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MAJOR ARTICLE

Isoniazid Monoresistance and Antituberculosis Treatment Outcome in Persons With Pulmonary Tuberculosis in Brazil

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Background. The high burden of drug-resistant tuberculosis (TB) is a problem to achieve the goals of the End TB Strategy by 2035. Whether isoniazid monoresistance (Hr) affects anti-TB treatment (ATT) outcomes remains unknown in high-burden countries.

Methods. We evaluated determinants of ATT outcome among pulmonary TB cases reported to the National Notifiable Disease Information System (SINAN) between June 2015 and June 2019, according to drug sensitivity testing (DST) results. Binomial logistic regression models were employed to evaluate whether Hr was associated with an unfavorable ATT outcome: death or failure, compared to cure or treatment completion.

Results. Among 60 804 TB cases reported in SINAN, 21 197 (34.9%) were included in the study. In this database, the frequency of unfavorable outcomes was significantly higher in those with Hr in contrast to isoniazid-sensitive persons with pulmonary TB (9.1% vs 3.05%; $P < .001$). Using a binomial logistic regression model, Hr was independently associated with unfavorable outcomes (odds ratio, 3.34 [95% confidence interval, 2.06–5.40]; $P < .001$).

Conclusions. Hr detected prior to ATT was predictive of unfavorable outcomes at the national level in Brazil. Our data reinforce the need for high-TB-burden countries to prioritize DST to detect Hr. Effective treatment regimens for Hr-TB are needed to improve outcomes.

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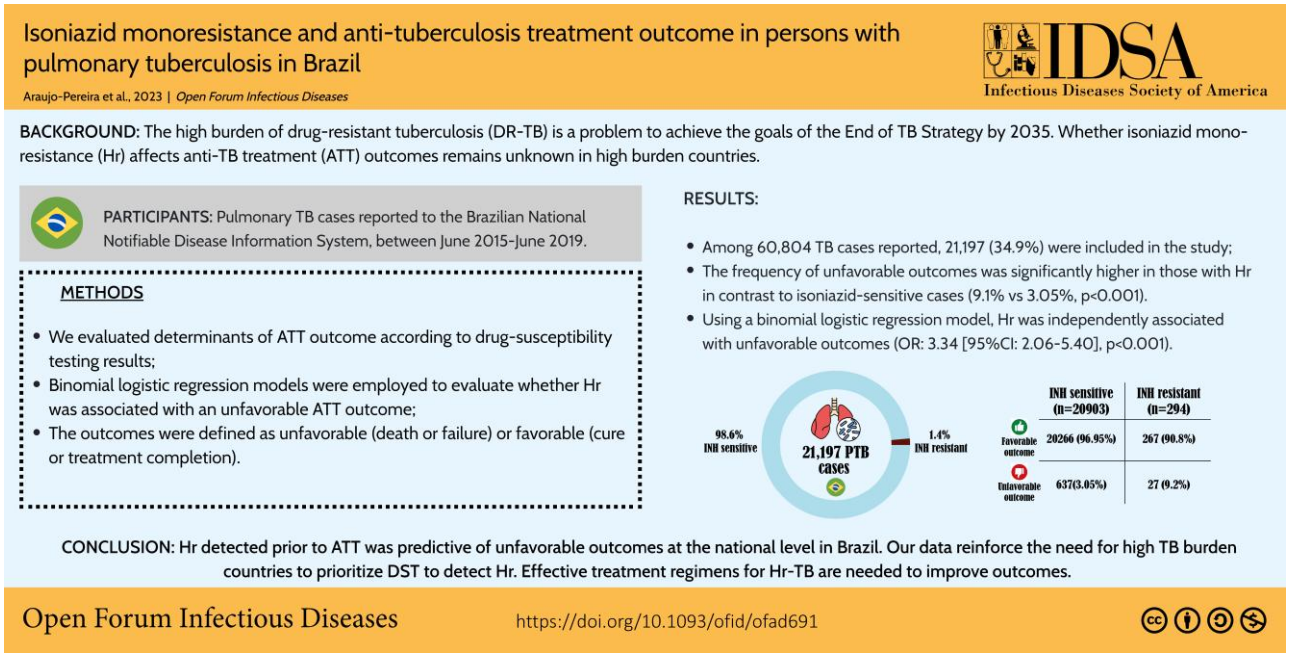
Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/isoniazid-monoresistance-and-anti-tuberculosis-treatment-outcome-in-persons-with-pulmonary-tuberculosis-in-brazil-36f503ef-d241-4583-adbe-e7c7a8ef4cec

Keywords. antitubercular treatment outcomes; death; isoniazid resistance; tuberculosis.

