

Epidemiological Characteristics Associated with Smoking in Patients with Tuberculosis: A Case-control Study

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Hypothesis

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Abstract

Objective: To analyze the factors associated with smoking in patients with tuberculosis

Methods: Case-control study conducted in the municipality of Foz do Iguaçu-PR, Brazil between 2009 and 2018. Odds Ratio (OR) and confidence intervals were calculated to analyze the chance of occurrence of smoking (cases) according to social demographic, clinical and diagnostic variables. Follow-up variables were submitted to descriptive analysis.

Results: Evidence of association was identified between smoking and individuals with no or a low education level (OR 2.10; CI95% 1.14-3.87), homelessness (OR 2.99; CI95% 1.,07-8.38), pulmonary tuberculosis (OR 3.57; CI95% 1.72-7.34), alcoholism (OR 3.58; CI95% 2.39-5.38), drug use (OR 8.11; CI95% 4.89-13.46), re-entry after default (OR 2.50; CI95% 1.32-4.74) and X-ray with tuberculosis-suspicion result (OR 3.53; CI95% 1.03-12.08). Smokers had a higher rate of treatment default when compared to non-smokers.

Conclusion: It was evidenced that smoking among tuberculosis cases is associated with low education levels, homelessness, and patients who use alcohol and illicit drugs. Moreover, smoking is directly linked to more severe radiological images of pulmonary tuberculosis and is more prevalent in cases that default treatment.

INTRODUCTION

Tuberculosis (TB) shows large incidence rate variability among countries, being among the top ten causes of death on the planet ^[1]. Data from the World Health Organization ^[1] estimate that one-third of the world's population is infected Mycobacterium tuberculosis (Mtb) and a large part of this population comes from underdeveloped and developing countries. About 10 million people became ill with TB in 2017, of which 1.3 million progressed to death ^[1]. A total of 73,864 new cases of the disease were reported in Brazil in 2019 ^[2]. Numerous comorbidities negatively affect the TB epidemiology, such as alcoholism, malnutrition, Diabetes mellitus, HIV infection, smoking, and others. Smoking is one of the aggravation factors of patients affected by pulmonary TB due to presenting complications arising from the use of tobacco, such as pulmonary emphysema, asthma, cancer, and hypertension, among others ^[3].

A study conducted in Georgia between 2011 and 2013 revealed that 24.4% of patients with TB were smokers and 31.9% were former smokers ^[4]. Regarding treatment outcomes, the risk of an unfavourable outcome in TB treatment is 70% higher in smokers compared to those who never smoke ^[4]. Therefore, smoking is associated with a delay in conversion of the sputum culture treatment default and deaths ^[3,5]. In this sense, it is worth highlighting the performance of the Tobacco Control Program in Brazil, which acts in order to reduce the prevalence of smokers and the consequent morbi-mortality related to consuming tobacco products in the country, along with the support and adoption or fulfilment of sanitary, legislative and economic measures in articulation with the healthcare network in the Unified Health System ^[6]. This program conducts campaigns and educational

activities to enhance the prevention of smoking initiation, promoting actions to quit smoking and encouraging the establishment of tobacco-free environments [6].

Considering the magnitude of TB as a national and global public health problem, as well as the fact that tobacco can damage the lungs and reduce lung function, increasing the risk of developing TB and unfavourable treatment outcome, this study aimed to analyse the factors associated with smoking in patients with TB, since the study hypothesizes that smoking in these patients is associated to social demographic, clinical and diagnostic factors. The study results can serve as elements to improve the care provided to these individuals in accordance with the National Policy on Tobacco Control and to maximize the success of anti-tuberculosis therapy.

MATERIALS AND METHODS

This is a case-control study conducted in the municipality of Foz do Iguaçu, which is located west in the state of Paraná, bordering Argentina and Paraguay. The municipality has an estimated population of 257,971 inhabitants for 2021 [7] has a Tobacco Control Program and a TB Control Program Reference Centre. The study population consisted of all diagnosed cases of active TB notified from 2009 to 2018 to the Epidemiological Surveillance sector of the municipality of Foz do Iguaçu - PR. Patients whose smoking variable was not filled in, as well as those fewer than 18 years old and with a change in diagnosis, were excluded. Invalid responses (blank/ignored) of the other study variables were not considered for the analyses; therefore, the sample size in some analyses did not correspond to the total population included in the study. "Cases" were defined as people with tuberculosis and who used tobacco. "Control" was defined as people with tuberculosis and who did not use tobacco. Such use is informed by the patient at the time of diagnosis and recorded in the TB case notification form. It is important to emphasize that the amount and time of use is not a variable to be filled out in the notification form, nor it is possible to identify former smokers. Cases and controls were paired according to age and sex in a matching ratio equal to 2, that is, two "controls" for each "case". In order to ensure data comparability, they were collected from the same data source and concomitantly for "cases" and "controls".

