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Associated risk factors with pulmonary tuberculosis relapses in Cali, Colombia

Factores asociados con recaídas por tuberculosis pulmonar en Cali, Colombia

Relapses in pulmonary tuberculosis

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Introduction: Relapses in Tuberculosis (TB) are caused by endogenous reactivations or by exogenous reinfections, with proportions that reach up to 27% of cases. Its importance lies in the risk of the appearance of multidrug-resistant to Mycobacterium tuberculosis strains. In Colombia, according to reports from the National Institute of Health, in 2011 there were 572 relapses reported, representing a 4,9%. Data of the TB Control Program (PCTB) of the Municipal Health Secretariat (SSM) of the city of Cali, reported a 6% relapse rate during the years 2013 and 2014; a rate higher than the national one.

Objective: To determine the risk factors associated with relapse in patients with pulmonary TB in Cali.

Materials and methods: Observational, analytical, case-control study (1: 1); performed with 81 cases of Pulmonary TB relapses detected through 2013 and 2014 years. Sociodemographic, clinical, lifestyle, and health services variables were collected to identify potential risk factors associated to TB relapses. A logistic regression was used to identify the risk factors.

Results: After adjustments for some variables, the multivariate logistic regression showed that Body Mass Index (BMI) OR = 0.90 95%CI 0,81-0,99, and Population Density, OR-0.99 95%CI 0.98-1.00; were inversely associated to TB relapses. Alcohol consumption increases the likelihood of TB relapse occurrence OR = 5.56, 95% CI 1.18 – 26.26.

Conclusions: BMI and Population density were inversely associated to Pulmonary TB relapses in Cali. By the other hand, alcohol consumption increases the likelihood of TB relapses occurrence.

Key words: Tuberculosis, pulmonary; recurrence; body mass index; Colombia

Introducción. Las recaídas en la tuberculosis (TB) son causadas por reactivaciones endógenas o por reinfecciones exógenas, con proporciones que alcanzan hasta el 27% de los casos. Su importancia radica en el riesgo de aparición de cepas *de Mycobacterium tuberculosis* resistentes a múltiples fármacos. En Colombia, según informes del Instituto Nacional de Salud, en 2011, se reportaron 572 recaídas, lo que representa un porcentaje del 4,9%. Datos del programa de TB (PCTB) de la Secretaría de Salud Municipal (SSM) de la ciudad de Cali registraron una tasa de recaídas del 6% durante los años 2013 y 2014; más alta que la tasa nacional.

Objetivo. Identificar factores asociados con la recaída en pacientes con TB pulmonar.

Materiales y métodos. Estudio observacional, analítico, de casos y controles; con pacientes diagnosticados con TB pulmonar detectados durante entre 2013 y 2014. Se estudiaron variables sociodemográficas, clínicas, de estilo de vida y programáticas. Se utilizó una regresión logística para identificar los factores de riesgo.

Resultados. Después de ajustar por otras variables, la regresión logística mostró dos factores inversamente asociados con las recaídas; el Índice de Masa Corporal (IMC), OR = 0,90 IC95% 0,81-0,99 y la Densidad Poblacional en las comunas, OR = 0,99 0,99-1,00. El consumo de alcohol aumenta la probabilidad de ocurrencia de la recaída por TB, OR = 5,56, IC95% 1,18 – 26,26.

Conclusiones. El IMC y la densidad poblacional están inversamente asociados con las recaídas por TB pulmonar, en Cali. El consumo de alcohol está directamente relacionado.

Palabras clave. Tuberculosis pulmonar, recurrencia, Índice de Masa Corporal, Cali.

Palabras clave: tuberculosis pulmonar; recurrencia; índice de masa corporal, Colombia

Tuberculosis relapses are caused by endogenous reactivations or by exogenous reinfections, with a prevalence near to 27%. Its importance lies in the risk of the appearance of multidrug-resistant to *Mycobacterium tuberculosis* strains. In Colombia, according to reports from the National Institute of Health, in 2011 there were 572 relapses reported, representing a prevalence of 4,9% (1). The data of the TB control program (PCTB) of the Municipal Health Secretariat (SSM) of the city of Cali, reported a 6% relapse prevalence during the years 2013 and 2014; a rate higher than the national one.