Tuberculosis (TB) remains a serious public health problem. The high burden of drug-resistant TB (DR-TB) observed in recent decades makes it difficult to achieve the goals of the End TB Strategy by 2035, proposed by the World Health Organization (WHO) [1, 2]. According to the WHO, it is estimated that 10.6 million people had active TB in 2021, and 1.6 million died, which ranks TB among the 10 leading causes of death in the world [1].

In 2020, a decrease in detection of multidrug-resistant (MDR) or rifampicin-resistant (RR) TB detection and treatment occurred worldwide due to disruption of health systems during the coronavirus disease 2019 (COVID-19) pandemic [1]. In 2018, for the first time, the WHO provided global estimates of the incidence of isoniazid resistance: there were 1.4 million incident cases of Hr-TB, of which 1.1 million were susceptible to rifampicin [2]. Importantly, most of these patients were not diagnosed with DR-TB by the WHO-recommended molecular test Xpert MTB/RIF (Xpert) and did not receive appropriate treatment [3, 4].

A meta-analysis based on individual Hr-TB patient data found that the addition of a fluoroquinolone to the treatment regimen was associated with higher odds of successful treatment [5]. In 2018, the WHO guidelines for the treatment of Hr-TB recommended a 4-drug regimen: rifampicin (R), ethambutol (E), pyrazinamide (Z), and levofloxacin (Lfx), with or without isoniazid ([H]RZE-Lfx) [6]. Recently, in high-income settings, early Hr-TB detection by molecular tests has been associated with shorter time to adequate treatment [7].

Brazil remains among the top 30 countries with a high TB burden, with 78 057 new cases reported in 2022, and an incidence of 36.3 cases/100 000 inhabitants [8]. There was an increase in the notification of RR-TB cases in Brazil after the incorporation of the Xpert assay in the national Unified Health System in 2014 [9], though it detected only 55% of the estimated MDR-TB incident cases in the country [10]. Resistance to other drugs is determined through culture and phenotypic drug sensitivity testing (DST). According to the Brazilian TB Ministry of Health Guidelines, DST has been indicated for all suspected TB cases since 2015. Nevertheless, culture for mycobacteria is performed only in 24% of new TB cases. In cases of retreatment, culture is performed in 28.4% of cases undergoing retreatment and DST in only 12.4% [8].

TB case data are reported in the Notifiable Diseases Information System (SINAN). Data of patients with DR-TB usually migrate to another National Disease Information System (Special Tuberculosis Treatment Information System [SITE-TB]). Therefore, there are few studies using SINAN data to evaluate the Hr effect on anti-TB treatment (ATT) outcomes in a national approach [9, 10]. In the present study, we evaluated the effect of isoniazid monoresistance (Hr) on ATT outcomes, evaluating a large cohort of persons with pulmonary TB (PTB) reported between 2015 and 2019 to the National SINAN TB cases registry [11].

