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Prediction Models for Adverse Drug Reactions During Tuberculosis Treatment in Brazil

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Background. Tuberculosis (TB) treatment–related adverse drug reactions (TB-ADRs) can negatively affect adherence and treatment success rates.

Methods. We developed prediction models for TB-ADRs, considering participants with drug-susceptible pulmonary TB who initiated standard TB therapy. TB-ADRs were determined by the physician attending the participant, assessing causality to TB drugs, the affected organ system, and grade. Potential baseline predictors of TB-ADR included concomitant medication (CM) use, human immunodeficiency virus (HIV) status, glycated hemoglobin (HbA1c), age, body mass index (BMI), sex, substance use, and TB drug metabolism variables (*NAT2* acetylator profiles). The models were developed through bootstrapped backward selection. Cox regression was used to evaluate TB-ADR risk.

Results. There were 156 TB-ADRs among 102 of the 945 (11%) participants included. Most TB-ADRs were hepatic (n = 82 [53%]), of moderate severity (grade 2; n = 121 [78%]), and occurred in *NAT2* slow acetylators (n = 62 [61%]). The main prediction model included CM use, HbA1c, alcohol use, HIV seropositivity, BMI, and age, with robust performance (c-statistic = 0.79 [95% confidence interval {CI}, .74–.83) and fit (optimism-corrected slope and intercept of −0.09 and 0.94, respectively). An alternative model replacing BMI with *NAT2* had similar performance. HIV seropositivity (hazard ratio [HR], 2.68 [95% CI, 1.75–4.09]) and CM use (HR, 5.26 [95% CI, 2.63–10.52]) increased TB-ADR risk.

Conclusions. The models, with clinical variables and with *NAT2*, were highly predictive of TB-ADRs.

Keywords. TB treatment; adverse drug reactions; prediction model; concomitant medication.

First-line tuberculosis (TB) treatment is effective, resulting in high cure rates for drug-susceptible disease when the standard 6-month regimen is completed [1–3]. However, adverse drug reactions (ADRs) influence rates of treatment completion and effectiveness, through interrupted therapy and the need to use alternative regimens [4]. Recent data from a prospective cohort study in Brazil found that more than three-quarters of participants experienced at least one ADR episode during TB treatment; more than half of all participants had clinical symptoms of an ADR, whereas the remainder were diagnosed based on laboratory measurements [5]. Moreover, treatment interruptions due to ADRs occur in up to 15% of patients, and often within the initial 2-month intensive phase of treatment [5, 6]. This can lead to treatment modification, requiring longer and less effective regimens, and drugs that are more expensive and more toxic. Even when ADRs do not result in treatment modification, they can potentially affect adherence and negatively impact treatment success rates [7].

Our group previously developed a prediction model for unsuccessful TB treatment outcomes, including death, treatment failure, regimen switch, and incomplete treatment [8]. However, the model did not evaluate ADR, which is a measure of drug safety and tolerability. Identifying persons at increased risk of TB treatment–related ADR (TB-ADR), especially modifiable risk factors, could facilitate interventions to lower the risk of ADR. Given the importance of TB drug tolerability for treatment completion and effectiveness, and the lack of models to predict TB-ADR, we developed prediction models for ADR during TB treatment in a large, prospective observational

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cohort in Brazil [9]. We developed two models: one with only clinical variables, and one that also included information on TB drug metabolizer polymorphisms.

METHODS

Study Design and Population

Our study included participants enrolled in the Regional Prospective Observational Research in Tuberculosis (RePORT) Brazil cohort. RePORT-Brazil is a prospective observational cohort study of persons with newly diagnosed, culture-confirmed, pulmonary TB at five sites across three regions in Brazil, enrolled between June 2015 and June 2019. Participants were followed for two years [9, 10]. RePORT-Brazil excluded participants who had previously received anti-TB therapy for ≥7 days, received >7 days of fluoroquinolone therapy within 30 days of enrollment, were pregnant or breastfeeding, or did not plan to remain in the enrollment region during follow-up. Sites were in Rio de Janeiro (Instituto Nacional de Infectologia Evandro Chagas, Clínica de Saúde Rinaldo Delmare, Secretaria de Saúde de Duque de Caxias), Salvador (Instituto Brasileiro para Investigação da Tuberculose), and Manaus (Fundação Medicina Tropical Dr Heitor Vieira Dourado). The study population has been shown to be representative of all TB cases reported to the national Brazilian TB registry (SINAN) [9].

For this study, we included RePORT-Brazil participants with drug-susceptible pulmonary TB who initiated standard TB therapy, comprising a 2-month intensive phase of isoniazid, rifampicin or rifabutin, pyrazinamide, and ethambutol, followed by a 4-month continuation phase of isoniazid with either rifampicin or rifabutin, all dosed according to the participant's weight [11, 12].

Data Collection and Definitions

Clinical, demographic, and outcome data were collected longitudinally at in-person study visits at baseline, month 1, month 2, and end of treatment (typically month 6), and then via telephone follow-up every 6 months until month 24. Data were stored in REDCap [13].

Our primary endpoint was TB-ADR after standard TB therapy was started. RePORT-Brazil used a symptom-based approach to identify ADRs during TB treatment. This analysis included any TB-ADR based on physician-assigned attribution of "possibly," "likely," or "definitely" related to TB treatment [14]. The physician attending the participant assessed whether a specific sign or symptom and/or laboratory alteration was related to TB treatment. Each RePORT-Brazil site had clinicians trained in identifying ADRs known to be related with TB drugs, who independently evaluated each participant. TB-ADRs were also described according to the affected organ system (hepatic, dermatologic, neurologic) and by grade (grades 2–5) [11, 15]. Grade 2 reactions were considered moderate severity; grade 3, severe; grade 4, life-threatening; and grade 5, death. Grade 1 reactions were not captured in RePORT-Brazil. TB treatment outcome definitions followed the recently updated World Health Organization TB treatment outcome definitions [16], in which treatment discontinuation due to ADRs is considered treatment failure.

