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Smoking and pulmonary tuberculosis treatment failure: a case-control study

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ABSTRACT

Objective: To determine the association between smoking and pulmonary tuberculosis treatment failure. **Methods:** This was a case-control study conducted at the Brazilian Institute for Tuberculosis Research in the city of Salvador, Brazil, between 2007 and 2015. We evaluated 284 patients treated for pulmonary tuberculosis, comparing 50 cases of treatment failure with 234 control cases in which the final outcome was cure. **Results:** Treatment failure was attributed to smoking and age rather than to gender, income, level of education, alcohol consumption, or marital status. Therefore, even after adjustment for age, the risk of treatment failure was 2.1 times (95% CI: 1.1-4.1) higher among the patients with a history of smoking. In addition, being over 50 years of age was found to increase the likelihood of treatment failure by 2.8 times (95% CI: 1.4-6.0). **Conclusions:** Smoking and aging are both associated with pulmonary tuberculosis treatment failure. Therefore, as part of a tuberculosis control program, health personnel should be prepared to offer strategies to promote smoking cessation and should be more careful with older patients.

Keywords: Tobacco use disorder; Tuberculosis; Treatment failure.

INTRODUCTION

Smoking and tuberculosis are public health problems worldwide.[1-3] Tuberculosis is considered one of fastest growing infectious diseases. According to data from the World Health Organization (WHO), there were 6.3 million reported new cases of tuberculosis, as well as 1.3 million reported deaths from the disease, in 2016.[3] Smoking is directly responsible for 6 million deaths worldwide each year[1] and is a risk factor for diseases with high mortality, such as pulmonary tuberculosis.[1,4] When both diseases act together, they increase their impact, and the product of this interaction can be considered a synergistic epidemic, or syndemic.[5]

Within the syndemic framework, it is estimated that smoking is responsible for 20%[6] of the burden of tuberculosis and that smoking will be responsible for a total of 18 million new cases and 40 million deaths in the 2010-2050 period.[7,8] Smoking is also associated with severe forms of tuberculosis in terms of sequelae and with poor tuberculosis treatment outcomes, such as recurrence and death.[6,9] That is due to the fact that the components of tobacco smoke cause numerous pathophysiological changes in the respiratory system, promoting local inflammatory and immunological changes, thus inhibiting cell growth and the action of some chemical mediators of innate immunity.[10,11] In addition, adherence to tuberculosis treatment has been found to be poor among patients who smoke during treatment, especially those who are male.[12,13]

Poor tuberculosis treatment outcomes include treatment failure, defined by the WHO as ". . . sputum smear or culture . . . positive at month 5 or later during treatment."[14] Treatment failure lengthens the period during which patients are infectious, and such patients may harbor resistant bacilli.[15,16] Although there have been few studies focusing on this type of poor outcome, it has been proposed that smoking doubles the risk of pulmonary tuberculosis treatment failure.[17,18] However, it remains unclear which variables can change the outcome of tuberculosis treatment; alcohol consumption, poverty, and gender should be considered potential confounders.[18,19] Therefore, the objective of this study was to determine the risk of pulmonary tuberculosis treatment failure in smokers and to analyze the potential confounders described in the literature.

METHODS

This was an unmatched case-control study including patients who received pulmonary tuberculosis treatment between 2007 and 2015 at the José Silveira Foundation *Instituto Brasileiro para Investigação da Tuberculose* (IBIT, Brazilian Institute for Tuberculosis Research), a referral center for tuberculosis control and treatment in the city of Salvador, Brazil.

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We included patients over 15 years of age who were diagnosed with pulmonary tuberculosis on the basis of a positive sputum smear or culture and who received treatment for drug-susceptible tuberculosis for 6 months, additional sputum smears being performed at months 2, 4, and 6 of treatment. We excluded patients with diabetes mellitus, HIV/AIDS, or comorbidities associated with drug abuse during treatment, as well as patients who dropped out of treatment or who did not comply with their follow-up visits.

Definitions of cases and controls

Cases were defined as pulmonary tuberculosis patients who experienced treatment failure. Treatment failure was defined by the criteria of the Brazilian National Guidelines for the Control of Tuberculosis[20]: remaining smear positive at the end of treatment; initiating treatment with a strongly positive (++ or +++) result and continuing to have this result up until month 4 of treatment; or having an initial positive result followed by negative results, then having new positive results for 2 consecutive months after month 4 of treatment. Controls were defined as pulmonary tuberculosis patients who, at the end of treatment, were classified as cured.