The research data were obtained in 2020 by accessing the TB case notifications registered in the Epidemiological Surveillance database of the municipality of Foz do Iguaçu - Paraná - Brazil. The following variables were selected in order to meet the study objective: social demographic variables (skin color; education; residential area; country of residence; special populations - imprisoned patients, homeless patients, health professionals and immigrant patients; and government cash transfer program benefit); clinical variables (clinical presentation, diseases and related aggravations - HIV; diabetes, mental disorder, alcoholism, drug use, other diseases); diagnostic variables (type of entry; sputum smear microscopy; rapid molecular test; sputum culture; susceptibility test; chest X-ray); follow-up variables (Directly Observed Treatment, treatment outcome). The variables smoking, age and gender were also requested to define the study population.

Statistical analyses were performed using the "R" statistical software program and summarized in frequency tables with descriptive analysis of the social demographic, clinical, diagnostic, and follow-up variables, according to the tobacco use status. In addition, the odds Ratio (OR) and their respective confidence intervals were calculated to analyse the chance of occurrence of the variable of smoking (cases) according to socio demographic, clinical and diagnostic variables, considering a significance level of 5%. The follow-up variables were not submitted to this type of analysis, as they occurred after the identification of smoking status. This project meets the recommendations of resolution no. 466/2012 of the Conselho Nacional de Saúde (National Health Council), with approval by the Research Ethics Committee of the Universidade Estadual do Oeste do Paraná (State University of West Paraná - Unioeste), and number 3.393.015.

RESULTS

There were 1,479 records of TB cases for the municipality of Foz do Iguaçu from 2009 to 2018 in the Epidemiological Surveillance Sector database. Among these cases, 470 individuals were excluded for not having the information on smoking status, 53 for being under 18 years old, and 21 for a change in diagnosis. Thus, among the population eligible for the study (n=935), 182 "cases" were identified and 364 "controls" were randomly included in the study. Among the "cases" included in the study, the mean age of participants was 41.4 (sd 14.0) years and 66.7% were male. In the analysis of the aspects associated with tobacco use in TB patients according to social demographic variables, evidence of a statistically significant association were identified between smoking and individuals with no education or with incomplete elementary education (OR 2.10; CI95% 1.14-3.87) and homeless people (OR 2.99; CI95% 1.07-8.38). The variables skin colour, residential area, country of residence, imprisoned patients, health practitioners, immigrant patients and government cash transfer program benefit were not associated with smoking (**Table 1**).

Table 1 Distribution of smokers and non-smokers diagnosed with tuberculosis according to their social demographic characteristics in Foz do Iguaçu - PR, from 2009 to 2018*.

| Sociodemographic characteristics | | Smokers | | Total N (%) | Odds Ratio |
|----------------------------------|--------------|------------------|------------------|------------------|------------------|
| | | Yes N (%) | No N (%) | | |
| Skin color | White | 108 (59.7) | 232 (64.8) | 340 (63.1) | 1 |
| | Non-white | 73 (40.3) | 126 (35.2) | 199 (37.0) | 1.24 (0.86-1.80) |
| | Total | 181 (100) | 358 (100) | 539 (100) | - |