All participants underwent human immunodeficiency virus (HIV) testing at baseline unless already known to be persons with HIV (PWH), and among PWH, we assessed baseline CD4 T-cell count and HIV-1 RNA (viral load [VL]), and both variables were evaluated as either continuous or categorical variables; we considered a breakpoint of 200 cells/mL for categorical CD4 T-cell count, and for VL a cutoff of <1000 copies/mL to define virologic suppression. We also considered timing of antiretroviral therapy (ART) initiation. Prior ART use was defined as exposure to any ART drug before TB diagnosis, and ART-naive was defined as having never received ART before TB diagnosis.

Diabetes status at baseline was based on both self-reported history of diabetes mellitus and glycated hemoglobin (HbA1c) level. HbA1c <5.7% was considered no diabetes, HbA1c 5.7% to <6.5% was considered prediabetes, and HbA1c ≥6.5% was considered diabetes [17, 18]. Age was considered in years at the time of enrollment, and body mass index (BMI) was categorized as underweight (BMI <18.5 kg/m^2), normal (18.5–25 kg/m^2), and overweight (>25 kg/m^2) [19]. Additional data, such as smear positivity at baseline, presence of cavitation on chest X-ray, and other concomitant chronic diseases, were also collected. The variable race was self-reported at baseline.

We also evaluated concomitant medication (CM) use (other than anti-TB treatment) at baseline, classified by mechanism of action (eg, antibacterial, oral hypoglycemic, analgesic, corticosteroids) and considering the number of CMs used, which were grouped into 4 categories: (1) medications for chronic disease treatment (eg, hypertension, diabetes, HIV); (2) pain/allergy medications, such as analgesic/antipyretic, antihistaminic, corticosteroid, and nonsteroidal anti-inflammatory; (3) antimicrobial medications, including antibiotics, antifungals, and antivirals other than antiretrovirals; and (4) miscellaneous medications, including antiemetic, vitamins, supplements, and any other medications not previously classified. Among PWH, each drug in an antiretroviral regimen (usually a 3-drug combination) was counted separately as a CM in the group of medications for chronic disease, as mentioned above.

Genotyping was done of selected single-nucleotide polymorphisms (SNPs) in genes relevant to metabolism of TB drugs. Genotyping was done by VANTAGE (Vanderbilt Technology for Advanced Genomics) using MassARRAY iPLEX Gold (Agena Bioscience) and TaqMan (ThermoFisher Scientific). We genotyped 4 SNPs to categorize *NAT2* acetylator groups,

