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Retreatment and Anti-tuberculosis Therapy Outcomes in Brazil Between 2015 and 2022: A Nationwide Study

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Background. Adherence to anti-tuberculosis treatment (ATT) in Brazil remains a challenge in achieving the goals set by the World Health Organization (WHO). Patients who are lost to follow-up during treatment pose a significant public health problem. This study aimed to investigate the factors associated with unfavorable ATT outcomes among those undergoing retreatment in Brazil.

Methods. We conducted an observational study of patients aged ≥18 years with tuberculosis (TB) reported to the Brazilian National Notifiable Disease Information System between 2015 and 2022. Clinical and epidemiologic variables were compared between the study groups (new cases and retreatment). Regression models identified variables associated with unfavorable outcomes.

Results. Among 743 823 reported TB cases in the study period, 555 632 cases were eligible, consisting of 462 061 new cases and 93 571 undergoing retreatments (44 642 recurrent and 48 929 retreatments after loss to follow-up [RLTFU]). RLTFU (odds ratio [OR], 3.96 [95% confidence interval {CI}, 3.83–4.1]) was a significant risk factor for any type of unfavorable ATT. Furthermore, RLTFU (OR, 4.93 [95% CI, 4.76–5.11]) was the main risk factor for subsequent LTFU. For death, aside from advanced age, living with HIV (OR, 6.28 [95% CI, 6.03–6.54]) was the top risk factor.

Conclusions. Retreatment is a substantial risk factor for unfavorable ATT outcomes, especially after LTFU. The rates of treatment success in RLTFU are distant from the WHO End TB Strategy targets throughout Brazil. These findings underscore the need for targeted interventions to improve treatment adherence and outcomes in persons who experience RLTFU.

Keywords. epidemiology; loss to follow-up; retreatment; treatment outcome; tuberculosis.

Tuberculosis (TB) remains the greatest cause of death by a single pathogen worldwide [1]. Importantly, TB treatment completion rates still fall short of the World Health Organization (WHO) targets [1]. Success rates are especially low in retreatment cases, which can lead to drug resistance and increased mortality and morbidity [1–3]. Thus, understanding the impact of a prior anti-TB therapy (ATT) on the outcomes of the current treatment is of utmost importance to guide the design of tailored public health interventions.

TB is a major public health concern in Brazil, identified by the WHO as one of the 30 countries with highest TB and TB–human immunodeficiency virus (HIV) burdens [4]. Hence, the Brazilian Ministry of Health (Br-MOH) operates the Brazilian Tuberculosis Database System (SINAN-TB) database, which captures information on all notified TB cases nationwide [5, 6]. However, subnational studies have still shown that Brazil's treatment abandonment rates are not only far higher than the targets set by the WHO, but also have a large association with both socioeconomic and biological factors [7, 8].

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As a component of pillar 1 of the End TB Strategy, the WHO aims to achieve a 90% treatment success rate for all reported cases of TB by 2035 [9]. To facilitate this, the strategy also recommends providing educational and economic assistance to TB patients, enabling them to complete their treatment [10]. Brazil has also committed to achieving these targets, with a specific focus on reducing treatment abandonment rates [6]. Importantly, treatment adherence interventions, including directly observed treatment (DOT) provided by trained healthcare professionals, as well as patient education and social protection, have been shown to greatly improve treatment success rates [11, 12]. Therefore, population-based, nationally representative studies from Brazil and other high-burden countries with close surveillance of retreatment and treatment outcomes among persons with TB are not available, but still needed to further understand progress and national TB control efforts in TB treatment [8].

Using the SINAN-TB database, we aimed to investigate the impact of previous TB treatment on the outcomes of new ATT in Brazil between 2015 and 2022. Specifically, we examined how retreatment, stratifying due to recurrent TB or retreatment after loss to follow-up (RLTFU), affects the likelihood of unfavorable outcomes, such as subsequent loss to follow-up (LTFU), treatment failure, or death. The analyses also explore the association between retreatment and other factors that may influence treatment outcomes, including comorbidities and epidemiologic and clinical features. By examining these factors, we sought to identify opportunities for targeted interventions that can improve treatment outcomes for TB patients in Brazil.

METHODS

Ethics Statement

All analyzed data were obtained from a public government program (SINAN-TB) and were preprocessed by the Br-MOH (https://datasus.saude.gov.br/informacoes-de-saude-tabnet/). Datasets were verified by eliminating duplicates and ensuring consistency and completeness of registered data, following the regulations dictated by Resolution No. 466/12 on Research Ethics of the National Health Council, Brazil. Written informed consent for participation was not required for this study following national legislation and institutional requirements.

