Center for Tuberculosis

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Blood-based Pathogen and Host Biomarker Signatures That Predict TB Treatment Outcomes

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BACKGROUND

Blood-based biomarkers have been sought as alternatives to traditional culture-based biomarkers for monitoring of tuberculosis (TB) treatment response. We integrated blood-based pathogen antigenic detection and host protein biomarkers to predict TB clinical outcomes.

METHODS

A total of 628 clinical trial and cohort participants were included in the analysis

Data	N	Treatment[a]	Serum collection (weeks)[b]	Sputum collection (weeks)[b]	Drug exposure data	Host and pathogen biomarkers
TBTC Study 29/29X[1,2] (Phase 2B)	538	6-month standard, R or P during intensive phase	0 and 8	0, 2, 4, 5, 6, 8, 12, 16, 20, and 24	N = 355	69 host
MARK-TB Biobank[c,3]	90 (60 cured, 30 recurrences)	6-month standard or 4-month experimental	0, 2, 4, 8, 17, 26, and 52	0, 2, 4, 8, 17, 26, and 52	Not available	54 host, 1 pathogen

[a]R = rifampicin, P = rifapentine, [b]Week 0 defined as a pretreatment sample, [c]MARK-TB = Markedly Accelerating Research with Knowledge of TB Biomarkers Biobank. 51 participants were from the REMoxTB trial (Phase 3) and 39 from the National TB Programme at the same sites at which REMoxTB was conducted.

Nonlinear mixed effect modeling and machine learning algorithms (recursive feature elimination for feature selection and decision trees for model development) were used to search for biomarker signatures that predict time to culture conversion (all participants), time to positivity in the MGIT assay (measure of bacterial burden) during treatment (N=538), and TB recurrence up to 18 months after start of treatment (N=90).

Log-transformed biomarker levels, ratio to pretreatment levels, and area under the biomarker concentration-time curve were tested simultaneously as predictors. Correlated variables (Spearman >0.75) were removed from analysis. A random 75% of the population was used for training and 25% for testing. Area under the receiver operating characteristic curve (ROC AUC) was used to assess model discrimination.

Host and pathogen biomarkers in serum drawn before and during the first 8 weeks of treatment show promise for predicting clinical outcomes.

RESULTS

Host signatures that included week 8 SAA1 with RANTES levels predict bacterial burden over time (Figures 1A and 1B).

ROC AUC for this signature to predict culture conversion was 0.77 to 0.79. Integration of drug exposure and clinical risk factors improved the ROC AUC to 0.86 (Figure 1C).

External validation with the MARK-TB database had an ROC AUC 0.72 (95% CI: 0.60-0.83) for prediction of culture conversion using week 8 SAA1 and RANTES.

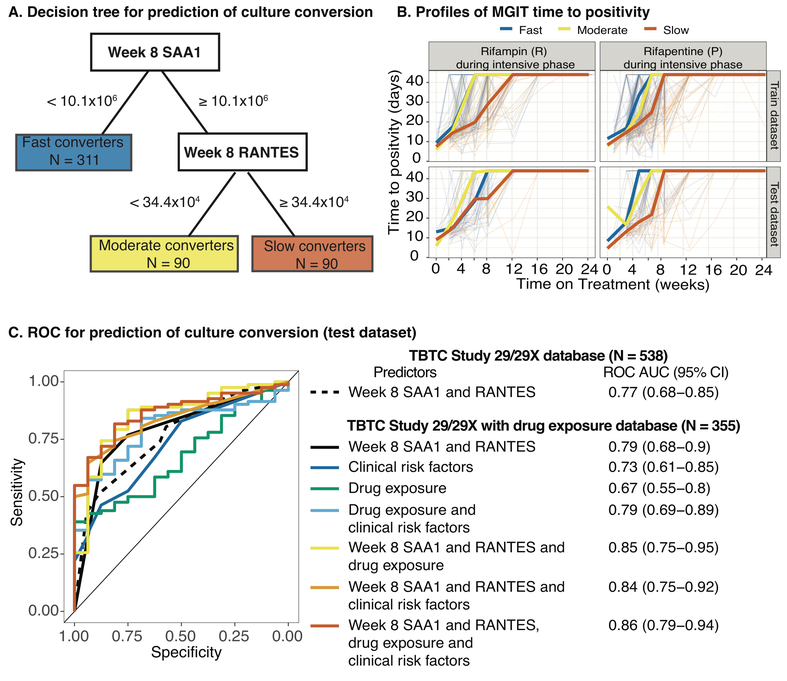


Figure 1. Prediction of MGIT time to positivity and MGIT culture conversion in TBTC Study 29/29X.

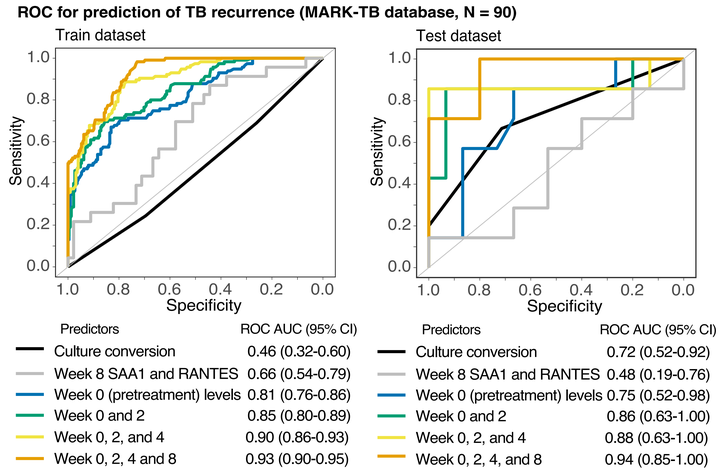


Figure 2. ROC for prediction of TB recurrence with the MARK-TB database (N = 90). Week 0 = Pretreatment biomarker levels

Week 8 SAA1 and RANTES poorly predicted TB recurrence with a ROC AUC < 0.50. Reanalysis of all biomarkers suggest TB recurrence can be predicted with signatures using pretreatment levels (ROC AUC = 0.75), pretreatment and week 2 levels (0.86), pretreatment and week 2 and 4 levels (0.88) and pretreatment and week 2, 4 and 8 levels (0.94) (Figure 2, test dataset).

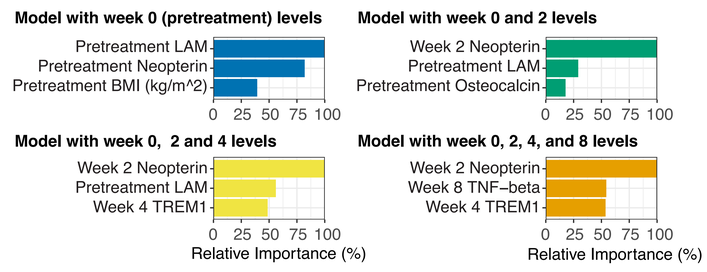


Figure 3. Top three most important predictors for models in Figure 2. Importance relative to the most important predictor in each model is shown. Importance is determined based on the decrease in accuracy when the variable is permuted (shuffled).

Early neopterin levels were consistently top predictors of TB recurrence. Pretreatment LAM levels were also important, but become less important as on-treatment biomarkers were included in the model.

References: 1. Dorman *et al., J. Infect. Dis.*, 2012.; 2. Dorman *et al., AJRCCM*, 2015; 3. www.mark-tb.org