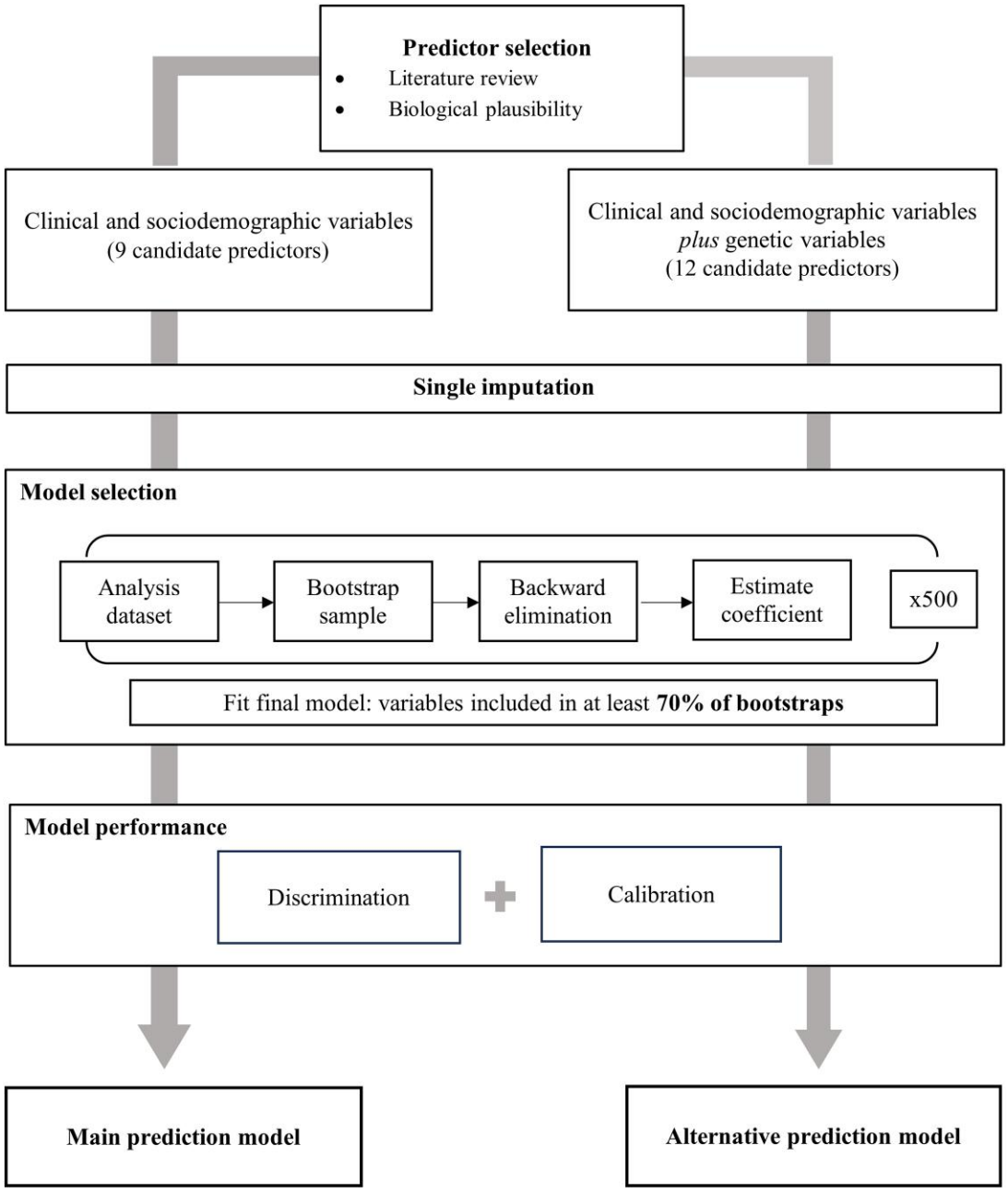


Figure 1 Flowchart with the steps followed to build the prediction models. Schematic representation of each model development step and assessment of model performance. Predictor selection. A comprehensive literature review, taking into account biological plausibility, was made to define which predictors to preselect for the models. Considering the applicability in daily practice, we included 9 easily available clinical and sociodemographic predictors for the main model. For the alternative model, we decided to also include genetic information related to metabolism of tuberculosis (TB) drugs, such as isoniazid and rifampicin. *NAT2* genotypes, related to isoniazid metabolism, were categorized based on combinations of gene variants rs1801280 (*NAT2**5), rs1799930 (*NAT2**6), rs1799931 (*NAT2**7), and rs1801279 (*NAT2**14). This categorization generates 3 *NAT2* acetylator profiles (slow, intermediate, and rapid) that represent the rate of isoniazid metabolism, and consequently, the drug serum levels; eg, *NAT2* slow acetylators metabolize isoniazid at a lower rate; thus, the isoniazid serum levels will be higher. The slow acetylator was defined as homozygous for the variant allele at any locus or heterozygous at 2 or more loci; intermediate as heterozygous at a single locus; or rapid if no variant allele. Two single-nucleotide polymorphisms related to hepatotoxicity and the metabolism of rifampicin, rs11045819 (gene *SLCO1B1*) and rs412543 (gene *GSTM1*), were also genotyped. Single imputation was used; with <1% of missing data, the added complexity of multiple imputation was not going to improve results. All continuous variables were modeled with restricted cubic splines with 3 knots to account for nonlinear relationships. Bootstrapped backward selection was used for model selection. This approach involved repeated iterations of backward selection in bootstrap samples (with replacement) from the data to evaluate the importance of each candidate predictor. After 500 iterations of bootstrapped backward selection, variables that were selected in at least 70% of bootstrap samples were included in the final model. Model performance was evaluated with discrimination and calibration measures to assess the accuracy and reliability of the prediction model. Discrimination was quantified with the c-statistic. Calibration was assessed using calibration plot, calibration intercept, and calibration slope. Internal validation with bootstrap resampling was used to estimate optimism-corrected performance measures. Predictions from the final model accounted for shrinkage according to the heuristic shrinkage factor, estimated as $\chi^2_{model} - df / \chi^2_{model}$, where "$\chi^2_{model}$" is the chi-square model and "df" is degrees of freedom.

Table 1. Clinical and Demographic Characteristics of the Study Population (N = 945) at Tuberculosis Treatment Initiation

Characteristics	Any TB-ADR (n = 102)	No TB-ADR (n = 843)
Age, y, median (Q1–Q3)	38 (26–49)	35 (25–49)
Female sex	33 (32)	284 (34)
Self-reported race		
Brown	13 (13)	228 (27)
Black	60 (59)	431 (51)
White	…	20 (2.3)
Other/Unknown	29 (28)	164 (19)
NAT2 acetylator group[a]		
Rapid	5 (5)	73 (9)
Intermediate	35 (34)	348 (41)
Slow	62 (61)	422 (50)
BMI at baseline, kg/m^2, median (Q1–Q3)	20.6 (19.1–22.2)	20.1 (18.2–22.5)
BMI category		
Underweight (<18.5 kg/m^2)	72 (71)	517 (61)
Normal (18.5–25 kg/m^2)	11 (11)	82 (9.7)
Overweight (>25 kg/m^2)	19 (19)	244 (29)
Sputum smear positive for acid-fast bacilli	76 (75)	694 (82)
Cavitation on chest X-ray	30 (31)	439 (52)
History of diabetes (self-report)	6 (5.9)	105 (12)
HbA1c at baseline, median (Q1–Q3)	5.8 (5.5–6.2)	5.9 (5.4–6.4)
Diabetes (HbA1c category)	6 (6)	105 (12)
Normal (<5.7%)	35 (35)	321 (38)
Prediabetes (5.7% to <6.5%)	47 (47)	312 (37)
Diabetes (≥6.5%)	19 (19)	204 (24)
PWH	38 (37)	145 (17)
Other chronic disease[b]	23 (23)	193 (23)
Receiving CM at baseline	82 (80)	336 (40)
Alcohol use		
Never	17 (17)	135 (16)
Former	56 (55)	310 (37)
Current	29 (28)	398 (47)
Tobacco use		
Never	50 (49)	406 (48)
Former	32 (31)	241 (29)
Current	20 (20)	196 (23)
Drug use[c]		
Never	69 (68)	555 (66)
Former	26 (25)	177 (21)
Current	7 (6.9)	110 (13)

Data are presented as No. (%) unless otherwise indicated. Column proportions do not include missing/unavailable values.

Abbreviations: BMI, body mass index; CM, concomitant medication; HbA1c, glycated hemoglobin; PWH, people with human immunodeficiency virus; Q1, quartile 1; Q3, quartile 3; TB-ADR, tuberculosis treatment–related adverse drug reaction.

[a]*NAT2* acetylator group is defined by 4 single gene polymorphisms.

