeable variability in the scores, as indicated by the relatively high standard deviation (Table 12).

Table 12: Descriptive Statistical Analysis of SGRQ – Impact Score

BK Status	N	Media	Standard Deviation	Mediana	Range	Minimum	Maximum
DS TB	149	33.0950	15.88072	37.6712	95.13	1.98	97.11
MDR TB	75	39.1415	17.60960	42.2939	80.74	10.09	90.83
Total	224	35.1195	16.68709	38.1056	95.13	1.98	97.11

Thus, it is observed that the differences between the two groups regarding the impact score are statistically significant, with higher scores for patients with MDR TB (Table 13).

Table 13: Mann-Whitney U Test – SGRQ Impact Score

	SGRQ - Scor Impact
Mann-Whitney U	4214.500
Wilcoxon W	15389.500
Z	-3.000
p (2-tails)	0.003

a. Grouping Variable: BK Bacteriological Status

By analyzing the independent role of each variable included in the statistical model, we found that only some of these variables independently predict the depression score. Based on the data in Table 14, we found that BK bacteriological status, age, sex, and the number of relapses before the confirmation of MDR TB/XDR TB diagnosis are statistically significant predictors. The regression coefficients and standard errors are provided in the table.

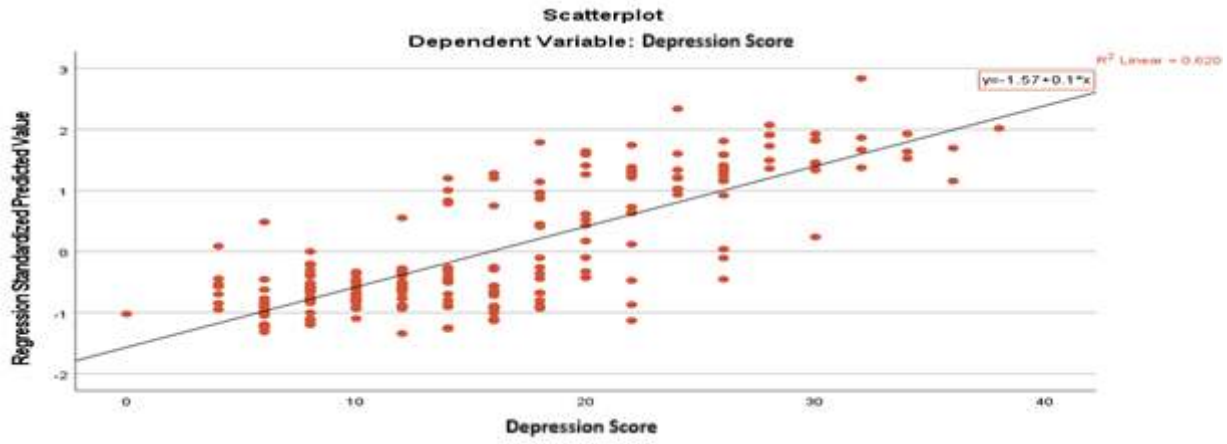

Figure 1: Scatterplot of the Variance in Depression Score Explained by the Multiple Linear Regression Model

Table 14: Regression Coefficients – Depression Score

Model	Unstandardized Coefficients		Standardized Coefficients			95% Confidence Interval for B	
	B	Standard error	Beta	t	P	Inferior limit	Superior limit
1(Constant)	2.193	2.274		0.964	0.336	-2.289	6.675
BK status	8.491	1.546	0.503	5.493	**<0.001**	5.444	11.538
Age	0.129	0.027	0.213	4.711	**<0.001**	0.075	0.183
Origin	-0.416	0.699	-0.026	-0.595	0.552	-1.793	0.961
Sex	1.845	0.760	0.106	2.427	**0.016**	0.346	3.344
Social status	0.303	0.214	0.063	1.418	0.158	-0.118	0.725
Number of Relapses Before the Confirmation of MDR TB/XDR TB Diagnosis	2.142	0.575	0.192	3.727	**<0.001**	1.009	3.275

Radiological form	-0.303	0.274	-0.048	-1.105	0.271	-0.843	0.237
Duration of Treatment (Months)	0.164	0.126	0.109	1.297	0.196	-0.085	0.413

By analyzing the independent role of each variable included in the statistical model, we found that only some of these variables independently predict the anxiety score. Based on the data in Table 15, we determined that BK bacteriological status, age, and the number of relapses before the confirmation of MDR TB/XDR TB diagnosis are statistically significant predictors. The regression coefficients and standard errors are provided in the table.