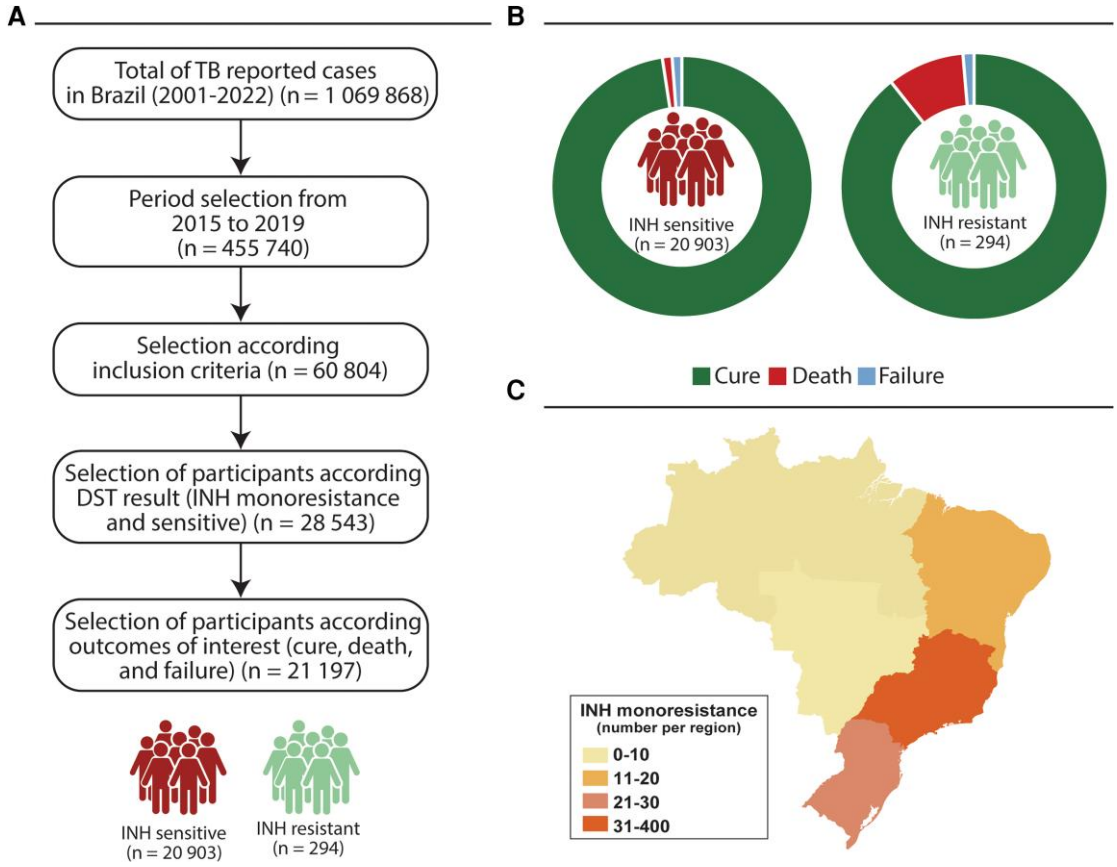


Figure 1. Study population. *A*, Study flowchart of tuberculosis (TB) cases reported in the Notifiable Diseases Information System (SINAN) database and selected according to RePORT-Brazil criteria. Of 1 069 868 TB cases reported in SINAN, 21 197 were selected following the inclusion and exclusion criteria. The inclusion criteria were patients aged ≥18 years, with culture-positive pulmonary TB and with drug sensitivity testing (DST) to isoniazid (INH) recorded. The exclusion criteria were TB patients without treatment outcome reported, vulnerable populations (pregnant, prisoners, and homeless), and those with rifampicin resistance by DST or with multidrug resistance. *B*, Of 20 903 drug-sensitive cases TB cases reported, 97% had cure as the main outcome (left). Of 294 INH-monoresistant TB cases reported in the SINAN cohort, 91% had cure as the main outcome (right). *C*, The geopolitical map of Brazil shows the different Brazilian regions. The states are plotted with colors that refer to INH monoresistance, in number of cases reported by state.

METHODS

Patient Consent Statement

The study was conducted according to the principles of the Declaration of Helsinki. For the data extracted from SINAN, among persons with PTB (PWPTB), the anonymity of study subjects was preserved, and all data were de-identified. All data available for the years 2015–2022 were obtained from the government platform (publicly available) and pre-processed by the Ministry of Health, which included verification of presumed duplicate registration, consistency, and completeness of registered data. Thus, this study does not include factors necessitating patient consent or ethical committee approval.

Study Design

We evaluated baseline clinical and sociodemographic characteristics, comorbidities, and the variables of outcomes among PTB cases reported to SINAN between 2015 and 2022, according to Hr or isoniazid sensitivity. The primary hypothesis was that patients with Hr-TB had a higher risk of unfavorable ATT outcomes compared to patients with isoniazid sensitivity. The inclusion criteria were age ≥18 years, with culture-positive PTB and with DST to isoniazid recorded. The exclusion criteria were TB patients without treatment outcome reported, with RR-TB by DST or with MDR-TB, and those who had as an outcome "lost to follow-up" or "transferred out." To characterize drug resistance, only the phenotypic DST result was used [8]. PWPTB reported to SINAN were treated with standard HRZE/HR [6].

