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A systematic review of prediction models for tuberculosis treatment outcomes

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ABSTRACT (word count: 261)

Objective: To systematically review and critically evaluate prediction models developed to predict tuberculosis (TB) treatment outcomes among persons with pulmonary tuberculosis.

Design: Systematic review

Data sources: PubMed, Embase, Web of Science, and Google Scholar were searched for studies published January 1, 1995 - January 9, 2020.

Study selection and data extraction: Studies that developed a model to predict pulmonary TB treatment outcomes were included. Study screening, data extraction, and quality assessment were conducted independently by two reviewers. Study quality was evaluated using the Prediction model Risk Of Bias Assessment Tool (PROBAST).

Results: 14,739 articles were identified, 536 underwent full-text review, and 33 studies presenting 37 prediction models were included. Model outcomes included death (n=16, 43%), treatment failure (n=6, 16%), default (n=6, 16%) or a composite outcome (n=9, 25%). Most models (n=29, 78%) measured discrimination (median c-statistic=0.75; IQR: 0.68-0.84), and 17 (46%) reported calibration, often the Hosmer-Lemeshow test (n=13). Nineteen (51%) models were internally validated, and six (16%) were externally validated. Eighteen studies (54%) mentioned missing data, and of those half (n=9) used complete case analysis. The most common predictors included age, sex, extrapulmonary TB, body mass index (BMI), chest x-ray results, previous TB, and HIV. Risk of bias varied across studies, but all studies had high risk of bias in their analysis.

Conclusions: TB outcome prediction models are heterogeneous with disparate outcome definitions, predictors, and methodology. We do not recommend applying any in clinical settings without external validation, and encourage future researchers adhere to guidelines for developing and reporting of prediction models.

Registration: The study was pre-registered on OSF (https://osf.io/rz3wp).

ARTICLE SUMMARY:

Strengths and limitations

- Prediction models for tuberculosis treatment outcomes have the potential to inform interventions or treatment management protocols to promote cure among tuberculosis patients at the greatest risk of unsuccessful treatment outcomes, but the methods and clinical utility of existing models had not been formally evaluated.
- This was the first systematic review of prediction models for tuberculosis treatment outcomes.
- The review used a comprehensive search strategy, conducted thorough bias assessment with the PROBAST tool, and offers recommendations for future model development and validation studies for predicting tuberculosis treatment outcomes.
- Evidence synthesis and quality assessment were limited by incomplete reporting in primary studies
- External validation studies or studies written in languages other than English, Spanish, Portuguese, or French were excluded.

BACKGROUND

Tuberculosis (TB) is one of the top ten causes of death worldwide and a leading cause of death from an infectious disease. In 2018, 10 million people developed TB and 1.45 million people died from it globally, despite widespread availability of curative treatment.(1) Global treatment success was 85% for all new and relapse TB patients in 2018. For HIV-associated TB, it was 75%. These proportions are lower than the End TB Strategy target of ≥90% treatment success.(2)

Heeding early recognition that *Mycobacterium tuberculosis* develops resistance rapidly in response to single-drug therapy, TB has been treated with combination therapy for more than 50 years.(3) Aside from weight-based dosing, the World Health Organization (WHO) and other TB guidelines authorities recommend a standardized approach for treatment of almost all TB patients.(4–6) The current recommendation for treatment of drug-susceptible TB includes 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin. However, actual treatment regimens may vary due to differences in drug tolerability, and other individual-level factors that can affect TB treatment outcomes.

Due to the long duration of TB treatment, it would be beneficial for TB outcome studies to identify early treatment predictors of unsuccessful TB treatment outcomes to identify patients needing tailored treatment approaches, such as directly observed therapy (DOT) or extended treatment course. Research suggests that individual characteristics, such as HIV, age, undernutrition, diabetes, TB disease severity, extrapulmonary TB, history of TB, adherence, alcohol use, and adverse drug reactions, are associated with unsuccessful TB treatment outcomes, but results vary by setting and patient population.(7–10)

Prediction models are defined as any combination or equation of two or more predictors, such as demographic factors, medical history, physical examination, and lab tests, used for estimating an individualized probability of a specific endpoint within a defined period of time.(11) The large number of prediction models for TB outcomes published in recent years highlights a common desire to identify TB patients at greatest risk of an unsuccessful treatment outcome in order to tailor treatment strategies and promote cure. However, to date, there has not been a formal synthesis or quality assessment of existing prediction models for TB treatment outcomes, which is essential to determine which models should inform clinical practice. This could also guide development of future models. Thus, we conducted a systematic review to identify, describe, compare, and synthesize clinical prediction models designed to predict TB treatment outcomes among persons with pulmonary TB.

METHODS AND ANALYSIS

All steps of the systematic review were carried out according to guidelines set by Cochrane Prognosis Methods Group (PMG) and PROGnosis RESearch Strategy (PROGRESS).(12–14) Reporting adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (**Supplemental File 1).** This study was pre-registered on OSF (https://osf.io/rz3wp).

Study eligibility criteria

The review question was defined according to the PICOTS framework (**Supplemental File 2)**. In brief, the goal was to identify prognostic models developed to predict TB treatment outcomes among pulmonary TB cases. The main outcome was unsuccessful TB treatment outcome, defined by the WHO as the combination of death, treatment failure, loss to follow-up, and/or not evaluated, as compared to successful TB treatment outcome, defined as the combination of cure or treatment completion (**Table 1**). Loss to follow-up was sometimes referred to as default or treatment abandonment.

Inclusion criteria were: 1) prognostic model studies with or without external validation(15); 2) study population included adult, drug-susceptible, pulmonary, TB cases; 3) written in English, Spanish, Portuguese, and French; 4) published between January 1, 1995 and January 9, 2020; 5) treatment outcome was one of the following: cure, treatment completion, death, treatment failure, loss to follow-up, or not evaluated.

Exclusion criteria were: 1) predictive value of more than one variable was evaluated but not combined in a prediction model; 2) study population was only multi-drug resistant (MDR) TB cases, only extrapulmonary TB cases, or only children (< 18 years-old); 3) outcome was evaluated during treatment such as: two-month smear/culture conversion, acquired resistance,

adverse events, quality of life; 4) long-term outcomes, such as relapse, recurrence, or post-treatment mortality.

The decision to include only articles in English, Spanish, Portuguese, and French was based on study team capabilities. The dates reflect modern TB treatment practice; first-line TB treatment regimens were not available until the early 1990s.(16,17) Articles that included a combination of drug-susceptible and drug-resistant cases, or a combination of children and adults were included.

Search strategy and selection criteria

The following electronic databases were searched on January 9, 2020: PubMed, Embase, Web of Science, and the first 200 references from Google Scholar. This combination of databases achieved best overall recall for systematic reviews in a recent study.(18) Clinicaltrials.gov and retractiondatabase.org were also searched for unpublished research. Reference lists of retrieved articles were checked to identify eligible studies.

Search terms relating to the "prediction model" component of the search were adapted from a PubMed search strategy that captured prediction model studies with sensitivity of 98%.(19) That component was combined with terms relating to TB treatment outcomes. The search strategy, developed in PubMed, was adapted for all other databases with assistance from a reference librarian (**Supplemental File 3**).

Article selection was conducted in three stages. The first stage was de-duplication and title screening, carried out using *revtools* in RStudio (version 1.2).(20) Remaining articles were imported into Covidence, a web-based software platform that streamlines systematic reviews, where abstracts (Stage 2) and full text (Stage 3) were screened.(21) Stages 2 and 3 were carried out by two independent reviewers (LSP and FMR). Discordance was discussed between

reviewers, and if consensus was not reached, a third party arbitrated (one of TRS, VCR, PFR, DL). In stage 3, reasons for exclusion were documented according to PRISMA.

Data analysis

Data from selected studies were recorded using a database designed in REDCap (Vanderbilt University).(22,23) Data extraction was informed by the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) and the Prediction Model Risk of Bias Assessment Tool (PROBAST).(15,24,25) CHARMS checklist and PROBAST are in **Supplemental Files 4 and 5,** respectively**.**

Quality assessment and applicability of included studies was assessed using PROBAST.(15,25) PROBAST was specifically designed to assess risk of bias of prediction model studies, which included identifying deficiencies in study design, conduct, or analysis that led to inaccurate estimates of predictive performance. PROBAST has 4 domains: participants, predictors, outcome, and analysis with 20 total signaling questions. Each question was answered on the scale: yes, probably yes, no, probably no, no information. Domains were scored as low, high, and unclear risk of bias. PROBAST also guides assessment of applicability of participants, predictors, and outcomes from each included study to the review question.

Results were summarized narratively and in tables and figures. Meta-analysis was not possible due to lack of external validation and use of disparate predictors, outcome definitions, and modeling methods. For studies that presented multiple models with the same set of predictors and outcomes, but different methods, the best-performing method was included in data synthesis. For studies presenting multiple models with different sets of predictors (i.e. baseline data vs. longitudinal data), the model developed using only baseline data was included. If studies developed multiple models for different outcomes or with different populations, all models were included.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, or reporting of the research, as it was not feasible or appropriate for this systematic review. The study protocol is publicly available at https://osf.io/rz3wp.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study selection

The search identified 14,739 unique studies. After excluding irrelevant titles, 6,426 abstracts were screened, 536 articles underwent full-text review, and 33 model development studies presenting 37 prediction models were included (**Figure 1**).

Study characteristics

Of the 33 studies, most were retrospective cohorts (n=25, 76%), three (9%) were prospective cohort studies, two (6%) were case-control studies, and three (9%) were nested case-control studies. Data from nearly half of studies (n=16, 48%) were collected from surveillance systems; eleven (33%) studies used a data collection form developed specifically for their study and six studies (18%) extracted data from medical records. Median sample size was 803 (interquartile range (IQR): 291-4167). Full details on included studies are in **Table 2**.

Thirteen studies (41%) took place in Asia, eight (25%) in Africa, six (19%) in Europe, four (12%) in North America, and one (3%) included sites in Europe and Argentina. Fewer than half (n=14, 45%) of the studies took place in high-burden TB settings.[1] One study did not report study location. (**Tables 2 and 3**).

Reporting of population characteristics varied by study (**Table 4**). Among 18 studies that reported a measure of central tendency (mean or median) for age, the median of those measures of central tendency was 41 years (IQR: 37-49). Eighteen studies reported including persons living with HIV (PLWH); 5 of these included only TB/HIV patients. Twelve studies reported including persons with diabetes; one of which includes only TB/DM. Eight studies reported including participants with MDR, ten studies included only hospitalized patients, and in 14 studies, all participants were on directly observed therapy (DOT).

Model characteristics

Model outcomes included death (n=16, 43%), treatment failure (n=6, 16%), default (n=6, 16%) or a composite outcome (n=8, 23%) (**Tables 2 and 5**). The complete outcome definition for all included studies is in **Supplemental File 6**.

Most models were developed using clinical/epidemiologic predictors (n=34, 92%), two (6%) used multiple biomarkers, and one (3%) used adherence data. The most common candidate predictors were age, sex, extrapulmonary TB, smear result, BMI, x-ray findings, and previous TB. The most common predictors retained in the final models were age, sex, extrapulmonary TB, BMI, chest x-ray results, previous TB, and HIV (**Figure 2**).

Only three models (8%) used survival analysis; most models used logistic regression (n=29, 78%) and five (14%) used a machine learning approach. More than half of studies (n=19, 51%) considered variables for inclusion in the multivariable model based on unadjusted associations with the outcome. Model building methods varied widely between models (**Table 5**).

Only 19 (51%) models were internally validated, including ten (53%) split-sample validation, five (26%) bootstrap resampling, and four (21%) cross-validation. Six (16%) models were externally validated.

Many models (n=30, 81%) reported discrimination with c-statistic (concordance statistic) or area under the receiver operating characteristic (AUROC), which are equivalent and quantify the ability of the model to distinguish between patients who do and do not develop an outcome. Only 17 (46%) reported calibration, the agreement between observed and predicted outcomes. Most studies assessed calibration with Hosmer-Lemeshow tests (n=13, 77%); only two studies provided a calibration plot, the preferred reporting method for prediction model

studies,(15,26,27) and one reported the calibration slope **(Table 2)**. Models were presented a variety of ways, the most common of which was a weighted risk score (n=16, 43%); details on model presentation are in **Supplemental File 7.**

Quality assessment

Grading of PROBAST signaling questions is summarized in **Figure 3**, and the summary risk of bias for the participants, predictors, outcome, and analysis domains and assessment of applicability are shown in **Figure 4**. More than half of the studies were at low risk of bias for the population and outcomes domains, but all studies were at high risk of bias in the analysis domain.

Common sources of population bias included use of non-nested case-control design(28,29), nested case-control design without proper estimation of baseline risk,(30,31) or inappropriate inclusion/exclusion criteria.(32,33) Sources of predictor bias included lack of standardized assessment of key predictors (i.e. HIV, diabetes, chest x-ray scoring)(9,28,30,33–35) or timing of data collection/availability that would limit the intended use of the model.(9,28,36) Within the outcomes domain, sources of bias included subjective(34) or non-standard(31,37) outcome measures and inconsistent outcome ascertainment.(28)

Bias in the analysis domain was widespread. More than half of the models included were likely overfit due to low events per variable (EPV) ratios (**Table 5**). Only 6 studies handled continuous and categorical variables appropriately (i.e., didn't dichotomize continuous variables, considered non-linearity of continuous variables).(30,38–42) Most studies used complete case-analysis or did not mention missing data; no study used multiple imputation in their main analysis. One study with low amounts of missing data (<5%) conducted sensitivity analysis with multiple imputation.(43) A different study excluded only two people out of a total sample size of

1007 with missing data, which would have little impact on model performance.(44) Fewer than half (n=14) of studies avoided univariable predictor selection, and only three studies used survival analysis, appropriately accounting for censoring.(35,44,45) Performance measures were appropriately reported (i.e. calibration assessed with plot and discrimination assessed with c-statistic/AUROC) in three studies.(40,43,46) Only two studies estimated optimism (degree to which data are overfit) or accounted for potential overfitting with penalization of model parameters.(34,40) Ten studies appropriately presented their model with model coefficients or nomograms, which prevents bias from rounding or transforming model coefficients to generate a risk score.(29,32,50–54,34,36,37,44,46–49)

About half of the models (n=19, 51%) were applicable to the review question in all domains. However, unclear reporting of target population or predictor and outcome definitions limited assessment of applicability for several studies.(37,48,49,55,56) Additionally, studies that included only hospitalized patients with specific laboratory parameters may not be routinely available in the clinical setting.(38,39,41)

DISCUSSION

In this comprehensive, systematic review of prediction models for pulmonary TB treatment outcomes, we identified 33 model development studies presenting 37 prediction models. These prediction models were developed for predicting death, treatment failure, default, or a composite unfavorable outcome during TB treatment. Most models reported good performance (c-statistic/AUROC>0.7), but all were evaluated to have high risk of bias due to poor reporting, exclusion of missing data, weak methodologic approaches, lack of calibration assessment, and limited validation. Predictor and outcome definitions varied by study and limited comparisons between models.

More than half of the models included in the review were developed in low burden TB settings, and none were developed specifically in South America. Prediction of TB treatment outcome is especially important in high burden TB settings, where resources may be limited, and risk assessment can guide resource allocation toward patients who need the most involved care protocols.

Common risk factors included in the models were consistent with well-established risk factors for poor TB treatment outcomes, including age, sex, HIV, extrapulmonary TB, baseline smear results, and previous TB treatment. Among studies that included PLWH, only three considered factors related to management/severity of HIV, such as receipt of antiretroviral therapy, CD4 cell count, or viral load, which likely impact TB treatment outcomes.(39,45,50) Laboratory values or metabolic biomarkers, such as hemoglobin, hemoglobin A1c or random blood glucose, may also be associated with treatment outcome and worth considering as candidate predictors. There is increasing evidence that diabetes impacts TB treatment outcomes, but caution is warranted about how to best define diabetes in the context of a prediction model to ensure consistency and reproducibility across studies.(57) Behavioral characteristics, such as

tobacco use, alcohol use, and drug use were rarely included in final prediction models and are difficult to collect objectively, suggesting their role in prediction models for TB treatment outcomes may be limited.

Additionally, several studies excluded participants with HIV, diabetes, extrapulmonary TB, or MDR TB, because these factors negatively influence treatment outcomes. However, careful consideration should be given to inclusion/exclusion criteria in prediction model studies. Information necessary to carry out inclusion/exclusions should be available at the of intended use of the model, which may not always hold for these aforementioned factors.(58) This point is especially questionable for MDR, given that conventional drug-susceptibility testing results are not available for several weeks after TB diagnosis; though more recent advances in rapid molecular methods such as GeneXpert or line-probe assays offer rapid screening for drug resistance.(59)

TB researchers should thoughtfully consider how to appropriately handle complexities of censoring and competing risks in TB outcomes research. Only three studies in this review used survival analysis, despite the long duration of TB treatment outcome assessment and relatively high rates of losses to follow-up across studies. Losses to follow-up were frequently excluded, which can lead to selection bias. Additionally, all studies that included death as the outcome considered all-cause mortality. Also, for studies that predict losses to follow-up/default, death (even due to TB) is a competing risk. Competing risk analyses are common in cardiovascular research, research in elderly populations, and there are specific recommendations for competing risk methods in prognostic research.(60,61)

Though all included studies were at high risk of bias in the analysis domain, we want to highlight two studies with some exemplary characteristics.(40,43) Pefura-Yone et al.(40) provide

clear explanations of study design, inclusion/exclusion criteria, and data collection procedures; TB diagnosis and treatment outcome definitions were standard.(62) Non-linearity of continuous variables was considered with restricted cubic splines, and no continuous variables were categorized or dichotomized; the final model includes four predictors that are easy to collect and routinely assessed in most TB control programs, especially those in high burden settings. The performance of the model was internally validated with bootstrap validation, and the discrimination (c-statistic=0.808) was corrected for optimism. Model calibration was presented graphically with calibration plots. The final model was presented as a nomogram with instructions for use, which facilitates use in external validation studies. Gupta-Wright and colleagues developed and externally validated a clinical risk score to predict mortality in high-burden, low-resource settings.[43] They used clinical trial data with very low amounts of missing data for model development, and externally validated the clinical risk score with data collected independently from two other studies (a clinical trial and a prospective cohort). Given high amounts (42%) of missing data in the validation cohort, they conducted sensitivity analysis using multiple imputation for missing data; the c-statistic differed slightly between complete case and multiple-imputation analyses in the validation cohort (0.68 vs. 0.64). Candidate predictors were based on *a priori* clinical knowledge, previous literature, and required variables were objective, reproducible, and available in low-resource settings, consistent with recommended approaches.(25,58,63) Additionally, they reported model performance with the c-statistics and calibration plots for development and validation cohorts, and reported results according to TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) guidance.(26,27) Regardless, each of these models requires external validation prior to use in clinical practice.

There are several limitations of this study. First, data extraction was subject to reporting the primary study, which varied widely across studies. Most studies reported discrimination, and several reported sensitivity and specificity; TRIPOD recommends all studies report, at minimum, calibration with a calibration plot and discrimination with c-statistic.(27) Measures of sensitivity and specificity require dichotomization of risks, which then only pertain to a specific risk stratum, rather than quantifying the overall model performance.(14,63) We did not include external validation studies, which is an essential step for translation to clinical practice. However, several studies in the review did not include the full model equation, which inhibits their ability to be externally validated. Upon searching for studies that externally validated prediction models in this review, we found three studies(64–66) that evaluated the same model (TBscore).(35) Briefly, these studies evaluated the ability of TBscore to monitor treatment response in a new setting(64), refined the instrument (TBccoreII) using exploratory factor analysis(65), and then evaluated TBscoreII for use in patients with TB/HIV.(66) To our knowledge, no other studies included in the review were externally validated by other sources. Finally, we excluded 10 studies that were not available in English, Spanish, Portuguese, or French; all abstracts were available in English, and none reported model performance metrics, so they likely would have been excluded for different reasons regardless.

The findings of this review not only serve as a comprehensive overview of existing TB outcome prediction models but can act as a resource for future model development and validation of prediction models for TB treatment outcomes. We encourage researchers to focus future TB outcome prediction models on easily collected and readily available predictors that are widely generalizable. We highlight age, sex, extrapulmonary TB, BMI, chest x-ray results, previous TB, and HIV as common predictors of TB treatment outcomes. Additionally, when

building a new prediction model, it is recommended to first prune the set of considered predictors based on expert opinion and previous literature, rather than univariable analysis or variable selection processes(25,58,63) Future model development or validation studies should adhere to the TRIPOD guidelines, which provide a 22-item checklist and aims to improve the reporting of prediction model development studies.(26,27) We also encourage researchers consider the PROBAST criteria when developing their model to limit sources of bias in design and conduct of prediction model studies.

Prediction models are an important tool in TB management, as they can lay the foundation for future intervention studies or clinical decision making by providing risk prediction that can aid in targeted treatment, resource allocation, or intensive case management at patients who are least likely to achieve cure and most likely to benefit from some form of intervention, especially in high-burden and low-resources areas. Though our findings suggest that none of the existing models are ready for clinical application without extensive external validation, we hope they direct future researchers to make use of guidelines for development and reporting of prediction models.

FOOTNOTES

Ethics approval: Not required.

Transparency statement: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted, and any discrepancies from the study as planned were explained.

Contributorship: LSP conceptualized the research question, designed the protocol, and drafted the manuscript. LSP and FMR screened studies. FMR, PFR, DL, VCR and TRS provided feedback on the research design, original protocol, and revised successive drafts of the manuscript. All authors approved the final version of the manuscript.

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Competing interests: None declared.

Data sharing: The study protocol is available online at https://osf.io/rz3wp. Most included studies are publicly available. Additional data and code are available upon request.

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Table 1. World Health Organization definition of treatment outcomes for TB patients(67)

Outcome	Definition
Treatment completion	Completion of treatment without evidence of failure, but without documentation of a negative sputum smear or culture in the last month of treatment and/or on at least one previous occasion, either because tests were not done or because results are unavailable
Cure	Bacteriologic confirmation of a negative smear or culture at the end of TB treatment and on at least one previous occasion
Treatment success	Composite of cured and treatment completed
Treatment failure	Sputum smear or culture is positive at month 5 or later during treatment
Death	TB patient who dies for any reason before starting or during the course of treatment
Loss to follow-up	TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated (transfer out)	TB patient for whom no treatment outcome was assigned, which includes cases who "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart of inclusion process

[See Figure 1]

Table 2. Study characteristics

First author, year	Population	Study years	Study design	Location	Validation	No. with outcome / sample size (%)	Predictors in final model	Performance measures	Model presentation	Risk of bias (population, predictor, outcome, analysis)
Death										
Abdelbary(9) / 2017	TB cases	2006 - 2013	Retrospective cohort	Mexico	Internal (split-sample)	*Development:* 261/4216 (6%) *Validation:* 260/4215 (6%)	Age (<41, 41-65, ≥65), sex, MDR, HIV, malnutrition, alcoholism, diabetes, pulmonary TB	c-statistic = 0.70 Sensitivity = 60% Specificity = 71%	Risk score	Low, High, Low, High
Abdelbary(9) / 2017 (TB-DM)	TB-DM cases	2006 - 2013	Retrospective cohort	Mexico	None	88/2121 (4%)	Sex, malnutrition, BCG vaccinated, AFB smear (positive vs. negative)	c-statistic = 0.68	Risk score	Unclear, High, Low, High
Aljohaney(68) / 2018	Hospitalized TB patients	Dec 2011 – Dec 2016	Retrospective cohort	Saudi Arabia	None	41/291 (14%)	Clinical model: Age, congestive heart failure Clinical + lab model:* Age > 65, congestive heart failure, bilateral disease on chest xray	Clinical model: Accuracy = 86% Clinical & lab model:* Accuracy = 90%	Odds ratios	Unclear, Unclear, Unclear, High
Bastos(69) / 2016	Inpatient and outpatient TB cases on DOT	2007 - 2013	Retrospective cohort	Portugal	External (setting)	*Development:* 121/681 (18%) *Validation:* 24/103 (23%)	Hypoxemic respiratory failure, age (≥50 vs. <50), bilateral involvement, comorbidities (at least one of HIV, diabetes, liver at least one of: HIV, diabetes, liver failure/cirrhosis, congestive heart failure, chronic respiratory disease), hemoglobin (<12 vs. ≥12)	AUROC = 0.84 (95% CI: 0.76-0.93) Sensitivity = 41.8% Specificity = 92.1%	Risk score	Low, Unclear, Low, High
Gupta-Wright(70) / 2019	Hospitalized TB-HIV patients	Oct 2015 – Sept 2017	Retrospective cohort	Malawi and South Africa	External (setting)	*Development:* 94/315 (30%) *Validation:* 147/644 (23%)	Sex, age 55+, currently taking ART, ability to walk unaided, severe anemia, positive TB-LAM	c-statistic = 0.68 (95% CI: 0.61-0.74) HL test: p=0.13 Calibration plot	Risk score	Low, Low, Low, High
Horita(71) / 2013	Hospitalized TB patients	Jan 2008 – Jul 2011	Retrospective cohort	Japan	External (setting)	*Development:* 36/179 (20%) *Validation:* 48/244 (20%)	Age, oxygen requirement, albumin, activities of daily living	AUROC = 0.893 Sensitivity = 0.92 Specificity = 0.73	Risk score	Low, Low, Low, High
Koegelenberg(39) / 2015	Hospitalized TB patients	Jan 2012 – May 2013	Retrospective cohort	South Africa	None	38/83 (46%)	Septic shock, HIV with CD4 < 200, creatinine > 140 (male) or >120 (female), P:F O2 ratio < 200, chest radiograph showing miliary pattern/parenchymal infiltrates, absence of TB treatment at admission	Mean score in survivors: 2.27 (SD=1.47) Mean score in non-survivors: 3.58 (SD=1.08)	Risk score	Low, Low, Low, High
Nguyen(52) (general pop) / 2018	TB cases	Jan 2010 – Dec 2016	Retrospective cohort	Texas	Internal (split-sample)	*Development:* 253/3378 (7%) *Validation:* 270/3377 (8%)	Age group (15-44, 44-64, >64), US born, homeless, resident of long term care facility, chronic kidney failure, meningeal TB, miliary TB, HIV positive, HIV unknown	AUROC = 0.80 (95% CI: 0.77-0.82) HL test:X^2=6.3, p=0.613	Risk score	Low, Unclear, Unclear, High
Nguyen(36) (TB-DM) / 2019	TB-DM patients	Jan 2010 – Dec 2016	Retrospective cohort	Texas	Internal (bootstrap)	112/1227 (9%)	Age ≥65, US-born, homeless, IDU, chronic kidney failure, TB meningitis, Miliary TB, AFB positive smear, HIV positive	AUROC = 0.82 (95% CI: 0.78-0.87) HL test: X^2=4.54, p=0.81 Brier score=0.07	Risk score	Unclear, Unclear, Unclear, High
Nguyen(51) (TB-HIV) / 2018	TB-HIV patients	Jan 2010 – Dec 2016	Retrospective cohort	Texas	Internal (bootstrap)	57/450 (13%)	Age ≥ 45, resident of LTCF, meningeal TB, abnormal CXR, diagnosis confirmed by positive culture of NAA, culture not converted or unknown	AUROC = 0.79 (95% CI 0.70-0.87) HL test: X^2=4.25, p=0.51 Brier score: 0.09	Risk score	Low, High, Unclear, High
Pefura-Yone(53) / 2017	TB patients	Jan 2012 – Dec 2013	Retrospective cohort	Cameroon	Internal (bootstrap)	213/2250 (9%)	Age, adjusted BMI, clinical form (PTB+, PTB-, EPTB), HIV	C-statistic: 0.808 HL test: X^2=6.44, p=0.60 Sensitivity = 80.7% Specificity = 68.2% Calibration plot	Model coefficients	Low, Low, Low, High
Podlekareva(72) / 2013	TB/HIV patients	Jan 2004 – Dec 2006	Retrospective cohort	52 cities in Europe and Argentina	None	995†	DST performed, treatment with RHZ, and cART at/near TB diagnosis	Crude RH = 0.62 (95% CI: 0.64-0.84)	Risk score	Low, Unclear, Low, High
Valade(41) / 2012	Hospitalized TB patients	Mar 2000 – Jul 2009	Retrospective cohort	France	Internal (bootstrap)	20/53 (38%)	Miliary TB, catecholamine infusion, mechanical ventilation on admission	AUROC = 0.92 (95% CI: 0.85-0.98) Brier score = 0.13	Risk score	Unclear, Low,

								Optimism = 0.03 Accuracy = 85% Sensitivity - 75% Specificity = 91%		Low, High
Wang(73) / 2019	HIV-negative, culture-confirmed, pulmonary TB cases	Jan 2014 – Dec 2016	Prospective cohort	China	External (setting)	*Development:* 36/287 (13%) *Validation:* 15/104 (14%)	Age, cavitary lesion, pleural effusion, drug resistance, disseminated, albumin, c-reactive protein, white blood cell count, IL-6, MIF	AUROC = 0.85 ± 0.028	Odds ratios	Low, Low, Low, High
Wejse(74) / 2008	Pulmonary TB patients on DOT	1996 - 2001	Retrospective cohort	Guinea Bissau	None	100/698 (14%)	Cough, hemoptysis, dyspnea, chest pain, night sweating, anemia conjunctivae, tachycardia, positive funding at lung auscultation, temperature >37, BMI <18, BMI<16, MUAC<220, MUAC<200	AUROC = 0.65 (95% CI: 0.6-0.7) Sensitivity = 0.45 Specificity = 0.75	Risk score	Low, High, Low, High
Zhang(44) / 2019	TB/HIV patients at end stage of AIDS	Aug 2009 – Jan 2018	Retrospective cohort	China	Internal (split-sample)	*Development:* 157/807 (19%) *Validation:* 40/200 (20%)	Anemia, TB meningitis, severe pneumonia, hypoalbuminemia, unexplained infection or space-occupying lesions, malignancy	AUROC = 0.867 (95% CI: 0.832-0.902) Sensitivity = 79.6% Specificity = 82.9%	Risk score	Low, Low, Low, High
Treatment failure										
Abdelbary(9) / 2017	TB cases	2006 - 2013	Retrospective cohort	Mexico	Internal (split-sample)	*Development:* 2109† *Validation:* 6322†	Education (no or low vs. higher than primary school), MDR, AFB smear (>+2, +1, negative)	c-statistic = 0.65 Sensitivity = 52% Specificity = 66%	Risk score	Low, High, Low, High
Kalhori(48) (logistic) / 2010	TB cases at DOTS registration	2005	Retrospective cohort	Iran	Internal (split-sample)	*Development:* 828/4836 (17%) *Validation:* 2418†	Gender, age, weight nationality, prison, case type	AUROC = 0.70 Accuracy = 81.64% HL test: X^2=11.935, df=8, p=0.154	Model coefficients	Unclear, Unclear, Unclear, High
Keane(29) / 1997	Smear-positive TB patients on standard first-line regimen with DOT	1990 - 1995	Non-nested case control	Vietnam	None	130/803 (16%)	3 month model: Extensive lesions, mediastinal shift, average smear score 3rd month, weight, progressive x-ray, any previous treatment Baseline model: Mediastinal shift, average smear score, extensive lesions, any previous treatment, cavities, weight	3 month: Sensitivity = 80% Specificity = 80% Baseline: Sensitivity = 70% Specificity = 80%	Model coefficients	High, Unclear, Unclear, High
Luies(32) / 2017	Smear-positive pulmonary TB cases on DOT	May 1999 – Jul 2002	Nested case-control	South Africa	Internal (cross-validation)	10/31 (32%)	3,5,-Dihydroxybenzoic acid, (3-(4-Hydroxy-3-methoxyphenyl) propionic acid	AUROC = 0.89 (95% CI: 0.7-1.00)	Model coefficients	High, Unclear, Unclear, High
Mburu(75) / 2018	Smear-positive TB patients	Feb 2014 – Aug 2015	Prospective cohort	Kenya	Internal (cross-validation)	13/321 (4%)	HbA1c, regimen (retreatment), age, weight, random blood glucose, BMI, BUN, HIV positive result, ever smoker, creatinine	AUROC = 0.56 ± 0.07	Relative score	Low, Low, Low, High
Default										
Thompson(76) / 2017	HIV uninfected adults with newly diagnosed pulmonary TB	Apr 2010 – Apr 2013	Retrospective cohort	South Africa	Internal (cross-validation) and external (setting)	6/99 (6%)	18 splice junctions and 13 genes	AUROC (internal) = 0.87 AUROC (external) = 0.63	Heatmap of differentially expressed genes	Low, Low, Low, High
Abdelbary(9) / 2017 (TB-DM)	TB cases	2006 - 2013	Retrospective cohort	Mexico	None	93/2121 (4%)	Age (<40 vs. ≥40), sex, HIV	c-statistic= 0.62	Risk score	Unclear, High, Unclear, High
Belilovsky(34) / 2010	Hospitalized TB patients	1993 - 2002	Retrospective cohort	Russia	External (geographical)	*Development:* 1326/3904 (34%) *Validation:* 4662/12803 (36%)	Sex, unemployment, retreatment case, alcohol abuse (yes, no, no data), severe TB form, residence (urban vs. rural), age (25-50 vs. other), pulmonary TB (vs extrapulmonary), prison history	Belgrood: AUROC = 0.75 Orel: AUROC = 0.75 Pskov: AUROC = 0.78 Yaroslavi: AUROC = 0.75 Calibration table	Model coefficients	Unclear, High, High, High
Chang(30) / 2004	All tuberculosis patients	Jan 1999 – Mar 1999	Nested case-control	China	None	102/408 (25%)	Baseline:* Ever smoker (current, former, never), retreatment (history of default, no history of default, not) Longitudinal: Smoking status (current, former, never), retreatment (with history of default, without history of default, never), unsatisfactory adherence in first two months (good, poor, fair, unknown), subsequent hospitalization, treatment side effects in last month of treatment	Baseline:* AUROC = 0.70 (95% CI: 0.63-0.76) HL test: X^2 = 1.448, df=5, p=0.919 Longitudinal: AUROC = 0.85 (95% CI: 0.80-0.90)	Odds ratios	High, High, Low, High

								HL test: $X^2 = 5.887$, df=6, p=0.436		
Chee(77) / 2000	TB cases	1996	Nested case-control	Singapore	None	38/71 (54%)	Chinese race, extent of family support, treatment duration	Accuracy = 74.6%	Model coefficients	High, Unclear, High, High
Cherkaoui(28) / 2014	TB patients with definite or probable pulmonary or extrapulmonary TB	Jun 2010 – Oct 2011	Non-nested case-control	Morocco	None	91/277 (33%)	Age <50, work interfering with ability to take TB treatment, retreatment regimen, daily DOT, moderate or severe side effects, told friends about TB, current smoker, never smoker, symptom resolution in <2 months, knowledge of TB treatment duration	AUROC = 0.85 (95% CI: 0.80-0.90) Sensitivity = 82.4% Specificity = 87.6% HL test: X^2=0.77, p-value=1.00	Survey tool	High, High, High, High
Rodrigo(78) / 2012	New TB cases	Jan 2006 – Dec 2009	Prospective cohort	Spain	Internal (split-sample)	*Development:* 92/1490 (6%) *Validation:* 103/1589 (6%)	Immigrant, living alone, living in an institution, previous TB treatment, linguistic barriers (poor understanding), IV drug use, unknown IV drug use	AUROC = 0.67 (95% CI: 0.65-0.70) Sensitivity = 65.05% Specificity = 67.36%	Risk score	Low, Low, Low, High
Unfavorable outcome										
Kalhori(49) (predicting) / 2009†	TB patients at DOT registration	2005	Retrospective cohort	Iran	Internal (split-sample)	*Development:* 6920† *Validation:* 2966†	Age, gender, nationality, prison, area, weight	Classification rate = 89.8% R2 = 0.45	Model coefficients	Unclear, Unclear, Unclear, High
Sauer(56) / 2018†	TB cases	Data available through March 2018	Retrospective cohort	Azerbaijan, Belarus, Georgia, Moldova, Romania	Internal (split-sample)	*Development:* 103/411 (25%) *Validation:* 44/176 (25%)	Forward selection (FS):* Drug sensitivity, employment status, smear microscopy, dissemination Backwards elimination (BE): Drug sensitivity, employment status, smear microscopy, dissemination Stepwise selection (SS): Drug sensitivity, employment status, smear microscopy, dissemination Lasso: Country, employment, extrapulmonary, cavity size, decrease in lung capacity, smear microscopy, drug sensitivity, chest imaging Random forest (RF): Top 5 by mean decrease accuracy: lung cavity size, type of resistance, employment status, country, total cavities Top 5 by mean decrease Gini index: Age of onset, drug regimen, lung cavity size, number of daily contacts, culture	FS:* AUROC = 0.74 (95% CI: 0.66-0.82) Sensitivity = 0.36 Specificity = 0.89 Misclassification = 0.24 BE: AUROC = 0.73 (95% CI: 0.65-0.81) Sensitivity = 0.3 Specificity = 0.88 Misclassification = 0.27 SS: AUROC = 0.73 (95% CI: 0.65-0.81) Sensitivity = 0.30 Specificity = 0.88 Misclassification = 0.27 Lasso: AUROC = 0.72 (95% CI: 0.64-0.80) Sensitivity = 0.21 Specificity = 0.96 Misclassification = 0.23 RF: AUROC = 0.73 (95% CI: 0.65-0.81) Sensitivity = 0.30 Specificity = 0.88 Misclassification = 0.27 SVM linear: AUROC = 0.69 (95% CI: 0.60-0.77) Sensitivity = 0.21 Specificity = 0.94 Misclassification = 0.24 SVM polynomial: AUROC = 0.69 (95% CI: 0.60-0.77) Sensitivity = 0 Specificity = 1 Misclassification = 0.25	List	Unclear, Unclear, Unclear, High

Baussano(46) / 2008§	Pulmonary TB cases	2001 - 2005	Retrospective cohort	Italy	Internal (bootstrap)	576/1242 (46%)	Residency (residential vs. homeless), sex, geographic origin (non-EU vs. EU), case definition (other than definite vs. definite), treatment setting (inpatient and unknown vs. outpatient), age (continuous)	AUROC= 0.75 Calibration slope = 0.98 R^2 = 0.24	Nomogram	Low, Unclear, Low, High
Costa-Veiga(47) / 2017§	Pulmonary TB cases	2000 - 2012	Retrospective cohort	Portugal	External (temporal)	*Development:* 1152/10766 (11%) *Validation:* 4714†	HIV, previous treatment, age class (25-44, 15-24, 45-64, >64), IV drug use, pathologies (other disease comorbidity)	AUROC= 75.9% (95% CI: 74.1-77.7) Sensitivity = 71% Specificity = 73%	Nomogram	Low, Low, Low, High
Killian(33) / 2019§	TB patients (99DOTS program)	Feb 2017 – Sep 2018	Retrospective cohort	India	None	433/4167 (10%)	LEAP:* Lstm rEal-time Adherence Predictor with 2 input layers, 1) LSTM with 64 hidden units and a dense layer with 48 units for the dense layer and 4 units for the penultimate layer w-misses: missed doses in last week t-misses: total missed doses in 35 days units and a dense layer with 48 units for the dense layer and 4 units for the penultimate layer Random forest: 150 trees and no max depth based on DAT from first 35 day	LEAP* AUROC = 0.743 lw-misses: AUROC = 0.607 t-misses: AUROC = 0.630 Random forest: AUROC = 0.722	None	High, High, Unclear, High
Madan(50) / 2018§	TB-HIV patients on DOT with first-line TB treatment	2015	Retrospective cohort	India	None	78/448 (17%)	Sputum smear grade, previous TB,; disease classification, HIV status, ART status, CD4 cell count, sex and age group (with interaction terms between age group and sex; sputum smear status and type of TB; HIV status at TB diagnosis and CD4 cell category).	AUROC = 0.783 HL test p-value = 0.149	Model coefficients	Low, Low, Low, High
Mburu(75) / 2018§	Smear-positive TB patients	Feb 2014 – Aug 2015	Prospective cohort	Kenya	Internal (cross-validation)	32/340 (9%)	HbA1c, treatment regimen (retreatment), creatinine, BMI, BUN, weight, age, random blood glucose, HIV positive result, male gender	AUROC = 0.65 ± 0.06	Relative score	Low, Low, Low, High
Other outcome										
Kalhori(79) (fuzzy) / 2009¶	TB patients at DOTS registration	2005	Retrospective cohort	Iran	Internal (split-sample)	*Development:* 7254† *Validation:* 2418†	Case type, treatment category, risky sex, prison, sex, recent TB infection, diabetes, low body weight, TB type, length, previous imprisonment, age, area, HIV	Mean absolute percentage error = 1.24	Learned parameters	Unclear, Unclear, High, High
Hussain(55) / 2019‖	Pulmonary and extrapulmonary TB patients (TB Reach)	2011 - 2014	Retrospective cohort	Unknown	Internal (split-sample)	*Development:* 3371† *Validation:* 842†	Random forest*, artificial neural networks, and SVM	Random forest:* Accuracy = 76.32%	None	Unclear, Unclear, Unclear, High

Abbreviations: AUROC=Area under receiver operating characteristic; c-statistic=concordance statistic; DOTS=Directly Observed Therapy, DM=Diabetes; HL=Hosmer-Lemeshow; TB=Tuberculosis;
*Indicates best-performing/most relevant model, which is included throughout the manuscript (see methods section for details). Performance measures are reported for highest level of validation performed (ranked from strongest to weakest: external validation, internal validation, no validation). If internal and external validation were performed, both are reported.
†Outcome number unknown
‡Outcome is composite of death and treatment failure (losses to follow-up and not evaluated (unknown) outcomes were excluded)
§Outcome is composite of death, treatment failure, loss to follow-up, and not evaluated
¶Outcome is a value from 1 to 5 (1= patient completed the treatment course in frame of DOTS, 2=cured, 3= quit treatment, 4=failed treatment and 5=death)
‖Outcome is treatment completion

Table 3. Characteristics of patient populations in the 33 included studies with prediction models for tuberculosis treatment outcomes

Characteristic	Studies reporting characteristic, n (% of total)	Categories	N(%) or Median [IQR]
Sample size	33 (11)	-	803 [291, 4167]
Study duration, years	32 (97)	-	4 [2,7]
Study design	33 (100)	Prospective cohort	3 (9)
		Retrospective cohort	25 (76)
		Nested case-control	3 (9)
		Non-nested case-control	2 (6)
Data source	33 (100)	Medical record	6 (18)
		National registry or surveillance system	13 (39)
		Local registry or surveillance system	1 (3)
		Regional registry or surveillance system	2 (6)
		Data collect form for study purposes	11 (33)
Study region	32 (97)	Africa	8 (25)
		Asia	13 (41)
		Europe	6 (19)
		North America	4 (12)
		South America	0 (0)
		Global	1 (3)
High burden TB setting*	31 (94)	All	143(42)
		Some	1 (3)
		None	17 (55)
Missing data	18 (54)	Complete case-analysis	9 (50)
		Missing indicator method	4 (22)
		Heckman's method	1 (6)
		Simple imputation	2 (12)
		Sensitivity analysis with imputation	1 (6)
		Other	1 (5)
Number of models developed	33 (100)	1	25 (76)
		2	4 (12)
		3	1 (3)

		4	2 (6)
		7	1 (3)
Reasons for multiple models developed	8 (24)	Different outcomes	1 (12)
		Different predictors considered	4 (50)
		Different methods	2 (25)
		Different outcomes	1 (12)
		Different populations and outcomes	1 (12)

*Determined based on study location and WHO list of 30 high-burden TB countries in the 2019 Global Tuberculosis Report (1).