Figure 2: Scatterplot of the Variance in Anxiety Score Explained by the Multiple Linear Regression Model

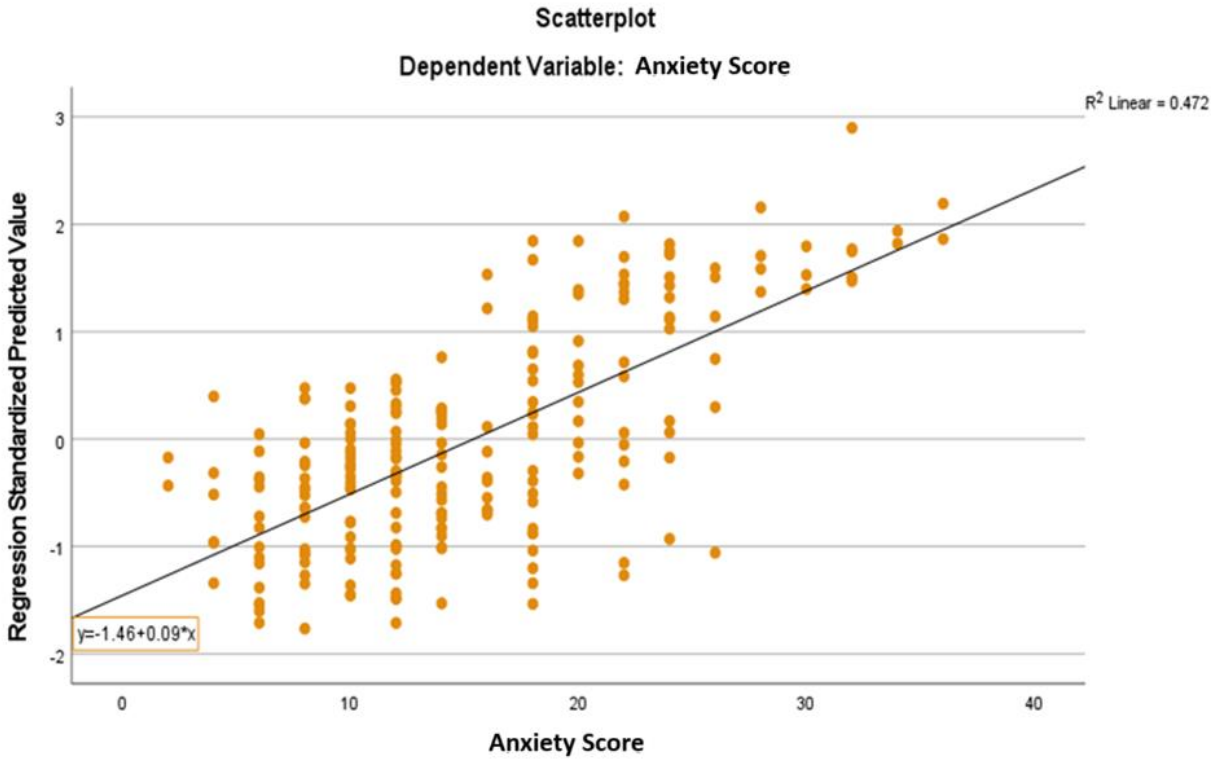

Table 15 Regression Coefficients – Anxiety Score

Model		Unstandardized Coefficients		Standardized Coefficients			95% Confidence Interval for B	
		B	Standard Error	Beta	t	p	Inferior limit	Superior limit
1	(Constant)	-1.641	2.447		-0.671	0.503	-6.465	3.182
	BK Status	5.932	1.663	0.385	3.566	**<0.001**	2.653	9.211
	Age	0.235	0.029	0.426	7.988	**<0.001**	0.177	0.293
	Origin	0.916	0.752	0.063	1.218	0.224	-0.566	2.398
	Sex	0.912	0.818	0.057	1.115	0.266	-0.701	2.525
	Social status	0.017	0.230	0.004	0.074	0.941	-0.437	0.471
	Number of Relapses Before the Confirmation of MDR TB/XDR TB Diagnosis	1.410	0.618	0.138	2.280	**0.024**	0.191	2.630