Notifiable Diseases Information System, Brazilian Ministry of Health

SINAN is a system for the investigation and notification of transmissible diseases that has been implemented, supported, and maintained by the Brazilian Ministry of Health [11]. All PWPTB reported to SINAN at national level were eligible. According to the Ministry of Health, TB patients reported to SINAN had 1 or more of the following criteria: (1) clinical

Table 1. Clinical Characteristics of the Notifiable Diseases Information System (SINAN) Cohort According to Isoniazid Resistance

Characteristic	Resistant (n = 294)	Susceptible (n = 20 903)	*P* Value
Male sex	219 (74.5)	14 711 (70.4)	.142
Race			.244
Black/Mixed	98 (35.4)	7517 (38.3)	
Indigenous	125 (45.1)	9120 (46.4)	
White	2 (0.7)	120 (0.6)	
Yellow	52 (18.8)	2894 (14.7)	
Years of schooling			.502
<5	37 (17.9)	2393 (15.0)	
5–8	73 (35.3)	5510 (34.5)	
9–12	78 (37.7)	6738 (42.2)	
>12	19 (9.2)	1323 (8.3)	
Abnormal chest X-ray	246 (96.9)	16 717 (97.3)	.804
TB type			.542
PTB	283 (96.3)	20 284 (97.0)	
PTB + EPTB	11 (3.7)	619 (2.9)	
Alcohol use	73 (25.1)	4826 (23.6)	.603
Diabetes	27 (9.3)	2229 (10.9)	.440
Mental illness	11 (3.8)	496 (2.4)	.177
Other comorbidities	18 (12.6)	1199 (11.2)	.705
HIV infection	27 (9.5)	1738 (8.9)	.812
Drug use	58 (20.3)	3837 (18.9)	.597
Tobacco use	87 (30.1)	6291 (30.8)	.845
Macro region			**<.001**
Midwest	3 (1.0)	833 (3.9)	
North East	15 (5.1)	2101 (10.1)	
North	1 (0.3)	1324 (6.3)	
Southeast	250 (85.0)	13 568 (64.9)	
South	25 (8.5)	3077 (14.7)	
Treatment outcome			**<.001**
Cure	267 (90.8)	20 266 (97.0)	
Death	26 (8.8)	610 (2.9)	
Failure	1 (0.3)	27 (0.1)	

Data are shown as number and frequency (%). Data were compared using the Pearson χ^2 test (categorical). In the *P* value column, bold font indicates a significant value ($P < .05$).

Abbreviations: EPTB, extrapulmonary tuberculosis; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis; TB, tuberculosis.

Table 2. Clinical Characteristics of the Notifiable Diseases Information System (SINAN) Cohort According to Treatment Outcomes

Characteristic	Favorable (n = 20 533)	Unfavorable (n = 664)	*P* Value
Male sex	14 416 (70.2)	514 (77.4)	**<.001**
Race			.567
Black/Mixed	7396 (38.3)	219 (36.0)	
Indigenous	8953 (46.3)	292 (47.9)	
White	117 (0.61)	5 (0.82)	
Yellow	2853 (14.8)	93 (15.3)	
Years of schooling			**<.001**
<5	2339 (14.8)	91 (23.7)	
5–8	5429 (34.4)	154 (40.1)	
9–12	6693 (42.4)	123 (32.0)	
>12	1326 (8.4)	16 (4.2)	
Abnormal chest X-ray	16 396 (97.3)	567 (98.1)	.283
TB type			**<.001**
PTB	19 959 (97.2)	608 (91.6)	
PTB + EPTB	574 (2.8)	56 (8.4)	
Alcohol use	4650 (23.1)	249 (39.6)	**<.001**
Diabetes	2165 (10.8)	91 (14.4)	**.004**
Mental illness	483 (2.4)	24 (3.8)	**.032**
Other comorbidities	1121 (10.7)	96 (29.4)	**<.001**
HIV infection	1733 (8.9)	32 (5.8)	**.013**
Drug use	3759 (18.8)	136 (21.7)	.074
Tobacco use	6125 (30.5)	253 (40.6)	**<.001**
Sensibility test			**<.001**
Isoniazid resistant	267 (1.3)	27 (4.1)	
Isoniazid susceptible	20 266 (98.7)	637 (95.9)	
Macro region			**<.001**
Midwest	787 (3.8)	49 (7.4)	
North East	2039 (9.9)	77 (11.6)	
North	1293 (6.3)	32 (4.8)	
Southeast	13 395 (65.2)	423 (63.7)	
South	3019 (14.7)	83 (12.5)	
Treatment outcome			NA
Cure	20 533 (100)	0 (0.00)	
Death	0 (0.00)	636 (95.8)	
Failure	0 (0.00)	28 (4.2)	

