

ASSOCIATION OF SMOKING WITH TUBERCULOSIS AND ITS NEGATIVE OUTCOMES: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To identify evidence of an association between tuberculosis and smoking, as well as the complications of tobacco for the tuberculosis patient.

Methods: This is a systematic literature review, structured by the PRISMA steps, using the population, exposure and outcome (PEO) strategy to elaborate the guiding question: "Is tobacco associated with tuberculosis?" "What are the complications resulting from smoking in the treatment of tuberculosis?". For searching the articles, a time limit was defined from 1999 to 2019, and was done in the PubMed, Cumulative Index to Nursing and Allied Health Literature and Latin American and Caribbean Health Sciences Literature databases. The descriptors "Tobacco", "Tobacco Use", "Tuberculosis", "Adult" isolated and/or combined were used. It Included full articles available in Portuguese, English and Spanish. State of the Art through Systematic Review software was used for database management.

Results: A total of 227 articles were retrieved, of which 25 were included and fully examined, in which only 3 were from Brazil. The results showed that there is an association between smoking and the development of tuberculosis. Complications in treatment include treatment failure, non-adherence and dropout, and mortality was higher among patients who were smokers. It also showed that the cure of tuberculosis was associated with the patient who never smoked.

Conclusion: The set of studies reviewed indicates that in addition to smoking being strongly associated with tuberculosis, tobacco use increases the chances of unfavorable outcomes of tuberculosis treatment.

Descriptors: Tobacco; Tobacco use; Tuberculosis.

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INTRODUCTION

Tuberculosis (TB) is among the top ten causes of death among infectious diseases in the world, with 10.4 million records in 2016, of which 1.8 million died. However, the World Health Organization (WHO) has launched the "End TB" strategy for the post-2015 period, which aims to eliminate the disease (<1 case per 100,000 inhabitants) and to further reduce TB mortality by 95% by the year 2035[1].

Thus, the fight against TB faces many challenges regarding the organization of health services, public policies for coping with the disease, as well as socioeconomic, clinical and behavioral factors. These include the association of TB with other comorbidities, such as smoking, which may hinder treatment, increase the chances of transmission and contribute to increased morbidity and mortality of individuals[2,3].

It is estimated that 1.3 billion people in the world use tobacco, with most of them living in underdeveloped or developing countries, where TB rates are higher[4,5].

In this context, there is currently an increasing smoking epidemic and TB control is still precarious, but future prospects are

worrying regarding the association of both diseases. A study that assessed the impact of smoking on TB incidence, based on the smoking trend curve and the projection of TB incidence, prevalence and mortality from 2010 to 2050, estimated that smoking will produce an excess of 18 million TB cases and 40 million deaths if the number of smokers in the world continues to follow the same trend, which will make it even more difficult to achieve the targets set by WHO[6].

In Brazil, smoking is still worrying, in 2013 there were 15% of smokers among adults, and a higher prevalence among Brazilians with lower education[7]. According to a cohort study, it was found that smokers are 2.5 times more likely to develop recurrent TB compared with nonsmokers; in addition, smokers show worse adherence to TB treatment[8].

Despite the evidence levels of the association between smoking and TB, the main worldwide guidelines on TB provide little information on the need to combat smoking to improve TB control[9], thus requiring further studies and evidence to prove such association and its possible causes. Given the above, the objective of this study was to identify the evidence of an association between tuberculosis and smoking, as well as

the complications of tobacco for the patient with tuberculosis.

METHOD

To identify the evidence of an association between tobacco and TB in the treatment complications of patients diagnosed with TB, a systematic literature review was conducted according to the PRISMA steps: 1) Identification; 2) Screening; 3) Eligibility, 4) Inclusion(10). In the first stage (identification) search strategies were developed based on two research questions structured according to the components 1) Population; 2) Exposure; 3) Outcome (PEO) (P - Population - Older people; E - exposure - Tobacco; O - Outcome - Tuberculosis).

Thus, to achieve the objective of the review, the following questions were asked: 1) Is tobacco associated with tuberculosis? 2) What are the complications arising from smoking in the treatment of tuberculosis? To perform the search strategy, studies published between January 1, 1999 and May 31, 2019 were retrieved.