[b]Other chronic disease includes cardiovascular disorders (eg, hypertension, coronary artery disease, peripheral artery disease, poststroke disorders), thyroid disorders (eg, hypo- and hyperthyroidism), pulmonary disorders (eg, asthma, chronic obstructive pulmonary disease), psychiatric disorders (eg, depression), and chronic kidney disorders.

[c]Drug use includes all drugs, such as marijuana, cocaine, crack, ecstasy, injectable drugs, inhaled solvents, oxycodone, and cocaine paste base.

which have been associated with higher isoniazid concentrations and higher incidence of TB-ADRs including hepatotoxicity [20–22], as slow, intermediate, or rapid acetylators.

Table 2. Distribution of All Tuberculosis Treatment–Related Adverse Drug Reactions (TB-ARDs; Event-Level) Among 102 Persons With a TB-ARD

Adverse Drug Reaction	No. (%) (N = 156 Episodes)
Grade	
Grade 2	121 (78)
Grade 3	25 (16)
Grade 4	9 (5.8)
Grade 5	1 (0.6)
Relation to TB treatment[a]	
Related	21 (13)
Likely	71 (46)
Possible	64 (41)
Type of TB-ADR	
Hepatic	82 (53)
Dermatologic	35 (22)
Neurologic[b]	17 (11)
Other[c]	22 (14)
Timing of ADR in relation to TB treatment start	
Within 1 mo	79 (51)
1–2 mo	41 (26)
2–3 mo	15 (9.7)
3–4 mo	5 (3.2)
4–5 mo	10 (6.5)
5–6 mo	4 (2.6)
≥6 mo	1 (0.6)

Abbreviations: ADR, adverse drug reaction; TB, tuberculosis.

[a]This classification establishes the causality of the ADR and is defined based on Naranjo et al [14]: "A 'related' reaction followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established, followed a recognized response to the suspected drug, and was confirmed by improvement on withdrawing the drug and reappeared on re-exposure. A 'likely' reaction has a reasonable temporal sequence after a drug, followed a recognized response to the suspected drug, was confirmed by withdrawal but not by exposure to the drug, and could not be reasonably explained by the known characteristics of the patient's clinical state. And a 'possible' reaction followed a temporal sequence after a drug, possibly followed a recognized pattern to the suspected drug, and could be explained by characteristics of the patient's disease."

[b]Neurologic is composed of 13 events of peripheral neuropathy and 4 other neurologic events.

[c]Other ADRs include anemia (n = 2), arthralgia (n = 5), cardiovascular/respiratory (n = 3), musculoskeletal (n = 2), reproductive (n = 2), sensory (n = 1), uric acid elevation (n = 6), and urinary/renal (n = 1).

We selected the candidate predictors for the 2 prediction models incorporating information from a comprehensive literature review and biological plausibility [20–25]. Considerable deliberation was given to the inclusion of the following variables: CM use, HIV status (positive or negative), HbA1c, age, BMI, alcohol use, tobacco use, drug use, sex, and genetic data. Substance use (alcohol, tobacco, and drugs), was categorized as former, current, or never use.

Statistical Analysis

Participant characteristics were described stratifying by TB-ADR occurrence (any TB-ADR and no TB-ADR). Details of each ADR were described, including the grade, physician-assigned attribution of relation to TB treatment, type of ADR (organ system affected), and timing of ADR. For all descriptive analyses, continuous variables were

Table 3. Prediction Models for Any Tuberculosis Treatment–Related Adverse Drug Reaction

Variable	Bootstrap Inclusion, %	Coefficient	Standard Error
Main prediction model			
Intercept	**100**	−6.8	± 2.16
Concomitant medications	**100**	1.83	± 0.28
HbA1c (%)	**100**	−0.88	± 0.64
Alcohol use (current)	**85**	−0.42	± 0.36
HIV	**83**	0.59	± 0.26
Age	**82**	0.03	± 0.03
BMI	**79**	−0.16	± 0.10
Tobacco use	61	…	…
Drug use	37	…	…
Sex	21	…	…
Alternative prediction model			
Intercept	**100**	−2.87	± 0.69
Concomitant medications	**100**	1.82	± 0.27
HbA1c (%)	**100**	−0.30	± 0.09
Alcohol use (current)	**91**	−0.45	± 0.33
NAT2 acetylator profile[a]	**79**	0.35	± 0.18
HIV	**77**	0.49	± 0.25
Age	**76**	0.02	± 0.01
BMI	62	…	…
Tobacco use	56	…	…
Drug use	45	…	…
rs11045819 (*SLCO1B1*)	40	…	…
rs412543 (*GSMT2*)	20	…	…
Sex	16	…	…

In bold, the variables selected >70% of bootstrap samples that were included in the final models.

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus.

[a] *NAT2* acetylator profile included rapid, intermediate, and slow groups. The interpretation of this variable within the model was that as the *NAT2* acetylator slowed, there was an increased probability of tuberculosis treatment–related adverse drug reactions to occur.

summarized with median and the lower and the higher interquartiles (Q1 and Q3, respectively) and categorical variables by frequency and percentages.

We used 2 approaches for the models to predict risk of any TB-ADR. First, we considered the applicability and utility of a prediction score in daily practice, and included 9 prespecified clinical and sociodemographic predictors to build the main model. Second, since we also had data on *NAT2* acetylator group, we built an alternative model, with 12 prespecified predictors. Bootstrapped backward selection was used for model selection [26]. After 500 iterations of bootstrapped backward selection, variables that were selected in at least 70% of bootstrap samples were included in the final model. Model performance was evaluated with discrimination and calibration measures. Discrimination was quantified with the c-statistic [27]. Calibration was assessed using calibration plot, calibration intercept, and calibration slope [28] (Figure 1). Internal validation with bootstrap resampling was used to estimate optimism-corrected performance measures, and predictions from the final model accounted for shrinkage using the heuristic shrinkage factor [29]. The methods used in prediction model development, including variable selection and model validation, have been described in detail elsewhere [8]. Moreover, we developed a nomogram with the variables included in the main prediction model to aid the model interpretation.

