

## Predictive Markers of Incident Tuberculosis in Close Contacts in Brazil and India

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There are insufficient predictors of progression to tuberculosis among contacts. A case-control study within RePORT-Brazil matched 20 QuantiFERON-positive progressors and 40 nonprogressors by sex, age, and exposure duration. Twenty-nine cytokines were measured using a Luminex assay with QuantiFERON-TB Gold Plus supernatants collected at baseline and evaluated using machine learning for tuberculosis prediction. The same markers were evaluated in 8 QuantiFERON-positive progressors and 12 nonprogressors from India. Interleukin 8, interleukin 10, and CCL3 levels predicted incident tuberculosis (area under the receiver operating characteristic curve, 0.75) in 2 years with sensitivity and specificity >80%, in both cohorts. This signature

predicted tuberculosis progression in close contacts meeting World Health Organization goals.

**Keywords.** tuberculosis; cytokine; biomarker prediction; QuantiFERON; multicentric study; Brazil; India.

Tuberculosis causes significant disease and death, particularly in low-and middle-income countries. Approximately 10.6 million people had newly diagnosed tuberculosis in 2022, a higher number than in 2019–2021, indicating that we are far from reaching the 50% reduction milestone of the End TB Strategy by 2025 [1].

Current diagnostic tools, such as interferon (IFN)  $\gamma$  release assays (IGRAs), are able to detect tuberculosis infection but do not adequately predict which individuals will develop tuberculosis disease [2, 3]. This limitation underscores the need for more precise biomarkers that can identify those at highest risk of disease progression. Identifying these markers could significantly enhance the predictive power of current diagnostic tools and allow for more targeted interventions, which are crucial for controlling tuberculosis transmission and improving outcomes [4].

The current study aimed to identify biomarkers in IGRA supernatants that predict progression to tuberculosis disease in contacts of patients with pulmonary tuberculosis (PTB) in Brazil and India.

### METHODS

#### Ethical Approval

This study adhered to the principles of the Declaration of Helsinki and was approved by the institutional review boards at all enrollment sites (CAAE 25102412.3.1001.5262) and at Vanderbilt University Medical Center. Written informed consent was obtained from all participants in the Regional Prospective Observational Research on Tuberculosis (RePORT)–Brazil cohort. The Indian parent study was approved by the institutional ethics committees of the Indian Council of Medical Research–National Institute for Research in Tuberculosis, Chennai, India; Bireme Jeejeebhoy Government Medical College, Pune, India; and Johns Hopkins University, Baltimore, Maryland.

#### Brazilian Study Cohort

The study subjects were participants of RePORT-Brazil [5]. Patients were enrolled between 2015 and 2019, resulting in 1188 cases of culture-confirmed PTB and 1930 close contacts. Contacts were followed up for 2 years. At enrollment, participants were evaluated for signs and symptoms of PTB; underwent an IGRA (QuantiFERON-TB Gold Plus; QFT-Plus), chest radiography, and human immunodeficiency virus (HIV) testing; and had blood and urine samples collected and stored in a

Received 12 September 2024; editorial decision 23 December 2024; accepted 23 December 2024; published online 7 January 2025

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The Journal of Infectious Diseases® 2025;232:567–72

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https://doi.org/10.1093/infdis/jiae642

biorepository. Tuberculosis-preventive treatment was prescribed if applicable. This analysis included all contacts from RePORT-Brazil in whom tuberculosis disease developed during follow-up and had a positive QFT-Plus result at baseline ( $n = 20$ ). There were 40 QFT-Plus-positive controls in whom tuberculosis did not develop, matched by sex, age, and tuberculosis exposure duration. We included only QFT-Plus-positive participants because only 4 progressors were IGRA negative, which could have skewed the analysis. The definitions used for stratification are described in [Supplementary Table 1](#).

### Study Design

A nested case-control (1:2) Brazilian study was conducted to identify cytokines in the supernatant of QFT-Plus samples associated with the risk of progression to tuberculosis disease in QFT-Plus-positive close contacts of individuals with PTB.