Overall Study Design

The primary hypothesis was that TB cases reported to have prior ATT are at increased risk of an unfavorable ATT outcome, predominantly LTFU. We performed an observational study in which we classified TB cases according to their history of previous ATT (new case: those without a prior TB treatment; retreatment [RLTFU]: those with prior TB treatment abandonment; or recurrence: a case with a previous history of TB cure) and characterized these populations by their clinical, socioeconomic, and epidemiological characteristics. Moreover, we tested whether prior ATT at the time of entry in the SINAN as a TB case was associated with increased odds of an unfavorable TB treatment outcome, evaluated as a composite (death, failure, and LTFU) or individual (death or LTFU) outcomes. To do that, we selected all individuals diagnosed with TB in the SINAN-TB database between 2015 and 2022 and assessed predictive factors in the group. Of note, we only included retreatment and new TB cases (removing cases notified as transferred, and postmortem diagnosed), while excluding adolescents and children (<18 years old) and cases without outcome information (incomplete cases). Furthermore, we excluded cases with treatment regimen switches (treatment change and/or TB drug resistant) and transferred them out of the notification system for the model development.

Data Collection

This study utilized data collected from adults (≥18 years old) diagnosed with TB in the SINAN-TB database from 2015 to 2022. The SINAN-TB database is maintained, verified, and supported by the Br-MOH. This database diagnosed TB by microbiologic confirmation (acid-fast bacilli or molecular test [GeneXpert MTB/RIF] in sputum smears and/or positive culture), chest radiography or histopathology, or clinical manifestations, according to the parameters established by the Manual of Recommendations for TB Control in Brazil [6]. In addition to the type of TB diagnosis, SINAN-TB also stores data on patients' characteristics, including clinical (HIV, diabetes, and mental illness) and epidemiologic (sex, age, consumption habits, treatment outcome) data. All variables used in this study are detailed in Table 1.

Entry Mode Definition

Entry mode is how the patient is notified in the system, which depends on previous TB history (Supplementary Figure 1): New cases are those without a history of TB treatment, including any patient who has never undergone TB treatment or has done so for ≤30 days. RLTFU is defined as a patient with a history of interruption of TB treatment for >30 days. Recurrence is a case with a previous history of TB cure. Postmortem is defined as cases identified late, that is, at the time of or after the patient's death.

Notification of TB Cases

The notification of TB cases in Brazil is mandatory and composed of 4 main steps:

1. Diagnosis: The diagnosis of TB generally takes place in a variety of healthcare settings, including primary healthcare units, family healthcare units, hospitals, and specialized and private clinics, through several possible combinations of epidemiologic, radiographic, clinical, and laboratory

Table 1. Characteristics of Brazilian Tuberculosis (TB) Cases Notified Between 2015 and 2022, According to the History of Prior TB and Anti-TB Therapy

Characteristics	RLTFU (n = 48 929)	Recurrent (n = 44 642)	New Case (n = 462 061)
Age, y			
18–34	22 535 (46.1)	14 720 (33.0)	189 107 (40.9)
35–49	17 993 (36.8)	15 039 (33.7)	128 858 (27.9)
50–64	6759 (13.8)	10 606 (23.8)	94 825 (20.5)
65–79	1420 (2.9)	3642 (8.1)	40 344 (8.8)
≥80	222 (0.4)	635 (1.4)	8927 (1.9)
Sex			
Female	11 169 (22.8)	10 522 (23.6)	140 988 (30.5)
Male	37 758 (77.2)	34 117 (76.4)	321 030 (69.5)
Missing	2 (<0.1)	3 (<0.1)	43 (0.1)
Race			
White	11 069 (22.6)	27 451 (61.5)	140 697 (30.4)
Non-White[a]	34 227 (70.0)	12 916 (28.9)	287 193 (62.2)
Missing	3633 (7.4)	4275 (9.6)	34 171 (7.4)
Schooling, y			
<5	5952 (12.2)	5687 (12.7)	48 581 (10.5)
5 to <9	14 319 (29.3)	12 823 (28.7)	102 982 (22.3)
9 to <12	11 320 (23.1)	10 779 (24.1)	132 009 (28.6)
≥12	930 (1.9)	1531 (3.4)	31 752 (6.9)
Missing	16 408 (33.5)	13 822 (31.0)	146 737 (31.8)
TB type			
PTB	44 979 (91.9)	40 634 (91.0)	390 629 (84.5)
EPTB	2503 (5.1)	3064 (6.9)	58 084 (12.6)
PTB + EPTB	1446 (3.0)	940 (2.1)	13 336 (2.9)
Directly observed therapy	12 843 (26.2)	15 617 (35.0)	15 617 (35.0)
Missing	6098 (12.5)	5326 (11.9)	40 521 (8.8)
Alcohol use[b]	17 449 (35.7)	9906 (22.2)	80 009 (17.3)
Missing	3252 (6.6)	2528 (5.7)	28 249 (6.1)
Smoking[c]	17 623 (36.0)	12 760 (28.6)	105 750 (22.9)
Missing	3822 (7.8)	2867 (6.4)	31 704 (6.9)
Drug use[d]	18 688 (38.2)	8433 (18.9)	60 516 (13.1)
Missing	3788 (7.7)	3111 (7.0)	33 767 (7.3)
HIV infection	9871 (20.2)	6015 (13.5)	41 737 (9.0)
Missing	7853 (16.0)	7020 (15.7)	73 475 (15.9)
ART	4309 (43.7)	3109 (51.7)	20 260 (48.5)
Missing	3446 (34.9)	2104 (35.0)	13 606 (32.6)
Diabetes	2183 (4.5)	3130 (7.0)	40 689 (8.8)
Missing	3597 (7.4)	2699 (6.0)	28 519 (6.2)
Mental illness	1790 (3.7)	1122 (2.5)	10 475 (2.3)
Missing	3802 (7.8)	2803 (6.3)	30 113 (6.5)
Abnormal chest X-ray	32 033 (65.5)	29 119 (65.2)	319 520 (69.2)
Missing	15 547 (31.8)	13 996 (31.4)	119 902 (25.9)
Smear grade			
Positive	25 110 (51.3)	23 136 (51.8)	232 567 (50.3)
Negative	9370 (19.2)	9493 (21.3)	83 990 (27.9)
Not performed	12 821 (26.2)	10 859 (24.3)	128 869 (27.9)
Missing	1628 (3.3)	1154 (2.6)	16 635 (3.6)
TB culture			
Positive	13 526 (27.6)	13 245 (29.7)	101 057 (21.9)
Negative	5968 (12.2)	6699 (15.0)	42 351 (9.2)
Not performed	28 402 (58.0)	23 783 (53.3)	309 781 (67.0)
Missing	1033 (2.1)	915 (2.0)	8872 (1.9)
Molecular test			
Detectable sensitive RIF	14 956 (30.6)	13 752 (30.8)	124 647 (27.0)
Detectable resistant RIF	461 (0.9)	359 (0.8)	2252 (0.5)
Not detectable	2952 (6.0)	2924 (6.5)	22 168 (4.8)
Not performed	24 934 (51.0)	22 639 (50.7)	265 303 (57.4)
Inconclusive	664 (1.4)	612 (1.4)	7078 (1.5)
Missing	4962 (10.1)	4356 (9.8)	40 613 (8.8)
Susceptibility test[e]			
Susceptible	7650 (15.6)	8399 (18.8)	54 971 (11.9)
Resistant to other first-line drugs	203 (0.4)	166 (0.4)	1020 (0.2)
Resistant to isoniazid	173 (0.4)	102 (0.2)	712 (0.2)
Resistant to isoniazid and rifampicin	102 (0.2)	47 (0.1)	170 (<0.1)
Resistant to rifampicin	86 (0.2)	57 (0.1)	278 (0.1)
Ongoing	916 (1.9)	720 (1.6)	5505 (1.2)
Not performed	14 081 (28.8)	15 414 (34.5)	172 344 (37.3)
Missing	25 718 (52.7)	19 737 (44.2)	227 061 (49.2)
Treatment outcomes			
Loss to follow-up	23 483 (48.0)	7557 (16.9)	62 154 (13.5)
Cure	20 217 (41.3)	32 519 (72.8)	358 014 (77.5)
Death	5165 (10.6)	4496 (10.1)	41 527 (9.0)
Failure	64 (0.1)	70 (0.2)	366 (0.1)

