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ORIGINAL ARTICLE

The impact of the stratification by degree of clinical severity and abandonment risk of tuberculosis treatment

Pedro Daibert de Navarro[1,2], João Paulo Amaral Haddad[3], Juliana Veiga Costa Rabelo[1], Claudia Hermínia de Lima e Silva[4], Isabela Neves de Almeida[2,5], Wânia da Silva Carvalho[6], Silvana Spíndola de Miranda[2]

1. Secretaria Municipal de Saúde, Prefeitura de Belo Horizonte, Belo Horizonte (MG) Brasil.
2. Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.
3. Departamento de Medicina Veterinária Preventiva, Escola de Veterinária, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.
4. Secretaria de Estado de Saúde de Minas Gerais, Belo Horizonte (MG) Brasil.
5. Faculdade de Farmácia, Universidade Federal de Ouro Preto, Ouro Preto (MG) Brasil.
6. Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.

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ABSTRACT

Objective: Evaluate the impact of the instrument of the "Stratification by Degree of Clinical Severity and Abandonment Risk of Tuberculosis Treatment" (SRTB) on the tuberculosis outcome. **Methods:** This study was a pragmatic clinical trial involving patients with a confirmed diagnosis of tuberculosis treated at one of the 152 primary health care units in the city of Belo Horizonte, Brazil, between May of 2016 and April of 2017. Cluster areas for tuberculosis were identified, and the units and their respective patients were divided into intervention (use of SRTB) and nonintervention groups. **Results:** The total sample comprised 432 participants, 223 and 209 of whom being allocated to the nonintervention and intervention groups, respectively. The risk of treatment abandonment in the nonintervention group was significantly higher than was that in the intervention group (OR = 15.010; $p < 0.001$), regardless of the number of risk factors identified. Kaplan-Meier curves showed a hazard ratio of 0.0753 ($p < 0.001$). **Conclusions:** The SRTB instrument was effective in reducing abandonment of tuberculosis treatment, regardless of the number of risk factors for that. This instrument is rapid and easy to use, and can be adapted to different realities. Its application showed characteristics predisposing to a non-adherence to the treatment and established bases to mitigate its impact.

Keywords: Tuberculosis; Patient compliance; Risk factors; Treatment adherence.

INTRODUCTION

In recent years, the number of tuberculosis cases has decreased globally. However, this reduction has been insufficient to reach the goals of the WHO End TB Strategy worldwide.[1] These goals will only be achieved if diagnosis, treatment, and prevention are focused on the patient and in their needs in a context of universal health care coverage.[1,2]

Tuberculosis remains one of the major 10 causes of death in the world, affecting 1.3 million people; there were approximately 10 million patients with tuberculosis in 2018.[2] Treatment success rates remain low, reinforcing the need for health care models that facilitate the adequate monitoring of people with tuberculosis.[1,2]

Brazil is one of the 20 countries with the highest burden of tuberculosis, with an estimated 91,000 cases and 7,000 annual deaths.[2] Belo Horizonte (BH) is the capital of the second most populous state in the country, with cure rates (72.5%) and treatment abandonment (11.8%) outside the recommended international parameters of at least 85% and at most 5%, respectively.[3]

Despite the high effectiveness of the recommended therapeutic procedures for the treatment and prevention of tuberculosis,[4,5] low adherence to the treatment is considered the main challenge for the global control of the disease.[6-9] The inadequate treatment interruption can cause consequences individual and collectively, such as death, sequelae, appearance of drug-resistant *Mycobacterium tuberculosis*, increased costs for health systems, in addition providing a place for the permanence of the source of infection in the community.[4,5,7,9-11]

International agencies have been advocating for the Directly Observed Treatment (DOT) since 1994 to strengthen treatment adherence. Its premise is to guarantee the visualization of the medication taken by the patient and to strengthen their bond with the health care team.[2,4-6] Various studies have shown that DOT alone does not provide greater treatment adherence and have pointed out the need for other measures.[5,7,8,10,12-14]

Strengthening adherence interventions can have a greater impact on the health of the population, when compared with any other improvements in