The searches were done in articulation with the research questions, and used the databases: PubMed, Cumulative Index

to Nursing and Allied Health Literature (CINAHL) and Latin American and Caribbean Health Sciences Literature (LILACS). The descriptors Mesh Terms were used for the international databases, ((Tuberculosis) AND (Smoking) OR (Tobacco) AND (adult)) and Health Sciences Descriptors (Decs) for national databases ((Adults) AND (Tobacco) AND (Tuberculosis)) and the Boolean operators AND and OR for combinations of these descriptors.

In the screening stage, which was characterized by reading the titles, abstracts and keywords of the 217 articles selected, the following eligibility criteria were adopted: adults over the age of 18; active tobacco use at some point in life and who were diagnosed/associated with TB.

And to read these articles used the State of the Art through Systematic Review (StArt) software that aims to perform the database management.

Thus, after the elimination of duplicates, the articles were screened, potentially eligible studies were pre-selected based on the reading of titles, abstracts and keywords, which were performed by two independent reviewers (ARS - MF) independent reading consists of an individualized analysis that

only after the screening has been completed will the articles be compared “included or excluded” if there is a discrepancy among the reviewers, the article go through a third analysis (MAMA).

In the eligibility stage, full reading of the potentially eligible studies is performed, being done by five reviewers (ARS - MF - LC - JA - MAMA).

At the inclusion stage, the evaluators performed the data extraction, based on the pre-defined protocol, thus, this protocol aimed to favor and guide the process of extracting information from the articles during their full reading. In the end, the references were exported to an Excel database for construction and analysis of results.

RESULTS

A total of 227 articles were retrieved, of which 110 were identified in the Pubmed database, 64 in CINAHL and 53 in LILACS. After removing duplicates and applying the inclusion criteria, 74 articles were selected for full text reading. Finally, 25 studies were included and examined by the authors. The search and selection processes are presented in (Figure 1), using the PRISMA flowchart[10].

