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Factors associated with loss to follow-up in tuberculosis treatment in Brazil: a retrospective cohort study

Fatores associados à perda de seguimento do tratamento para tuberculose no Brasil: coorte retrospectiva

Factores asociados a la pérdida de seguimiento del tratamiento para la tuberculosis en Brasil: cohorte retrospectiva

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ABSTRACT

Objective: To analyze the factors associated with loss to follow-up in tuberculosis cases among adults in Brazil in 2020 and 2021.
Method: Retrospective cohort with secondary data from the Brazilian Notifiable Diseases Information System. A total of 24,344 people diagnosed with tuberculosis whose information was complete in the database were included. Adjusted odds ratios and confidence intervals were estimated by binary logistic regression.
Results: Higher odds of loss to follow-up were observed for males, non-white ethnicity/color, with lower education level, homeless or deprived of liberty, who used drugs, alcohol and/or tobacco, with admission due to recurrence or re-entry after abandonment, and with unknown or positive serology for HIV. On the other hand, older age, extrapulmonary tuberculosis, deprivation of libertyand supervised treatment were associated with lower odds of loss to follow-up.
Conclusion: Demographic, socioeconomic and clinical-epidemiological factors were associated with the loss to follow-up in tuberculosis cases, which reiterates the various vulnerabilities intertwined with the illness and treatment of this disease. Therefore, there is a need to promote strategies aimed at adherence and linkage to the care for groups most vulnerable to loss to follow-up in tuberculosis treatment in Brazil.
Descriptors: Tuberculosis. Lost to follow-up. Cohort studies. Logistic models. Continuity of patient care.

RESUMO

Objetivo: Analisar os fatores associados à perda de seguimento dos casos de tuberculose entre adultos no Brasil em 2020 e 2021.
Método: Coorte retrospectiva com dados secundários provenientes do Sistema de Informação de Agravos de Notificação do Brasil. Foram incluídas 24.344 pessoas diagnosticadas com tuberculose cujas informações estavam completas no banco de dados. Razões de chances ajustadas eintervalos de confiança foram estimados por regressão logística binária.
Resultados: Observaram-se maiores chances de perda de seguimento para pessoas do sexo masculino, deetnia/cor não branca, combaixa escolaridade, em situação de rua, que faziamuso de drogas, álcool e/outabaco, com entrada porrecorrênciaou reingressoapós abandono, e com sorologia desconhecida oupositiva para HIV. Por outro lado, a idade mais avançada, a forma extrapulmonar da tuberculose, a privação de liberdade eo tratamento supervisionado associaram-se a menores chances.
Conclusão: Fatores demográficos, socioeconômicos e clínico-epidemiológicos estiveram associadosà perda de seguimento dos casos de tuberculose, o que reitera as diversas vulnerabilidades imbricadas ao adoecimento e ao tratamento dessa doença. Portanto, constata-se a necessidade depromoção de estratégias que visem à adesão e à vinculação ao cuidado dos grupos mais vulneráveis à perda de seguimento do tratamento para tuberculoseno Brasil.
Descritores: Tuberculose. Perda de seguimento. Estudos de coortes. Modelos logísticos. Continuidade da assistência ao paciente.

RESUMEN

Objetivo: Analizar los factores asociados a la pérdida de seguimiento de los casos de tuberculosis entre adultos en Brasil en 2020 y 2021.
Método: Cohorte retrospectiva con datos secundarios del Sistema de Información de Enfermedades de Declaración Obligatoria de Brasil. Se incluyeron un total de 24.344 personas diagnosticadas con tuberculosis cuya información estaba completa en la base de datos. Las razones de probabilidad ajustadas y los intervalos de confianza se estimaron mediante regresión logística binaria.
Resultados: Se observaron mayores posibilidades de perder el seguimiento para el sexo masculino, de etnia/color no blanco, con baja escolaridad, sin hogar, que usaban drogas, alcohol y/o tabaco, con ingreso por recidiva o reingreso tras abandono, y con serología desconocida o positiva para VIH. Por otro lado, la edad avanzada, la forma extrapulmonar de tuberculosis, la privación de libertad y el tratamiento supervisado se asociaron con menores probabilidades.
Conclusión: Factores demográficos, socioeconómicos y clínico-epidemiológicos se asociaron a la pérdida del seguimiento de los casos de tuberculosis, lo que reitera las diversas vulnerabilidades entrelazadas con la enfermedad y el tratamiento de esta enfermedad. Por lo tanto, existe la necesidad de promover estrategias dirigidas a la adherencia y la vinculación a la atención de los grupos más vulnerables a la pérdida del tratamiento de seguimiento de la tuberculosis en Brasil.
Descriptores: Tuberculosis. Perdida de seguimiento. Estudios de cohortes. Modelos logísticos. Continuidad de la atención al paciente.