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| | | | | | |
|---|-----------------------------------|------------|------------|------------|------------------|
| Education | Illiterate or Elementary inc. | 130 (76.0) | 219 (67.6) | 349 (70.5) | 2.10 (1.14-3.87) |
| | Elementary comp. | 26 (15.2) | 52 (16.0) | 78 (15.8) | 1.77 (0.84-3.71) |
| | High School comp. or higher comp. | 15 (8.8) | 53 (16.4) | 68 (13.7) | 1 |
| | Total | 171 (100) | 324 (100) | 495 (100) | - |
| Residential area | Urban | 159 (98.8) | 322 (97.3) | 481 (97.8) | 1 |
| | Periphery/rural | 2 (1.2) | 9 (2.7) | 11 (2.2) | 0.45 (0.10-2.11) |
| | Total | 161 (100) | 331 (100) | 492 (100) | - |
| Country of residence | Brazil | 179 (98.4) | 358 (98.4) | 537 (98.4) | 1 |
| | Paraguay | 3 (1.6) | 6 (1.6) | 9 (1.6) | 1.00 (0.25-4.05) |
| | Total | 182 (100) | 364 (100) | 546 (100) | - |
| Imprisoned patients | Yes | 31 (17.5) | 39 (12.7) | 70 (14.5) | 1.45 (0.87-2.43) |
| | No | 146 (82.5) | 267 (87.3) | 413 (85.5) | 1 |
| | Total | 177 (100) | 306 (100) | 483 (100) | - |
| Homeless patients | Yes | 10 (5.6) | 6 (2.0) | 16 (3.3) | 2.99 (1.07-8.38) |
| | No | 167 (94.4) | 300 (98.0) | 467 (96.7) | 1 |
| | Total | 177 (100) | 306 (100) | 483 (100) | - |
| Health practitioners | Yes | 1 (0.6) | 2 (0.7) | 3 (0.6) | 0.86 (0.78-9.59) |
| | No | 176 (99.4) | 304 (99.3) | 480 (99.4) | 1 |
| | Total | 177 (100) | 306 (100) | 483 (100) | - |
| Immigrant patients | Yes | 2 (1.1) | 8 (2.6) | 10 (2.1) | 0.43 (0.09-2.04) |
| | No | 174 (98.9) | 298 (97.4) | 472 (97.9) | 1 |
| | Total | 176 (100) | 306 (100) | 482 (100) | - |
| Government cash transfer program recipients | Yes | 7 (4.0) | 4 (1.3) | 11 (2.3) | 3.17 (0.92-11.0) |
| | No | 166 (96.0) | 301 (98.7) | 467 (97.7) | 1 |
| | Total | 173 (100) | 305 (100) | 478 (100) | - |

Regarding the clinical characteristics, the study showed a statistically significant association between smokers and pulmonary clinical form (OR 3.57; CI95% 1.72-7.34), alcoholism (OR 3.58; CI95% 2.39-5.38), and drug use (OR 8.11; CI95% 4.89-13.46). No association was found between smoking and HIV, diabetes, mental disorder, or other diseases (**Table 2**).

Table 2 Distribution of smokers and non-smokers diagnosed with tuberculosis, according to clinical characteristics in Foz do Iguacu - PR, in the period from 2009 to 2018.

| Clinical characteristics | | Smokers | | Total N (%) | Odds Ratio |
|--------------------------|------------------------------------|--------------|-------------|----------------|-------------------|
| | | Yes N (%) | No N (%) | | |
| Clinical presentation | Pulmonary | 173 (95.1) | 307 (84.3) | 480 (87.9) | 3.57(1.72-7.34) |
| | Extra-pulmonary or Pulmonary-extra | 9 (4.9) | 57 (15.7) | 66 (12.1) | 1 |
| | Total | 182 (100) | 364 (100) | 546 (100) | - |
| HIV | Yes | 20 (11.2) | 42 (13.5) | 62 (12.7) | 0.81 (0.46-1.44) |
| | No | 158 (88.8) | 270 (86.5) | 428 (87.3) | 1 |
| | Total | 178 (100) | 312 (100) | 490 (100) | - |
| Diabetes | Yes | 8 (4.4) | 24 (6.6) | 32 (5.9) | 0.66 (0.29-1.49) |
| | No | 173 (95.6) | 340 (93.4) | 513 (94.1) | 1 |
| | Total | 181 (100) | 364 (100) | 545 (100) | - |
| Mental disorder | Yes | 9 (5.0) | 12 (3.3) | 21 (3.9) | 1.54 (0.64-3.72) |
| | No | 171 (95.0) | 351 (96.7) | 522 (96.1) | 1 |
| | Total | 180 (100) | 363 (100) | 543 (100) | - |
| Alcoholism | Yes | 75 (41.4) | 60 (16.5) | 135 (24.8) | 3.58 (2.39-5.38) |
| | No | 106 (58.6) | 304 (83.5) | 410 (75.2) | 1 |
| | Total | 181 (100) | 364 (100) | 545 (100) | - |
| Drug use | Yes | 67 (37.4) | 25 (6.9) | 92 (16.9) | 8.11 (4.89-13.46) |
| | No | 112 (62.6) | 339 (93.1) | 451 (83.1) | 1 |
| | Total | 179 (100) | 364 (100) | 543 (100) | - |