### QuantIFERON-TB Assay

Whole blood was incubated in stimulated (TB1 and TB2 antigens), positive control (mitogen), and unstimulated (Nil) tubes, processed according to the manufacturer's instructions (Qiagen). After incubation, supernatants were harvested to measure the IFN- $\gamma$  response, and the remaining supernatants were stored at  $-80^{\circ}\text{C}$  for analysis.

### Multiplex Cytokine Assay

The immunology assays were performed with QFT-Plus supernatants (TB1 tubes only), using the Luminex xMAP INTELLIFLEX System to measure the following biomarkers from a commercially available kit: epidermal growth factor, eotaxin, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, IFN- $\alpha$ 2, IFN- $\gamma$ , interleukin 1 $\alpha$ , 1 $\beta$ , 2, 3, 4, 5, 6, 7, 12p40, 12p70, 13, 15, and 17, interleukin 1 receptor antagonist, interleukin 8 (IL-8), interleukin 10 (IL-10), IFN- $\gamma$  inducible protein, 10 kDa (chemokine [CXC motif] ligand 10 [CXCL10]), chemokine (C-C motif) ligand 2 (CCL2), CCL3, CCL4, tumor necrosis factor (TNF), TNF- $\beta$ , and vascular endothelial growth factor. Biomarker levels were background corrected before analysis, subtracting the signal from a blank sample included in the Luminex assay, according manufacturer instructions, using BELYSA software (version 1.1.0).

### Indian Study Cohort

We evaluated our findings in an Indian cohort of tuberculosis household contacts from the Cohort for Tuberculosis Research by the Indo-US Medical Partnership (C-TRIUMPH) study [6], which followed up participants from August 2014 to December 2017. Immunology assays measured the same cytokines, except for interleukin 12p40 and TNF- $\beta$ , in QuantiFERON Gold supernatants using the Human XL Cytokine Magnetic Luminex Performance Assay 45-plex Fixed Panel (R&D Systems) [7].

This cohort included 20 QFT-positive contacts (8 progressors and 12 nonprogressors).

### Statistical Analysis

#### Descriptive Analysis

For continuous variables, we reported median values and interquartile ranges (IQRs) as measures of central tendency and dispersion. Categorical variables were summarized using frequency counts and proportions (number and percentage). The  $\chi^2$  test was used to compare categorical variables across different study groups. For continuous variables between 2 unmatched groups, we used the Mann-Whitney  $U$  test.  $P$  values  $<.05$  after adjustment for multiple comparisons (false discovery rates) were considered to indicate statistical significance.

#### Inflammatory Profile Analysis

Cytokine data underwent logarithmic transformation ( $\log_{10}$ ), followed by unsupervised hierarchical cluster analysis using Ward's method. Dendrograms were created to visualize Euclidean distances between data points.

#### Feature Selection With a Random Forest Algorithm

To discern variables with the greatest discriminatory potential, we leveraged the random forest algorithm, using all available variables. This machine-learning technique allows us to rank the importance of each variable in distinguishing between progressors and nonprogressors. We used the mean decrease in impurities (MDI) metric for each marker to select the most important variables. Higher MDI values signify greater variable importance, reflecting their contribution to the classification. We established a prespecified MDI threshold of 1 to identify the most important variables.

To validate the accuracy of our selected variables, we executed a random forest validation procedure using a 5-fold cross-validation strategy. In this approach, we divided our data set into 5 mutually exclusive subsets. During each iteration, 4 subsets were used for model training, while the remaining served for testing. We repeated this process 5 times, each time using a different subset for testing. This procedure provided a robust assessment of the predictive power of our model, guarding against overfitting. The average performance score obtained from this validation serves as a reliable indicator of the accuracy of the model.