All cases in the IBIT database (MV System) that met the inclusion criteria were selected. Controls were selected by using the Predictive Analytics Software package, version 18.0 (SPSS Inc., Chicago, IL, USA) as a random number generator from the IBIT database. We considered a case/control ratio of 1:4. Sociodemographic and microbiological data were extracted from the medical records of each selected patient. Laboratory test results were obtained from the IBIT database.

Definition of exposure

Patients were categorized, by smoking status, as follows: current smokers—those who, at the time of diagnosis and during treatment, reported smoking; former smokers—those who, at the time of diagnosis, reported having stopped smoking and who did not smoke during treatment; and never smokers—those who had not smoked before being diagnosed and still did not smoke when they were classified as cured.

In addition to data on the exposure variable, we collected data on variables that could have an effect on tuberculosis treatment outcomes. We identified the following variables in the literature[18,19]: patient income; history of alcohol consumption; gender; age; level of education; and marital status.

Sample size and statistical analysis

Between 2007 and 2015, a total of 2,437 patients were diagnosed with pulmonary tuberculosis and treated at the IBIT. Our initial sample size calculation indicated that 60 cases and 240 controls were required in order to achieve a confidence interval of 95% and a power of 80%. We based our calculation on a previous study, conducted by Tachfouti et al.,[17] in which treatment failure was found to be associated with smoking (OR = 2.25).

Data analysis was performed with the Predictive Analytics Software package, version 18.0 (SPSS Inc.). Categorical variables were described as absolute and relative frequencies; age and income were stratified into categories. The smoking variable was grouped into two categories, current smokers and former smokers being grouped together and compared with never smokers, because the risk of having poor tuberculosis treatment outcomes is similar in current and former smokers.[21] Pearson's chi-square test was used in order to determine the statistical difference among the variables. We calculated ORs as a measure of association between treatment failure and the variables of interest, using a confidence interval of 95%. Values of $p < 0.05$ were considered statistically significant.

Covariates (gender, age, income, level of education, marital status, and alcohol consumption) were analyzed with the use of the Mantel-Haenszel test to determine whether any of them behaved as an effect-modifying factor in the association between smoking and treatment failure. We employed multivariate binary logistic regression analysis to adjust the effect of this association and the covariates, using a combined backward-forward procedure. The final logistic regression model included variables that changed the OR by at least 10%.

Ethical aspects

This study was approved by the Research Ethics Committee of the Federal University of Bahia Climério de Oliveira Maternity Hospital (CAAE protocol no. 51244415.4.0000.5543). All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

We included 284 patients (50 cases and 234 controls), 180 (63.3%) of whom were male. Of those 284 patients, 97 (34.1%) were current or former smokers. The mean age was 40.5 ± 14.7 years. The number of cases of treatment failure was higher among patients over 50 years of age (OR = 3.4; 95% CI: 1.8-6.4; Table 1 and Figure 1). The risk of treatment failure was 2.5 times higher (95% CI: 1.3-4.6) among the current or former smokers than among the never smokers (52.0% vs. 30.3%). However, gender, alcohol consumption, level of education, income, and marital status had similar distributions between the groups (Table 1).

After being adjusted for age, the OR for pulmonary tuberculosis treatment failure in current or former smokers was 2.1 (95% CI: 1.1-4.1; Table 2).

Stratified analysis showed that being a woman and being a current smoker collectively increase the risk of treatment failure (OR = 6.0; 95% CI: 1.5-23.3 vs. OR = 3.1; 95% CI: 1.3-7.3 for being a man and a current smoker; Table 3). However, the homogeneity tests were not significant, and, during multivariate

Table 1. Characteristics of the study population, including cases (of treatment failure) and controls, at the José Silveira Foundation Brazilian Institute for Tuberculosis Research, Salvador, Brazil, 2007-2015.

