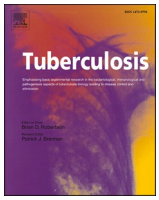
Tuberculosis 156 (2026) 102720

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: www.elsevier.com/locate/tube



Plasma biomarkers CRP, iFABP, and zonulin as predictors of tuberculosis progression in household contacts of pulmonary TB patients

Anuradha Rajamanickam [a,*], Evangeline Ann Daniel [b,c], Nikhil Gupte [d,e], Kannan Thiruvengadam [f], Padmapriyadarsini Chandrasekaran [b,c], Sathyamurthi Pattabiraman [b,c], Brindha Bhanu [b,c], Amsaveni Sivaprakasam [b,c], Mandar Paradkar [d,e], Vandana Kulkarni [d,e], Rajesh Karyakarte [g], Vidya Mave [d,e,h], Amita Gupta [h], Luke Elizabeth Hanna [b,c], Subash Babu [a,i]

[a] National Institute of Health-National Institute of Allergy and Infectious Diseases-International Center for Excellence in Research, Chennai, India
[b] Indian Council of Medical Research (ICMR)- National Institute for Research in Tuberculosis, Chennai, India
[c] University of Madras, Chennai, India
[d] BJ Government Medical College-Johns Hopkins Clinical Research Site, Pune, India
[e] Johns Hopkins Center for Infectious Diseases in India, Pune, India
[f] Indian Council of Medical Research (ICMR)- Vector Control Research Centre, Puducherry, India
[g] BJ Government Medical College and Sassoon General Hospitals, Pune, India
[h] Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[i] Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

ARTICLE INFO

Keywords:
Plasma biomarkers
Tuberculosis
Latent tuberculosis
Progression
APP
MTMs

ABSTRACT

Background: Identifying host biomarkers associated with progression from *Mycobacterium tuberculosis* infection to active tuberculosis (TB) could support early risk stratification in household contacts (HHCs). This exploratory study evaluated baseline plasma immune biomarkers in HHCs of pulmonary TB (PTB) patients to assess their association with subsequent disease development.

Methods: We analyzed baseline plasma samples from 15 progressors and 29 non-progressors enrolled from PTB-affected households. Acute-phase proteins (α-2-macroglobulin (α-2-M), C-reactive protein [CRP], haptoglobin (Hp), serum amyloid P (SAP)) and microbial translocation markers (lipopolysaccharide, lipid-binding protein, endotoxin core antibodies IgG, intestinal fatty acid-binding protein [iFABP], sCD14, and zonulin) were measured using Luminex and ELISA. Logistic regression and ROC analyses were performed as exploratory assessments of biomarker associations.

Results: Higher baseline levels of CRP, iFABP, and zonulin were observed among progressors compared with non-progressors. In univariable analyses, these biomarkers showed strong discriminatory ability (AUC $\geq$0.90), although estimates should be interpreted cautiously given the small sample size. A combined model including CRP, iFABP, and zonulin demonstrated high discriminatory performance (AUC 0.99 [95 % CI: 0.97–1.00]), but confidence intervals reflect the imprecision inherent to the limited dataset.

Conclusions: In this exploratory cohort, elevated CRP, iFABP, and zonulin were associated with progression to active TB among household contacts. These preliminary findings suggest potential involvement of inflammatory and gut-barrier pathways in TB progression and warrant validation in larger, independent cohorts to define their translational utility.

1. Introduction

Mycobacterium tuberculosis (M.tb) remains a major global health threat, with an estimated 10.8 million new cases reported in 2023. Although nearly one-quarter of the world's population carries latent TB infection (LTBI), only 5–10 % will progress to active TB disease over

* Corresponding author. Department of ICER, #1, Mayor Sathyamoorthy Road, National Institute for Research in Tuberculosis, Chennai, 600031, India.
E-mail addresses: anuradha@icerindia.org, anuradha.icer@gmail.com (A. Rajamanickam).

https://doi.org/10.1016/j.tube.2025.102720
Received 10 September 2025; Received in revised form 26 November 2025; Accepted 8 December 2025
Available online 11 December 2025

their lifetime [1]. Progression is influenced by complex host–pathogen interactions, and understanding these mechanisms is critical for TB control, particularly in high-burden settings [2,3].