#### Receiver Operating Characteristic Curve Analysis

We conducted a receiver operating characteristic (ROC) curve analysis using the most relevant variables identified in the feature selection step, to quantify the sensitivity, specificity, and overall discriminatory ability of the model. Performance of the ROC curves were internally validated by averaging the area under the ROC curve (AUC) analyses of repeated

**Table 1. Clinical and Demographic Characteristics of the RePORT-Brazil Study Population**

Characteristic	Study Participants, No. (%) <sup>a</sup>		P Value <sup>b</sup>
	Progressors (n = 20)	Nonprogressors (n = 40)	
Age, median (IQR), y	26.3 (18.3–49.1)	26.4 (17.9–49.9)	.86
Male sex	6 (30.0)	12 (30.0)	>.99
Race			
White	5 (25.0)	2 (5.00)	.30
Black	6 (30.0)	15 (37.5)	
Brown	9 (45.0)	22 (55.0)	
Other	0 (0.00)	1 (2.50)	
Literacy	19 (95.0)	37 (92.5)	>.99
Monthly income			
Above minimal wage	3 (15)	14 (35.0)	.40
Minimal wage or less	9 (45.0)	17 (42.5)	
No income	6 (30.0)	7 (17.5)	
Missing	2 (10)	2 (5)	
BCG vaccine scar	17 (85.0)	37 (92.5)	.58
HIV-positive status	0 (0.00)	0 (0.00)	...
Smoker status	3 (15.0)	10 (25.0)	.74
Secondary smoking	8 (40.0)	17 (42.5)	>.99
Alcohol consumption	6 (30.0)	22 (55.0)	.29
Illicit drug use	1 (5.00)	4 (10.0)	.83
Diabetes mellitus	0 (0.00)	4 (10.0)	.45
Duration of contact per month, median (IQR), h	23.0 (8.00–24.2)	18.0 (5.00–64.5)	.83
Tuberculosis-preventive therapy	5 (25.0)	20 (50.0)	.06

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.

<sup>a</sup>Data represent no. (%) of participants unless otherwise specified.

<sup>b</sup>Comparisons between progressors and nonprogressors were conducted using the Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical variables. *P* values indicate the level of statistical significance for differences between the groups.

(100 times) 10-fold cross-validations. Statistical analyses were performed using R software (version 4.4.2).

## RESULTS

### Baseline Characteristics of Study Participants

The RePORT-Brazil cohort comprised 60 QFT-positive close contacts of patients with PTB, classified based on tuberculosis progression: 20 progressors and 40 nonprogressors. Overall, 70% were female; the median age (IQR) was 26.3 (17.8–49.3) years. The median duration (IQR) from study inclusion to disease in progressors was 8.4 (4.2–15.3) months. Demographic and clinical variables, including age, race, income, HIV status, and consumption habits, did not differ significantly between groups (Table 1). Characteristics of the index case patients were similar for both groups of contacts (Supplementary Table 2).

### Inflammatory Profile of Close Contacts at Baseline According to Tuberculosis Progression Classification

At baseline, progressors exhibited a distinct inflammatory profile compared with nonprogressors, with significantly higher median (IQR) levels of IFN- $\gamma$  (970 [592–1961] vs 444 [335–879] pg/mL; *P* = .02), interleukin 13 (16.4 [8.04–31.3] vs 7.00 [1.49–11.2] pg/mL; *P* = .02), and interleukin 2 (90.6 [59.3–208] vs 33.4 [25.7–84.9]; *P* = .02), respectively. Conversely, median (IQR)