	Radiological Form	-0.131	0.295	-0.023	-0.445	0.657	-0.713	0.450
	Duration of Treatment (Months)	0.015	0.136	0.011	0.113	0.910	-0.253	0.284

a. Dependent Variable: Anxiety Score

By analyzing the independent role of each variable included in the statistical model, we found that only some of these variables independently predict the stress score. Based on the data in Table 16, we determined that BK bacteriological status, age, and sex are statistically significant predictors. The regression coefficients and standard errors are provided in the table.

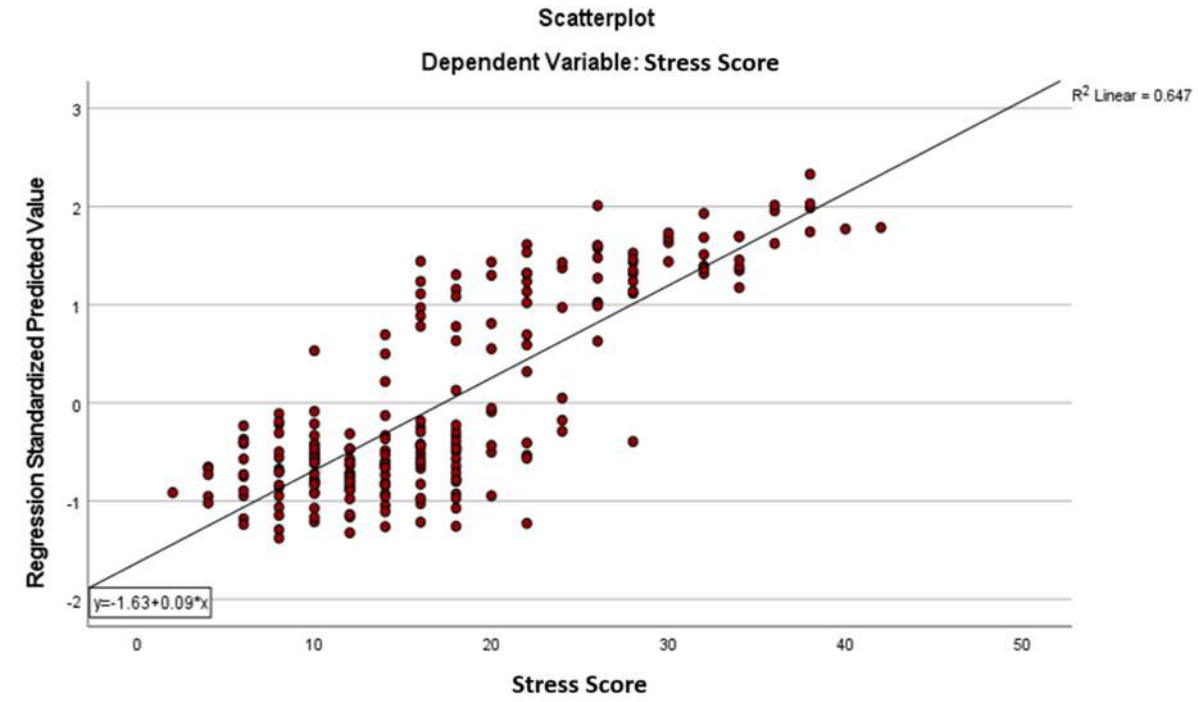

Figure 3: Scatterplot of the Variance in Stress Score Explained by the Multiple Linear Regression Model