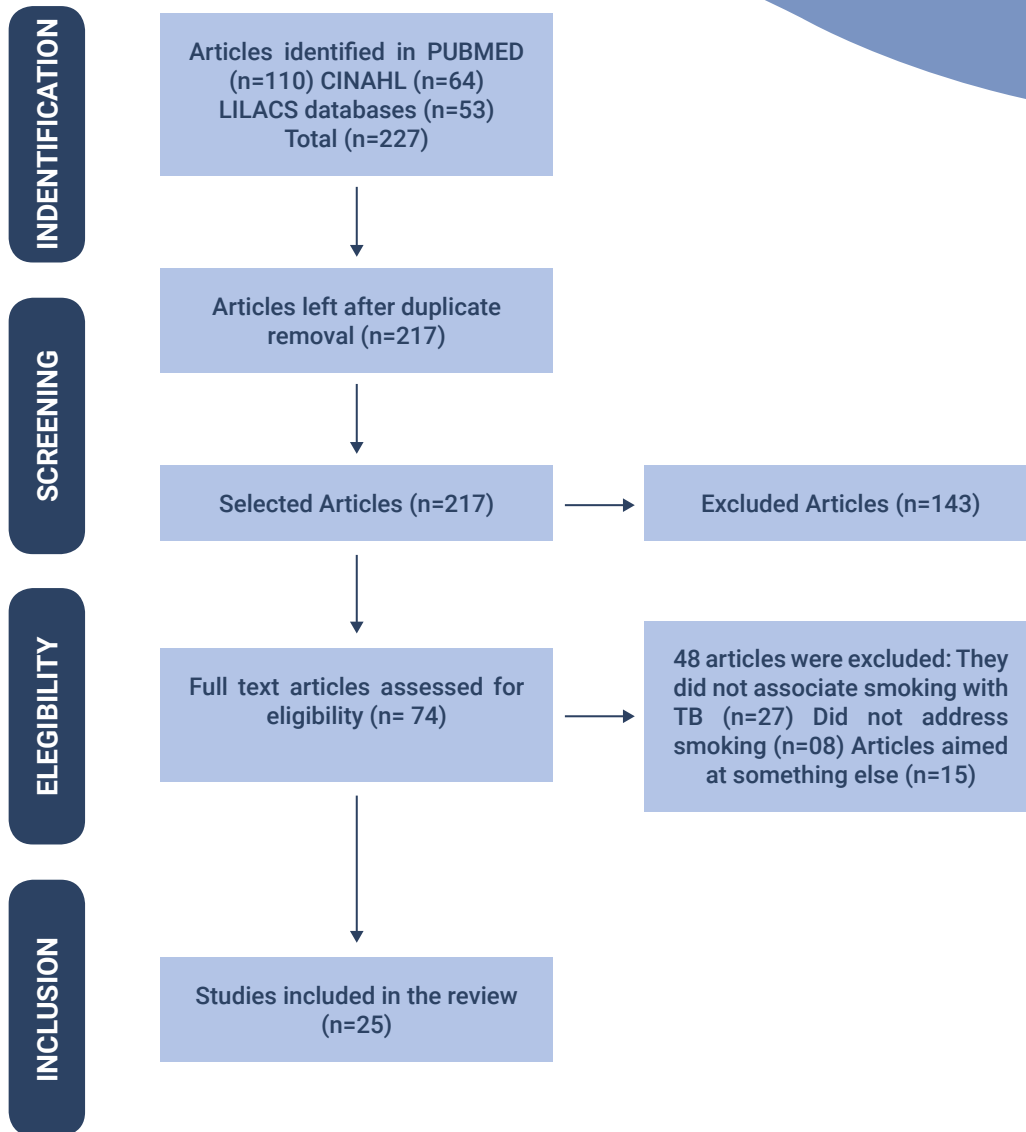


Chart 1 - Flowchart of the studies included in the systematic review.

The essential data extracted from the included articles are summarized in (Chart 2). The results of the literature review pointed to an important association between smoking and the development of TB.

The results showed that six studies addressed treatment problems (failure, non-adherence and dropout) as one of the main complications of smoking for TB patients (ID - 3,9,16,22,23,25). One study mentioned that smoking negatively influences the con-

DISCUSSION

centration of pyrazinamide, a drug used to treat TB (ID-13).

In addition to tobacco, other drugs were also related to TB and its complications, including alcohol that was mentioned in six studies (ID - 1,10,6,18,20,22).

Regarding mortality, three studies found that mortality from TB was higher among patients who were smokers (ID - 9,10,24).

This review aims to identify scientific evidence of an association between passive or active tobacco use with TB, based on findings about the complications and outcome of TB treatment among smokers. It was possible to identify that there were a total of 25 articles, and the majority, 22 articles were international studies, with the scenarios located in the Asian continent.

ID	AUTHOS	YEAR	COUNTRY	TITLE	OBJECTIVE	RESULTS
1	Balakrishnan S. et al(11).	2019	India	Higher risk of developing active TB among adult diabetics exposed to TB during childhood: A study from Kerala, India	To identify individual risk factors for TB.	Contact in childhood and recent contact with TB, smoking more than 10 cigarettes a day and consuming more than 10 drinks per week was considered an associated factor for TB.
2	Nandasena S. et al(12).	2019	Sri Lanka	Characteristics and sputum conversion of tuberculosis (TB) patients in Kalutara, Sri Lanka	To describe the characteristics of TB patients and evaluate factors associated with sputum conversion.	Those who smoke tobacco are less likely to have sputum conversion in 2-3 months compared to non-smokers. Smoking and alcohol withdrawal are important factors for the conversion of sputum in patients with pulmonary TB.
3	Oliveira SM. et al(13).	2018	Brazil	Predictors of noncompliance to pulmonary tuberculosis treatment: An insight from South America	To investigate factors associated with increased risk of TB treatment dropout in Porto Alegre, Brazil.	Factors associated with nonadherence to treatment were 72% higher in individuals who smoke and 173% higher among individuals who used drugs. Living in a low-income area with drug abuse and a history of smoking remained associated with treatment dropout.
4	Tahseen S. et al(14).	2018	Pakistan	Systematic case finding for tuberculosis in HIV-infected people who inject drugs: experience from Pakistan.	To evaluate the prevalence of TB among HIV-infected injecting drug users referred for antiretroviral treatment and to assess the diagnostic value of cough as a screening symptom.	A higher prevalence of TB occurred among smokers with a history of more than 10 cigarettes/day than those with less than 10 cigarettes/day.
6	Mwiru RS. et al(15).	2017	Tanzania	Prevalence and patterns of cigarette smoking among patients co-infected with human immunodeficiency virus and tuberculosis in Tanzania.	To determine smoking pattern and prevalence among co-infected patients with HIV and TB in Dar es Salaam, Tanzania.	Men who were smokers and consumed alcohol were seven times more likely to develop TB.
7	Lindsay RP. et al(16).	2014	United States	The Association between Active and Passive Smoking and Latent Tuberculosis Infection in Adults and Children in the United States: Results from NHANES	To determine the association between active and passive smoking in latent TB infection in a representative sample of US adults and children.	Active smokers were significantly more likely to have latent TB infection than nonsmokers. Passive adult smokers also had a higher chance of latent TB infection compared to nonsmokers.
8	Alavi-Naini R. et al(17).	2012	Iran	Association Between Tuberculosis and Smoking	To determine the association between TB and smoking in southeastern Iran, an endemic area for tuberculosis.	Cigarette smokers were 3.1 times more frequent in TB patients compared to nonsmokers. Other factors that showed significant differences between TB patients were the use of non-parenteral drugs; family history of TB, family history of smoking and smoking history of more than 10 years.