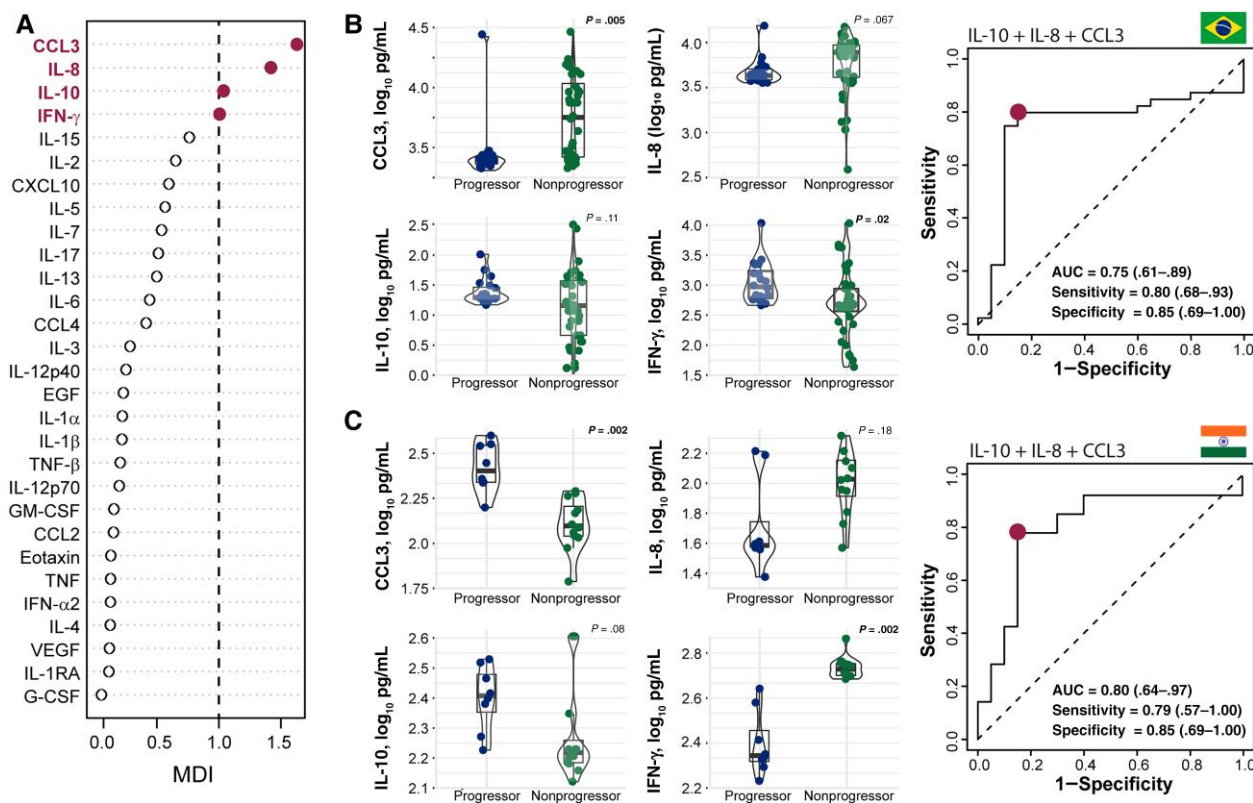
CCL3/macrophage inflammatory protein 1 $\alpha$  levels were lower in progressors (1778 [1626–1910] pg/mL) than in nonprogressors (4475 [1892–9401] pg/mL; *P* = .005). All cytokine measurements are detailed in Supplementary Table 3.

### Biomarker Selection to Distinguish Tuberculosis Progressors

To identify the most relevant biomarkers differentiating groups, we used a random forest algorithm. This analysis revealed that IL-8, IL-10, IFN- $\gamma$ , and CCL3 were the most significant cytokines, with an MDI >1 (Figure 1A), with the last 2 showing a statistically significant difference between groups (Figure 1B). ROC curve analysis demonstrated that CCL3 alone provided the highest AUC of 0.79 (95% confidence interval [CI], .67–.91) with .65 sensitivity (.50–.8) and .90 specificity (.77–1.0). However, the combination of IL-8, IL-10, and CCL3 enhanced predictive performance, with an AUC of 0.75 (95% CI, .61–.90), a sensitivity of .80 (.61–.88), and a specificity of .85 (.69–1.00) (Figure 1B). The ROC analysis assessing each variable individually, and all combinations are described in Supplementary Table 4.