Correspondence to:
Silvana Spíndola de Miranda. Avenida Alfredo Balena, 190, Santa Efigênia, CEP 30130-100, Belo Horizonte, MG, Brasil.
Tel.: 55 31 3409-9905. E-mail: silvanaspindola@gmail.com
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medical treatment.[15,16] Low adherence is a primary determinant of treatment effectiveness, because it reduces the expected clinical benefits. It is believed that its magnitude and effect are even greater, especially in developing countries, given the scarcity of resources and the inequalities in access to the health care system.[6,7] The ideal care organization requires coordination of patient needs and the identification of possible barriers to treatment.[9-11,17,18]

Health systems such as Primary Health Care (PHC) consider this level of care to be the preferred access to the care network. PHC uses technologies of high complexity and low technological density that should solve health problems of greater frequency and relevance in its territory,[19] including tuberculosis.[4-7,9,10,20]

Proper management of chronic health conditions imposes the need to stratify cases so that patients receive differentiated care, which is an attribute of a rational and resolving health care system. The population stratification process is central to health care models because it allows the identification of people and groups with similar health needs that must be cared by specific technologies and resources, based on different approach of people and groups that present similar risks.[21,22] Usually, without risk stratification, the services supply follows demand criteria, generating unnecessary interventions, depriving differentiated attention according to people's needs.[16-18]

Tuberculosis is considered a chronic disease, and it is extremely important to recognize the social determinants involved in the process. Patients need an individualized approach, as the frequency of associated diseases is high, as well as other vulnerabilities. Many factors are associated with adherence to the TB treatment, including patient characteristics, the relationship between the health care provider and the patient, the prolonged treatment regime and the organization of health systems.[4-10]

This study aims to assess the impact of the instrument of the "Stratification by Degree of Clinical Severity and Abandonment Risk of Tuberculosis Treatment" (SRTB) on the tuberculosis outcome.

METHODS

This was a pragmatic clinical trial involving patients with a confirmed diagnosis of tuberculosis who were treated at one of the 152 PHC units in the city of Belo Horizonte, Brazil, between May of 2016 and April of 2017. All of the PHC units in the city were divided into two groups, taking into consideration the administrative organization of the health care network, the presence of cluster areas for tuberculosis in the territory, and social vulnerability indexes, in order to avoid selection bias in the sample.

We used a georeferencing software (https://www.mapdevelopers.com/batch_geocode_tool.php) and the addresses of the participants with the objective of determining the geographic location of 70-90% of the cases between 2012 and 2015 in order to define the existence of possible clusters. Maps were created for each of those years, as was one for the four years as a whole, using the TerraView software (www.dpi.inpe.br/terraview). In order to assess the presence of clusters we used the SaTScan software (https://www.satscan.org/download_satscan.html), which was adopted to search for high rates with the purely spatial discrete Poisson scan model.

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (Protocol no. 43320015.4.0000.5149), and all participants agreed to participate and signed a free an informed consent form.

The SRTB instrument (Chart 1) was developed considering international guidelines for the management of tuberculosis.[4,5,10,15,20,23] The instrument is structured into two parts: the degree of clinical risk (low/medium/high/very high), according to disease presentation, presence of comorbidities, bacterial resistance and clinical complications, with the premise of referring the patient to the ideal level of health care (PHC, Secondary Reference - medical specialties, Tertiary Reference – emergency hospitals/health units); and the risk degree of abandoning the treatment - low/high - in order to strengthen compliance measures linking it to the PHC unit).

All of the patients diagnosed with tuberculosis who were 18 years or older and agreed to participate in the study were interviewed by trained researchers and had their home address linked to the respective PHC unit. The PHC units were divided into two groups: nonintervention and intervention. In both, a questionnaire was applied, validated for research, which contains sociodemographic characteristics (sex, race/color self declaration, education, marital status and income), individual characteristics (homeless person, freedom deprivation), clinical characteristics (signs/symptoms, comorbidities: people living with the Human Immunodeficiency Virus (HIV/AIDS), alcoholism, smoking and use of illicit drugs), characteristics of treatment (history of previous treatment for TB, adverse reaction to drugs, DOT, report of symptoms improvement after the second month of treatment) and operational characteristics of the health system (epidemiological surveillance and case monitoring). The SRTB instrument was used only in the intervention group, and the patients in this group were monitored regarding the implementation of the recommendations in the instrument. Treatment outcomes were as follows: cure (considering clinical, radiological, and/or bacteriological results), treatment abandonment (i.e., not taking the medication for a period longer than 30 consecutive days), and death.