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INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease that represents a global socio-sanitary challenge, especially in the post-COVID-19 scenario. This is because the pandemic impacted TB diagnosis and treatment actions, reversing historical progress in its control[1,2]. Worldwide, 6.4 million new cases of TB were recorded in 2021, of which around 25.0% progressed to death[1]. Brazil, a country with a high TB burden, recorded 78,057 cases in 2022, representing a rate of 36.3 per 100 thousand inhabitants[2].

The health-disease process related to TB is intertwined with the social development of the population, with poor living conditions considered one of the main enhancers of illness[1–3].In this sense, it is recognized that TB is a disease related to and perpetuating poverty, stemming from overlapping socioeconomic difficulties and resulting in contexts of vulnerability, marginalization, stigma and discrimination, experiences often endured by affected people[3].

People with TB are susceptible to different outcomes. A cross-sectional study conducted in Werder, Ethiopia, showed that 71.1% of cases completed treatment and 16.6% were lost to follow-up[4], a situation in which treatment is not started or is interrupted for 30 consecutive days[5]. In this same research, it was evidenced that the age of 55 to 64 years old, the male gender, the distance ≥ 10 km to access the healthcare service and the history of TB treatment showed a significant association with the occurrence of this outcome[4].

An exploratory study conducted in Gwalior, India, which aimed to understand the aspects related to the loss to follow-up in TB cases, revealed that the side effects of medications, financial restrictions related to job loss, abuse of chemical substances, low education level, social stigma, lack of family support, lack of knowledge about the disease and lack of advice from healthcare professionals were the main barriers to treatment adherence[6].

In addition to the possibility of worsening the clinical picture and unfavorable treatment outcome, loss to follow-up can result in the continued spread of the disease, as in the absence of medication, it allows the affected person to become infectious once again[7]. Furthermore, this situation can favor the development and spread of strains resistant to standard antibiotic therapy recommended by the Brazilian Ministry of Health, leading to drug-resistant TB (DR-TB)[7].

In Brazil, TB treatment is available in the Unified Health System (*Sistema* Único *de Saúde* – SUS) and occurs, in most cases, in Primary Health Care (PHC)[8].However, the percentage of loss to follow-up among people with TB has been increasing since 2016, rising from 11.2% to 14.0% in 2021; on the other hand, cure has reduced, going from 76.2% to 66.5% in the same period[2]. Furthermore, it is worth highlighting that when comparing the two-year periods 2018-2019 and 2020–2021, the loss to follow-up in TB cases increased by 10.4%[2].

Strategies have been sought to minimize this problem, such as directly observed treatment (DOT), an action in which the healthcare professional observes, at least three times a week, the person's medication intake throughout the entire TB treatment[5]. However, the implementation of DOT may be challenging in cases of social vulnerability, such as drug abuse and homelessness, which emphasizes the existence of numerous individual, social and programmatic factors that affect treatment adherence[9].

Considering the complexity of synergistic and intrinsic aspects of illness and treatment adherence for TB in the Brazilian population, the guiding question of this study was raised: what are the factors possibly associated with the occurrence of loss to follow-up in treatment among people affected by TB in the country? Therefore, this research aimed to analyze the factors associated with loss to follow-up in tuberculosis cases among adults in Brazil in 2020 and 2021.

METHOD

Retrospective cohort study, complied with the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). This research was developed with data from the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* – SINAN) in Brazil, accessed in November 2022 by the Information Technology Department of the Unified Health System (DATASUS). SINAN is a decentralized system that allows the recording and monitoring of notifiable diseases and conditions at a national level.

Brazil, the setting of this study, has 210 million inhabitants and is divided into five regions: North, Northeast, Southeast, South, and Midwest. It is worth noting that, since 2017, the fight against the disease has been guided by the National Plan to End TB, aligned with the Global End TB Strategy and the Sustainable Development Goals (SDGs). Among the goals set for 2035, the aim is to reduce the number of cases to less than 10 per 100 thousand inhabitants and to reduce the number of deaths to less than 230 per year in the country[2].

To reduce the number of cases and deaths from TB, early diagnosis and adequate treatment of those affected are essential. In Brazil, TB management is decentralized to PHC, which is responsible, in typical cases of the disease, for diagnosing and treating people for at least six months[5]. This follow-up and closure information is recorded by healthcare

professionals in the TB case monitoring form and subsequently notified on SINAN[5].

Cases of TB in individuals aged 18 and above were analyzed, categorized as new cases (person never subjected to treatment or treated for < 30 days), recurrence (person who presented reinfection or recurrence of the previous one) and re-entry after abandonment (person who started new treatment after abandonment)[5].The period 2020 and 2021 was considered as COVID-19 hampered the monitoring of TB cases[2] and, therefore, the inclusion of data prior to and concomitant with the pandemic could obscure the associations being tested.