Characteristic	Cases (n = 50) n (%)	Controls (n = 234) n (%)	OR	(95% CI)
Male gender	33 (66.0)	146 (62.4)	1.17	(0.62-2.22)
Age, years				
< 50	26 (52.0)	184 (78.6)	Reference values	
< 30	8 (16.0)	74 (31.6)		
31-50	18 (36.0)	110 (47.0)		
> 50	24 (48.0)	50 (21.4)	3.40	(1.80-6.42)
Being in a stable relationship[a]	37 (74.0)	179 (76.5)	0.87	(0.43-1.76)
≤ 8 years of schooling	32 (64.0)	138 (59.0)	1.24	(0.66-2.33)
Income ≤ the Brazilian NMW[b]	23 (46.0)	127 (54.3)	0.72	(0.39-1.32)
Alcohol consumption[c]	29 (59.2)	122 (52.1)	1.33	(0.71-2.49)
Smoking status				
Current or former smoker	26 (52.0)	71 (30.3)	2.49	(1.34-4.63)
Current smoker	20 (40.0)	37 (15.8)	3.67	(1.83-7.34)
Former smoker	6 (12.0)	34 (14.5)	1.19	(0.45-3.16)
Never smoker	24 (48.0)	163 (69.7)	Reference values	

NMW: national (monthly) minimum wage. [a]Being in a stable relationship (marital status option) was defined as cohabiting or being married. [b]880 Brazilian reals (245 US dollars) in 2015. [c]Alcohol consumers were defined as patients who reported having consumed alcohol on a regular basis before or after being diagnosed with tuberculosis and were compared with patients who reported never having consumed alcohol.

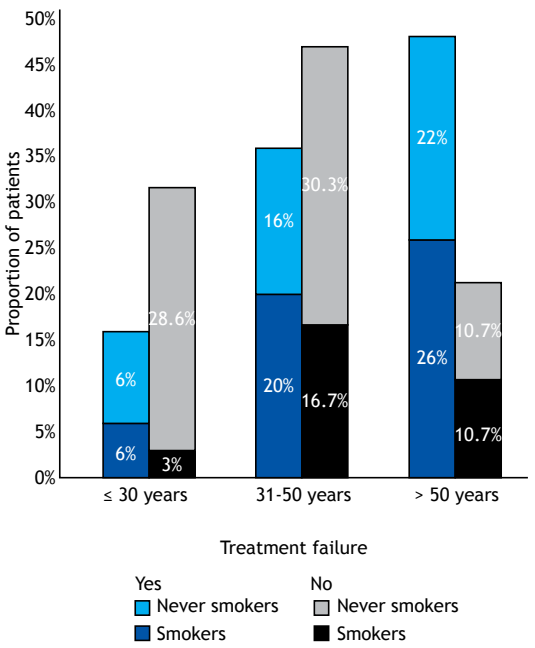


Figure 1. Distribution of the patients in whom treatment failed and those who were cured, by age and smoking status, at the José Silveira Foundation Brazilian Institute for Tuberculosis Research, Salvador, Brazil, 2007-2015.

adjustment, the gender variable was not found to be a determining factor in the model.

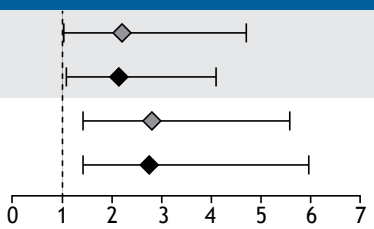
DISCUSSION

In the group of patients who were treated at the IBIT and selected for inclusion during the 8-year study period, we found that being a current or former smoker increased the risk of pulmonary tuberculosis treatment failure. That association persisted even after adjustment for potential confounders. We also found that, among the patients in whom treatment failed, the proportion of smokers was higher in the > 50-year age group. Previous studies have identified an association between treatment failure and smoking.[9,17] However, such studies have grouped treatment failure with other poor outcomes, such as treatment nonadherence and death, rather than measuring it separately.[9] In the Tachfouti et al. study,[17] which was conducted in Morocco, the model was adjusted for age and monthly income, and the risk of treatment failure was found to be higher in patients with a low income and in those who smoked. Of the covariates in our study (age, gender, income, level of education, marital status, and alcohol consumption), age had the greatest effect in the final model. Data stratification by age showed a higher proportion of current smokers over 50 years of age in the case group. This result is similar to that reported in the study conducted in China by Wang et al.,[22] in which the risk of treatment failure was shown to increase with age. However, that could be related to the fact that the prevalence of tuberculosis in the > 50-year age group is high in China and in Brazil.[23]