Table 16: Regression Coefficients – Stress Score

Model		Unstandardized Coefficients		Standardized Coefficient			95% Confidence Interval for B	
		B	Standard error	Beta	t	p	Inferior limit	Superior limit
1	(Constant)	0.717	2.353		0.305	0.761	-3.922	5.356
	BK status	11.503	1.600	0.634	7.190	**<0.001**	8.349	14.656
	Age	0.159	0.028	0.246	5.631	**<0.001**	0.103	0.215
	Origin	-0.289	0.723	-0.017	-0.400	0.690	-1.714	1.136
	Sex	2.776	0.787	0.148	3.528	**<0.001**	1.225	4.327

Social status	0.205	0.221	0.040	0.925	0.356	-0.232	0.641
Number of Relapses Before the Confirmation of MDR TB/XDR TB Diagnosis	1.133	0.595	0.094	1.905	0.058	-0.039	2.306
Radiological form	-0.185	0.284	-0.027	-0.653	0.514	-0.744	0.374
Duration of Treatment (Months)	0.090	0.131	0.056	0.686	0.493	-0.168	0.348

a. Dependent Variable: Stress Score

By analyzing the independent role of each variable included in the statistical model, we found that only some of these variables independently predict the symptom score. Based on the data, we determined that BK bacteriological status is the only statistically significant predictor. The regression coefficients and standard errors are provided in Table 17.

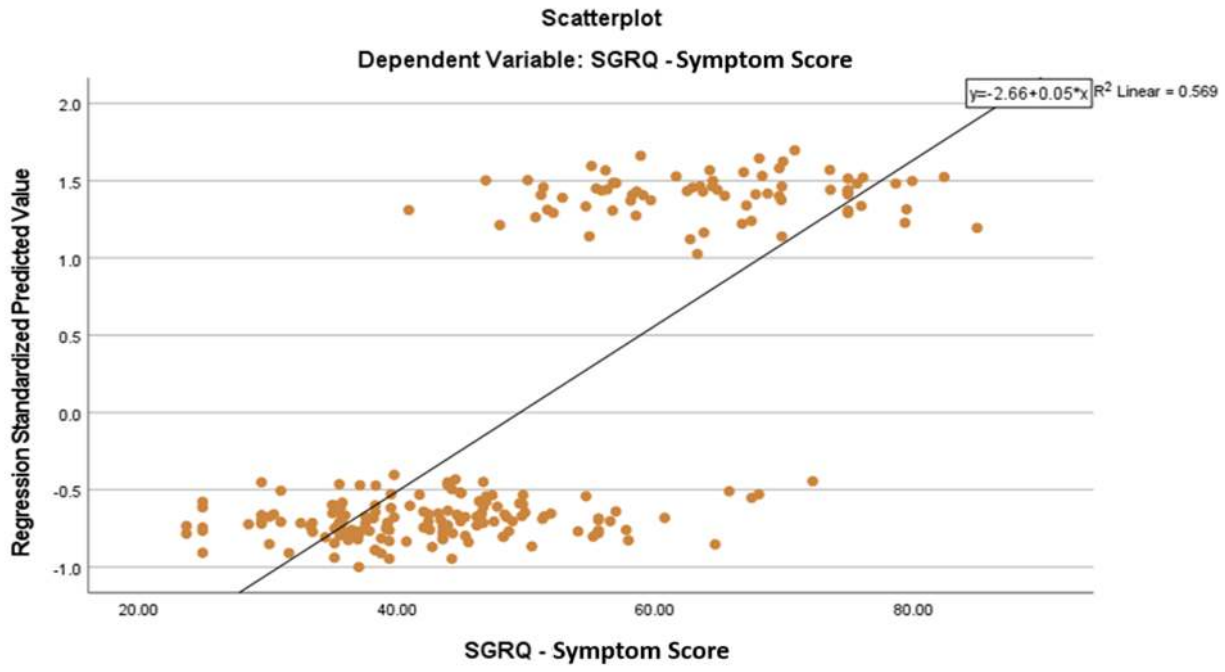

Figure 4: Scatterplot of the Variance in SGRQ – Symptom Score Explained by the Multiple Linear Regression Model