Participants were selected based on their classification in the SINAN as either primary abandonment (< 30 days) and abandonment (≥ 30 days), hereinafter referred to as loss to follow-up; and as cured (treatment completed as recommended)[5]. Cases in progress or with other closures were excluded due to the impossibility of categorizing their follow-up status. Furthermore, complete cases were analyzed to ensure the accuracy of the information, removing records with at least one ignored/blank variable (Figure 1).

The following demographic and socioeconomic variables were considered: gender (male and female); age (in years); age group (18 to 34, 35 to 64 and 65 years and over); ethnicity/color (white and non-white); region of residence (North, Northeast, South, Southeast and Midwest); education level (illiterate, ≤ 8 years and > 8 years of education); beneficiary of a government income transfer program (yes and no); immigrant population (yes and no); homeless population (yes and no); and population deprived of liberty (yes and no).

The clinical-epidemiological variables extracted were: type of entry (new case, recurrence and reentry after abandonment); clinical form (pulmonary, extrapulmonary and mixed); treatment modality (self-administered or supervised); alcohol use (yes and no); use of illicit drugs (yes and no); tobacco use (yes and no); diabetes (yes and no); mental disorder (yes and no); and co-infection with HIV (yes, no and doesn't know – this subcategory encompasses people who have not been tested or have ongoing testing for HIV).

The data was exported to a Microsoft Excel 2016® spreadsheet and organized into contingency tables. For the descriptive analysis, the absolute and relative frequencies were presented for each categorical variable, according to the case outcome (cure and loss to follow-up). In the analytical component, to verify the relationship between the dependent and independent variables, the binary logistic regression model was used, given the categorical and dichotomous nature of the dependent variable[10].

Initially, a diagnosis of collinearity of the variables was performed, and it was found the absence of multicollinearity (tolerance test with values greater than 0.10 and variance inflation factor less than 10.00). Following this, bivariate analyzes were made using regression models, calculating unadjusted odds ratios (uOR) and their 95% confidence intervals (95%CI). Variables were considered significant if their 95%CI did not cross the null value (1.00).

Afterwards, initial multivariate models were constructed. To this end, selection was used by the stepwise backward method, in which the independent variables with p-value ≤ 0.10 in bivariate analysis were inserted together and then removed one by one, respecting the significance criterion by likelihood ratio. In the end, only variables with a p-value ≤ 0.05 remained. With this, the adjusted odds ratios (aOR) for the final set of variables and their 95%CI were estimated.

These odds ratios represented the increased or reduced chance of each subvariable for loss to follow-up outcome in relation to the reference categories, selected based on theoretical hypotheses, in the respective independent variables. Furthermore, to test the robustness of the findings and avoid association bias regarding the exclusion of cases with unknown information, a *post hoc* analysis was conducted including missing data as a subcategory of the independent variables of the final multiple model.

The p-values of the Wald tests referring to the regression coefficients were presented (p-value ≤ 0.05 was intended). The final model was evaluated by the omnibus test, whose chi-square statistic (χ^2) compares the difference in variation between the adjusted and null models (with a desired p-value ≤ 0.05). Additionally, the Nagelkerke pseudo-$r^2$was used to represent the explanatory capacity of the final model with respect to the analyzed outcome (1.00 was considered)[10]. The analyses were conducted using the SPSS Statistics® software, version 20.1.

This study is part of an institutional project aimed at improving assistance and surveillance of communicable diseases through diagnoses and situational analyses. Therefore, it is approved by the Research Ethics Committee (opinion no. 5.721.740/2022 and certificate of presentation for ethical appreciation no. 63981922,6,0000,0104), according to Resolution No. 466/2012 of the National Health Council. Since these are secondary data, the requirement for informed consent was waived.