We additionally performed Cox proportional hazard regression to evaluate associations between each variable selected for the final primary prediction model and the risk of TB-ADR (but not for the alternative model); we considered any grade 2 or higher TB-ADR, related to any organ system. Participants could experience multiple ADRs over the course of treatment, but each analysis evaluated time until the first ADR. Individuals who were lost to follow-up were censored at their last kept study visit [30]. For all analyses, confounders were selected a priori and included age, sex, and tobacco and alcohol use at baseline. We considered the age of 35 as reference for adjustment based on the study population median age. For the diabetes variable, HbA1c was considered as a continuous variable (modeled with a restricted cubic spline with 3 knots) and as a categorical variable, of no diabetes, prediabetes, and diabetes, as described above. Less than 1% of participants had any missing data. Data were assumed to be missing completely at random, so single imputation with predictive mean matching was used in the analysis. All analyses were conducted using the significance level of .05 and using R software (version 4.2.0).

RESULTS

Of the 945 participants included, 102 (11%) experienced an ADR (Supplementary Figure 1). Among those who experienced ADRs, most were men (68% [n = 69]), 37% (n = 38) were PWH, 80% (n = 82) had CM use at baseline, and most were slow *NAT2* acetylators (61% [n = 62]) (Table 1). Overall, there were 156 TB-ADR episodes reported; most TB-ADRs occurred during the intensive phase of TB treatment (n = 120 [77%]). Most TB-ADRs were grade 2 (n = 121 [78%]), and the most frequent type was hepatic (n = 82 [53%]), followed by dermatologic (n = 35 [22%]), and neurologic (n = 17 [11%]) (Table 2).

After bootstrapped backward selection, 6 variables were most predictive of TB-ADRs and were included in the main model: CM use at baseline, HbA1c, alcohol use, HIV status, BMI, and age (Table 3). The main model with these variables, including restricted cubic splines with 3 knots for HbA1c and age, demonstrated good performance with a c-statistic of 0.79 (95% confidence interval [CI], .75–.83) and the calibration curve indicated a good fit, with an optimism-corrected intercept and slope of −0.22 and 0.87, respectively. A shrinkage factor of 0.90 was applied to correct for uncertainties introduced in model development and improve fit in external validation (Figure 2*A* and 2*B*). The alternative prediction model included the following variables: CM use, HbA1c, alcohol use, *NAT2* acetylator group, age, and HIV status (Table 3). This model