Table 17: Regression Coefficients – SGRQ Symptom Score

Model		Unstandardized Coefficients		Standardized Coefficients			95% Confidence Interval for B	
		B	Standard error	Beta	t	p	Inferior limit	Superior limit
1	(Constant)	42.274	4.276		9.887	<0.001	33.845	50.702
	BK status	22.898	2.907	0.768	7.877	**<0.001**	17.168	28.628
	Age	0.039	0.051	0.036	0.756	0.451	-0.062	0.140
	Origin	-1.876	1.314	-0.067	-1.428	0.155	-4.465	0.714
	Sex	-0.700	1.430	-0.023	-0.490	0.625	-3.519	2.118
	Social Status	0.345	0.402	0.041	0.857	0.392	-0.448	1.138
	Number of Relapses Before the Confirmation of MDR TB/XDR TB Diagnosis	-1.153	1.081	-0.058	-1.066	0.287	-3.283	0.978
	Radiological Form	0.280	0.515	0.025	0.544	0.587	-0.736	1.296
	Duration of Treatment (Months)	0.008	0.238	0.003	0.034	0.973	-0.461	0.477

a. Dependent Variable: Symptom Score

By analyzing the independent role of each variable included in the statistical model, we found that only some of these variables independently predict the activity score. Based on the data in Table 18, we determined that BK bacteriological status and age are statistically significant predictors. The regression coefficients and standard errors are provided in the table.