Data are presented as No. (%).

Abbreviations: ART, antiretroviral therapy; EPTB, extrapulmonary tuberculosis; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis; RIF, rifampin; RLTFU, retreatment after loss to follow-up; TB, tuberculosis.

[a]Non-White race includes black, mixed, pardo, yellow, and indigenous.

[b]Past or current consumption of alcohol.

[c]Past or current smoking of tobacco.

[d]Past or current drug use (marijuana, cocaine, heroin, or crack).

[e]Resistant to other first-line drugs (ethambutol and/or pyrazinamide).

[f]Other comorbidities include cancer, kidney disease, chronic obstructive pulmonary disease, emphysema, allergies, and asthma.

tests. TB cases are only reported after confirmation, whether laboratory or clinical criteria.

2. Notification: SINAN-TB is notified by the healthcare worker. This happens for each TB case, and notification accompanies the patient's clinical and epidemiologic data.
3. Access to treatment: TB treatment is provided free of charge by the Unified Health System (Sistema Único de Saúde [SUS]). The standard treatment for drug-susceptible TB usually consists of an initial 2-month phase with 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol), followed by a continuation phase of at least 4 months with isoniazid and rifampicin. Importantly, only SUS provides the treatment countrywide, and all the patients must follow up in a public health clinic.
4. Update notification: Data on the treatment outcome are mandatorily updated in SINAN-TB [5, 13].

Variable Definitions

SINAN-TB contains a wide variety of clinical and demographic characteristics of persons diagnosed with TB. These include the participant's race, substance use (smoking, alcohol, and/or drug use), comorbidities, and characteristics that led to the TB

diagnosis such as chest X-ray status and GeneXpert MTB/RIF test result. A full list of variables and their definitions is included in the Supplementary Methods.

Outcome Definition

An unfavorable outcome was defined as TB treatment failure (positive sputum smear results remain until the end of treatment), LTFU (if the patient has taken >30 consecutive days to return to a treatment unit after the expected return date), or death (the knowledge of a patient's death during treatment), while a favorable treatment outcome was defined as cure (clinical and bacteriologic). The definitions for clinical or bacteriological cure, as well as for each specific unfavorable outcome, were determined following criteria found in the Manual of Recommendations for the Control of TB in Brazil and are depicted in detail in Supplementary Table 1 [5, 14]. Registries of other outcomes—such as transferred (patient sent to another healthcare unit to finalize the treatment), treatment modification (factors that cause treatment modification: due to drug-resistant TB), change in diagnosis (patient diagnosed with another disease other than TB), and "ongoing treatment"—were excluded from the analyses due to the lack of information on the final treatment outcome (Figure 1). Characteristics of each population included in the study are provided in Table 1.