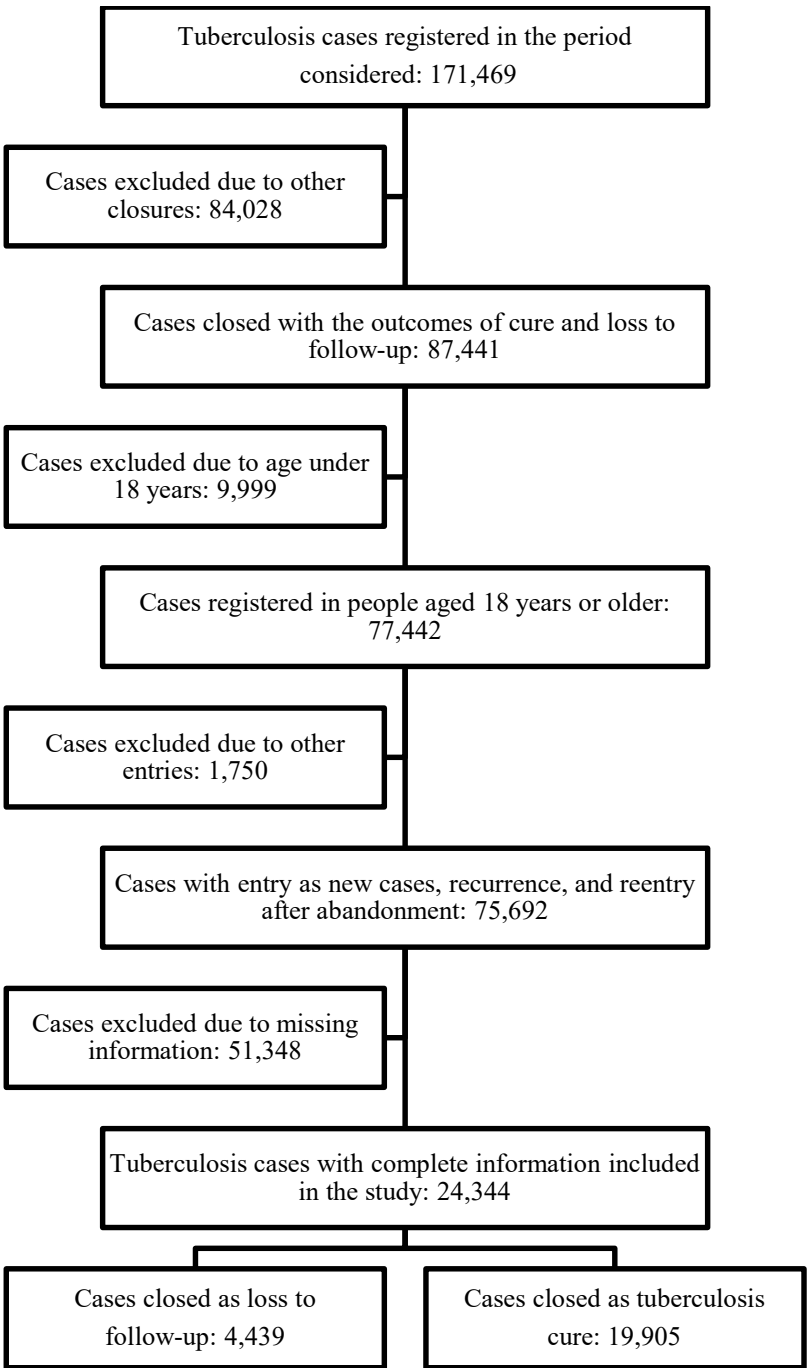

Figure 1 – Flowchart of the selection process for tuberculosis cases registered in Brazil between 2020 and 2021.
Source: Prepared by the authors, 2022.

RESULTS

There were 171,469 cases of TB reported in Brazil between 2020 and 2021, of which 14.19% were included. Exclusions due to missing data occurred in the following variables in the respective order: government beneficiary (31,366); education level (21,903); treatment type (20,190); ethnicity/color (5,655); drug use (4,676); tobacco use (4,495); mental disorder (4,466); alcohol use (4,359); diabetes (4,219); immigrant (3,805); homelessness (3,289); not deprived of liberty (2,524); HIV co-infection (296); region of residence (9); gender (8); and clinical form (4).

The proportion loss to follow-up was 18.23% in Brazil, with variation between regions, namely: South (22.94%), Southeast (19.61%), Midwest (17.64%), Northeast (15.66%) and North (15.10%). A higher occurrence was observed in males (75.65%), aged 18 to 34 (52.76%), non-white (76.08%), with up to 8 years of study (68.51 %), non-beneficiaries of income transfer programs (90.22%), who were not deprived of liberty (92.45%) or homeless (89.93%) and non-immigrants (99.53%) (Table 1).

Regarding clinical-epidemiological aspects, the proportion of loss to follow-up was higher among new cases (64.09%), with clinical pulmonary form of TB (91.05%) and who did not undergo supervised treatment (69.70%). Furthermore, there was a predominance of people who did not use alcohol (69.86%), illicit drugs (64.02%) and tobacco (57.74%), who did not have any mental disorder (96.31%), who did not have diabetes (93.99%) and did not have HIV co-infection (70.79%) (Table 1).

In bivariate analysis, high odds of loss to follow-up were evidenced among male people, with low education level, non-white and homeless, whose entry was due to recurrence or re-entry after abandonment, with a mixed form (pulmonary and extrapulmonary), in use of alcohol, drugs and tobacco, with mental disorders and with TB-HIV co-infection. On the other hand, increasing age, deprivation of liberty, extrapulmonary form, DOT and diabetes reduced the odds (Table 2).