Table 4. Study population characteristics of 33 included studies

	Included?			
Characteristic	**Yes**	**No**	**Unknown**	**Median [IQR]‡, n**
Age*	18	-	15	41 [37, 49],
HIV	18	7	8	23% [10-100], n=17
Diabetes	12	2	19	12% [5-21], n=11
MDR	8	7	18	1% [1-3], n=8
Other drug resistance	12	1	20	6% [4-12], n=10
Extrapulmonary TB†	22	4	7	11% [4-17], n=16
Previous TB	20	1	12	19% [9-30], n=17
DOT	14	0	19	100% [100-100], n=14
Hospitalized patients	13	1	19	100% [100-100], n=10

Abbreviations: DOT=directly observed therapy; IQR=interquartile range; MDR=multi-drug resistance; TB=tuberculosis

*Based on the measure of central tendency reported in the study (mean: n=11; median: n=7)

†Forms of extrapulmonary TB differ by study but included some of the following: Miliary, meningeal, pleural, peritoneal, disseminated, blood/bone, abdominal

‡Other than age (which is reported in years), this is the percentage of the population that has the characteristic among studies that include patients with the characteristic. For example, among the 18 studies that include persons with HIV, 17 report how many people had HIV and among those, the median percentage of the population with HIV is 23%.

Table 5. Methods reported for the 37 models of the 33 included studies with prediction models for tuberculosis treatment outcomes

Characteristic	Studies reporting characteristic, n (%)	Categories	N(%) or median [IQR]
Type of outcome	37 (100)	Single	29 (78)
		Composite	8 (22)
Outcome	37 (100)	Death	16 (43)
		Treatment failure	6 (16)
		Default, Loss to follow-up, or treatment interruption	6 (16)
		Unfavorable outcome	6 (16)
		Treatment success	2 (6)
		Other‡	1 (3)
Number - prevalence of outcome*	32 (87)	-	94 [38-171] 15% [9-26]
Events per candidate variable†	30 (81)	-	6 [3-11]
Events per variable (in final model)	29 (78)	-	14 [9-26]
Predictor types		Clinical/epidemiologic	34 (92)
		Adherence	1 (3)
		Biomarker	2 (5)
Analysis	37 (100)	Logistic regression	29 (78)
		Survival analysis	3 (8)
		Machine learning	5 (14)
Method for considering predictors in multivariable models	36 (97)	All candidate predictors	12 (32)
		Based on unadjusted association with outcome	19 (51)
		Based on clinical relevance	1 (3)
		Other§	4 (14)
Selection of predictors during modeling	31 (84)	Full model approach	2 (6)
		Forward selection	7 (23)
		Backwards elimination	5 (16)
		Stepwise selection	8 (26)
		Random Forest	1 (3)
		Hosmer-Lemeshow model building criteria	4 (13)
		Bayesian model averaging	3 (10)
		Pairwise selection	1 (3)

P-value for consideration in model	17 (46)	0·01	2 (12)
		0·05	3 (18)
		0·11	1 (6)
		0·2	6 (35)
		0·25	5 (29)
P-value for retention in MV model	20 (54)	0·05	9 (45)
		0·1	9 (45)
		0·15	1 (5)
		0·2	1 (5)
Internal validation	19 (51)	Split-sample	10 (53)
		Bootstrap	5 (26)
		Cross-validation	4 (21)
External validation	6 (16)	Temporal	1 (17)
		Geographic	1 (4)
		Setting	4 (67)
Calibration	17 (46)	Calibration plot¶	2 (12)
		Calibration slope¶	1 (6)
		Hosmer-Lemeshow goodness of fit p-value¶	13 (77)
			0·51 [0·20, 0·79]
		Calibration table¶	2 (12)
		Mean absolute error¶	1 (6)
Discrimination	30 (81)	C-statistic (AUROC) ¶	30 (100)
			0·75 [0·68-0·84]
		Log rank test¶	2 (5)
Classification	18 (49)	Sensitivity‖	14 (78)
			70 [54, 78]
		Specificity‖	13 (72)
			75 [71, 88]
		Accuracy	2 (11)
		Other**	2 (11)
Model presentation	34 (92)	Risk score	16 (43)
		Model coefficient	8 (22)
		Nomogram	2 (6)
		Odds ratios/relative scores	4 (12)
		Survey tool	1 (3)

Abbreviations: AUROC=area under receiver operating characteristic; c-statistic=concordance statistic

*Prevalence of outcome in the population used to develop the prediction model (i.e. derivation/development subset if split-sample technique was used or full sample if the model was not validated or if bootstrap/cross-validation was used)

†Only 5 studies report the exact number of predictors considered. Otherwise, the number of candidate predictors was estimated from the provided tables or lists of candidate predictors in the source paper.
‡Outcome is a value from 1 to 5 (1= patient completed the treatment course in frame of DOTS, 2=cured, 3= quit treatment, 4=failed treatment and 5=death)
§Other methods of determining which variables to consider for prediction model include: principal components analysis (n=1), screening for multi-collinearity via correlation coefficient (n=1), one study used a combination of a priori and selection via univariable association, and the other used machine learning pre-processing (n=1)
¶Sums to more than 100%, because some studies report multiple measures of calibration or discrimination
‖Based on the following cut-off methods: Youden (n=4) concordance probability (n=1), estimated at nearest 0,1 for studies that present a range of sensitivity and specificity in a table or figure (n=4), or unknown (n=5)
**Other includes one study that reports false positive rate and one study that includes a graph of sensitivity vs. specificity.

Figure 2. Most common predictors considered and included

[See Figure 2]

Figure 2 legend**:**
Considered: the predictor as evaluated as a candidate predictor prior to multivariable modeling
Included: the predictor was considered and subsequently included in the final multivariable model

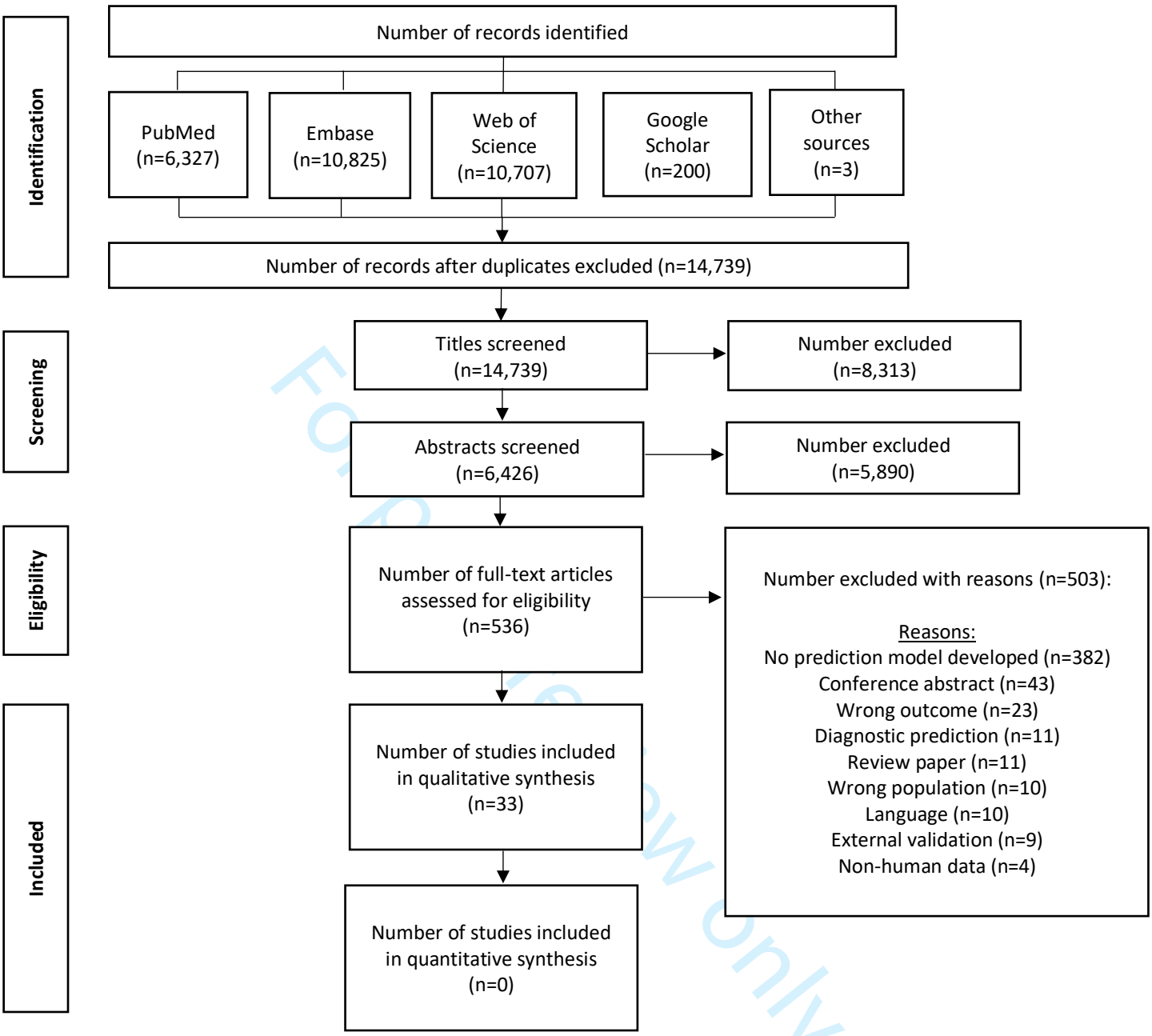
Figure 3. Heatmap of signaling questions from risk of bias assessment with PROBAST

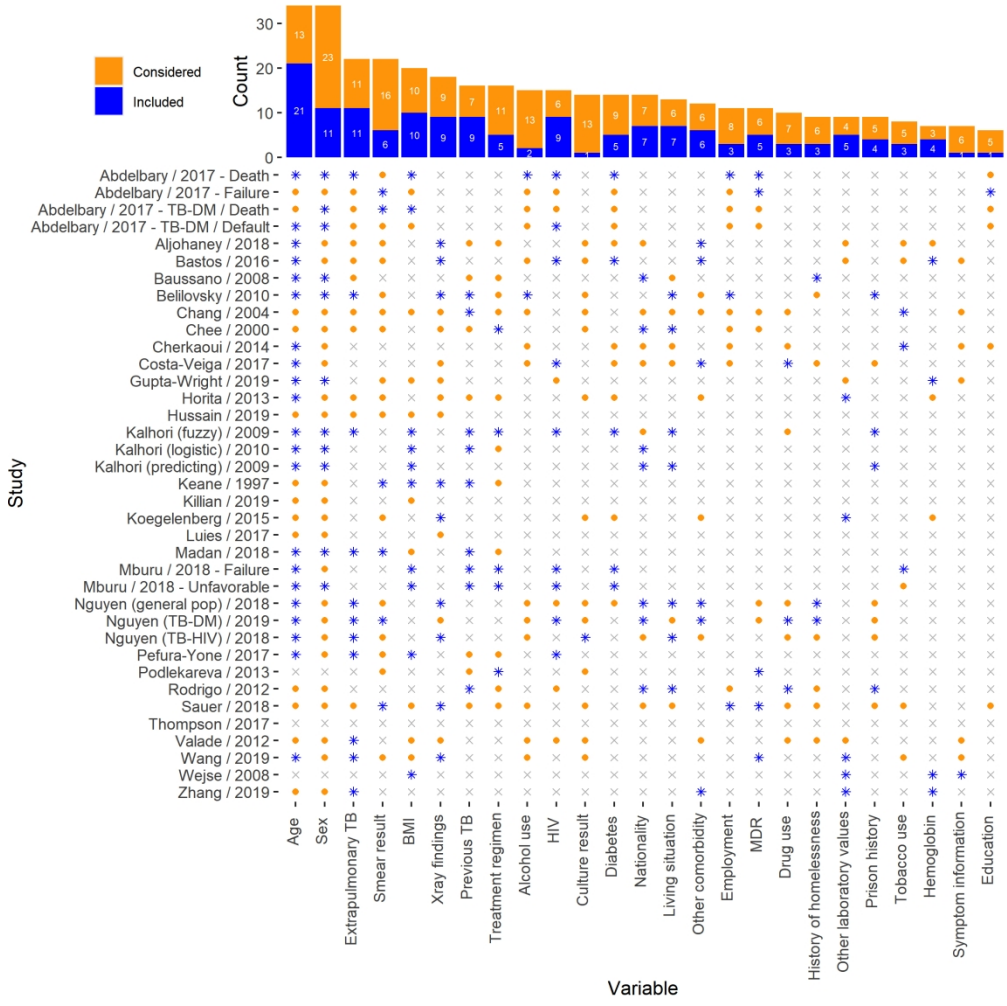
[See Figure 3]

Figure 3 legend**:**
PROBAST questions (additional details in Supplemental File 5)
Participants 1: What study design was used and was it appropriate?
Participants 2: Were all inclusion and exclusion criteria appropriate?
Predictors 1: Were predictors defined as assessed the same way for all participants?
Predictors 2: Were predictor assessments made without knowledge of data outcome?
Predictors 3: Are all predictors available at the time the model was intended to be used?
Outcome 1: Was the outcome determined appropriately?
Outcome 2: Was the outcome pre-specified or standard?
Outcome 3: Were predictors excluded from outcome definition?
Outcome 4: Was the outcome defined and determined in a similar way for all participants?
Outcome 5: Was the outcome determined without predictor information?
Outcome 6: Was the time interval between predictor assessment and outcome determination appropriate?
Analysis 1: Were there a reasonable number of participants with the outcome?
Analysis 2: Were continuous and categorical variables handled appropriately?
Analysis 3: Were all enrolled participants included in the analysis?
Analysis 4: Were participants with missing data handled appropriately?
Analysis 5: Was selection of predictors based on univariable analysis avoided?
Analysis 6: Were complexities in data (censoring, competing risks, sampling of control participants) accounted for appropriately?
Analysis 7: Were relevant model performance measures evaluated appropriately?
Analysis 8: Were model overfitting, underfitting, and optimism in the model performance accounted for?
Analysis 9: Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?

Figure 4. Summary of risk of bias and applicability assessment with PROBAST

[See Figure 4]





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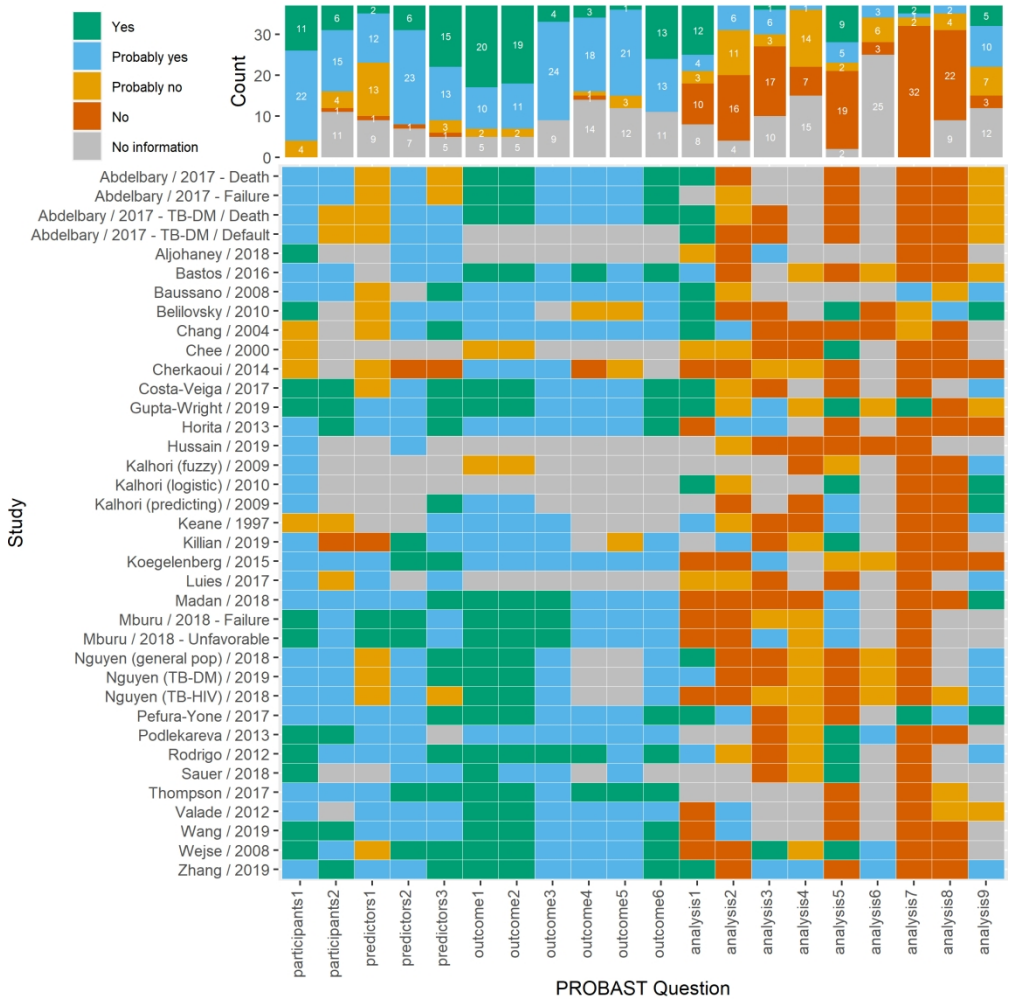

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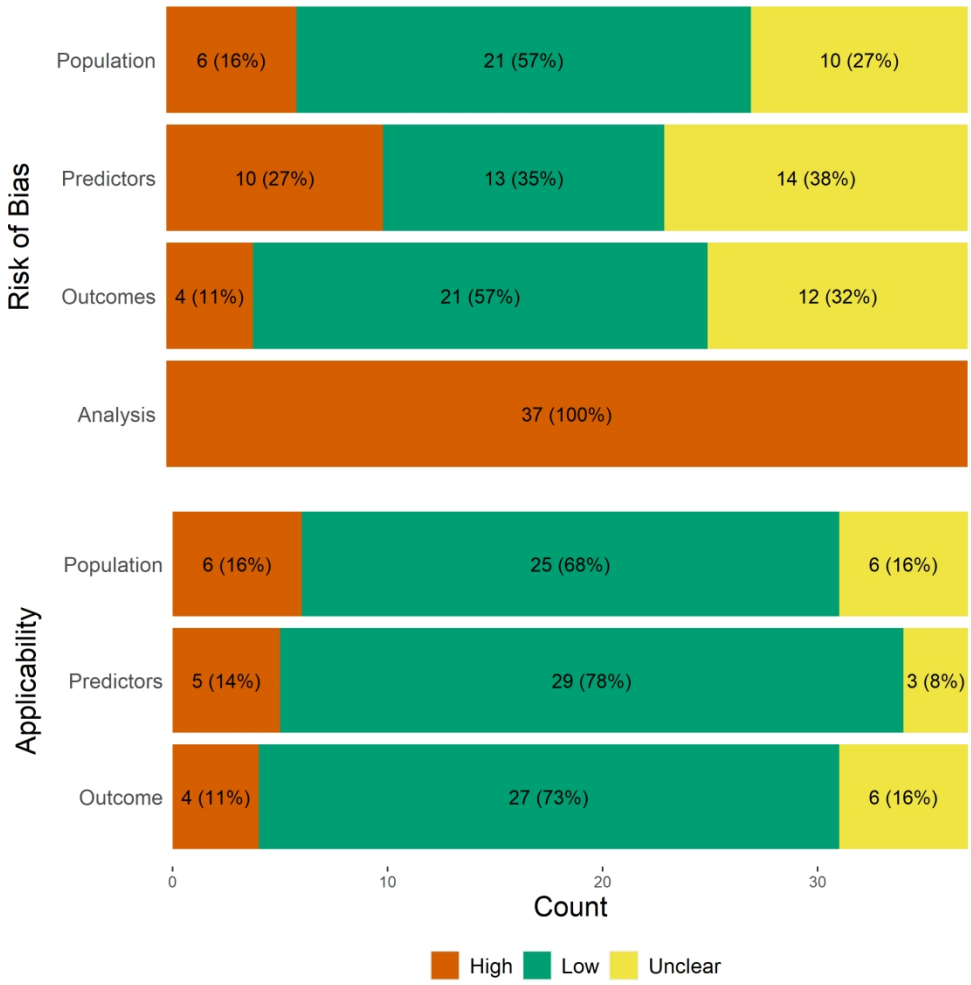

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Supplemental File 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Supplemental File 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract and p. 7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9; Supplemental Files 4 and 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9; Supplemental File 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-13; Table 3, 4, 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14; Figures 3 and 4

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-14; Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplemental File 2. PICOTS System

Population	Pulmonary tuberculosis cases
Intervention	Any prognostic model developed to predict tuberculosis treatment outcome. This includes model development studies with and without external validation
Comparator	Models will be compared to each other, as there is no other relevant comparator for this systematic review
Outcome	TB treatment outcome. The primary outcome of interest is the probability of unsuccessful TB treatment outcome, defined by the WHO as the combination of death, treatment failure, default, and/or not evaluated, as compared to successful TB treatment outcome, defined as the combination of cure and treatment completion. Included studies should evaluate at least one of the following outcomes: cure, treatment completion, death, treatment failure, default, and not evaluated. Default and not evaluated are sometimes referred to collectively as lost to follow-up. Some prediction models will look at only single endpoints, whereas other look at composite outcomes.
Timing	The timespan of prediction may vary between studies, depending on the duration of treatment and follow-up, but we expect most studies will evaluate endpoints around 6-9 months.
Setting	Model designed for use in clinical or hospital setting at the time of TB treatment initiation to aid in targeted treatment or programmatic support for individuals at greatest risk for unsuccessful TB treatment outcomes.

Supplemental File 3. Search Strategy

Database	*Search terms*
PubMed	1. ((validat*[tiab] OR predict*[ti] OR rule*[tiab]) OR (predict*[tiab] AND (outcome*[tiab] OR risk*[tiab] OR model*[tiab])) OR ((history[tiab] OR variable*[tiab] OR criteria[tiab] OR scor*[tiab] OR characteristic*[tiab] OR finding*[tiab] OR factor*[tiab]) AND (predict*[tiab] OR model*[tiab] OR decision*[tiab] OR identif*[tiab] OR prognos*[tiab])) OR (decision*[tiab] AND (model*[tiab] OR clinical*[tiab] OR "Logistic Models"[Mesh])) OR (prognostic[tiab] AND (history[tiab] OR variable*[tiab] OR criteria[tiab] OR scor*[tiab] OR characteristic*[tiab] OR finding*[tiab] OR factor*[tiab] OR model*[tiab])) 2. (stratification[tiab] OR "ROC Curve"[Mesh] OR discrimination[tiab] OR discriminate[tiab] OR "c-statistic"[tiab] OR "c statistic"[tiab] OR "area under the curve"[tiab] OR AUC[tiab] OR calibration[tiab] OR indices[tiab] OR algorithm[tiab] OR multivariable[tiab]) 3. (tuberculosis[Mesh] OR tuberculosis[tiab]) 4. (outcome*[tiab] OR mortality*[tiab] OR death*[tiab] OR fail*[tiab] OR recur*[tiab] OR relapse*[tiab] OR default*[tiab] OR abandon*[tiab] OR loss*[tiab] OR cure*[tiab] OR success*[tiab] OR unsuccess*[tiab] OR die[tiab] OR died[tiab] OR dies[tiab])) 5. 1 OR 2 6. 3 AND 4 7. 5 AND 6 AND (humans[Filter]) AND ("1995"[Date - Publication] : "3000"[Date - Publication])
Embase	1. (validat$ or predict$ or rule$).ti. OR (predict$ and (outcome$ or risk$ or model$)).ti,ab. OR ((history or variable$ or criteria or scor$ or characteristic$ or finding$ or factor$) and (predict$ or model$ or decision$ or identif$ or prognos$)).ti,ab. OR (decision$.ti,ab. and ((model$ or clinical$).ti,ab. or "statistical model"/)) OR (prognostic and (history or variable$ or criteria or scor$ or characteristic$ or finding$ or factor$ or model$)).ti,ab. 2. (stratification or discrimination or discriminate or c-statistic or "c statistic" or "area under the curve" or AUC or calibration or indices or algorithm or multivarriable).ti,ab. or "receiver operating characteristic"/ 3. tuberculosis/ or tuberculosis.ti,ab 4. (outcome$ or mortality$ or death$ or fail$ or recur$ or relapse$ or default$ or abandon$ or loss$ or cure$ or success$ or unsuccess$ or die or died or dies).ti,ab. 5. 1 or 2 6. 3 and 4 7. 5 and 6 8. limit 7 to (human and yr="1995 -Current")
Web of Science	1. TI=(validat* or predict*. or rule*) OR TS=(predict* and (outcome* or risk* or model*)) OR TS=((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)) OR TS=(decision* and ((model* or clinical*). or "statistical model")) OR TS=(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)) 2. TS=(stratification or discrimination or discriminate or c-statistic or "c statistic" or "area under the curve" or AUC or calibration or indices or algorithm or multivariable or "receiver operating characteristic") 3. TS=(tuberculosis) 4. TS=(outcome* or mortality* or death* or fail* or recur* or relapse* or default* or abandon* or loss* or cure* or success* or unsuccess* or die or died or dies) 5. 1 or 2 6. 3 and 4 7. 5 and 6; IC Timespan=1995-2019
Google scholar	tuberculosis treatment outcome prediction prognostic model development validation

Supplemental File 4. CHARMS Checklist

Domain	Key items	Reported on page #
SOURCE OF DATA	Source of data (e.g., cohort, case-control, randomized trial participants, or registry data)	
PARTICIPANTS	Participant eligibility and recruitment method (e.g., consecutive participants, location, number of centers, setting, inclusion and exclusion criteria)	
	Participant description	
	Details of treatments received, if relevant	
	Study dates	
OUTCOME(S) TO BE PREDICTED	Definition and method for measurement of outcome	
	Was the same outcome definition (and method for measurement) used in all patients?	
	Type of outcome (e.g., single or combined endpoints)	
	Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)?	
	Were candidate predictors part of the outcome (e.g., in panel or consensus diagnosis)?	
	Time of outcome occurrence or summary of duration of follow-up	
CANDIDATE PREDICTORS (OR INDEX TESTS)	Number and type of predictors (e.g., demographics, patient history, physical examination, additional testing, disease characteristics)	
	Definition and method for measurement of candidate predictors	
	Timing of predictor measurement (e.g., at patient presentation, at diagnosis, at treatment initiation)	
	Were predictors assessed blinded for outcome, and for each other (if relevant)?	
	Handling of predictors in the modelling (e.g., continuous, linear, non-linear transformations or categorised)	
SAMPLE SIZE	Number of participants and number of outcomes/events	
	Number of outcomes/events in relation to the number of candidate predictors (Events Per Variable)	
MISSING DATA	Number of participants with any missing value (include predictors and outcomes)	
	Number of participants with missing data for each predictor	
	Handling of missing data (e.g., complete-case analysis, imputation, or other methods)	
MODEL DEVELOPMENT	Modelling method (e.g., logistic, survival, neural network, or machine learning techniques)	
	Modelling assumptions satisfied	
	Method for selection of predictors **for inclusion** in multivariable modelling (e.g., all candidate predictors, pre-selection based on unadjusted association with the outcome)	
	Method for selection of predictors **during multivariable modelling** (e.g., full model approach, backward or forward selection) and criteria used (e.g., p-value, Akaike Information Criterion)	
	Shrinkage of predictor weights or regression coefficients (e.g., no shrinkage, uniform shrinkage, penalized estimation)	
MODEL PERFORMANCE	Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log-rank) measures with confidence intervals	
	Classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement) and whether a-priori cut points were used	
MODEL EVALUATION	Method used for testing model performance: development dataset only (random split of data, resampling methods e.g. bootstrap or cross-validation, none) or separate external validation (e.g. temporal, geographical, different setting, different investigators)	
	In case of poor validation, whether model was adjusted or updated (e.g., intercept recalibrated, predictor effects adjusted, or new predictors added)	
RESULTS	Final and other multivariable models (e.g., basic, extended, simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, model performance measures (with standard errors or confidence intervals)	
	Any alternative presentation of the final prediction models, e.g., sum score, nomogram, score chart, predictions for specific risk subgroups with performance	

	Comparison of the distribution of predictors (including missing data) for development and validation datasets	
INTERPRETATION AND DISCUSSION	Interpretation of presented models (confirmatory, i.e., model useful for practice versus exploratory, i.e., more research needed)	
	Comparison with other studies, discussion of generalizability, strengths and limitations.	

Supplemental File 5. Prediction model Risk Of Bias Assessment Tool (PROBAST)

Link to full explanation and elaboration document
Citation: Moons KG, Wolff RF, Riley RD, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med. 2019;170:W1–W33. doi: https://doi.org/10.7326/M18-1377

Domain 1: Participants
The overall aim for prediction models is to generate absolute risk predictions that are correct in new individuals. Certain data sources or designs are not suited to generate absolute probabilities. Problems may also arise if a study inappropriately includes or excludes participant groups from entering the study

	Signaling question	Yes/probably yes	No/probably no	No information
1	What study design was used and was it appropriate?	Yes: If a cohort design (including RCT or proper registry data) was used and you have confidence in data quality and participant enrollment is clearly described Probably yes: a nested case–control or case–cohort design (with proper adjustment of the baseline risk/hazard in the analysis) has been used or a cohort design was used but participant enrollment was data quality is unclear	No: If a non-nested case–control design has been used Probably no: a nested case-control study was used without proper adjustment of baseline risk/hazard	If the method of participant sampling is unclear.
2	Were all inclusion and exclusion criteria appropriate?	Yes: Inclusion and exclusion are clear and selection participants was appropriate, so participants correspond to unselected participants of interest (i.e. the target population). Probably yes: Inclusion and exclusion criteria are not entirely clear, but it seems like the population is representative of the target population	No: If participants are included who would already have been identified as having the outcome and so are no longer at risk of developing outcome, or if specific subgroups are excluded that may have altered the performance of the prediction model for the intended target population. Probably no: inclusion and exclusion criteria are unclear and it seems possible that there was bias in selection of participants that could lead to the model being applied to a population that is unrepresentative of the target population.	When there is no information on whether inappropriate inclusions or exclusions took place.

Low risk of bias	High risk of bias	Unclear risk of bias
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 2: Predictors
Bias in model performance can occur when the definition and measurement of predictors is flawed. Predictors are the variables evaluated for their association with the outcome of interest. Bias can occur, for example, when predictors are not defined in a similar way for all participants or knowledge of the outcome influences

	Signaling question	Yes/probably yes	No/probably no	No information
1	Were predictors defined and assessed in a similar way for all participants?	Yes: It is clear that definitions of predictors and their assessment were similar for all participants. Probably yes: Some predictors were based off subjective judgement, but carried out by persons with the necessary skills to evaluate the predictor, or if data from multiple sources was used but predictor definitions were standardized between sources.	No: If different definitions were used for the same predictor or if predictors requiring subjective interpretation were assessed by differently experienced assessors Probably no: Data from multiple sources was used and its unclear whether definitions were standardized between sources or if subjective measurements were likely not carried out by persons with appropriate training.	If there is no information on how predictors were defined or assessed.
2	Were predictor assessments made without knowledge of data outcome?	Yes: If outcome information was stated as not used during predictor assessment or was clearly not (yet) available to those assessing predictors (i.e. prospective data collection).	If it is clear that outcome information was used when assessing predictors.	No information on whether predictors were assessed without knowledge of outcome information.

		Probably yes: If it is likely that outcome information was not used during predictor assessment, but not entirely clear (retrospective data collection/surveillance data)		
3	Are all predictors available at the time the model was intended to be used?	All included predictors would be available at the time the model is intended to be used for prediction	Predictors would not be available at the time the model is intended to be used for prediction.	No information on whether predictors would be available at the time the model is intended to be used for prediction.

Low risk of bias	**High risk of bias**	**Unclear risk of bias**
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 3: Outcome

Bias in model performance can occur when methods used to determine outcomes incorrectly classify participants with or without the outcome. Bias in methods of outcome determination can result from use of suboptimal methods, tests, or criteria that lead to unacceptably high levels of errors in outcome determination, when methods are inconsistently applied across participants, or when knowledge of predictors influence outcome determination. Incorrect timing of outcome determination can also result in bias.

	Signaling question	**Yes/probably yes**	**No/probably no**	**No information**
1	Was the outcome determined appropriately?	If a method of outcome determination has been used which is considered optimal or acceptable by guidelines or previous publications on the topic Note: This is about level of measurement error within the method of determining the outcome (see concerns for applicability about whether the definition of the outcome method is appropriate).	If a clearly suboptimal method has been used that causes unacceptable error in determining outcome status in participants	No information on how outcome was determined
2	Was the outcome pre-specified or standard?	Yes: If the method of outcome determination is objective, or if a standard outcome definition is used, or if prespecified categories are used to group outcomes. (i.e. outcome assessment is based on previously published studies, published study protocol, or clinical guidelines) Probably yes: The outcome determination is not clearly based on guidelines or previous research, but outcome assessment is objective and would not inadvertently alter study results	No: If the outcome definition was not standard and not prespecified Probably no: a non-standard or non-prespecified outcome was used, and it is unclear whether the outcome definition could introduce bias. *Caution with composite outcomes that favor a better model by excluding typical outcome components or including atypical events	No information on whether the outcome definition was prespecified or standard
3	Were predictors excluded from outcome definition?	Yes: None of the predictors are included in the outcome definition (clearly stated) Probably yes: None of the predictors are included in the outcome definition (assumed)	If ≥1 of the predictors forms part of the outcome definition	No information on whether predictors are excluded from the outcome definition
4	Was the outcome defined and determined in a similar way for all participants?	Yes: If outcomes were defined and determined in a similar way for all participants (clearly stated) Probably yes: If outcomes were defined and determined in a similar way for all participants (assumed)	If outcomes were clearly defined and determined in a different way for some participants	No information on whether outcomes were defined or determined in a similar way for all participants
5	Was the outcome determined without predictor information	Yes: If predictor information was not known when determining the outcome status, or outcome status determination is clearly reported as determined without knowledge of predictor information. Probably yes: predictor information might have been available at time of outcome assessment, but outcome definition is objective and knowing information about predictors would not influence outcome	No: If it is clear that predictor information was used when determining the outcome status Probably no: it is likely predictor information was available at the time of outcome assessment, and outcome definition is subjective and knowledge of predictors could influence outcome determination.	No information on whether outcome was determined without knowledge of predictor information

		assessment (i.e death, treatment failure based on culture results, etc)		
6	Was the time interval between predictor assessment and outcome determination appropriate	If the time interval between predictor assessment and outcome determination was appropriate to enable the correct type and representative number of relevant outcomes to be recorded, or if no information on the time interval is required to allow a representative number of the relevant outcome occur or if predictor assessment and outcome determination were from information taken within an appropriate time interval.	If the time interval between predictor assessment and outcome determination is too short or too long to enable the correct type and representative number of relevant outcomes to be recorded.	If no information was provided on the time interval between predictor assessment and outcome determination.

