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Depression and anxiety symptoms among people with rifampicin-resistant tuberculosis receiving in-patient care in the National Pulmonology Reference Institute in Romania

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Abstract

Mental health comorbidities are common among tuberculosis patients, with higher prevalence among people with rifampicin-resistant/multidrug-resistant (RR/MDR) tuberculosis. TB and depression share common risk factors adding to the overall disease burden. There is limited evidence about prevalence of depression and anxiety symptoms among tuberculosis patients in Romania. We assessed the prevalence of depression and anxiety symptoms and their evolution over the course of the treatment in RR/MDR-TB patients receiving in-patient care at the National Institute of Pneumonology (NIP) "Marius Nasta" in Romania during May-September 2020. We conducted a cohort study and used the Hospital Anxiety and Depression Scale (HADS) to assess the prevalence of depression and anxiety (defined as score≥ 8) symptoms at admission (baseline) and the second month of in-patient treatment (follow-up). Difference between baseline and follow-up depression and anxiety symptoms were assessed using McNemar test. Binary logistic regression was used to evaluate the association between sociodemographic and clinical characteristics with the presence of depression and anxiety symptoms at baseline. The cohort included 46 patients, 63% were male, mean age was 46 (±13.3) years. The prevalence of depression and anxiety in our cohort was 46% and 43% at baseline respectively, and 50% and 39%, at the follow-up respectively. About one third (7/25) of patients who had normal HADS depression score at baseline, had an increase above the threshold at the second month of treatment. No statistical difference in prevalence of depression or anxiety was found between the baseline and second month of treatment. Unadjusted analysis showed that odds of depression at baseline was lower in patients with education above 8th grade compared to patients with education below 8th grade (odds ratio=0.2, 95% confidence interval: 0.1,0.8, p=0.026). The study revealed high prevalence of depression and anxiety among RR/MDR-TB patients admitted to the NIP, underlining the necessity of evaluating the mental health of TB patients and linking them to appropriate care.

Introduction

Tuberculosis (TB) remains one of the major public health threats globally [1]. Around 10 million people fall ill with TB each year [1], of which about 3% is estimated to occur in the World Health Organization (WHO) European Region [2]. Globally and regionally, TB incidence rate has been declining with the average annual rate of 1.6% and 5% respectively in the period 2000-2018 [1]. This decline in the Region, however, is driven by drug-susceptible (DS) TB, whereas the rates of drug-resistance (DR) have been increasing [1,3]). WHO European Region accounts for 23% of all patients with rifampicin-resistant/multidrug-resistant tuberculosis (RR/MDR-TB) globally [2].

Romania is one of the 18 high-priority countries for TB control in the WHO European Region [2]. Although the TB incidence rate continues to decline on an annual average rate of 5.5%, the country has the highest incidence rate of TB (68 per 100,000 population) [4] accounting for 23% of all TB patients in the European Union (EU) [2]. The RR/MDR-TB burden is one of the public health challenges in the country. In 2018, the estimated RR/MDR-TB incidence was 3.6 (range 2.9-4.5) per 100,000 population; however, of the expected 710 patients, only 470 were reported, meaning that the detection rate was only 66% [2,4]. During the same year, the estimated proportion of RR/MDR-TB among new patients was 2.7% (range 2.3-3.2), among previously treated patients was 15% (range 13-16%) [2,4]. The lower RR/MDR-TB detection rate may be due to the limited access to rapid-diagnostic test and to drug-susceptibility testing [2,4,5] and could contribute to delayed diagnosis of RR/MDR-TB, as well as delayed initiation of treatment and respectively to poor treatment outcomes. The RR/MDR-TB treatment success rate for those who started treatment from 2015 to 2016 was around 50%, which is lower than WHO target of 75% [2]. RR/MDR-TB treatment is complex, has a long duration and requires multiple drugs, including injectables [6,7].