Regarding diagnosis, a statistically significant association was found between smoking and re-entry after default (OR 2.50; CI95% 1.32-4.74) and X-ray with TB-suspicion result (OR 3.53; CI95% 1.03-12.08). No association was identified between smoking and the variables sputum smear microscopy, rapid molecular testing, sputum culture or susceptibility testing (**Table 3**).

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Table 3 Distribution of smokers and non-smokers diagnosed with tuberculosis, according to the characteristics of the diagnosis in Foz do Iguaçu - PR, from 2009 to 2018*.

| Diagnosis Characteristics | | Smokers | | Total N (%) | Odds Ratio |
|---------------------------|------------------------|------------|------------|----------------|-------------------|
| | | Yes | No | | |
| | | N (%) | N (%) | | |
| Type of entry | New case | 131 (72.0) | 298 (82.1) | 429 (78.7) | 1 |
| | Relapse | 21 (11.5) | 29 (8.0) | 50 (9.2) | 1.65 (0.91-3.00) |
| | Re-entry after default | 22 (12.1) | 20 (5.5) | 42 (7.7) | 2.50 (1.32-4.74) |
| | Transfer/after death | 8 (4.2) | 16 (4.4) | 24 (4.5) | 1.14 (0.48-2.72) |
| | Total | 182 (100) | 363 (100) | 545 (100) | |
| Sputum smear microscopy | Positive | 91 (80.5) | 192 (75.3) | 283 (76.9) | 1.35(0.79-2.34) |
| | Negative | 22 (19.5) | 63 (24.7) | 85 (23.1) | 1 |
| | Total | 113 (100) | 255 (100) | 368 (100) | - |
| Rapid molecular test | Detectable | 93 (86.1) | 112 (79.4) | 205 (82.3) | 1.61 (0.81-3.17) |
| | Non-detectable | 15 (13.9) | 29 (20.6) | 44 (17.7) | 1 |
| | Total | 108 (100) | 141 (100) | 249 (100) | - |
| Sputum Culture | Positive | 110 (69.6) | 166 (60.4) | 276 (63.7) | 1.50 (0.99-2.28) |
| | Negative | 48 (30.4) | 109 (39.6) | 157 (36.3) | 1 |
| | Total | 158 (100) | 271 (100) | 433 (100) | - |
| Susceptibility test | Resistant | 14 (14.7) | 11 (8.8) | 25 (11.4) | 1.79 (0.77-4.15) |
| | Sensitive | 81 (85.3) | 114 (91.2) | 195 (88.6) | 1 |
| | Total | 95 (100) | 120(100) | 220 (100) | - |
| Chest X-rays | Suspect | 150 (98.0) | 283 (93.4) | 433 (95.0) | 3.53 (1.03-12.08) |
| | Normal/other disease | 3 (2.0) | 20 (6.6) | 23 (5.0) | 1 |
| | Total | 153 (100) | 303 (100) | 456 (100) | - |

Directly Observed Treatment has been indicated for a large portion of individuals affected by TB, regardless of being a smoker or not. Smokers had higher rates of abandoning treatment when compared to non-smokers (Table 4).

Table 4 Distribution of smokers and non-smokers with a diagnosis of tuberculosis, according to follow-up of patients in Foz does Iguaçu - PR, in the period from 2009 to 2018*.