Low risk of bias	High risk of bias	Unclear risk of bias
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 4: Analysis

Statistical analysis is a critical part of prediction model development and validation. The use of inappropriate statistical analysis methods increases the potential for bias in reported model performance measures. Model development studies include many steps where flawed methods can distort results. We recommend reviewers seek statistical advice when completing

	Signaling question	Yes/probably yes	No/probably no	No information
1	Were there a reasonable number of participants with the outcome?	For model development studies, if the number of participants with the outcome relative to the number of candidate predictor parameters is ≥20 (EPV ≥20).* For model validation studies, if the number of participants with the outcome is ≥100.	For model development studies, if the number of participants with the outcome relative to the number of candidate predictor parameters is <10 (EPV <10).* For model validation studies, if the number of participants with the outcome is <100.	For model development studies, no information on the number of candidate predictor parameters or number of participants with the outcome, such that the EPV cannot be calculated. For model validation studies, no information on the number of participants with the outcome.
		* For EPVs between 10 and 20, the item should be rated as either probably yes or probably no, depending on the outcome frequency, overall model performance, and distribution of the predictors in the model. For more guidance, see references 145 to 147.		
2	Were continuous and categorical predictors handled appropriately?	Yes: If continuous predictors are kept as continuous or if continuous predictors are examined as linear or non-linear using restricted cubic splines or fractional polynomials. Probably yes: If continuous predictors are not converted into >2 categories when included in the model (i.e., dichotomized or categorized) using a prespecified method or in a way that avoids sparse data/would not intentionally improve statistical significance. For model validation studies, if continuous predictors are included using the same definitions or transformations, and categorical variables are categorized using the same cut points, ascompared with the development study.	No: For model development studies, if continuous predictors are converted into 2 categories when included in the model. Probably no: If categorical predictor group definitions do not use a prespecified method or continuous variables were split into >2 groups, but the decision of how to split variables is unclear. For model validation studies, if continuous predictors are included using different definitions or transformations, or categorical variables are categorized using different cut points, as compared with the development study.	No information on whether continuous predictors are examined for nonlinearity and no information on how categorical predictor groups are defined. For model validation studies, no information on whether the same definitions or transformations and the same cut points are used, as compared with the development study.
3	Were all enrolled participants included in the analysis?	If all participants enrolled in the study are included in the data analysis.	If some or a subgroup of participants are inappropriately excluded from the analysis (because they were missing data, unknown outcome, outliers)	No information on whether all enrolled participants are included in the analysis.
4	Were participants with missing data handled appropriately?	Yes: If there are no missing values of predictors or outcomes and the study explicitly reports that participants are not excluded on the basis of missing data, or if missing values are handled using multiple imputation.	No: If participants with missing data are omitted from the analysis, or if the method of handling missing data is clearly flawed, e.g., missing indicator method or inappropriate use of last value carried forward, or	If there is insufficient information to determine if the method of handling missing data is appropriate

		Probably yes: If a small percentage of persons with missing data were excluded and authors provide comparison of included vs. excluded participants or if sensitivity analysis with imputation methods are convincing that bias is low	if the study had no explicit mention of methods to handle missing data. Probably no: If authors provide comparison of included vs. excluded participants or if sensitivity analysis with imputation methods are reported, but the results are not convincing to rule out bias from excluding missing data	
5	Was selection of predictors based on univariable analysis avoided?	If the predictors are not selected on the basis of univariable analysis prior to multivariable modeling.	If the predictors are selected on the basis of univariable analysis prior to multivariable modeling.	If there is no information to indicate that univariable selection is avoided.
6	Were complexities in the data (censoring, competing risks, sampling of control participants) accounted for appropriately?	If any complexities in the data are accounted for appropriately, or if it is clear that any potential data complexities have been identified appropriately as unimportant.	If complexities in the data that could affect model performance are ignore. For example, case-control studies that do not estimate baseline risk or studies with censoring or competing risks that do not use survival analysis or other appropriate methods.	No information is provided on whether complexities in the data are present or accounted for appropriately if present.
7	Were relevant model performance measures evaluated appropriately?	Yes: If both calibration (via calibration plot) and discrimination (c-index) are evaluated appropriately (including relevant measures tailored for models predicting survival outcomes). Probably yes: if authors present a table of predicted probabilities with confidence intervals and corresponding outcome frequencies across subgroups	If both calibration and discrimination are not evaluated, or if only goodness-of-fit tests (Hosmer-Lemeshow test), are used to evaluate calibration or if for models predicting survival outcomes performance measures accounting for censoring are not used, or if classification measures (like sensitivity, specificity, or predictive values) were presented using predicted probability thresholds derived from the data set at hand, but calibration is not otherwise evaluated.	Either calibration or discrimination are not reported, or no information is provided as to whether appropriate performance measures for survival outcomes are used (e.g., references to relevant literature or specific mention of methods, such as using Kaplan–Meier estimates), or no information on thresholds for estimating classification measures is given.
8	Were model overfitting, underfitting, and optimism in model performance accounted for?	Yes: If internal validation techniques (bootstrapping and cross-validation) including all model development procedures, were used to account for any optimism in model fitting, and subsequent adjustment of the model performance estimates were applied. Probably yes: If internal validation was used and optimism was estimated as very low, and then optimism-corrected performance measures were not appropriately calculated (accounting for all model development procedures)	No: If no internal validation has been performed, or if internal validation consists only of a single random split-sample of participant data, Probably no: Internal validation with bootstrapping or cross-validation was conducted but did not include all model development procedures including any variable selection or were not used to correct model performance measures.	No information: No information is provided on whether internal validation techniques, including all model development procedures, have been applied.
9	Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?	If the predictors and regression coefficients in the final model correspond to reported results from multivariable analysis.	If the predictors and regression coefficients in the final model do not correspond to reported results from multivariable analysis. (i.e. rounding of model coefficients to create a "risk score" are inappropriately determined).	If it is unclear whether the regression coefficients in the final model correspond to reported results from multivariable analysis.

Low risk of bias	**High risk of bias**	**Unclear risk of bias**
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Applicability				
	Domain	**Low concern**	**High concern**	**Unclear concern**

	Participants: do you have concern that the included participants or setting do not match the review question?	Included participants and clinical setting match the review question.	Included participants and clinical setting were different from the review question.	If relevant information about the participants and clinical setting are not reported.
	Predictors: does the definition, assessment, or timing of predictors match the review questions?	Definition, assessment, and timing of predictors match the review question.	Definition, assessment, or timing of predictors were different from the review question	If relevant information about the predictors is not reported.
	Outcome: does the definition, timing, or determination of outcome match the review question?	Outcome definition, timing, and method of determination defines the outcome as intended by the review question.	Choice of outcome definition, timing, and method of outcome determination defines another outcome as intended by the review question	If relevant information about the outcome, timing, and method of determination is not reported.

Supplemental File 6. Model outcome definitions

Study ID	Outcome category	Full outcome definition from the source paper
Hussain / 2019	Treatment completion	The target variable TreatmentComplete consists of 64.37% positive (treatment complete) and 35.62% negative (treatment incomplete)
Abdelbary / 2017 - Death	Death	All causes of death (TB or non-TB related) during the course of TB treatment
Abdelbary / 2017 - TB-DM / Death	Death	Death included all causes of death (TB and non-TB related) during the course of TB treatment
Aljohaney / 2018	Death	Not defined, but seems to be death during hospitalization.
Bastos / 2016	Death	Deaths that occurred during the first 6 months after diagnosis were classified as TB death
Gupta-Wright / 2019	Death	The outcome was mortality risk at 2 months after admission.
Horita / 2013	Death	'Discharged alive' was defined as being discharged alive and satisfying the discharge criteria, i.e., when the patient was receiving effective treatment, showed clinical improvement and negative conversion was confirrmed. Negative conversion was defined as three or more consecutive sputum samples obtained on different days being smear-negative for acid-fast bacilli or when appropriate sputum sample(s) were culture-negative. 'Died in hospital' was defined as death from any cause.
Koegelenberg / 2015	Death	Patients were categorised as either ICU/hospital survivors or non-survivors.
Nguyen (general pop) / 2018	Death	Documented treatment outcome of 'completed' or 'died'
Nguyen (TB-DM) / 2019	Death	TB treatment outcome of either 'completed' or 'died'
Nguyen (TB-HIV) / 2018	Death	Given the main purpose of our study is to predict the mortality during TB treatment in HIV-infected patients against the treatment completion, patients who had an outcome coding other than completed or died.
Pefura-Yone / 2017	Death	At treatment completion, patients are ranked into the following mutually exclusive categories 1) cured-patient with negative smear at the last month of treatment and at least one of the preceding months; 2) treatment completed-patient who has completed the treatment and for whom the smear results at the end of the last month are not available; 3) failure-patient with positive smear at the 5th month or later during treatment; 4) death-death from any cause during treatment; 5) defaulter-patient who's treatment has been interrupted for at least two consecutive months; 6) transfer-patient transferred to complete his treatment in another center and who's treatment outcome is unknown Cured and treatment completed are considered successful treatment
Podlekareva / 2013	Death	Death within 12 months of TB diagnosis
Valade / 2012	Death	Final outcomes of survival or death were recorded
Wang / 2019	Death	The outcome was estimated with all-cause mortality, with the mortality in 12 months as the primary outcome and the mortality in 3, 6, 9 months as other outcome
Wejse / 2008	Death	Mortality: ability to predict death
Zhang / 2019	Death	Primary treatment outcome was documented either survival or death when HIV/TB co-infected patients left hospital. Patients who survived when discharged received 12-month follow-up, and the date of last known alive was documented in electronical medical records base on records of last follow-up
Abdelbary / 2017 - Failure	Treatment failure	Treatment failure indicated smear-positive persistence at or after 5 months of treatment with first-line anti-TB medications.
Kalhori (logistic) / 2010	Treatment failure	The dependent variable was failing in treatment course completion.
Keane / 1997	Treatment failure	Failing to clear the sputum of acid-fast bacilli with standard treatment and having to start second line therapy
Luies / 2017	Treatment failure	From the original samples, all treatment failure cases were included.
Mburu / 2018 - Failure	Treatment failure	The secondary analyses only compared 'cures' versus 'failures' at similar time points as is the standard practice when examining chemotherapy efficacy
Thompson / 2017	Treatment failure	Patients' clinical outcomes were classified as 'cured' if they proved and maintained sputum culture negativity by month 6 after treatment initiation (M6), 'failed' if the M6 culture was still positive, and 'un-evaluable' if contamination caused uncertainty in outcome. We note that none of the treatment failures achieved culture negativity at any time point during treatment.
Abdelbary / 2017 - TB-DM / Default	Default, Abandon, or LTF (interruption >2 months)	Never defined
Belilovsky / 2010	Default, Abandon, or LTF (interruption >2 months)	We evaluated TI initiated by the patient (significant noncompliance with the doctor's prescribed course of treatment and serious violations of public order in hospitals) resulting in inpatient treatment cancellation.
Chang / 2004	Default, Abandon, or LTF	Default was defined as failure to collect drugs for 2 months or more after registration

	(interruption >2 months)	
Chee / 2000	Default, Abandon, or LTF (interruption >2 months)	Defaulter or cases were defined as patients on anti-tuberculosis treatment at the TBCU who failed to turn up for their scheduled appointments despite usual attempts to recall them by phone or mail, as described below, and from whom at least one home visit during the study was recorded
Cherkaoui / 2014	Default, Abandon, or LTF (interruption >2 months)	Treatment default was defined as an interruption in TB treatment for >=2 consecutive months.
Rodrigo / 2012	Default, Abandon, or LTF (interruption >2 months)	Interruption of treatment for any reason for more than 2 months, non-completion of treatment within 9 months when the patient is placed on a 6 month regimen. or drug intake of <80% the prescribed dose.
Kalhori (predicting) / 2009	Treatment success (cure + completion)	For each patient dependent variable was recorded whether or not the patient finished the treatment course and get cured.
Sauer / 2018	Unfavorable outcome (death + failure)	The primary outcome was treatment failure, which we defined as failure of therapy or death.
Baussano / 2008	Unfavorable outcome (death, failure, LTF, NE)	Treatment interruption or default, treatment failure, transferred out cases and those lost to follow-up were grouped as 'unsuccessful outcomes
Costa-Veiga / 2017	Unfavorable outcome (death, failure, LTF, NE)	In line with WHO criteria, SVIG-TB categorized a six possible and mutually exclusive categories for treatment outcomes, grouped in this study into a binary outcome: (i) Successful outcome-if PTB patients were treated before and declared cured, including both negative smear microscopy at the end of treatment at least one previous follow-up test and in case of not providing sputum samples, cure is declared if treatment completed and absent of disease clinical evidences (categories 1 and 2). (ii) Unsuccessful outcome-if treatment of PTB patients resulted in failure (i.e. remaining smear-positive after 5 months of treatment, cat. 3), default (i.e. patients who interrupted their treatment for two consecutive months or more after registration, cat. 4), death (cat. 5) or were transferred-out (cat. 6)
Killian / 2019	Unfavorable outcome (death, failure, LTF, NE)	We label 'Cured' and 'Treatment Complete' to be favorable outcomes and 'Died', 'Treatment failed', and 'Lost to follow-up' to be unfavorable outcomes
Madan / 2018	Unfavorable outcome (death, failure, LTF, NE)	Favourable treatment outcomes included cure and treatment completed. Unfavourable treatment outcomes included death, loss to follow-up, treatment failure, transfer out, or a switch to MDR TB treatment.
Mburu / 2018 - Unfavorable	Unfavorable outcome (death, failure, LTF, NE)	The primary analyses compared favorable versus unfavorable outcomes at end of treatment
Kalhori (fuzzy) / 2009	Other composite outcome	The values of outcomes might be any values from 1 to 5 which means different outcomes. Value 1 means patient completed the treatment course in frame of DOTS, 2 means the patient has been cured, 3 means patients has quitted the course, 4 means patients has failed and finally 5 is a sign of dead as outcome of TB treatment course

Supplemental File 7. Model presentation

Study ID	Final model
Abdelbary / 2017 - Death	2 + 2*(Age 41-65) + 5*(Age>=65) + 2*(Male gender) + 4*(MDR TB) + 3*(HIV) + 3*(Malnutrition) + 2*(Alcoholism) + 2*(Male*diabetes) + 3*(HIV*pulmonary TB) - 1*(diabetes) - 1*(pulmonary TB)
Abdelbary / 2017 - Failure	8*(No or low education) + 40*(MDR) + 10*(AFB smear +2) + 15*(AFB smear +3)
Abdelbary / 2017 - TB-DM / Death	2 + 3*(Male gender) + 3*(Malnutrition) - 1*(BCG vaccinated) - 1*(AFB smear positive)
Abdelbary / 2017 - TB-DM / Default	2 + 2*(Age<40) + 2*(Male gender) + 4*(HIV)
Aljohaney / 2018	Don't report final model, but show the beta coefficients. The coefficients are written as predictor (beta-coefficient): age ³ 65 (2.497), congestive heart failure (1.231), bilateral disease on chest x-ray (1.192)
Bastos / 2016	3*(Hypoxemic respiratory failure) + 2*(Age>=50) + 1*(Bilateral involvement) + 1*(At least one of: HIV, diabetes, liver failure/cirrhosis, congestive heart failure, chronic respiratory disease) + 1*(Hemoglobin<12)
Baussano / 2008	Nomogram with: residency status (residential vs. homeless), sex, geographic origin (non-EU vs. EU), case definition (other than definite vs. definite), treatment setting (inpatient and unknown vs. outpatient), age (continuous)
Belilovsky / 2010	-3.2 + 0.8*(male gender) + 0.7*(unemployment) + 0.4*(retreatment case) + 1.1*(alcohol abuse) + 0.6*(no data about alcohol) + 0.8*(severe TB form) - 0.3*(urban residence) + 0.4*(age 25-50) + 0.8*(pulmonary TB) + 0.5*(prison history)
Chang / 2004	Dont report final model. Just show odds ratios of predictors but don't report intercept term, which are written as predictor (OR) as follows: Current smokers (3.44), ex-smokers (2.48), history of default (10.74), no history of default (0.80),
Chee / 2000	The OR for each predictor is as follow in the format predictor (OR): Non-Chinese race (8.08), Living with family vs. living alone/with friends (0.08), Treatment duration (1.85). Treatment duration is categorical as 6 months, 9 months, and >9 months, but only one OR is presented.
Cherkaoui / 2014	2 points for yes to the following questions: Are you younger than 50 years of age? Do you feel work is interfering with your ability to take TB treatment? Are you taking a retreatment regimen for TB? Do you or doctor think you are having moderate or severe side effects from TB treatment Are you required to get your TB treatment daily? Have you told your friends that you have TB? (1 point for no) Are you a current smoker (1 point for yes) Did you TB symptoms go away within 2 months of starting TB treatment (1 point for yes) Do you know how long your TB treatment is supposed to last (1 point for no) Have you ever smoked cigarettes (-1 point for no)
Costa-Veiga / 2017	Nomogram with: HIV, previous treatment, age class (25-44, 15-24, 45-64, >64), IV drug use, pathologies (other disease comorbidity: yes/no)
Gupta-Wright / 2019	9*(Male sex) + 7*(patient aged 55+) + 6*(currently taking ART) + 7*(unable to walk unaided) + 7*(hemoglobin <80, severe anemia) + 6*(positive on urine TB-LAM)
Horita / 2013	1*Age (years) + 10*(oxygen requirement) - 20*(albumin) + 5*(semi-dependent, ADL) + 10*(total dependent, ADL)
Hussain / 2019	None
Kalhori (fuzzy) / 2009	Learned parameters by training set for each predictor written as predictor (learned parameter): Case type (0.467), treatment category (-0.079), risky sex (-0.945), prison (0.992), sex (0.400), recent TB infection (0.793), diabetes (2.445), low body weight (1.313), TB type (0.950), length (-0.235), previous imprisonment (2.398), age (0.237), area (0.8895), HIV (0.731)
Kalhori (logistic) / 2010	exp(-0.93 - 0.71*(gender) + 0.02*(age) - 0.02*(weight) + 0.5*(nationality) + 0.99*(prison) + 0.16*(case type))
Kalhori (predicting) / 2009	exp(-(1.58 - 0.12*(age) + 0.807*(gender) - 0.039*(nationality) - 0.263*(prison) + 0.15*(area) + 0.021*(weight))
Keane / 1997	Unclear. No constant term provided. Here are the predictor (OR): Mediastinal shift (2.1), average smear score (1.5), extensive lesions (3.6), any previous treatment (2.3), cavities (1.7), weight (0.98)
Killian / 2019	LEAP = Lstm rEal-time Adherence Predictor with 2 input layers, 1) LSTM with 64 hidden units and a dense layer with 48 units for the dense layer and 4 units for the penultimate layer
Koegelenberg / 2015	One point for each parameter: septic shock, HIV with CD4 < 200, creatinine > 140 (male) or >120 (female), P:F O2 ratio < 200, chest radiograph showing miliary pattern/parenchymal infiltrates, absence of TB treatment at admission
Luies / 2017	Written as predictor (OR): 3,5,-Dihydroxybenzoic acid (25.6), 3-(4-Hydroxy-3-methoxyphenyl) propionic acid (1.3)
Madan / 2018	Written as predictor (OR): New TB with 1+ smear grade (5.78), New TB with 2+ smear grade (2.69), New TB with 3+ smear grade (1.69), New TB without smear (1.67), New TB with smear positive, unknown grade (1.00), Previously treated, smear negative TB (1.35), previously treated with scanty smear (4.74), previously treated with 1+ smear grade (1.61), previously treated with 2+ smear grade (1.05), previously treated with 3+ smear grade (7.54), previously treated with no sputum smear (2.46), previously treated with unknown grade (30.37), pulmonary TB (1.83), pulmonary and extrapulmonary TB (5.86), HIV+ on ART with CD4 350-500 (8.09), HIV+ on ART with CD4 200-350 (6.14), HIV+ on ART with CD4 50-200 (16.35), HIV+ on ART with CD4 <50 (38.76), HIV+ not on ART with CD4 350-500 (53.44), HIV+ not on ART with CD4 200-350 (65.98), HIV+ not on ART with CD4 50-200 (6.94), HIV+ not on ART with CD4 <50 (49.20), HIV+ diagnosed after TB with CD4>500 (1.05), HIV+ diagnosed after TB with CD4 350-500 (2.49), HIV+ diagnosed after TB with CD4 200-350 (8.88), HIV+ diagnosed after TB with CD4 50-200 (6.79), HIV+ diagnosed after TB with CD4 <50 (13.99), Female 25-34 (9.41), Female 35-44 (1.75), Female >= 45 (4.49), Male 15-24 (10.63), Male 25-34 (2.74), Male 35-44 (2.9), Male >= 45 (3.96)
Mburu / 2018 - Failure	Present relative scores for each covariate included with scores of 100, 72.61, 69.19, 55.39, 49.87, 48.74, 48.18, 46.51, 39.69, and 37.69 for hba1c, regimen, age, weight, random blood glucose, BMI, BUN, HIV positive result, ever smoker, creatinine, respectively
Mburu / 2018 - Unfavorable	Present relative scores for each covariate included, not sure if this was how it should be used. Relative scores are 100, 79.38, 70.09, 63.93, 62.47, 62.63, 61.63, 55.62, 39.21, 34.48 for hba1c, regimen, creatinine, BMI, BUN, weight, age, random blood glucose, HIV positive result, male gender, respectively
Nguyen (general pop) / 2018	6*[Age 45-64] + 12*[Age>65] + 2*[US born] + 2*[Homeless] + 4*[Resident of LTCF] + 8*[Chronic kidney failure] + 10*[Meningeal TB] + 4*[Miliary TB] + 6*[TB-CXR] + 6*[HIV positive] + 6*[HIV unknown]
Nguyen (TB-DM) / 2019	16*[Age >= 65] + 5*[US-born] + 11*[Homeless] + 20*[IDU] + 20*[Chronic kidney failure] + 20*[TB meningitis] + 13*[Miliary TB] + 6*[AFB positive smear] + 24*[Positive HIV]
Nguyen (TB-HIV) / 2018	Prognostic score: 5*[Age >= 65] + 12*[Resident of LTCF] + 9*[Meningeal TB] + 6*[abnormal CXR] + 9*[diagnosis confirmed with positive culture or NAA] + 10*[culture not converted or unknown]

	Model: -6.994499 + 1.069024*[Age >= 65] + 2.541147*[Resident of LTCF] + 1.998852*[Meningeal TB] + 1.37995*[abnormal CXR] + 1.899108*[diagnosis confirmed with positive culture or NAA] + 2.186305*[culture not converted or unknown]
Pefura-Yone / 2017	1/(1 + exp(-1.3120 + 0.0474*[age] - 0.1866*[adjusted BMI] + 1.1637*[PTB-] + 0.5418*[ETB] + 1.3820*[HIV]
Podlekareva / 2013	1*[DST performed] + 2*[Initial treatment with RHZ] + 2*[cART started before or up to 1 month after TB diagnosis]
Rodrigo / 2012	1*[Immigrant] + 1*[Living alone] + 1*[Living in an institution] + 2*[Previous TB treatment] + 2*[Linguistic barriers] + 4*[IV drug use] + 1*[Unknown IV drug use]
Sauer / 2018	Negatively correlated: drug sensitivity (sensitive), employment status (employed), microscopy: 1 to 99 acid-resistant bacteria in 100 fields of view when stained by Ziehl-Nielsen, dissemination (diffuse pulmonary nodules detected)
Thompson / 2017	Heatmap of differentially expressed genes
Valade / 2012	Sum of three parameters: military tuberculosis (yes: +1, no: 0), required mechanical ventilation on ICU admission (yes: +1, no: 0), and required vasopressor infusion (yes: +1, no: 0).
Wang / 2019	Unknown
Wejse / 2008	1 point for each variable: cough, hemoptysis, dyspnea, chest pain, night sweating, anemia conjunctivae, tachycardia, positive funding at lung auscultation, temperature >37, BMI <18, BMI<16, MUAC<220, MUAC<200
Zhang / 2019	2*[Anemia (HGB < 90g/L)]+ 2*[Tuberculous meningitis] + 5*[Severe pneumonia] + 2*[Hypoalbuminemia] + 7* [Unexplained infections or space-occupying lesions] + 5* [Malignancies]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Supplemental File 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract and p. 7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9; Supplemental Files 4 and 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9; Supplemental File 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-13; Table 3, 4, 5

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14; Figures 3 and 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-14; Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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A systematic review of prediction models for pulmonary tuberculosis treatment outcomes in adults

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ABSTRACT

Objective: To systematically review and critically evaluate prediction models developed to predict tuberculosis (TB) treatment outcomes among adults with pulmonary tuberculosis.

Design: Systematic review

Data sources: PubMed, Embase, Web of Science, and Google Scholar were searched for studies published January 1, 1995 - January 9, 2020.

Study selection and data extraction: Studies that developed a model to predict pulmonary TB treatment outcomes were included. Study screening, data extraction, and quality assessment were conducted independently by two reviewers. Study quality was evaluated using the Prediction model Risk Of Bias Assessment Tool (PROBAST). Data were synthesized with narrative review and in tables and figures.

Results: 14,739 articles were identified, 536 underwent full-text review, and 33 studies presenting 37 prediction models were included. Model outcomes included death (n=16, 43%), treatment failure (n=6, 16%), default (n=6, 16%) or a composite outcome (n=9, 25%). Most models (n=29, 78%) measured discrimination (median c-statistic=0.75; interquartile range: 0.68-0.84), and 17 (46%) reported calibration, often the Hosmer-Lemeshow test (n=13). Nineteen (51%) models were internally validated, and six (16%) were externally validated. Eighteen studies (54%) mentioned missing data, and of those, half (n=9) used complete case analysis. The most common predictors included age, sex, extrapulmonary TB, body mass index (BMI), chest x-ray results, previous TB, and HIV. Risk of bias varied across studies, but all studies had high risk of bias in their analysis.

Conclusions: TB outcome prediction models are heterogeneous with disparate outcome definitions, predictors, and methodology. We do not recommend applying any in clinical settings

without external validation, and encourage future researchers adhere to guidelines for developing and reporting of prediction models.

Registration: The study was registered on the international prospective register of systematic reviews PROSPERO (CRD42020155782)

ARTICLE SUMMARY:

Strengths and limitations

- Prediction models for tuberculosis treatment outcomes have the potential to inform interventions or treatment management protocols to promote cure among tuberculosis patients at the greatest risk of unsuccessful treatment outcomes, but the methods and clinical utility of existing models had not been formally evaluated.
- This was the first systematic review of prediction models for tuberculosis treatment outcomes.
- The review used a comprehensive search strategy, conducted thorough bias assessment with the Prediction Model Risk of Bias Assessment Tool (PROBAST) tool, and offers recommendations for future model development and validation studies for predicting tuberculosis treatment outcomes.
- Evidence synthesis and quality assessment were limited by incomplete reporting in primary studies
- External validation studies or studies written in languages other than English, Spanish, Portuguese, or French were excluded.

BACKGROUND

Tuberculosis (TB) is one of the top ten causes of death worldwide and a leading cause of death from an infectious disease. In 2018, 10 million people developed TB and 1.45 million people died from it globally, despite widespread availability of curative treatment.[1] Global treatment success was 85% for all new and relapse TB patients in 2018. For HIV-associated TB, it was 75%. These proportions are lower than the End TB Strategy target of ≥90% treatment success.[2]

Heeding early recognition that *Mycobacterium tuberculosis* develops resistance rapidly in response to single-drug therapy, TB has been treated with combination therapy for more than 50 years.[3] Aside from weight-based dosing, the World Health Organization (WHO) and other TB guidelines authorities recommend a standardized approach for treatment of almost all TB patients.[4–6] The current recommendation for treatment of drug-susceptible TB includes 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin. However, actual treatment regimens may vary due to differences in drug tolerability, and other individual-level factors that can affect TB treatment outcomes.

Due to the long duration of TB treatment, it would be beneficial for TB outcome studies to identify early treatment predictors of unsuccessful TB treatment outcomes to identify patients needing tailored treatment approaches, such as directly observed therapy (DOT) or extended treatment course. Research suggests that individual characteristics, such as HIV, age, undernutrition, diabetes, TB disease severity, extrapulmonary TB, history of TB, adherence, alcohol use, and adverse drug reactions, are associated with unsuccessful TB treatment outcomes, but results vary by setting and patient population.[7–10]

Prediction models are defined as any combination or equation of two or more predictors, such as demographic factors, medical history, physical examination, and lab tests, used for estimating an individualized probability of a specific endpoint within a defined period of time.[11] The large number of prediction models for TB outcomes published in recent years highlights a common desire to identify TB patients at greatest risk of an unsuccessful treatment outcome in order to tailor treatment strategies and promote cure. However, to date, there has not been a formal synthesis or quality assessment of existing prediction models for TB treatment outcomes, which is essential to determine which models should inform clinical practice. This could also guide development of future models. Thus, we conducted a systematic review to identify, describe, compare, and synthesize clinical prediction models designed to predict TB treatment outcomes among persons with pulmonary TB.

METHODS AND ANALYSIS

All steps of the systematic review were carried out according to guidelines set by Cochrane Prognosis Methods Group (PMG) and PROGnosis RESearch Strategy (PROGRESS).[12–14] Reporting adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (**Supplemental File 1).** This study was pre-registered on Open Science Framework (OSF) (https://osf.io/rz3wp) and the international prospective register of systematic reviews (PROSPERO; CRD42020155782).

Study eligibility criteria

The review question was defined according to the PICOTS (Population, Intervention, Comaparator, Outcomes, Timing, Setting) framework (**Supplemental File 2)**. In brief, the goal was to identify prognostic models developed to predict TB treatment outcomes among pulmonary TB cases. The main outcome was unsuccessful TB treatment outcome, defined by the WHO as the combination of death, treatment failure, loss to follow-up, and/or not evaluated, as compared to successful TB treatment outcome, defined as the combination of cure or treatment completion (**Table 1**) [15]. Loss to follow-up was sometimes referred to as default or treatment abandonment.

Inclusion criteria were: 1) prognostic model studies with or without external validation[16]; 2) study population included adult, drug-susceptible, pulmonary, TB cases; 3) written in English, Spanish, Portuguese, and French; 4) published between January 1, 1995 and January 9, 2020; 5) treatment outcome was one of the following: cure, treatment completion, death, treatment failure, loss to follow-up, or not evaluated.

Exclusion criteria were: 1) predictive value of more than one variable was evaluated but not combined in a prediction model; 2) study population was only multi-drug resistant (MDR) TB cases, only extrapulmonary TB cases, or only children (< 18 years-old); 3) outcome was

evaluated during treatment such as: two-month smear/culture conversion, acquired resistance, adverse events, quality of life; 4) long-term outcomes, such as relapse, recurrence, or post-treatment mortality.

The decision to include only articles in English, Spanish, Portuguese, and French was based on study team capabilities. The dates reflect modern TB treatment practice; first-line TB treatment regimens were not available until the early 1990s.[17,18] Articles that included a combination of drug-susceptible and drug-resistant cases, or a combination of children and adults were included.

Search strategy and selection criteria

The following electronic databases were searched on January 9, 2020: PubMed, Embase, Web of Science, and the first 200 references from Google Scholar. This combination of databases achieved best overall recall for systematic reviews in a recent study.[19] Clinicaltrials.gov and retractiondatabase.org were also searched for unpublished research. Reference lists of retrieved articles were checked to identify eligible studies.

Search terms relating to the "prediction model" component of the search were adapted from a PubMed search strategy that captured prediction model studies with sensitivity of 98%.[20] That component was combined with terms relating to TB treatment outcomes. The search strategy, developed in PubMed, was adapted for all other databases with assistance from a reference librarian (**Supplemental File 3**).

Article selection was conducted in three stages. The first stage was automatic de-duplication and title screening, carried out using *revtools* in RStudio (version 1.2).[21] Remaining articles were imported into Covidence, a web-based software platform that streamlines systematic reviews, where abstracts (Stage 2) and full text (Stage 3) were manually screened.[22] Stages 2 and 3 were carried out by two independent reviewers (LSP and FMR).

Discordance was discussed between reviewers, and if consensus was not reached, a third party arbitrated (one of TRS, VCR, PFR, DL). In stage 3, reasons for exclusion were documented according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Data analysis

Data from selected studies were recorded using a database designed in REDCap (Vanderbilt University).[23,24] Data extraction was informed by the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) and the Prediction Model Risk of Bias Assessment Tool (PROBAST).[16,25,26] CHARMS checklist and PROBAST are in **Supplemental Files 4 and 5,** respectively**.**

Quality assessment and applicability of included studies was assessed using PROBAST by dual independent review.[16,26] PROBAST was specifically designed to assess risk of bias of prediction model studies, which included identifying deficiencies in study design, conduct, or analysis that led to inaccurate estimates of predictive performance. PROBAST has 4 domains: participants, predictors, outcome, and analysis with 20 total signaling questions. Each question was answered on the scale: yes, probably yes, no, probably no, no information. Domains were scored as low, high, and unclear risk of bias. PROBAST also guides assessment of applicability of participants, predictors, and outcomes from each included study to the review question.

Results were summarized narratively and in tables and figures. Meta-analysis was not possible due to lack of external validation and use of disparate predictors, outcome definitions, and modeling methods. For studies that presented multiple models with the same set of predictors and outcomes, but different methods, the best-performing method was included in data synthesis. For studies presenting multiple models with different sets of predictors (i.e. baseline data vs. longitudinal data), the model developed using only baseline data was included. If studies

developed multiple models for different outcomes or with different populations, all models were included.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, or reporting of the research, as it was not feasible or appropriate for this systematic review. The study protocol is publicly available at https://osf.io/rz3wp.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study selection

The search identified 14,739 unique studies. After excluding irrelevant titles, 6,426 abstracts were screened, 536 articles underwent full-text review, and 33 model development studies presenting 37 prediction models were included (**Figure 1**).

Study characteristics

Of the 33 studies, most were retrospective cohorts (n=25, 76%), three (9%) were prospective cohort studies, two (6%) were case-control studies, and three (9%) were nested case-control studies. Data from nearly half of studies (n=16, 48%) were collected from surveillance systems; eleven (33%) studies used a data collection form developed specifically for their study and six studies (18%) extracted data from medical records. Median sample size was 803 (interquartile range (IQR): 291-4167). Full details on included studies are in **Table 2**.

Thirteen studies (41%) took place in Asia, eight (25%) in Africa, six (19%) in Europe, four (12%) in North America, and one (3%) included sites in Europe and Argentina. Fewer than half (n=14, 45%) of the studies took place in high-burden TB settings.[1] One study did not report study location. (**Tables 2 and 3**).

Reporting of population characteristics varied by study (**Table 4**). Among 18 studies that reported a measure of central tendency (mean or median) for age, the median of those measures of central tendency was 41 years (IQR: 37-49). Of 17 studies that reported the minimum age of participants, seven (41%) had a minimum age of 15, one (6%) had a minimum age of 16, one (6%) had a minimum age of 17, and the remainder had minimum age of 18. Eighteen studies reported including persons living with HIV (PLWH); 5 of these included only TB/HIV patients. Twelve studies reported including persons with diabetes; one of which includes only TB/DM.

Eight studies reported including some participants with MDR, though prevalence of MDR was low in all studies. Ten studies included only hospitalized patients, and in 14 studies, all participants were on directly observed therapy (DOT).

Model characteristics

Model outcomes included death (n=16, 43%), treatment failure (n=6, 16%), default (n=6, 16%) or a composite outcome (n=8, 23%) (**Tables 2 and 5**). The complete outcome definition for all included studies is in **Supplemental File 6**.

Most models were developed using clinical/epidemiologic predictors (n=34, 92%), two (6%) used multiple biomarkers, and one (3%) used adherence data. The most common candidate predictors were age, sex, extrapulmonary TB, smear result, BMI, x-ray findings, and previous TB. The most common predictors retained in the final models were age, sex, extrapulmonary TB, BMI, chest x-ray results, previous TB, and HIV (**Figure 2**).

Only three models (8%) used survival analysis; most models used logistic regression (n=29, 78%) and five (14%) used a machine learning approach. More than half of studies (n=19, 51%) considered variables for inclusion in the multivariable model based on unadjusted associations with the outcome. Model building methods varied widely between models (**Table 5).**

Only 19 (51%) models were internally validated, including ten (53%) split-sample validation, five (26%) bootstrap resampling, and four (21%) cross-validation. Six (16%) models were externally validated.

Many models (n=30, 81%) reported discrimination with c-statistic (concordance statistic) or area under the receiver operating characteristic (AUROC), which are equivalent and quantify the ability of the model to distinguish between patients who do and do not develop an outcome.

Only 17 (46%) reported calibration, the agreement between observed and predicted outcomes. Most studies assessed calibration with Hosmer-Lemeshow tests (n=13, 77%); only two studies provided a calibration plot, the preferred reporting method for prediction model studies,[16,27,28] and one reported the calibration slope **(Table 2)**. Models were presented a variety of ways, the most common of which was a weighted risk score (n=16, 43%); details on model presentation are in **Supplemental File 7.**

Quality assessment

Grading of PROBAST signaling questions is summarized in **Figure 3**, and the summary risk of bias for the participants, predictors, outcome, and analysis domains and assessment of applicability are shown in **Figure 4**. More than half of the studies were at low risk of bias for the population and outcomes domains, but all studies were at high risk of bias in the analysis domain.

Common sources of population bias included use of non-nested case-control design[29,30], nested case-control design without proper estimation of baseline risk,[31,32] or inappropriate inclusion/exclusion criteria.[33,34] Sources of predictor bias included lack of standardized assessment of key predictors (i.e. HIV, diabetes, chest x-ray scoring)[9,29,31,34–36] or timing of data collection/availability that would limit the intended use of the model.[9,29,37] Within the outcomes domain, sources of bias included subjective[35] or non-standard[32,38] outcome measures and inconsistent outcome ascertainment.[29]

Bias in the analysis domain was widespread. More than half of the models included were likely overfit due to low events per variable (EPV) ratios (**Table 5**). Only 6 studies handled continuous and categorical variables appropriately (i.e., didn't dichotomize continuous variables, considered non-linearity of continuous variables).[31,39–43] Most studies used complete case-

analysis or did not mention missing data; no study used multiple imputation in their main analysis. One study with low amounts of missing data (<5%) conducted sensitivity analysis with multiple imputation.[44] A different study excluded only two people out of a total sample size of 1007 with missing data, which would have little impact on model performance.[45] Fewer than half (n=14) of studies avoided univariable predictor selection, and only three studies used survival analysis, appropriately accounting for censoring.[36,45,46] Performance measures were appropriately reported (i.e. calibration assessed with plot and discrimination assessed with c-statistic/AUROC) in three studies.[41,44,47] Only two studies estimated optimism (degree to which data are overfit) or accounted for potential overfitting with penalization of model parameters.[35,41] Ten studies appropriately presented their model with model coefficients or nomograms, which prevents bias from rounding or transforming model coefficients to generate a risk score.[30,33,35,37,38,45,47–55]

About half of the models (n=19, 51%) were applicable to the review question in all domains. However, unclear reporting of target population or predictor and outcome definitions limited assessment of applicability for several studies.[38,49,50,56,57] Additionally, studies that included only hospitalized patients with specific laboratory parameters may not be routinely available in the clinical setting.[39,40,42]

DISCUSSION

In this comprehensive, systematic review of prediction models for pulmonary TB treatment outcomes, we identified 33 model development studies presenting 37 prediction models. Although diagnostic prediction models for prevalent TB were previously systematically reviewed, this is the first systematic review of TB treatment outcomes.[58] The included prediction models were developed for predicting death, treatment failure, default, or a composite unfavorable outcome during TB treatment. Most models reported good performance (c-statistic/AUROC>0.7), but all were evaluated to have high risk of bias due to poor reporting, exclusion of missing data, weak methodologic approaches, lack of calibration assessment, and limited validation. Predictor and outcome definitions varied by study and limited comparisons between models.

More than half of the models included in the review were developed in low burden TB settings, and none were developed specifically in South America. Prediction of TB treatment outcome is especially important in high burden TB settings, where resources may be limited, and risk assessment can guide resource allocation toward patients who need the most involved care protocols.

