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Do catastrophic costs impact treatment outcomes in people with rifampicin-resistant tuberculosis in the Republic of Moldova?

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Abstract

The Republic of Moldova is among the 30 rifampicin-resistant and/or multidrug-resistant (RR/MDR) tuberculosis (TB) high burden countries in the world. Despite free TB diagnostics and treatment, TB patients face substantial economic losses and this may impact overall treatment outcomes. We assessed if there is an association between TB-related catastrophic costs and TB treatment outcomes. We conducted a cohort study using data from patient records and a survey that quantified catastrophic costs among RR/MDR-TB affected households in the Republic of Moldova in 2016. We included adult patients (age ≥18 years) with RR/MDR-TB who had been in inpatient (intensive phase) or outpatient (continuous phase) treatment for at least 2 months. Unfavourable treatment outcome, such as failure, death or lost to follow-up, was the primary outcome variable. The definition of catastrophic TB-related costs followed the World Health Organisation (WHO) guidelines: costs due to TB ≥20% of annual household income. Log-binomial regression was used to assess association between the outcome and catastrophic TB-related costs adjusting for other socio-demographic, behavioural and clinical covariates. In total 287 RR/MDR-TB patients (78% males, mean age 42 years) were included. Of them, 30% experienced catastrophic TB-related costs. Overall, one in five patients (21%) had unfavourable treatment outcome, such as treatment failure (5%), death (8%) or lost to follow-up (8%). The experience of catastrophic TB-related costs was not associated with unfavourable treatment outcome [adjusted relative risk (aRR)=0.88, 95% CI: 0.50–1.50]. Major factors independently associated with unfavourable TB treatment outcomes were poverty (aRR=2.07; 95% CI: 1.06-4.07), urban residence (aRR=1.99; 95% CI: 1.12-3.52) and positive HIV (Human Immunodeficiency Virus) status (aRR=2.61; 95% CI: 1.31-4.89). As a result, we failed to find an association between catastrophic costs and treatment outcomes of RR/MDR-TB patients in the Republic of Moldova. However, we found that patients from poor households and urban areas were twice more likely to achieve unfavourable TB treatment outcomes disregarding whether they experienced catastrophic costs or not. Also, TB/HIV patients and urban residents were identified as the most vulnerable groups with higher risk of unfavourable treatment outcome and TB-related costs.

Introduction

Globally, about 400 million people lack access to one of seven essential services for Millennium Development Goal priority areas annually [1,2]. It is estimated that over 100 million people fall below the poverty line every year as a result of out-of-pocket expenditures on health [3] and about 150 million people suffer catastrophic health expenditure because they pay for health services [4]. Universal health coverage, along with cutting down the socioeconomic burden to eliminate the catastrophic costs incurred by tuberculosis (TB)-affected households, and interventions to improve quality of life for patients while enabling adherence to treatment are key objectives of the World Health Organisation (WHO) End TB Strategy 2016-2035 [5]. WHO defined catastrophic cost as costs exceeding 20% of annual household income and which are incurred during patients' pre-diagnostic, diagnostic, and treatment stages [6].

The Republic of Moldova is a lower-middle-income country where 44% of current health expenditure are paid out-of-pocket [7,8]. It is among the countries in Europe that is facing the most economic difficulties [8] contributing to poverty and public health challenges, including TB. As is it known TB often results in severe economic consequences for TB-affected households [9]. The burden of TB places the country among the 18 high-priority countries in the WHO European Region and among 30 countries with a high Rifampicin-Resistant or Multi-Drug-Resistance (RR/MDR) TB burden in the world [10]. Besides, it is among 8 countries of the East Europe and central Asia (Azerbaijan, Kyrgyzstan, Republic of Moldova, Romania, Russian Federation, Tajikistan, Ukraine, and Uzbekistan) showing significant increases in trends of RR/MDR-TB among new TB patients [11].