Descriptive analyses were performed with the Stata statistical software package, version 14 (StataCorp LP, College Station, TX, USA), according to the selected characteristics stratified by group, by means of frequency of distribution and measures of central tendency and dispersion for the characteristics studied.

Chart 1. Stratification by degree of clinical severity and abandonment risk of tuberculosis treatment.

STRATIFICATION BY DEGREE OF CLINICAL SEVERITY AND ABANDONMENT RISK OF TUBERCULOSIS TREATMENT			
1st STEP RISK OF ABANDONMENT OF TREATMENT	I	**LOW RISK** TB without identified risk of abandonment	**DOT** (preferably at the health unit or other place to be agreed). **Guidance regarding the disease and drug treatment.** **Involvement of the multidisciplinary team.**
	II	**HIGH RISK** TB with identified risk of abandonment; (1) Social vulnerability; (2) Abusive / harmful use of alcohol and other drugs; (3) History of previous TB treatment abandonment; (4) Homeless situation; (5) HIV infection; (6) Freedom deprivation.	**DOT** (preferably at the health unit or other place to be agreed). **Guidance regarding the disease and drug treatment.** **Involvement of the multidisciplinary team.** (1) Social service; (2) Mental Health Services; (3) Identification and intervention in previous abandonment factors; (4) Social Work and Mental Health; (5) Teams from the Secondary Reference Centers for HIV / AIDS; (6) Immediately report to the epidemiological surveillance service, informing the probable prison unit.
2nd STEP CLINICAL RISK	A	**LOW RISK** - Pulmonary, ganglionic and/or pleural TB	**Primary Health Care:** - Basic health unit
	B	**MEDIUM RISK** - Confirmed extrapulmonary TB (except, ganglion and pleural); - TB with severe comorbidities; - TB with clinical complications and/or major adverse effects to treatment; - Treatment failure; - TB resistant to a medication.	**Secondary Reference Clinic:** - Children: Reference center for pediatric TB; - Adults: Reference center in TB in adults; - HIV / AIDS: Reference center in TB-HIV - infectious diseases.
	C	**HIGH RISK** - TB + clinical/surgical criteria for hospitalization - MDR or XDR - Confirmed tuberculous meningoencephalitis	**Tertiary Reference Clinic or hospitalization:** - Children: Reference hospital for pediatric TB; - Adults: Reference hospital for TB in adults; - HIV / AIDS: Reference hospital in TB-HIV - infectious diseases
	D	**VERY HIGH RISK** - Suspected tuberculous meningitis; - TB with signs of severity: respiratory failure (hypoxemia or tachydyspnea), circulatory failure (oliguria or hypotension) and severe change in mental status; - TB with complications that require immediate assistance intervention	**Emergency Health Unit**

DOT: directly observed treatment; TB: tuberculosis; MDR: multidrug resistant; and XDR: extensively drug resistant.

The magnitude of the association between the explanatory variables and the "treatment abandonment" event was estimated using odds ratio and its corresponding 95% CI for each variable, obtained by logistic regression. In the univariate analysis, variables with $p \leq 0.20$ in the Wald test were manually selected for the multivariate analysis. The level of significance required for inclusion in the final model was $p < 0.05$. The likelihood ratio test was used in order to compare the models. The goodness of fit of the final models was assessed by the Hosmer-Lemeshow test. Survival analysis was performed, according to Cox's semi parametric model, to estimate the occurrence of treatment abandonment between groups.

RESULTS

During the study period, 623 tuberculosis patients were identified, of whom 476 were interviewed. Of those, 44 patients were excluded from the study: a change in the diagnosis (n = 16), place of residence other than Belo Horizonte (n = 6); and a lack of follow up at the PHC unit (n = 22). Therefore, the study sample comprised 432 participants, who were divided into the nonintervention (n = 223) and intervention (n = 209) groups.