Separately, depression and TB [8] are recognized as important public health concerns. WHO estimated that globally, the total number of people with depression exceeds 300 million and approximately the same number of people suffer from anxiety disorders [8]. Out of the estimated number of people with depression and anxiety in the world, 12% and 14% respectively are in WHO European Region [8]. In Romania, the estimated prevalence of depressive and anxiety disorders in general population was about 5% and 4%, respectively [8].

Several studies have reported that mental health comorbidities are common in TB patients [9-12]. Previous studies from the WHO European Region, report a prevalence of depression and depressive symptoms among TB patients ranging from 19-65% [13-17]. Among them two were conducted in Romania and the reported prevalence of depression among hospitalized TB patients was 38.9% [15] and 65% [17]. Results of a meta-analysis study showed that among TB patients the pooled estimated prevalence of depression is 45% [(18]. The prevalence of depression is higher among RR/MDR-TB patients [19]. Studies done outside of the WHO European Region reported that the prevalence of depression is higher than in the general population and ranging from 13% to 72% in pulmonary TB patients [11,20-23] and from 23% to 70% in RR/MDR-TB patients [24].

A literature search reveals that mental disorders are associated with poor adherence to medication which could lead to irregular treatment especially in the treatment of illnesses with long duration [19].

Many people with depression are also exposed to TB risk factors including alcohol abuse, poverty, homelessness and congregate housing, thus they are at higher risk of developing the disease [25-27]. On the other hand, TB patients are at higher risk of developing depression due to several risk factors including drugs used for the treatment of RR/MDR-TB [27-30] poverty, social exclusion and drug abuse [27]. Thus, TB and depression act synergistically to worsen the overall disease burden. Hence, evaluating these comorbidities and linking them to appropriate care is crucial. There is limited evidence on this issue symptoms in Europe and in Romania [15,17]. In this study, we addressed this knowledge gap by assessing the prevalence of depression and anxiety symptoms and their change over the course of treatment among RR/MDR-TB patients receiving in-patient care in the National Institute of Pneumonology "Marius Nasta" in Romania during May-September 2020. In addition, the study explored factors associated with depression and anxiety symptoms at the baseline.

Materials and Methods

Study design and population

We conducted a cohort study. The study enrolled all consecutive adult (≥18 years old) RR/MDR-TB patients receiving in-patient care in the NIP in Romania during May-September 2020. Only patients who were able to speak Romanian and provided written informed consent were included into the study.

Study setting

In Romania, the Ministry of Health (MoH) has the primary responsibility for TB control in the country and exercises power through the central unit of National Tuberculosis Programme (NTP) - the National Institute of Pneumonology "Marius Nasta" (NIP).

Integrated patient-centred care and prevention services are some of the key interventions in implementing NTP and include social and psychological support for TB patients. Since July 2014, some of the RR/MDR-TB patients have been benefitted from psychological counselling and social support in ambulatory care through internationally funded projects provided by NGOs. Moreover, psychological and social support is given to TB patients by four TB hospitals, including NIP since 2015. The services are free and are provided by psychologists and social workers.

Study instrument

We used the Hospital Anxiety and Depression Scale (HADS) to evaluate presence of depression and anxiety symptoms [31]. The questionnaire has been validated in many countries, languages and settings [32-34), and can be used free of charge. The instrument was not validated for Romanian population.

It consists of 14 questions, of which seven measure presence of depression symptoms and the remaining seven measure presence of anxiety symptoms. The evaluation of symptoms is done by scoring each response from 0 to 3. A cumulative score is calculated after the interview, which is the sum of all responses. This is done separately for depression and anxiety. A score between 0-7 represents the absence of symptoms, a score between 8-10 represents a borderline case, whilst a score between 11-21 represents the presence of the symptoms. A review paper on the validity of the questionnaire showed that the optimal cut-off score for 'caseness' (the degree to which diagnostic criteria for depression and anxiety symptoms are applicable to a given patient) of depression and anxiety is 8 or above [32].