The country has taken substantial steps to improve TB care in the last two decades, by implementing reforms according to international recommendations [5,12,13]. These efforts improved the key impact indicators such as TB mortality and TB notification rate which decreased respectively by 66% (from 18 to 6 per 100,000) and 38% (from 113 to 72 per 100,000) from 2010 to 2019 [14,15]. However, the treatment success rate among MDR-TB patients remains low (55%) and has not reached the target of 75% for WHO European region [12,15].

TB diagnosis and TB treatment are free of charge in the Republic of Moldova. Nevertheless, TB patients may face medical costs during the pre-diagnostic stage if they are not insured for health, for high-performance procedures (magnetic resonance tomography, computed tomography etc.), for private medicine, for treatment of side effects, especially in the ambulatory stage of TB treatment, and for co-morbidities (except HIV). Non-medical financial burden is a result of inability to work during TB treatment or limited support from the family. To address these barriers in the Republic of Moldova, a system of incentives for TB patients was introduced in 2009 and universal coverage was achieved in 2011. Still, a survey conducted in 2016 showed that catastrophic costs were experienced by 26% of households at over 20% cut-off value of annual household income, and by 7% of households at over 40% cut-off value [16].

These findings are in line with evidence from other parts of the word which quantified the costs associated to TB and identified various barriers in terms of access to health care but none examined the relationship between catastrophic costs and treatment outcomes [17-23].

Taking into account the high RR/MDR-TB burden in the Republic of Moldova, suboptimal treatment outcomes and high level of catastrophic costs while accessing health care, we decided to assess the association between treatment outcomes and costs related to TB. We hypothesized that RR/MDR-TB patients with catastrophic TB-related costs were more likely to have unfavourable TB treatment outcomes.

Methods

Study design

This is a cohort study following-up the TB patients identified in a survey on TB-related costs conducted in 2016 [16]. The baseline study was a cross-sectional assessment of direct and indirect costs incurred by the households with RR/MDR-TB patients. At the end of 2018, we extracted TB treatment details and outcomes of patients enrolled in the baseline study and merged them with the data on costs.

General setting

The Republic of Moldova is situated in the South eastern Europe, bordering Romania and Ukraine. The part of the country, informally referred to as the Left Bank of the Dniester River, is not controlled by official authorities. The Right Bank of the Dniester River has a total population of about 3 million and has a population density of 90 people per square kilometre.

National TB control

The primary responsibility for TB care and control in the Republic of Moldova lies with the Ministry of Health, Labour and Social Protection. TB care services are implemented by the National Tuberculosis Program (NTP), in collaboration with other governmental entities, development partners and civil society organizations. The diagnosis and management of TB are in accordance with WHO guidelines [24]. There is a national TB case-based database in the country – Information System for Monitoring and Evaluation TB patients (SIME TB) – for TB patients' notification and their follow-up [15]. Welfare benefits are available in the Republic of Moldova for RR/MDR-TB patients, including temporary disability allowances and incentives provided to patients adhering to treatment during outpatient care. Various incentive systems have been in place over the years [25]. During the baseline study period, outpatient RR/MDR-TB patients received adherence incentives for 90% of doses taken (20 USD per month before 1st of July 2015 and 56 USD per month in period after 1st of July 2015 (Supplementary Table 1).

Study population

The baseline study (June-November 2016) included 287 adult (≥18 years) RR/MDR-TB patients who had undergone inpatient care for at least 2 months during the intensive phase (150 patients) and outpatient care for at least two months during the continuation phase (137 patients). Patients from Left Bank of the Dniester River and incarcerated patients were excluded. RR-TB patients have infections that are resistant to rifampicin (RIF), while MDR-TB patients have infections resistant to at least rifampicin (RIF) and isoniazid (INH), confirmed by culture, line probe assay, or any other drug susceptibility test.

Data sources and variables

We used two data sources: i) the baseline survey conducted in 2016 (socio-demographical characteristics of patients, quantifica-

tion of income and catastrophic costs) [16], and ii) national database - SIME TB (treatment outcomes and clinical characteristics of patients).