After the similarity test between the groups and the univariate logistic regression, no significant differences were found, unless for income, presence

of comorbidities and adverse reaction, demonstrating the homogeneity of the sample.

The descriptive analysis (Table 1) revealed a predominance of male individuals, and approximately half of the total sample had a low level of education (≤ 8 years of schooling). In addition, 319 patients (73.8%) had comorbidities, 123 (28.5%) were alcoholics, 170 (39.4%) were current smokers, 69 (16.0%) made use of illicit drugs, and 203 (47.0%) presented with adverse reactions to medications in the second month of treatment (Table 1).

In the nonintervention group, in the univariate analysis, several characteristics were associated with treatment abandonment: non-white color, single marital status, low income (criteria used by the Brazilian Federal Government which considers families that have a monthly income per capita of up to half a minimum wage or a total family income up to three minimum wages), homeless person, presence of comorbidities, alcoholism, smoking, use of illicit drugs, retreatment by re-entry after abandonment, presence of one or more risk factors identified (low income, homeless person, retreatment for re-entry after abandonment, alcoholism and/or use of illicit drugs). In the intervention group, none of these characteristics were associated with treatment abandonment.

The variables sex, education, DOT performance, presence of adverse reaction to medications and improvement of symptoms, assessed in the second month of treatment, as well as HIV/AIDS co-infection, did not show an association in both groups.

In the multivariate analysis, we adjusted the variables related to treatment abandonment, producing two models (Table 2): one taking into consideration the number of risk factors identified; and one using the following variables: low income, retreatment, use of illicit drugs and/or alcohol, and homeless people. In both models, adherence to DOT and the use of the SRTB instrument reduced the risk of treatment abandonment.

The impact of income on tuberculosis treatment was evident (Figure 1). Low income was associated with a greater chance of dropping out. The abandonment risk decreases when the income increases, showing an inverse relation. The income effect under the risk of abandonment practically disappears for people with an income above R$ 5,000 per month.

Treatment abandonment was more likely to occur in the nonintervention group, when compared with the intervention group (OR = 15.010; p < 0.001). The application of the SRTB instrument reduced the impact of all characteristics associated with treatment abandonment.

The number of risk factors directly increased the "abandonment" outcome in the nonintervention group. However, this outcome was not significant in the intervention group, regardless of the number of risk factors identified (Figure 2).

The Kaplan-Meier curves followed by the log-rank test (Figure 3) were statistically different (p < 0.001), showing that the intervention was effective in reducing treatment abandonment in the intervention group. The Cox proportional hazards model showed an association between the exposure factor, whether or not it was part of the intervention group (hazard ratio = 0.0753).

DISCUSSION

Treatment success for patients with tuberculosis at a high risk of abandonment is exceptionally difficult, requiring intense commitment and innovative approaches. The use of the SRTB instrument significantly reduced the risk of treatment abandonment (OR = 15.010; p < 0.001), even in the presence of one or more risk factors (OR:4.376 p=0.001 to 12.240 p<0.001). Studies that promoted a set of treatment adherence interventions reported lower treatment abandonment rates.[6-12,14,15] The greater adherence of patients to drug treatment can be achieved by combining interventions aimed at the identified risk factors. Even considering that these measures have a cost, it is still less than the consequences of the abandonment.[2,6,7,14,24] Due to the set of interventions performed, a reduction in abandonment was observed in intervention group (with SRTB it was 92.5% more slow at any time of follow-up - HR:0.0753) when compared to nonintervention group, showing a strong association between the occurrence of abandonment and the proposed strategy by SRTB.

Abandonment among non-white patients may be associated with social issues evidenced in the present study, because low income is more common in that population in Brazil.[19] Therefore, poverty is one of the main reasons for patients not to understand the benefit of clinical treatment. Other studies[2,20,25-27] corroborate the connection between social capital and health: as the family income increased, treatment abandonment significantly decreased. Poor people generally have less access to health care services or have access to health care facilities with fewer resources. In addition, that population is exposed to social determinants of tuberculosis, which indicates the need for further government actions in order to promote equity.[2,20,25-27]