It is estimated that 20% of the incidence of pulmonary tuberculosis can be attributed to smoking.[6] In the patient cohort from which the cases of this study were extracted, the overall prevalence of smoking at the time of diagnosis of pulmonary tuberculosis was 15.8%. That is higher than the prevalence of smoking in Brazil and in the city of Salvador, which was 12.0% and 5.1%, respectively, in 2016.[24] Other authors have also found a high prevalence of smoking among tuberculosis patients.[25,26]

Table 2. Multiple logistic regression of associations of smoking and age with the risk of pulmonary tuberculosis treatment failure at the José Silveira Foundation Brazilian Institute for Tuberculosis Research, Salvador, Brazil, 2007-2015.

Variable	Model	OR (95% CI)
Somoking[a]	Saturated	2.2 (1.1 - 4.7)
	Final	2.1 (1.1 - 4.1)
Age > 50 years	Saturated	2.8 (1.4 - 5.6)
	Final	2.2 (1.4 - 6.0)



[a]Before and during treatment. Saturated model adjusted for smoking, age, gender, level of education, marital status, income, and alcohol consumption. Final model adjusted for smoking and age.

Table 3. Associations between smoking and pulmonary tuberculosis treatment failure, by gender, among cases (of treatment failure) and controls at the José Silveira Foundation Brazilian Institute for Tuberculosis Research, Salvador, Brazil, 2007-2015.

Gender	Smoking status	Cases (n = 50) n (%)	Controls (n = 234) n (%)	OR	95% CI
Male	Current or former smoker	19 (57.6)	55 (37.7)	2.25	1.04-4.83
	Current smoker	15 (45.5)	31 (21.2)	3.15	1.37-7.25
	Former smoker	4 (12.1)	24 (16.4)	1.08	0.28-3.48
	Never smoker	14 (42.4)	91 (62.3)	Reference values	
Female	Current or former smoker	7 (41.2)	16 (6.8)	3.15	1.04-9.53
	Current smoker	5 (29.4)	6 (6.8)	6.00	1.54-23.35
	Former smoker	2 (11.8)	10 (11.4)	1.43	0.19-7.04
	Never smoker	10 (58.8)	72 (81.8)	Reference values	

There have been few studies addressing the associations of gender and smoking with poor pulmonary tuberculosis treatment outcomes, because the trend is to use age-matched controls or to select only men.[27-30] There is a disconnect between studies showing that gender is not associated with poor tuberculosis treatment outcomes[31,32] and those showing that being male is the strongest predictor of a poor outcome.[33,34] In our stratified analysis, female smokers were at greater risk of treatment failure than were male smokers, although the difference was not statistically significant, perhaps because of the small number of women in our sample. One likely explanation is related to the context or the socioeconomic profile of women, in terms of variables such as malnutrition, access to health care services, and stigma.[35,36] In addition, there is a trend toward gender equality in smoking prevalence rates with the passing of the epidemic.[37-39] We believe that this association should be further explored in future studies and that reporting of poor tuberculosis treatment outcomes by gender should be encouraged.

Although our study covered a relatively long period of time (8 years), its major limitation is that the number of available cases was small and, consequently, the sample size was smaller than the required sample size calculated, because treatment failure is an uncommon event, as was observed in a cohort in the state of Pernambuco, Brazil, in which the reported treatment failure rate was 2.1%.[40] However, the final number of patients included was large enough to demonstrate the association and achieve the major objective. Another important limitation is that inherent to retrospective studies, which is the use of clinical records to try to obtain data, because complete data were not available for all patients. Nevertheless, it was possible to adjust the model for the main variables described in the literature as potential confounders,[6,19] and we managed to use other data sources in addition to clinical records.

Smoking is a modifiable risk factor that has a major impact on pulmonary tuberculosis. To meet the objective of reducing the prevalence of smokers in the general population, in order to reduce the risk of pulmonary tuberculosis and poor treatment outcomes such as treatment failure, it is necessary to devise tuberculosis control strategies that include anti-smoking interventions, such as offering smoking cessation treatment at the time of diagnosis, as a means of achieving success in the treatment of tuberculosis.

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