TB treatment outcome and catastrophic cost definitions were in line with WHO guidelines. We considered treatment cure or completion as favourable treatment outcome and failure, death or loss to follow-up as unfavourable outcome. Household income was categorized by Wealth Index, based on Multiple Indicator Cluster Surveys methodology [26]. We also included a variable based on World Bank definition of poverty, such as an income of ≤1.90 USD per capita per day [27]. Catastrophic TB-related costs were defined as ≥20% of annual income for TB-affected households. Details on costs (direct, indirect, welfare benefits) and definitions for other variables are provided in Supplementary Table 1.

Data analysis

The survey data were entered into IBM® SPSS® Statistics (version 20.0). Clinical data exported from SIME TB was merged with SPSS database by the Patient ID. Final dataset was checked for consistency with original data sources. Analysis was done using R, version 3.5.2 software (©R Foundation for Statistical Computing, 2016). We described patients' characteristics with frequencies and percentages for categorical variables and mean (and standard deviation) or median (and interquartile range) for continuous variables, as appropriate. Patients' profile was stratified by the experience of TB-related catastrophic costs and we measured differences using Chi-square tests for categorical variables and *t*-tests for continuous variables. If expected cell frequency was less than 5, Fisher's exact test was used instead of Chi-square test. *t*-test was replaced with Kruskal-Wallis test for continuous variables deviating from the nor-

Table 1. Socio-demographic, behavioural and clinical characteristics of RR/MDR-TB patients with and without TB-related catastrophic costs, Republic of Moldova, 2016.

Characteristics	Total (%)	Percent of TB-related costs from the household income		p-value°
		≤19% n (%)	≥20% n (%)	
Total	287	201	86	
Sex				0.773
Male	225 (78.4)	159 (70.7)	66 (29.3)	
Female	62 (21.6)	42 (67.7)	20 (32.3)	
Mean age (standard deviation), years	42 (12)	42 (12)	41 (12)	0.585
Age group, years				0.609
18-44	175 (61.0)	125 (71.4)	50 (28.6)	
45-78	112 (39.0)	76 (67.9)	36 (32.1)	
Type of residence				0.660
Urban	103 (35.9)	70 (68.0)	33 (32.0)	
Rural	184 (64.1)	131 (71.2)	53 (28.8)	
Household size, persons				0.368
1	56 (19.5)	35 (62.5)	21 (37.5)	
2-3	138 (48.1)	98 (71.0)	40 (29.0)	
4-9	93 (32.4)	68 (73.1)	25 (26.9)	
Household in the poverty, World Bank criterion				0.221
≤1.90 USD per person per day	146 (50.9)	97 (66.4)	49 (33.6)	
>1.90 USD per person per day	141 (49.1)	104 (73.8)	37 (26.2)	
Wealth index				0.964
Poorest	57 (19.9)	40 (70.2)	17 (29.8)	
Poor	58 (20.2)	40 (69.0)	18 (31.0)	
Middle	57 (19.9)	41 (71.9)	16 (28.1)	
Rich	58 (20.2)	42 (72.4)	16 (27.6)	
Richest	57 (19.8)	38 (66.7)	19 (33.3)	
Married or cohabitation				0.211
Yes	148 (51.6)	109 (73.6)	39 (26.4)	
No	139 (48.4)	92 (66.2)	47 (33.8)	
Education				0.897
Primary or no education	103 (35.9)	72 (69.9)	31 (30.1)	
Secondary	138 (48.1)	98 (71.0)	40 (29.0)	
Secondary professional / Higher	46 (16.0)	31 (67.4)	15 (32.6)	
Employment				0.006
Officially employed	117 (40.8)	93 (79.5)	24 (20.5)	
Unofficially employed or not employed	170 (59.2)	108 (63.5)	62 (36.5)	
Labor migration				0.128
Yes	50 (17.4)	40 (80.0)	10 (20.0)	
No	237 (82.6)	161 (67.9)	76 (32.1)	