In the final model, increased odds of loss to follow-up were observed for the following variables: male (aOR: 1.35); non-white ethnicity/color (aOR: 1.16); illiterate education level (aOR: 1.60) and with up to 8 years of study (aOR: 1.66); homelessness people (HP) (aOR: 2.55); drug use (aOR: 1.84), alcohol use (aOR: 1.14) and tobacco use (aOR: 1.38); entry as recurrence (aOR: 1.33) and re-entry after abandonment (aOR: 4.31); and unknown serology (aOR: 1.69) and TB-HIV co-infection (aOR: 1.90) (Table 3).

On the other hand, the following variables were associated with a lower odds of loss to follow-up: age (aOR: 0.97); population deprived of liberty (PDL) (aOR: 0.32); completion of DOT (aOR: 0.46); and extrapulmonary form (aOR: 0.82) (Table 3). When evaluating the model adjustment, a Nagelkerke pseudo-r^2 of 0.249 was obtained: the model explains 24.90% of the variation in the dependent variable. The omnibus test showed a p-value < 0.001 (χ^2:4,025.83), indicating that the adjusted model is better than the model without variables.

In the *post hoc* sensitivity analysis, when including the missing data as a subcategory of the independent variables of the final model, it was noted that most of association measures maintained similar values to the complete case approach. A significant difference was observed in the odds ratios and their 95%CI, compared to the main model, for education level ≤ 8 years of study and for carrying out the DOT. However, these variables maintained their association with the studied outcome (Table 4).

Table 1 – Descriptive analysis of the demographic, socioeconomic, and clinical-epidemiological characteristics of individuals affected by tuberculosis in Brazil between 2020 and 2021.

Characteristics	Total	Loss to follow-up	Cure
	n (%)	n (%)	n (%)
Gender			
Female	7,786 (31.98)	1,081 (24.35)	6,705 (33.69)
Male	16,558 (68.02)	3,358 (75.65)	13,200 (66.31)
Age group			
18 to 34 years old	10,732 (44.08)	2,342 (52.76)	8,390 (42.15)
35 to 64 years old	11,486 (47.18)	1,920 (43.25)	9,566 (48.06)
≥ 65 years old	2,126 (8.73)	177 (3.99)	1,949 (9.79)

Table 1 – Cont.

Characteristics	Total	Loss to follow-up	Cure
	n (%)	n (%)	n (%)
Ethnicity/color			
White	6,912 (28.39)	1,062 (23.92)	5,850 (29.39)
Non-white	17,432 (71.61)	3,377 (76.08)	14,055 (70.61)
Education level			
Illiterate	1,085 (4.46)	168 (3.78)	917 (4.61)
≤ 8 years	13,511 (55.50)	3,041 (68.51)	10,470 (52.60)
> 8 years	9,748 (40.04)	1,230 (27.71)	8,518 (42.79)
Income transfer			
No	21,802 (89.56)	4,005 (90.22)	17,797 (89.41)
Yes	2,542 (10.44)	434 (9.78)	2,108 (10.59)
Deprivation of liberty			
No	21,766 (89.41)	4,104 (92.45)	17,662 (88.73)
Yes	2,578 (10.59)	335 (7.55)	2,243 (11.27)
Homelessness			
No	23,625 (97.05)	3,992 (89.93)	19,633 (98.63)
Yes	719 (2.95)	447 (10.07)	272 (1.37)
Immigrant			
No	24,234 (99.55)	4,418 (99.53)	19,816 (99.55)
Yes	110 (0.45)	21 (0.47)	89 (0.45)
Entry Type			
New case	20,262 (83.23)	2,845 (64.09)	17,416 (87.50)
Recurrence	1,653 (6.79)	300 (6.76)	1,353 (6.80)
Re-entry after abandonment	2,430 (9.98)	1,294 (29.15)	1,136 (5.70)
Clinical form			
Pulmonary	21,505 (88.33)	4,042 (91.05)	17,463 (87.73)

Table 1 – Cont.

Characteristics	Total	Loss to follow-up	Cure
	n (%)	n (%)	n (%)
Extrapulmonary	2,353 (9.67)	287 (6.47)	2,066 (10.38)
Mixed	486 (2.00)	110 (2.48)	376 (1.89)
Treatment modality			
Self-administered	13,428 (55.16)	3,094 (69.70)	10,334 (51.92)
Supervised	10,916 (44.84)	1,345 (30.30)	9,571 (48.08)
Alcohol use			
No	19,913 (81.80)	3,101 (69.86)	16,812 (84.46)
Yes	4,431 (18.20)	1,338 (30.14)	3,093 (15.54)
Illicit drugs use			
No	20,191 (82.94)	2,842 (64.02)	17,349 (87.16)
Yes	4,153 (17.06)	1,597 (35.98)	2,556 (12.84)
Tobacco use			
No	17,780 (73.04)	2,563 (57.74)	15,217 (76.45)
Yes	6,564 (26.96)	1,876 (42.26)	4,688 (23.55)
Mental disorder			
No	23,711 (97.40)	4,275 (96.31)	19,436 (97.64)
Yes	633 (2.60)	164 (3.69)	469 (2.36)
Diabetes			
No	22,010 (90.41)	4,172 (93.99)	17,838 (89.62)
Yes	2,334 (9.59)	267 (6.01)	2,067 (10.38)
HIV co-infection			
No	19,867 (81.60)	3,142 (70.79)	16,725 (84.02)
Doesn't know	2.645 (10.87)	615 (13.85)	2,030 (10.20)
Yes	1,832 (7.53)	682 (15.36)	1,150 (5.78)