The reported risk factors associated with Pulmonary TB relapse are multiple and well documented all over the world. Among them are, failure to adhere to treatment, persistence of pulmonary cavitation, and multidrug resistance to medications (2). The importance of sociodemographic, cultural, clinical, and behavioral determinants are still under discussion. Studies conducted in Colombia, as well as in other Latin American countries have shown that residing in urban areas, overcrowding and irregular treatment are factors associated with relapse in patients with pulmonary TB confirmed by bacilloscopy (3). Toledano Y. et al, mentions that high relapse rates, used to be related to high population density (4); and also with alcoholism, smoking (5). In 2015, a study found that malnutrition, intra-home TB infection, urban marginal people, harmful habits such as alcoholism, smoking, presence of comorbidities such as diabetes mellitus, chronic renal failure, silicosis; were related to relapses (6).

Another factor to take into account is the nutritional status, and the Body Mass Index (BMI) has been used as a proxy indicator of nutritional status, to examine its association with relapses among patients with pulmonary tuberculosis (7). A study conducted in India, in 2014, found that malnutrition increased the incidence of tuberculosis cases in men and women of the tribes included in the study (8).

The city of Cali is an urban area with a high TB burden, with a relapse rate higher than the national one. However, to date, there are no published studies focused in the identification of the factors associated with relapses and, as a consequence, there is a lack of information that allow making informed decisions for their control. This situation implies a serious public health problem, since there are treated patients who continue transmitting the infection in their communities. In addition, it represents an additional cost for the control programs given that these patients must undergo additional procedures such as microbiological cultures, molecular tests, and antimicrobial sensitivity tests (9). The objective of this study was to determine the risk factors associated with relapse in patients with pulmonary TB in Cali, Colombia.

Materials and methods

Observational, analytical, Case-Control study (1:1) performed in a sample taken from the TB Control Program (TBCP) database, between January 2013 and December 2014. During this period, 81 cases were detected, and 81 controls were selected from the same database, this sample size represent 85% of statistical power. The criteria used to estimate the power were P_o = 0,35, P_1 = 0,57, OR = 2,5 (10,11).

Inclusion/exclusion criteria and case/control definitions

Patients diagnosed with pulmonary TB, confirmed by bacilloscopy, residents in the city of Cali, and with at least 80% of the defined variables available on the database, were included. Records of patients who had as admission condition to the TBCP, those who left the program or recorded a therapeutic failure, were excluded. Cases were defined as patients whose condition of readmission to the TBCP was relapse, as defined by the WHO recommendation: a patient previously treated for TB who had been declared as cured, based on three successive negative smears or negative cultures in the last 4 months after treatment. Controls were defined as patients with a first episode of TB, diagnosed in the same year as the case, who had no relapse after the same follow-up period as the cases (12). Study subjects were selected from the same database using well-known methods (13,14).

Evaluated risk factors

The independent variables collected were grouped as follows: 1) Sociodemographic factors: such as sex, age, ethnic group by self-report (indigenous, mestizo or afro-descendant), socioeconomic status, marital status, level of education, job occupation, vulnerability condition as population (street dweller or displaced), 'commune' (political subdivision of the city), overcrowding and social security affiliation regime. 2) Clinical/biological factors: body mass index (BMI), chest radiological findings, coinfection with HIV, diabetes, and kidney disease. 3) Lifestyle factors: tobacco use, alcohol consumption, and use of illicit drugs, such as marijuana, heroin, and cocaine, among others. 4) Health care factors: variables related to the intake of antiretroviral drugs (ARV), rotation of TB control program officials, and duration of the tuberculosis symptoms.

Data management and analysis

Data were collected from three different sources: the TBCP databases, the individual treatment card, and medical records. Data were entered into Microsoft®-Excel tables (v2010, Redmond, WA), with double digitization to warrant data quality and then exported to the SPSS v21 package (15). An exploratory analysis of each of the variables was carried out to evaluate their distribution. Proportions were estimated with their respective 95% confidence interval. In the case of quantitative variables, measures of central tendency and variability were used as indicated. During the bivariate analysis, the objective was to evaluate numerical problems such as collinearity, complete separation, and cells with zeroes or less than five expected observations. In this phase, the variables that would enter to the multivariate analysis were identified and the fundamental criterion for this selection was the presence of randomness effect on the association with the dependent or response variable, with each of the independent or predictive variables.