Data are shown as No. (%) for categorical variables. Data were compared using the Pearson χ^2 test (categorical). In the *P* value column, bold font indicates a significant value ($P < .05$).

Abbreviations: EPTB, extrapulmonary tuberculosis; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis; TB, tuberculosis.

factors (presumptive diagnosis); (2) bacteriology (sputum smear positive) or positive culture (solid or liquid); (3) positive Xpert result; (4) chest radiography; or (5) in the case of extrapulmonary TB, histopathology. After TB diagnosis, the information collected and the laboratory results were recorded on a national electronic form that included the clinical form of TB, individual characteristics (sex, age, race, education level, alcohol consumption, drug use, smoking habits, and associated conditions and diseases), and the presence of TB/human immunodeficiency virus (HIV) coinfection and test results, among others. Information regarding the ATT outcome was also provided, 12 months after the case was reported notification. We opted to evaluate data only from 2015 onward because there was a notification system update at the end of 2014, which became effective in 2015 and has been in place since. This allowed us to eliminate the potential bias that could arise from different data collection methods, devices, or software. Additionally, we restricted the data up to 2019 to avoid potential bias associated with the COVID-19 pandemic.

Isoniazid Resistance Definition and Treatment Recommendation

To define Hr, we used the 2018 WHO guideline criteria [6] that refer to *Mycobacterium tuberculosis* strains with resistance to isoniazid and documented susceptibility to rifampicin [3]. The addition of levofloxacin to (H)RZE is recommended in all patients with Hr-TB, with exception of the following: (1) known or suspected resistance to levofloxacin; (2) known

intolerance to fluoroquinolones; and (3) known or suspected risk for prolonged QTc interval. In Hr-TB cases in whom a fluoroquinolone cannot be used, the patients may still be treated with 6(H)RZE.

TB Treatment Outcome Definition

A favorable treatment outcome was defined as cure or treatment completed (at least 6 months of standard treatment). An unfavorable outcome was defined as treatment failure, or TB-related death during treatment. The definitions for clinical and bacteriological cure, failure, and death corresponded with the recently updated WHO guideline [6]. Patients with PTB are considered cured if they have at least 2 negative sputum smears during treatment. Treatment completion is based on clinical and radiological criteria. Death is defined when a patient dies during treatment. Finally, treatment failure is defined as persistent sputum positivity at the end of treatment or specific patterns of sputum positivity, including strong initial positivity maintained until the fourth month or initial positivity followed by negativity and then new positivity for 2 consecutive months starting from the fourth month of treatment.

Table 3. Clinical Outcomes in the Notifiable Diseases Information System (SINAN) Cohort According to Isoniazid Resistance

Outcome	Isoniazid Sensitivity (n = 20 903)	Isoniazid Resistance (n = 294)	*P* Value
Treatment success	20 266 (96.95)	267 (90.8)	**<.001**
Unfavorable	637 (3.05)	27 (9.2)	
Death	610 (2.92)	26 (8.84)	
Failure	27 (0.13)	1 (0.34)	

Data are presented as No. (%) unless otherwise indicated. Bold font indicates a significant value ($P < .05$).