The present study showed that DOT reduced the risk of treatment abandonment when associated with other measures, but only in the intervention group. The effectiveness of DOT, a globally recommended strategy to strengthen treatment adherence, is questioned in some studies,[26,27] being especially directed at vulnerable groups.[28,29] Other authors have demonstrated that DOT reduced dropout, especially when other support measures are involved, such as educational and psychological support programs.[14,30]

It is evident that good health care services are necessary to ensure that patients benefit from the treatment, but this alone is insufficient; the autonomy

Table 1. Characteristics of the sample of patients diagnosed with tuberculosis in the nonintervention and intervention groups, Belo Horizonte, Brazil (N = 432).[a]

Characteristic	Group		p*
	Nonintervention (n = 223)	Intervention (n = 209)	
Sociodemographic			
Sex			
Male	162 (72.65)	141 (67.46)	0.240
Female	61 (27.35)	68 (32.54)	
Self-reported race/skin color			
White	47 (21.08)	39 (18.66)	0.530
Non-White	176 (78.92)	170 (81.34)	
Level of education			
> 8 years of schooling	96 (43.05)	92 (44.02)	0.847
≤ 8 years of schooling	127 (56.95)	117 (55.98)	
Marital status			
Not single	109 (48.88)	120 (57.42)	0.076
Single	114 (51.12)	89 (42.58)	
Income[b]			
Not low	110 (49.33)	125 (59.81)	0.033
Low	113 (50.67)	84 (40.19)	
Clinical			
Comorbidities			
No	71 (31.84)	42 (20.10)	0.006
Yes	152 (68.16)	167 (79.90)	
HIV			
No	206 (92.38)	190 (90.91)	0.581
Yes	17 (07.62)	19 (09.09)	
Alcoholism			
No	155 (69.51)	154 (73.68)	0.336
Yes	68 (30.49)	55 (26.32)	
Smoking status			
Never smoker	100 (44.84)	95 (45.45)	0.318
Former smoker	40 (17.94)	27 (12.92)	
Smoker	83 (37.22)	87 (41.63)	
Illicit drug use			
No	188 (84.68)	173 (83.17)	0.670
Yes	34 (15.32)	35 (16.83)	
Monitoring			
Why did you seek a health care unit?			
Physician or family referral	87 (39.01)	96 (45.93)	0.146
Self-referral	136 (60.99)	113 (54.07)	
Adverse reactions to medications in the 2nd month			
No	151 (69.59)	71 (34.13)	< 0.001
Yes	66 (30.41)	137 (65.87)	
Treatment outcome			
Cure	183 (82.06)	206 (98.56)	> 0.001
Abandonment	40 (17.94)	3 (1.44)	

[a]Values expressed as n (%). [b]In accordance with the Brazilian Federal Government criteria, families that have a monthly income per capita of up to half the minimum wage or a total family income up to three minimum wages are considered as having low income (minimum wage: R$1,045 [US$209 on 2020/01/07]). *Qui-square test.

of patients, who choose whether they will take their medication or not, should be considered. This point of view emphasizes that a health care system should be targeted to the needs of patients and not only to mechanisms for monitoring behavior, such as DOT; usually, patients with chronic diseases have difficulty in adhering to the recommended protocols.[19,21]

Other characteristics showed a strong association with treatment abandonment in the nonintervention group: people on the street,[17,27] presence of comorbidities,[4,20]

alcohol abuse and/or illicit drugs use,[14,17] smoking,[14,26] and re-entry into treatment.[20,26] Thus, the identification of these characteristics provides more precise strategies for reducing initial risks with the use of the SRTB instrument.

The interaction between people on the street and abusive use of alcohol and/or illicit drugs was evidenced, revealing a ten times greater chance of abandoning treatment (OR:10.769 p=0.002); being five times greater than the presence of only the variable abuse of alcohol and/or illicit drugs. Homeless people are recognized as one of the groups with the highest prediction of abandonment, especially when the use of associated licit and/or illicit drugs are identified.[27,31] The SRTB mitigated the impact of all these interactions by targeting strategic interventions and organized in order to promote greater adherence to treatment, such as social support and care with a multidisciplinary team.