To compare the characteristics between the Cases and Controls, the Student test or the Chi-square test was applied, according to the measurement scale used in each variable. Each test was evaluated with a level of significance of 5% and their respective intervals at 95% of confidence.

A multivariate analysis was carried out using a binary logistic regression model, to evaluate the goodness of fit of the global model and to identify the factors associated with relapse for pulmonary TB. The Stepwise procedure was used to select the independent variables, using an alpha equal to 0.15 to enter the model, and an alpha equal 0.10 to stay in it. Additional, those variables that, in the bivariate analysis, were not statistically significant, but reported by other authors as biological or public health important factors related to pulmonary TB relapses, were also included in the statistical model.

Logistic regression is based on a number of assumptions, which are extremely reasonable. As the dependent variable is the proportion of individuals who present a binary attribute, and that proportion follows a binomial distribution, most of the linear regression assumptions do not apply in logistic regression. Logistic regression assumes a linear regression between the logit of the dependent variable and all independent variables, which in turn, can be binary, ordinal, and interval. The observations must be independent, there also can be no presence of multicollinarity between independent variables and the outliers' data, responsible for the leverage of estimates, should be check and explained. All these problems can be prevented throughout a good study design and analysis. The adequacy of the model was tested based on the analysis of deviance. This model validation was done by computing the maximum likelihood of a null model and taking the ratio of the maximum likelihoods of the null model to the model we were interested in. Base on this ratio, a measure called deviance is defined, which is twice the different between the likelihood of a perfect fitted model and the likelihood of the model we are interesting in. This quantity is called the log-likelihood ratio, because the different between the two likelihoods is equal to the logarithm of the ratio of the two likelihoods. Thus, the better the model fits the data, the smaller the deviance and the log-likelihood ratio.

Therefore, all we have to find is the difference between the minus 2 likelihood of the null and the model we are interesting in. This result is known as Log-likelihood Ratio test, which follows a chi-square distribution with degrees equal to the number of independent variables in the model we are evaluating.

We also evaluated how effective was the model describing the outcome variable, this procedure is known as goodness of fit. As its name points out, these measures are based in the difference between the observed and fitted values, so the smaller the difference, the better the fit of the model. We used the Hosmer-Lemeshow test, who through multiple modulations demonstrated that, when $J = n$ and the fitted logistic regression model is the correct model, the distribution of this test is well approximated by the chi-square distribution with $g - 2$ degrees of freedom(14,16,17).

After the statistical analysis, the interpretation was performed to contextualize the results and try to respond to the research question related to the associated risk factors to TB relapse, and to identify practical public health interventions. The measure of association reported was OR and its respective 95%CI for each risk factors identified as associated with the relapses.

Ethical issues

The research project was reviewed and endorsed by the Research Ethics Committee of Universidad Libre, Seccional Cali. The authorities from the Municipal Health Secretary of Cali gave a written consent for using the database. Given that this is a research based on records, this study was classified as a risk-free research, as established in article 11 of Resolution 8430 of 1993 of the Ministry of National Health of Colombia.

Access to the data was coded to comply with the terms of the Helsinki Declaration to ensure the confidentiality and identity protection of the participants and their data.

Results

Sociodemographic factors comparison. The age mean was close to 50 years old, in both groups, and its distribution was almost equal in both groups, cases and controls, was give us the confidence that this variable will not be a confounder. Male and mestizo ethnic group were predominant in both groups, with 63.0% and 80.2% in cases, and 58% and 87.7%, respectively. The most frequent socioeconomic stratum was low, with 66.7% in both groups, which is consistent with the subsidized health care affiliation regime, and the predominant educational levels were elementary and high school with 39.2% and 47.2%, in cases; and 35.1% and 40.2% in controls, respectively. The high level of unemployment in both groups was 47.5% in cases and 38.3% in controls. Most of the study subjects were single, 33.3% in cases, and 38.3% in controls.

The incidence by ‘commune’ was similar in both groups, 60,7 for cases, and 60,8 for controls. None of these variables yielded statistically significant. The only one that became statistical significance was the population density by commune, being much higher in the control group (table 1).