Common risk factors included in the models were consistent with well-established risk factors for poor TB treatment outcomes, including age, sex, HIV, extrapulmonary TB, baseline smear results, and previous TB treatment. Among studies that included PLWH, only three considered factors related to management/severity of HIV, such as receipt of antiretroviral therapy, CD4 cell count, or viral load, which likely impact TB treatment outcomes.[40,46,51] Laboratory values or metabolic biomarkers, such as hemoglobin, hemoglobin A1c or random blood glucose, may also be associated with treatment outcome and worth considering as candidate predictors. There is increasing evidence that diabetes impacts TB treatment outcomes,

but caution is warranted about how to best define diabetes in the context of a prediction model to ensure consistency and reproducibility across studies.[59] Behavioral characteristics, such as tobacco use, alcohol use, and drug use were rarely included in final prediction models and are difficult to collect objectively, suggesting their role in prediction models for TB treatment outcomes may be limited.

Additionally, several studies excluded participants with HIV, diabetes, extrapulmonary TB, or MDR TB, because these factors negatively influence treatment outcomes. However, careful consideration should be given to inclusion/exclusion criteria in prediction model studies. Information necessary to carry out inclusion/exclusions should be available at the of intended use of the model, which may not always hold for these aforementioned factors.[60] This point is especially questionable for MDR, given that conventional drug-susceptibility testing results are not available for several weeks after TB diagnosis; though more recent advances in rapid molecular methods such as GeneXpert or line-probe assays offer rapid screening for drug resistance.[61]

TB researchers should thoughtfully consider how to appropriately handle complexities of censoring and competing risks in TB outcomes research. Only three studies in this review used survival analysis, despite the long duration of TB treatment outcome assessment and relatively high rates of losses to follow-up across studies. Losses to follow-up were frequently excluded, which can lead to selection bias. Additionally, all studies that included death as the outcome considered all-cause mortality. Also, for studies that predict losses to follow-up/default, death (even due to TB) is a competing risk. Competing risk analyses are common in cardiovascular research, research in elderly populations, and there are specific recommendations for competing risk methods in prognostic research.[62,63]

Though all included studies were at high risk of bias in the analysis domain, we want to highlight two studies with some exemplary characteristics.[41,44] Pefura-Yone et al.[41] provide clear explanations of study design, inclusion/exclusion criteria, and data collection procedures; TB diagnosis and treatment outcome definitions were standard.[64] Non-linearity of continuous variables was considered with restricted cubic splines, and no continuous variables were categorized or dichotomized; the final model includes four predictors that are easy to collect and routinely assessed in most TB control programs, especially those in high burden settings. The performance of the model was internally validated with bootstrap validation, and the discrimination (c-statistic=0.808) was corrected for optimism. Model calibration was presented graphically with calibration plots. The final model was presented as a nomogram with instructions for use, which facilitates use in external validation studies. Gupta-Wright and colleagues developed and externally validated a clinical risk score to predict mortality in high-burden, low-resource settings.[43] They used clinical trial data with very low amounts of missing data for model development, and externally validated the clinical risk score with data collected independently from two other studies (a clinical trial and a prospective cohort). Given high amounts (42%) of missing data in the validation cohort, they conducted sensitivity analysis using multiple imputation for missing data; the c-statistic differed slightly between complete case and multiple-imputation analyses in the validation cohort (0.68 vs. 0.64). Candidate predictors were based on *a priori* clinical knowledge, previous literature, and required variables were objective, reproducible, and available in low-resource settings, consistent with recommended approaches.[26,60,65] Additionally, they reported model performance with the c-statistics and calibration plots for development and validation cohorts, and reported results according to TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or

diagnosis) guidance.[27,28] Regardless, each of these models requires external validation prior to use in clinical practice.

There are several limitations of this study. First, data extraction was subject to reporting the primary study, which varied widely across studies. Most studies reported discrimination, and several reported sensitivity and specificity; TRIPOD recommends all studies report, at minimum, calibration with a calibration plot and discrimination with c-statistic.[28] Measures of sensitivity and specificity require dichotomization of risks, which then only pertain to a specific risk stratum, rather than quantifying the overall model performance.[14,65] We did not include external validation studies, which is an essential step for translation to clinical practice. However, several studies in the review did not include the full model equation, which inhibits their ability to be externally validated. Upon searching for studies that externally validated prediction models in this review, we found three studies[66–68] that evaluated the same model (TBscore).[36] Briefly, these studies evaluated the ability of TBscore to monitor treatment response in a new setting[66], refined the instrument (TBccoreII) using exploratory factor analysis[67], and then evaluated TBscoreII for use in patients with TB/HIV.[68] To our knowledge, no other studies included in the review were externally validated by other sources. Finally, we excluded 10 studies that were not available in English, Spanish, Portuguese, or French; all abstracts were available in English, and none reported model performance metrics, so they likely would have been excluded for different reasons regardless.

The findings of this review not only serve as a comprehensive overview of existing TB outcome prediction models but can act as a resource for future model development and validation of prediction models for TB treatment outcomes. We encourage researchers to focus future TB outcome prediction models on easily collected and readily available predictors that are

widely generalizable. We highlight age, sex, extrapulmonary TB, BMI, chest x-ray results, previous TB, and HIV as common predictors of TB treatment outcomes. Additionally, when building a new prediction model, it is recommended to first prune the set of considered predictors based on expert opinion and previous literature, rather than univariable analysis or variable selection processes[26,60,65] Future model development or validation studies should adhere to the TRIPOD guidelines, which provide a 22-item checklist and aims to improve the reporting of prediction model development studies.[27,28] We also encourage researchers consider the PROBAST criteria when developing their model to limit sources of bias in design and conduct of prediction model studies.

Prediction models are an important tool in TB management, as they can lay the foundation for future intervention studies or clinical decision making by providing risk prediction that can aid in targeted treatment, resource allocation, or intensive case management at patients who are least likely to achieve cure and most likely to benefit from some form of intervention, especially in high-burden and low-resources areas. Use of prediction models can potentially help guide tuberculosis treatment practices to achieve the End TB Strategy target of >90% treatment success, but methodologic rigor and detailed reporting must be improved. Though our findings suggest that none of the existing models are ready for clinical application without extensive external validation, we hope they direct future researchers to make use of guidelines for development and reporting of prediction models.

FOOTNOTES

Ethics approval: Not required.

Transparency statement: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted, and any discrepancies from the study as planned were explained.

Contributorship: LSP conceptualized the research question, designed the protocol, and drafted the manuscript. LSP and FMR screened studies. FMR, PFR, DL, VCR and TRS provided feedback on the research design, original protocol, and revised successive drafts of the manuscript. All authors approved the final version of the manuscript.

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Data sharing: The study protocol is available online at https://osf.io/rz3wp. Most included studies are publicly available. Additional data and code are available upon request.

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Table 1. World Health Organization definition of treatment outcomes for TB patients

Outcome	Definition
Treatment completion	Completion of treatment without evidence of failure, but without documentation of a negative sputum smear or culture in the last month of treatment and/or on at least one previous occasion, either because tests were not done or because results are unavailable
Cure	Bacteriologic confirmation of a negative smear or culture at the end of TB treatment and on at least one previous occasion
Treatment success	Composite of cured and treatment completed
Treatment failure	Sputum smear or culture is positive at month 5 or later during treatment
Death	TB patient who dies for any reason before starting or during the course of treatment
Loss to follow-up	TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated (transfer out)	TB patient for whom no treatment outcome was assigned, which includes cases who "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart of inclusion process

[See Figure 1]

Table 2. Study characteristics

First author, year	Population	Study years	Study design	Location	Validation	No. with outcome / sample size (%)	Predictors in final model	Performance measures	Model presentation	Risk of bias (population, predictor, outcome, analysis)
Death										
Abdelbary[9] / 2017	TB cases	2006 - 2013	Retrospective cohort	Mexico	Internal (split-sample)	*Development:* 261/4216 (6%) *Validation:* 260/4215 (6%)	Age (<41, 41-65, ≥65), sex, MDR, HIV, malnutrition, alcoholism, diabetes, pulmonary TB	c-statistic = 0.70 Sensitivity = 60% Specificity = 71%	Risk score	Low, High, Low, High
Abdelbary[9] / 2017 (TB-DM)	TB-DM cases	2006 - 2013	Retrospective cohort	Mexico	None	88/2121 (4%)	Sex, malnutrition, BCG vaccinated, AFB smear (positive vs. negative)	c-statistic = 0.68	Risk score	Unclear, High, Low, High
Aljohaney[69] / 2018	Hospitalized TB patients	Dec 2011 – Dec 2016	Retrospective cohort	Saudi Arabia	None	41/291 (14%)	Clinical model: Age, congestive heart failure Clinical + lab model:* Age > 65, congestive heart failure, bilateral disease on chest xray	Clinical model: Accuracy = 86% Clinical & lab model:* Accuracy = 90%	Odds ratios	Unclear, Unclear, Unclear, High
Bastos[70] / 2016	Inpatient and outpatient TB cases on DOT	2007 - 2013	Retrospective cohort	Portugal	External (setting)	*Development:* 121/681 (18%) *Validation:* 24/103 (23%)	Hypoxemic respiratory failure, age (≥50 vs. <50), bilateral involvement, comorbidities (at least one of HIV, diabetes, liver at least one of: HIV, diabetes, liver failure/cirrhosis, congestive heart failure, chronic respiratory disease), hemoglobin (<12 vs. ≥12)	AUROC = 0.84 (95% CI: 0.76-0.93) Sensitivity = 41.8% Specificity = 92.1%	Risk score	Low, Unclear, Low, High
Gupta-Wright[71] / 2019	Hospitalized TB-HIV patients	Oct 2015 – Sept 2017	Retrospective cohort	Malawi and South Africa	External (setting)	*Development:* 94/315 (30%) *Validation:* 147/644 (23%)	Sex, age 55+, currently taking ART, ability to walk unaided, severe anemia, positive TB-LAM	c-statistic = 0.68 (95% CI: 0.61-0.74) HL test: p=0.13 Calibration plot	Risk score	Low, Low, Low, High
Horita[72] / 2013	Hospitalized TB patients	Jan 2008 – Jul 2011	Retrospective cohort	Japan	External (setting)	*Development:* 36/179 (20%) *Validation:* 48/244 (20%)	Age, oxygen requirement, albumin, activities of daily living	AUROC = 0.893 Sensitivity = 0.92 Specificity = 0.73	Risk score	Low, Low, Low, High
Koegelenberg[40] / 2015	Hospitalized TB patients	Jan 2012 – May 2013	Retrospective cohort	South Africa	None	38/83 (46%)	Septic shock, HIV with CD4 < 200, creatinine > 140 (male) or >120 (female), P:F O2 ratio < 200, chest radiograph showing miliary pattern/parenchymal infiltrates, absence of TB treatment at admission	Mean score in survivors: 2.27 (SD=1.47) Mean score in non-survivors: 3.58 (SD=1.08)	Risk score	Low, Low, Low, High
Nguyen[53] (general pop) / 2018	TB cases	Jan 2010 – Dec 2016	Retrospective cohort	Texas	Internal (split-sample)	*Development:* 253/3378 (7%) *Validation:* 270/3377 (8%)	Age group (15-44, 44-64, >64), US born, homeless, resident of long term care facility, chronic kidney failure, meningeal TB, miliary TB, HIV positive, HIV unknown	AUROC = 0.80 (95% CI: 0.77-0.82) HL test:X^2=6.3, p=0.613	Risk score	Low, Unclear, Unclear, High
Nguyen[37] (TB-DM) / 2019	TB-DM patients	Jan 2010 – Dec 2016	Retrospective cohort	Texas	Internal (bootstrap)	112/1227 (9%)	Age ≥65, US-born, homeless, IDU, chronic kidney failure, TB meningitis, Miliary TB, AFB positive smear, HIV positive	AUROC = 0.82 (95% CI: 0.78-0.87) HL test: X^2=4.54, p=0.81 Brier score=0.07	Risk score	Unclear, Unclear, Unclear, High
Nguyen[52] (TB-HIV) / 2018	TB-HIV patients	Jan 2010 – Dec 2016	Retrospective cohort	Texas	Internal (bootstrap)	57/450 (13%)	Age ≥ 45, resident of LTCF, meningeal TB, abnormal CXR, diagnosis confirmed by positive culture of NAA, culture not converted or unknown	AUROC = 0.79 (95% CI 0.70-0.87) HL test: X^2=4.25, p=0.51 Brier score: 0.09	Risk score	Low, High, Unclear, High
Pefura-Yone[54] / 2017	TB patients	Jan 2012 – Dec 2013	Retrospective cohort	Cameroon	Internal (bootstrap)	213/2250 (9%)	Age, adjusted BMI, clinical form (PTB+, PTB-, EPTB), HIV	C-statistic: 0.808 HL test: X^2=6.44, p=0.60 Sensitivity = 80.7% Specificity = 68.2% Calibration plot	Model coefficients	Low, Low, Low, High
Podlekareva[73] / 2013	TB/HIV patients	Jan 2004 – Dec 2006	Retrospective cohort	52 cities in Europe and Argentina	None	995†	DST performed, treatment with RHZ, and cART at/near TB diagnosis	Crude RH = 0.62 (95% CI: 0.64-0.84)	Risk score	Low, Unclear, Low, High
Valade[42] / 2012	Hospitalized TB patients	Mar 2000 – Jul 2009	Retrospective cohort	France	Internal (bootstrap)	20/53 (38%)	Miliary TB, catecholamine infusion, mechanical ventilation on admission	AUROC = 0.92 (95% CI: 0.85-0.98) Brier score = 0.13	Risk score	Unclear, Low,

								Optimism = 0.03 Accuracy = 85% Sensitivity - 75% Specificity = 91%		Low, High
Wang[74] / 2019	HIV-negative, culture-confirmed, pulmonary TB cases	Jan 2014 – Dec 2016	Prospective cohort	China	External (setting)	*Development:* 36/287 (13%) *Validation:* 15/104 (14%)	Age, cavitary lesion, pleural effusion, drug resistance, disseminated, albumin, c-reactive protein, white blood cell count, IL-6, MIF	AUROC = 0.85 ± 0.028	Odds ratios	Low, Low, Low, High
Wejse[75] / 2008	Pulmonary TB patients on DOT	1996 - 2001	Retrospective cohort	Guinea Bissau	None	100/698 (14%)	Cough, hemoptysis, dyspnea, chest pain, night sweating, anemia conjunctivae, tachycardia, positive funding at lung auscultation, temperature >37, BMI <18, BMI<16, MUAC<220, MUAC<200	AUROC = 0.65 (95% CI: 0.6-0.7) Sensitivity = 0.45 Specificity = 0.75	Risk score	Low, High, Low, High
Zhang[45] / 2019	TB/HIV patients at end stage of AIDS	Aug 2009 – Jan 2018	Retrospective cohort	China	Internal (split-sample)	*Development:* 157/807 (19%) *Validation:* 40/200 (20%)	Anemia, TB meningitis, severe pneumonia, hypoalbuminemia, unexplained infection or space-occupying lesions, malignancy	AUROC = 0.867 (95% CI: 0.832-0.902) Sensitivity = 79.6% Specificity = 82.9%	Risk score	Low, Low, Low, High
Treatment failure										
Abdelbary[9] / 2017	TB cases	2006 - 2013	Retrospective cohort	Mexico	Internal (split-sample)	*Development:* 2109† *Validation:* 6322†	Education (no or low vs. higher than primary school), MDR, AFB smear (>+2, +1, negative)	c-statistic = 0.65 Sensitivity = 52% Specificity = 66%	Risk score	Low, High, Low, High
Kalhori[49] (logistic) / 2010	TB cases at DOTS registration	2005	Retrospective cohort	Iran	Internal (split-sample)	*Development:* 828/4836 (17%) *Validation:* 2418†	Gender, age, weight nationality, prison, case type	AUROC = 0.70 Accuracy = 81.64% HL test: X^2=11.935, df=8, p=0.154	Model coefficients	Unclear, Unclear, Unclear, High
Keane[30] / 1997	Smear-positive TB patients on standard first-line regimen with DOT	1990 - 1995	Non-nested case control	Vietnam	None	130/803 (16%)	3 month model: Extensive lesions, mediastinal shift, average smear score 3rd month, weight, progressive x-ray, any previous treatment Baseline model: Mediastinal shift, average smear score, extensive lesions, any previous treatment, cavities, weight	3 month: Sensitivity = 80% Specificity = 80% Baseline: Sensitivity = 70% Specificity = 80%	Model coefficients	High, Unclear, Unclear, High
Luies[33] / 2017	Smear-positive pulmonary TB cases on DOT	May 1999 – Jul 2002	Nested case-control	South Africa	Internal (cross-validation)	10/31 (32%)	3,5,-Dihydroxybenzoic acid, (3-(4-Hydroxy-3-methoxyphenyl) propionic acid	AUROC = 0.89 (95% CI: 0.7-1.00)	Model coefficients	High, Unclear, Unclear, High
Mburu[76] / 2018	Smear-positive TB patients	Feb 2014 – Aug 2015	Prospective cohort	Kenya	Internal (cross-validation)	13/321 (4%)	HbA1c, regimen (retreatment), age, weight, random blood glucose, BMI, BUN, HIV positive result, ever smoker, creatinine	AUROC = 0.56 ± 0.07	Relative score	Low, Low, Low, High
Default										
Thompson[77] / 2017	HIV uninfected adults with newly diagnosed pulmonary TB	Apr 2010 – Apr 2013	Retrospective cohort	South Africa	Internal (cross-validation) and external (setting)	6/99 (6%)	18 splice junctions and 13 genes	AUROC (internal) = 0.87 AUROC (external) = 0.63	Heatmap of differentially expressed genes	Low, Low, Low, High
Abdelbary[9] / 2017 (TB-DM)	TB cases	2006 - 2013	Retrospective cohort	Mexico	None	93/2121 (4%)	Age (<40 vs. ≥40), sex, HIV	c-statistic= 0.62	Risk score	Unclear, High, Unclear, High
Belilovsky[35] / 2010	Hospitalized TB patients	1993 - 2002	Retrospective cohort	Russia	External (geographical)	*Development:* 1326/3904 (34%) *Validation:* 4662/12803 (36%)	Sex, unemployment, retreatment case, alcohol abuse (yes, no, no data), severe TB form, residence (urban vs. rural), age (25-50 vs. other), pulmonary TB (vs extrapulmonary), prison history	Belgrood: AUROC = 0.75 Orel: AUROC = 0.75 Pskov: AUROC = 0.78 Yaroslavi: AUROC = 0.75 Calibration table	Model coefficients	Unclear, High, High, High
Chang[31] / 2004	All tuberculosis patients	Jan 1999 – Mar 1999	Nested case-control	China	None	102/408 (25%)	Baseline:* Ever smoker (current, former, never), retreatment (history of default, no history of default, not) Longitudinal: Smoking status (current, former, never), retreatment (with history of default, without history of default, never), unsatisfactory adherence in first two months (good, poor, fair, unknown), subsequent hospitalization, treatment side effects in last month of treatment	Baseline:* AUROC = 0.70 (95% CI: 0.63-0.76) HL test: X^2 = 1.448, df=5, p=0.919 Longitudinal: AUROC = 0.85 (95% CI: 0.80-0.90)	Odds ratios	High, High, Low, High

								HL test: $X^2 = 5.887$, df=6, p=0.436		
Chee[78] / 2000	TB cases	1996	Nested case-control	Singapore	None	38/71 (54%)	Chinese race, extent of family support, treatment duration	Accuracy = 74.6%	Model coefficients	High, Unclear, High, High
Cherkaoui[29] / 2014	TB patients with definite or probable pulmonary or extrapulmonary TB	Jun 2010 – Oct 2011	Non-nested case-control	Morocco	None	91/277 (33%)	Age <50, work interfering with ability to take TB treatment, retreatment regimen, daily DOT, moderate or severe side effects, told friends about TB, current smoker, never smoker, symptom resolution in <2 months, knowledge of TB treatment duration	AUROC = 0.85 (95% CI: 0.80-0.90) Sensitivity = 82.4% Specificity = 87.6% HL test: X^2=0.77, p-value=1.00	Survey tool	High, High, High, High
Rodrigo[79] / 2012	New TB cases	Jan 2006 – Dec 2009	Prospective cohort	Spain	Internal (split-sample)	*Development:* 92/1490 (6%) *Validation:* 103/1589 (6%)	Immigrant, living alone, living in an institution, previous TB treatment, linguistic barriers (poor understanding), IV drug use, unknown IV drug use	AUROC = 0.67 (95% CI: 0.65-0.70) Sensitivity = 65.05% Specificity = 67.36%	Risk score	Low, Low, Low, High
Unfavorable outcome										
Kalhori[50] (predicting) / 2009†	TB patients at DOT registration	2005	Retrospective cohort	Iran	Internal (split-sample)	*Development:* 6920† *Validation:* 2966†	Age, gender, nationality, prison, area, weight	Classification rate = 89.8% R2 = 0.45	Model coefficients	Unclear, Unclear, Unclear, High
Sauer[57] / 2018†	TB cases	Data available through March 2018	Retrospective cohort	Azerbaijan, Belarus, Georgia, Moldova, Romania	Internal (split-sample)	*Development:* 103/411 (25%) *Validation:* 44/176 (25%)	Forward selection (FS):* Drug sensitivity, employment status, smear microscopy, dissemination Backwards elimination (BE): Drug sensitivity, employment status, smear microscopy, dissemination Stepwise selection (SS): Drug sensitivity, employment status, smear microscopy, dissemination Lasso: Country, employment, extrapulmonary, cavity size, decrease in lung capacity, smear microscopy, drug sensitivity, chest imaging Random forest (RF): Top 5 by mean decrease accuracy: lung cavity size, type of resistance, employment status, country, total cavities Top 5 by mean decrease Gini index: Age of onset, drug regimen, lung cavity size, number of daily contacts, culture	FS:* AUROC = 0.74 (95% CI: 0.66-0.82) Sensitivity = 0.36 Specificity = 0.89 Misclassification = 0.24 BE: AUROC = 0.73 (95% CI: 0.65-0.81) Sensitivity = 0.3 Specificity = 0.88 Misclassification = 0.27 SS: AUROC = 0.73 (95% CI: 0.65-0.81) Sensitivity = 0.30 Specificity = 0.88 Misclassification = 0.27 Lasso: AUROC = 0.72 (95% CI: 0.64-0.80) Sensitivity = 0.21 Specificity = 0.96 Misclassification = 0.23 RF: AUROC = 0.73 (95% CI: 0.65-0.81) Sensitivity = 0.30 Specificity = 0.88 Misclassification = 0.27 SVM linear: AUROC = 0.69 (95% CI: 0.60-0.77) Sensitivity = 0.21 Specificity = 0.94 Misclassification = 0.24 SVM polynomial: AUROC = 0.69 (95% CI: 0.60-0.77) Sensitivity = 0 Specificity = 1 Misclassification = 0.25	List	Unclear, Unclear, Unclear, High

Baussano[47] / 2008§	Pulmonary TB cases	2001 - 2005	Retrospective cohort	Italy	Internal (bootstrap)	576/1242 (46%)	Residency (residential vs. homeless), sex, geographic origin (non-EU vs. EU), case definition (other than definite vs. definite), treatment setting (inpatient and unknown vs. outpatient), age (continuous)	AUROC= 0.75 Calibration slope = 0.98 R^2 = 0.24	Nomogram	Low, Unclear, Low, High
Costa-Veiga[48] / 2017§	Pulmonary TB cases	2000 - 2012	Retrospective cohort	Portugal	External (temporal)	*Development:* 1152/10766 (11%) *Validation:* 4714†	HIV, previous treatment, age class (25-44, 15-24, 45-64, >64), IV drug use, pathologies (other disease comorbidity)	AUROC= 75.9% (95% CI: 74.1-77.7) Sensitivity = 71% Specificity = 73%	Nomogram	Low, Low, Low, High
Killian[34] / 2019§	TB patients (99DOTS program)	Feb 2017 – Sep 2018	Retrospective cohort	India	None	433/4167 (10%)	LEAP:* Lstm rEal-time Adherence Predictor with 2 input layers, 1) LSTM with 64 hidden units and a dense layer with 48 units for the dense layer and 4 units for the penultimate layer w-misses: missed doses in last week t-misses: total missed doses in 35 days units and a dense layer with 48 units for the dense layer and 4 units for the penultimate layer Random forest: 150 trees and no max depth based on DAT from first 35 day	LEAP* AUROC = 0.743 lw-misses: AUROC = 0.607 t-misses: AUROC = 0.630 Random forest: AUROC = 0.722	None	High, High, Unclear, High
Madan[51] / 2018§	TB-HIV patients on DOT with first-line TB treatment	2015	Retrospective cohort	India	None	78/448 (17%)	Sputum smear grade, previous TB,; disease classification, HIV status, ART status, CD4 cell count, sex and age group (with interaction terms between age group and sex; sputum smear status and type of TB; HIV status at TB diagnosis and CD4 cell category).	AUROC = 0.783 HL test p-value = 0.149	Model coefficients	Low, Low, Low, High
Mburu[76] / 2018§	Smear-positive TB patients	Feb 2014 – Aug 2015	Prospective cohort	Kenya	Internal (cross-validation)	32/340 (9%)	HbA1c, treatment regimen (retreatment), creatinine, BMI, BUN, weight, age, random blood glucose, HIV positive result, male gender	AUROC = 0.65 ± 0.06	Relative score	Low, Low, Low, High
Other outcome										
Kalhori[80] (fuzzy) / 2009¶	TB patients at DOTS registration	2005	Retrospective cohort	Iran	Internal (split-sample)	*Development:* 7254† *Validation:* 2418†	Case type, treatment category, risky sex, prison, sex, recent TB infection, diabetes, low body weight, TB type, length, previous imprisonment, age, area, HIV	Mean absolute percentage error = 1.24	Learned parameters	Unclear, Unclear, High, High
Hussain[56] / 2019‖	Pulmonary and extrapulmonary TB patients (TB Reach)	2011 - 2014	Retrospective cohort	Unknown	Internal (split-sample)	*Development:* 3371† *Validation:* 842†	Random forest*, artificial neural networks, and SVM	Random forest:* Accuracy = 76.32%	None	Unclear, Unclear, Unclear, High

Abbreviations: AUROC=Area under receiver operating characteristic; c-statistic=concordance statistic; DOTS=Directly Observed Therapy, DM=Diabetes; HL=Hosmer-Lemeshow; TB=Tuberculosis;
*Indicates best-performing/most relevant model, which is included throughout the manuscript (see methods section for details). Performance measures are reported for highest level of validation performed (ranked from strongest to weakest: external validation, internal validation, no validation). If internal and external validation were performed, both are reported.
†Outcome number unknown
‡Outcome is composite of death and treatment failure (losses to follow-up and not evaluated (unknown) outcomes were excluded)
§Outcome is composite of death, treatment failure, loss to follow-up, and not evaluated
¶Outcome is a value from 1 to 5 (1= patient completed the treatment course in frame of DOTS, 2=cured, 3= quit treatment, 4=failed treatment and 5=death)
‖Outcome is treatment completion

Table 3. Characteristics of patient populations in the 33 included studies with prediction models for tuberculosis treatment outcomes

Characteristic	Studies reporting characteristic, n (% of total)	Categories	N(%) or Median [IQR]
Sample size	33 (11)	-	803 [291, 4167]
Study duration, years	32 (97)	-	4 [2,7]
Study design	33 (100)	Prospective cohort	3 (9)
		Retrospective cohort	25 (76)
		Nested case-control	3 (9)
		Non-nested case-control	2 (6)
Data source	33 (100)	Medical record	6 (18)
		National registry or surveillance system	13 (39)
		Local registry or surveillance system	1 (3)
		Regional registry or surveillance system	2 (6)
		Data collect form for study purposes	11 (33)
Study region	32 (97)	Africa	8 (25)
		Asia	13 (41)
		Europe	6 (19)
		North America	4 (12)
		South America	0 (0)
		Global	1 (3)
High burden TB setting*	31 (94)	All	143(42)
		Some	1 (3)
		None	17 (55)
Missing data	18 (54)	Complete case-analysis	9 (50)
		Missing indicator method	4 (22)
		Heckman's method	1 (6)
		Simple imputation	2 (12)
		Sensitivity analysis with imputation	1 (6)
		Other	1 (5)
Number of models developed	33 (100)	1	25 (76)
		2	4 (12)
		3	1 (3)

		4	2 (6)
		7	1 (3)
Reasons for multiple models developed	8 (24)	Different outcomes	1 (12)
		Different predictors considered	4 (50)
		Different methods	2 (25)
		Different outcomes	1 (12)
		Different populations and outcomes	1 (12)

*Determined based on study location and WHO list of 30 high-burden TB countries in the 2019 Global Tuberculosis Report (1).

Table 4. Study population characteristics of 33 included studies

	Included?			
Characteristic	**Yes**	**No**	**Unknown**	**Median [IQR]‡, n**
Age*	-	-	15	41 [37, 49], n=18
HIV	18	7	8	23% [10-100], n=17
Diabetes	12	2	19	12% [5-21], n=11
MDR	8	7	18	1% [1-3], n=8
Other drug resistance	12	1	20	6% [4-12], n=10
Extrapulmonary TB†	22	4	7	11% [4-17], n=16
Previous TB	20	1	12	19% [9-30], n=17
DOT	14	0	19	100% [100-100], n=14
Hospitalized patients	13	1	19	100% [100-100], n=10

Abbreviations: DOT=directly observed therapy; IQR=interquartile range; MDR=multi-drug resistance; TB=tuberculosis

*Based on the measure of central tendency reported in the study (mean: n=11; median: n=7)

†Forms of extrapulmonary TB differ by study but included some of the following: Miliary, meningeal, pleural, peritoneal, disseminated, blood/bone, abdominal

‡Other than age (which is reported in years), this is the percentage of the population that has the characteristic among studies that include patients with the characteristic. For example, among the 18 studies that include persons with HIV, 17 report how many people had HIV and among those, the median percentage of the population with HIV is 23%.

Table 5. Methods reported for the 37 models of the 33 included studies with prediction models for tuberculosis treatment outcomes

Characteristic	Studies reporting characteristic, n (%)	Categories	N(%) or median [IQR]
Type of outcome	37 (100)	Single	29 (78)
		Composite	8 (22)
Outcome	37 (100)	Death	16 (43)
		Treatment failure	6 (16)
		Default, Loss to follow-up, or treatment interruption	6 (16)
		Unfavorable outcome	6 (16)
		Treatment success	2 (6)
		Other‡	1 (3)
Number - prevalence of outcome*	32 (87)	-	94 [38-171] 15% [9-26]
Events per candidate variable†	30 (81)	-	6 [3-11]
Events per variable (in final model)	29 (78)	-	14 [9-26]
Predictor types		Clinical/epidemiologic	34 (92)
		Adherence	1 (3)
		Biomarker	2 (5)
Analysis	37 (100)	Logistic regression	29 (78)
		Survival analysis	3 (8)
		Machine learning	5 (14)
Method for considering predictors in multivariable models	36 (97)	All candidate predictors	12 (32)
		Based on unadjusted association with outcome	19 (51)
		Based on clinical relevance	1 (3)
		Other§	4 (14)
Selection of predictors during modeling	31 (84)	Full model approach	2 (6)
		Forward selection	7 (23)
		Backwards elimination	5 (16)
		Stepwise selection	8 (26)
		Random Forest	1 (3)
		Hosmer-Lemeshow model building criteria	4 (13)
		Bayesian model averaging	3 (10)
		Pairwise selection	1 (3)

P-value for consideration in model	17 (46)	0·01	2 (12)
		0·05	3 (18)
		0·11	1 (6)
		0·2	6 (35)
		0·25	5 (29)
P-value for retention in MV model	20 (54)	0·05	9 (45)
		0·1	9 (45)
		0·15	1 (5)
		0·2	1 (5)
Internal validation	19 (51)	Split-sample	10 (53)
		Bootstrap	5 (26)
		Cross-validation	4 (21)
External validation	6 (16)	Temporal	1 (17)
		Geographic	1 (4)
		Setting	4 (67)
Calibration	17 (46)	Calibration plot¶	2 (12)
		Calibration slope¶	1 (6)
		Hosmer-Lemeshow goodness of fit p-value¶	13 (77)
			0·51 [0·20, 0·79]
		Calibration table¶	2 (12)
		Mean absolute error¶	1 (6)
Discrimination	30 (81)	C-statistic (AUROC) ¶	30 (100)
			0·75 [0·68-0·84]
		Log rank test¶	2 (5)
Classification	18 (49)	Sensitivity‖	14 (78)
			70 [54, 78]
		Specificity‖	13 (72)
			75 [71, 88]
		Accuracy	2 (11)
		Other**	2 (11)
Model presentation	34 (92)	Risk score	16 (43)
		Model coefficient	8 (22)
		Nomogram	2 (6)
		Odds ratios/relative scores	4 (12)
		Survey tool	1 (3)

Abbreviations: AUROC=area under receiver operating characteristic; c-statistic=concordance statistic

*Prevalence of outcome in the population used to develop the prediction model (i.e. derivation/development subset if split-sample technique was used or full sample if the model was not validated or if bootstrap/cross-validation was used)

†Only 5 studies report the exact number of predictors considered. Otherwise, the number of candidate predictors was estimated from the provided tables or lists of candidate predictors in the source paper.

‡Outcome is a value from 1 to 5 (1= patient completed the treatment course in frame of DOTS, 2=cured, 3= quit treatment, 4=failed treatment and 5=death)

§Other methods of determining which variables to consider for prediction model include: principal components analysis (n=1), screening for multi-collinearity via correlation coefficient (n=1), one study used a combination of a priori and selection via univariable association, and the other used machine learning pre-processing (n=1)

¶Sums to more than 100%, because some studies report multiple measures of calibration or discrimination

‖Based on the following cut-off methods: Youden (n=4) concordance probability (n=1), estimated at nearest 0,1 for studies that present a range of sensitivity and specificity in a table or figure (n=4), or unknown (n=5)

**Other includes one study that reports false positive rate and one study that includes a graph of sensitivity vs. specificity.

Figure 2. Most common predictors considered and included

[See Figure 2]

Figure 2 legend**:**
Considered: the predictor as evaluated as a candidate predictor prior to multivariable modeling
Included: the predictor was considered and subsequently included in the final multivariable model

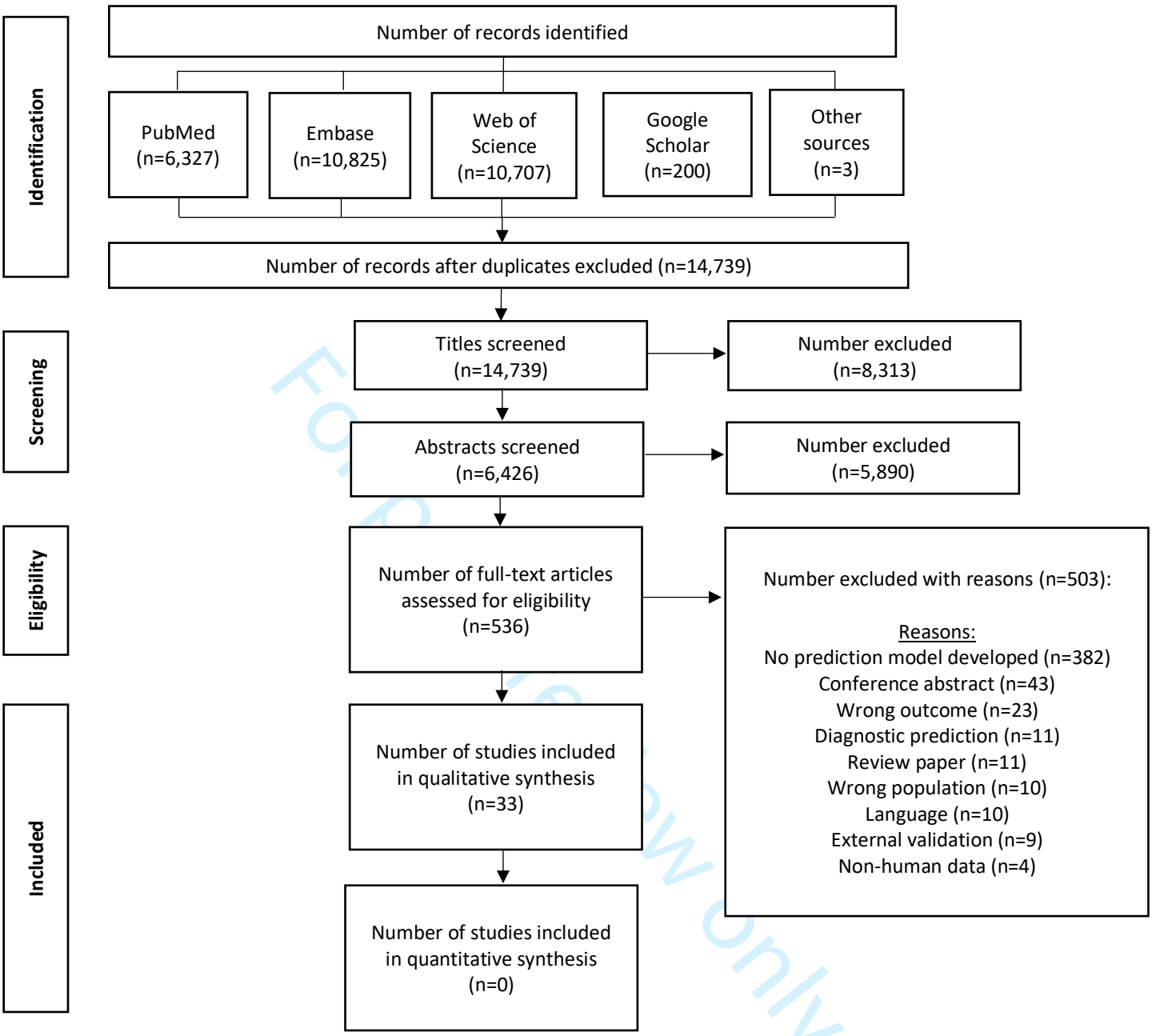
Figure 3. Heatmap of signaling questions from risk of bias assessment with PROBAST

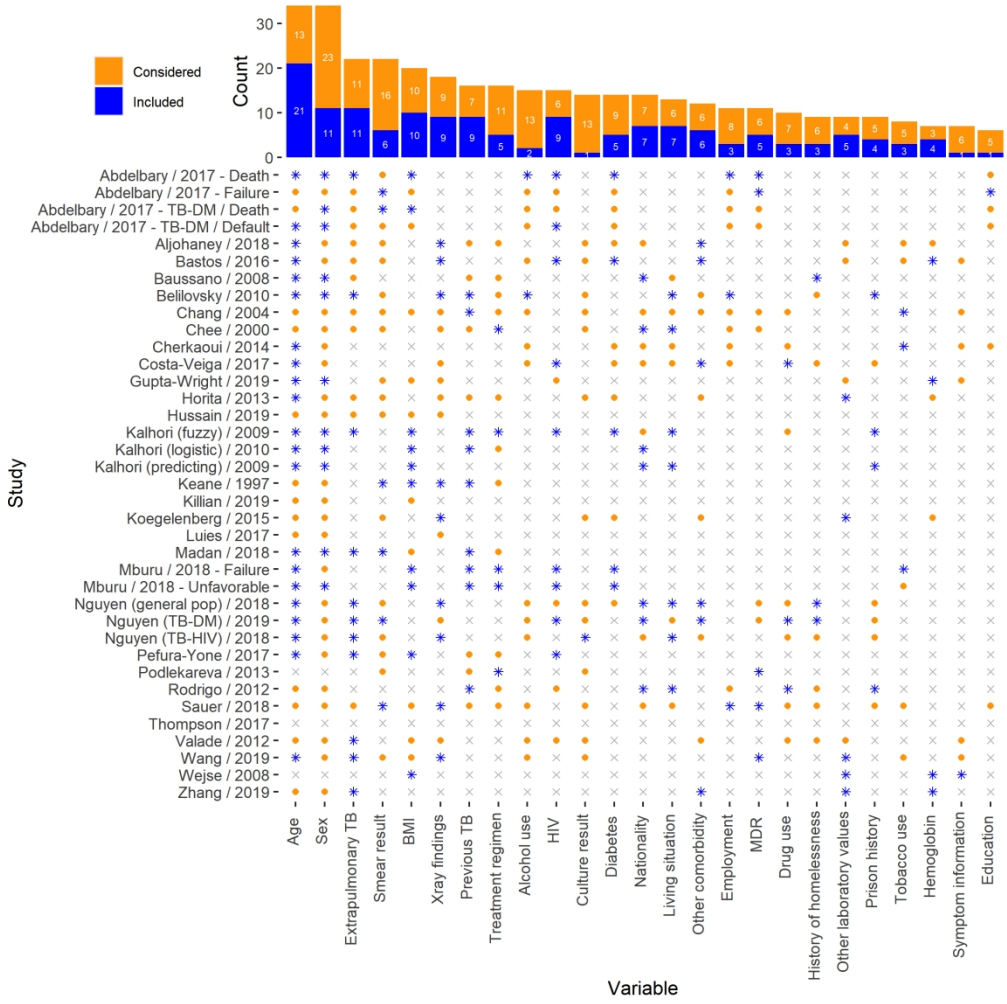
[See Figure 3]

Figure 3 legend**:**
PROBAST questions (additional details in Supplemental File 5)
Participants 1: What study design was used and was it appropriate?
Participants 2: Were all inclusion and exclusion criteria appropriate?
Predictors 1: Were predictors defined as assessed the same way for all participants?
Predictors 2: Were predictor assessments made without knowledge of data outcome?
Predictors 3: Are all predictors available at the time the model was intended to be used?
Outcome 1: Was the outcome determined appropriately?
Outcome 2: Was the outcome pre-specified or standard?
Outcome 3: Were predictors excluded from outcome definition?
Outcome 4: Was the outcome defined and determined in a similar way for all participants?
Outcome 5: Was the outcome determined without predictor information?
Outcome 6: Was the time interval between predictor assessment and outcome determination appropriate?
Analysis 1: Were there a reasonable number of participants with the outcome?
Analysis 2: Were continuous and categorical variables handled appropriately?
Analysis 3: Were all enrolled participants included in the analysis?
Analysis 4: Were participants with missing data handled appropriately?
Analysis 5: Was selection of predictors based on univariable analysis avoided?
Analysis 6: Were complexities in data (censoring, competing risks, sampling of control participants) accounted for appropriately?
Analysis 7: Were relevant model performance measures evaluated appropriately?
Analysis 8: Were model overfitting, underfitting, and optimism in the model performance accounted for?
Analysis 9: Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?