Vulnerability Definition

Following the WHO, we defined vulnerable populations as groups who have an increased risk of developing active TB and have a worse prognosis. The vulnerabilities evaluated in this study were pregnancy, healthcare work, incarceration, homelessness, and immigration at the time of diagnosis [13]. We used the vulnerabilities in descriptive analyses to adjust for potential confounding, which are described in table notes and figure legends. We did not consider people with HIV, people who use drugs, and people who use alcohol as specific vulnerable populations due to the overlap with the vulnerability groups included. Instead, HIV status and drug and alcohol use were used to characterize the subpopulations and were included in the association analyses. We adjusted the regression models according to the vulnerabilities presented by the population.

Statistical Analysis

Clinical and epidemiologic variables were presented in this study as frequency (%) if categorical or as median (interquartile range) if continuous. Due to the large sample size and the nature of most analyzed variables (binary: yes/no), no imputation was performed for incomplete data. Exploratory data analysis was conducted to check the distribution and main characteristics of (1) new TB cases, (2) retreatment cases (RLTFU), and (3) recurrent cases. Then, we computed odds ratios (ORs) and 95% confidence intervals (CIs) for the association of each factor with separate dichotomous outcomes (ie, favorable or unfavorable TB treatment outcome) using logistic regression. Furthermore, to quantify the association of each characteristic with a given outcome in the presence of others (ie, death, cure, and LTFU), we fit a multinomial model. The outcome of treatment failure was not included in the multinomial analyses due to the very small number of cases compared with the other outcomes. To assess the impacts of the coronavirus disease 2019 (COVID-19) pandemic on TB treatment outcomes, we created dichotomous variables indicating whether the case was notified before or after 1 January 2020, and sensitivity analysis was performed (Supplementary Figure 2 and Supplementary Figure 3). Before we constructed our models, we first eliminated any variable with >30% of missing values, then we checked for multicollinearity among remaining predictors using their variance inflation factor values. The model fit was checked using visual inspection based on the distribution of the residuals. All analyses were conducted using R software (R Development Core Team 2023).

RESULTS

Characteristics of the Study Participants

Our analysis included 594 513 TB cases from the SINAN-TB database between 2015 and 2022. We classified our population based on their entry mode into the healthcare system, with 462 061 people classified as new cases and 93 571 as retreatment cases (48 929 reentry after prior LTFU and 44 642 recurrent cases) during this period. In this analysis, we decided to assess clinical characteristics and risk factors associated with unfavorable ATT based on their history of prior TB and ATT. Notably, 39 417 people were excluded because they were under the age of 18; 25 160 cases were excluded due to not meeting the entry mode criterion (19 647 transferred from another healthcare unit [HCU] and 5513 were postmortem diagnosis), 84 733 did not meet the outcome inclusion criteria (11 985 treatment change, 8804 diagnostic change, 63 944 missing outcomes), and 38 881 transferred to another HCU (Figure 1).

Characteristics of our study's population can be found in Table 1. First, while the RLFTU and new cases groups presented most of the cases with age between 18 and 34 years (46.1% and 40.9%, respectively), all populations were mostly reported as being male, with a non-White race, as well as fewer schooling years (Table 1). However, regarding TB type, whereas all groups were mostly composed of pulmonary TB, this condition was more common in RLTFU cases (91.9%). In addition, RLTFU cases also presented more frequent substance use than new and recurrent TB cases; the rates of alcohol consumption (35.7%), drug use (38.2%), and smoking (36.0%) were all higher in this group. This was in contrast with the proportion of DOT (26.2%), which was lower among RLTFU and equal among both recurrent (35.0%) and new (35.0%) TB cases (Table 1).

Moreover, our study revealed that diabetes was observed in a higher percentage (8.8%) of new TB cases, whereas the