Sources of data

In the study are used two data sources: primary data obtained through the HADS questionnaire and secondary data acquired from the patients' medical records.

Data collection and variables

Each patient was assessed for presence of depression and anxiety symptoms at admission (baseline) and the second month of in-patient treatment (follow-up) using the HADS questionnaire. The questionnaire was self-administered. For those who were not able to complete the questionnaire on their own, it was administered by trained and experienced psychologist working at the facility.

Socio-demographic (age, sex, level of education, residence, marital status, employment, smoking status and alcohol consumption), and clinical characteristics (history of TB, laboratory assessment, chest X-Ray, comorbidities and clinical symptoms (defined as key symptoms if cough, fever and haemoptysis were present) were extracted from patients' charts and entered into the EpiData dataset by the study team. Data entry errors were identified and corrected through random checking of a sample of records.

Analysis and statistics

The study variables are summarized using frequencies for categorical variables and measures of central tendency for continuous variables.

Scoring of depression and anxiety symptoms was performed according to the HADS manual. We used a cut-off point of 8/21 as a threshold for abnormal level of depression or anxiety symptoms. Prevalence of depression and anxiety was calculated for the whole sample and for each category in socio-demographic and clinical variables. Difference between the baseline and follow-up measurements was tested using McNemar test. Binary logistic regression was used to evaluate the association between sociodemographic and clinical characteristics and the presence of depression and anxiety symptoms at baseline. Respective crude odds ratios (OR) and 95% confidence intervals (CI) were reported. The level of significance was set at $p<0.05$. The data analysis was conducted using SPSS (v.23, IBM, USA).

Results

The study cohort included 46 participants out of 76 eligible patients identified during the study period (Figure 1). Sociodemographic and clinical characteristics of the study population are presented in Table 1. Mean age of the study population was 46 (±13.3) years, majority of them were male (29/46, 63%) and 61% (28/46) were married or living with a partner. About 65% (30/46) of the study population had an education level above 8th grade, and majority 54% (25/46) resided in rural areas. The majority of the participants (38/46, 83%) were current smokers and about one third of them reported high alcohol consumption (35%, 16/46). About half of the participants (24/46, 52%) were previously treated patients. X-ray assessment revealed cavities in about one third of the patients (18/46, 39%). Diabetes was diagnosed in four (9%) and HIV infection in two (4%) patients. Majority of the participants (36/46, 78%) had one or two key symptoms (cough, fever, haemoptysis) and about 15% (7/46) had all three symptoms. All patients had pulmonary TB.

The prevalence of depression and anxiety in our cohort at baseline were 46% (21/46) and 43% (20/46) respectively, and at follow-up were 50% (23/46) and 39% (18/46) respectively. At baseline 28% (13/46) and at follow-up 22% (10/46) of the participants had both depression and anxiety. Seven study participants who had normal HADS score at baseline (7/25, 28%), developed depression at the follow-up, of which five moved to the borderline category and two to the abnormal category. Five study participants whose depression score was classified as abnormal (borderline and abnormal categories combined) at the baseline (5/21, 24%), showed normal scores at the follow-up. Detailed depiction of changes in the