ID	AUTHORS	YEAR	COUNTRY	TITLE	OBJECTIVE	RESULTS
9	Gillani S. et al(18).	2010	Malaysia	Clinical Modalities and Therapeutic Outcomes; Between Ever-Smokers Versus Never-Smokers of Tuberculosis Patients in Penang, Malaysia.	To identify the impact of smoking on the clinical characteristics and outcome of TB treatment, and emphasizing this association, may be helpful in treating TB cases.	Most cured patients never smoked, while those who dropped out treatment or died were smokers; There was a high risk of death in TB patients who were smokers.
10	Lindoso AABP. et al(19).	2008	Brazil	Perfil de pacientes que evoluem para óbito por tuberculose no município de São Paulo, 2002	To describe the profile of adult patients living in the city of São Paulo who evolved to death associated with TB, according to biological, environmental and institutional factors.	Among the patients who died, 71% were smokers and 64% were alcohol dependent.
11	Watkins RE. et al(20).	2006	Australia	Does smoking explain sex differences in the global tuberculosis epidemic?	To determine whether smoking makes a significant contribution to gender differences in TB distribution among high-burden countries.	Cigarette smoking was a significant predictor for TB reports. Smoking is an important modifiable factor that has a significant impact on the global epidemiology of TB, and emphasizes the importance of tobacco control in countries with a high incidence of TB.
12	Gajalakshmi V. et al(21).	2003	India	Smoking and mortality from TB and other diseases in India: retrospective study of 43000 adult male deaths and 35000 controls.	To assess the age-specific mortality of smoking among men (since few women smoke) in urban and rural India.	Smoking increases the incidence of clinical tuberculosis, causing half of all male TB deaths and a quarter of all middle-aged male deaths.
13	Hemantkumar AK. et al(22).	2016	India	Pharmacokinetics of thrice-weekly rifampicin, isoniazid and pyrazinamide in adult tuberculosis patients in India.	To study the pharmacokinetics of rifampicin, isoniazid and pyrazinamide in adult tuberculosis patients and to examine factors that influence drug pharmacokinetics.	Smoking was a factor that negatively influenced the concentration of pyrazinamide, a TB treatment drug.
14	Baghaei P. et al(23).	2018	Iran	Diagnosing active and latent tuberculosis among Iranian HIV-infected patients.	To screen TB among HIV-positive patients through history and symptomatology, physical examination, chest X-ray, tuberculin test, as well as sputum smear and TB culture.	Smoking remains associated with the development of TB.
15	Ephrem T. et al(24).	2015	Ethiopia	Determinants of active pulmonary tuberculosis in Ambo Hospital, West Ethiopia	To determine the factors associated with active pulmonary TB observed in cases at Ambo Hospital in Ethiopia.	Having one or more family members with a history of TB, marital status, male, rural residence, current or past smoker, BMI <18.5, HIV infection, and a history of worm infestation remained as significant factors related to active TB.
16	Gegia M. et al(25).	2015	Georgia	Tobacco smoking and tuberculosis treatment outcomes: a prospective cohort study in Georgia.	To evaluate the effect of smoking on TB treatment outcome in Tbilisi, Georgia.	Active smokers had an increased risk of poor treatment outcome. Those who stopped smoking more than two months before starting treatment had no increased risk.
17	Kirenga BJ. et al(26).	2015	Uganda	Tuberculosis risk factors among tuberculosis patients in Kampala, Uganda: implications for tuberculosis control.	To determine the prevalence of different tuberculosis risk factors and TB presentation among tuberculosis patients in Kampala Uganda.	The prevalence of risk factors for TB were HIV, diabetes, close contact, family history, smoking, poverty, overcrowding and alcohol use.
18	Ajagbe O. et al(27).	2014	Ireland	Survival analysis of adult tuberculosis disease.	To estimate survival time, including median survival time, and assess the association and impact of covariates (TB risk factors) for the event.	The risk for TB was drug abuse (2.2 times), smoking (1.8 times), alcohol (1.8 times) and immunosuppressive medication (3.0 times).
19	Magee MJ. et al(28).	2014	Georgia	Diabetes mellitus, smoking status, and rate of sputum culture conversion in patients with multidrug-resistant tuberculosis: a cohort study from the country of Georgia.	To estimate the association between DM and conversion time of sputum culture in adult patients with pulmonary TB. Secondly, determine factors associated with sputum culture conversion rates.	The sputum culture conversion rate was significantly lower in active smokers, low body mass index, resistance to second-line drugs, pulmonary cavities, and disseminated TB.
20	Naidoo P. et al(29).	2013	South Africa	Predictors of TB and antiretroviral medication non-adherence in public primary care patients in South Africa: a cross sectional study.	To investigate factors associated with adherence to anti-TB and HIV drugs.	Predictors of noncompliance with both anti-TB and dual therapy (antiretroviral and anti-TB drugs) included poverty, one or more co-morbid health status, alcohol use, having an HIV-positive partner, and tobacco use.
21	Singh PN. et al(30).	2013	Cambodia	Cigarette smoking and tuberculosis in Cambodia: findings from a national sample.	To examine the relationship between daily smoking and life history of tuberculosis in a national sample of adults in Cambodia.	There was a significant positive relationship between TB and number of cigarettes smoked per day and packs per year.