Clinical/biological factors comparison. Weight was similar between the two groups, cases = 52,6 kg, and controls = 54,5, t Student = - 1,20, DF = 60, p-value = 0,23. Height was also similar, cases = 1,64 mts, controls = 1,63 mts, t Student = 0.70, DF = 156, p-value = 0,48. As expected, there was a high percentage of positive radiological findings in both groups, 92,6 for cases and 91,4 for controls. The majority of the study subjects did not have coinfection with HIV, diabetes, or kidney disease. There was no statistically significant differences among these variables either (table 1).

Lifestyle factors comparison. Cases had a higher prevalence of smoking 11,1% and 3,7%; alcohol consumption was higher among the cases, 12,3% and 2,5%; illicit drug use 3,7% and 0,0%, respectively. Nevertheless, the difference was only statistical significant for alcohol consumption, Chi-square = 5,76, DF = 1, p = 0,01; and Population density, t Student = -2,99, DF = 86,6, p = 0.000; equal variances not assumed F Snedecor = 37,2, p = 0,000.

Health services factors comparison. Although none variable turned out to be statistically significant, it is important to point out that time lapse between the first symptoms and diagnosis was, on average, 108,5 days for cases and 96,8 days for controls, this result was not statistically significant, t Student = 0,43, DF = 160, p = 0,66 (table 1).

After the bivariate analysis, the following variables were include in the logistic model: Population density p = 0,03, diabetes p = 0,19, tobacco consumption p = 0,07, alcohol use p = 0,02, drug uses p = 0,08, VIH treatment p = 0.11 and malnutrition p = 0,97 (table 2).

The Logistic regression results, shows alcohol consumption OR =5,56, 95%CI = 1,18 – 26,26; BMI OR = 0,90, 0,81 – 0,99, and population density OR = 0,99, 0,98 – 1,00; as the three risk factors associated to TB relapses (table 3).

The Logistic model adjusted the data quite well, the Hosmer-Lemeshow test yielded a Chi-square = 9,9, DF = 8. P = 0,29. The Omnibus test for the regression coefficients in the model showed statistical significance, Chi-square = 15,5, DF = 3, p = 0,001. The finding points to that, at least, one of the regression coefficient contributes significantly to TB relapses, increasing or decreasing the probability of its occurrence. The summary of the Logistic model is on the table 3.

Discussion

The findings point to that BMI and Population Density factors are inversely related to pulmonary TB relapses occurrence in Cali, Colombia; after adjusted for other factors. The alcohol consumption is positive related to TB relapses.

Muñoz P. et al, also refers that as the BMI decreases, the risk of tuberculosis increases. This relationship remain after controlling for socio-economic level, high alcohol consumption, history of gastrectomy, and prior vaccination with the BCG (7). In our study, having normal nutritional status, measured through the BMI, acted as a protective factor for relapses due to tuberculosis.

Bhargava A et al 2014, they estimated that 60% of the registered incidence of TB, among women living in the center and east of the Indian states, was attributable to malnutrition (8).

We did not get the same results.

Thomas and Narayanan conducted a prospective study, in 2005, to measure the relapse rate among patients who successfully completed TB treatment and cured by the control program, and to identify the risk factors associated to relapse. They found that irregularity in treatment ORa = 2,5, 95%CI: 1,4- 4,7, initial drug resistance profile ORa = 4,8, 95%CI 2,0- 11.6, smoking ORa = 3,1, 95%CI 1,6-6,0, and alcoholism ORa = 2,3, 95%CI 1,3-4,1, p 0,01 (18), were all associated to TB relapse.

San Martín *et al.* 2015, reported relapses associated to malnutrition OR = 6,57, bacillary load OR = 4,03, intradomicilliary TB infections OR = 24,75, urban-marginal settings OR = 2,7, and harmful habits, such as alcoholism OR = 5,26, and smoking = OR: 3,6.(6).

Toledo et al, in 2010, found in a cross-sectional study, that the most prevalent toxic habit among TB patients was alcohol consumption in 83,3%. Also in their discussions they mention that the prevalence of patients with relapses might be related to high population density (4). Which is similar to what was found in our study.