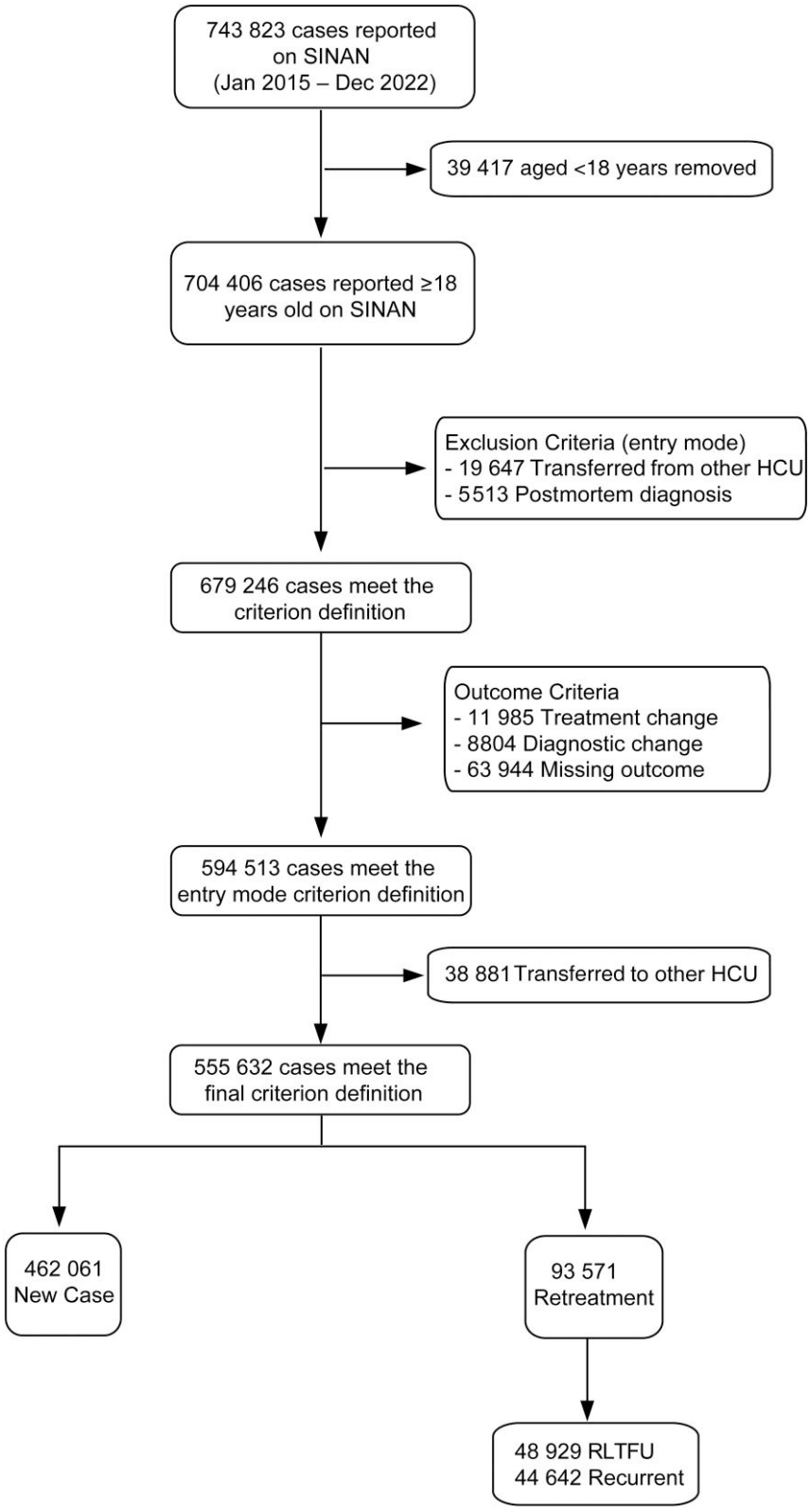

Figure 1. Flowchart of tuberculosis (TB) cases notified in Brazil between 2015 and 2021, stratified according to the history of prior TB and anti-TB therapy. Abbreviations: HCU, healthcare unit; RLTFU, retreatment after loss to follow-up; SINAN, Brazilian Tuberculosis Database System.

prevalence of HIV (20.2%) and mental illness (3.7%) were more pronounced in the RLTFU group, as indicated in Table 1. Additionally, while all groups showed similar rates of positive smear grade, abnormal chest X-rays were most common in new cases (69.2%) (Table 1).

Furthermore, features such as TB culture, susceptibility test, and molecular test results were either scarcely carried out in all groups or had considerable missing data (Table 1). Finally, regarding treatment outcomes, the RLFTU group more frequently had composite unfavorable treatment outcome, marked especially by subsequent LTFU (48.0%) (Figure 2).

Determinants of Anti-TB Unfavorable Outcomes in the Overall Study Population

Our analysis of determinants of unfavorable treatment outcomes in TB cases in the overall study population highlighted the contribution of previous unfavorable treatment outcomes to subsequent unfavorable treatment outcomes. We also adjusted this model for social vulnerabilities.

Our findings indicated that RLTFU (OR, 3.87 [95% CI, 3.73–4]) was the strongest determinant of a composite unfavorable outcome, which includes LTFU, failure, and death, followed by HIV infection (OR, 2.72 [95% CI, 2.64–2.8]), and drug use (OR, 1.75 [95% CI, 1.7–1.81]). Notably, age, alcohol use, tobacco use, mental illness, male sex, and non-White race also presented noteworthy associations with unfavorable outcomes in the overall population. Also, cases notified during the COVID-19 pandemic (OR, 1.51 [95% CI, 1.47–1.55]) were at increased risk of unfavorable outcomes. As expected, DOT use (OR, 0.43 [95% CI, .42–.44]), was identified as an independent protective factor against unfavorable outcomes (Figure 3).