Current diagnostic tools such as the tuberculin skin test (TST) and interferon-gamma release assays (IGRA) have important limitations: they cannot distinguish LTBI from active TB (ATB), nor can they reliably reflect dynamic stages of *M.tb* infection [4,5]. LTBI is increasingly recognized as a spectrum of asymptomatic states with variable risks of progression, underscoring the need for affordable and accessible risk-stratification biomarkers. Such tools are essential for reducing TB morbidity and mortality and for advancing global TB elimination goals [6,7].

Host–pathogen interactions in TB involve distinct immune signatures, including acute-phase proteins (APPs) and microbial translocation markers (MTMs), both of which have shown promise as diagnostic or prognostic indicators [8]. Microbial translocation, resulting from increased intestinal permeability, can lead to endotoxemia and systemic immune activation, a phenomenon observed in *M.tb* infections [9,10]. MTMs such as lipopolysaccharide (LPS), lipid-binding protein (LBP), soluble CD14 (sCD14), and endotoxin core antibodies (EndoCAb) are altered in TB, HIV, and parasitic infections [11–13].

Among APPs, C-reactive protein (CRP) and haptoglobin have been associated with TB disease activity. CRP is widely used as a diagnostic adjunct, especially in pediatric TB, while haptoglobin has been proposed as a marker of TB progression [14–16]. Despite these findings, data from high-burden regions such as India remain limited, particularly regarding how these markers behave in household contacts at risk of progression [17,18].

In this study, we evaluated APPs and MTMs in household contacts of pulmonary TB patients to identify biomarker patterns associated with subsequent disease progression. By comparing progressors (those who developed active TB) with non-progressors, we aimed to explore a biomarker signature that may assist early identification of individuals at higher risk of developing active TB.

2. Methods

2.1. Informed consent and ethical approval

This study was approved by the Institutional Review Boards and Ethics Committees of Johns Hopkins University (JHU), USA; Byramjee Jeejeebhoy Government Medical College (BJGMC), Pune, India; and the ICMR-National Institute for Research in Tuberculosis (ICMR-NIRT), Chennai, India (ICMR-NIRT-NIRT-ICE-2020-021), and was conducted in accordance with ethical guidelines. Written informed consent/assent was obtained from all the recruited study participants.

2.2. Study cohort

A cohort of healthy household contacts (HHCs) of newly diagnosed pulmonary TB patients was enrolled from two sites: ICMR-NIRT (Chennai) and BJGMC (Pune), India, as part of the Indo-US C-TRI-UMPH study. Participants, including both progressors and non-progressors, were followed longitudinally between August 2014 and December 2017. Study design and methodology have been described previously [19].

2.3. Participant classification

Study participants were grouped according to predefined criteria (Suppl.Table 1). All HHCs underwent comprehensive clinical and laboratory evaluations for TB at baseline and during scheduled follow-ups. Definitions for TB progressors, distinguishing between confirmed and probable cases are included in SupplTable II. Additional sample collection was discontinued if a participant was diagnosed with active TB.

2.4. Screening and monitoring

At enrollment, all participants underwent tuberculin skin testing (TST) and an interferon-gamma release assay (IGRA). Those who initially tested negative were retested during follow-up. T-SPOT.TB was not performed in this study; IGRA was used as the immunological test for detecting *M. tuberculosis* infection. TST and IGRA results were compared between progressors and non-progressors.

Active TB was diagnosed using a combination of chest radiography, sputum smear microscopy, culture, and GeneXpert MTB/RIF testing. Individuals with evidence of active TB at baseline were excluded. Progressors were defined as HHCs who developed active TB during follow-up, while non-progressors were randomly selected HHCs who remained disease-free throughout the study.