To be continued on next page

mal distribution. Relative risk was selected as a measure of association in the analysis of treatment outcome factors. We calculated unadjusted and adjusted relative risks and their confidence intervals using log-binomial regressions. The adjusted model included factors associated with the outcome at $p<0.1$ in binary regressions and age and sex disregarding their significance as common confounders. We also consecutively measured interactions between TB-related catastrophic costs and other selected covariates, so that the effect of TB-related catastrophic costs on TB treatment outcome was allowed to vary depending on the value of other variables. Significance of interactions was measured by Wald tests. Considering that catastrophic TB-related costs could be on the causal pathway between income and treatment outcomes, we calculated proportion of patients with unfavourable outcome stratified by the experience of catastrophic costs and wealth index, and measured the association by the Mantel-Haenszel Chi-square test. Levels of significance throughout the analysis was set at 5%.

Results

A total of 287 RR/MDR-TB patients were included in the analysis. Mean age was 42 (SD 12) years; most of them were male (225/287, 78%) and lived in a rural area (184/287, 64%) (Table 1). Over half of patients (146/287, 51%) came from the households living below the poverty line as per the World Bank definition. According to the Wealth Index, 115 (40%) patients belonged to the poorest or poor households. Median percentage of TB-related costs from the household income was 15% (inter-quartile range: 9-22%).

Table 1. Continued from previous page.

Characteristics	Total (%)	Percent of TB-related costs from the household income		p-value°
		≤19% n (%)	≥20% n (%)	
Total	287	201	86	
Medical insurance status before TB*				1.000
Yes	127 (45.0)	88 (69.3)	39 (30.7)	
No	155 (55.0)	108 (69.7)	47 (30.3)	
History of imprisonment*				0.150
Yes	31 (11.2)	18 (58.1)	13 (41.9)	
No	246 (88.8)	178 (72.4)	68 (27.6)	
Excessive alcohol consumption				1.000
Yes	32 (11.1)	22 (68.8)	10 (31.2)	
No	255 (88.9)	179 (70.2)	76 (29.8)	
HIV status				0.651
Negative	262 (91.3)	182 (69.5)	80 (30.5)	
Positive	25 (8.7)	19 (76.0)	6 (24.0)	
Presence of diabetes mellitus				0.055
Yes	8 (2.8)	3 (37.5)	5 (62.5)	
No	279 (97.2)	198 (71.0)	81 (29.0)	
Type of TB case				0.294
New	189 (65.9)	128 (67.7)	61 (32.3)	
Retreatment	98 (34.1)	73 (74.5)	25 (25.5)	
Presence of side-effects during TB treatment				1.000
Yes	244 (85.0)	171 (70.1)	73 (29.9)	
No	43 (15.0)	30 (69.8)	13 (30.2)	
Perceived needs – family support*				0.813
Yes	150 (55.4)	106 (70.7)	44 (29.3)	
No	121 (44.6)	83 (68.6)	38 (31.4)	
Perceived needs – better alimentation*				0.762
Yes	210 (77.5)	145 (69.0)	65 (31.0)	
No	61 (22.5)	44 (72.1)	17 (27.9)	
Perceived treatment barriers – smoking*				0.973
Yes	117 (44.0)	82 (70.1)	35 (29.9)	
No	149 (56.0)	103 (69.1)	46 (30.9)	
Perceived treatment barriers – side effects*				0.754
Yes	127 (47.7)	90 (70.9)	37 (29.1)	
No	139 (52.3)	95 (68.3)	44 (31.7)	
Perceived concerns – treatment without effect*				1.000
Yes	115 (48.9)	78 (67.8)	37 (32.2)	
No	120 (51.1)	81 (67.5)	39 (32.5)	
Perceived concerns – spread TB to my family*				0.356
Yes	115 (48.9)	74 (64.3)	41 (35.7)	
No	120 (51.1)	85 (70.8)	35 (29.2)	

°Chi-square tests for categorical variables and t-test for age: missing data was excluded during hypothesis testing; *missing data was excluded: medical insurance status before TB (n=2); history of imprisonment (n=8); perceived needs – family support or better alimentation (n=15); perceived treatment barriers – smoking or side effects (n=20); perceived concerns – treatment without effect or spread TB to my family (n=45); TB, tuberculosis; RR/MDR-TB, rifampicin resistant or multi-drug resistant tuberculosis; HIV, human immunodeficiency viruses.