The factors associated with TB relapses found in those studies were classified as behavioral factors, which correspond to unhealthy lifestyles. This finding is consistent with the declaration of Health Determinants issued by the World Health Organization (WHO), which includes stress, social exclusion, addictions such as alcohol consumption, drugs and tobacco use, unhealthy diet, overcrowding, and other adverse life conditions as multidimensional poverty, measured by poor housing conditions, low income, and unemployment (19,20). These health determinants can be directly related to some of the sociodemographic factors found in our study, although they did not showed statistical significance.

Nevertheless, they showed greater prevalence among the cases, for instance, unemployment (47%), low socioeconomic stratum (66,7%), and low educational level (39,7%). It also agrees with the report published by Millet J, in 2012, on the influencing factors to the epidemiology of TB, including poverty, overcrowding, and malnutrition. And other factors such as social inequalities, HIV infection and drugs or alcohol abuse(20). Gadoev at al, found some factors associated with recurrence in tuberculosis, such as age between 35 and 55 years, having pulmonary tuberculosis with positive smear, having some comorbidities, including chronic obstructive pulmonary disease (21).

Kim L et al, found that relapses were associated with age, having HIV infection, being a foreigner, and consumption of psychoactive substances (22).

On the other hand, Núñez et al, found that Tb treatment failures, living far away from the health center, and having a conflicting family environment, increase the risk of relapse (23).

Mehdi M et al, pointed out that some factors of the host, which are independent of the Tb control program activities, predispose to relapsing, such as gender, malnutrition, diabetes, kidney failure and HIV infections (24). Rutledge et al, found that multi-drug resistance, non-adherence to treatment, and non-supervision of the same; were related to relapse (25).

Naidoo K, based on a systematic review, says that distinguishing between relapse and reinfection is of paramount importance in addressing the burden of recurrent TB disease. High rates of relapse demand renewed interventions to improve individual patient care while high rates of reinfection demand improved infection and epidemic control measures. Urgent attention is required to address challenges of adherence, such as social and health care worker support systems and step-down management facilities (26).

Most of the disagreement, in the findings, between our and other studies can be explained by the source of the data used, our data was collected for administrative purposes rather than for research ones, and because of this, it was not possible to evaluate some important variables reported by other researches.

Among the strengths of the study is the fact of using incident cases, and the inclusion criteria that allowed the participation and representation of patient's records with a wide variety of socioeconomic characteristics, biological and clinical conditions, from different health care institutions that perform TB control programs, and residents from different communes of the city. Another important weakness in the study lies in the deficiencies in the quality of the clinical records and their underreporting, a situation that did not allow for the collection of some variables reported as important by other studies. Other weakness is that being a secondary information source, with the described characteristics, it is usual to have a bias of non-differential misclassification, which is preferable to differential misclassification bias; because it is known that its impact is towards the null hypothesis. Finally, the lack of genetic tools to differentiate reinfection and reactivation as the cause of the relapse is an important limitation. We believe that selection bias is unlikely, because all cases should be reported to the Municipal Health Secretary database; otherwise, patients would be left without treatment. By the other hand, there are two ways for controlling potential confounder variables, during the study design and during the analysis, we tried both. During the analysis, the multivariate analysis is the strongest way to control them, since the independent variables are usually associated with one another and may have different distributions within levels of the outcome variable. One goal of such analysis is to statistically adjust the estimate effects of each variable in the model for differences in the distribution of and associations among independent variables. Applying this concept to a multivariate logistic regression model, it is surmised that each estimate coefficient provides an estimate of the odds adjusting for all other variables included in the model.

Nevertheless, there will always be a residual confounding due to variables not included in the model.

In conclusion, the BMI, and Population density were risk factors inversely associated to pulmonary TB relapses. No significant association was found with biological and programmatic factors analyzed. In order to get some more evidence in this regard, it seems necessary to carry out more studies including other factors and larger sample sizes.

Based on the finding it is recommended, in order to reduce relapses incidence from Pulmonary TB in the city of Cali: 1) to implement strategies that allow the municipal TB control program to prioritize low BMI; 2) to provide comprehensive health care, taking into account the social determinants of tuberculosis; and 3) The TBCP program should articulated with other social programs, such as mental health, food security, and nutrition program.