2.5. Sample collection, transport, and storage

Blood samples were collected via venipuncture under standardized conditions to minimize pre-analytical variability. Plasma was transported at ambient temperature, centrifuged upon arrival, aliquoted into single-use tubes to avoid freeze–thaw cycles, and stored at −80 °C until analysis.

2.6. Diagnostic tests for active TB

Sputum samples were tested using GeneXpert MTB/RIF, Löwenstein–Jensen (LJ) culture, and/or Mycobacterial Growth Indicator Tube (MGIT) liquid culture. Participants with a positive result by any method were classified as confirmed TB cases. For progressors, drug-susceptibility testing (DST) was performed using GeneXpert and MGIT 960 phenotypic DST. All available isolates were confirmed to be drug-susceptible *M. tuberculosis* with no rifampicin or isoniazid resistance detected.

2.7. Biomarker measurements

Plasma levels of α-2 macroglobulin, CRP, haptoglobin, and SAP were measured using the Milliplex MAP Human CVD Panel (Millipore) on a multiplex platform. Samples were heat-treated at 75 °C for 5 min to inactivate endotoxin inhibitors. Microbial translocation markers were measured using commercial ELISA kits: LPS by LAL assay; LBP, EndoCAb IgG, iFABP, and sCD14 from Cell Sciences/Hycult Biotech; and zonulin from MyBiosource. All biomarkers were measured from baseline plasma collected at enrollment, prior to the development of active TB.

2.8. Statistical analysis

Data were analyzed using R (v4.2.0) and JMP (v17.0.0). Baseline characteristics were compared between progressors and non-progressors using the Mann–Whitney *U* test (continuous variables) and Fisher's exact test (categorical variables). Median biomarker levels were compared using the Mann–Whitney *U* test, with $p \leq 0.05$ considered significant.

Logistic regression and ROC analyses were used to evaluate the association and exploratory discriminatory performance of individual biomarkers. Cut-off thresholds for sensitivity and specificity were identified using the Youden Index. Because of the small sample size and case–control design, sensitivity and specificity values are presented as exploratory point estimates, and confidence intervals were generated to reflect uncertainty. Random Forest analysis was performed to identify biomarkers contributing most strongly to group separation while accounting for variable correlations. Given the limited number of progressors, multivariable analyses were exploratory; biomarkers were evaluated with and without adjustment for key covariates (IGRA status, diabetes, and nutritional indicators) to assess robustness. PPV and NPV were interpreted cautiously because they are highly sensitive to

prevalence assumptions inherent to case–control designs.

3. Results

3.1. Study cohort

Among 1051 household contacts (HHCs) enrolled between August 2014 and December 2017, [19]. 20 individuals (1.9 %) developed active TB within two years, with time to onset ranging from 3 to 21 months. Baseline plasma samples were available for 15 of these progressors, and 29 non-progressors were randomly selected for comparison. None of the participants were HIV-positive, and no progressors had diabetes at baseline. The study design is shown in Supplementary Fig. 1, and cohort characteristics are presented in Table 1. TST and IGRA results were available for all participants. Although IGRA positivity was more frequent among progressors than non-progressors, the difference was not statistically significant ($p = 0.11$). Similarly, TST positivity did not differ significantly between the two groups. These findings suggest that baseline TST/IGRA status alone had limited ability to distinguish individuals who progressed to active TB in this cohort, in contrast to the biomarker differences observed in plasma.

3.2. Levels of acute phase proteins in progressors and non-progressors

Plasma levels of acute-phase proteins were higher in TB progressors compared to non-progressors (Fig. 1). Median concentrations were: α-2-M (1423 vs. 1075 pg/mL), CRP (34.4 vs. 18.6 pg/mL), haptoglobin (205 vs. 140 pg/mL), and SAP (3.5 vs. 1.8 pg/mL). Table 2 summarizes biomarker levels by progressor status. As shown in Fig. 2, progressors had significantly elevated levels of all four acute-phase proteins.