One-third of patients (86/287, 30%) experienced catastrophic TB-related costs. The proportion of patients with catastrophic costs was higher among unofficially employed or unemployed (62/170, 37%) compared to employed (24/117, 21%, p=0.006). There was no difference by other variables.

In the survey, most of the patients (210/287, 78%) emphasized unmet needs for better alimentation, and over half of the sample (150/287, 55%) needed more family support. Patients considered side effects (127/287, 48%) and smoking (117/287, 44%) as major treatment barriers. Nearly half of the study participants (115/287, 49%) had concerns that TB treatment would not be successful. Perceived needs, barriers and concerns were not associated with the experience of catastrophic TB-related costs.

Of the 287 patients, 60 (21%) had unfavourable treatment outcome, such as treatment failure (15/287, 5%), death (22/287, 8%) or loss to follow-up (23/287, 8%). In the unadjusted analysis, the experience of catastrophic TB-related costs was not associated with unfavourable outcome [relative risk (RR)=0.92, 95% confidence interval (CI): 0.54–1.49] (Table 2). Proportion of unfavourable treatment outcomes was 20% (17/86) among patients with catastrophic TB-related costs and 21% (43/201) among patients with non-catastrophic costs (p=0.756) (Table 3). In analysis adjusted for sex, age, material status, type of residence, and HIV comorbidity, the link between catastrophic TB-related costs and unfavourable outcome remained insignificant [adjusted RR (aRR)=0.90, 95% CI: 0.50–1.56]. We did not find an interaction between TB catastrophic costs and wealth. In both groups of patients with and without catastrophic costs, poor patients had higher proportion of unfavourable treatment outcome than patients from middle/rich income groups (Figure 1).

Major factors independently associated with unfavourable TB treatment outcomes were poverty by the Wealth index (aRR=2.07; 95% CI: 1.06-4.07), urban residence (aRR=1.99; 95% CI: 1.12-3.52) and positive HIV status (aRR=2.61; 95% CI: 1.31-4.89).

Discussion

This research is a continuation of the baseline study where TB-related costs were quantified [16] for the Republic of Moldova. Besides, this is the first study assessing the association between catastrophic costs and treatment outcomes in the country and in the WHO European Region. Contrary to our expectation, we found no

Table 2. Treatment outcomes of RR/MDR-TB patients with and without TB-related catastrophic costs, Republic of Moldova, 2016.

Treatment outcomes	Total n (%)	Percent of TB-related costs from the household income		Two Proportion Z-Test p-value
		≤19% n (%)	≥20% n (%)	
Total	287	201	86	
Favourable	227 (79.1)	158 (78.6)	69 (80.2)	0.879
Unfavourable	60 (20.9)	43 (21.4)	17 (19.8)	0.879
Failure	15 (5.2)	10 (5.0)	5 (5.8)	0.998
Lost to follow-up	23 (8.0)	17 (8.5)	6 (7.0)	0.852
Died	22 (7.7)	16 (8.0)	6 (7.0)	0.964

TB, tuberculosis; RR/MDR-TB, rifampicin resistant or multi-drug resistant tuberculosis.