Figure 4. Summary of risk of bias and applicability assessment with PROBAST

[See Figure 4]





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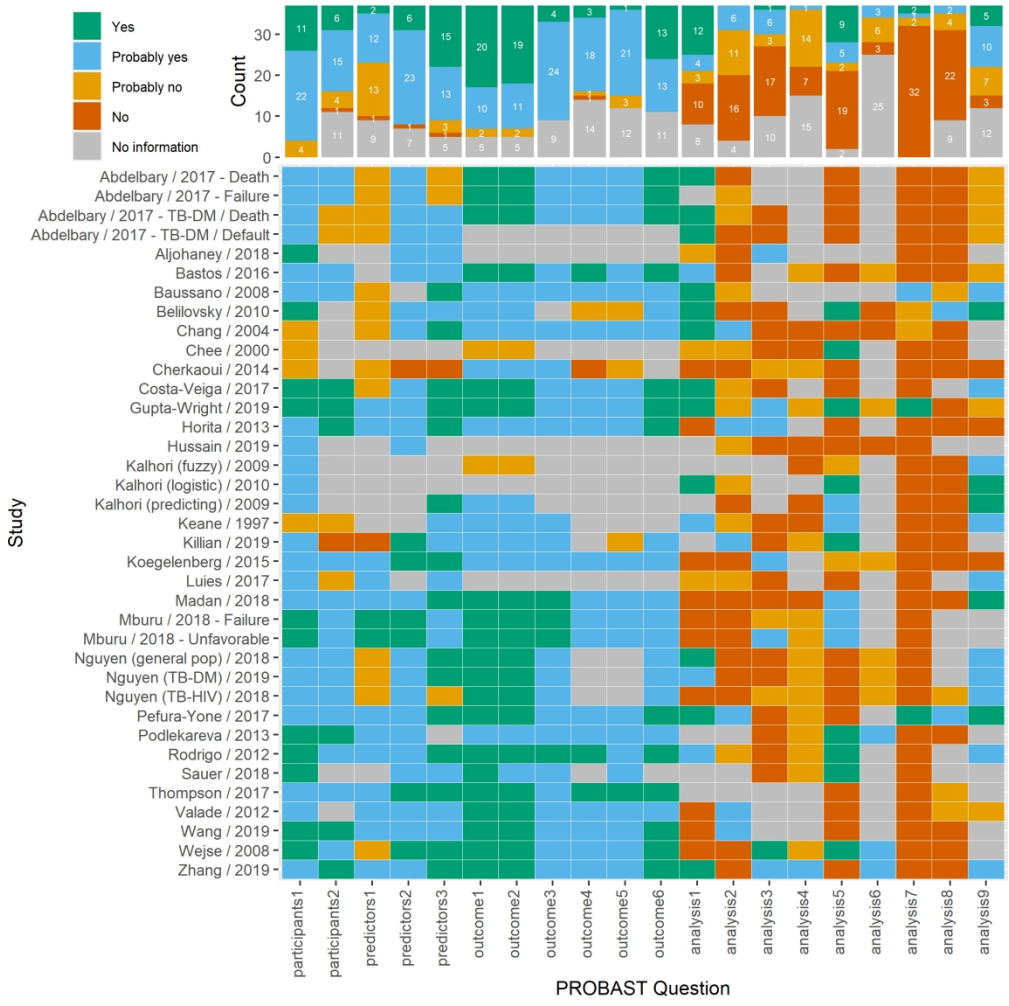

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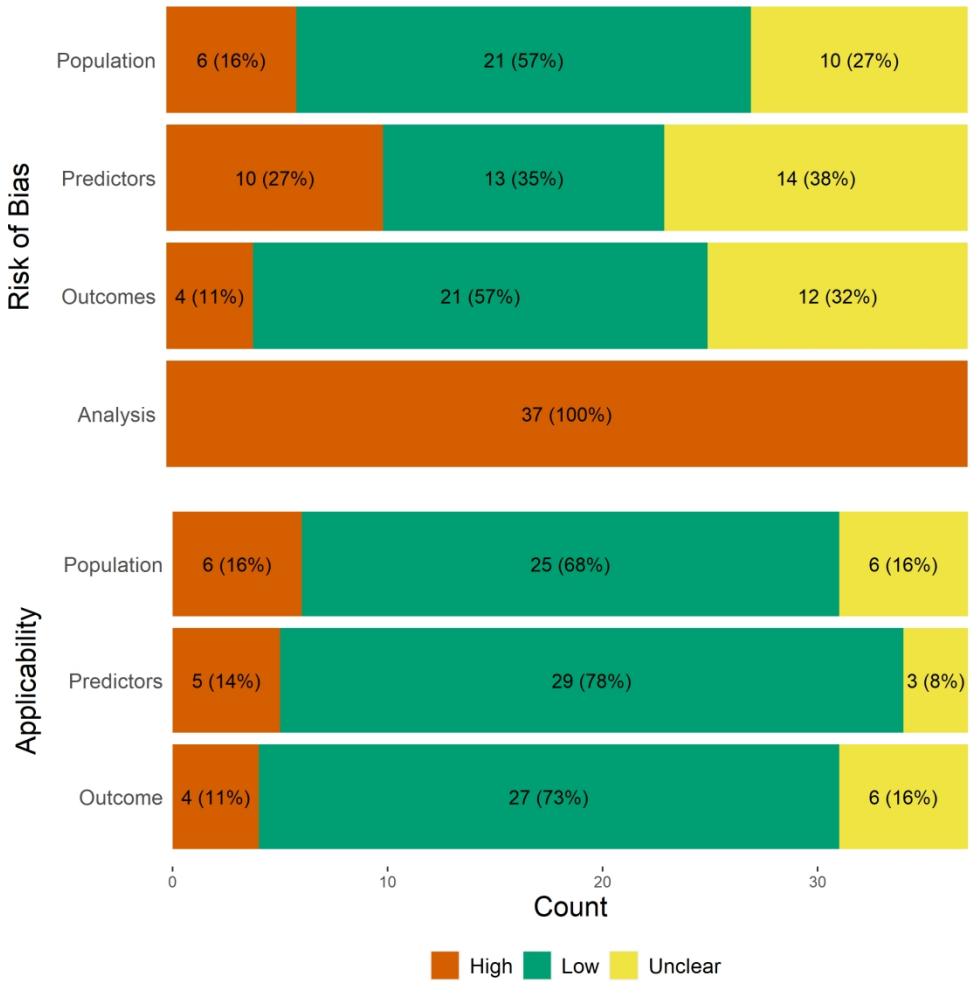

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Supplemental File 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Supplemental File 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract and p. 7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9; Supplemental Files 4 and 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9; Supplemental File 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-13; Table 3, 4, 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14; Figures 3 and 4

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-14; Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplemental File 2. PICOTS System

Population	Pulmonary tuberculosis cases
Intervention	Any prognostic model developed to predict tuberculosis treatment outcome. This includes model development studies with and without external validation
Comparator	Models will be compared to each other, as there is no other relevant comparator for this systematic review
Outcome	TB treatment outcome. The primary outcome of interest is the probability of unsuccessful TB treatment outcome, defined by the WHO as the combination of death, treatment failure, default, and/or not evaluated, as compared to successful TB treatment outcome, defined as the combination of cure and treatment completion. Included studies should evaluate at least one of the following outcomes: cure, treatment completion, death, treatment failure, default, and not evaluated. Default and not evaluated are sometimes referred to collectively as lost to follow-up. Some prediction models will look at only single endpoints, whereas other look at composite outcomes.
Timing	The timespan of prediction may vary between studies, depending on the duration of treatment and follow-up, but we expect most studies will evaluate endpoints around 6-9 months.
Setting	Model designed for use in clinical or hospital setting at the time of TB treatment initiation to aid in targeted treatment or programmatic support for individuals at greatest risk for unsuccessful TB treatment outcomes.

Supplemental File 3. Search Strategy

Database	*Search terms*
PubMed	1. ((validat*[tiab] OR predict*[ti] OR rule*[tiab]) OR (predict*[tiab] AND (outcome*[tiab] OR risk*[tiab] OR model*[tiab])) OR ((history[tiab] OR variable*[tiab] OR criteria[tiab] OR scor*[tiab] OR characteristic*[tiab] OR finding*[tiab] OR factor*[tiab]) AND (predict*[tiab] OR model*[tiab] OR decision*[tiab] OR identif*[tiab] OR prognos*[tiab])) OR (decision*[tiab] AND (model*[tiab] OR clinical*[tiab] OR "Logistic Models"[Mesh])) OR (prognostic[tiab] AND (history[tiab] OR variable*[tiab] OR criteria[tiab] OR scor*[tiab] OR characteristic*[tiab] OR finding*[tiab] OR factor*[tiab] OR model*[tiab])) 2. (stratification[tiab] OR "ROC Curve"[Mesh] OR discrimination[tiab] OR discriminate[tiab] OR "c-statistic"[tiab] OR "c statistic"[tiab] OR "area under the curve"[tiab] OR AUC[tiab] OR calibration[tiab] OR indices[tiab] OR algorithm[tiab] OR multivariable[tiab]) 3. (tuberculosis[Mesh] OR tuberculosis[tiab]) 4. (outcome*[tiab] OR mortality*[tiab] OR death*[tiab] OR fail*[tiab] OR recur*[tiab] OR relapse*[tiab] OR default*[tiab] OR abandon*[tiab] OR loss*[tiab] OR cure*[tiab] OR success*[tiab] OR unsuccess*[tiab] OR die[tiab] OR died[tiab] OR dies[tiab])) 5. 1 OR 2 6. 3 AND 4 7. 5 AND 6 AND (humans[Filter]) AND ("1995"[Date - Publication] : "3000"[Date - Publication])
Embase	1. (validat$ or predict$ or rule$).ti. OR (predict$ and (outcome$ or risk$ or model$)).ti,ab. OR ((history or variable$ or criteria or scor$ or characteristic$ or finding$ or factor$) and (predict$ or model$ or decision$ or identif$ or prognos$)).ti,ab. OR (decision$.ti,ab. and ((model$ or clinical$).ti,ab. or "statistical model"/)) OR (prognostic and (history or variable$ or criteria or scor$ or characteristic$ or finding$ or factor$ or model$)).ti,ab. 2. (stratification or discrimination or discriminate or c-statistic or "c statistic" or "area under the curve" or AUC or calibration or indices or algorithm or multivarriable).ti,ab. or "receiver operating characteristic"/ 3. tuberculosis/ or tuberculosis.ti,ab 4. (outcome$ or mortality$ or death$ or fail$ or recur$ or relapse$ or default$ or abandon$ or loss$ or cure$ or success$ or unsuccess$ or die or died or dies).ti,ab. 5. 1 or 2 6. 3 and 4 7. 5 and 6 8. limit 7 to (human and yr="1995 -Current")
Web of Science	1. TI=(validat* or predict*. or rule*) OR TS=(predict* and (outcome* or risk* or model*)) OR TS=((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)) OR TS=(decision* and ((model* or clinical*). or "statistical model")) OR TS=(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)) 2. TS=(stratification or discrimination or discriminate or c-statistic or "c statistic" or "area under the curve" or AUC or calibration or indices or algorithm or multivariable or "receiver operating characteristic") 3. TS=(tuberculosis) 4. TS=(outcome* or mortality* or death* or fail* or recur* or relapse* or default* or abandon* or loss* or cure* or success* or unsuccess* or die or died or dies) 5. 1 or 2 6. 3 and 4 7. 5 and 6; IC Timespan=1995-2019
Google scholar	tuberculosis treatment outcome prediction prognostic model development validation

Supplemental File 4. CHARMS Checklist

Domain	Key items	Reported on page #
SOURCE OF DATA	Source of data (e.g., cohort, case-control, randomized trial participants, or registry data)	
PARTICIPANTS	Participant eligibility and recruitment method (e.g., consecutive participants, location, number of centers, setting, inclusion and exclusion criteria)	
	Participant description	
	Details of treatments received, if relevant	
	Study dates	
OUTCOME(S) TO BE PREDICTED	Definition and method for measurement of outcome	
	Was the same outcome definition (and method for measurement) used in all patients?	
	Type of outcome (e.g., single or combined endpoints)	
	Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)?	
	Were candidate predictors part of the outcome (e.g., in panel or consensus diagnosis)?	
	Time of outcome occurrence or summary of duration of follow-up	
CANDIDATE PREDICTORS (OR INDEX TESTS)	Number and type of predictors (e.g., demographics, patient history, physical examination, additional testing, disease characteristics)	
	Definition and method for measurement of candidate predictors	
	Timing of predictor measurement (e.g., at patient presentation, at diagnosis, at treatment initiation)	
	Were predictors assessed blinded for outcome, and for each other (if relevant)?	
	Handling of predictors in the modelling (e.g., continuous, linear, non-linear transformations or categorised)	
SAMPLE SIZE	Number of participants and number of outcomes/events	
	Number of outcomes/events in relation to the number of candidate predictors (Events Per Variable)	
MISSING DATA	Number of participants with any missing value (include predictors and outcomes)	
	Number of participants with missing data for each predictor	
	Handling of missing data (e.g., complete-case analysis, imputation, or other methods)	
MODEL DEVELOPMENT	Modelling method (e.g., logistic, survival, neural network, or machine learning techniques)	
	Modelling assumptions satisfied	
	Method for selection of predictors **for inclusion** in multivariable modelling (e.g., all candidate predictors, pre-selection based on unadjusted association with the outcome)	
	Method for selection of predictors **during multivariable modelling** (e.g., full model approach, backward or forward selection) and criteria used (e.g., p-value, Akaike Information Criterion)	
	Shrinkage of predictor weights or regression coefficients (e.g., no shrinkage, uniform shrinkage, penalized estimation)	
MODEL PERFORMANCE	Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log-rank) measures with confidence intervals	
	Classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement) and whether a-priori cut points were used	
MODEL EVALUATION	Method used for testing model performance: development dataset only (random split of data, resampling methods e.g. bootstrap or cross-validation, none) or separate external validation (e.g. temporal, geographical, different setting, different investigators)	
	In case of poor validation, whether model was adjusted or updated (e.g., intercept recalibrated, predictor effects adjusted, or new predictors added)	
RESULTS	Final and other multivariable models (e.g., basic, extended, simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, model performance measures (with standard errors or confidence intervals)	
	Any alternative presentation of the final prediction models, e.g., sum score, nomogram, score chart, predictions for specific risk subgroups with performance	

	Comparison of the distribution of predictors (including missing data) for development and validation datasets	
INTERPRETATION AND DISCUSSION	Interpretation of presented models (confirmatory, i.e., model useful for practice versus exploratory, i.e., more research needed)	
	Comparison with other studies, discussion of generalizability, strengths and limitations.	

Supplemental File 5. Prediction model Risk Of Bias Assessment Tool (PROBAST)

Link to full explanation and elaboration document
Citation: Moons KG, Wolff RF, Riley RD, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med. 2019;170:W1–W33. doi: https://doi.org/10.7326/M18-1377

Domain 1: Participants
The overall aim for prediction models is to generate absolute risk predictions that are correct in new individuals. Certain data sources or designs are not suited to generate absolute probabilities. Problems may also arise if a study inappropriately includes or excludes participant groups from entering the study

	Signaling question	Yes/probably yes	No/probably no	No information
1	What study design was used and was it appropriate?	Yes: If a cohort design (including RCT or proper registry data) was used and you have confidence in data quality and participant enrollment is clearly described Probably yes: a nested case–control or case–cohort design (with proper adjustment of the baseline risk/hazard in the analysis) has been used or a cohort design was used but participant enrollment was data quality is unclear	No: If a non-nested case–control design has been used Probably no: a nested case-control study was used without proper adjustment of baseline risk/hazard	If the method of participant sampling is unclear.
2	Were all inclusion and exclusion criteria appropriate?	Yes: Inclusion and exclusion are clear and selection participants was appropriate, so participants correspond to unselected participants of interest (i.e. the target population). Probably yes: Inclusion and exclusion criteria are not entirely clear, but it seems like the population is representative of the target population	No: If participants are included who would already have been identified as having the outcome and so are no longer at risk of developing outcome, or if specific subgroups are excluded that may have altered the performance of the prediction model for the intended target population. Probably no: inclusion and exclusion criteria are unclear and it seems possible that there was bias in selection of participants that could lead to the model being applied to a population that is unrepresentative of the target population.	When there is no information on whether inappropriate inclusions or exclusions took place.

Low risk of bias	High risk of bias	Unclear risk of bias
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 2: Predictors
Bias in model performance can occur when the definition and measurement of predictors is flawed. Predictors are the variables evaluated for their association with the outcome of interest. Bias can occur, for example, when predictors are not defined in a similar way for all participants or knowledge of the outcome influences

	Signaling question	Yes/probably yes	No/probably no	No information
1	Were predictors defined and assessed in a similar way for all participants?	Yes: It is clear that definitions of predictors and their assessment were similar for all participants. Probably yes: Some predictors were based off subjective judgement, but carried out by persons with the necessary skills to evaluate the predictor, or if data from multiple sources was used but predictor definitions were standardized between sources.	No: If different definitions were used for the same predictor or if predictors requiring subjective interpretation were assessed by differently experienced assessors Probably no: Data from multiple sources was used and its unclear whether definitions were standardized between sources or if subjective measurements were likely not carried out by persons with appropriate training.	If there is no information on how predictors were defined or assessed.
2	Were predictor assessments made without knowledge of data outcome?	Yes: If outcome information was stated as not used during predictor assessment or was clearly not (yet) available to those assessing predictors (i.e. prospective data collection).	If it is clear that outcome information was used when assessing predictors.	No information on whether predictors were assessed without knowledge of outcome information.

		Probably yes: If it is likely that outcome information was not used during predictor assessment, but not entirely clear (retrospective data collection/surveillance data)		
3	Are all predictors available at the time the model was intended to be used?	All included predictors would be available at the time the model is intended to be used for prediction	Predictors would not be available at the time the model is intended to be used for prediction.	No information on whether predictors would be available at the time the model is intended to be used for prediction.

Low risk of bias	**High risk of bias**	**Unclear risk of bias**
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 3: Outcome

Bias in model performance can occur when methods used to determine outcomes incorrectly classify participants with or without the outcome. Bias in methods of outcome determination can result from use of suboptimal methods, tests, or criteria that lead to unacceptably high levels of errors in outcome determination, when methods are inconsistently applied across participants, or when knowledge of predictors influence outcome determination. Incorrect timing of outcome determination can also result in bias.

	Signaling question	**Yes/probably yes**	**No/probably no**	**No information**
1	Was the outcome determined appropriately?	If a method of outcome determination has been used which is considered optimal or acceptable by guidelines or previous publications on the topic Note: This is about level of measurement error within the method of determining the outcome (see concerns for applicability about whether the definition of the outcome method is appropriate).	If a clearly suboptimal method has been used that causes unacceptable error in determining outcome status in participants	No information on how outcome was determined
2	Was the outcome pre-specified or standard?	Yes: If the method of outcome determination is objective, or if a standard outcome definition is used, or if prespecified categories are used to group outcomes. (i.e. outcome assessment is based on previously published studies, published study protocol, or clinical guidelines) Probably yes: The outcome determination is not clearly based on guidelines or previous research, but outcome assessment is objective and would not inadvertently alter study results	No: If the outcome definition was not standard and not prespecified Probably no: a non-standard or non-prespecified outcome was used, and it is unclear whether the outcome definition could introduce bias. *Caution with composite outcomes that favor a better model by excluding typical outcome components or including atypical events	No information on whether the outcome definition was prespecified or standard
3	Were predictors excluded from outcome definition?	Yes: None of the predictors are included in the outcome definition (clearly stated) Probably yes: None of the predictors are included in the outcome definition (assumed)	If ≥1 of the predictors forms part of the outcome definition	No information on whether predictors are excluded from the outcome definition
4	Was the outcome defined and determined in a similar way for all participants?	Yes: If outcomes were defined and determined in a similar way for all participants (clearly stated) Probably yes: If outcomes were defined and determined in a similar way for all participants (assumed)	If outcomes were clearly defined and determined in a different way for some participants	No information on whether outcomes were defined or determined in a similar way for all participants
5	Was the outcome determined without predictor information	Yes: If predictor information was not known when determining the outcome status, or outcome status determination is clearly reported as determined without knowledge of predictor information. Probably yes: predictor information might have been available at time of outcome assessment, but outcome definition is objective and knowing information about predictors would not influence outcome	No: If it is clear that predictor information was used when determining the outcome status Probably no: it is likely predictor information was available at the time of outcome assessment, and outcome definition is subjective and knowledge of predictors could influence outcome determination.	No information on whether outcome was determined without knowledge of predictor information

		assessment (i.e death, treatment failure based on culture results, etc)		
6	Was the time interval between predictor assessment and outcome determination appropriate	If the time interval between predictor assessment and outcome determination was appropriate to enable the correct type and representative number of relevant outcomes to be recorded, or if no information on the time interval is required to allow a representative number of the relevant outcome occur or if predictor assessment and outcome determination were from information taken within an appropriate time interval.	If the time interval between predictor assessment and outcome determination is too short or too long to enable the correct type and representative number of relevant outcomes to be recorded.	If no information was provided on the time interval between predictor assessment and outcome determination.

Low risk of bias	High risk of bias	Unclear risk of bias
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 4: Analysis

Statistical analysis is a critical part of prediction model development and validation. The use of inappropriate statistical analysis methods increases the potential for bias in reported model performance measures. Model development studies include many steps where flawed methods can distort results. We recommend reviewers seek statistical advice when completing

	Signaling question	Yes/probably yes	No/probably no	No information
1	Were there a reasonable number of participants with the outcome?	For model development studies, if the number of participants with the outcome relative to the number of candidate predictor parameters is ≥20 (EPV ≥20).* For model validation studies, if the number of participants with the outcome is ≥100.	For model development studies, if the number of participants with the outcome relative to the number of candidate predictor parameters is <10 (EPV <10).* For model validation studies, if the number of participants with the outcome is <100.	For model development studies, no information on the number of candidate predictor parameters or number of participants with the outcome, such that the EPV cannot be calculated. For model validation studies, no information on the number of participants with the outcome.
		* For EPVs between 10 and 20, the item should be rated as either probably yes or probably no, depending on the outcome frequency, overall model performance, and distribution of the predictors in the model. For more guidance, see references 145 to 147.		
2	Were continuous and categorical predictors handled appropriately?	Yes: If continuous predictors are kept as continuous or if continuous predictors are examined as linear or non-linear using restricted cubic splines or fractional polynomials. Probably yes: If continuous predictors are not converted into >2 categories when included in the model (i.e., dichotomized or categorized) using a prespecified method or in a way that avoids sparse data/would not intentionally improve statistical significance. For model validation studies, if continuous predictors are included using the same definitions or transformations, and categorical variables are categorized using the same cut points, ascompared with the development study.	No: For model development studies, if continuous predictors are converted into 2 categories when included in the model. Probably no: If categorical predictor group definitions do not use a prespecified method or continuous variables were split into >2 groups, but the decision of how to split variables is unclear. For model validation studies, if continuous predictors are included using different definitions or transformations, or categorical variables are categorized using different cut points, as compared with the development study.	No information on whether continuous predictors are examined for nonlinearity and no information on how categorical predictor groups are defined. For model validation studies, no information on whether the same definitions or transformations and the same cut points are used, as compared with the development study.
3	Were all enrolled participants included in the analysis?	If all participants enrolled in the study are included in the data analysis.	If some or a subgroup of participants are inappropriately excluded from the analysis (because they were missing data, unknown outcome, outliers)	No information on whether all enrolled participants are included in the analysis.
4	Were participants with missing data handled appropriately?	Yes: If there are no missing values of predictors or outcomes and the study explicitly reports that participants are not excluded on the basis of missing data, or if missing values are handled using multiple imputation.	No: If participants with missing data are omitted from the analysis, or if the method of handling missing data is clearly flawed, e.g., missing indicator method or inappropriate use of last value carried forward, or	If there is insufficient information to determine if the method of handling missing data is appropriate

		Probably yes: If a small percentage of persons with missing data were excluded and authors provide comparison of included vs. excluded participants or if sensitivity analysis with imputation methods are convincing that bias is low	if the study had no explicit mention of methods to handle missing data. Probably no: If authors provide comparison of included vs. excluded participants or if sensitivity analysis with imputation methods are reported, but the results are not convincing to rule out bias from excluding missing data	
5	Was selection of predictors based on univariable analysis avoided?	If the predictors are not selected on the basis of univariable analysis prior to multivariable modeling.	If the predictors are selected on the basis of univariable analysis prior to multivariable modeling.	If there is no information to indicate that univariable selection is avoided.
6	Were complexities in the data (censoring, competing risks, sampling of control participants) accounted for appropriately?	If any complexities in the data are accounted for appropriately, or if it is clear that any potential data complexities have been identified appropriately as unimportant.	If complexities in the data that could affect model performance are ignore. For example, case-control studies that do not estimate baseline risk or studies with censoring or competing risks that do not use survival analysis or other appropriate methods.	No information is provided on whether complexities in the data are present or accounted for appropriately if present.
7	Were relevant model performance measures evaluated appropriately?	Yes: If both calibration (via calibration plot) and discrimination (c-index) are evaluated appropriately (including relevant measures tailored for models predicting survival outcomes). Probably yes: if authors present a table of predicted probabilities with confidence intervals and corresponding outcome frequencies across subgroups	If both calibration and discrimination are not evaluated, or if only goodness-of-fit tests (Hosmer-Lemeshow test), are used to evaluate calibration or if for models predicting survival outcomes performance measures accounting for censoring are not used, or if classification measures (like sensitivity, specificity, or predictive values) were presented using predicted probability thresholds derived from the data set at hand, but calibration is not otherwise evaluated.	Either calibration or discrimination are not reported, or no information is provided as to whether appropriate performance measures for survival outcomes are used (e.g., references to relevant literature or specific mention of methods, such as using Kaplan–Meier estimates), or no information on thresholds for estimating classification measures is given.
8	Were model overfitting, underfitting, and optimism in model performance accounted for?	Yes: If internal validation techniques (bootstrapping and cross-validation) including all model development procedures, were used to account for any optimism in model fitting, and subsequent adjustment of the model performance estimates were applied. Probably yes: If internal validation was used and optimism was estimated as very low, and then optimism-corrected performance measures were not appropriately calculated (accounting for all model development procedures)	No: If no internal validation has been performed, or if internal validation consists only of a single random split-sample of participant data, Probably no: Internal validation with bootstrapping or cross-validation was conducted but did not include all model development procedures including any variable selection or were not used to correct model performance measures.	No information: No information is provided on whether internal validation techniques, including all model development procedures, have been applied.
9	Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?	If the predictors and regression coefficients in the final model correspond to reported results from multivariable analysis.	If the predictors and regression coefficients in the final model do not correspond to reported results from multivariable analysis. (i.e. rounding of model coefficients to create a "risk score" are inappropriately determined).	If it is unclear whether the regression coefficients in the final model correspond to reported results from multivariable analysis.

Low risk of bias	**High risk of bias**	**Unclear risk of bias**
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Applicability				
	Domain	**Low concern**	**High concern**	**Unclear concern**

	Participants: do you have concern that the included participants or setting do not match the review question?	Included participants and clinical setting match the review question.	Included participants and clinical setting were different from the review question.	If relevant information about the participants and clinical setting are not reported.
	Predictors: does the definition, assessment, or timing of predictors match the review questions?	Definition, assessment, and timing of predictors match the review question.	Definition, assessment, or timing of predictors were different from the review question	If relevant information about the predictors is not reported.
	Outcome: does the definition, timing, or determination of outcome match the review question?	Outcome definition, timing, and method of determination defines the outcome as intended by the review question.	Choice of outcome definition, timing, and method of outcome determination defines another outcome as intended by the review question	If relevant information about the outcome, timing, and method of determination is not reported.

Supplemental File 6. Model outcome definitions

Study ID	Outcome category	Full outcome definition from the source paper
Hussain / 2019	Treatment completion	The target variable TreatmentComplete consists of 64.37% positive (treatment complete) and 35.62% negative (treatment incomplete)
Abdelbary / 2017 - Death	Death	All causes of death (TB or non-TB related) during the course of TB treatment
Abdelbary / 2017 - TB-DM / Death	Death	Death included all causes of death (TB and non-TB related) during the course of TB treatment
Aljohaney / 2018	Death	Not defined, but seems to be death during hospitalization.
Bastos / 2016	Death	Deaths that occurred during the first 6 months after diagnosis were classified as TB death
Gupta-Wright / 2019	Death	The outcome was mortality risk at 2 months after admission.
Horita / 2013	Death	'Discharged alive' was defined as being discharged alive and satisfying the discharge criteria, i.e., when the patient was receiving effective treatment, showed clinical improvement and negative conversion was confirrmed. Negative conversion was defined as three or more consecutive sputum samples obtained on different days being smear-negative for acid-fast bacilli or when appropriate sputum sample(s) were culture-negative. 'Died in hospital' was defined as death from any cause.
Koegelenberg / 2015	Death	Patients were categorised as either ICU/hospital survivors or non-survivors.
Nguyen (general pop) / 2018	Death	Documented treatment outcome of 'completed' or 'died'
Nguyen (TB-DM) / 2019	Death	TB treatment outcome of either 'completed' or 'died'
Nguyen (TB-HIV) / 2018	Death	Given the main purpose of our study is to predict the mortality during TB treatment in HIV-infected patients against the treatment completion, patients who had an outcome coding other than completed or died.
Pefura-Yone / 2017	Death	At treatment completion, patients are ranked into the following mutually exclusive categories 1) cured-patient with negative smear at the last month of treatment and at least one of the preceding months; 2) treatment completed-patient who has completed the treatment and for whom the smear results at the end of the last month are not available; 3) failure-patient with positive smear at the 5th month or later during treatment; 4) death-death from any cause during treatment; 5) defaulter-patient who's treatment has been interrupted for at least two consecutive months; 6) transfer-patient transferred to complete his treatment in another center and who's treatment outcome is unknown Cured and treatment completed are considered successful treatment
Podlekareva / 2013	Death	Death within 12 months of TB diagnosis
Valade / 2012	Death	Final outcomes of survival or death were recorded
Wang / 2019	Death	The outcome was estimated with all-cause mortality, with the mortality in 12 months as the primary outcome and the mortality in 3, 6, 9 months as other outcome
Wejse / 2008	Death	Mortality: ability to predict death
Zhang / 2019	Death	Primary treatment outcome was documented either survival or death when HIV/TB co-infected patients left hospital. Patients who survived when discharged received 12-month follow-up, and the date of last known alive was documented in electronical medical records base on records of last follow-up
Abdelbary / 2017 - Failure	Treatment failure	Treatment failure indicated smear-positive persistence at or after 5 months of treatment with first-line anti-TB medications.
Kalhori (logistic) / 2010	Treatment failure	The dependent variable was failing in treatment course completion.
Keane / 1997	Treatment failure	Failing to clear the sputum of acid-fast bacilli with standard treatment and having to start second line therapy
Luies / 2017	Treatment failure	From the original samples, all treatment failure cases were included.
Mburu / 2018 - Failure	Treatment failure	The secondary analyses only compared 'cures' versus 'failures' at similar time points as is the standard practice when examining chemotherapy efficacy
Thompson / 2017	Treatment failure	Patients' clinical outcomes were classified as 'cured' if they proved and maintained sputum culture negativity by month 6 after treatment initiation (M6), 'failed' if the M6 culture was still positive, and 'un-evaluable' if contamination caused uncertainty in outcome. We note that none of the treatment failures achieved culture negativity at any time point during treatment.
Abdelbary / 2017 - TB-DM / Default	Default, Abandon, or LTF (interruption >2 months)	Never defined
Belilovsky / 2010	Default, Abandon, or LTF (interruption >2 months)	We evaluated TI initiated by the patient (significant noncompliance with the doctor's prescribed course of treatment and serious violations of public order in hospitals) resulting in inpatient treatment cancellation.
Chang / 2004	Default, Abandon, or LTF	Default was defined as failure to collect drugs for 2 months or more after registration

	(interruption >2 months)	
Chee / 2000	Default, Abandon, or LTF (interruption >2 months)	Defaulter or cases were defined as patients on anti-tuberculosis treatment at the TBCU who failed to turn up for their scheduled appointments despite usual attempts to recall them by phone or mail, as described below, and from whom at least one home visit during the study was recorded
Cherkaoui / 2014	Default, Abandon, or LTF (interruption >2 months)	Treatment default was defined as an interruption in TB treatment for >=2 consecutive months.
Rodrigo / 2012	Default, Abandon, or LTF (interruption >2 months)	Interruption of treatment for any reason for more than 2 months, non-completion of treatment within 9 months when the patient is placed on a 6 month regimen. or drug intake of <80% the prescribed dose.
Kalhori (predicting) / 2009	Treatment success (cure + completion)	For each patient dependent variable was recorded whether or not the patient finished the treatment course and get cured.
Sauer / 2018	Unfavorable outcome (death + failure)	The primary outcome was treatment failure, which we defined as failure of therapy or death.
Baussano / 2008	Unfavorable outcome (death, failure, LTF, NE)	Treatment interruption or default, treatment failure, transferred out cases and those lost to follow-up were grouped as 'unsuccessful outcomes
Costa-Veiga / 2017	Unfavorable outcome (death, failure, LTF, NE)	In line with WHO criteria, SVIG-TB categorized a six possible and mutually exclusive categories for treatment outcomes, grouped in this study into a binary outcome: (i) Successful outcome-if PTB patients were treated before and declared cured, including both negative smear microscopy at the end of treatment at least one previous follow-up test and in case of not providing sputum samples, cure is declared if treatment completed and absent of disease clinical evidences (categories 1 and 2). (ii) Unsuccessful outcome-if treatment of PTB patients resulted in failure (i.e. remaining smear-positive after 5 months of treatment, cat. 3), default (i.e. patients who interrupted their treatment for two consecutive months or more after registration, cat. 4), death (cat. 5) or were transferred-out (cat. 6)
Killian / 2019	Unfavorable outcome (death, failure, LTF, NE)	We label 'Cured' and 'Treatment Complete' to be favorable outcomes and 'Died', 'Treatment failed', and 'Lost to follow-up' to be unfavorable outcomes
Madan / 2018	Unfavorable outcome (death, failure, LTF, NE)	Favourable treatment outcomes included cure and treatment completed. Unfavourable treatment outcomes included death, loss to follow-up, treatment failure, transfer out, or a switch to MDR TB treatment.
Mburu / 2018 - Unfavorable	Unfavorable outcome (death, failure, LTF, NE)	The primary analyses compared favorable versus unfavorable outcomes at end of treatment
Kalhori (fuzzy) / 2009	Other composite outcome	The values of outcomes might be any values from 1 to 5 which means different outcomes. Value 1 means patient completed the treatment course in frame of DOTS, 2 means the patient has been cured, 3 means patients has quitted the course, 4 means patients has failed and finally 5 is a sign of dead as outcome of TB treatment course