Source: Notifiable Diseases Information System, 2022.

Table 2 – Bivariate analysis of demographic, socioeconomic, and clinical-epidemiological characteristics associated with loss to follow-up in tuberculosis cases in Brazil between 2020 and 2021.

Characteristics	uOR*	95%CI (min.–max.)†	p-value‡
Gender			
Female		Reference	
Male	1.57	1.46–1.70	< 0.001
Age (in years)			
Continuous variable	0.97	0.97–0.98	< 0.001
Ethnicity/color			
White		Reference	
Non-white	1.32	1.22–1.42	< 0.001
Education level			
Illiterate	1.26	1.06–1.51	0.008
≤ 8 years	2.01	1.87–2.16	< 0.001
> 8 years		Reference	
Income transfer			
No		Reference	
Yes	0.91	0.82–1.02	0.109
Deprivation of liberty			
No		Reference	
Yes	0.64	0.57–0.72	< 0.001
Homelessness			
No		Reference	
Yes	8.08	6.92–9.43	< 0.001
Immigrant			
No		Reference	
Yes	1.05	0.65–1.70	0.816
Entry Type			
New case		Reference	
Recurrence	1.35	1.19–1.54	< 0.001
Re-entry after abandonment	6.97	6.37–7.62	< 0.001

Table 2 – Cont.

Characteristics	uOR*	95%CI (min.–max.)†	p-value‡
Clinical form			
Pulmonary		Reference	
Extrapulmonary	0.60	0.52–0.68	< 0.001
Mixed	1.26	1.01–1.56	0.011
Treatment modality			
Self-administered		Reference	
Supervised	0.46	0.43–0.50	< 0.001
Alcohol use			
No		Reference	
Yes	2.34	2.17–2.52	< 0.001
Illicit drugs use			
No		Reference	
Yes	3.81	3.54–4.10	< 0.001
Tobacco use			
No		Reference	
Yes	2.37	2.22–2.54	< 0.001
Mental disorder			
No		Reference	
Yes	1.59	1.32–1.90	< 0.001
Diabetes			
No		Reference	
Yes	0.55	0.48–0.63	< 0.001
HIV co-infection			
No		Reference	
Doesn't know	1.61	1.46–1.77	< 0.001
Yes	3.15	2.85–3.49	< 0.001

Source: Notifiable Diseases Information System, 2022.
*Unadjusted odds ratio. †95% confidence interval (minimum–maximum). ‡Wald test.

Table 3 – Multivariate analysis of demographic, socioeconomic and clinical-epidemiological characteristics associated with loss to follow-up of tuberculosis cases in Brazil between 2020 and 2021.

Characteristics	aOR*	95%CI (min.–max.)†	p-value‡
Gender			
Female		Reference	
Male	1.34	1.23–1.46	< 0.001
Age (in years)			
Continuous variable	0.97	0.97–0.97	< 0.001
Ethnicity/color			
White		Reference	
Non-white	1.16	1.07–1.26	< 0.001
Education level			
Illiterate	1.60	1.31–1.95	< 0.001
≤ 8 years	1.80	1.66–1.96	< 0.001
> 8 years		Reference	
Deprivation of liberty			
No		Reference	
Yes	0.32	0.28–0.37	< 0.001
Homelessness			
No		Reference	
Yes	2.55	2.12–3.06	< 0.001
Entry Type			
New case		Reference	
Recurrence	1.33	1.15–1.53	< 0.001
Re-entry after abandonment	4.31	3.90–4.77	< 0.001

Table 3 – Cont.

Characteristics	aOR*	95%CI (min.–max.)†	p-value‡
Clinical form			
Pulmonary		Reference	
Extrapulmonary	0.82	0.71–0.94	0.007
Mixed	1.05	0.82–1.34	0.687
Treatment modality			
Self-administered		Reference	
Supervised	0.46	0.43–0.50	< 0.001
Alcohol use			
No		Reference	
Yes	1.14	1.04–1.26	0.005
Illicit drugs use			
No		Reference	
Yes	1.84	1.66–2.04	< 0.001
Tobacco use			
No		Reference	
Yes	1.38	1.26–1.51	< 0.001
HIV co-infection			
No		Reference	
Doesn't know	1.69	1.52–1.89	< 0.001
Yes	1.90	1.69–2.15	< 0.001

Source: Notifiable Diseases Information System, 2022.
*Adjusted odds ratio. †95% confidence interval (minimum–maximum). ‡Wald test.