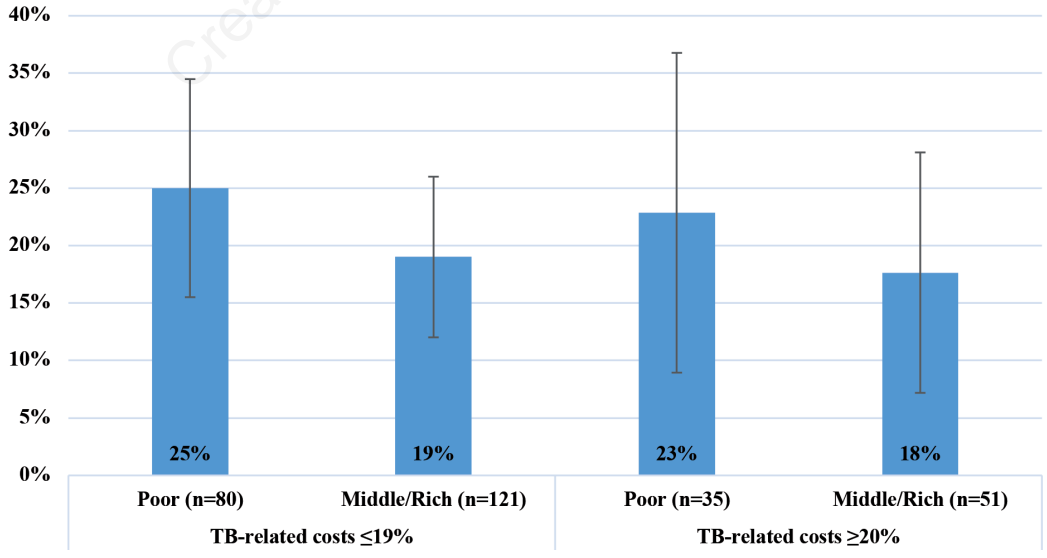

Figure 1. Proportion of unfavourable TB treatment outcomes by the Wealth index groups and experience of catastrophic TB-related costs (≥20%), Republic of Moldova, 2016. Mantel-Haenszel Chi-squared test for the stratified table: p=0.306.

association between catastrophic costs and unfavourable TB outcome in this setting. In contrast, a study from Peru identified an association between the costs and RR/MDR-TB in similar proportions of unfavourable outcomes [28].

Several factors were associated with unfavourable TB treatment outcomes in our study, and primarily poverty. A study conducted in Georgia among susceptible TB patients found that patients with lower household income were at greater risk of unfavourable TB treatment outcomes [29]. We can explain this with the fact that treatment of RR/MDR-TB is complex and prolonged over time. Thus, poverty caused by health-related payments could rise sharply in poorer households. Far more, temporary disability due to TB, as well as TB-related costs experienced in accessing diagnostic and treatment services, worsen their financial situation, affecting the well-being of patients and households, which are actually the main factors of poverty and both can lead to adverse outcomes of TB. Another explanation can be that TB patients who come from the poorest households and have a low welfare level are not able to face health expenditure, for diagnosis as well as for treatment. In the Republic of Moldova usually, people from poor households do not seek medical care in the same way as the wealthier [30]. Hereby, this can lead to delayed diagnosis and TB treatment, and, of course, to non-adherence with the long-term treatment regimen for RR/MDR-TB. Besides, people with low welfare level have less satisfactory living conditions compared to those who have higher welfare level. At the same

Table 3. Associated factors contributing to unfavourable outcomes among RR/MDR-TB patients who experienced TB-related catastrophic costs, Republic of Moldova, 2016.