Several other factors are associated with non-adherence to TB treatment, such as ignorance about the disease and its treatment, stigma, absence of a psychosocial approach; interventions are recommended to address these determinants in the routine of services.[4,5,14,27] Another predisposing cause of treatment abandonment is the improvement of

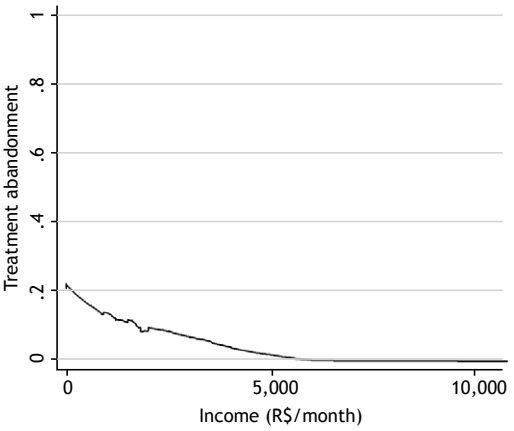

Figure 1. Impact of income on the abandonment of tuberculosis treatment. Reference: R$1.00 was equivalent to US$0.20 on Jan 7, 2020.

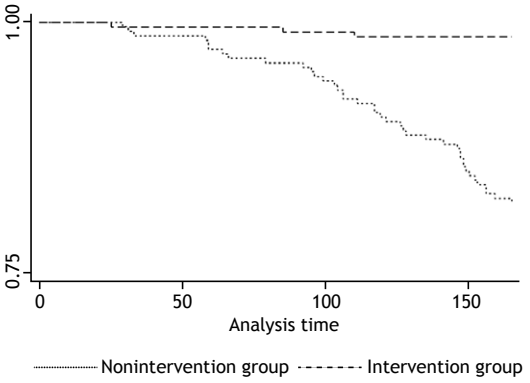

Figure 3. Kaplan-Meier curves comparing treatment abandonment between the nonintervention and intervention groups.

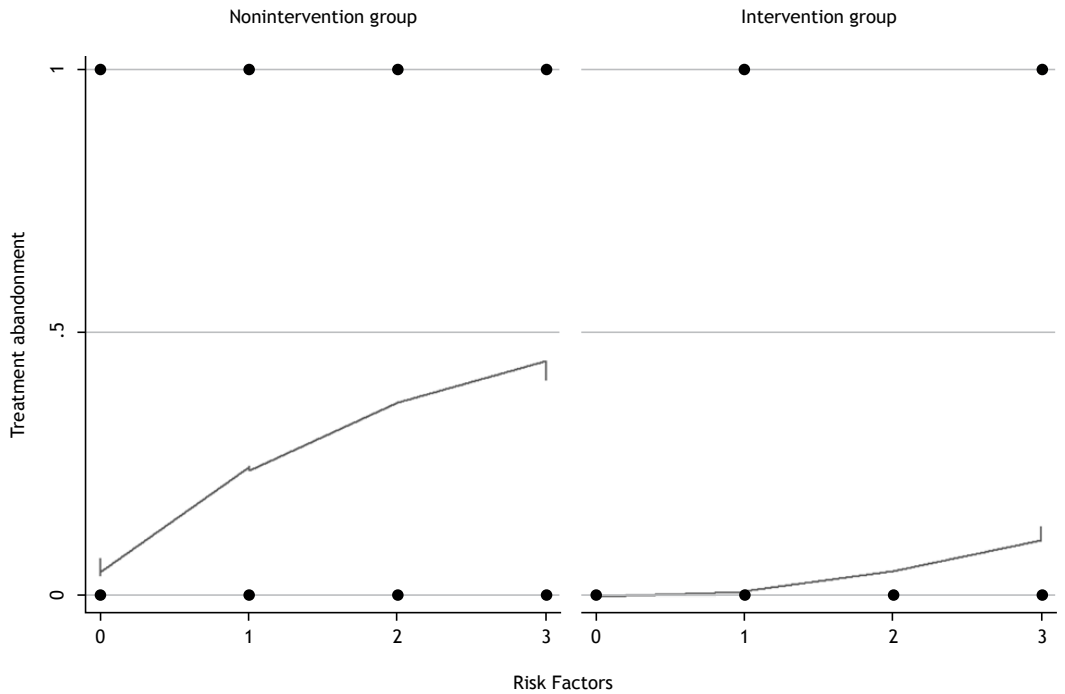

Figure 2. Risk of treatment abandonment in the nonintervention and intervention groups, by number of risk factors for treatment abandonment.