3.3. Levels of microbial translocation markers in progressors and non-progressors

Plasma levels of microbial translocation markers were also evaluated in both groups. The median levels were LPS (0.064 ng/mL in progressors vs. 0.05 ng/mL in non-progressors), LBP (458 pg/mL in progressors vs. 378 pg/mL in non-progressors), EndoCAb (469 GMU/mL in progressors vs. 312 GMU/mL in non-progressors), sCD14 (23026 pg/mL in progressors vs. 17838 pg/mL in non-progressors), iFABP (268 pg/mL in progressors vs. 170 pg/mL in non-progressors), and zonulin (34 ng/mL in progressors vs. 27 ng/mL in non-progressors). As depicted in Fig. 3, progressors demonstrated significantly elevated levels of all these markers compared to non-progressors.

Table 1
Baseline characteristics by progressor status.

Characteristic	Non Progressors N = 29[a]	Progressors N = 15[a]	p-value[b]
Age	28 (25, 32)	29 (21, 38)	0.6
Gender			0.8
Female	14 (48 %)	8 (53 %)	
Male	15 (52 %)	7 (47 %)	
IGRA Status			0.11
Negative	19 (66 %)	6 (40 %)	
Positive	10 (34 %)	9 (60 %)	
TST Status[c]			0.18[d]
– <10 mm	18 (62 %)	7 (47 %)	
– ≥10 mm	11 (38 %)	8 (53 %)	
HIV Status	All are Negative	All are Negative	
T2 Diabetes Status	All are Negative	All are Negative	

[a] Median (Q1, Q3); n (%).
[b] Wilcoxon rank sum test; Pearson's Chi-squared test; Wilcoxon rank sum exact test.
[c] TST performed at baseline; individuals negative at baseline were retested per protocol.
[d] p-value from Fisher's exact test.

Table 2
Summary of biomarkers by progressor status.

Characteristic	Non-Progressors N = 29[a]	Progressors N = 15[a]	p-value[b]
α-2- Macroglobin (pg/ml)	1075 (681, 1323)	1423 (1,072, 1532)	0.036
CRP (pg/ml)	19 (13, 26)	34 (31, 38)	<0.001
Haptoglobin (pg/ml)	140 (108, 171)	205 (157, 237)	<0.001
Serum Amyloid-P (pg/ml)	1.79 (1.35, 2.59)	3.45 (2.63, 4.15)	<0.001
LPS EU/ml	0.050 (0.043, 0.058)	0.064 (0.058, 0.073)	<0.001
sCD14 (pg/ml)	17,838 (13,152, 20,354)	23,026 (21,064, 27,867)	<0.001
LBP (ng/ml)	378 (336, 451)	458 (393, 476)	0.015
EndoCAb (GMU/ml)	312 (241, 368)	469 (355, 502)	<0.001
iFABP (pg/ml)	170 (150, 189)	268 (224, 296)	<0.001
Zonulin (ng/ml)	27.0 (26.0, 29.0)	34.0 (32.0, 37.0)	<0.001

[a] Median (Q1, Q3); n (%).
[b] Wilcoxon rank sum test; Wilcoxon rank sum exact test.

3.4. Biomarkers by progressors status

We compared biomarkers of inflammation, microbial translocation, and gut epithelial integrity between non-progressors (n = 29) and progressors (n = 15). The results demonstrated significantly higher levels of several biomarkers among progressors compared to non-progressors (Table II).

Inflammatory markers, including α-2-M, CRP, Hp, and SAP, were significantly elevated in progressors. Median α-2-M levels were 1423 (1072–1532) in progressors compared to 1075 (681–1323) in non-progressors ($p = 0.036$). Similarly, CRP [34 (31–38) vs. 19 (13–26); $p < 0.001$], Hp [205 (157–237) vs. 140 (108–171); $p < 0.001$], and SAP [3.45 (2.63–4.15) vs. 1.79 (1.35–2.59); $p < 0.001$] levels were significantly higher in progressors.