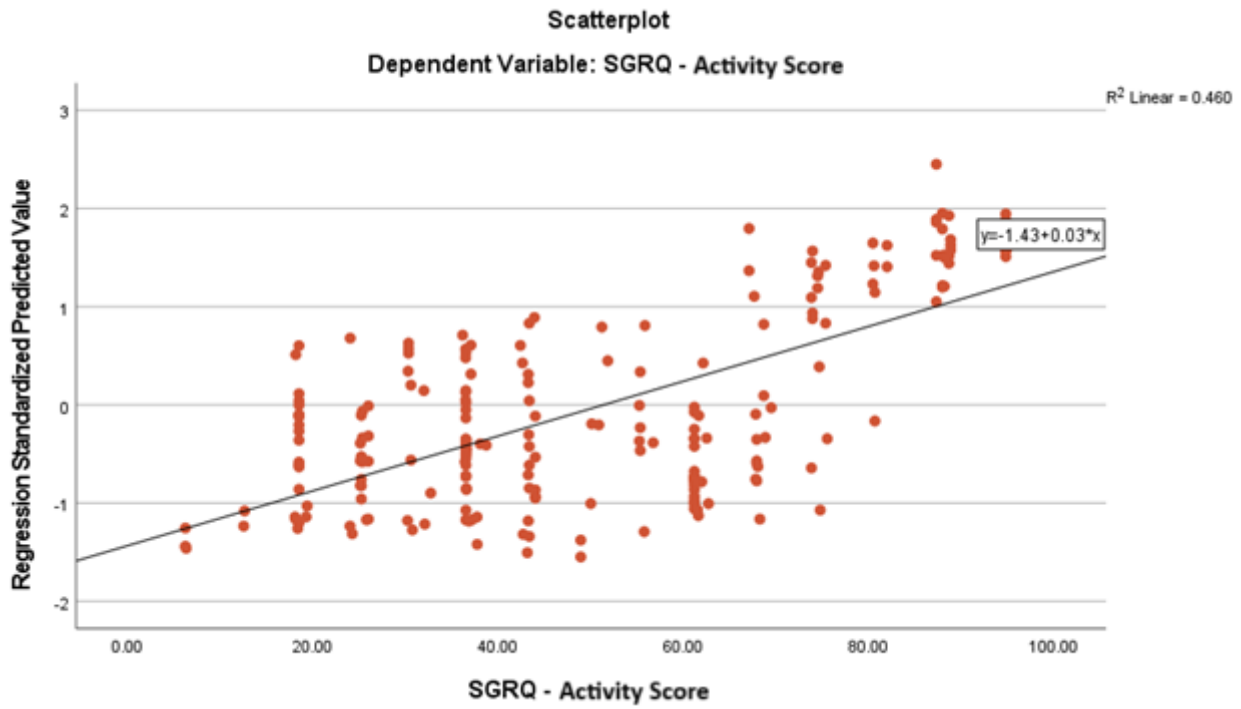

Figure 5: Scatterplot of the Variance in SGRQ – Activity Score Explained by the Multiple Linear Regression Model

Table 18: Regression Coefficients – SGRQ Activity Score

Model		Unstandardized Coefficients		Standardized Coefficients			95% Confidence Interval for B	
		B	Standard error	Beta	t	p	Inferior limit	Superior limit
1	(Constant)	9.688	8.273		1.171	0.243	-6.620	25.996
	BK Status	26.570	5.624	0.515	4.724	**<0.001**	15.484	37.657
	Age	0.638	0.099	0.346	6.419	**<0.001**	0.442	0.834
	Origin	-0.391	2.542	-0.008	-0.154	0.878	-5.402	4.620
	Sex	0.839	2.766	0.016	0.303	0.762	-4.614	6.292
	Social Status	-0.036	0.778	-0.002	-0.046	0.964	-1.570	1.499

Number of Relapses Before the Confirmation of MDR TB/XDR TB Diagnosis	1.765	2.091	0.052	0.844	0.400	-2.357	5.887
Radiological form	-0.539	0.997	-0.028	-0.540	0.589	-2.505	1.427
Duration of Treatment (Months)	0.008	0.460	0.002	0.017	0.986	-0.899	0.915

Regression Coefficients – Activity Score

6. DISCUSSIONS

Sharma et al. (2013) investigated the mental health of patients with MDR and DS TB, concluding that MDR TB patients had higher scores on the anxiety and depression scales according to the DASS 21 R assessment, similar to the values observed in our study [37]. Pachi et al. (2013) observed that MDR TB patients had significantly higher depression scores, which can be explained by additional stress factors such as the prolonged duration of treatment and uncertainty about prognosis [38].

Patients with MDR TB had an average anxiety score of 20.37 ± 7.96, nearly double that of DS TB patients, who had an average score of 12.85 ± 5.29. This difference reflects the stress and uncertainty associated with managing this more severe and difficult-to-treat form of the disease.

Dhingra et al. (2017) identified higher anxiety scores in MDR TB patients and emphasized that anxiety is often exacerbated by the long duration of treatment and fear of treatment failure [39]. In the DS TB patient group, over two-thirds exhibited normal stress levels, indicating a better ability to manage the disease and a lower psychological impact. Approximately one-quarter of these patients had low stress levels, suggesting minimal emotional disturbance in this group. The near absence of severe and extremely severe cases in this group highlights the relatively stable emotional state of DS TB patients.

Doherty et al. (2013) emphasized that MDR TB patients are subjected to a higher level of stress compared to chemoresponsive forms [40]. MDR TB patients had an average symptom score of 64.59 ± 9.45, significantly higher than the average score of 42.08 ± 9.23 in DS TB patients, suggesting that MDR TB patients experience much greater severity of respiratory symptoms, which may be related to the complexity of treatment and a poorer response to therapy.

Baral et al. (2016) also identified higher symptom scores in MDR TB patients compared to those with DS TB, demonstrating the increased severity of respiratory symptoms in this group [41].

7. Conclusions

1. BK Bacteriological Status: This is the most consistent predictor with a statistically significant role in increasing depression, anxiety, and stress scores, as well as symptom, activity, and impact scores.

2. Depression Scores: The average depression score was approximately twice as high for MDR TB patients compared to DS TB patients. Among DS TB patients, 30% exhibited mild or moderate depression, and about 5% were classified with severe or extremely severe depression. In MDR TB patients, the distribution was as follows: 29.3% had moderate depression, 37.3% had severe depression, and 32% had extremely severe depression.