| Patients' Follow-up | | Smokers | | Total N (%) |
|---------------------------|------------------|-----------|------------|----------------|
| | | Yes | No | |
| | | N (%) | N (%) | |
| Directly Observed Therapy | Yes | 35 (87.5) | 135 (79.4) | 170 (81.0) |
| | No | 5 (12.5) | 35 (20.6) | 40 (19.0) |
| | Total | 40 (100) | 170 (100) | 210 (100) |
| Treatment Outcome | Cure | 88 (48.6) | 234 (64.3) | 322 (59.1) |
| | Default | 42 (23.2) | 50 (13.7) | 92 (16.9) |
| | Death | 23 (12.7) | 38 (10.4) | 61 (11.2) |
| | Transfer | 12 (6.6) | 29 (8.0) | 41 (7.5) |
| | Resistant | 14 (7.7) | 7 (1.9) | 21 (3.9) |
| | Change of scheme | 2 (1.1) | 6 (1.7) | 8 (1.5) |
| | Total | 181 (100) | 364 (100) | 545 (100) |

DISCUSSION

Several aspects, such as smoking-related tobacco use, may interfere in the incidence and prognosis of TB cases and are associated with unfavourable outcomes. Therefore, the identifying the aspects associated with tobacco use in TB patients with an investigation of social demographic, clinical, diagnostic, and follow-up aspects can contribute to an adequate and focused care provided to these individuals in order to overcome the challenges involving the achievement of treatment success among them. The results of the study indicate that tobacco use is affecting patients with TB with a mean age of about 40 years old. These people come from a generation in which the smoking habit was fashionable in their cultural context and from a period when the consequences were unknown and there was no social critique in relation to this act. Moreover, it leads to a reflection regarding active and economically productive individuals that may be more predisposed to smoking due to exhausting daily routines, stress, and anxiety, among others. It is also important to mention that such individuals end up in environments with greater circulation and contact with other people, predisposing themselves to contact and develop TB. Results of the study regarding gender shows that there was a high number of males among TB patient smokers, concurring with other findings^[8] which cited that the proportion of TB attributable to smoking was more than 6 times higher in men than in women It is hypothesized that men are exposed to riskier behaviours and work activities, as well as being less concerned with their health, as verified by their low visits to physicians and low attendance at health services for routine consultations, situations which predispose them to tobacco use and to the onset of diseases such as TB. As a consequence of this culture in the male population, a longer life expectancy is observed among