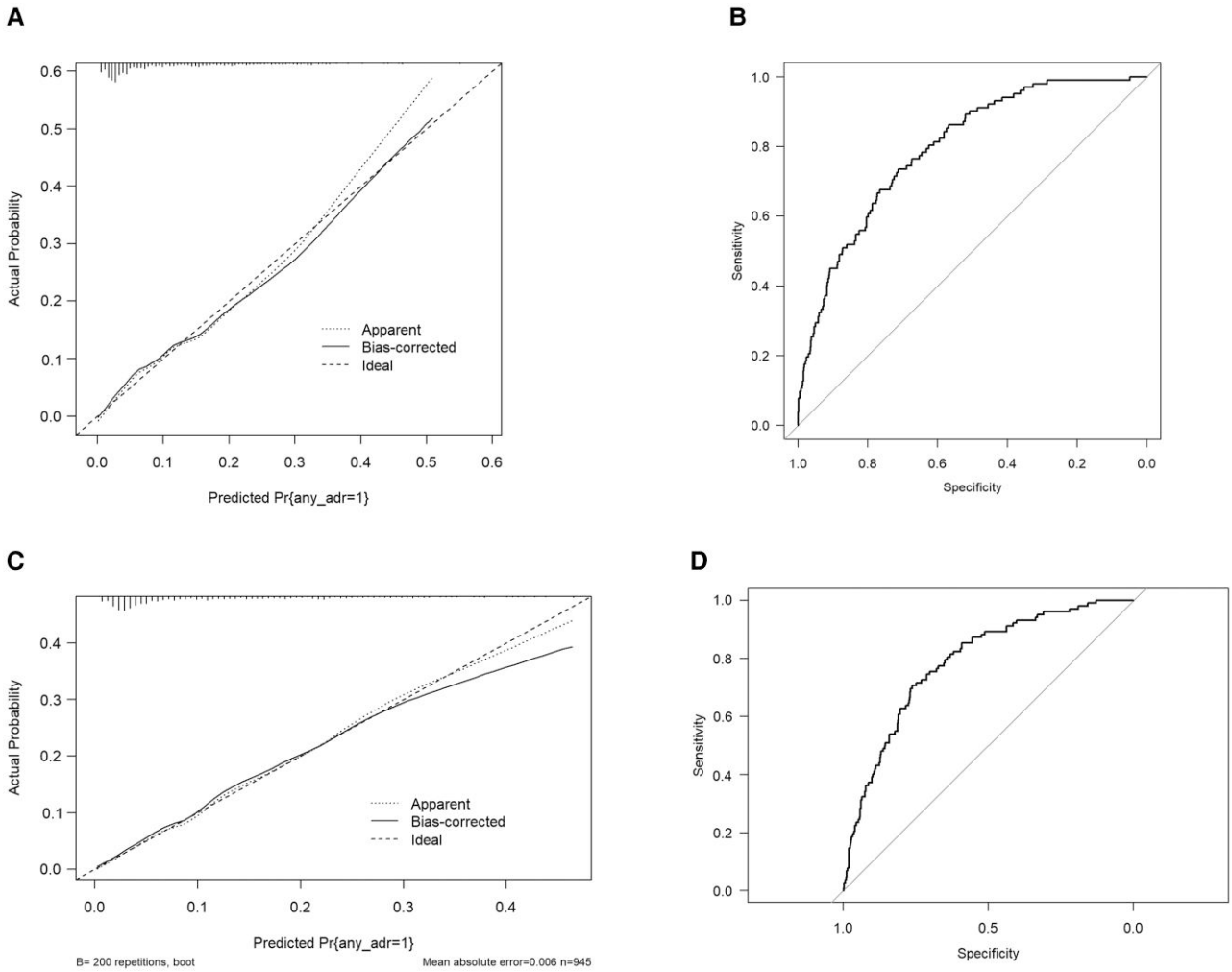


Figure 2. Performance of main prediction model (*A* and *B*) and of alternative prediction model (*C* and *D*). *A*, The calibration plot displays agreement between observed and predicted outcome probabilities across deciles of outcome (tuberculosis treatment–related adverse drug reaction [TB-ADR]) risk. An ideal calibration curve has an intercept of 0 and a slope of 1 (dashed line). The apparent calibration (dotted line) is calibration of the model in the original data, and the bias-corrected line is corrected for overfitting using 500 bootstrap samples. The bias-corrected calibration intercept and slope were −0.22 and 0.87, respectively. The top of the plot displays a histogram of the distribution of predicted probabilities of TB-ADR for the 945 participants with culture-confirmed, drug-susceptible pulmonary TB included in the study. A shrinkage factor of 0.90 was applied to correct uncertainties introduced in model development and improve fit in external validation. *B*, The receiver operating characteristic (ROC) curve measures discrimination of the model, ie, how well the model can differentiate between those with and without an outcome. The area under the ROC curve, which is equivalent to the c-statistic, is 0.79 (95% confidence interval [CI], .75–.83). *C*, The calibration plot displays agreement between observed and predicted outcome probabilities across deciles of outcome (TB-ADR) risk. An ideal calibration curve has an intercept of 0 and a slope of 1 (dashed line). The apparent calibration (dotted line) is calibration of the model in the original data, and the bias-corrected line is corrected for overfitting using 500 bootstrap samples. The bias-corrected calibration intercept and slope were −0.09 and 0.94, respectively. The top of the plot displays a histogram of the distribution of predicted probabilities of TB-ADR for the 945 participants with culture-confirmed, drug-susceptible pulmonary TB included in the study. A shrinkage factor of 0.90 was applied to correct uncertainties introduced in model development and improve fit in external validation. *D*, The ROC curve measures discrimination of the model, ie, how well the model can differentiate between those with and without an outcome. The area under the ROC curve, which is equivalent to the c-statistic, is 0.79 (95% CI, .74–.83).

also demonstrated good performance, with a c-statistic of 0.79 (95% CI, .74–.83). The calibration curve indicated a good fit, with an optimism-corrected intercept and slope of −0.09 and 0.94, respectively (Figure 2*C* and 2*D*). The predicted risks from the main model can be applied to new populations using a nomogram (Supplementary Figure 2).

In addition to the prediction model, we evaluated the association of each predictor included in the main model, individually, with TB-ADR occurrence. CM use at baseline increased by approximately 5 times the risk of any TB-ADR (hazard ratio [HR], 5.38 [95% CI, 3.25–8.89]). PWH also had an increased risk of any TB-ADR (HR, 2.68 [95% CI, 1.75–4.09]) and of hepatic TB-ADR (HR, 5.26 [95% CI, 2.63–10.52]; graph not shown). Higher levels of HbA1c were associated with decreased risk of having TB-ADR (Figure 3). For example, compared to individuals with HbA1c of 5.5%, individuals with an

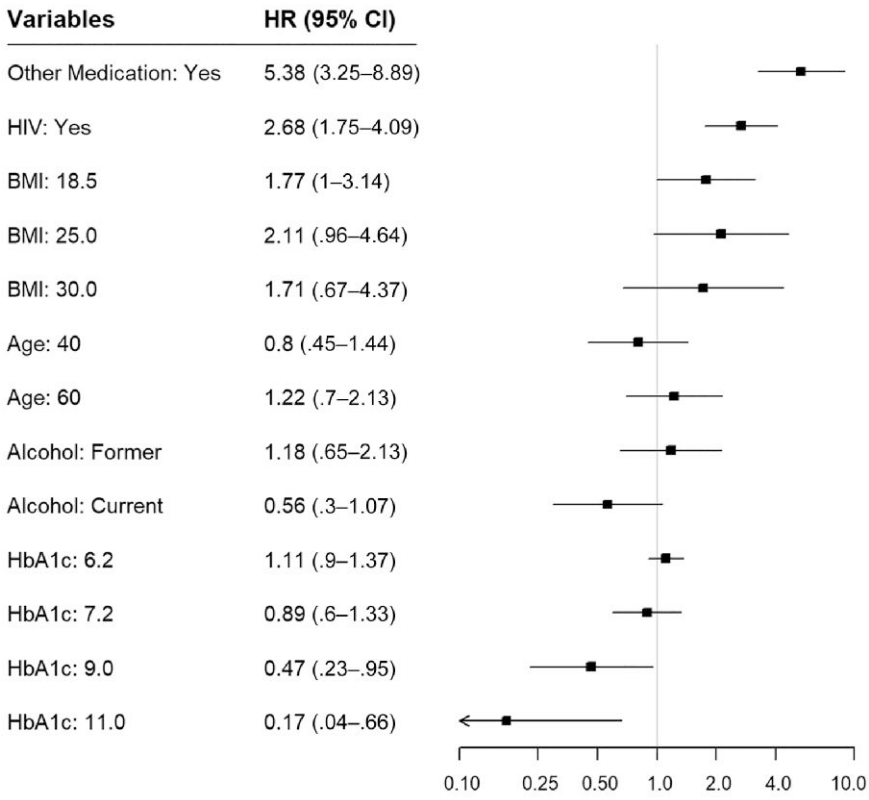


Figure 3. Coefficient plot of variables and associations with tuberculosis treatment–related adverse drug reactions. Abbreviations: BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; HR, hazard ratio. Reference categories: for other medication, no; for HIV, no/HIV negative; for body mass index, 15 kg/m^2; for age, 20 years; for alcohol, never; for HbA1c: 5.5%.