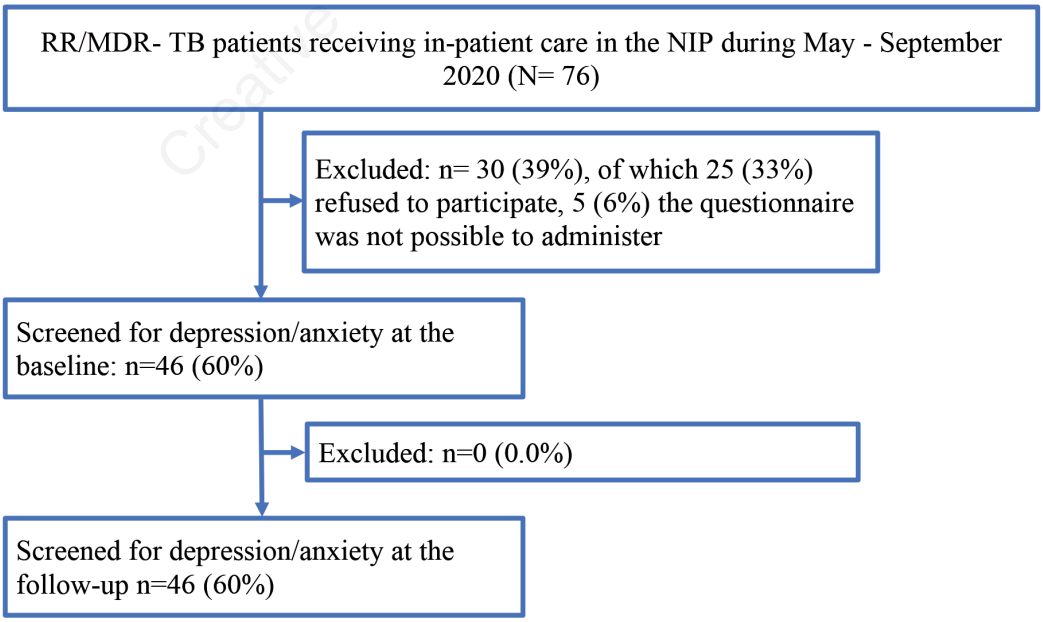

Figure 1. Flow chart of the study participants: MDR-TB patients receiving in-patient care in the National institute of Pneumology "Marius Nasta" (NIP) in Romania (May-September 2020).

Table 1. Baseline sociodemographic and clinical characteristics of patients with rifampicin-resistant/multidrug-resistant tuberculosis receiving in-patient care in the National Institute of Pneumonology (May-September) (N=46).