Characteristics	TB treatment outcome		RR [95% CI]	Adjusted RR [95% CI]
	Favourable n (%)	Unfavourable n (%)		
Total	227	60		
Sex				
Male	175 (77.8)	50 (22.2)	1.38 [0.78;2.74]	1.57 [0.82;3.31]
Female	52 (83.9)	10 (16.1)	ref.	–
Age group, years				
18-44	135 (77.1)	40 (22.9)	ref.	ref.
45-78	92 (82.1)	20 (17.9)	0.78 [0.47;1.25]	0.88 [0.50;1.50]
Percent of TB-related costs from the household income				
≤19%	158 (78.6)	43 (21.4)	ref.	ref.
≥20%	69 (80.2)	17 (19.8)	0.92 [0.54;1.49]	0.90 [0.50;1.56]
Type of residence				
Urban	75 (72.8)	28 (27.2)	1.56 [0.99;2.44]	1.99 [1.12;3.52]
Rural	152 (82.6)	32 (17.4)	ref.	ref.
Household size, persons				
1	41 (73.2)	15 (26.8)	1.56 [0.83;2.92]	–
2-3	109 (79.0)	29 (21.0)	1.22 [0.71;2.18]	–
4-9	77 (82.8)	16 (17.2)	ref.	–
Household in the poverty by the World Bank criterion				
≤1.90 USD per person per day	115 (78.8)	31 (21.2)	1.03 [0.66;1.63]	–
>1.90 USD per person per day	112 (79.4)	29 (20.6)	ref.	–
Wealth index				
Poor	87 (75.7)	28 (24.3)	1.47 [0.88;2.53]	2.07 [1.06;4.07]
Middle	44 (77.2)	13 (22.8)	1.38 [0.71;2.57]	1.72 [0.80;3.56]
Rich	96 (83.5)	19 (16.5)	ref.	–
Married or cohabitation				
Yes	126 (85.1)	22 (14.9)	0.54 [0.33;0.86]	0.72 [0.40;1.24]
No	101 (72.7)	38 (27.3)	ref.	ref.
Education				
Primary or no education	80 (77.7)	23 (22.3)	2.05 [0.91;5.82]	–
Secondary	106 (76.8)	32 (23.2)	2.13 [0.98;5.96]	–
Secondary professional/Higher	41 (89.1)	5 (10.9)	ref.	–
Employment				
Officially employed	94 (80.3)	23 (19.7)	ref.	–
Unofficially employed or not employed	133 (78.2)	37 (21.8)	1.11 [0.70;1.79]	–
Labor migration				
Yes	39 (78.0)	11 (22.0)	1.06 [0.56;1.81]	–
No	188 (79.3)	49 (20.7)	ref.	–
Medical insurance status before TB°				
Yes	106 (83.5)	21 (16.5)	0.71 [0.43;1.14]	–
No	119 (76.8)	36 (23.2)	ref.	–

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time, the causal pathway between poverty and unfavourable TB treatment outcomes is complex and involved multiple additional factors. Some studies determined that the accumulated psychosocial stress caused by sickness may be one plausible biological mechanism explaining the increased odds of poor TB treatment outcome among patients with low socioeconomic status [31,32].

Living in an urban area was identified as a risk factor for an unfavourable outcome such as loss to follow-up for the RR/MDR-TB patients in the study conducted in the Republic of Moldova in 2019 [33]. In our study living in an urban area was independently associated with unfavourable outcome. The poverty assessment reports [34,35] highlight on continuing differences in the standard of living between urban and rural populations, with the level of poverty in rural areas being higher than in urban areas. On the other hand, the rural population have access to non-financial resources (own livestock and garden) in comparison with the urban population and may be less dependent on wages [34]. One of the additional explanations can be that during the years, community services (information, education, peer support, adherence programs) has been more concentrated in rural areas considering that rural area has less access to medical services [36].

As expected, patients with TB/HIV coinfection to have higher rates of unfavourable TB outcomes. A survey conducted on financial burden of HIV and TB among patients in Ethiopia [37] revealed that TB patients face TB-related costs during the treatment and after treatment completion, TB patients are less likely to face additional costs while people living with HIV face costs over their lifetime because HIV infection is a chronic disease that needs lifelong treatment. This fact could influence TB treatment results as well. Usually, HIV-positive patients are more likely than HIV-

Table 3. Continued from previous page.