HbA1c of 9% had 63% decreased risk of TB-ADR (HR, 0.47 [95% CI, .23–.95]) and individuals with HbA1c of 11% had 83% decreased risk of TB-ADR (HR, 0.17 [95% CI, .04–.66]) (Supplementary Figure 3).

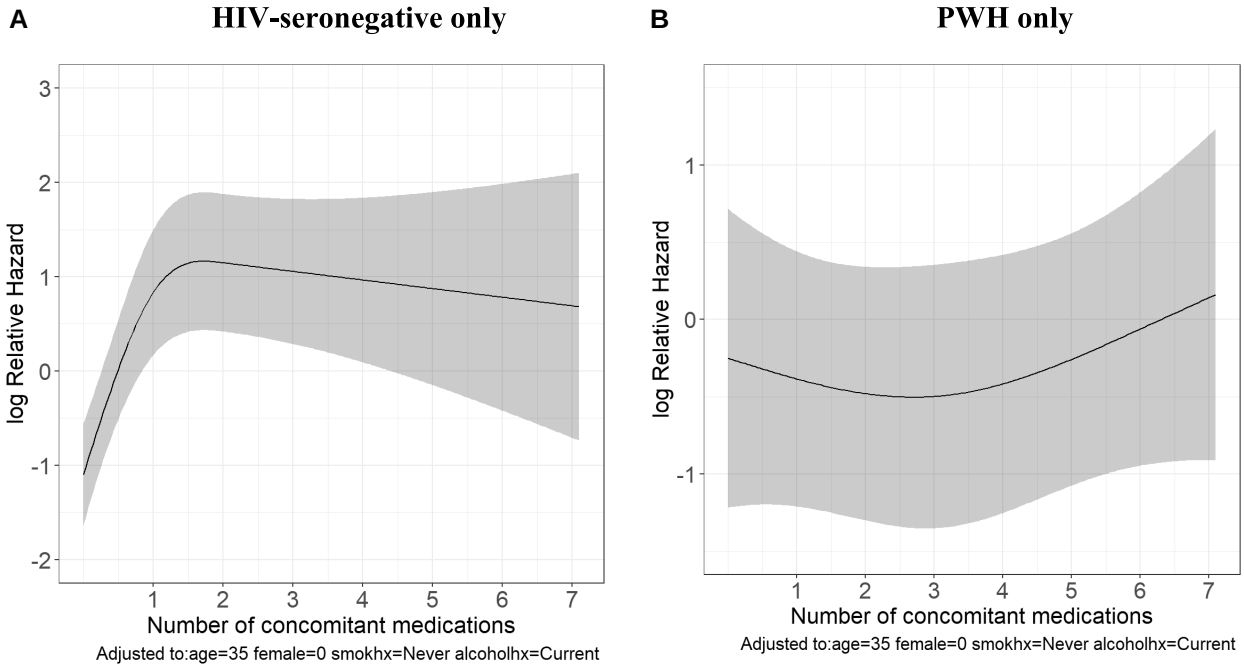
Since CM use and HIV status were highly associated with TB-ADR, we performed additional subanalysis to assess the association of CM and TB-ADR, stratifying by HIV status. A subset of patients (n = 315) also had information about the type and number of medications used at baseline, allowing us to assess the effect of polypharmacy on the outcome instead of a simple binary (yes/no) exposure. HIV-seronegative participants who were prescribed at least 1 CM at baseline had a higher risk of having a TB-ADR compared to participants with no CM (adjusted HR [aHR], 6.89 [95% CI, 3.63–13.07]). As the number of CM increased among HIV-negative participants, no substantial increase in the TB-ADR risk was observed. We also assessed the interaction of CM, which includes ART, and HIV seropositivity. In addition, among PWH, no association with number of CM and TB-ADRs was found (Figure 4). Regarding the type of CM, we categorized 27 classes of CM into 4 groups. Among participants, taking 4 or more CM medications for chronic diseases and antimicrobials was more frequent. Most participants taking only 1 CM were using pain medication (70.6%), and within this group, only 12% (n = 13) were acetaminophen-containing drugs (Supplementary Table 1).

Further analysis considering HIV-related variables found no association with TB-ADR when comparing CD4 T-cell counts (>200 vs <200 cells/mL), VL (suppressed vs nonsuppressed), or ART exposure (ART-experienced vs ART-naive) (Supplementary Figure 4)

DISCUSSION

This analysis highlights several important findings. Most TB-ADRs were of moderate severity (grade 2), were hepatic, and occurred in the intensive phase of TB treatment. Use of CM at baseline, HbA1c, alcohol use, HIV status, BMI, and age were predictive of TB-ADR. Our findings of ADR severity, of organ system affected, and of the timing of ADR during TB treatment are consistent with previous studies [5, 23].