Table 2. Multiple analysis of the characteristics related to the treatment dropout among the groups studied, Belo Horizonte, Minas Gerais, Brazil.§

Description	Number of risk factors		According to risk factors	
	P-value	OR (95% CI)	P-value	OR (95% CI)
Group				
A (non-intervention)		1 (reference)		1 (reference)
B (intervention)	< 0,001	0,07 (0,02 - 0,23)	< 0,001	0,07 (0,90 - 0,22)
Self-reported race / skin color				
White		1 (reference)		1 (reference)
Not white	0,016	6,52 (1,41 - 30,13)	0,068	4,07 (0,90 - 19,40)
Directly Observed Treatment				
Not		1 (reference)		1 (reference)
Yes	0,025	0,42 (0,20 - 0,90)	0,009	0,34 (0,15 - 0,77)
Number of risk factors				
None		1 (reference)		---
1 (one)	0,001	4,38 (1,78 - 10,75)		---
2 (two)	< 0,001	11,80 (3,80 - 36,79)		---
≥ 3 (three or more)	< 0,001	12,24 (3,84 - 39,02)		---
According to risk factors				
Interaction: use of illicit drugs and/or alcohol and homeless				
does not use illicit drugs and/or alcohol and is not homeless		---		1 (reference)
does not use illicit drugs and/or alcohol and is homeless		---		***
uses illicit drugs and/or alcohol and is not homeless		---	0,015	2,71 (1,22 - 6,05)
uses illicit drugs and/or alcohol and is homeless		---	0,002	10,77 (2,32 - 50,04)
Income				
Not low		---		1 (reference)
Low		---	0,020	0,99 (0,98 - 0,99)
Retreatment for re-entry after abandonment				
Not		---		1 (reference)
Yes		---	0,018	3,08 (1,21 - 7,80)

(§) Two final models have been proposed. (***) In the study, none of the patients were on the street without using illicit drugs and/or alcohol, which is why it is not possible to estimate the OR of this class.

symptoms in the second month of treatment,[31] but this factor showed no associations with treatment abandonment in the present study, corroborating the findings of other authors.[32] In addition, no associations were found related to adverse reactions to medications, sex, or level of education.[17,33,34]

Care models that integrate the different attention levels are recommended to achieve better results in the treatment of TB.[2,19-21] This disease is managed on an outpatient basis, except for cases that require greater propaedeutic support and therapeutic.[4,5,11,14,20,35] Patients monitored at other levels of care have lower adherence to treatment,[32,35] in addition to the poor-quality health care services that enhance abandonment.[14,27,34]

The limitations of the present study were the impossibility of interviewing patients with severe tuberculosis who died prior to the interview and the impossibility of interviewing those coinfected with HIV/AIDS, whose follow-up was carried out in secondary/tertiary referral centers.

In conclusion, the SRTB instrument was effective in reducing abandonment of tuberculosis treatment, even in the presence of one or more risk factors. The implementation of the SRTB instrument and the monitoring of the process of the explained recommendations and its application not only showed characteristics predisposing to non-adherence to treatment, but also established bases to mitigate its impact. The SRTB instrument organizes the levels of care by stratifying the cases, as well as demonstrating the need for a set of person-centered interventions to achieve greater treatment success. It is an instrument of easy and quick applicability that can be adapted to different realities, considering the potential of the local health network and available resources

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AUTHOR CONTRIBUTIONS

PDN: main author, study design and execution; analysis of results; scientific writing of the manuscript; and approval of the final version. JPAH: statistical analysis; scientific review of the article; and approval of the final version. JVCR: study execution; analysis of results; scientific writing of the manuscript; and approval of the final version. CHLS: study execution; scientific review of the article; and approval of the final version. INA: study execution; analysis of results; scientific review of the article; and approval of the final version. WSC: supervision; manuscript correction; scientific review of the article; and approval of the final version. SSM: study design; coordination; manuscript correction; scientific review of the article; and approval of the final version.

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