Characteristics	Total	TB treatment outcome: Favourable n (%)	TB treatment outcome: Unfavourable n (%)	RR [95% CI]	Adjusted RR [95% CI]
		227	60		
History of imprisonment°					
Yes		22 (71.0)	9 (29.0)	1.46 [0.73;2.51]	–
No		197 (80.1)	49 (19.9)	ref.	–
Excessive alcohol consumption					
Yes		23 (71.9)	9 (28.1)	1.41 [0.71;2.42]	–
No		204 (80.0)	51 (20.0)	ref.	–
HIV status					
Negative		215 (82.1)	47 (17.9)	ref.	ref.
Positive		12 (48.0)	13 (52.0)	2.90 [1.74;4.42]	2.61 [1.31;4.89]
Presence of diabetes mellitus					
Yes		6 (75.0)	2 (25.0)	1.20 [0.22;2.97]	–
No		221 (79.2)	58 (20.8)	ref.	–
Type of TB case					
New		152 (80.4)	37 (19.6)	ref.	–
Retreatment		75 (76.5)	23 (23.5)	1.20 [0.74;1.88]	–
Presence of side-effects during TB treatment					
Yes		193 (79.1)	51 (20.9)	1.00 [0.57;2.03]	–
No		34 (79.1)	9 (20.9)	ref.	–
Perceived needs – family support°					
Yes		121 (80.7)	29 (19.3)	0.78 [0.49;1.23]	–
No		91 (75.2)	30 (24.8)	ref.	–
Perceived needs – better alimentation°					
Yes		163 (77.6)	47 (22.4)	1.14 [0.67;2.12]	–
No		49 (80.3)	12 (19.7)	ref.	–
Perceived treatment barriers – smoking°					
Yes		87 (74.4)	30 (25.6)	1.32 [0.84;2.08]	–
No		120 (80.5)	29 (19.5)	ref.	–
Perceived treatment barriers – side effects°					
Yes		99 (78.0)	28 (22.0)	0.99 [0.63;1.55]	–
No		108 (77.7)	31 (22.3)	ref.	–
Perceived concerns – treatment without effect°					
Yes		84 (73.0)	31 (27.0)	1.47 [0.91;2.42]	–
No		98 (81.7)	22 (18.3)	ref.	–
Perceived concerns – spread TB to my family°					
Yes		95 (82.6)	20 (17.4)	0.63 [0.38;1.02]	–
No		87 (72.5)	33 (27.5)	ref.	–

°Missing data was excluded: medical insurance status before TB (n=2); history of imprisonment (n=8); perceived needs, family support or better alimentation (n=15); perceived treatment barriers, smoking or side effects (n=20); perceived concerns, treatment without effect or spread TB to my family (n=45); HIV, human immunodeficiency viruses; RR, relative risk; ref., reference category; CI, confidence interval; TB, tuberculosis; RR/MDR, rifampicin resistant or multi-drug resistant tuberculosis. Descriptive statistics were summarized as n (%).

negative patients to have extrapulmonary TB or smear-negative pulmonary TB [38]. This may lead to a delay in TB diagnosis and treatment initiation, increasing the chance of unfavourable outcomes and the patient may face additional costs during in pre-treatment period. Delayed TB diagnosis and later initiation of RR/MDR-TB treatment can also affect the outcome of treatment [33]. TB and HIV drugs must be supplemented with higher food intake [39,40]. It has been suggested that HIV positive TB patients are more likely to become malnourished due to constant sickness [41], which can be associated to unfavourable treatment results. Another reason for unfavourable outcomes among HIV-associated TB patients could be poor uptake of anti-retroviral therapy and death due to HIV-related causes [42].

There are some limitations in this study related to the parent study methodology: first the use of self-reported data on respondent's income and expenditures, then not taking into account the time spent (for medical consultations, investigations, or to pick up medicines from the treatment site) and the study population. The criteria for enrolment in the baseline study (RR/MDR-TB patients who were in inpatient or outpatient TB care for at least for 2 months for intensive and continuation phases, respectively) led to an overestimation of favourable outcomes, given one third of deaths among TB patients occur within the first two months of treatment (27%). In our study the proportion with successful outcome was higher (79%) than the treatment success rate of 60% reported by NTP for Right Bank of the Dniester River (without penitentiaries) for 2016 cohort.

Conclusions

In the Republic of Moldova, we failed to find an association between catastrophic costs and treatment outcomes of RR/MDR-TB patients. However, our study found that patients from poor households were twice more likely to experience unfavourable TB treatment outcomes regardless of whether they experienced TB catastrophic costs or not. Also, TB/HIV patients and urban residents were identified as the most vulnerable groups with higher risk of unfavourable treatment outcome. The patient-centred care approach and expanded social and financial risk protection measures are needed to minimise the high patient cost of TB care and improve treatment outcomes in special groups such as coming from poverty households, living in urban area, and having TB/HIV coinfection.

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