Supplemental File 7. Model presentation

Study ID	Final model
Abdelbary / 2017 - Death	2 + 2*(Age 41-65) + 5*(Age>=65) + 2*(Male gender) + 4*(MDR TB) + 3*(HIV) + 3*(Malnutrition) + 2*(Alcoholism) + 2*(Male*diabetes) + 3*(HIV*pulmonary TB) - 1*(diabetes) - 1*(pulmonary TB)
Abdelbary / 2017 - Failure	8*(No or low education) + 40*(MDR) + 10*(AFB smear +2) + 15*(AFB smear +3)
Abdelbary / 2017 - TB-DM / Death	2 + 3*(Male gender) + 3*(Malnutrition) - 1*(BCG vaccinated) - 1*(AFB smear positive)
Abdelbary / 2017 - TB-DM / Default	2 + 2*(Age<40) + 2*(Male gender) + 4*(HIV)
Aljohaney / 2018	Don't report final model, but show the beta coefficients. The coefficients are written as predictor (beta-coefficient): age ³ 65 (2.497), congestive heart failure (1.231), bilateral disease on chest x-ray (1.192)
Bastos / 2016	3*(Hypoxemic respiratory failure) + 2*(Age>=50) + 1*(Bilateral involvement) + 1*(At least one of: HIV, diabetes, liver failure/cirrhosis, congestive heart failure, chronic respiratory disease) + 1*(Hemoglobin<12)
Baussano / 2008	Nomogram with: residency status (residential vs. homeless), sex, geographic origin (non-EU vs. EU), case definition (other than definite vs. definite), treatment setting (inpatient and unknown vs. outpatient), age (continuous)
Belilovsky / 2010	-3.2 + 0.8*(male gender) + 0.7*(unemployment) + 0.4*(retreatment case) + 1.1*(alcohol abuse) + 0.6*(no data about alcohol) + 0.8*(severe TB form) - 0.3*(urban residence) + 0.4*(age 25-50) + 0.8*(pulmonary TB) + 0.5*(prison history)
Chang / 2004	Dont report final model. Just show odds ratios of predictors but don't report intercept term, which are written as predictor (OR) as follows: Current smokers (3.44), ex-smokers (2.48), history of default (10.74), no history of default (0.80),
Chee / 2000	The OR for each predictor is as follow in the format predictor (OR): Non-Chinese race (8.08), Living with family vs. living alone/with friends (0.08), Treatment duration (1.85). Treatment duration is categorical as 6 months, 9 months, and >9 months, but only one OR is presented.
Cherkaoui / 2014	2 points for yes to the following questions: Are you younger than 50 years of age? Do you feel work is interfering with your ability to take TB treatment? Are you taking a retreatment regimen for TB? Do you or doctor think you are having moderate or severe side effects from TB treatment Are you required to get your TB treatment daily? Have you told your friends that you have TB? (1 point for no) Are you a current smoker (1 point for yes) Did you TB symptoms go away within 2 months of starting TB treatment (1 point for yes) Do you know how long your TB treatment is supposed to last (1 point for no) Have you ever smoked cigarettes (-1 point for no)
Costa-Veiga / 2017	Nomogram with: HIV, previous treatment, age class (25-44, 15-24, 45-64, >64), IV drug use, pathologies (other disease comorbidity: yes/no)
Gupta-Wright / 2019	9*(Male sex) + 7*(patient aged 55+) + 6*(currently taking ART) + 7*(unable to walk unaided) + 7*(hemoglobin <80, severe anemia) + 6*(positive on urine TB-LAM)
Horita / 2013	1*Age (years) + 10*(oxygen requirement) - 20*(albumin) + 5*(semi-dependent, ADL) + 10*(total dependent, ADL)
Hussain / 2019	None
Kalhori (fuzzy) / 2009	Learned parameters by training set for each predictor written as predictor (learned parameter): Case type (0.467), treatment category (-0.079), risky sex (-0.945), prison (0.992), sex (0.400), recent TB infection (0.793), diabetes (2.445), low body weight (1.313), TB type (0.950), length (-0.235), previous imprisonment (2.398), age (0.237), area (0.8895), HIV (0.731)
Kalhori (logistic) / 2010	exp(-0.93 - 0.71*(gender) + 0.02*(age) - 0.02*(weight) + 0.5*(nationality) + 0.99*(prison) + 0.16*(case type))
Kalhori (predicting) / 2009	exp(-(1.58 - 0.12*(age) + 0.807*(gender) - 0.039*(nationality) - 0.263*(prison) + 0.15*(area) + 0.021*(weight))
Keane / 1997	Unclear. No constant term provided. Here are the predictor (OR): Mediastinal shift (2.1), average smear score (1.5), extensive lesions (3.6), any previous treatment (2.3), cavities (1.7), weight (0.98)
Killian / 2019	LEAP = Lstm rEal-time Adherence Predictor with 2 input layers, 1) LSTM with 64 hidden units and a dense layer with 48 units for the dense layer and 4 units for the penultimate layer
Koegelenberg / 2015	One point for each parameter: septic shock, HIV with CD4 < 200, creatinine > 140 (male) or >120 (female), P:F O2 ratio < 200, chest radiograph showing miliary pattern/parenchymal infiltrates, absence of TB treatment at admission
Luies / 2017	Written as predictor (OR): 3,5,-Dihydroxybenzoic acid (25.6), 3-(4-Hydroxy-3-methoxyphenyl) propionic acid (1.3)
Madan / 2018	Written as predictor (OR): New TB with 1+ smear grade (5.78), New TB with 2+ smear grade (2.69), New TB with 3+ smear grade (1.69), New TB without smear (1.67), New TB with smear positive, unknown grade (1.00), Previously treated, smear negative TB (1.35), previously treated with scanty smear (4.74), previously treated with 1+ smear grade (1.61), previously treated with 2+ smear grade (1.05), previously treated with 3+ smear grade (7.54), previously treated with no sputum smear (2.46), previously treated with unknown grade (30.37), pulmonary TB (1.83), pulmonary and extrapulmonary TB (5.86), HIV+ on ART with CD4 350-500 (8.09), HIV+ on ART with CD4 200-350 (6.14), HIV+ on ART with CD4 50-200 (16.35), HIV+ on ART with CD4 <50 (38.76), HIV+ not on ART with CD4 350-500 (53.44), HIV+ not on ART with CD4 200-350 (65.98), HIV+ not on ART with CD4 50-200 (6.94), HIV+ not on ART with CD4 <50 (49.20), HIV+ diagnosed after TB with CD4>500 (1.05), HIV+ diagnosed after TB with CD4 350-500 (2.49), HIV+ diagnosed after TB with CD4 200-350 (8.88), HIV+ diagnosed after TB with CD4 50-200 (6.79), HIV+ diagnosed after TB with CD4 <50 (13.99), Female 25-34 (9.41), Female 35-44 (1.75), Female >= 45 (4.49), Male 15-24 (10.63), Male 25-34 (2.74), Male 35-44 (2.9), Male >= 45 (3.96)
Mburu / 2018 - Failure	Present relative scores for each covariate included with scores of 100, 72.61, 69.19, 55.39, 49.87, 48.74, 48.18, 46.51, 39.69, and 37.69 for hba1c, regimen, age, weight, random blood glucose, BMI, BUN, HIV positive result, ever smoker, creatinine, respectively
Mburu / 2018 - Unfavorable	Present relative scores for each covariate included, not sure if this was how it should be used. Relative scores are 100, 79.38, 70.09, 63.93, 62.47, 62.63, 61.63, 55.62, 39.21, 34.48 for hba1c, regimen, creatinine, BMI, BUN, weight, age, random blood glucose, HIV positive result, male gender, respectively
Nguyen (general pop) / 2018	6*[Age 45-64] + 12*[Age>65] + 2*[US born] + 2*[Homeless] + 4*[Resident of LTCF] + 8*[Chronic kidney failure] + 10*[Meningeal TB] + 4*[Miliary TB] + 6*[TB-CXR] + 6*[HIV positive] + 6*[HIV unknown]
Nguyen (TB-DM) / 2019	16*[Age >= 65] + 5*[US-born] + 11*[Homeless] + 20*[IDU] + 20*[Chronic kidney failure] + 20*[TB meningitis] + 13*[Miliary TB] + 6*[AFB positive smear] + 24*[Positive HIV]
Nguyen (TB-HIV) / 2018	Prognostic score: 5*[Age >= 65] + 12*[Resident of LTCF] + 9*[Meningeal TB] + 6*[abnormal CXR] + 9*[diagnosis confirmed with positive culture or NAA] + 10*[culture not converted or unknown]

	Model: -6.994499 + 1.069024*[Age >= 65] + 2.541147*[Resident of LTCF] + 1.998852*[Meningeal TB] + 1.37995*[abnormal CXR] + 1.899108*[diagnosis confirmed with positive culture or NAA] + 2.186305*[culture not converted or unknown]
Pefura-Yone / 2017	1/(1 + exp(-1.3120 + 0.0474*[age] - 0.1866*[adjusted BMI] + 1.1637*[PTB-] + 0.5418*[ETB] + 1.3820*[HIV]
Podlekareva / 2013	1*[DST performed] + 2*[Initial treatment with RHZ] + 2*[cART started before or up to 1 month after TB diagnosis]
Rodrigo / 2012	1*[Immigrant] + 1*[Living alone] + 1*[Living in an institution] + 2*[Previous TB treatment] + 2*[Linguistic barriers] + 4*[IV drug use] + 1*[Unknown IV drug use]
Sauer / 2018	Negatively correlated: drug sensitivity (sensitive), employment status (employed), microscopy: 1 to 99 acid-resistant bacteria in 100 fields of view when stained by Ziehl-Nielsen, dissemination (diffuse pulmonary nodules detected)
Thompson / 2017	Heatmap of differentially expressed genes
Valade / 2012	Sum of three parameters: military tuberculosis (yes: +1, no: 0), required mechanical ventilation on ICU admission (yes: +1, no: 0), and required vasopressor infusion (yes: +1, no: 0).
Wang / 2019	Unknown
Wejse / 2008	1 point for each variable: cough, hemoptysis, dyspnea, chest pain, night sweating, anemia conjunctivae, tachycardia, positive funding at lung auscultation, temperature >37, BMI <18, BMI<16, MUAC<220, MUAC<200
Zhang / 2019	2*[Anemia (HGB < 90g/L)]+ 2*[Tuberculous meningitis] + 5*[Severe pneumonia] + 2*[Hypoalbuminemia] + 7* [Unexplained infections or space-occupying lesions] + 5* [Malignancies]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Supplemental File 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract and p. 7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9; Supplemental Files 4 and 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9; Supplemental File 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-13; Table 3, 4, 5

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14; Figures 3 and 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-14; Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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A systematic review of prediction models for pulmonary tuberculosis treatment outcomes in adults

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ABSTRACT

Objective: To systematically review and critically evaluate prediction models developed to predict tuberculosis (TB) treatment outcomes among adults with pulmonary tuberculosis.

Design: Systematic review

Data sources: PubMed, Embase, Web of Science, and Google Scholar were searched for studies published January 1, 1995 - January 9, 2020.

Study selection and data extraction: Studies that developed a model to predict pulmonary TB treatment outcomes were included. Study screening, data extraction, and quality assessment were conducted independently by two reviewers. Study quality was evaluated using the Prediction model Risk Of Bias Assessment Tool (PROBAST). Data were synthesized with narrative review and in tables and figures.

Results: 14,739 articles were identified, 536 underwent full-text review, and 33 studies presenting 37 prediction models were included. Model outcomes included death (n=16, 43%), treatment failure (n=6, 16%), default (n=6, 16%) or a composite outcome (n=9, 25%). Most models (n=29, 78%) measured discrimination (median c-statistic=0.75; interquartile range: 0.68-0.84), and 17 (46%) reported calibration, often the Hosmer-Lemeshow test (n=13). Nineteen (51%) models were internally validated, and six (16%) were externally validated. Eighteen studies (54%) mentioned missing data, and of those, half (n=9) used complete case analysis. The most common predictors included age, sex, extrapulmonary TB, body mass index (BMI), chest x-ray results, previous TB, and HIV. Risk of bias varied across studies, but all studies had high risk of bias in their analysis.

Conclusions: TB outcome prediction models are heterogeneous with disparate outcome definitions, predictors, and methodology. We do not recommend applying any in clinical settings

without external validation, and encourage future researchers adhere to guidelines for developing and reporting of prediction models.

Registration: The study was registered on the international prospective register of systematic reviews PROSPERO (CRD42020155782)

ARTICLE SUMMARY:

Strengths and limitations

- Prediction models for tuberculosis treatment outcomes have the potential to inform interventions or treatment management protocols to promote cure among tuberculosis patients at the greatest risk of unsuccessful treatment outcomes, but the methods and clinical utility of existing models had not been formally evaluated.
- This was the first systematic review of prediction models for tuberculosis treatment outcomes.
- The review used a comprehensive search strategy, conducted thorough bias assessment with the Prediction Model Risk of Bias Assessment Tool (PROBAST) tool, and offers recommendations for future model development and validation studies for predicting tuberculosis treatment outcomes.
- Evidence synthesis and quality assessment were limited by incomplete reporting in primary studies, as well as heterogeneities in study populations, such as multi-drug resistance and age.
- External validation studies or studies written in languages other than English, Spanish, Portuguese, or French were excluded.

BACKGROUND

Tuberculosis (TB) is one of the top ten causes of death worldwide and a leading cause of death from an infectious disease. In 2018, 10 million people developed TB and 1.45 million people died from it globally, despite widespread availability of curative treatment.[1] Global treatment success was 85% for all new and relapse TB patients in 2018. For HIV-associated TB, it was 75%. These proportions are lower than the End TB Strategy target of ≥90% treatment success.[2]

Heeding early recognition that *Mycobacterium tuberculosis* develops resistance rapidly in response to single-drug therapy, TB has been treated with combination regimens for more than 50 years.[3] Aside from weight-based dosing, the World Health Organization (WHO) and other TB guidelines authorities recommend a standardized approach for treatment of almost all TB patients.[4–6] The current recommendation for drug-susceptible TB includes 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin.

Due to the long duration of TB treatment, it would be beneficial to understand early predictors of unsuccessful TB treatment outcomes to identify patients needing tailored treatment approaches, such as directly observed therapy (DOT) or extended treatment course. Research suggests that individual characteristics, such as HIV, age, undernutrition, diabetes, TB disease severity, extrapulmonary TB, history of TB, adherence, alcohol use, and adverse drug reactions, are associated with unsuccessful TB treatment outcomes, but results vary by setting and patient population.[7–10]

Prediction models, defined as any combination or equation of two or more predictors to estimate an individualized probability of a specific endpoint within a defined period of time, are

increasingly common in TB research.[11] The large number of recent prediction models for TB outcomes highlights the common desire to identify TB patients at greatest risk of an unsuccessful treatment outcome. However, to date, there has not been a formal synthesis or quality assessment of existing prediction models for TB treatment outcomes, which is essential to determine whether they should be used to inform care and may help guide development of future models. Thus, we conducted a systematic review to identify, describe, compare, and synthesize clinical prediction models designed to predict TB treatment outcomes among persons with pulmonary TB.

METHODS AND ANALYSIS

All steps of the systematic review were carried out according to guidelines set by Cochrane Prognosis Methods Group (PMG) and PROGnosis RESearch Strategy (PROGRESS).[12–14] Reporting adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (**Supplemental File 1).** This study was pre-registered on Open Science Framework (OSF) (https://osf.io/rz3wp) and the international prospective register of systematic reviews (PROSPERO; CRD42020155782).

Study eligibility criteria

The review question was defined according to the PICOTS (Population, Intervention, Comaparator, Outcomes, Timing, Setting) framework (**Supplemental File 2)**. In brief, the goal was to identify prognostic models developed to predict TB treatment outcomes among pulmonary TB cases. The main endpoint was unsuccessful TB treatment outcome, defined by the WHO as the combination of death, treatment failure, loss to follow-up, and/or not evaluated, as compared to successful TB treatment outcome, defined as the combination of cure or treatment completion (**Table 1**) [15]. Loss to follow-up was sometimes referred to as default or treatment abandonment.

Inclusion criteria were: 1) prognostic model studies with or without external validation[16]; 2) study population included adult, drug-susceptible, pulmonary, TB cases; 3) written in English, Spanish, Portuguese, and French; 4) published between January 1, 1995 and January 9, 2020; 5) treatment outcome was one of the following: cure, treatment completion, death, treatment failure, loss to follow-up, or not evaluated.

Exclusion criteria were: 1) predictive value of more than one variable was evaluated but not combined in a prediction model; 2) study population was only multi-drug resistant (MDR) TB cases, only extrapulmonary TB cases, or only children (< 18 years-old); 3) outcome was

evaluated during treatment such as: two-month smear/culture conversion, acquired resistance, adverse events, quality of life; 4) long-term outcomes, such as relapse, recurrence, or post-treatment mortality.

The decision to include only articles in English, Spanish, Portuguese, and French was based on study team capabilities. The dates reflect modern TB treatment practice; first-line TB treatment regimens were not available until the early 1990s.[17,18] Articles that included a combination of drug-susceptible and drug-resistant cases, or a combination of children and adults were included.

Search strategy and selection criteria

The following electronic databases were searched on January 9, 2020: PubMed, Embase, Web of Science, and the first 200 references from Google Scholar. This combination of databases achieved best overall recall for systematic reviews in a recent study.[19] Clinicaltrials.gov and retractiondatabase.org were also searched for unpublished research. Reference lists of retrieved articles were checked to identify eligible studies.

Search terms relating to the "prediction model" component of the search were adapted from a PubMed search strategy that captured prediction model studies with sensitivity of 98%.[20] That component was combined with terms relating to TB treatment outcomes. The search strategy, developed in PubMed, was adapted for all other databases with assistance from a reference librarian (**Supplemental File 3**).

Article selection was conducted in three stages. The first stage was automatic de-duplication and title screening, carried out using *revtools* in RStudio (version 1.2).[21] Remaining articles were imported into Covidence, a web-based software platform that streamlines systematic reviews, where abstracts (Stage 2) and full text (Stage 3) were manually screened.[22] Stages 2 and 3 were carried out by two independent reviewers (LSP and FMR).

Discordance was discussed between reviewers, and if consensus was not reached, a third party arbitrated (one of TRS, VCR, PFR, DL). In stage 3, reasons for exclusion were documented according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Data analysis

Data from selected studies were recorded using a database designed in REDCap (Vanderbilt University).[23,24] Data extraction was informed by the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) and the Prediction Model Risk of Bias Assessment Tool (PROBAST).[16,25,26] CHARMS checklist and PROBAST are in **Supplemental Files 4 and 5,** respectively**.**

Quality assessment and applicability of included studies was assessed using PROBAST by dual independent review.[16,26] PROBAST was specifically designed to assess risk of bias of prediction model studies, which included identifying deficiencies in study design, conduct, or analysis that led to inaccurate estimates of predictive performance. PROBAST has 4 domains: participants, predictors, outcome, and analysis with 20 total signaling questions. Each question was answered on the scale: yes, probably yes, no, probably no, no information. Domains were scored as low, high, and unclear risk of bias. PROBAST also guides assessment of applicability of participants, predictors, and outcomes from each included study to the review question.

Results were summarized narratively and in tables and figures. Meta-analysis was not possible due to lack of external validation and use of disparate predictors, outcome definitions, and modeling methods. For studies that presented multiple models with the same set of predictors and outcomes, but different methods, the best-performing method was included in data synthesis. For studies presenting multiple models with different sets of predictors (i.e. baseline data vs. longitudinal data), the model developed using only baseline data was included. If studies developed multiple models for different outcomes or with different populations, all models were

included. To further evaluate the impact of study population heterogeneities on prediction model performance, we additionally examined results after stratifying studies by inclusion/exclusion of MDR and younger age groups.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, or reporting of the research, as it was not feasible or appropriate for this systematic review. The study protocol is publicly available at https://osf.io/rz3wp.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study selection

The search identified 14,739 unique studies. After excluding irrelevant titles, 6,426 abstracts were screened, 536 articles underwent full-text review, and 33 model development studies presenting 37 prediction models were included (**Figure 1**).

Study characteristics

Of the 33 studies, most were retrospective cohorts (n=25, 76%), three (9%) were prospective cohort studies, two (6%) were case-control studies, and three (9%) were nested case-control studies. Data from nearly half of studies (n=16, 48%) were collected from surveillance systems; eleven (33%) studies used a data collection form developed specifically for their study and six studies (18%) extracted data from medical records. Median sample size was 803 (interquartile range (IQR): 291-4167). Full details on included studies are in **Table 2**.

Thirteen studies (41%) took place in Asia, eight (25%) in Africa, six (19%) in Europe, four (12%) in North America, and one (3%) included sites in Europe and Argentina. Fewer than half (n=14, 45%) took place in high-burden TB settings.[1] One study did not report study location. (**Tables 2 and 3**).

Reporting of population characteristics varied by study (**Table 4**). Among 18 studies that reported a measure of central tendency (mean or median) for age, the median of those measures was 41 years (IQR: 37-49). Of 17 studies that reported the minimum age of participants, seven (41%) had a minimum age of 15, one (6%) had a minimum age of 16, one (6%) had a minimum age of 17, and the remainder had minimum age of 18. Eighteen studies reported including persons living with HIV (PLWH); 5 of these included only TB/HIV patients. Thirteen studies reported including persons with diabetes; one of which included only TB/DM. Eight studies

reported including some participants with MDR, though prevalence of MDR was low in all studies. Ten studies included only hospitalized patients, and in 14 studies, all participants were on directly observed therapy (DOT).

Model characteristics

Model outcomes included death (n=16, 43%), treatment failure (n=6, 16%), default (n=6, 16%) or a composite outcome (n=8, 23%) (**Tables 2 and 5**). The complete outcome definition for all included studies is in **Supplemental File 6**.

Most models were developed using clinical/epidemiologic predictors (n=34, 92%), two (6%) used multiple biomarkers, and one (3%) used adherence data. The most common candidate predictors were age, sex, extrapulmonary TB, smear result, BMI, x-ray findings, and previous TB. The most common predictors retained in the final models were age, sex, extrapulmonary TB, BMI, chest x-ray results, previous TB, and HIV (**Figure 2**).

Only three models (8%) used survival analysis; most models used logistic regression (n=29, 78%) and five (14%) used a machine learning approach. More than half of studies (n=19, 51%) considered variables for inclusion in the multivariable model based on unadjusted associations with the outcome. Model building methods varied widely between models (**Table 5).**

Only 19 (51%) models were internally validated, including ten (53%) split-sample validation, five (26%) bootstrap resampling, and four (21%) cross-validation. Six (16%) models were externally validated. Many models (n=30, 81%) reported discrimination with c-statistic (concordance statistic) or area under the receiver operating characteristic (AUROC), which are equivalent and quantify the ability of the model to distinguish between patients who do and do not develop an outcome. Only 17 (46%) reported calibration, the agreement between observed

and predicted outcomes. Most studies assessed calibration with Hosmer-Lemeshow tests (n=13, 77%); only two studies provided a calibration plot, the preferred reporting method for prediction model studies,[16,27,28] and one reported the calibration slope **(Table 2)**. Models were presented a variety of ways, the most common of which was a weighted risk score (n=16, 43%); details on model presentation are in **Supplemental File 7.**

Quality assessment

Grading of PROBAST signaling questions is summarized in **Figure 3**, and the summary risk of bias for the participants, predictors, outcome, and analysis domains and assessment of applicability are shown in **Figure 4**. More than half of the studies were at low risk of bias for the population and outcomes domains, but all studies were at high risk of bias in the analysis domain.

Common sources of population bias included use of non-nested case-control design[29,30], nested case-control design without proper estimation of baseline risk,[31,32] or inappropriate inclusion/exclusion criteria.[33,34] Sources of predictor bias included lack of standardized assessment of key predictors (i.e. HIV, diabetes, chest x-ray scoring)[9,29,31,34–36] or timing of data collection/availability that would limit the intended use of the model.[9,29,37] Within the outcomes domain, sources of bias included subjective[35] or non-standard[32,38] outcome measures and inconsistent outcome ascertainment.[29]

Bias in the analysis domain was widespread. More than half of the models included were likely overfit due to low events per variable (EPV) ratios (**Table 5**). Only 6 studies handled continuous and categorical variables appropriately (i.e., didn't dichotomize continuous variables, considered non-linearity of continuous variables).[31,39–43] Most studies used complete case-analysis or did not mention missing data; no study used multiple imputation in their main

analysis. One study with low amounts of missing data (<5%) conducted sensitivity analysis with multiple imputation.[44] A different study excluded only two people out of a total sample size of 1007 with missing data, which would have little impact on model performance.[45] Fewer than half (n=14) of studies avoided univariable predictor selection, and only three studies used survival analysis, appropriately accounting for censoring.[36,45,46] Performance measures were appropriately reported (i.e. calibration assessed with plot and discrimination assessed with c-statistic/AUROC) in three studies.[41,44,47] Only two studies estimated optimism (degree to which data are overfit) or accounted for potential overfitting with penalization of model parameters.[35,41] Ten studies appropriately presented their model with model coefficients or nomograms, which prevents bias from rounding or transforming model coefficients to generate a risk score.[30,33,35,37,38,45,47–55]

About half of the models (n=19, 51%) were applicable to the review question in all domains. However, unclear reporting of target population or predictor and outcome definitions limited assessment of applicability for several studies.[38,49,50,56,57] Additionally, studies that included only hospitalized patients with specific laboratory parameters may not be routinely available in the clinical setting.[39,40,42] Results from analyses stratified by inclusion of patients with MDR and minimum age <18 are presented in **Supplemental File 8.**

DISCUSSION

In this comprehensive, systematic review of prediction models for pulmonary TB treatment outcomes, we identified 33 model development studies presenting 37 prediction models. Although diagnostic prediction models for prevalent TB were previously systematically reviewed, this is the first review of TB treatment outcomes.[58] The included prediction models were developed for predicting death, treatment failure, default, or a composite unfavorable outcome during TB treatment. Most models reported good performance (c-statistic/AUROC>0.7), but all were evaluated to have high risk of bias due to poor reporting, exclusion of missing data, weak methodologic approaches, lack of calibration assessment, and limited validation. Population heterogeneities, such as differences in inclusion/exclusion of individuals with MDR and younger ages, and varying predictor and outcome definitions limited comparisons between models.

More than half of the models included in the review were developed in low burden TB settings, and none were developed specifically in South America. Prediction of TB treatment outcome is especially important in high burden TB settings, where resources may be limited, and risk assessment can guide resource allocation toward patients who need the most involved care.

Common risk factors included in the models were consistent with well-established risk factors for poor TB treatment outcomes, including age, sex, HIV, extrapulmonary TB, baseline smear results, and previous TB treatment. Among studies that included PLWH, only three considered factors related to management/severity of HIV, such as receipt of antiretroviral therapy, CD4 cell count, or viral load, which likely impacted TB treatment outcomes.[40,46,51] Laboratory values or metabolic biomarkers, such as hemoglobin, hemoglobin A1c or random blood glucose, may also be associated with treatment outcome and worth considering as candidate predictors. There is increasing evidence that diabetes impacts TB treatment outcomes,

but caution is warranted about how to best define diabetes in the context of a prediction model to ensure consistency and reproducibility across studies.[59] Behavioral characteristics, such as tobacco use, alcohol use, and drug use were rarely included in final prediction models and are difficult to collect objectively, suggesting their role in prediction models for TB treatment outcomes may be limited.

Additionally, several studies excluded participants with HIV, diabetes, extrapulmonary TB, or MDR TB, because these factors negatively influence treatment outcomes. However, careful consideration should be given to inclusion/exclusion criteria in prediction model studies, given that information should be available at the time of intended model use, which may not always hold for these aforementioned factors.[60] This is especially questionable for MDR, given that conventional drug-susceptibility testing results are not available for several weeks after TB diagnosis; though more recent advances in rapid molecular methods such as GeneXpert or line-probe assays offer rapid screening.[61]

TB researchers should thoughtfully consider how to appropriately handle complexities of censoring and competing risks in TB outcomes research. Only three studies in this review used survival analysis, despite the long duration of TB treatment outcome assessment and relatively high rates of losses to follow-up across studies, and no studies considered competing risks, such as death due to other causes.[62] Losses to follow-up were frequently excluded, which can lead to selection bias.

Though all included studies were at high risk of bias in the analysis domain, we want to highlight two studies with some exemplary characteristics.[41,44] Pefura-Yone et al.[41] provide clear explanations of study design, inclusion/exclusion criteria, and data collection procedures; TB diagnosis and treatment outcome definitions were standard.[63] Non-linearity of continuous

variables was considered with restricted cubic splines, and no continuous variables were categorized or dichotomized; the final model includes four predictors that are easy to collect and routinely assessed in most TB control programs, especially those in high burden settings. The performance of the model was internally validated with bootstrap validation, and the discrimination (c-statistic=0.808) was corrected for optimism. Model calibration was presented graphically with calibration plots. The final model was presented as a nomogram with instructions for use, which facilitates use in external validation studies. Gupta-Wright and colleagues developed and externally validated a clinical risk score to predict mortality in high-burden, low-resource settings.[43] They used clinical trial data with very low amounts of missing data for model development, and externally validated the clinical risk score with data collected independently from two other studies (a clinical trial and a prospective cohort). Given high amounts (42%) of missing data in the validation cohort, they conducted sensitivity analysis using multiple imputation for missing data; the c-statistic differed slightly between complete case and multiple-imputation analyses in the validation cohort (0.68 vs. 0.64). Candidate predictors were based on *a priori* clinical knowledge, previous literature, and required variables were objective, reproducible, and available in low-resource settings, consistent with recommended approaches.[26,60,64] Additionally, they reported model performance with the c-statistics and calibration plots for development and validation cohorts, and reported results according to TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) guidance.[27,28] Regardless, each of these models requires external validation prior to use in clinical practice.

There are several limitations of this study. Data extraction was subject to reporting in the primary study, which varied widely and was often incomplete, leading to challenges evaluating

differences in model performance due to heterogeneities in study populations. Additionally, though most studies reported discrimination, few presented a calibration curve, arguably the most important measure of model performance, further inhibiting assessment and comparison of model performance.[28,65] We did not include external validation studies, which is an essential step for translation to clinical practice. However, several studies in the review did not include the full model equation, which impedes their ability to be externally validated. Upon searching for studies that externally validated prediction models in this review, we found three studies[66–68] that evaluated the same model (TBscore).[36] Briefly, these studies evaluated the ability of TBscore to monitor treatment response in a new setting[66], refined the instrument (TBccoreII) using exploratory factor analysis[67], and then evaluated TBscoreII for use in patients with TB/HIV.[68] To our knowledge, no other studies included in the review were externally validated by other sources. Finally, we excluded 10 studies that were not available in English, Spanish, Portuguese, or French; all abstracts were available in English, and none reported model performance metrics, so they likely would have been excluded for different reasons regardless.

The findings of this review not only serve as a comprehensive overview of existing TB outcome prediction models but can act as a resource for future model development and validation of prediction models for TB treatment outcomes. We encourage researchers to focus future TB outcome prediction models on easily collected and readily available predictors that are widely generalizable. We highlight age, sex, extrapulmonary TB, BMI, chest x-ray results, previous TB, and HIV as common predictors of TB treatment outcomes. Additionally, when building a new prediction model, it is recommended to first prune the set of considered predictors based on expert opinion and previous literature, rather than univariable analysis or variable selection processes[26,60,64] Future model development or validation studies should

adhere to the TRIPOD guidelines, which provide a 22-item checklist and aims to improve the reporting of prediction model development studies.[27,28] We also encourage researchers consider PROBAST criteria to limit bias in design and conduct of prognostic studies.

Prediction models are an important tool in TB management. They can lay the foundation for future impact studies by providing risk estimation to target novel treatment approaches, resource allocation, or intensive case management towards patients who are least likely to achieve cure and most likely to benefit from intervention, especially in high-burden and low-resources areas. Use of prediction models can potentially help guide tuberculosis treatment practices to achieve the End TB Strategy goal of >90% treatment success, but methodologic rigor and detailed reporting must be improved. Though our findings suggest that none of the existing models are ready for clinical application without extensive external validation, we hope they direct future researchers to make use of guidelines for development and reporting of prediction models.

FOOTNOTES

Ethics approval: Not required.

Transparency statement: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted, and any discrepancies from the study as planned were explained.

Contributorship: LSP conceptualized the research question, designed the protocol, and drafted the manuscript. LSP and FMR screened studies. FMR, PFR, DL, VCR and TRS provided feedback on the research design, original protocol, and revised successive drafts of the manuscript. All authors approved the final version of the manuscript.

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Competing interests: None declared.

Data sharing: The study protocol is available online at https://osf.io/rz3wp. Most included studies are publicly available. Additional data and code are available upon request.

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Table 1. World Health Organization definition of treatment outcomes for TB patients

Outcome	Definition
Treatment completion	Completion of treatment without evidence of failure, but without documentation of a negative sputum smear or culture in the last month of treatment and/or on at least one previous occasion, either because tests were not done or because results are unavailable
Cure	Bacteriologic confirmation of a negative smear or culture at the end of TB treatment and on at least one previous occasion
Treatment success	Composite of cured and treatment completed
Treatment failure	Sputum smear or culture is positive at month 5 or later during treatment
Death	TB patient who dies for any reason before starting or during the course of treatment
Loss to follow-up	TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated (transfer out)	TB patient for whom no treatment outcome was assigned, which includes cases who "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart of inclusion process

[See Figure 1]

Table 2. Study characteristics

First author, year	Population	Study years	Study design	Location	Validation	No. with outcome / sample size (%)	Predictors in final model	Performance measures	Model presentation	Risk of bias (population, predictor, outcome, analysis)
Death										
Abdelbary[9] / 2017	TB cases	2006 - 2013	Retrospective cohort	Mexico	Internal (split-sample)	*Development:* 261/4216 (6%) *Validation:* 260/4215 (6%)	Age (<41, 41-65, ≥65), sex, MDR, HIV, malnutrition, alcoholism, diabetes, pulmonary TB	c-statistic = 0.70 Sensitivity = 60% Specificity = 71%	Risk score	Low, High, Low, High
Abdelbary[9] / 2017 (TB-DM)	TB-DM cases	2006 - 2013	Retrospective cohort	Mexico	None	88/2121 (4%)	Sex, malnutrition, BCG vaccinated, AFB smear (positive vs. negative)	c-statistic = 0.68	Risk score	Unclear, High, Low, High
Aljohaney[69] / 2018	Hospitalized TB patients	Dec 2011 – Dec 2016	Retrospective cohort	Saudi Arabia	None	41/291 (14%)	Clinical model: Age, congestive heart failure Clinical + lab model:* Age > 65, congestive heart failure, bilateral disease on chest xray	Clinical model: Accuracy = 86% Clinical & lab model:* Accuracy = 90%	Odds ratios	Unclear, Unclear, Unclear, High
Bastos[70] / 2016	Inpatient and outpatient TB cases on DOT	2007 - 2013	Retrospective cohort	Portugal	External (setting)	*Development:* 121/681 (18%) *Validation:* 24/103 (23%)	Hypoxemic respiratory failure, age (≥50 vs. <50), bilateral involvement, comorbidities (at least one of HIV, diabetes, liver at least one of: HIV, diabetes, liver failure/cirrhosis, congestive heart failure, chronic respiratory disease), hemoglobin (<12 vs. ≥12)	AUROC = 0.84 (95% CI: 0.76-0.93) Sensitivity = 41.8% Specificity = 92.1%	Risk score	Low, Unclear, Low, High
Gupta-Wright[71] / 2019	Hospitalized TB-HIV patients	Oct 2015 – Sept 2017	Retrospective cohort	Malawi and South Africa	External (setting)	*Development:* 94/315 (30%) *Validation:* 147/644 (23%)	Sex, age 55+, currently taking ART, ability to walk unaided, severe anemia, positive TB-LAM	c-statistic = 0.68 (95% CI: 0.61-0.74) HL test: p=0.13 Calibration plot	Risk score	Low, Low, Low, High
Horita[72] / 2013	Hospitalized TB patients	Jan 2008 – Jul 2011	Retrospective cohort	Japan	External (setting)	*Development:* 36/179 (20%) *Validation:* 48/244 (20%)	Age, oxygen requirement, albumin, activities of daily living	AUROC = 0.893 Sensitivity = 0.92 Specificity = 0.73	Risk score	Low, Low, Low, High
Koegelenberg[40] / 2015	Hospitalized TB patients	Jan 2012 – May 2013	Retrospective cohort	South Africa	None	38/83 (46%)	Septic shock, HIV with CD4 < 200, creatinine > 140 (male) or >120 (female), P:F O2 ratio < 200, chest radiograph showing miliary pattern/parenchymal infiltrates, absence of TB treatment at admission	Mean score in survivors: 2.27 (SD=1.47) Mean score in non-survivors: 3.58 (SD=1.08)	Risk score	Low, Low, Low, High
Nguyen[53] (general pop) / 2018	TB cases	Jan 2010 – Dec 2016	Retrospective cohort	Texas	Internal (split-sample)	*Development:* 253/3378 (7%) *Validation:* 270/3377 (8%)	Age group (15-44, 44-64, >64), US born, homeless, resident of long term care facility, chronic kidney failure, meningeal TB, miliary TB, HIV positive, HIV unknown	AUROC = 0.80 (95% CI: 0.77-0.82) HL test:X^2=6.3, p=0.613	Risk score	Low, Unclear, Unclear, High
Nguyen[37] (TB-DM) / 2019	TB-DM patients	Jan 2010 – Dec 2016	Retrospective cohort	Texas	Internal (bootstrap)	112/1227 (9%)	Age ≥65, US-born, homeless, IDU, chronic kidney failure, TB meningitis, Miliary TB, AFB positive smear, HIV positive	AUROC = 0.82 (95% CI: 0.78-0.87) HL test: X^2=4.54, p=0.81 Brier score=0.07	Risk score	Unclear, Unclear, Unclear, High
Nguyen[52] (TB-HIV) / 2018	TB-HIV patients	Jan 2010 – Dec 2016	Retrospective cohort	Texas	Internal (bootstrap)	57/450 (13%)	Age ≥ 45, resident of LTCF, meningeal TB, abnormal CXR, diagnosis confirmed by positive culture of NAA, culture not converted or unknown	AUROC = 0.79 (95% CI 0.70-0.87) HL test: X^2=4.25, p=0.51 Brier score: 0.09	Risk score	Low, High, Unclear, High
Pefura-Yone[54] / 2017	TB patients	Jan 2012 – Dec 2013	Retrospective cohort	Cameroon	Internal (bootstrap)	213/2250 (9%)	Age, adjusted BMI, clinical form (PTB+, PTB-, EPTB), HIV	C-statistic: 0.808 HL test: X^2=6.44, p=0.60 Sensitivity = 80.7% Specificity = 68.2% Calibration plot	Model coefficients	Low, Low, Low, High
Podlekareva[73] / 2013	TB/HIV patients	Jan 2004 – Dec 2006	Retrospective cohort	52 cities in Europe and Argentina	None	995†	DST performed, treatment with RHZ, and cART at/near TB diagnosis	Crude RH = 0.62 (95% CI: 0.64-0.84)	Risk score	Low, Unclear, Low, High
Valade[42] / 2012	Hospitalized TB patients	Mar 2000 – Jul 2009	Retrospective cohort	France	Internal (bootstrap)	20/53 (38%)	Miliary TB, catecholamine infusion, mechanical ventilation on admission	AUROC = 0.92 (95% CI: 0.85-0.98) Brier score = 0.13	Risk score	Unclear, Low,