Markers of microbial translocation also showed significant differences. Progressors had higher levels of LPS [0.064 (0.058–0.073) vs. 0.050 (0.043–0.058); $p < 0.001$], sCD14 [23,026 (21,064–27,867) vs. 17,838 (13,152–20,354); $p < 0.001$], LBP [458 (393–476) vs. 378 (336–451); $p = 0.015$], and EndoCAb [469 (355–502) vs. 312 (241–368); $p < 0.001$].

Furthermore, markers of gut epithelial damage, including iFABP and zonulin, were also significantly elevated in progressors. iFABP levels were 268 (224–296) compared to 170 (150–189) in non-progressors ($p < 0.001$), while zonulin levels were 34.0 (32.0–37.0) versus 27.0 (26.0–29.0), respectively ($p < 0.001$).

These findings collectively indicate a heightened inflammatory and microbial translocation profile in individuals who progressed, supporting the role of gut barrier dysfunction and systemic immune activation in disease progression.

Determination to assess the differences in the biomarkers using Univariable Logistic Regression analysis.

To identify biomarkers associated with disease progression, we performed univariable logistic regression analysis (Table 3). Several biomarkers showed significant associations with progression status.

3.5. Plasma signature of acute phase proteins and microbial translocation markers as biomarkers for active tuberculosis progression

Random forest followed by multiple logistic regression was used to evaluate the independent association of selected biomarkers with disease progression. The model included iFABP, CRP, and zonulin, based on their biological relevance and significance in univariable analyses.

Among these, zonulin emerged as the strongest predictor, with an odds ratio (OR) of 2.23 [95 % CI: 1.21–8.6; $p = 0.07$], suggesting a trend toward statistical significance and a potential independent role in predicting disease progression. Although iFABP demonstrated excellent diagnostic performance with a sensitivity of 93 % and specificity of 100

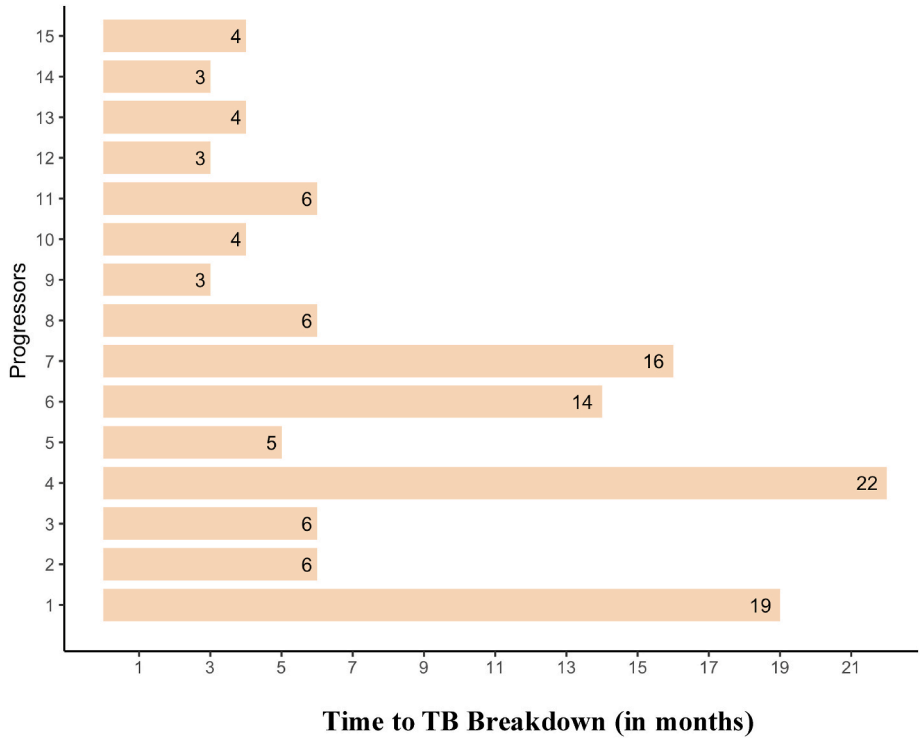


Fig. 1. Time to TB breakdown in the Progressor Group This figure displays the time to TB breakdown among the recruited progressor individuals (n = 15). The X-axis represents the time to TB breakdown in months, and the Y-axis represents individual progressors.