Prior TB Treatment as a Risk Factor for LTFU and Death

Moreover, the results remained consistent when analyzing each unfavorable outcome separately (LTFU or death) (Figure 4). To

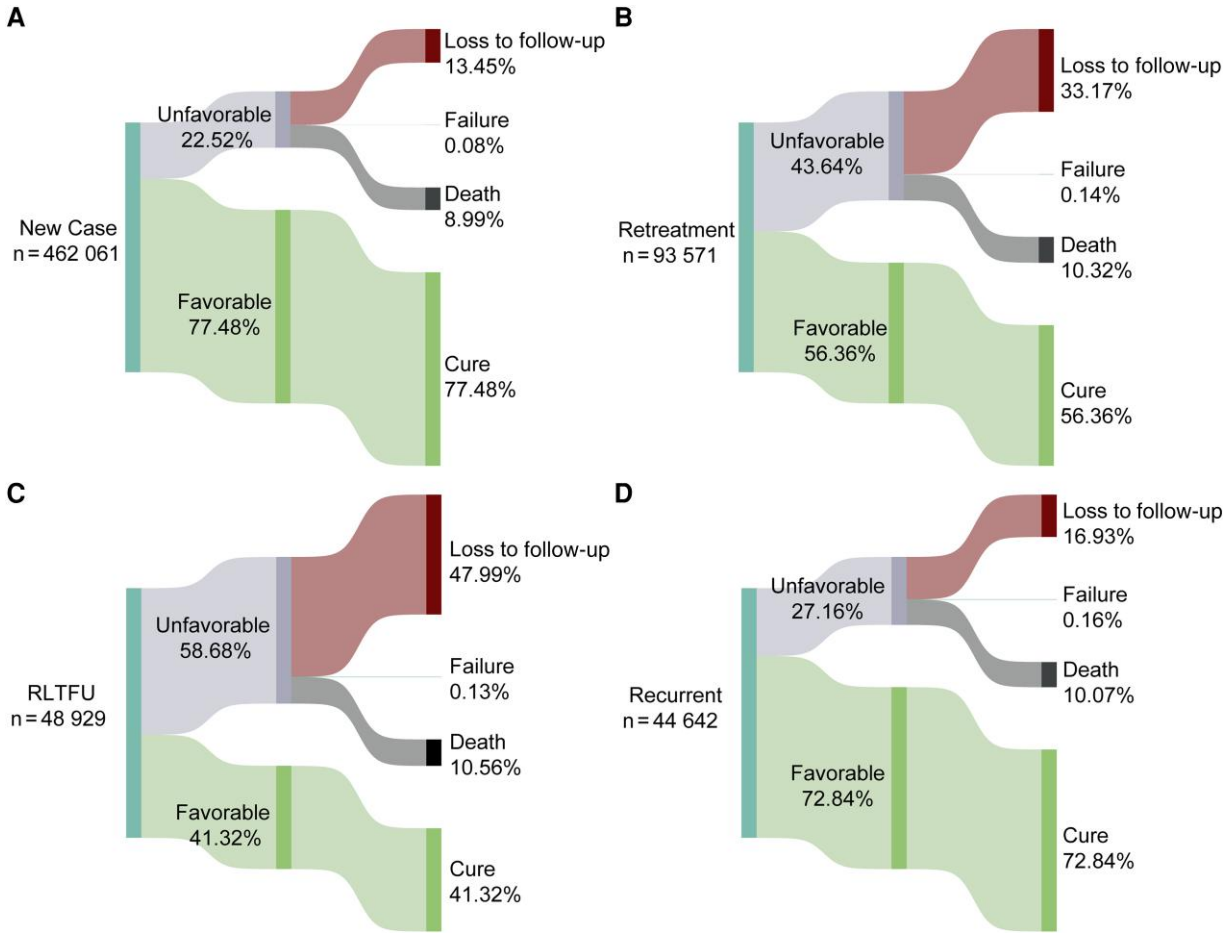

Figure 2. Distribution of tuberculosis (TB) treatment outcomes, stratified according to entry mode in the healthcare system. Sankey diagrams show frequencies of each TB treatment outcome in the Brazilian Tuberculosis Database System (SINAN) registry of TB cases identified between 2015 and 2022 among new cases (*A*), retreatment cases (*B*), TB cases reported among retreatment after loss to follow-up (*C*), and recurrent cases (a case with a previous history of TB cure) (*D*). Loss to follow-up: the patient has taken >30 consecutive days to return to a treatment unit after the expected return date; unfavorable outcome: TB treatment failure (positive sputum smear results remain until the end of treatment); death: the knowledge of a patient's death during treatment.