Statistical Analysis

Median values and interquartile range (IQR) were used as measures of central tendency and dispersion. The Mann-Whitney *U* test (for 2 unmatched groups), the Wilcoxon matched-pairs test (for 2 matched groups), or the Kruskal-Wallis test (for >2 unmatched groups) were used to compare continuous variables. Categorical variables were compared using Pearson χ^2 test and were displayed as numbers and frequency (%). Differences with $P \leq .05$ were considered statistically significant. A binomial logistic regression model (stepwise method) using all variables in SINAN (age, sex, region, race, educational level, tobacco use, alcohol consumption, drug use, prior TB, chest X-ray status, HIV infection, DST) in the first step was performed to assess the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of clinical and sociodemographic characteristics associated with unfavorable outcomes. Statistical analyses were performed using R language (version 4.5.1), with the following packages: compareGroups (version 4.5.1), nnet (version 7.3.17), MASS (version 7.3.58.1), and ggplot2 (version 3.3.6).

RESULTS

Study Sites and Population

Figure 1 shows that, among 1 069 868 TB cases reported in SINAN, 60 804 PTB cases met the inclusion criteria. Of the 39 607 individuals excluded in this second step, 22 889 (57.8%) were excluded due to of a lack of DST results

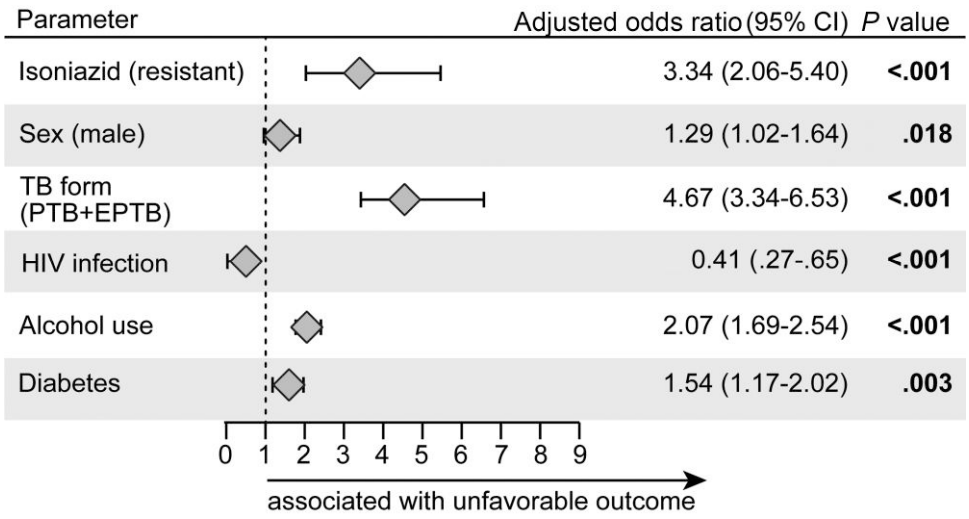


Figure 2. Binomial logistic regression to assess the association of isoniazid resistance with unfavorable tuberculosis treatment outcomes. One model of binomial logistic regression analysis (stepwise method) was employed using all the available variables in the first step. The final model is described in the figure. The main outcome was a combination of unfavorable outcomes (death and failure), and the reference was a favorable outcome (cure). *P* values are statistically significant. Abbreviations: CI, confidence interval; EPTB, extrapulmonary tuberculosis; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis; TB, tuberculosis.

(Figure 1*A*). Among the 21 197 PWPTB included, all of them had DST results available, and outcomes of interest recorded (cure, failure, or death due to TB). Hr patients had a higher frequency of unfavorable outcomes (9.18% vs 3.03%; $P < .001$) (Figure 1*B*). Of these, 294 (1.4%) were Hr, with higher frequency in Southeast (85%) than in South (8.5%) and Northeast (5.1%) regions (Table 1 and Figure 1*C*).

Patients with TB included in the analyses differed from those who were excluded. There was a higher proportion of men, self-reported *pardo (individuals of mixed-race ancestry)*, alcohol users, TB in the past, and higher proportions of people living with HIV and tobacco and drug users among patients included in the analyses versus those who were not included (Supplementary Table 1).