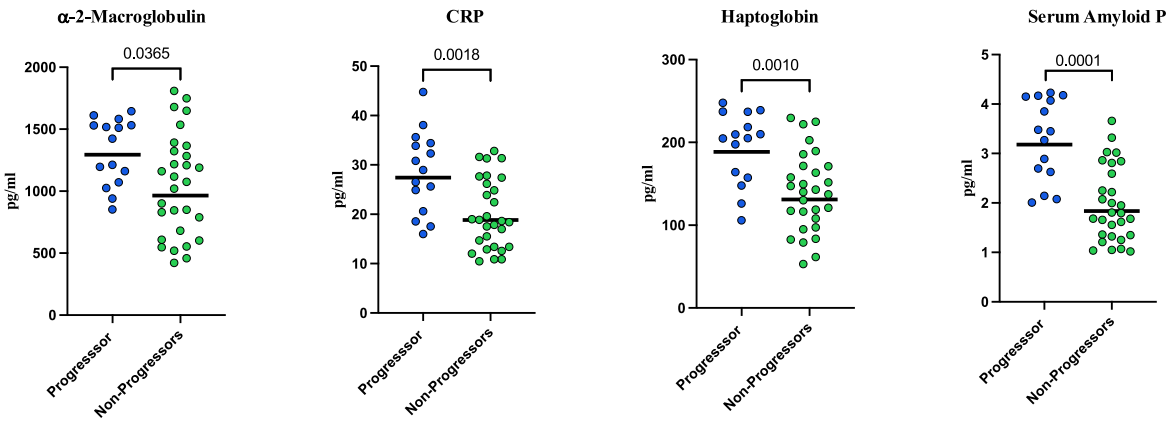


Fig. 2. Levels of acute phase proteins of Progressors and Non-progressors: Plasma levels of α-2-M, CRP, haptoglobin, and SAP were measured in progressors (n = 15) and non-progressors (n = 29). The data are presented as scattered plots, with each circle representing an individual. p-values were calculated using the Mann-Whitney *U* test, followed by Holm's multiple correction.

%, its association in the adjusted model did not reach statistical significance (OR: 1.04 [0.99–1.16]; $p = 0.21$). Despite a wide confidence interval, CRP showed a modest association with progression (OR: 1.30 [0.86–2.9]; $p = 0.21$). The combined model showed strong discriminatory power with an AUC of 0.99 [95 % CI: 0.97–1.00], indicating near-perfect classification performance, largely driven by iFABP and zonulin (Table 4).

3.6. Sensitivity analysis excluding early progressors

To determine whether elevated biomarker levels reflected incipient disease rather than associations with subsequent progression, we repeated the analyses after excluding the six progressors diagnosed within the first four months of follow-up. The patterns observed in the main analysis remained consistent: CRP, iFABP, and zonulin showed similar effect sizes and AUC values, although confidence intervals widened and p-values increased due to the smaller sample size (Supplementary Table III). These findings indicate that early, subclinical disease did not fully account for the biomarker differences observed at baseline.