3. Anxiety Levels: The majority of MDR TB patients (60.0%) had extremely severe anxiety levels compared to only 11.4% of DS TB patients.

4. Stress Scores: The average stress score was twice as high for MDR TB patients. Among DS TB patients, two-thirds had normal stress levels, and 25% had elevated stress levels, compared to MDR TB patients, where severe (37.3%), moderate (24%), and extremely severe (20%) stress levels predominated.

5. Symptom Scores: MDR TB patients had a significantly higher average symptom score, suggesting increased severity of respiratory symptoms compared to the DS TB group.

8. Originality of the Thesis

The doctoral thesis achieved the scientific research objectives set. Our study highlighted that patients diagnosed with multidrug-resistant tuberculosis (MDR-TB) develop significantly higher levels of anxiety and depression compared to those with chemoresponsive forms of TB. This observation is based on the elevated scores obtained in psychological assessments using the DASS 21R scale, indicating a greater psychological burden among MDR-TB patients. The difference can be explained by the longer duration of treatment, its complexity, associated stigma, and uncertainty about prognosis, all contributing to the intense psychological stress experienced by these patients.

BK bacteriological status, age, and sex were identified as key factors in the development of significantly higher levels of anxiety, depression, and stress, associated with a massive impact on quality of life and activities as evaluated by the SGRQ questionnaire, in MDR-TB patients compared to the DS TB group. Thus, BK bacteriological status proved to be a significant predictor across all categories, demonstrating its major influence on both

mental and physical health, associated with a higher likelihood of developing symptoms of depression, anxiety, and stress, and having a negative impact on symptomatology and quality of life, in accordance with the existing literature.

For the first part, 130 bibliographic references were consulted, analyzing the history of M. tuberculosis infection, epidemiology, definition, mechanisms of chemoresistance, diagnosis, treatment, and side effects.

The original contribution included developing patient inclusion criteria, data collection, statistical analysis, drawing statistically significant conclusions, and comparing them with the existing literature.

Limitations encountered include data accuracy or availability issues, difficult access to medical information, human factors (inability or refusal to participate), and the relatively small number of patients.

Action Plan

To address this issue at a national level, we propose an action plan involving a collaborative network among various health entities and specialists. The action plan will focus on reducing depression and anxiety among MDR TB patients through an integrated and personalized approach.

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Appendices

Figures

LIST OF PUBLISHED SCIENTIFIC WORKS

1. "Prevalence of Depression and Anxiety in Patients with Multidrug-Resistant Tuberculosis: An Analysis With DASS-21R" **Popoiag Ciprian-Constantin**, Gache Alexandra-Cristiana, Iosif Alexandru-Cătălin and Rugină Sorin. ARS Medica Tomitana, BDI**,** vol.30, no.1, 2024, pp.1-5. https://doi.org/10.2478/arsm-2024-0001

2. "Fitness for Work in the Long Journey of Tuberculosis Infection to Chronic Posttuberculosis Disease Case Report and Literature Review", Arghir Ioan Anton, **Popoiag Ciprian Constantin**, Arghir Ana Adina, Ion Ileana, Tofolean Doina Ecaterina, Cambrea Simona Claudia, Fildan Ariadna Petronela, Trenchea Mihaela and Oțelea Marina Ruxandra. Romanian Journal of Occupational Medicine, vol.74, no.1, 2023, pp.16 22. BDI https://2.org/10/2478/rjom-2023-0003

3. "The Long-Term Impact on Patients with MDR-TB Using the Saint George's Respiratory Questionnaire", **Popoiag Ciprian-Constantin,** Gache Alexandra-Cristiana, Iosif Alexandru-Catalin, Gache Teodor-Nicolae and Rugina Sorin. ARS Medica Tomitana, vol.30, no.1, 2024, pp.24-28**.** BDI https://doi.org/10.2478/arsm-2024-0005