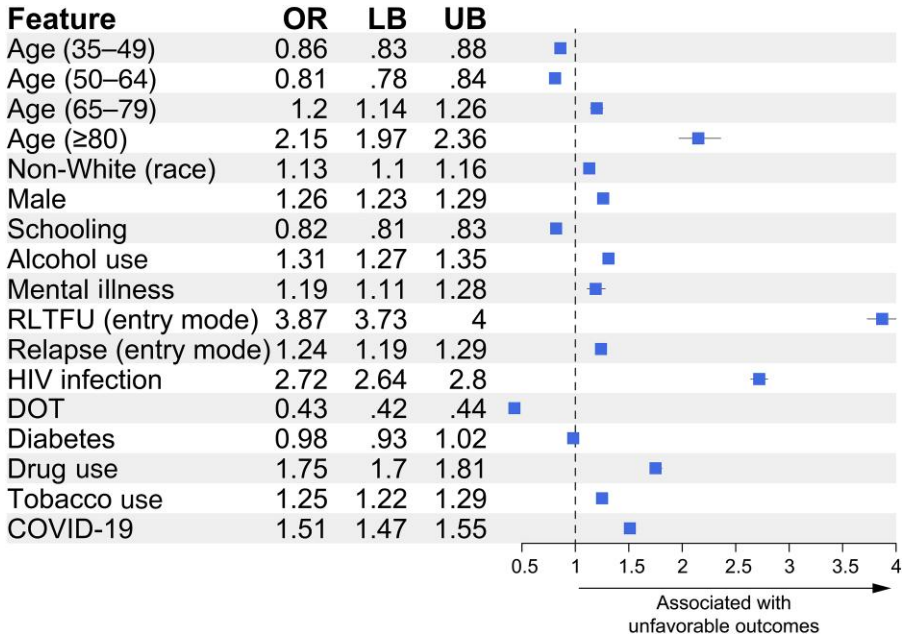

Figure 3. Results from the logistic regression model quantifying the associations between various risk factors for unfavorable treatment outcomes in the overall population of the study. We adjusted the model for social vulnerabilities: homelessness, pregnancy, immigration incarceration, and healthcare work. Each feature represents an independent association removing the effect of the other features in the model. Abbreviations: COVID-19, coronavirus disease 2019; DOT, directly observed treatment; HIV, human immunodeficiency virus; LB, lower boundary of the 95% confidence interval; OR, odds ratio; RLTFU, retreatment after loss to follow-up; UB, upper boundary of the 95% confidence interval.

do so, we performed a multinomial regression model to determine associations between clinical and epidemiologic characteristics and each outcome (Figure 4). Still, some characteristics such as RLTFU (OR, 4.78 [95% CI, 4.61–4.96]) and drug use (OR, 1.96 [95% CI, 1.89–2.03]) exhibited a significantly stronger association with LTFU, while age ≥80 years (OR, 11.76 [95% CI, 10.60–13.04]) and HIV infection (OR, 6.40 [95% CI, 6.13–6.67]) were the most important risk factors for death. Furthermore, being notified during the COVID-19 pandemic was also linked to increased odds for LTFU (OR, 1.49 [95% CI, 1.45–1.54]) and death (OR, 1.55 [95% CI, 1.49–1.62]). Protective factors such as DOT and higher years of schooling showed a stronger association with LTFU than with death (Figure 4).

DISCUSSION

To the best of our knowledge, this study is pioneering in its national evaluation of retreatment TB. Corroborating these findings, prior research [8, 15–17] conducted on our study population indicated that patient-related factors, drug abuse, and socioeconomic status are the key determinants of noncompletion of TB treatment.

Successful treatment is an important tool for measuring the quality of national TB programs [18, 19]. To improve the ATT success rates, the WHO has widely advocated for the use of DOT, especially in key and hard-to-reach populations. Despite the Br-MOH proposing a unique therapeutic plan, individuals undergoing retreatment, unless resistant, currently undergo the same care cascade as new cases [6]. This approach has not proven to be the best option, as retreatment can occur multiple times for a single patient. Therefore, a more comprehensive strategy that includes evaluating both the pathogen resistance and the specific context of retreatment is necessary to ensure treatment completion for this group. In our study, being a case of RLTFU was the most important risk factor associated with subsequent unfavorable ATT outcomes in the overall population. The top risk factors for poor outcomes also included HIV infection, drug use, and mental illness, which is consistent with previous studies [19–24]. Interestingly, the association between retreatment and unfavorable outcomes persisted when LTFU was evaluated individually. This indicates that patients undergoing retreatment, especially after abandonment, are at a higher risk of abandoning treatment again, which poses a potential problem in the TB care cascade. This underscores the need for the Brazilian TB program to focus on high-risk groups such as RLTFU to reduce the risk of LTFU, achieve an immediate impact on interrupting TB transmission, and decrease the incidence of the disease in the long term.

The same relationship was found for HIV infection and death, emphasizing the need to address HIV-TB coinfection as a major problem and to improve HIV care among TB