								Optimism = 0.03 Accuracy = 85% Sensitivity - 75% Specificity = 91%		Low, High
Wang[74] / 2019	HIV-negative, culture-confirmed, pulmonary TB cases	Jan 2014 – Dec 2016	Prospective cohort	China	External (setting)	*Development:* 36/287 (13%) *Validation:* 15/104 (14%)	Age, cavitary lesion, pleural effusion, drug resistance, disseminated, albumin, c-reactive protein, white blood cell count, IL-6, MIF	AUROC = 0.85 ± 0.028	Odds ratios	Low, Low, Low, High
Wejse[75] / 2008	Pulmonary TB patients on DOT	1996 - 2001	Retrospective cohort	Guinea Bissau	None	100/698 (14%)	Cough, hemoptysis, dyspnea, chest pain, night sweating, anemia conjunctivae, tachycardia, positive funding at lung auscultation, temperature >37, BMI <18, BMI<16, MUAC<220, MUAC<200	AUROC = 0.65 (95% CI: 0.6-0.7) Sensitivity = 0.45 Specificity = 0.75	Risk score	Low, High, Low, High
Zhang[45] / 2019	TB/HIV patients at end stage of AIDS	Aug 2009 – Jan 2018	Retrospective cohort	China	Internal (split-sample)	*Development:* 157/807 (19%) *Validation:* 40/200 (20%)	Anemia, TB meningitis, severe pneumonia, hypoalbuminemia, unexplained infection or space-occupying lesions, malignancy	AUROC = 0.867 (95% CI: 0.832-0.902) Sensitivity = 79.6% Specificity = 82.9%	Risk score	Low, Low, Low, High
Treatment failure										
Abdelbary[9] / 2017	TB cases	2006 - 2013	Retrospective cohort	Mexico	Internal (split-sample)	*Development:* 2109† *Validation:* 6322†	Education (no or low vs. higher than primary school), MDR, AFB smear (>+2, +1, negative)	c-statistic = 0.65 Sensitivity = 52% Specificity = 66%	Risk score	Low, High, Low, High
Kalhori[49] (logistic) / 2010	TB cases at DOTS registration	2005	Retrospective cohort	Iran	Internal (split-sample)	*Development:* 828/4836 (17%) *Validation:* 2418†	Gender, age, weight nationality, prison, case type	AUROC = 0.70 Accuracy = 81.64% HL test: X^2=11.935, df=8, p=0.154	Model coefficients	Unclear, Unclear, Unclear, High
Keane[30] / 1997	Smear-positive TB patients on standard first-line regimen with DOT	1990 - 1995	Non-nested case control	Vietnam	None	130/803 (16%)	3 month model: Extensive lesions, mediastinal shift, average smear score 3rd month, weight, progressive x-ray, any previous treatment Baseline model: Mediastinal shift, average smear score, extensive lesions, any previous treatment, cavities, weight	3 month: Sensitivity = 80% Specificity = 80% Baseline: Sensitivity = 70% Specificity = 80%	Model coefficients	High, Unclear, Unclear, High
Luies[33] / 2017	Smear-positive pulmonary TB cases on DOT	May 1999 – Jul 2002	Nested case-control	South Africa	Internal (cross-validation)	10/31 (32%)	3,5,-Dihydroxybenzoic acid, (3-(4-Hydroxy-3-methoxyphenyl) propionic acid	AUROC = 0.89 (95% CI: 0.7-1.00)	Model coefficients	High, Unclear, Unclear, High
Mburu[76] / 2018	Smear-positive TB patients	Feb 2014 – Aug 2015	Prospective cohort	Kenya	Internal (cross-validation)	13/321 (4%)	HbA1c, regimen (retreatment), age, weight, random blood glucose, BMI, BUN, HIV positive result, ever smoker, creatinine	AUROC = 0.56 ± 0.07	Relative score	Low, Low, Low, High
Default										
Thompson[77] / 2017	HIV uninfected adults with newly diagnosed pulmonary TB	Apr 2010 – Apr 2013	Retrospective cohort	South Africa	Internal (cross-validation) and external (setting)	6/99 (6%)	18 splice junctions and 13 genes	AUROC (internal) = 0.87 AUROC (external) = 0.63	Heatmap of differentially expressed genes	Low, Low, Low, High
Abdelbary[9] / 2017 (TB-DM)	TB cases	2006 - 2013	Retrospective cohort	Mexico	None	93/2121 (4%)	Age (<40 vs. ≥40), sex, HIV	c-statistic= 0.62	Risk score	Unclear, High, Unclear, High
Belilovsky[35] / 2010	Hospitalized TB patients	1993 - 2002	Retrospective cohort	Russia	External (geographical)	*Development:* 1326/3904 (34%) *Validation:* 4662/12803 (36%)	Sex, unemployment, retreatment case, alcohol abuse (yes, no, no data), severe TB form, residence (urban vs. rural), age (25-50 vs. other), pulmonary TB (vs extrapulmonary), prison history	Belgrood: AUROC = 0.75 Orel: AUROC = 0.75 Pskov: AUROC = 0.78 Yaroslavi: AUROC = 0.75 Calibration table	Model coefficients	Unclear, High, High, High
Chang[31] / 2004	All tuberculosis patients	Jan 1999 – Mar 1999	Nested case-control	China	None	102/408 (25%)	Baseline:* Ever smoker (current, former, never), retreatment (history of default, no history of default, not) Longitudinal: Smoking status (current, former, never), retreatment (with history of default, without history of default, never), unsatisfactory adherence in first two months (good, poor, fair, unknown), subsequent hospitalization, treatment side effects in last month of treatment	Baseline:* AUROC = 0.70 (95% CI: 0.63-0.76) HL test: X^2 = 1.448, df=5, p=0.919 Longitudinal: AUROC = 0.85 (95% CI: 0.80-0.90)	Odds ratios	High, High, Low, High

								HL test: $X^2 = 5.887$, df=6, p=0.436		
Chee[78] / 2000	TB cases	1996	Nested case-control	Singapore	None	38/71 (54%)	Chinese race, extent of family support, treatment duration	Accuracy = 74.6%	Model coefficients	High, Unclear, High, High
Cherkaoui[29] / 2014	TB patients with definite or probable pulmonary or extrapulmonary TB	Jun 2010 – Oct 2011	Non-nested case-control	Morocco	None	91/277 (33%)	Age <50, work interfering with ability to take TB treatment, retreatment regimen, daily DOT, moderate or severe side effects, told friends about TB, current smoker, never smoker, symptom resolution in <2 months, knowledge of TB treatment duration	AUROC = 0.85 (95% CI: 0.80-0.90) Sensitivity = 82.4% Specificity = 87.6% HL test: X^2=0.77, p-value=1.00	Survey tool	High, High, High, High
Rodrigo[79] / 2012	New TB cases	Jan 2006 – Dec 2009	Prospective cohort	Spain	Internal (split-sample)	*Development:* 92/1490 (6%) *Validation:* 103/1589 (6%)	Immigrant, living alone, living in an institution, previous TB treatment, linguistic barriers (poor understanding), IV drug use, unknown IV drug use	AUROC = 0.67 (95% CI: 0.65-0.70) Sensitivity = 65.05% Specificity = 67.36%	Risk score	Low, Low, Low, High
Unfavorable outcome										
Kalhori[50] (predicting) / 2009†	TB patients at DOT registration	2005	Retrospective cohort	Iran	Internal (split-sample)	*Development:* 6920† *Validation:* 2966†	Age, gender, nationality, prison, area, weight	Classification rate = 89.8% R2 = 0.45	Model coefficients	Unclear, Unclear, Unclear, High
Sauer[57] / 2018†	TB cases	Data available through March 2018	Retrospective cohort	Azerbaijan, Belarus, Georgia, Moldova, Romania	Internal (split-sample)	*Development:* 103/411 (25%) *Validation:* 44/176 (25%)	Forward selection (FS):* Drug sensitivity, employment status, smear microscopy, dissemination Backwards elimination (BE): Drug sensitivity, employment status, smear microscopy, dissemination Stepwise selection (SS): Drug sensitivity, employment status, smear microscopy, dissemination Lasso: Country, employment, extrapulmonary, cavity size, decrease in lung capacity, smear microscopy, drug sensitivity, chest imaging Random forest (RF): Top 5 by mean decrease accuracy: lung cavity size, type of resistance, employment status, country, total cavities Top 5 by mean decrease Gini index: Age of onset, drug regimen, lung cavity size, number of daily contacts, culture	FS:* AUROC = 0.74 (95% CI: 0.66-0.82) Sensitivity = 0.36 Specificity = 0.89 Misclassification = 0.24 BE: AUROC = 0.73 (95% CI: 0.65-0.81) Sensitivity = 0.3 Specificity = 0.88 Misclassification = 0.27 SS: AUROC = 0.73 (95% CI: 0.65-0.81) Sensitivity = 0.30 Specificity = 0.88 Misclassification = 0.27 Lasso: AUROC = 0.72 (95% CI: 0.64-0.80) Sensitivity = 0.21 Specificity = 0.96 Misclassification = 0.23 RF: AUROC = 0.73 (95% CI: 0.65-0.81) Sensitivity = 0.30 Specificity = 0.88 Misclassification = 0.27 SVM linear: AUROC = 0.69 (95% CI: 0.60-0.77) Sensitivity = 0.21 Specificity = 0.94 Misclassification = 0.24 SVM polynomial: AUROC = 0.69 (95% CI: 0.60-0.77) Sensitivity = 0 Specificity = 1 Misclassification = 0.25	List	Unclear, Unclear, Unclear, High

Baussano[47] / 2008§	Pulmonary TB cases	2001 - 2005	Retrospective cohort	Italy	Internal (bootstrap)	576/1242 (46%)	Residency (residential vs. homeless), sex, geographic origin (non-EU vs. EU), case definition (other than definite vs. definite), treatment setting (inpatient and unknown vs. outpatient), age (continuous)	AUROC= 0.75 Calibration slope = 0.98 R^2 = 0.24	Nomogram	Low, Unclear, Low, High
Costa-Veiga[48] / 2017§	Pulmonary TB cases	2000 - 2012	Retrospective cohort	Portugal	External (temporal)	*Development:* 1152/10766 (11%) *Validation:* 4714†	HIV, previous treatment, age class (25-44, 15-24, 45-64, >64), IV drug use, pathologies (other disease comorbidity)	AUROC= 75.9% (95% CI: 74.1-77.7) Sensitivity = 71% Specificity = 73%	Nomogram	Low, Low, Low, High
Killian[34] / 2019§	TB patients (99DOTS program)	Feb 2017 – Sep 2018	Retrospective cohort	India	None	433/4167 (10%)	LEAP:* Lstm rEal-time Adherence Predictor with 2 input layers, 1) LSTM with 64 hidden units and a dense layer with 48 units for the dense layer and 4 units for the penultimate layer w-misses: missed doses in last week t-misses: total missed doses in 35 days units and a dense layer with 48 units for the dense layer and 4 units for the penultimate layer Random forest: 150 trees and no max depth based on DAT from first 35 day	LEAP* AUROC = 0.743 lw-misses: AUROC = 0.607 t-misses: AUROC = 0.630 Random forest: AUROC = 0.722	None	High, High, Unclear, High
Madan[51] / 2018§	TB-HIV patients on DOT with first-line TB treatment	2015	Retrospective cohort	India	None	78/448 (17%)	Sputum smear grade, previous TB,; disease classification, HIV status, ART status, CD4 cell count, sex and age group (with interaction terms between age group and sex; sputum smear status and type of TB; HIV status at TB diagnosis and CD4 cell category).	AUROC = 0.783 HL test p-value = 0.149	Model coefficients	Low, Low, Low, High
Mburu[76] / 2018§	Smear-positive TB patients	Feb 2014 – Aug 2015	Prospective cohort	Kenya	Internal (cross-validation)	32/340 (9%)	HbA1c, treatment regimen (retreatment), creatinine, BMI, BUN, weight, age, random blood glucose, HIV positive result, male gender	AUROC = 0.65 ± 0.06	Relative score	Low, Low, Low, High
Other outcome										
Kalhori[80] (fuzzy) / 2009¶	TB patients at DOTS registration	2005	Retrospective cohort	Iran	Internal (split-sample)	*Development:* 7254† *Validation:* 2418†	Case type, treatment category, risky sex, prison, sex, recent TB infection, diabetes, low body weight, TB type, length, previous imprisonment, age, area, HIV	Mean absolute percentage error = 1.24	Learned parameters	Unclear, Unclear, High, High
Hussain[56] / 2019‖	Pulmonary and extrapulmonary TB patients (TB Reach)	2011 - 2014	Retrospective cohort	Unknown	Internal (split-sample)	*Development:* 3371† *Validation:* 842†	Random forest*, artificial neural networks, and SVM	Random forest:* Accuracy = 76.32%	None	Unclear, Unclear, Unclear, High

Abbreviations: AUROC=Area under receiver operating characteristic; c-statistic=concordance statistic; DOTS=Directly Observed Therapy, DM=Diabetes; HL=Hosmer-Lemeshow; TB=Tuberculosis;
*Indicates best-performing/most relevant model, which is included throughout the manuscript (see methods section for details). Performance measures are reported for highest level of validation performed (ranked from strongest to weakest: external validation, internal validation, no validation). If internal and external validation were performed, both are reported.
†Outcome number unknown
‡Outcome is composite of death and treatment failure (losses to follow-up and not evaluated (unknown) outcomes were excluded)
§Outcome is composite of death, treatment failure, loss to follow-up, and not evaluated
¶Outcome is a value from 1 to 5 (1= patient completed the treatment course in frame of DOTS, 2=cured, 3= quit treatment, 4=failed treatment and 5=death)
‖Outcome is treatment completion

Table 3. Characteristics of patient populations in the 33 included studies with prediction models for tuberculosis treatment outcomes

Characteristic	Studies reporting characteristic, n (% of total)	Categories	N(%) or Median [IQR]
Sample size	33 (11)	-	803 [291, 4167]
Study duration, years	32 (97)	-	4 [2,7]
Study design	33 (100)	Prospective cohort	3 (9)
		Retrospective cohort	25 (76)
		Nested case-control	3 (9)
		Non-nested case-control	2 (6)
Data source	33 (100)	Medical record	6 (18)
		National registry or surveillance system	13 (39)
		Local registry or surveillance system	1 (3)
		Regional registry or surveillance system	2 (6)
		Data collect form for study purposes	11 (33)
Study region	32 (97)	Africa	8 (25)
		Asia	13 (41)
		Europe	6 (19)
		North America	4 (12)
		South America	0 (0)
		Global	1 (3)
High burden TB setting*	31 (94)	All	143(42)
		Some	1 (3)
		None	17 (55)
Missing data	18 (54)	Complete case-analysis	9 (50)
		Missing indicator method	4 (22)
		Heckman's method	1 (6)
		Simple imputation	2 (12)
		Sensitivity analysis with imputation	1 (6)
		Other	1 (5)
Number of models developed	33 (100)	1	25 (76)
		2	4 (12)
		3	1 (3)

		4	2 (6)
		7	1 (3)
Reasons for multiple models developed	8 (24)	Different outcomes	1 (12)
		Different predictors considered	4 (50)
		Different methods	2 (25)
		Different outcomes	1 (12)
		Different populations and outcomes	1 (12)

*Determined based on study location and WHO list of 30 high-burden TB countries in the 2019 Global Tuberculosis Report (1).

Table 4. Study population characteristics of 33 included studies

	Included?			
Characteristic	**Yes**	**No**	**Unknown**	**Median [IQR]‡, n**
Age*	-	-	15	41 [37-49], n=18
HIV	18	7	8	23% [10-100], n=17
Diabetes	13	1	19	12% [5-21], n=11
MDR	8	7	18	1% [1-3], n=8
Other drug resistance	12	1	20	6% [4-12], n=10
Extrapulmonary TB†	22	4	7	11% [4-17], n=16
Previous TB	20	1	12	19% [9-30], n=17
DOT	14	0	19	100% [100-100], n=14
Hospitalized patients	13	1	19	100% [100-100], n=10

Abbreviations: DOT=directly observed therapy; IQR=interquartile range; MDR=multi-drug resistance; TB=tuberculosis

*Based on the measure of central tendency reported in the study (mean: n=11; median: n=7)

†Forms of extrapulmonary TB differ by study but included some of the following: Miliary, meningeal, pleural, peritoneal, disseminated, blood/bone, abdominal

‡Other than age (which is reported in years), this is the percentage of the population that has the characteristic among studies that include patients with the characteristic. For example, among the 18 studies that include persons with HIV, 17 report how many people had HIV and among those, the median percentage of the population with HIV is 23%.

Table 5. Methods reported for the 37 models of the 33 included studies with prediction models for tuberculosis treatment outcomes

Characteristic	Studies reporting characteristic, n (%)	Categories	N(%) or median [IQR]
Type of outcome	37 (100)	Single	29 (78)
		Composite	8 (22)
Outcome	37 (100)	Death	16 (43)
		Treatment failure	6 (16)
		Default, Loss to follow-up, or treatment interruption	6 (16)
		Unfavorable outcome	6 (16)
		Treatment success	2 (6)
		Other‡	1 (3)
Number - prevalence of outcome*	32 (87)	-	94 [38-171] 15% [9-26]
Events per candidate variable†	30 (81)	-	6 [3-11]
Events per variable (in final model)	29 (78)	-	14 [9-26]
Predictor types		Clinical/epidemiologic	34 (92)
		Adherence	1 (3)
		Biomarker	2 (5)
Analysis	37 (100)	Logistic regression	29 (78)
		Survival analysis	3 (8)
		Machine learning	5 (14)
Method for considering predictors in multivariable models	36 (97)	All candidate predictors	12 (32)
		Based on unadjusted association with outcome	19 (51)
		Based on clinical relevance	1 (3)
		Other§	4 (14)
Selection of predictors during modeling	31 (84)	Full model approach	2 (6)
		Forward selection	7 (23)
		Backwards elimination	5 (16)
		Stepwise selection	8 (26)
		Random Forest	1 (3)
		Hosmer-Lemeshow model building criteria	4 (13)
		Bayesian model averaging	3 (10)
		Pairwise selection	1 (3)

P-value for consideration in model	17 (46)	0·01	2 (12)
		0·05	3 (18)
		0·11	1 (6)
		0·2	6 (35)
		0·25	5 (29)
P-value for retention in MV model	20 (54)	0·05	9 (45)
		0·1	9 (45)
		0·15	1 (5)
		0·2	1 (5)
Internal validation	19 (51)	Split-sample	10 (53)
		Bootstrap	5 (26)
		Cross-validation	4 (21)
External validation	6 (16)	Temporal	1 (17)
		Geographic	1 (4)
		Setting	4 (67)
Calibration	17 (46)	Calibration plot¶	2 (12)
		Calibration slope¶	1 (6)
		Hosmer-Lemeshow goodness of fit p-value¶	13 (77)
			0·51 [0·20, 0·79]
		Calibration table¶	2 (12)
		Mean absolute error¶	1 (6)
Discrimination	30 (81)	C-statistic (AUROC) ¶	30 (100)
			0·75 [0·68-0·84]
		Log rank test¶	2 (5)
Classification	18 (49)	Sensitivity‖	14 (78)
			70 [54, 78]
		Specificity‖	13 (72)
			75 [71, 88]
		Accuracy	2 (11)
		Other**	2 (11)
Model presentation	34 (92)	Risk score	16 (43)
		Model coefficient	8 (22)
		Nomogram	2 (6)
		Odds ratios/relative scores	4 (12)
		Survey tool	1 (3)

Abbreviations: AUROC=area under receiver operating characteristic; c-statistic=concordance statistic

*Prevalence of outcome in the population used to develop the prediction model (i.e. derivation/development subset if split-sample technique was used or full sample if the model was not validated or if bootstrap/cross-validation was used)

†Only 5 studies report the exact number of predictors considered. Otherwise, the number of candidate predictors was estimated from the provided tables or lists of candidate predictors in the source paper.

‡Outcome is a value from 1 to 5 (1= patient completed the treatment course in frame of DOTS, 2=cured, 3= quit treatment, 4=failed treatment and 5=death)

§Other methods of determining which variables to consider for prediction model include: principal components analysis (n=1), screening for multi-collinearity via correlation coefficient (n=1), one study used a combination of a priori and selection via univariable association, and the other used machine learning pre-processing (n=1)

¶Sums to more than 100%, because some studies report multiple measures of calibration or discrimination

‖Based on the following cut-off methods: Youden (n=4) concordance probability (n=1), estimated at nearest 0,1 for studies that present a range of sensitivity and specificity in a table or figure (n=4), or unknown (n=5)

**Other includes one study that reports false positive rate and one study that includes a graph of sensitivity vs. specificity.

Figure 2. Most common predictors considered and included

[See Figure 2]

Figure 2 legend**:**
Considered: the predictor as evaluated as a candidate predictor prior to multivariable modeling
Included: the predictor was considered and subsequently included in the final multivariable model

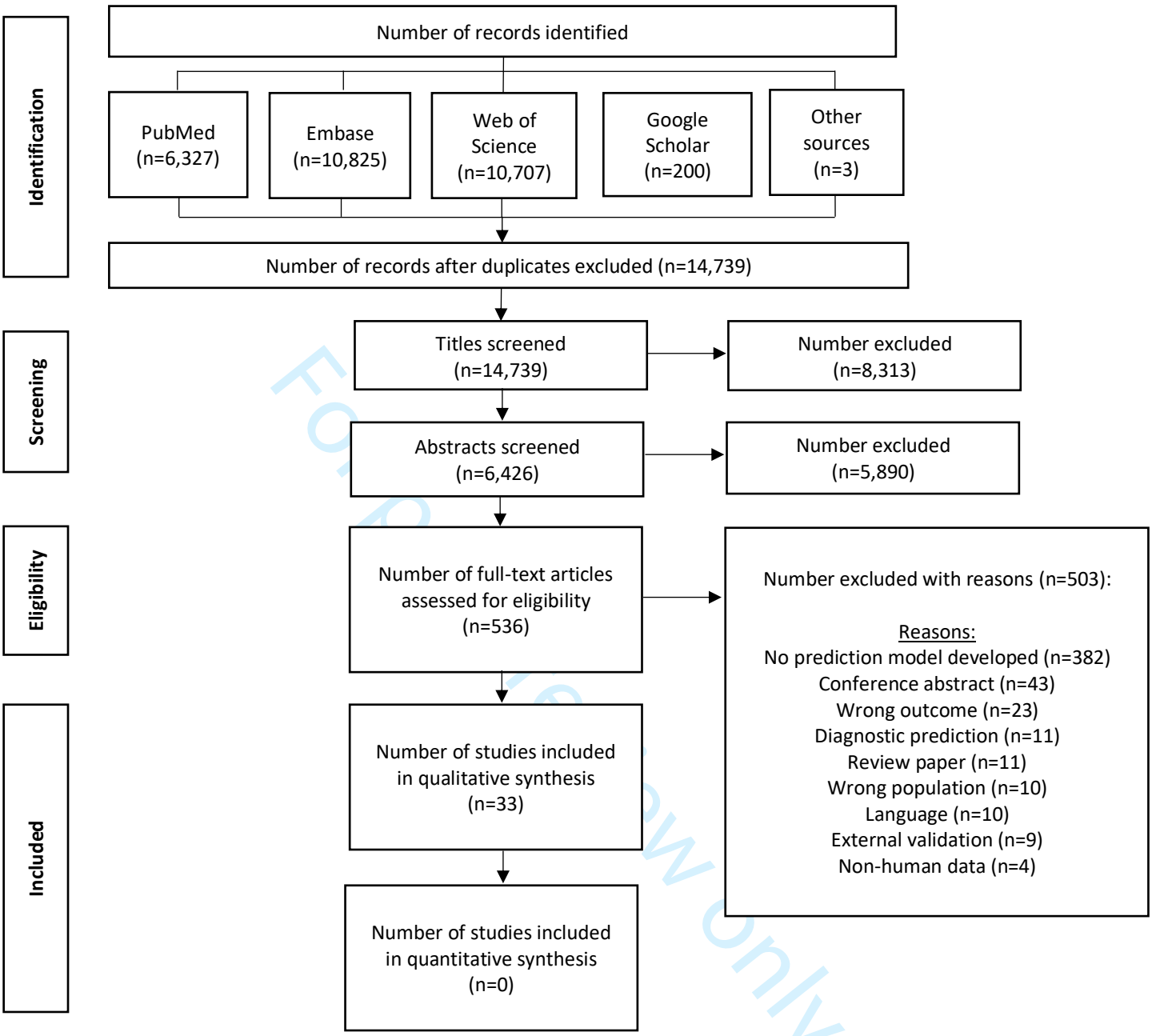
Figure 3. Heatmap of signaling questions from risk of bias assessment with PROBAST

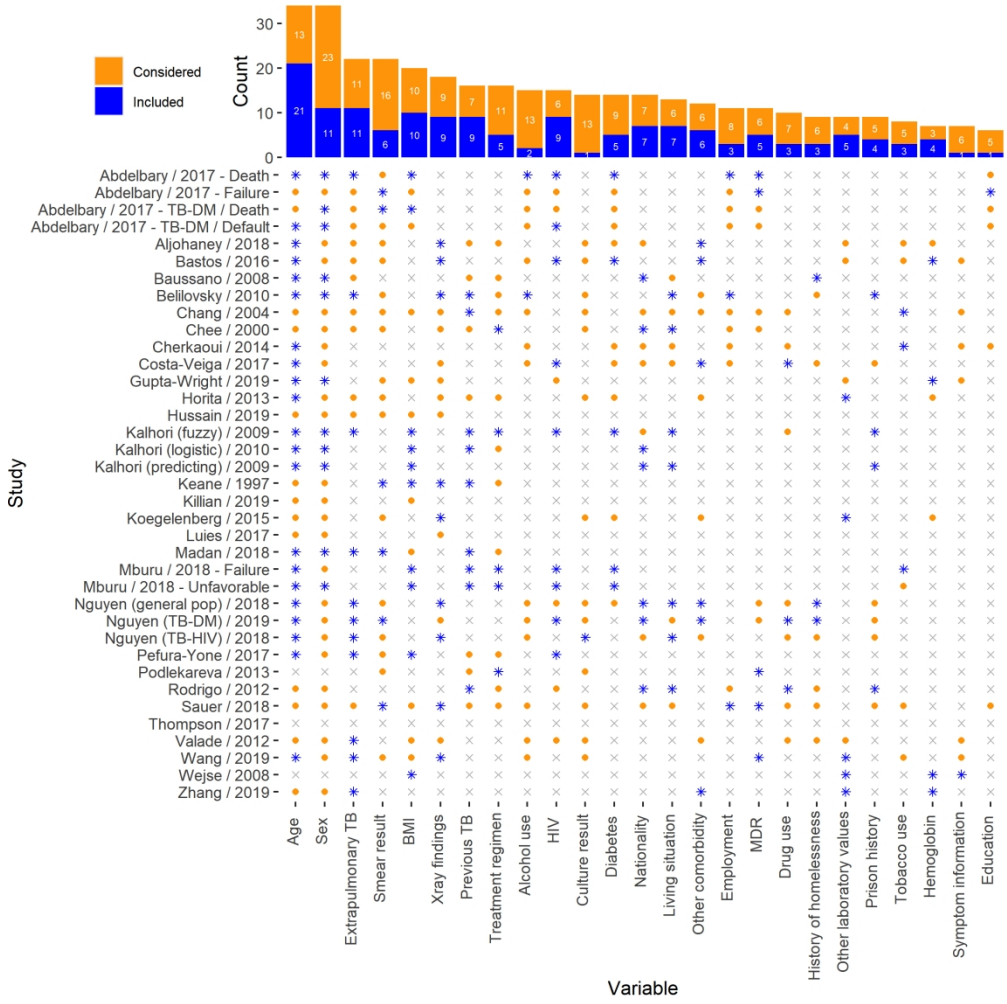
[See Figure 3]

Figure 3 legend**:**
PROBAST questions (additional details in Supplemental File 5)
Participants 1: What study design was used and was it appropriate?
Participants 2: Were all inclusion and exclusion criteria appropriate?
Predictors 1: Were predictors defined as assessed the same way for all participants?
Predictors 2: Were predictor assessments made without knowledge of data outcome?
Predictors 3: Are all predictors available at the time the model was intended to be used?
Outcome 1: Was the outcome determined appropriately?
Outcome 2: Was the outcome pre-specified or standard?
Outcome 3: Were predictors excluded from outcome definition?
Outcome 4: Was the outcome defined and determined in a similar way for all participants?
Outcome 5: Was the outcome determined without predictor information?
Outcome 6: Was the time interval between predictor assessment and outcome determination appropriate?
Analysis 1: Were there a reasonable number of participants with the outcome?
Analysis 2: Were continuous and categorical variables handled appropriately?
Analysis 3: Were all enrolled participants included in the analysis?
Analysis 4: Were participants with missing data handled appropriately?
Analysis 5: Was selection of predictors based on univariable analysis avoided?
Analysis 6: Were complexities in data (censoring, competing risks, sampling of control participants) accounted for appropriately?
Analysis 7: Were relevant model performance measures evaluated appropriately?
Analysis 8: Were model overfitting, underfitting, and optimism in the model performance accounted for?
Analysis 9: Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?

Figure 4. Summary of risk of bias and applicability assessment with PROBAST

[See Figure 4]





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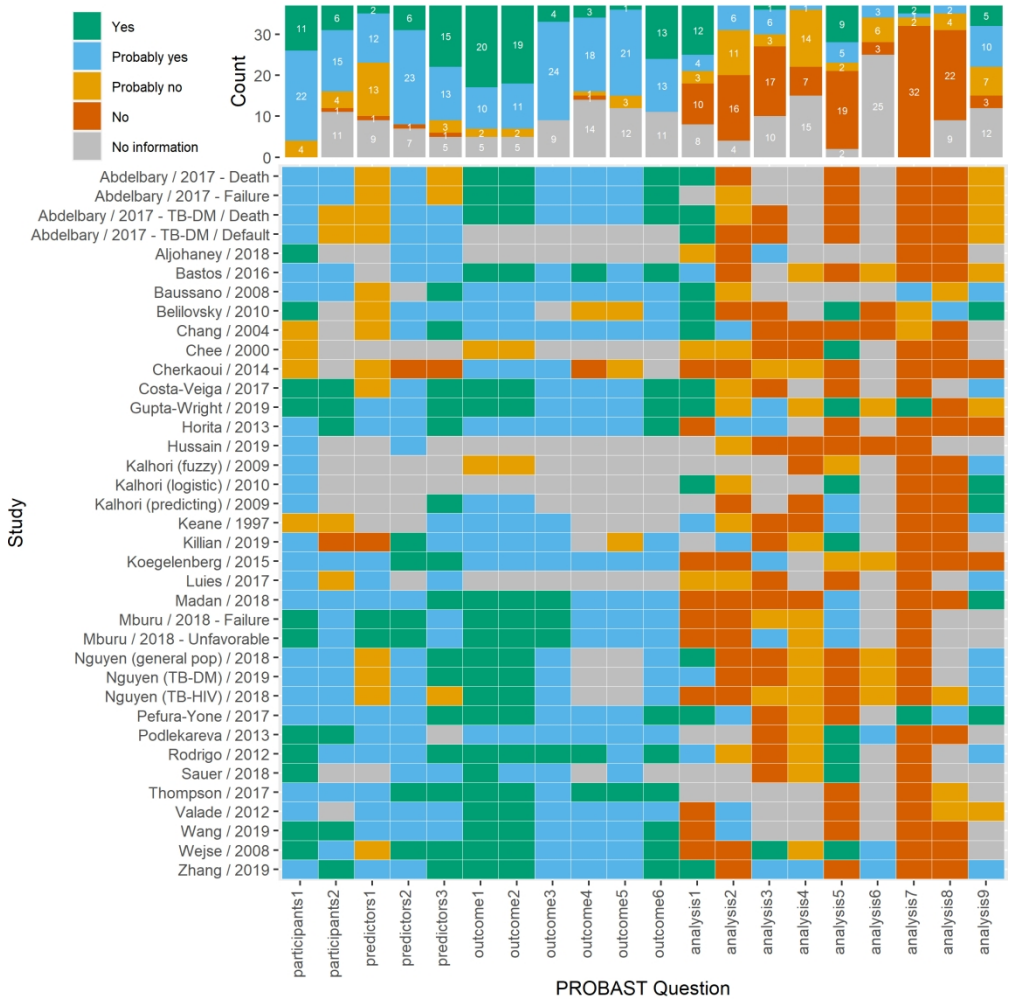

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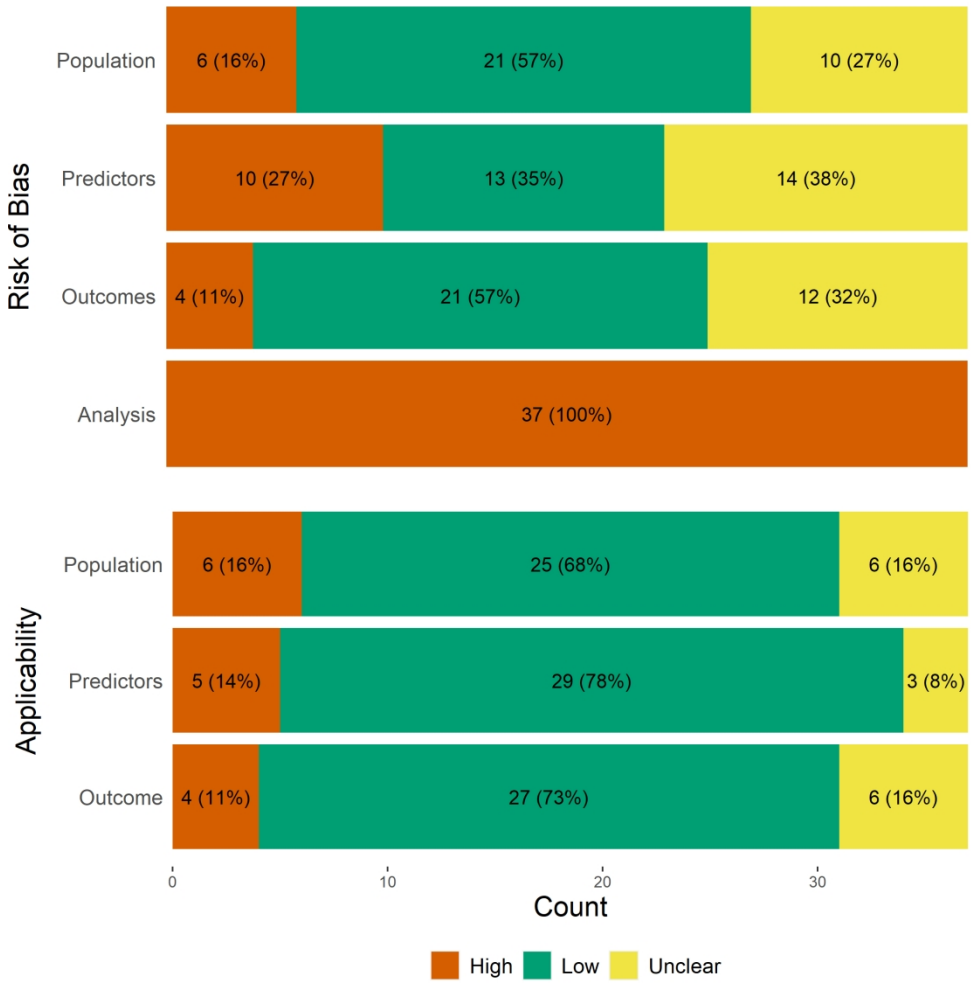

203x203mm (300 x 300 DPI)

Supplemental File 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Supplemental File 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract and p. 7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9; Supplemental Files 4 and 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9; Supplemental File 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-13; Table 3, 4, 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14; Figures 3 and 4

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-14; Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplemental File 2. PICOTS System

Population	Pulmonary tuberculosis cases
Intervention	Any prognostic model developed to predict tuberculosis treatment outcome. This includes model development studies with and without external validation
Comparator	Models will be compared to each other, as there is no other relevant comparator for this systematic review
Outcome	TB treatment outcome. The primary outcome of interest is the probability of unsuccessful TB treatment outcome, defined by the WHO as the combination of death, treatment failure, default, and/or not evaluated, as compared to successful TB treatment outcome, defined as the combination of cure and treatment completion. Included studies should evaluate at least one of the following outcomes: cure, treatment completion, death, treatment failure, default, and not evaluated. Default and not evaluated are sometimes referred to collectively as lost to follow-up. Some prediction models will look at only single endpoints, whereas other look at composite outcomes.
Timing	The timespan of prediction may vary between studies, depending on the duration of treatment and follow-up, but we expect most studies will evaluate endpoints around 6-9 months.
Setting	Model designed for use in clinical or hospital setting at the time of TB treatment initiation to aid in targeted treatment or programmatic support for individuals at greatest risk for unsuccessful TB treatment outcomes.

Supplemental File 3. Search Strategy

Database	*Search terms*
PubMed	1. ((validat*[tiab] OR predict*[ti] OR rule*[tiab]) OR (predict*[tiab] AND (outcome*[tiab] OR risk*[tiab] OR model*[tiab])) OR ((history[tiab] OR variable*[tiab] OR criteria[tiab] OR scor*[tiab] OR characteristic*[tiab] OR finding*[tiab] OR factor*[tiab]) AND (predict*[tiab] OR model*[tiab] OR decision*[tiab] OR identif*[tiab] OR prognos*[tiab])) OR (decision*[tiab] AND (model*[tiab] OR clinical*[tiab] OR "Logistic Models"[Mesh])) OR (prognostic[tiab] AND (history[tiab] OR variable*[tiab] OR criteria[tiab] OR scor*[tiab] OR characteristic*[tiab] OR finding*[tiab] OR factor*[tiab] OR model*[tiab])) 2. (stratification[tiab] OR "ROC Curve"[Mesh] OR discrimination[tiab] OR discriminate[tiab] OR "c-statistic"[tiab] OR "c statistic"[tiab] OR "area under the curve"[tiab] OR AUC[tiab] OR calibration[tiab] OR indices[tiab] OR algorithm[tiab] OR multivariable[tiab]) 3. (tuberculosis[Mesh] OR tuberculosis[tiab]) 4. (outcome*[tiab] OR mortality*[tiab] OR death*[tiab] OR fail*[tiab] OR recur*[tiab] OR relapse*[tiab] OR default*[tiab] OR abandon*[tiab] OR loss*[tiab] OR cure*[tiab] OR success*[tiab] OR unsuccess*[tiab] OR die[tiab] OR died[tiab] OR dies[tiab])) 5. 1 OR 2 6. 3 AND 4 7. 5 AND 6 AND (humans[Filter]) AND ("1995"[Date - Publication] : "3000"[Date - Publication])
Embase	1. (validat$ or predict$ or rule$).ti. OR (predict$ and (outcome$ or risk$ or model$)).ti,ab. OR ((history or variable$ or criteria or scor$ or characteristic$ or finding$ or factor$) and (predict$ or model$ or decision$ or identif$ or prognos$)).ti,ab. OR (decision$.ti,ab. and ((model$ or clinical$).ti,ab. or "statistical model"/)) OR (prognostic and (history or variable$ or criteria or scor$ or characteristic$ or finding$ or factor$ or model$)).ti,ab. 2. (stratification or discrimination or discriminate or c-statistic or "c statistic" or "area under the curve" or AUC or calibration or indices or algorithm or multivarriable).ti,ab. or "receiver operating characteristic"/ 3. tuberculosis/ or tuberculosis.ti,ab 4. (outcome$ or mortality$ or death$ or fail$ or recur$ or relapse$ or default$ or abandon$ or loss$ or cure$ or success$ or unsuccess$ or die or died or dies).ti,ab. 5. 1 or 2 6. 3 and 4 7. 5 and 6 8. limit 7 to (human and yr="1995 -Current")
Web of Science	1. TI=(validat* or predict*. or rule*) OR TS=(predict* and (outcome* or risk* or model*)) OR TS=((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)) OR TS=(decision* and ((model* or clinical*). or "statistical model")) OR TS=(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)) 2. TS=(stratification or discrimination or discriminate or c-statistic or "c statistic" or "area under the curve" or AUC or calibration or indices or algorithm or multivariable or "receiver operating characteristic") 3. TS=(tuberculosis) 4. TS=(outcome* or mortality* or death* or fail* or recur* or relapse* or default* or abandon* or loss* or cure* or success* or unsuccess* or die or died or dies) 5. 1 or 2 6. 3 and 4 7. 5 and 6; IC Timespan=1995-2019
Google scholar	tuberculosis treatment outcome prediction prognostic model development validation

Supplemental File 4. CHARMS Checklist

Domain	Key items	Reported on page #
SOURCE OF DATA	Source of data (e.g., cohort, case-control, randomized trial participants, or registry data)	
PARTICIPANTS	Participant eligibility and recruitment method (e.g., consecutive participants, location, number of centers, setting, inclusion and exclusion criteria)	
	Participant description	
	Details of treatments received, if relevant	
	Study dates	
OUTCOME(S) TO BE PREDICTED	Definition and method for measurement of outcome	
	Was the same outcome definition (and method for measurement) used in all patients?	
	Type of outcome (e.g., single or combined endpoints)	
	Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)?	
	Were candidate predictors part of the outcome (e.g., in panel or consensus diagnosis)?	
	Time of outcome occurrence or summary of duration of follow-up	
CANDIDATE PREDICTORS (OR INDEX TESTS)	Number and type of predictors (e.g., demographics, patient history, physical examination, additional testing, disease characteristics)	
	Definition and method for measurement of candidate predictors	
	Timing of predictor measurement (e.g., at patient presentation, at diagnosis, at treatment initiation)	
	Were predictors assessed blinded for outcome, and for each other (if relevant)?	
	Handling of predictors in the modelling (e.g., continuous, linear, non-linear transformations or categorised)	
SAMPLE SIZE	Number of participants and number of outcomes/events	
	Number of outcomes/events in relation to the number of candidate predictors (Events Per Variable)	
MISSING DATA	Number of participants with any missing value (include predictors and outcomes)	
	Number of participants with missing data for each predictor	
	Handling of missing data (e.g., complete-case analysis, imputation, or other methods)	
MODEL DEVELOPMENT	Modelling method (e.g., logistic, survival, neural network, or machine learning techniques)	
	Modelling assumptions satisfied	
	Method for selection of predictors **for inclusion** in multivariable modelling (e.g., all candidate predictors, pre-selection based on unadjusted association with the outcome)	
	Method for selection of predictors **during multivariable modelling** (e.g., full model approach, backward or forward selection) and criteria used (e.g., p-value, Akaike Information Criterion)	
	Shrinkage of predictor weights or regression coefficients (e.g., no shrinkage, uniform shrinkage, penalized estimation)	
MODEL PERFORMANCE	Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log-rank) measures with confidence intervals	
	Classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement) and whether a-priori cut points were used	
MODEL EVALUATION	Method used for testing model performance: development dataset only (random split of data, resampling methods e.g. bootstrap or cross-validation, none) or separate external validation (e.g. temporal, geographical, different setting, different investigators)	
	In case of poor validation, whether model was adjusted or updated (e.g., intercept recalibrated, predictor effects adjusted, or new predictors added)	
RESULTS	Final and other multivariable models (e.g., basic, extended, simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, model performance measures (with standard errors or confidence intervals)	
	Any alternative presentation of the final prediction models, e.g., sum score, nomogram, score chart, predictions for specific risk subgroups with performance	

	Comparison of the distribution of predictors (including missing data) for development and validation datasets	
INTERPRETATION AND DISCUSSION	Interpretation of presented models (confirmatory, i.e., model useful for practice versus exploratory, i.e., more research needed)	
	Comparison with other studies, discussion of generalizability, strengths and limitations.	