The 2 models developed were highly predictive of TB-ADR. Interestingly, most of the predictors were common to both models. The main model included variables that can be easily obtained in the clinical setting and can promptly demonstrate



Number of concomitant medications[1]	Hazard Ratio	95% Confidence Interval
0	Reference	
1	**6.90**	**3.63-13.10***
2	**9.42**	**4.60-19.29***
3	**8.60**	**4.19-17.67***
4+	**7.85**	**3.53-17.45***

Number of concomitant medications[2]	Hazard Ratio	95% Confidence Interval
0	Reference	
1	0.87	0.60-1.27
2	0.79	0.40-1.58
3	0.78	0.33-1.85
4+	0.85	0.35-2.06

Figure 4. Association between concomitant medication and tuberculosis treatment–related adverse drug reactions, stratified by HIV status. *(A)* Risk of TB-ADR among participants HIV-seronegative, according to the number of concomitant medications. *(B)* Among participants living with HIV, no risk of TB-ADR was observed according to the number of concomitant medications, which include the antiretrovirals. Abbreviations: HIV, human immunodeficiency virus; PWH: people with HIV; TB-ADR: TB treatment-related adverse drug reaction. Adjusted to: age = 35; female = 0; smoking = never; alcohol use = current. [1] Number of participants in each subgroup: for 0, N=469; for 1, N=129; for 2, N=49, for 3, N=13, for 4+, N=19. [2] Number of participants in each subgroup: for 0, N=40; for 1, N=14; for 2, N=15, for 3, N=25, for 4+, N=69. ***** The risk of TB-ADR increases the highest from 0 to 1 concomitant medication.

the risk of TB-ADR in a person starting TB treatment. The alternative model included the same variables plus the *NAT2* acetylator profiles, which are generally not readily available in clinical practice. However, such information may be useful for evaluating interventions that could improve the tolerability of TB treatment, such as isoniazid dose adjustment.

When evaluating associations between predictors and risk of TB-ADR, CM use at baseline and HIV coinfection were associated with increased risk for TB-ADR, whereas high levels of HbA1c were associated with decreased risk for TB-ADR. Among HIV-seronegative participants, CM use at baseline was strongly associated with risk of TB-ADR, especially when comparing no CM versus 1 CM. The most common class of CM used by participants taking only 1 CM was non-acetaminophen-containing pain medication. In Brazil, dipyrone (ie, Metamizole) is a very commonly used analgesic and antipyretic drug and is available without prescription. Dipyrone has a potential hepatotoxic effect; however, the most well-known ADR for this drug is agranulocytosis, which occurs infrequently and was not observed in our study [31, 32]. Among PWH, there was no significant association between CM use, which included ART, and the risk of TB-ADR. There are limited previous studies evaluating this association; however, the available literature is not in accordance with our findings. A previous study demonstrated that hepatotoxicity risk increased with concomitant anti-TB-HIV therapy and that ART alone was associated with 3 times the risk of ADR compared to TB treatment alone [33]. Moreover, a recent study found higher incident rates of liver injury among patients with TB-HIV coinfection, especially when starting ART during the intensive phase of TB treatment [34].

In the present analysis, PWH were at increased risk for TB-ADR, including hepatic ADRs, which is consistent with several previous studies [34, 35] and therefore an expected finding. However, we did not find an association between HIV-related factors, such as CD4 T-cell count or VL, and TB-ADR in our study.

Interestingly, the risk of TB-ADR decreased as baseline HbA1c increased; that is, participants with higher HbA1c levels had lower risk of TB-ADR. Although the reason for this association is unclear, it could be due to decreased drug absorption among persons with poor diabetes control, and therefore lower TB drug exposures [36]. The association between BMI, age, and alcohol use was inconclusive for ADR risk. Moreover, there was a higher frequency of TB-ADR among slow *NAT2* acetylators, which is in accordance with the literature [21, 22, 37].

There were several limitations of this study. We considered only the first TB-ADR occurrence; TB-ADRs can overlap or occur more than once during TB treatment. In addition, the determination of attribution of ADRs to TB drugs by local care providers in this open-label study could be biased. Due to the high number of classes of CM received by the study population (ie, 27), we could not assess the association between any specific class (eg, antiretroviral, antihypertensives) and ADR risk with TB treatment. We considered only baseline information regarding CM use, which may not fully capture medications that are used intermittently, but which has the benefit of being readily applicable at TB treatment initiation. Depending on the type of medication, it may be taken regularly (eg, for chronic diseases) or intermittently (eg, for symptom relief). There was a relatively low rate of TB-ADR (11%) compared to rates in the literature [38, 39] and this may have affected the performance of the prediction model. Moreover, the lack of association between CM and risk of TB-ADR among PWH may have been due to the sample size, and because we only considered baseline information about ART, and not the possible time-varying association of ART and TB-ADR. We included only participants with culture-confirmed, drug-susceptible, pulmonary TB on standard therapy regimens for 6 months, which could affect the generalizability of the results.

This study had several strengths. This was a large multicenter prospective cohort study, representative of persons with TB in Brazil [9], with uniform data collection and regularly scheduled visits. Additionally, the variables included in the model are readily available in clinical settings, which, in turn, can make implementation of the prediction model feasible. We also developed an alternative model that included genetic information. We are not aware of previous studies that developed a prediction model for ADRs during TB treatment. Compared to the prediction model for unfavorable TB treatment outcomes developed by Peetluk et al [8, 40], the prediction models we developed can be an additional tool in TB treatment management. Although we did not perform external validation, the nomogram generated through the main prediction model can be easily applied to the target population—persons receiving standard TB treatment in Brazil.

In conclusion, we developed 2 models that were highly predictive of TB treatment–related ADRs; 1 with easy-to-assess variables, and another that included genetic data. Additionally, we evaluated associations between important risk factors and TB-ADR. Knowledge of these factors at the time of TB treatment initiation, and interventions to decrease their contribution (eg, fewer concomitant medications or isoniazid dose adjustment) could improve TB treatment tolerability.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Ethical approval. All clinical investigations were conducted according to the principles of the Declaration of Helsinki. The

RePORT-Brazil protocol, informed consent, and study documents were approved by the institutional review boards at each study site and at Vanderbilt University Medical Center. Participation in RePORT-Brazil was voluntary, and written informed consent was obtained from all such participants.

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

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