Among 21 197 patients included, 664 (3.1%) experienced an unfavorable ATT outcome. Unfavorable outcomes were more frequently reported in the Midwest and Northeast regions with frequencies equivalent to 5.8% and 3.8% respectively (Table 2). Patients with TB who experienced an unfavorable TB treatment outcome were more frequently male (77.4% vs 70.2%; $P < .001$), more often had 5–9 years of schooling (40.1% vs 34.4%; $P < .001$), and more commonly reported use of tobacco (40.6% vs 30.5%; $P < .001$), alcohol (39.6% vs 23.1%; $P < .001$), diabetes (14.4% vs 10.8%; $P = .004$), mental illness (3.83% vs 2.40%; $P = .032$), and other comorbidities (29.4% vs 10.7%; $P < .001$) than those who were successfully treated for TB (Table 2). Moreover, patients who had an unfavorable treatment outcome more frequently had PTB plus extrapulmonary TB (8.4%% vs 2.8%; $P < .001$), and more often had isoniazid monoresistance (4.1% vs 1.3%; $P < .001$) (Table 2). The detailed outcomes are described in Table 3.

Variables of TB Treatment Outcomes

We performed analyses to assess the association between the occurrence of Hr and each type of unfavorable outcome (treatment failure and death), using a favorable outcome as the reference. Compared to patients with isoniazid sensitivity, Hr was strongly associated with unfavorable ATT outcomes (9.2% vs 3.1%; $P < .001$). A model of binomial logistic regression analysis was employed using the following variables: sex, age, race, Directly Observed Therapy, site of disease (pulmonary/extrapulmonary), HIV infection, alcohol consumption, tobacco use, drug use, diabetes mellitus, and resistance to isoniazid (Figure 2). The main outcome was a combination of unfavorable outcomes (death and failure), and the reference was a favorable outcome (cure). Together, these results show that Hr was an independent factor associated with unfavorable outcomes in the SINAN cohort (aOR, 3.34 [95% CI, 2.06–5.40]; $P < .001$).

DISCUSSION

To our knowledge, no previous study has explored the patterns of Hr in Brazil or similar settings and its association with unfavorable treatment outcomes. The present study investigated a large cohort of PWPTB diagnosed and treated in Brazil. Of note, Hr in the SINAN database (1.4%) was lower than that estimated at a global level by the WHO (11%) [2] but similar to that described by Karo et al [12] (3.4%) in Europe and by Valencia et al [13] in Mozambique, where 4.6% and 2.6% of new and retreatment cases, respectively, were Hr. It is important to point out that the proportion of Hr cases in SINAN may be underestimated because DST was not uniformly performed. Bartholomay et al [10] evaluated DR-TB cases registered in SINAN/SITE-TB and observed that 24.9% of patients with DR-TB registered in the National Laboratory System were not found in SINAN or in SITE-TB, an electronic information system that was developed to monitor patients using special TB treatment regimens, including regimens for DR-TB.

Comparing to patients who were isoniazid drug sensitive, those with Hr more frequently experienced unfavorable TB treatment outcomes. The data observed are similar to those reported by studies from high-burden areas such as Peru [14], Mexico [15], Georgia [16], South Africa [17], and Europe [12]. In our regression analysis, Hr was independently linked to higher risk of an unfavorable TB treatment outcome, where the main outcome was a combination of unfavorable outcomes: death and failure.

The study has several limitations. In SINAN, endpoints were collected passively, and patients were followed only until the end of treatment. We also should mention the high proportion of PWPTB excluded in this cohort, due to unavailability of DST results (60.1%) and loss to follow-up (14.5%). Such data confirm the low proportion of phenotypic and molecular DST (Xpert) performed in Brazil [10]. We did not evaluate the PWPTB cases registered at SINAN that had a treatment modification and migrated to the SITE-TB system [10]. In the SINAN database, it was not possible to access the proportion of patients with Hr who modified the therapeutic regimen after the availability of Hr results. Such information could be useful to analyze the impact on treatment outcomes in patients with Hr who used an individualized regimen. Another limitation related to DST is that no information is available on the level of Hr resistance and the type of Hr mutations involved, which has been shown to influence treatment outcome [6].

In conclusion, our study confirms the independent association of Hr with unfavorable ATT outcomes. Such data reinforce the WHO recommendation that high-TB-burden countries prioritize the use of universal DST, preferably with molecular tests, aiming at the early detection of RR, but also of Hr, that allows the adoption of adequate initial treatment for patients with DR-TB, reducing morbidity, mortality, and transmission in the community.

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

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