ID	AUTORES	AÑO	PAÍS	TÍTULO	OBJETIVO	RESULTADOS
22	Slama K. et al(31).	2013	Morocco	Factors associated with treatment default by tuberculosis patients in Fez, Morocco.	To identify the determinants of TB treatment pattern in Fez, Morocco.	Predictive factors for treatment pattern were: relapse, current smoking, alcohol use, being more than 30 minutes from the health center and perception of having received insufficient explanation about the disease.
23	Dujaili JA. et al(32).	2010/2011	Malaysia	Outcomes of tuberculosis treatment: a retrospective cohort analysis of smoking versus non-smoking patients in Penang, Malaysia.	To determine smoking prevalence among TB patients in Penang and compare treatment outcomes between smokers and non-smokers.	TB patients and smokers were about seven times more likely to fail treatment or stop treatment and were less likely to be cured of TB compared to never smokers.
24	Pednekar MS. et al(33).	2007	India	Prospective study of smoking and tuberculosis in India.	To examine the association between smoking (mainly cigarette smoking) and tuberculosis in Mumbai, India.	The risk of TB mortality among smokers was 2.6 times higher than non-smokers, with a significant tendency for the daily frequency of smoked cigarettes. The prevalence of self-reported TB among smokers was also 5.2 times higher than non-smokers.
25	Maruza M. et al(34).	2011	Brazil	Risk factors for default from TB treatment in HIV-infected individuals in the state of Pernambuco, Brazil: a prospective cohort study.	To identify risk factors for the standard of TB treatment in people living with HIV.	The variables associated with treatment dropout were: gender, age, smoking, education level, CD4 T-cell count and highly effective antiretroviral therapy.

Chart 2 - General characteristics of the studies included in the literature review.

Analyzing the articles of this review, there is a knowledge gap regarding publications/development of researches that relate tobacco with TB in Brazil, and there were only three studies developed at national level. Of these, two associated that the practice of smoking in the past or current smoker is a behavior that increases the chances of treatment dropout when compared with a population with TB that did not have the habit or history of smoking[13,34].