Table 4 – Multivariate *post hoc* analysis of demographic, socioeconomic and clinical-epidemiological characteristics associated with loss to follow-up in tuberculosis cases in Brazil between 2020 and 2021.

Characteristics	aOR*	95%CI (min.–max.)†	p-value‡
Gender			
Female		Reference	
Male	1.36	1.30–1.43	< 0.001
Age (in years)			
Continuous variable	0.97	0.97–0.97	< 0.001
Ethnicity/color			
White		Reference	
Non-white	1.21	1.15–1.26	< 0.001
Education level			
Illiterate	1.47	1.28–1.68	< 0.001
≤ 8 years§	1.58	1.50–1.66	< 0.001
> 8 years		Reference	
Deprivation of liberty			
No		Reference	
Yes	0.37	0.35–0.40	< 0.001
Homelessness			
No		Reference	
Yes	3.10	2.84–3.39	< 0.001
Entry Type			
New case		Reference	
Recurrence	1.33	1.24–1.43	< 0.001
Re-entry after abandonment	3.93	3.72–4.15	< 0.001
Clinical form			
Pulmonary		Reference	

Table 4 – Cont.

Characteristics	aOR*	95%CI (min.–max.)†	p-value‡
Extrapulmonary	0.78	0.72–0.83	< 0.001
Mixed	0.94	0.83–1.07	0.398
Treatment modality			
Self-administered		Reference	
Supervised§	0.37	0.35–0.39	< 0.001
Alcohol use			
No		Reference	
Yes	1.24	1.18–1.31	< 0.001
Illicit drugs use			
No		Reference	
Yes	1.81	1.71–1.92	< 0.001
Tobacco use			
No		Reference	
Yes	1.27	1.21–1.33	< 0.001
HIV co-infection			
No		Reference	
Doesn't know	1.89	1.79–1.99	< 0.001
Yes	1.82	1.70–1.94	< 0.001

Source: Notifiable Diseases Information System, 2022.
*Adjusted odds ratio. †95% confidence interval (minimum–maximum). ‡Wald test. §There was a significant difference in the estimates from the analyses of complete cases and missing indicators.

DISCUSSION

This retrospective cohort study portrayed the complexity of factors that affect the follow-up of TB cases in the Brazilian population. A proportion of loss to follow-up of almost 19.0% was evidenced between 2020 and 2021, after applying the eligibility criteria, with disparity between the country's geographic regions. This value is more than three times higher than that recommended by the World Health Organization (WHO), which recommends a treatment abandonment rate of less than 5.0%[11].

A systematic review, which sought to identify the factors associated with this outcome in Brazil, revealed the lack of studies in this scope, especially those with robust statistical methods[12]. In this regard, it is important to highlight the potential of this study, which revealed various demographic,

socioeconomic, and epidemiological factors associated with loss to follow-up in TB cases, acting as an alert in the sense of requiring intersectoral efforts to promote treatment adherence strategies.

The profile of men, young, and of non-white ethnicity/color was in line with research that identified that DR-TB cases were predominant[13,14]. In these studies, the rate of treatment discontinuation was higher among this group, with most being re-entry after failure or abandonment[13,14]. Such fact suggests that young, non-white men still have difficulties in identifying their health demands and needs, which may influence the (non) adoption of protective practices.

Other factors commonly associated with loss to follow-up are alcohol use, tobacco or drugs and low educational level[12,15]. Education level is a proxy variable for income; therefore, it is possible to infer that the low perception of risk, combined with financial restrictions, could have made difficult the access to healthcare services for follow-up. Furthermore, the use of chemical substances may be associated with other risk practices and an increase in adverse drug effects, which could also harm adherence to TB treatment.

Among the priority groups for TB control in Brazil, PDL and HP stand out, as they share certain characteristics such as poverty, weakened or nonexistent family bonds, precarious housing and living conditions, and social exclusion, particularly when affected by TB[16,17]. In this study, it was observed that homeless people had a high chance of losing TB treatment follow-up, while people deprived of their liberty had lower odds.

These findings are similar to other studies using data from SINAN[15,18]. This may be related to the more proximal care offered to PDL, with the possibility of obtaining samples for diagnosis and treatment support through DOT[15,19]. Furthermore, it is worth noting that beyond the quality of the actions offered and despite the overlap of multiple vulnerabilities, confinement and restriction to an apparently controlled environment may have facilitated better treatment adherence.