Supplemental File 5. Prediction model Risk Of Bias Assessment Tool (PROBAST)

Link to full explanation and elaboration document
Citation: Moons KG, Wolff RF, Riley RD, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med. 2019;170:W1–W33. doi: https://doi.org/10.7326/M18-1377

Domain 1: Participants
The overall aim for prediction models is to generate absolute risk predictions that are correct in new individuals. Certain data sources or designs are not suited to generate absolute probabilities. Problems may also arise if a study inappropriately includes or excludes participant groups from entering the study

	Signaling question	Yes/probably yes	No/probably no	No information
1	What study design was used and was it appropriate?	Yes: If a cohort design (including RCT or proper registry data) was used and you have confidence in data quality and participant enrollment is clearly described Probably yes: a nested case–control or case–cohort design (with proper adjustment of the baseline risk/hazard in the analysis) has been used or a cohort design was used but participant enrollment was data quality is unclear	No: If a non-nested case–control design has been used Probably no: a nested case-control study was used without proper adjustment of baseline risk/hazard	If the method of participant sampling is unclear.
2	Were all inclusion and exclusion criteria appropriate?	Yes: Inclusion and exclusion are clear and selection participants was appropriate, so participants correspond to unselected participants of interest (i.e. the target population). Probably yes: Inclusion and exclusion criteria are not entirely clear, but it seems like the population is representative of the target population	No: If participants are included who would already have been identified as having the outcome and so are no longer at risk of developing outcome, or if specific subgroups are excluded that may have altered the performance of the prediction model for the intended target population. Probably no: inclusion and exclusion criteria are unclear and it seems possible that there was bias in selection of participants that could lead to the model being applied to a population that is unrepresentative of the target population.	When there is no information on whether inappropriate inclusions or exclusions took place.

Low risk of bias	High risk of bias	Unclear risk of bias
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 2: Predictors
Bias in model performance can occur when the definition and measurement of predictors is flawed. Predictors are the variables evaluated for their association with the outcome of interest. Bias can occur, for example, when predictors are not defined in a similar way for all participants or knowledge of the outcome influences

	Signaling question	Yes/probably yes	No/probably no	No information
1	Were predictors defined and assessed in a similar way for all participants?	Yes: It is clear that definitions of predictors and their assessment were similar for all participants. Probably yes: Some predictors were based off subjective judgement, but carried out by persons with the necessary skills to evaluate the predictor, or if data from multiple sources was used but predictor definitions were standardized between sources.	No: If different definitions were used for the same predictor or if predictors requiring subjective interpretation were assessed by differently experienced assessors Probably no: Data from multiple sources was used and its unclear whether definitions were standardized between sources or if subjective measurements were likely not carried out by persons with appropriate training.	If there is no information on how predictors were defined or assessed.
2	Were predictor assessments made without knowledge of data outcome?	Yes: If outcome information was stated as not used during predictor assessment or was clearly not (yet) available to those assessing predictors (i.e. prospective data collection).	If it is clear that outcome information was used when assessing predictors.	No information on whether predictors were assessed without knowledge of outcome information.

		Probably yes: If it is likely that outcome information was not used during predictor assessment, but not entirely clear (retrospective data collection/surveillance data)		
3	Are all predictors available at the time the model was intended to be used?	All included predictors would be available at the time the model is intended to be used for prediction	Predictors would not be available at the time the model is intended to be used for prediction.	No information on whether predictors would be available at the time the model is intended to be used for prediction.

Low risk of bias	**High risk of bias**	**Unclear risk of bias**
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 3: Outcome

Bias in model performance can occur when methods used to determine outcomes incorrectly classify participants with or without the outcome. Bias in methods of outcome determination can result from use of suboptimal methods, tests, or criteria that lead to unacceptably high levels of errors in outcome determination, when methods are inconsistently applied across participants, or when knowledge of predictors influence outcome determination. Incorrect timing of outcome determination can also result in bias.

	Signaling question	**Yes/probably yes**	**No/probably no**	**No information**
1	Was the outcome determined appropriately?	If a method of outcome determination has been used which is considered optimal or acceptable by guidelines or previous publications on the topic Note: This is about level of measurement error within the method of determining the outcome (see concerns for applicability about whether the definition of the outcome method is appropriate).	If a clearly suboptimal method has been used that causes unacceptable error in determining outcome status in participants	No information on how outcome was determined
2	Was the outcome pre-specified or standard?	Yes: If the method of outcome determination is objective, or if a standard outcome definition is used, or if prespecified categories are used to group outcomes. (i.e. outcome assessment is based on previously published studies, published study protocol, or clinical guidelines) Probably yes: The outcome determination is not clearly based on guidelines or previous research, but outcome assessment is objective and would not inadvertently alter study results	No: If the outcome definition was not standard and not prespecified Probably no: a non-standard or non-prespecified outcome was used, and it is unclear whether the outcome definition could introduce bias. *Caution with composite outcomes that favor a better model by excluding typical outcome components or including atypical events	No information on whether the outcome definition was prespecified or standard
3	Were predictors excluded from outcome definition?	Yes: None of the predictors are included in the outcome definition (clearly stated) Probably yes: None of the predictors are included in the outcome definition (assumed)	If ≥1 of the predictors forms part of the outcome definition	No information on whether predictors are excluded from the outcome definition
4	Was the outcome defined and determined in a similar way for all participants?	Yes: If outcomes were defined and determined in a similar way for all participants (clearly stated) Probably yes: If outcomes were defined and determined in a similar way for all participants (assumed)	If outcomes were clearly defined and determined in a different way for some participants	No information on whether outcomes were defined or determined in a similar way for all participants
5	Was the outcome determined without predictor information	Yes: If predictor information was not known when determining the outcome status, or outcome status determination is clearly reported as determined without knowledge of predictor information. Probably yes: predictor information might have been available at time of outcome assessment, but outcome definition is objective and knowing information about predictors would not influence outcome	No: If it is clear that predictor information was used when determining the outcome status Probably no: it is likely predictor information was available at the time of outcome assessment, and outcome definition is subjective and knowledge of predictors could influence outcome determination.	No information on whether outcome was determined without knowledge of predictor information

		assessment (i.e death, treatment failure based on culture results, etc)		
6	Was the time interval between predictor assessment and outcome determination appropriate	If the time interval between predictor assessment and outcome determination was appropriate to enable the correct type and representative number of relevant outcomes to be recorded, or if no information on the time interval is required to allow a representative number of the relevant outcome occur or if predictor assessment and outcome determination were from information taken within an appropriate time interval.	If the time interval between predictor assessment and outcome determination is too short or too long to enable the correct type and representative number of relevant outcomes to be recorded.	If no information was provided on the time interval between predictor assessment and outcome determination.

Low risk of bias	High risk of bias	Unclear risk of bias
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Domain 4: Analysis

Statistical analysis is a critical part of prediction model development and validation. The use of inappropriate statistical analysis methods increases the potential for bias in reported model performance measures. Model development studies include many steps where flawed methods can distort results. We recommend reviewers seek statistical advice when completing

	Signaling question	Yes/probably yes	No/probably no	No information
1	Were there a reasonable number of participants with the outcome?	For model development studies, if the number of participants with the outcome relative to the number of candidate predictor parameters is ≥20 (EPV ≥20).* For model validation studies, if the number of participants with the outcome is ≥100.	For model development studies, if the number of participants with the outcome relative to the number of candidate predictor parameters is <10 (EPV <10).* For model validation studies, if the number of participants with the outcome is <100.	For model development studies, no information on the number of candidate predictor parameters or number of participants with the outcome, such that the EPV cannot be calculated. For model validation studies, no information on the number of participants with the outcome.
		* For EPVs between 10 and 20, the item should be rated as either probably yes or probably no, depending on the outcome frequency, overall model performance, and distribution of the predictors in the model. For more guidance, see references 145 to 147.		
2	Were continuous and categorical predictors handled appropriately?	Yes: If continuous predictors are kept as continuous or if continuous predictors are examined as linear or non-linear using restricted cubic splines or fractional polynomials. Probably yes: If continuous predictors are not converted into >2 categories when included in the model (i.e., dichotomized or categorized) using a prespecified method or in a way that avoids sparse data/would not intentionally improve statistical significance. For model validation studies, if continuous predictors are included using the same definitions or transformations, and categorical variables are categorized using the same cut points, ascompared with the development study.	No: For model development studies, if continuous predictors are converted into 2 categories when included in the model. Probably no: If categorical predictor group definitions do not use a prespecified method or continuous variables were split into >2 groups, but the decision of how to split variables is unclear. For model validation studies, if continuous predictors are included using different definitions or transformations, or categorical variables are categorized using different cut points, as compared with the development study.	No information on whether continuous predictors are examined for nonlinearity and no information on how categorical predictor groups are defined. For model validation studies, no information on whether the same definitions or transformations and the same cut points are used, as compared with the development study.
3	Were all enrolled participants included in the analysis?	If all participants enrolled in the study are included in the data analysis.	If some or a subgroup of participants are inappropriately excluded from the analysis (because they were missing data, unknown outcome, outliers)	No information on whether all enrolled participants are included in the analysis.
4	Were participants with missing data handled appropriately?	Yes: If there are no missing values of predictors or outcomes and the study explicitly reports that participants are not excluded on the basis of missing data, or if missing values are handled using multiple imputation.	No: If participants with missing data are omitted from the analysis, or if the method of handling missing data is clearly flawed, e.g., missing indicator method or inappropriate use of last value carried forward, or	If there is insufficient information to determine if the method of handling missing data is appropriate

		Probably yes: If a small percentage of persons with missing data were excluded and authors provide comparison of included vs. excluded participants or if sensitivity analysis with imputation methods are convincing that bias is low	if the study had no explicit mention of methods to handle missing data. Probably no: If authors provide comparison of included vs. excluded participants or if sensitivity analysis with imputation methods are reported, but the results are not convincing to rule out bias from excluding missing data	
5	Was selection of predictors based on univariable analysis avoided?	If the predictors are not selected on the basis of univariable analysis prior to multivariable modeling.	If the predictors are selected on the basis of univariable analysis prior to multivariable modeling.	If there is no information to indicate that univariable selection is avoided.
6	Were complexities in the data (censoring, competing risks, sampling of control participants) accounted for appropriately?	If any complexities in the data are accounted for appropriately, or if it is clear that any potential data complexities have been identified appropriately as unimportant.	If complexities in the data that could affect model performance are ignore. For example, case-control studies that do not estimate baseline risk or studies with censoring or competing risks that do not use survival analysis or other appropriate methods.	No information is provided on whether complexities in the data are present or accounted for appropriately if present.
7	Were relevant model performance measures evaluated appropriately?	Yes: If both calibration (via calibration plot) and discrimination (c-index) are evaluated appropriately (including relevant measures tailored for models predicting survival outcomes). Probably yes: if authors present a table of predicted probabilities with confidence intervals and corresponding outcome frequencies across subgroups	If both calibration and discrimination are not evaluated, or if only goodness-of-fit tests (Hosmer-Lemeshow test), are used to evaluate calibration or if for models predicting survival outcomes performance measures accounting for censoring are not used, or if classification measures (like sensitivity, specificity, or predictive values) were presented using predicted probability thresholds derived from the data set at hand, but calibration is not otherwise evaluated.	Either calibration or discrimination are not reported, or no information is provided as to whether appropriate performance measures for survival outcomes are used (e.g., references to relevant literature or specific mention of methods, such as using Kaplan–Meier estimates), or no information on thresholds for estimating classification measures is given.
8	Were model overfitting, underfitting, and optimism in model performance accounted for?	Yes: If internal validation techniques (bootstrapping and cross-validation) including all model development procedures, were used to account for any optimism in model fitting, and subsequent adjustment of the model performance estimates were applied. Probably yes: If internal validation was used and optimism was estimated as very low, and then optimism-corrected performance measures were not appropriately calculated (accounting for all model development procedures)	No: If no internal validation has been performed, or if internal validation consists only of a single random split-sample of participant data, Probably no: Internal validation with bootstrapping or cross-validation was conducted but did not include all model development procedures including any variable selection or were not used to correct model performance measures.	No information: No information is provided on whether internal validation techniques, including all model development procedures, have been applied.
9	Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?	If the predictors and regression coefficients in the final model correspond to reported results from multivariable analysis.	If the predictors and regression coefficients in the final model do not correspond to reported results from multivariable analysis. (i.e. rounding of model coefficients to create a "risk score" are inappropriately determined).	If it is unclear whether the regression coefficients in the final model correspond to reported results from multivariable analysis.

Low risk of bias	**High risk of bias**	**Unclear risk of bias**
If the answer to all signaling questions is "Yes" or "Probably yes," then risk of bias can be considered low. If ≥1 of the answers is "No" or "Probably no," the judgment could still be "Low risk of bias" but specific reasons should be provided why the risk of bias can be considered low.	If the answer to any of the signaling questions is "No" or "Probably no," there is a potential for bias, except if defined at low risk of bias above.	If relevant information is missing for some of the signaling questions and none of the signaling questions is judged to put this domain at high risk of bias.

Applicability				
	Domain	**Low concern**	**High concern**	**Unclear concern**

	Participants: do you have concern that the included participants or setting do not match the review question?	Included participants and clinical setting match the review question.	Included participants and clinical setting were different from the review question.	If relevant information about the participants and clinical setting are not reported.
	Predictors: does the definition, assessment, or timing of predictors match the review questions?	Definition, assessment, and timing of predictors match the review question.	Definition, assessment, or timing of predictors were different from the review question	If relevant information about the predictors is not reported.
	Outcome: does the definition, timing, or determination of outcome match the review question?	Outcome definition, timing, and method of determination defines the outcome as intended by the review question.	Choice of outcome definition, timing, and method of outcome determination defines another outcome as intended by the review question	If relevant information about the outcome, timing, and method of determination is not reported.

Supplemental File 6. Model outcome definitions

Study ID	Outcome category	Full outcome definition from the source paper
Hussain / 2019	Treatment completion	The target variable TreatmentComplete consists of 64.37% positive (treatment complete) and 35.62% negative (treatment incomplete)
Abdelbary / 2017 - Death	Death	All causes of death (TB or non-TB related) during the course of TB treatment
Abdelbary / 2017 - TB-DM / Death	Death	Death included all causes of death (TB and non-TB related) during the course of TB treatment
Aljohaney / 2018	Death	Not defined, but seems to be death during hospitalization.
Bastos / 2016	Death	Deaths that occurred during the first 6 months after diagnosis were classified as TB death
Gupta-Wright / 2019	Death	The outcome was mortality risk at 2 months after admission.
Horita / 2013	Death	'Discharged alive' was defined as being discharged alive and satisfying the discharge criteria, i.e., when the patient was receiving effective treatment, showed clinical improvement and negative conversion was confirrmed. Negative conversion was defined as three or more consecutive sputum samples obtained on different days being smear-negative for acid-fast bacilli or when appropriate sputum sample(s) were culture-negative. 'Died in hospital' was defined as death from any cause.
Koegelenberg / 2015	Death	Patients were categorised as either ICU/hospital survivors or non-survivors.
Nguyen (general pop) / 2018	Death	Documented treatment outcome of 'completed' or 'died'
Nguyen (TB-DM) / 2019	Death	TB treatment outcome of either 'completed' or 'died'
Nguyen (TB-HIV) / 2018	Death	Given the main purpose of our study is to predict the mortality during TB treatment in HIV-infected patients against the treatment completion, patients who had an outcome coding other than completed or died.
Pefura-Yone / 2017	Death	At treatment completion, patients are ranked into the following mutually exclusive categories 1) cured-patient with negative smear at the last month of treatment and at least one of the preceding months; 2) treatment completed-patient who has completed the treatment and for whom the smear results at the end of the last month are not available; 3) failure-patient with positive smear at the 5th month or later during treatment; 4) death-death from any cause during treatment; 5) defaulter-patient who's treatment has been interrupted for at least two consecutive months; 6) transfer-patient transferred to complete his treatment in another center and who's treatment outcome is unknown Cured and treatment completed are considered successful treatment
Podlekareva / 2013	Death	Death within 12 months of TB diagnosis
Valade / 2012	Death	Final outcomes of survival or death were recorded
Wang / 2019	Death	The outcome was estimated with all-cause mortality, with the mortality in 12 months as the primary outcome and the mortality in 3, 6, 9 months as other outcome
Wejse / 2008	Death	Mortality: ability to predict death
Zhang / 2019	Death	Primary treatment outcome was documented either survival or death when HIV/TB co-infected patients left hospital. Patients who survived when discharged received 12-month follow-up, and the date of last known alive was documented in electronical medical records base on records of last follow-up
Abdelbary / 2017 - Failure	Treatment failure	Treatment failure indicated smear-positive persistence at or after 5 months of treatment with first-line anti-TB medications.
Kalhori (logistic) / 2010	Treatment failure	The dependent variable was failing in treatment course completion.
Keane / 1997	Treatment failure	Failing to clear the sputum of acid-fast bacilli with standard treatment and having to start second line therapy
Luies / 2017	Treatment failure	From the original samples, all treatment failure cases were included.
Mburu / 2018 - Failure	Treatment failure	The secondary analyses only compared 'cures' versus 'failures' at similar time points as is the standard practice when examining chemotherapy efficacy
Thompson / 2017	Treatment failure	Patients' clinical outcomes were classified as 'cured' if they proved and maintained sputum culture negativity by month 6 after treatment initiation (M6), 'failed' if the M6 culture was still positive, and 'un-evaluable' if contamination caused uncertainty in outcome. We note that none of the treatment failures achieved culture negativity at any time point during treatment.
Abdelbary / 2017 - TB-DM / Default	Default, Abandon, or LTF (interruption >2 months)	Never defined
Belilovsky / 2010	Default, Abandon, or LTF (interruption >2 months)	We evaluated TI initiated by the patient (significant noncompliance with the doctor's prescribed course of treatment and serious violations of public order in hospitals) resulting in inpatient treatment cancellation.
Chang / 2004	Default, Abandon, or LTF	Default was defined as failure to collect drugs for 2 months or more after registration

	(interruption >2 months)	
Chee / 2000	Default, Abandon, or LTF (interruption >2 months)	Defaulter or cases were defined as patients on anti-tuberculosis treatment at the TBCU who failed to turn up for their scheduled appointments despite usual attempts to recall them by phone or mail, as described below, and from whom at least one home visit during the study was recorded
Cherkaoui / 2014	Default, Abandon, or LTF (interruption >2 months)	Treatment default was defined as an interruption in TB treatment for >=2 consecutive months.
Rodrigo / 2012	Default, Abandon, or LTF (interruption >2 months)	Interruption of treatment for any reason for more than 2 months, non-completion of treatment within 9 months when the patient is placed on a 6 month regimen. or drug intake of <80% the prescribed dose.
Kalhori (predicting) / 2009	Treatment success (cure + completion)	For each patient dependent variable was recorded whether or not the patient finished the treatment course and get cured.
Sauer / 2018	Unfavorable outcome (death + failure)	The primary outcome was treatment failure, which we defined as failure of therapy or death.
Baussano / 2008	Unfavorable outcome (death, failure, LTF, NE)	Treatment interruption or default, treatment failure, transferred out cases and those lost to follow-up were grouped as 'unsuccessful outcomes
Costa-Veiga / 2017	Unfavorable outcome (death, failure, LTF, NE)	In line with WHO criteria, SVIG-TB categorized a six possible and mutually exclusive categories for treatment outcomes, grouped in this study into a binary outcome: (i) Successful outcome-if PTB patients were treated before and declared cured, including both negative smear microscopy at the end of treatment at least one previous follow-up test and in case of not providing sputum samples, cure is declared if treatment completed and absent of disease clinical evidences (categories 1 and 2). (ii) Unsuccessful outcome-if treatment of PTB patients resulted in failure (i.e. remaining smear-positive after 5 months of treatment, cat. 3), default (i.e. patients who interrupted their treatment for two consecutive months or more after registration, cat. 4), death (cat. 5) or were transferred-out (cat. 6)
Killian / 2019	Unfavorable outcome (death, failure, LTF, NE)	We label 'Cured' and 'Treatment Complete' to be favorable outcomes and 'Died', 'Treatment failed', and 'Lost to follow-up' to be unfavorable outcomes
Madan / 2018	Unfavorable outcome (death, failure, LTF, NE)	Favourable treatment outcomes included cure and treatment completed. Unfavourable treatment outcomes included death, loss to follow-up, treatment failure, transfer out, or a switch to MDR TB treatment.
Mburu / 2018 - Unfavorable	Unfavorable outcome (death, failure, LTF, NE)	The primary analyses compared favorable versus unfavorable outcomes at end of treatment
Kalhori (fuzzy) / 2009	Other composite outcome	The values of outcomes might be any values from 1 to 5 which means different outcomes. Value 1 means patient completed the treatment course in frame of DOTS, 2 means the patient has been cured, 3 means patients has quitted the course, 4 means patients has failed and finally 5 is a sign of dead as outcome of TB treatment course

Supplemental File 7. Model presentation

Study ID	Final model
Abdelbary / 2017 - Death	2 + 2*(Age 41-65) + 5*(Age>=65) + 2*(Male gender) + 4*(MDR TB) + 3*(HIV) + 3*(Malnutrition) + 2*(Alcoholism) + 2*(Male*diabetes) + 3*(HIV*pulmonary TB) - 1*(diabetes) - 1*(pulmonary TB)
Abdelbary / 2017 - Failure	8*(No or low education) + 40*(MDR) + 10*(AFB smear +2) + 15*(AFB smear +3)
Abdelbary / 2017 - TB-DM / Death	2 + 3*(Male gender) + 3*(Malnutrition) - 1*(BCG vaccinated) - 1*(AFB smear positive)
Abdelbary / 2017 - TB-DM / Default	2 + 2*(Age<40) + 2*(Male gender) + 4*(HIV)
Aljohaney / 2018	Don't report final model, but show the beta coefficients. The coefficients are written as predictor (beta-coefficient): age ³ 65 (2.497), congestive heart failure (1.231), bilateral disease on chest x-ray (1.192)
Bastos / 2016	3*(Hypoxemic respiratory failure) + 2*(Age>=50) + 1*(Bilateral involvement) + 1*(At least one of: HIV, diabetes, liver failure/cirrhosis, congestive heart failure, chronic respiratory disease) + 1*(Hemoglobin<12)
Baussano / 2008	Nomogram with: residency status (residential vs. homeless), sex, geographic origin (non-EU vs. EU), case definition (other than definite vs. definite), treatment setting (inpatient and unknown vs. outpatient), age (continuous)
Belilovsky / 2010	-3.2 + 0.8*(male gender) + 0.7*(unemployment) + 0.4*(retreatment case) + 1.1*(alcohol abuse) + 0.6*(no data about alcohol) + 0.8*(severe TB form) - 0.3*(urban residence) + 0.4*(age 25-50) + 0.8*(pulmonary TB) + 0.5*(prison history)
Chang / 2004	Dont report final model. Just show odds ratios of predictors but don't report intercept term, which are written as predictor (OR) as follows: Current smokers (3.44), ex-smokers (2.48), history of default (10.74), no history of default (0.80),
Chee / 2000	The OR for each predictor is as follow in the format predictor (OR): Non-Chinese race (8.08), Living with family vs. living alone/with friends (0.08), Treatment duration (1.85). Treatment duration is categorical as 6 months, 9 months, and >9 months, but only one OR is presented.
Cherkaoui / 2014	2 points for yes to the following questions: Are you younger than 50 years of age? Do you feel work is interfering with your ability to take TB treatment? Are you taking a retreatment regimen for TB? Do you or doctor think you are having moderate or severe side effects from TB treatment Are you required to get your TB treatment daily? Have you told your friends that you have TB? (1 point for no) Are you a current smoker (1 point for yes) Did you TB symptoms go away within 2 months of starting TB treatment (1 point for yes) Do you know how long your TB treatment is supposed to last (1 point for no) Have you ever smoked cigarettes (-1 point for no)
Costa-Veiga / 2017	Nomogram with: HIV, previous treatment, age class (25-44, 15-24, 45-64, >64), IV drug use, pathologies (other disease comorbidity: yes/no)
Gupta-Wright / 2019	9*(Male sex) + 7*(patient aged 55+) + 6*(currently taking ART) + 7*(unable to walk unaided) + 7*(hemoglobin <80, severe anemia) + 6*(positive on urine TB-LAM)
Horita / 2013	1*Age (years) + 10*(oxygen requirement) - 20*(albumin) + 5*(semi-dependent, ADL) + 10*(total dependent, ADL)
Hussain / 2019	None
Kalhori (fuzzy) / 2009	Learned parameters by training set for each predictor written as predictor (learned parameter): Case type (0.467), treatment category (-0.079), risky sex (-0.945), prison (0.992), sex (0.400), recent TB infection (0.793), diabetes (2.445), low body weight (1.313), TB type (0.950), length (-0.235), previous imprisonment (2.398), age (0.237), area (0.8895), HIV (0.731)
Kalhori (logistic) / 2010	exp(-0.93 - 0.71*(gender) + 0.02*(age) - 0.02*(weight) + 0.5*(nationality) + 0.99*(prison) + 0.16*(case type))
Kalhori (predicting) / 2009	exp(-(1.58 - 0.12*(age) + 0.807*(gender) - 0.039*(nationality) - 0.263*(prison) + 0.15*(area) + 0.021*(weight))
Keane / 1997	Unclear. No constant term provided. Here are the predictor (OR): Mediastinal shift (2.1), average smear score (1.5), extensive lesions (3.6), any previous treatment (2.3), cavities (1.7), weight (0.98)
Killian / 2019	LEAP = Lstm rEal-time Adherence Predictor with 2 input layers, 1) LSTM with 64 hidden units and a dense layer with 48 units for the dense layer and 4 units for the penultimate layer
Koegelenberg / 2015	One point for each parameter: septic shock, HIV with CD4 < 200, creatinine > 140 (male) or >120 (female), P:F O2 ratio < 200, chest radiograph showing miliary pattern/parenchymal infiltrates, absence of TB treatment at admission
Luies / 2017	Written as predictor (OR): 3,5,-Dihydroxybenzoic acid (25.6), 3-(4-Hydroxy-3-methoxyphenyl) propionic acid (1.3)
Madan / 2018	Written as predictor (OR): New TB with 1+ smear grade (5.78), New TB with 2+ smear grade (2.69), New TB with 3+ smear grade (1.69), New TB without smear (1.67), New TB with smear positive, unknown grade (1.00), Previously treated, smear negative TB (1.35), previously treated with scanty smear (4.74), previously treated with 1+ smear grade (1.61), previously treated with 2+ smear grade (1.05), previously treated with 3+ smear grade (7.54), previously treated with no sputum smear (2.46), previously treated with unknown grade (30.37), pulmonary TB (1.83), pulmonary and extrapulmonary TB (5.86), HIV+ on ART with CD4 350-500 (8.09), HIV+ on ART with CD4 200-350 (6.14), HIV+ on ART with CD4 50-200 (16.35), HIV+ on ART with CD4 <50 (38.76), HIV+ not on ART with CD4 350-500 (53.44), HIV+ not on ART with CD4 200-350 (65.98), HIV+ not on ART with CD4 50-200 (6.94), HIV+ not on ART with CD4 <50 (49.20), HIV+ diagnosed after TB with CD4>500 (1.05), HIV+ diagnosed after TB with CD4 350-500 (2.49), HIV+ diagnosed after TB with CD4 200-350 (8.88), HIV+ diagnosed after TB with CD4 50-200 (6.79), HIV+ diagnosed after TB with CD4 <50 (13.99), Female 25-34 (9.41), Female 35-44 (1.75), Female >= 45 (4.49), Male 15-24 (10.63), Male 25-34 (2.74), Male 35-44 (2.9), Male >= 45 (3.96)
Mburu / 2018 - Failure	Present relative scores for each covariate included with scores of 100, 72.61, 69.19, 55.39, 49.87, 48.74, 48.18, 46.51, 39.69, and 37.69 for hba1c, regimen, age, weight, random blood glucose, BMI, BUN, HIV positive result, ever smoker, creatinine, respectively
Mburu / 2018 - Unfavorable	Present relative scores for each covariate included, not sure if this was how it should be used. Relative scores are 100, 79.38, 70.09, 63.93, 62.47, 62.63, 61.63, 55.62, 39.21, 34.48 for hba1c, regimen, creatinine, BMI, BUN, weight, age, random blood glucose, HIV positive result, male gender, respectively
Nguyen (general pop) / 2018	6*[Age 45-64] + 12*[Age>65] + 2*[US born] + 2*[Homeless] + 4*[Resident of LTCF] + 8*[Chronic kidney failure] + 10*[Meningeal TB] + 4*[Miliary TB] + 6*[TB-CXR] + 6*[HIV positive] + 6*[HIV unknown]
Nguyen (TB-DM) / 2019	16*[Age >= 65] + 5*[US-born] + 11*[Homeless] + 20*[IDU] + 20*[Chronic kidney failure] + 20*[TB meningitis] + 13*[Miliary TB] + 6*[AFB positive smear] + 24*[Positive HIV]
Nguyen (TB-HIV) / 2018	Prognostic score: 5*[Age >= 65] + 12*[Resident of LTCF] + 9*[Meningeal TB] + 6*[abnormal CXR] + 9*[diagnosis confirmed with positive culture or NAA] + 10*[culture not converted or unknown]

	Model: -6.994499 + 1.069024*[Age >= 65] + 2.541147*[Resident of LTCF] + 1.998852*[Meningeal TB] + 1.37995*[abnormal CXR] + 1.899108*[diagnosis confirmed with positive culture or NAA] + 2.186305*[culture not converted or unknown]
Pefura-Yone / 2017	1/(1 + exp(-1.3120 + 0.0474*[age] - 0.1866*[adjusted BMI] + 1.1637*[PTB-] + 0.5418*[ETB] + 1.3820*[HIV]
Podlekareva / 2013	1*[DST performed] + 2*[Initial treatment with RHZ] + 2*[cART started before or up to 1 month after TB diagnosis]
Rodrigo / 2012	1*[Immigrant] + 1*[Living alone] + 1*[Living in an institution] + 2*[Previous TB treatment] + 2*[Linguistic barriers] + 4*[IV drug use] + 1*[Unknown IV drug use]
Sauer / 2018	Negatively correlated: drug sensitivity (sensitive), employment status (employed), microscopy: 1 to 99 acid-resistant bacteria in 100 fields of view when stained by Ziehl-Nielsen, dissemination (diffuse pulmonary nodules detected)
Thompson / 2017	Heatmap of differentially expressed genes
Valade / 2012	Sum of three parameters: military tuberculosis (yes: +1, no: 0), required mechanical ventilation on ICU admission (yes: +1, no: 0), and required vasopressor infusion (yes: +1, no: 0).
Wang / 2019	Unknown
Wejse / 2008	1 point for each variable: cough, hemoptysis, dyspnea, chest pain, night sweating, anemia conjunctivae, tachycardia, positive funding at lung auscultation, temperature >37, BMI <18, BMI<16, MUAC<220, MUAC<200
Zhang / 2019	2*[Anemia (HGB < 90g/L)]+ 2*[Tuberculous meningitis] + 5*[Severe pneumonia] + 2*[Hypoalbuminemia] + 7* [Unexplained infections or space-occupying lesions] + 5* [Malignancies]

Supplemental File 8. Comparison of model performance and quality by population characteristics.

For each analysis below, results were stratified on the basis of whether the study population included, excluded, or did not report on two population characteristics of interest: MDR and younger age group (minimum age <18 vs. minimum age ≥18).

Note: The unit of measure for these analyses is the model (N=37) not the study (N=33), which explains differences in numbers between this and Table 4 of the main manuscript.

A) MDR

	Included (N=11)	**Excluded (N= 7)**	**Unknown (N=19)**
Prevalence of MDR, Median [IQR]	1% [1%-1%]	0% [0%-0%]	
C-statistic, Median [IQR]	0.77 [0.69-0.81]	0.77 [0.73-0.81]	0.75 [0.69-0.85]
Unknown	1	3	4
Outcome			
Death	7 (64%)	1 (14%)	8 (42%)
Treatment failure	2 (18%)	1 (14%)	3 (16%)
Default, LTF, or treatment interruption	1 (9.1%)	2 (29%)	3 (16%)
Composite outcome*	1 (9.1%)	3 (43%)	5 (26%)
Risk of Bias (Population)			
Low	6 (55%)	4 (57%)	11 (58%)
High	0 (0%)	2 (29%)	4 (21%)
Unclear	5 (45%)	1 (14%)	4 (21%)
Risk of Bias (Predictors)			
Low	1 (9.1%)	3 (43%)	9 (47%)
High	5 (45%)	0 (0%)	5 (26%)
Unclear	5 (45%)	4 (57%)	5 (26%)
Risk of Bias (Outcomes)			
Low	5 (45%)	4 (57%)	12 (63%)
High	0 (0%)	1 (14%)	3 (16%)
Unclear	6 (55%)	2 (29%)	4 (21%)
Risk of Bias (Analysis)			
Low	0 (0%)	0 (0%)	0 (0%)
High	11 (100%)	7 (100%)	19 (100%)
Unclear	0 (0%)	0 (0%)	0 (0%)
Top 5 predictors included^	Age (7), x-ray findings (5), extrapulmonary TB (4), HIV (4), other comorbidities (4), smear result (4)	Nationality (3), Age (2), HIV (2), living situation (2), previous TB (2), sex (2), treatment regimen (2)	Age (12), previous TB (9), BMI (8), extrapulmonary TB (6), sex (6)

Abbreviations: BMI=body mass index, LTF=losses to follow-up, MDR=multi-drug resistance, TB=tuberculosis
*Composite outcome includes unfavorable outcome (combination of death, failure, and default/LTF/treatment interruption) or treatment success (combination of cure and treatment completion)
^Witten as predictor (number of models included in). Top 5 unless there was a tie, in which case more predictors were listed.

Summary: Overall, the study population for 11 models included individuals with MDR, whereas 7 excluded patients with MDR, and the inclusion of MDR was unknown in 19 models. In models that included patients with MDR, the overall prevalence of MDR was low, with a median 1% prevalence. Model performance, as measured by the c-statistic, of studies that included and excluded patients with MDR was comparable and both were slightly higher than in studies where the prevalence of MDR was unknown. There were notable differences in outcome definition for the studies that included vs. excluded MDR patients, such as most studies that included patients with MDR examined death as the primary endpoint, whereas studies that excluded patients with MDR were more likely to use a composite outcome or evaluate default/LTF/treatment interruptions. Risk of bias assessment for the population and analysis domains were similar between all groups, but studies that included patients with MDR seemed to have higher amounts of bias in the predictors domain and more unclear risk of bias in the outcomes domain. For all groups, age was an important predictor of treatment outcome, but the other frequently included predictors varied between groups.

B) Age <18

	Included (N=10)	Excluded (N= 11)	Unknown (N=16)
Minimum age			
15	8 (80%)	0 (0%)	-
16	1 (10%)	0 (0%)	-
17	1 (10%)	0 (0%)	-
18	0 (0%)	10 (91%)	-
20	0 (0%)	1 (9.1%)	-
Age[#], Median [IQR]	34 [32-38]	43 [43-50]	44 [40-49]
Unknown	4	3	8
C-statistic, Median [IQR]	0.78 (0.65, 0.80)	0.70 (0.68, 0.84)	0.75 (0.74, 0.85)
Unknown	1	0	7
Outcome			
Death	5 (50%)	7 (64%)	4 (25%)
Treatment failure	2 (20%)	1 (9.1%)	3 (19%)
Default, LTF, or treatment interruption	0 (0%)	3 (27%)	3 (19%)
Composite outcome*	3 (30%)	0 (0%)	6 (38%)
Risk of Bias (Population)			
Low	10 (100%)	9 (82%)	2 (12%)
High	0 (0%)	0 (0%)	6 (38%)
Unclear	0 (0%)	2 (18%)	8 (50%)
Risk of Bias (Predictors)			
Low	6 (60%)	5 (45%)	2 (12%)
High	2 (20%)	5 (45%)	3 (19%)
Unclear	2 (20%)	1 (9.1%)	11 (69%)
Risk of Bias (Outcomes)			
Low	8 (80%)	9 (82%)	4 (25%)
High	0 (0%)	1 (9.1%)	3 (19%)
Unclear	2 (20%)	1 (9.1%)	9 (56%)
Risk of Bias (Analysis)			
Low	0 (0%)	0 (0%)	0 (0%)
High	10 (100%)	11 (100%)	16 (100%)
Unclear	0 (0%)	0 (0%)	0 (0%)
Top 5 predictors included^	Age (7), HIV (5), BMI (4), extrapulmonary TB (4), previous TB (4)	Age (7), sex (5), extrapulmonary TB (4), hemoglobin (3), HIV (3), MDR (3), other lab values (3), x-ray findings (3)	Age (7), nationality (5), previous TB (5), BMI (4), sex (4), treatment regimen (4), x-ray findings (4)

Abbreviations: BMI=body mass index, LTF=losses to follow-up

[#]Based on measure of central tendency reported in the study

*Composite outcome includes unfavorable outcome (combination of death, failure, and default/LTF/treatment interruption) or treatment success (combination of cure and treatment completion)

^Witten as predictor (number of models included in). Top 5 unless there was a tie, in which case more predictors were listed.

Summary: In total, the study population of 10 models included individuals younger than 18, 11 had a minimum age of 18, and the minimum age of participants was not reported for 16 models. The age distribution of studies that included patients less than 18 was lower than that of studies with a minimum age of 18 or unreported minimum age. The c-statistic of studies that included younger patients (minimum age <18) was seemingly higher than studies with a minimum age of 18. Treatment outcome definitions varied between groups, such that none of the studies including younger patients examined default/LTF/treatment interruption as an outcome and none of the studies with age 18 as the minimum age used a composite outcome. Risk of bias for the population and predictors domain was somewhat lower for studies with a younger age population, and studies with unknown minimum age were more likely to be regarded as having unclear risk of bias. Across all groups, age was the most important predictor of outcome, but other important predictors varied between groups.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Supplemental File 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract and p. 7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9; Supplemental Files 4 and 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9; Supplemental File 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-13; Table 3, 4, 5

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14; Figures 3 and 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-14; Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20