Characteristics	Total	Depression symptoms at baseline				Anxiety symptoms at baseline			
		HADS score <8 (Normal)	HADS score ≥8 (Abnormal)	p-value	Crude OR (95% CI)	HADS score <8 (Normal)	HADS score ≥8 (Abnormal)	p-value	Crude OR (95% CI)
	N (col%)	N (row%)	N (row%)			N (row%)	N (row%)		
Total	46 (100)	25 (54)	21 (46)		–	26 (57)	20 (43)	–	–
Socio-demographic									
Age category									
≤30	6 (13)	3 (50)	3 (50)		ref.	3 (50)	3 (50)		ref.
31-45	11 (24)	5 (45)	6 (55)	0.460	0.5 (0.1-3.1)	5 (45)	6 (55)	0.858	1.2 (0.2-8.8)
46-60	21 (46)	14 (67)	7 (33)	0.641	1.7 (0.2-14.3)	15 (71)	6 (29)	0.334	0.4 (0.1-2.6)
61+	8 (17)	3 (38)	5 (63)	1.000	1 (0-0)	3 (38)	5 (63)	0.641	1.7 (0.2-14.3)
Patient's sex									
Male	29 (63)	18 (62)	11 (38)		ref.	18 (62)	11 (38)		ref.
Female	17 (37)	7 (41)	10 (59)	0.174	2.3 (0.7-7.9)	8 (47)	9 (53)	0.324	1.8 (0.5-6.2)
Level of education									
Below 8th grade	16 (35)	5 (31)	11 (69)		ref	8 (50)	8 (50)		ref
Above 8th grade	30 (65)	20 (67)	10 (33)	0.026	0.2 (0.1-0.8)	18 (60)	12 (40)	0.516	0.7 (0.2-2.3)
Place of current residence									
Urban	21 (46)	13 (62)	8 (38)		ref	13 (62)	8 (38)		ref
Rural	25 (54)	12 (48)	13 (52)	0.347	1.8 (0.5-5.7)	13 (52)	12 (48)	0.500	1.5 (0.5-4.9)
Marital status									
Single	18 (39)	10 (56)	8 (44)		ref	10 (56)	8 (44)		ref
Married/Co-habitation	28 (61)	15 (54)	13 (46)	0.895	1.1 (0.3-3.6)	16 (57)	12 (43)	0.916	0.9 (0.3-3.1)
Employment status									
Employed	27 (59)	17 (63)	10 (37)		ref	18 (67)	9 (33)		ref
Unemployed	19 (41)	8 (42)	11 (58)	0.165	2.3 (0.7-7.8)	8 (42)	11 (58)	0.102	2.7 (0.8-9.2)
Current smoking status									
Non-smoker	8 (17)	4 (50)	4 (50)		ref	5 (63)	3 (38)		ref
Smoker	38 (83)	21 (55)	17 (45)	0.786	0.8 (0.2-3.7)	21 (55)	17 (45)	0.708	1.3 (0.3-6.5)
Level of alcohol consumption									
Low or no	30 (65)	15 (50)	15 (50)		ref	14 (47)	16 (53)		ref
High	16 (35)	10 (63)	6 (38)	0.419	0.6 (0.2-2.1)	12 (75)	4 (25)	0.071	0.3 (0.1-1.1)
Clinical									
Type of TB case									
New	22 (48)	12 (55)	10 (45)		ref	14 (64)	8 (36)		ref
Retreatment	24 (52)	13 (54)	11 (46)	0.979	1 (0.3-3.2)	12 (50)	12 (50)	0.353	1.7 (0.5-5.7)
Baseline smear microscopy									
Positive	30 (65)	16 (53)	14 (47)		ref	17 (57)	13 (43)		ref
Negative	15 (33)	8 (53)	7 (47)	1.000	1 (0.3-3.5)	8 (53)	7 (47)	0.832	1.1 (0.3-4)
Not done	1 (2)	1 (100)	0 (0)	1.000	0 (0-0)	1 (100)	0 (0)	1.000	0 (0-0)
Baseline culture									
Positive	31 (67)	17 (55)	14 (45)		ref	17 (55)	14 (45)		ref
Negative	14 (30)	7 (50)	7 (50)	0.763	1.2 (0.3-4.3)	8 (57)	6 (43)	0.886	0.9 (0.3-3.3)
Not done	1 (2)	1 (100)	0 (0)	1.000	0 (0-0)	1 (100)	0 (0)	1.000	0 (0-0)
Resistance category									
Rifampicin resistance	16 (36)	7 (44)	9 (56)		ref	7 (44)	9 (56)		ref
Rifampicin and isoniazid resistance	20 (44)	11 (55)	9 (45)	0.503	0.6 (0.2-2.4)	11 (55)	9 (45)	0.503	0.6 (0.2-2.4)
Resistance to FLD	9 (20)	6 (67)	3 (33)	0.277	0.4 (0.1-2.1)	7 (78)	2 (22)	0.112	0.2 (0-1.4)
RX pulmonary cavities									
No	28 (61)	13 (46)	15 (54)		ref	16 (57)	12 (43)		ref
Yes	18 (39)	12 (67)	6 (33)	0.183	0.4 (0.1-1.5)	10 (56)	8 (44)	0.916	1.1 (0.3-3.5)
Adverse reaction°									
No	29 (63)	16 (55)	13 (45)		ref	15 (52)	14 (48)		ref
Yes	17 (37)	9 (53)	8 (47)	0.883	1.1 (0.3-3.6)	11 (65)	6 (35)	0.393	0.6 (0.2-2)
Having diabetes									
No	42 (91)	21 (50)	21 (50)		ref	24 (57)	18 (43)		ref
Yes	4 (9)	4 (100)	0 (0)	0.999	0 (0-0)	2 (50)	2 (50)	0.784	1.3 (0.2-10.4)
Associated HIV infection									
No	44 (96)	23 (52)	21 (48)		ref	25 (57)	19 (43)		ref
Yes	2 (4)	2 (100)	0 (0)	0.999	0 (0-0)	1 (50)	1 (50)	0.850	1.3 (0.1-22.4)
Presence of key symptoms (cough, fever, haemoptysis)									
None	3 (7)	1 (33)	2 (67)		ref	2 (67)	1 (33)	3 (7)	1 (33)
At least one	36 (78)	21 (58)	15 (42)	0.418	0.4 (0-4.3)	20 (56)	16 (44)	36 (78)	21 (58)
All	7 (15)	3 (43)	4 (57)	0.779	0.7 (0-11.3)	4 (57)	3 (43)	7 (15)	3 (43)