In relation to HP, there is precarious access and provision of care throughout the follow-up[16,19], which can hinder the bond between professional and user and harm adherence to TB treatment. This reinforces the markers of social and health inequity associated with TB, as both HP and PDL experience situations of deprivation of basic human rights[16,19], which demands the implementation of specific healthcare strategies to the realities faced with a view to proper management and control of the disease.

A retrospective cohort study developed in the city of Nekemte, Ethiopia, identified a treatment failure rate for TB among people with HIV of 41.90%[20]. In this study, individuals without HIV had approximately 10 times higher odds of treatment success compared to those with TB-HIV coinfection[20]. These findings may be linked to the concomitant treatment of both infections, which requires a greater number of medications and, as a consequence, may cause side effects more frequently.

In this context, the need for actions that aim to provide access and continuity to TB treatment, with emphasis on the most vulnerable groups. In view of this, DOT is a strategy that has been implemented worldwide and shown effectiveness in results, leading to improved adherence to treatment and, thus, reducing unfavorable outcomes in people affected by TB, as demonstrated in studies conducted in Brazil, England, United States and Ethiopia[21–24].

Nationally, since 2000, it has been recommended that DOT be performed in a decentralized manner for PHC, with support from the Specialized Assistance Service (SAS) in cases of TB-HIV co-infection, and with nursing action[25]. This strategy ensures the link between services and people, allowing early identification and/or making abandonment difficult[26]. Such information is corroborated by the findings, which revealed that performing the DOT reduced the odds of loss to follow-up by 54.0%.

Among the attributes of PHC, as a gateway, care coordinator and flow organizer within the scope of the Health Care Network (HCN), is attention focused on the family and community guidance[27]. In the interface with TB, PHC is essential to provide co-participation of the person affected by the disease in their care, respecting and encouraging their role and autonomy, especially with regard to performing DOT as a strategy to reduce unsuccessful outcomes[26,27].

Additionally to DOT, social protection strategies, such as income transfer programs, contribute to improving TB control, as they have positive effects on treatment, adherence to care, cure rates and service provision, especially for changing ways of life[15,28,29]. However, it is mentioned that no significant association was perceived between obtaining benefits and following treatment in this study, possibly due to the high rate of missing information in the database.

It is worth noting that this study must be interpreted considering some limitations. By using data from the COVID-19 pandemic period, the frequency of missing data and the proportion of abandonments may have been overestimated. The models were not adjusted for any specific confounders. Another limitation is on the impossibility of identifying at which level of care the loss to follow-up occurred, considering that adherence to treatment can be different in outpatient/hospital care compared to PHC.

It's also important to note that grouping individuals by black, brown, indigenous, and yellow ethnicity/color into a single category did not allow the identification of social and racial inequalities linked to the loss to follow-up in TB cases. Furthermore, it is mentioned that the removal of absentees may have underestimated the associations. However, research with SINAN data that used the imputation technique or the analysis of missing data showed results similar to the complete case approach[15,18].

Specifically with regard to this study, although the extent and nature of the missing data may act as limitations regarding the generalization of the findings when considering the significant number of exclusions, the specific and similar estimates evidenced for the aOR and the 95%CI of the final models from the analyzes of complete cases and missing indicators suggest that there is little possibility that the exclusions have interfered with the identified associations.

It should also be noted that despite this study uses data from the pandemic period, the outcome related to treatment interruption was already an emerging issue. It is a fact that the disruption of services and the recommendation to reduce the frequency of care due to COVID-19 impacted the increase in loss to follow-up. However, social and programmatic factors remain important predictors of this outcome, as demonstrated in a study in another South American country[30].

In view of the above, it is essential that the planning and delivery of care for people and communities with TB are developed in an articulated manner between health and other sectors, such as social assistance, justice and public safety, as well as society civil society and non-governmental organizations, in order to join efforts to enable comprehensive care for TB and other demands and needs that are related to well-being and the ability to successfully follow and complete the treatment.

CONCLUSION

A high proportion of TB treatment loss to follow-up was observed in Brazil between 2020 and 2021. Increased odds of this outcome were associated with males, non-white ethnicity, low education level; the use of alcohol, tobacco, and illicit drugs; entry due to recurrence or re-entry after abandonment; being a homelessness person; and have TB-HIV co-infection. On the other hand, older age, being deprived of liberty, using DOT and having the extrapulmonary form were associated with lower odds.

The potential contribution of these findings to public health is presumed, as they provided the opportunity to identify situations of individual, socioeconomic and programmatic vulnerability linked to TB treatment. In this way, the results can support the development and/or improvement of robust health and social assistance strategies and policies aimed at centralizing care in the figure of the affected person, as recommended by the pillars of the strategy for ending TB in Brazil by 2035.

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