And, the third study showed that about 71% of patients who had TB and were smokers died and alcohol dependence was present in 64% of deaths[19].

Smoking is one of the main risk factors for over 20 types of diseases, including chronic obstructive pulmonary disease, cardiovascular disease, stroke, multiple cancers/ lung[35].

The relationship between tobacco and TB occurs because nicotine is a risk factor for the decline in lung function, finding that smoking triggers a greater vulnerability to reduced expiratory volume and cigarette smoke causes damage to the body affecting the parenchyma and pulmonary arteries, which causes irreversible obstruction of the pulmonary branches[36]. Therefore, tobacco will cause histopathological damage to the lung, affect

ting the immune system, making it susceptible to pulmonary infections, including TB[17].

In this context, passive/active or current/past history of tobacco use is directly associated with a worse prognosis in the treatment of TB[37]. Thus, a serious public health problem is seen in countries where there is a high prevalence of smokers, considering that when there is a population that triggers a high standard of smoking this habit increases the risks for the persistence or emergence of new cases. in addition to decreasing cure rates.

It is evident that there is an association between TB and smoking in several studies[12,14-18,20-18,20-27,30-32]. However, this review advances the knowledge by pointing out how this association interferes with the prognosis of TB treatment, that is, to which unfavorable outcomes of TB treatment the abuse of tobacco would be associated[11-14,18,20,22,28,31].

In this sense, an unfavorable outcome identified in this review was the treatment dropout. Thus, treatment dropout is considered when the patient stays for about 30 consecutive days without going to the health unit after the return date[38]. Also, it emphasizes

that the therapeutic scheme for the treatment of TB at national level is free and developed in primary care, which is highly effective with a satisfactory cure rate[39]. As long as the patient follows the therapeutic scheme correctly and without interruption.

Data show that the TB treatment dropout rate in Brazil is approximately 17%, in this sense this dropout causes many negative consequences for the patient and the public health system, since, when a dropout occurs, there is also a need for re-entry of the therapeutic regimen, which causes difficulty in reducing the number of new TB cases and the emergence of multidrug-resistant TB[40].

Thus, four studies[13,25,32,34] pointed that smokers were about seven times more likely to fail or stop treatment and were less likely to be cured of TB(34). It showed that, among patients who never smoked or quit smoking at least two months before starting the therapeutic regimen, they were more likely to evolve to cure when compared with smokers[25].

Other factors were also associated with treatment dropout, such as alcohol use, being more than 30 minutes from the health center, receiving insufficient explanation about the disease by health professionals[13,31].

Therefore, the literature mentions the negative consequences caused by tobacco in the general population, it is estimated that more than 7 million people die each year from tobacco-related illnesses, and predicts that by 2030 this number will increase to 8.3 million, especially in low and middle income countries[41]. It is also worth noting that tobacco is one of the leading causes of preventable death worldwide.

In this scenario, patients diagnosed with TB who are smokers have a more susceptible immune system to other comorbidities leading to higher death rates. This outcome was found through this review, since it showed that the risk of TB mortality among smokers is 2.6 times higher than non-smokers[21,33], as well as an association between TB and tobacco use with deaths[34].

In order to provide greater control and elimination of TB, it is necessary to develop strategies that seek to reduce or stop smoking among the general population, since the habit of smoking exposes the individual to higher risks of lung infections, therefore, emphasis should be placed on smoking control in countries with a high incidence of TB cases. As well as seeking strategies for screening and screening for TB among smokers, since these

individuals are a population at risk, which are more likely to become ill with TB.

CONCLUSION

In this context, there is a serious public health problem worldwide, especially in countries where smoking is high, as this study showed a strong association that tobacco use increases the chances of unfavorable outcomes of TB treatment, such as treatment failure/dropout and death.

Therefore, it is necessary to develop prevention and promotion strategies in primary care aiming at a reduction/cessation of tobacco use among the general population, considering that when the individual has a smoking habit, he/she is vulnerable to having TB and in diagnosed patients, it is central to implement harm reduction actions, as well as tobacco cessation, through therapeutic consultations and active listening in the family health strategy.

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