HIV, human immunodeficiency virus; RX, X-ray; TB, tuberculosis; FLD, first line drugs; OR, odds ratio; CI, confidence interval; °adverse events during the first two months of TB treatment.

depression scores are presented in Figure 2. Four participants who at baseline had normal HADS score for anxiety (4/26, 15%), developed anxiety at the follow-up, specifically three of them had borderline HADS score and one abnormal HADS score.

No statistical difference was found between the depression and anxiety symptoms at baseline and at the second month of the treatment (Figures 2 and 3). Unadjusted analysis revealed that odds of depression decreased in patients with higher education (8th grade and above) compared to lower education (below 8th grade) (odds ratio=0.2, 95% confidence interval: 0.1,0.8, p=0.026) (Table 1).

Discussion

We describe the prevalence of depression symptoms as high as 46% among RR/MDR TB patients at admission. The prevalence estimate is comparable to other studies. In a meta-analysis of 4,903 patients with TB from seven countries, pooled estimated prevalence of depression was 45% (95% CI 38.04-52.55), with higher prevalence among MDR-TB 52.34% (95% CI 38.09-66.22) patients [18]. Other observational studies report the prevalence of depression and depressive symptoms ranging from 19-65% [13-17]. Among them two studies conducted in Romania with the reported prevalence of depression 38.9% [15] and 65% [17]. These studies were conducted in a single site and include-susceptible TB patients only. One of these studies reported no statistical difference between depression at baseline and at 6 weeks of hospital treatment among 63 DS TB patients [17]. This is in line with our findings, though both studies had small sample sizes and were not powered adequately to detect statistical differences. In contrast, a study conducted in Armenia found that at baseline the prevalence of depression among 395 DS TB patients was 22%, which decreased significantly to 11% at the end of the TB treatment course.

The prevalence of depression among TB patients is reported to be higher compared to the general population. Our findings confirm this, as the prevalence of depressive and anxiety disorders in general population in Romania was much lower at 5% and 4%, respectively [8]. A study from Romania with head-to-head comparison shows that the prevalence of depression is significantly higher among patients compared to the healthy individuals without TB (65% *vs* 11%, p<0.05).

We have identified seven studies that estimated the prevalence of depression and anxiety symptoms among TB patients using HADS questionnaire. Of them, only one was comparable to our study in terms of drug resistance profile, enrolment of hospitalized study population and usage of cut of point 8+ for categorization of caseness (the degree to which diagnostic criteria for depression and anxiety symptoms are applicable to a given patient) of depression and anxiety. The study was conducted in India and reported prevalence of depression was 55% and 56% for anxiety [35]. Prevalence of anxiety symptoms in our study was lower (43%).

Another study assessing the prevalence of depression among TB patients using HADS questionnaire was conducted in China among 1,252 DS TB patients receiving directly observed treatment [36]. The study reported a prevalence of 18% depression and 19% anxiety. In addition, the study identified independent risk factors associated with depression, including dyspnoea, tracheobronchial TB, lower education and low income [36]. Unadjusted analysis in our study also found association between the lower education and higher odds of depression.