women. It was found that skin colour was not associated with smoking in people with TB. However, a study carried out in the United States showed that black people were less likely to quit smoking^[9]. Regarding education, the study did not point out a statistically significant association between smoking and individuals with lower education. This result is different from another study^[10] which showed a higher prevalence of smokers among individuals with low education level and a probable association of smoking with a lack of knowledge about healthcare and diseases. There was no evidence of association between smoking and the residential area, although most TB cases live in an urban area. This profile reflects the urbanization of the municipality of Foz do Iguaçu, which recorded a rate of 99.2% in the 2010 census^[7] as well as the ease of access to cheap cigarettes from Paraguay. Among the inmates, there are a large proportion of individuals with addiction to psychoactive substances, but tobacco use was not observed. However, the prison population is exposed to greater TB infection because they experiment conditions conducive to the transmission and prevalence of the disease among these patients, since they are confined to closed environments with higher occupancy rates than the predefined capacity and with poor lighting and ventilation^[14]. An association with smokers was identified for homeless patients, reinforcing that socially vulnerable conditions are linked to this habit, as well as behaviours that put their own health at risk. Moreover, it is noteworthy that these same aspects that surround the social vulnerability of smokers are the same that expose them to develop pulmonary TB^[12]. Still regarding these aspects^[13] studies have shown that the homeless population knows little about the disease, only seeking healthcare when in extreme need, since they depend on others to refer them. Although health professionals have a significant prevalence of cigarette use^[14] the study did not indicate an association between these variables. In addition, evidence of an association between smoking and being an international immigrant was also not observed, however in other studies^[15,16] we can see that being an immigrant is a protective factor for substance use. An indication that smoking in people with tuberculosis is associated with social issues could be shown by the receipt of benefits from the government's cash transfer program, since it is known that the beneficiaries are people from families in the poverty line or in extreme poverty. However, the study did not identify such an association, showing that the actions developed by the Tobacco Control Programs at the national, state and municipal levels may be effective in different social groups. It is described that there is a decrease in phagocytic capacity and monocyte/macrophage activity in the lungs in smoking patients with TB, which together with the numerous harmful substances present in tobacco justify the significant association between the pulmonary clinical form of TB and smoking^[17]. Such results also lead to the understanding of increased pulmonary cavitation finding in chest radiographs among smoking patients, a result that has also been found in other studies^[18,19]. Despite being considered risk factors associated with tuberculosis infection, HIV, diabetes and mental disorder showed no association with smoking. This result indicates that the complications arising from the use of tobacco, whose risk of death from tuberculosis is nine times higher compared to non-smokers, are not overlapping the complications inherent to these diseases, bringing expectations of favourable treatment results among the affected cases by TB and who present comorbidities or who are smokers. Alcoholism was identified as one of the aspects associated with tobacco use among pulmonary TB patients. The association between these variables can lead to increased severity in relation to the prognosis of the disease, and greater failure of pharmacological therapy as a consequence, whether due to drug-alcohol reactions, to bacterial resistance, or even to the patient treatment default, which worsens the damage to the patient and the transmissibility of TB, generating an impact on public health. In the results found, it may be that alcoholism is also associated with men for genetic and cultural reasons, who were mostly in the smoking group. The research also found the use of illicit drugs as a factor associated with smoking among individuals with TB showing the need for a comprehensive approach to patients and an integrated assistance to other specialties such as mental health, with strategies for harm reduction or cessation in the use of these substances in order to maximize the results of anti-tuberculosis therapy, since they are proven to be harmful to treatment and patient health^[15] Therefore, the importance of programs to reduce or stop tobacco use is evidenced, which can contribute to relieve the burden of TB infection, and such programs should be extended to drug and alcohol users^[20]. Bacterial resistance in anti-tuberculosis therapy is another worrisome determinant of smoking among TB patients. It is hypothesized that this occurs due to the drop in immunity of patients who use tobacco, with a reduction in the activity of defense cells^[15] as well as a higher number of relapse cases and re-entry to treatment after abandoning. In addition, it has been found that smokers tend to have unsuccessful TB treatment outcomes and relapses which lead to treatment relapse^[21] Moreover, it is mentioned that the use of tobacco, in addition to aggravating the disease, can compromise the treatment with a higher risk of TB recurrence compared to non-smokers^[17] There was no evidence of an association between smoking and the results of the microscopy, TRM, sputum culture and sensitivity tests in this study. However, results from X-ray tests for suspected TB in this study were associated with smoking, showing the importance of imaging in the diagnosis of TB in people who use tobacco. Moreover, this result exposes the increased vulnerability of the respiratory system of smoker patients to *Mtb*, making it susceptible to infections and sequelae which compromise lung function^[5,22] Finally, the study showed a higher DOT indication and a higher percentage of treatment default and drug resistance cases among patients who smoke. Among smokers, 23.2% did not complete treatment, which leads us to think about if DOT is actually offered and the transmission risks of bacillus to other individuals, as well as future returns to treatment and drug resistance if death does not occur, with greater epidemiological consequences and financial investments of the healthcare system if such situations occur. The results of this study are consistent with a study^[19] that showed the high rate of treatment abandonment and resistance among smokers with TB. In view of the above, the importance of the TB Control Program teams working in conjunction with multidisciplinary teams and other social sectors to combat the use of tobacco in accordance with the National Policy on the Smoking Control^[6] should be emphasized, promoting actions to promote health and prevent diseases that reduce smoking among the entire population, since anyone can develop TB, as well as to provide therapeutic follow-up in order to reduce harm or to stop using tobacco. Thus, diagnosis and anti-tuberculosis therapy alone are not enough; it is essential for the patients to be aware of the complications arising from smoking, thus providing comprehensive care to the individual and a positive result in the treatment of TB and in the fight against smoking through recognition of the associated

aspects. Possible information bias may be cited among the limitations of the study, since the data were collected from secondary sources of information; smoking variable does not allow quantifying the gradients and the dependence time on the habit in question; lastly, we did not control the confounding variables.

CONCLUSION

According to the analyses of the aspects associated with tobacco use among the cases of TB, low education levels, homeless patients, patients with pulmonary TB and health risk behaviors, such as the use of alcohol and illicit drugs were identified. Such aspects associated must be considered for the delivery of individual/collective care, as well as for undertaking actions and strategies to overcome the challenges that involve such health needs and vulnerabilities. Furthermore, the study associates smoking with re-entry after default and severe chest radiological images, with smokers being more prone to treatment abandonment and drug-resistant TB, showing the urgency of dialogues between the TB Control Program and the National Smoking Control Policy in order to improve TB treatment outcome.

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