The results of this study could, eventually, be extrapolated to other places, given that factor such as harmful alcohol intake, body mass index and population density; are common factors in different settings.

The fact that population density has yielded as a protective factor was an unexpected result, which requires further evaluation.

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Conflicts of interests

None declared.

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Table 1. Characteristics of the study subjects.

Variable	*Descriptor*	*Cases n=81 (%)*	*Controls n=81 (%)*	*P-Value*
Sociodemographic factors				
**Age*	*Mean*	*51,4*	*51,7*	*0,90*
Sex	*Male*	*63,0*	*58,0*	
	Female	*37,0*	*42,0*	*0,50*
Ethnic group	*Afrocolombian*	*17,3*	*11,1*	
	Brown	*80,2*	*87,7*	*0,40*
	Indígenous	*2,5*	*1,2*	
Socioeconomic status	*High*	*2,5*	*1,2*	
	Medium	*30,9*	*32,1*	*1,00*
	Low	*66,7*	*66,7*	
Civil status	*Single*	*33,3*	*38,3*	
	Married	*30,9*	*37,1*	
	Free union	*17,3*	*8,6*	*0,20*
	Divorced	*4,9*	*8,6*	
	Widower	*13,6*	*7,4*	
Education level	*None*	*5,4*	*11,7*	
	Elementary school	*39,2*	*35,1*	
	High school	*47,3*	*40,3*	
	Technical	*4,1*	*9,1*	*0,60*
	Academic	*4,0*	*3,8*	
Occupation	*Employee*	*52,0*	*61,7*	
	Unemployed	*47,0*	*38,3*	*0,10*
	Missing data	*0,6*	*--*	
Health regime	*Contributory*	*23,5*	*38,3*	
	Subsidize	*64,2*	*50,6*	*0,10*
	Linked	*12,3*	*11,1*	
**TTB incidence by Commune*	*Mean*	*60,7*	*60,8*	*1,00*
**Pop density by commune*	*Mean*	*283,8*	*525,9*	*0,03*
Clinical-Biological factors				
Weight	*Mean*	*52.6*	*54.5*	*0,23*
Height	*Mean*	*1.64*	*1.63*	*0,48*
BMI	*Normal weight*	*49,0*	*48,0*	*0,53*
	Subnormal weight	*23,0*	*28,0*	
Positive radiological findings	*Positives*	*92,6*	*91,4*	*0,60*
	Negatives	*1,2*	*3,7*	
	Missing data	*6,2*	*4,9*	
HIV coinfection	*Yes*	*11,1*	*7,4*	*0,40*
	No	*85,2*	*91,4*	
	Misisng data	*3,7*	*1,2*	
Diabetes	*Yes*	*8,6*	*3,7*	*0,10*
	No	*91,4*	*96,3*	
Renal desease	*Yes*	*1,2*	*0,0*	*0,30*
	No	*98,8*	*100*	
Lifestyle factors				
Tobacco use	*Yes*	*11,1*	*3,7*	*0,01*
	No	*88,9*	*96,3*	
Alcohol consumption	*Yes*	*12,3*	*2,5*	*0,01*
	No	*87,7*	*97,5*	
Drug use	*Yes*	*3,7*	*0,0*	*0,10*
	No	*96,3*	*100*	

Health services factors				
Intake of antiretroviral drugs	*Yes*	*7,4*	*7,4*	*0,20*
	No	*0,0*	*3,7*	
	Missing data	*92,6*	*88,9*	
Rotation of the care personnel	*Yes*	*23,5*	*21,0*	*0,70*
	No	*76,5*	*79,0*	
Synptomatology elapsed	*Mean*	*108,5*	*96,8*	*0,70*

*Mean

Table 2. Associated risk factors

Variable	OR	SE*	95 % CI Lower limit - Upper limit	
Alcohol consumption	5,56	0,792	1,18	26,26
Body Mass Index	0,90	0,054	0,81	0,99
Population density	0,99	0,001	0,98	1,00

* Standard error.

Table 3. Model summary

Test	Result
-2 Log likelihood	203,559[a]
Cox & Snell R Square	,093
Nagelkerke R Square	,124

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.