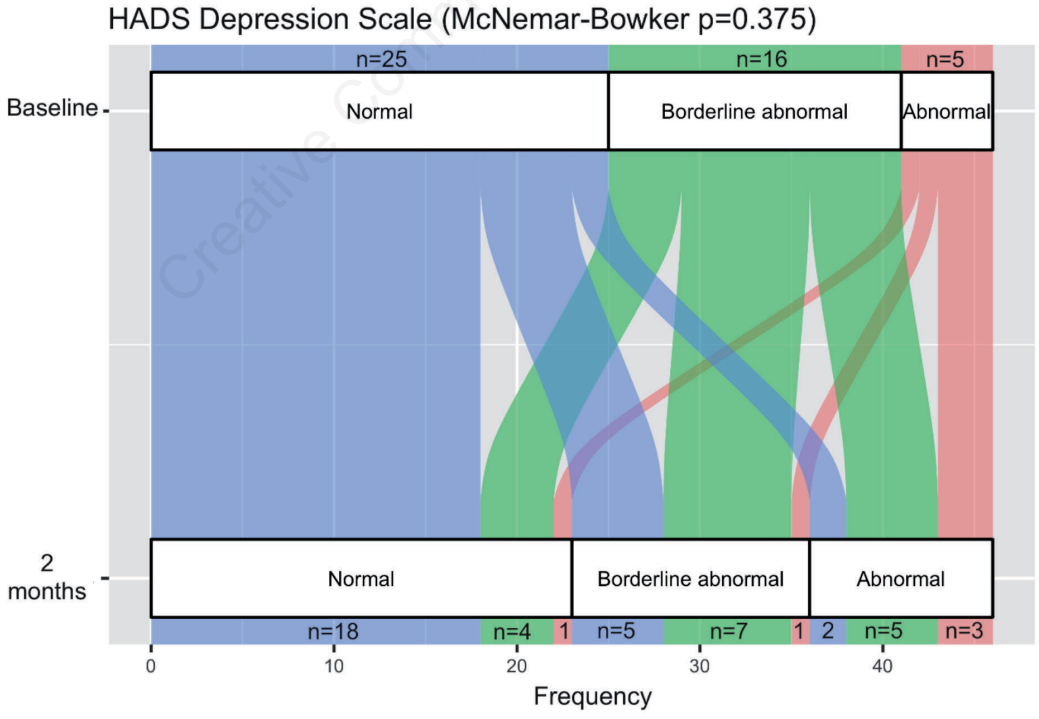

Figure 2. Comparison of depression symptoms at admission (baseline) and the second month of in-patient treatment (follow-up) among rifampicin-resistant/multidrug-resistant tuberculosis receiving in-patient care in the National Institute of Pneumonology (May-September 2020).

We report for the first time the prevalence of depression and anxiety symptoms among RR/MDR-TB patients in Romania. An independent, trained psychologist enrolled the study participants and facilitated the data collection. the physicians or healthcare workers who were involved in delivery of care were not involved in recruitment or administration of the questionnaire. This helped in minimizing the desirability bias and patients felt free in their responses.

The HADS questionnaire has been validated in other settings and widely used globally. A systematic review study of validation works for HADS questionnaire showed that with cut of point ≥8, HADS questionnaire assures optimal sensitivity and specificity. However, there is also a growing criticism of latent structure of HADS questionnaire in the literature [37]. In clinical practice the HADS questionnaire is a convenient tool for the assessment of depression and anxiety symptoms and their evolution. It has been recommended by the National Institute for Health and Care Excellence (NICE) in UK as one of the tools for assessing the psychological conditions [38]. However, depression and anxiety symptoms cannot be attributed to a depression as a psychiatric diagnosis.