### Indian Cohort Analysis

Of the 20 contacts from the Indian cohort, 55% were female; the median age (IQR) was 32 (6–38) years for progressors and



**Figure 1.** Identification and Validation of an Immune Signature Predicting TB Progression. (A) The MDI plot ranks the importance of cytokines and chemokines in distinguishing progressors from non-progressors. CCL3, IL-8, IL-10, and IFN- $\gamma$  are highlighted as the most important variables with a MDI greater than 1. (B) Violin plots display the distribution of these cytokine levels (log-transformed) in the Brazilian cohort, comparing TB progressors and non-progressors. The ROC curve demonstrates the predictive power of the combined IL-8, IL-10, and CCL3 model in the Brazilian cohort. (C) Evaluation of the immune signature in an independent Indian cohort. Violin plots display the distribution of the same cytokines, showing a similar pattern of differential expression and ROC metrics between progressors and non-progressors if compared to Brazil. Parenthetical ranges in C represent 95% confidence intervals. Abbreviations: AUC, area under the receiver operating characteristic curve; CCL2 and CCL3, chemokine (C-C motif) ligand 2 and 3; CXCL10, chemokine (CXC motif) ligand 10; EGF, epidermal growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL-8 (etc), interleukin 8 (etc); MDI, mean decrease in impurities; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

28 (17–51) years for nonprogressors. Only 1 individual lived with HIV. The median time (IQR) from inclusion to diagnosis of tuberculosis disease was 5.5 (3–16) months (Supplementary Table 5). Similarly to our results, in the ROC analysis of this cohort the IL-8 + IL-10 + CCL3 combination achieved an AUC of 0.80 (95% CI, .67–.94), with a sensitivity of .79 (.57–1.00) and a specificity of .85 (.69–1.00). The complete ROC analysis regarding this cohort is described in Supplementary Table 6.

## DISCUSSION

This study evaluated 2 unique prospective cohorts with a 2-year follow-up of tuberculosis disease development among close contacts of individuals with PTB. We identified an immune signature (IL-8, IL-10, and CCL3) that may predict tuberculosis progression risk in both cohorts. These markers are vital for recruiting immune response cells, regulating inflammation, and supporting granuloma formation to contain the infection [8]. The final model demonstrated strong predictive capability,

underscoring its potential utility in identifying individuals at high risk for PTB. Notably, this model met the World Health Organization (WHO) target product profile (TPP), which specifies a minimum sensitivity and specificity of 75% [4].

To our knowledge, this is the first study to identify a QFT-based immune signature that meets the WHO-TPP for predicting tuberculosis disease progression in contacts. While previous studies have identified potential biomarkers using unbiased omics technologies, these have not fully met the WHO's TPP criteria for sensitivity and specificity [8, 9]. Few prior studies evaluated the inflammatory profile of close contacts using QuantiFERON supernatants, as most biomarker research in tuberculosis has focused on other sample types or methodologies. Among studies with this approach, the one by Daniel et al [7] identified the CXCL10/CCL19 ratio as an accurate predictor of short-term risk of tuberculosis disease progression in a cohort that included both QFT-positive and QFT-negative contacts.

Interestingly, comparing the Brazilian and Indian populations, we observed different trends in the levels of CCL3

and IFN- $\gamma$  in progressors versus nonprogressors. Previous studies analyzing antigen-stimulated cytokines have shown variation in IFN- $\gamma$  responses. Typically, progressors exhibit higher IFN- $\gamma$  levels [10, 11], contrasting with our findings in the Indian cohort, where IFN- $\gamma$  was down-regulated in progressors. However, similar down-regulation has been reported in mice with disseminated tuberculosis [12] and in a study where IFN- $\gamma$ -related genes were down-regulated in progressors after tuberculosis-specific antigen stimulation [13]. Possible explanations include variation in tuberculosis immune response due to genetic and environmental factors, such as exposure levels to tuberculosis and circulating *Mycobacterium tuberculosis* strains across populations. We believe that this finding does not invalidate the signature, as it did not affect the accuracy in predicting tuberculosis disease in the 2 cohorts. It underscores the difficulty of finding an accurate signature for different settings, since tuberculosis immune response can vary.