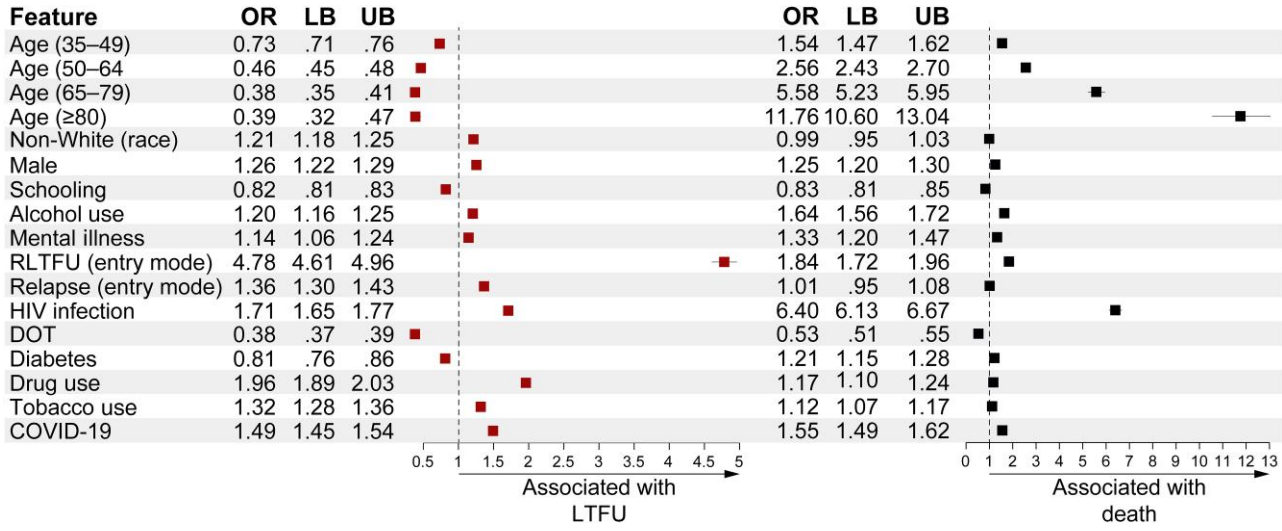

Figure 4. Results from multinomial regression models to quantify the associations between risk factors for death and loss to follow-up in the overall study population. We adjusted the model for social vulnerabilities: homelessness, pregnancy, immigration incarceration, and healthcare work. Each feature represents an independent association removing the effect of the other features in the model. Abbreviations: COVID-19, coronavirus disease 2019; DOT, directly observed treatment; HIV, human immunodeficiency virus; LB, lower boundary of the 95% confidence interval; LTFU, loss to follow-up; OR, odds ratio; RLTFU, retreatment after loss to follow-up; UB, upper boundary of the 95% confidence interval.

patients to reduce mortality rates as proposed by WHO [25]. Of note, notifications that occurred during the COVID-19 pandemic were also significantly associated with heightened odds for either a composite unfavorable outcome or LFTU and death. We hypothesize that these important findings can be explained by a decrease in treatment adhesion resulting from the restriction measures adopted during the pandemic, as previously reported in other studies [26].

Furthermore, DOT and higher levels of schooling were also associated with favorable ATT outcomes. Our findings reinforce that, at TB diagnosis, the rapid identification of mental disorders, depression, and substance use, such as alcohol consumption, drug use, and smoking, followed by supervised treatment and a better understanding of the significance of treatment, are keys for improved outcomes [27–30]. This also buttresses the argument that the Brazilian population would benefit from straightforward interventions such as universal DOT implementation and educational measures to improve overall education levels.

This study had some limitations. Although the reporting system is universally used in the country, there are still many variables with important missing data rates. Due to the data being anonymized by the Brazilian government, it is not possible to identify how many times the same patient abandoned treatment and reentered the notification system. Also, this is a study carried out with secondary data, mostly epidemiological and clinical, it was not possible to correlate these biological factors that may have influenced the treatment outcome. Of note, the low proportion of TB culture and drug susceptibility test results prevented the evaluation of the role of drug resistance at TB diagnosis among RLTFU and recurrence and new cases. We did not include children and adolescents due to the different treatment regimen and risk characteristics; future studies must focus on this population. Furthermore, the lack of a variable for COVID-19 in the TB notification form limited our ability to assess the impact of the pandemic on TB treatment outcomes at the individual level. To estimate the impact, we considered COVID-19 as an exposure.

Our study assesses the TB retreatment as a risk factor for unfavorable treatment outcomes in the Brazilian healthcare system. Our findings highlight the necessity for personalized patient-centered TB care for RLTFU cases. We provide important insights for policymakers, community stakeholders, and healthcare workers to understand that patients who have previously abandoned TB treatment should be prioritized for interventions to prevent subsequent LTFU and death. Recognizing the need to provide better care and varied incentives is also vital, ensuring that patients who have previously stopped TB therapy can complete their treatment, thereby interrupting TB transmission.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conceptualization: B. B.-D., M. M. R., and B. B. A. Data verification and curation: B. B.-D., M. M. R., M. A.-P., and B. B. A. Investigation: B. B.-D., M. M. R., M. C. F., B. D., A. L. K., V. C. R.,

T. R. S., M. C. S., and B. B. A. Formal analysis: B. B.-D., M. M. R., and B. B. A. Funding acquisition: A. L. K., V. C. R., T. R. S., M. C. S., M. M. R., and B. B. A. Methodology: B. B.-D., M. M. R., and B. B. A. Project administration: M. M. R., M. C. F., T. R. S., and B. B. A. Resources: B. B.-D., T. R. S., and B. B. A. Software: B. B.-D., M. M. R., M. A.-P., and B. B. A. Supervision: M. M. R. and B. B. A. Writing—original draft: B. B.-D., M. M. R., and B. B. A. Writing—review and editing: all authors.

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Data sharing. The data that support the findings of this study will be available upon reasonable request to the corresponding author of the study.

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Potential conflicts of interest. All authors: No reported conflicts.

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