The study had several limitations. First, the small sample size, did not provide sufficient power to detect any adjusted associations between depression or anxiety and other clinical and socio-demographic variables. For the same reason, the study was underpowered to detect changes in depression levels during the course of treatment. Second, the study was conducted in a single site, which limits generalizability of findings. However, the NIP is a central and the largest hospital for the treatment of the RR/MDR-TB patients in Romania, accounting for 59% of all RR/MDR-TB cases. Third, we had a high non-response rate. We do not know if non-responders were similar to responders and hence the effect of non-response on prevalence estimates cannot be ruled out. Fourth, behavioural characteristics, including smoking and alcohol abuse were self-reported, which could influence the data quality. Finally, we were not able to obtain information on important clinical co-variates, such as co-infection with HCV.

The study revealed high prevalence of depression and anxiety among RR/MDR-TB patients admitted to The National Institute of Pneumology "Marius Nasta". This calls routine assessment of all TB patients for depression and anxiety and linking them to appropriate care. This is likely to improve the overall quality of life for TB patients, complementing the evaluation and potential rehabilitation of post-TB treatment sequelae as recently discussed within the scientific community [37,39].

Future research on depression and anxiety with higher sample size is recommended to estimate independent risk factors for depression and anxiety, as well as factors associated with the change in the depression and anxiety score during the course of long treatment duration.

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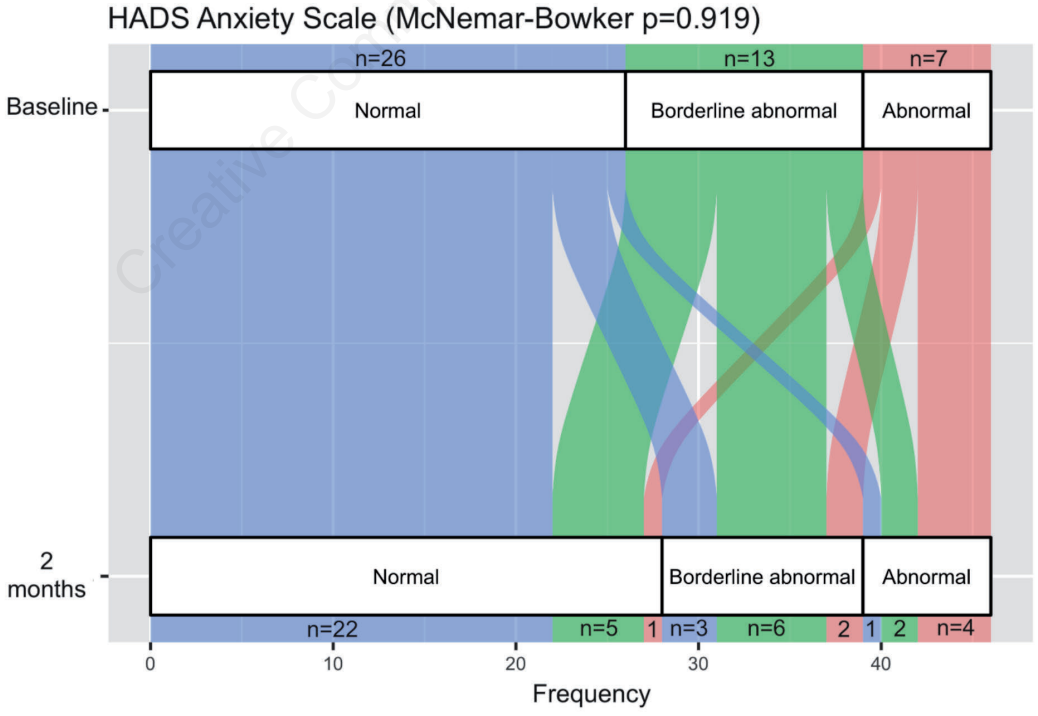

Figure 3. Comparison of anxiety symptoms at admission (baseline) and the second month of in-patient treatment (follow-up) among rifampicin-resistant/multidrug-resistant tuberculosis patients receiving in-patient care in the National Institute of Pneumonology (May-September 2020).

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