Despite its promising findings, the current study has several limitations. First, the sample size, while sufficient for initial validation, remains small, which may limit the generalizability of our results. Although evaluated in an independent cohort, our biomarker assessment was limited to QFT-positive individuals, including only 1 person living with HIV. Thus, the applicability of our findings to QFT-negative contacts and people with HIV remains to be explored. There was no sputum testing for tuberculosis contacts, which may have missed subclinical or asymptomatic tuberculosis cases. Moreover, while our study included 2 ethnically and geographically distinct populations, the potential influence of genetic and environmental factors from the host and pathogen, was not fully assessed. Finally, this study did not allow us to fully understand the temporal dynamics of these biomarkers in tuberculosis progression, emphasizing the need for longitudinal studies.

Despite these limitations, the current study identifies a novel plasmatic immune signature (IL-8, IL-10, and CCL3) that may offer a way to predict tuberculosis disease progression in close contacts. Our findings meet the WHO-TPP for tuberculosis predictive tools across distinct populations. Ultimately, these biomarkers hold significant potential to improve diagnosis and intervention for early tuberculosis disease progressors, particularly in high-burden settings, thereby contributing to global tuberculosis control efforts.

### Supplementary Data

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

### Notes

**Acknowledgments.** The authors thank the study participants and the clinical and laboratory platform teams of RePORT Brazil. Special thanks to Elze Leite (FIOCRUZ, Salvador, Brazil), Eduardo Gama (FIOCRUZ, Rio de Janeiro, Brazil), Allyson Guimarães Costa, Bruna da Costa Oliveira Lima, and Amanda Araújo da Costa (Fundação de Medicina Tropical Dr. Heitor Vieira Dourado, Manaus, Brazil), and Hilary Vansell (Vanderbilt University Medical Center, Nashville, Tennessee) for administrative and logistical support.

**Author contributions.** Conceptualization: B. M. F. N., M. A. P., and B. B. A. Data curation: M. C. F., C. S., M. A. P., and B. B. A. Investigation: B. M. F. N., E. A. D., M. C. F., V. C. R., A. L. K., M. C. S., T. R. S., M. A. P., A. G., L. E. H., and B. B. A. Formal analysis: M. A. P., and B. B. A. Funding acquisition: A. G., L. E. H., T. R. S., and B. B. A. Methodology: F. R., A. M. S. A., M. A. P., and B. B. A. Project administration: M. C. F., T. R. S., M. A. P., and B. B. A. Resources: B. M. F. N., T. R. S., M. A. P., and B. B. A. Software: M. A. P. and B. B. A. Supervision: T. R. S. and B. B. A. Writing—original draft: B. M. F. N., M. A. P., and B. B. A. Writing—review and editing: All authors.

**Disclaimer.** The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

**Financial support.** This work was supported by the Fundação Oswaldo Cruz (B. B. A.); the Intramural Research Program of the Fundação José Silveira (B. B. A.); Departamento de Ciência e Tecnologia—Secretaria de Ciência e Tecnologia, Ministério da Saúde (grant 25029.000507/2013-07 to V. C. R.); the National Institute of Allergy and Infectious Diseases (grant U01-AI069923 to M. C. F., V. C. R., A. L. K., T. R. S., and B. B. A.); the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), USA (NIH R01 AI147765, to B.B.A. and T.R.S.); the Conselho Nacional de Desenvolvimento Científico e Tecnológico (support to V. C. R., A. L. K., M. C. S., and B. B. A. as senior investigators and fellowship to M. A. P.); and the Rio de Janeiro Research Council/FAPERJ (Scientist of Our State fellowship to A. L. K.). The Indian study was supported by the Indian Council of Medical Research (grant 5/8/5/45/Adhoc/2022/ECD-1); the Regional Prospective Observational Research for Tuberculosis India Consortium, supported by federal funds from the government of India's Department of Biotechnology; and the Office of AIDS Research, National Institute of Allergy and Infectious Diseases, with funds distributed in part by CRDF Global (awards DAA3-19-65671-1 and DAA3-18-64774).

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

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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