4. Discussion

Accurate TB diagnosis remains challenging due to the lack of a definitive gold-standard test. This hampers the discovery of reliable biomarkers, especially for identifying individuals with latent TB infection (LTBI) who are at high risk of progressing to active disease—key for targeted preventive therapy [20,21]. Current diagnostic tools like TST and IGRA offer useful insights but have key limitations [22–24]. Therefore, identifying sensitive biomarkers to predict progression from

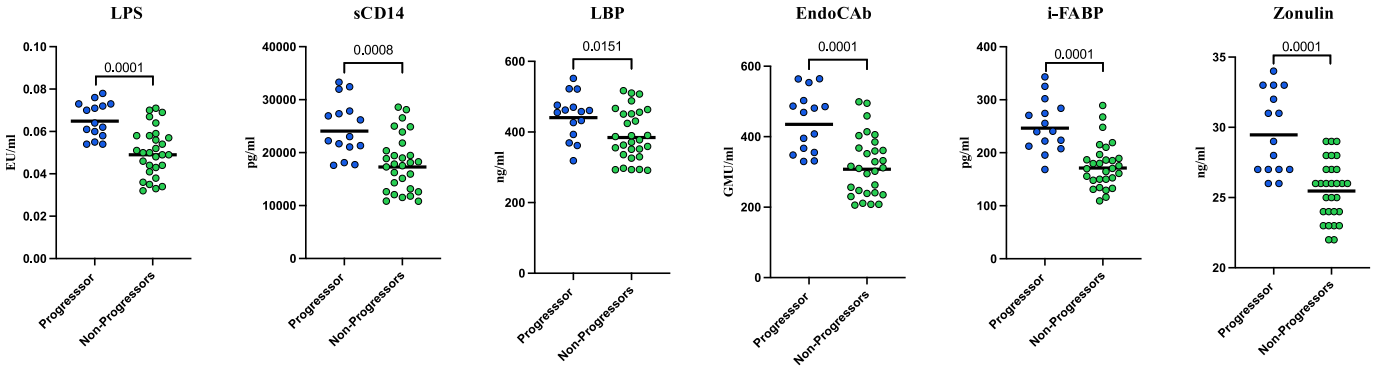


Fig. 3. Levels of microbial translocation markers in Progressors and Non-progressors: Plasma levels of LPS, LBP, EndoCAb, iFABP, sCD14, and zonulin were measured in progressors (n = 15) and non-progressors (n = 29). The data are presented as scattered plots, with each circle representing an individual. p-values were calculated using the Mann-Whitney *U* test, followed by Holm's multiple correction.

Table 3
Univariable Logistic Regression analysis to assess the differences in the biomarkers.

Characteristics	OR [CI] (p-value)	Sensitivity	Specificity	ROC [CI]
α-2- Macroglobin (pg/ml)	1 [1.00, 1.00] (0.033)	1	0.41	0.69 [0.54–0.85]
CRP (pg/ml)	1.44 [1.20, 1.96] (0.002)	0.87	0.86	0.94 [0.87–1]
Haptoglobin (pg/ml)	1.03 [1.01, 1.04] (0.003)	0.67	0.86	0.8 [0.66–0.94]
Serum Amyloid-P (pg/ml)	6.31 [2.53, 22.1] (<0.001)	1	0.62	0.88 [0.78–0.98]
sCD14 (pg/ml)	1 [1.00, 1.00] (0.003)	0.80	0.76	0.8 [0.67–0.93]
LBP (ng/ml)	1.01 [1.00, 1.02] (0.024)	0.80	0.62	0.72 [0.57–0.88]
EndoCAb (GMU/ml)	1.02 [1.01, 1.03] (0.001)	1	0.59	0.84 [0.72–0.95]
iFABP (pg/ml)	1.04 [1.02, 1.08] (<0.001)	1	0.79	0.93 [0.86–1]
Zonulin (ng/ml)	2.33 [1.53, 4.92] (0.003)	1	0.79	0.94 [0.88–1]
IGRA Status		0.6	0.66	0.63 [0.47–0.78]
Negative				
Positive	2.85 [0.80, 10.8] (0.11)			

Among inflammatory markers, CRP was a strongly associated with progression status with an odds ratio (OR) of 1.44 [95 % CI: 1.20–1.96; p = 0.002], demonstrating high sensitivity (87 %) and specificity (86 %), and an area under the ROC curve (AUC) of 0.94 [0.87–1.00]. Serum amyloid P exhibited an even stronger association with progression (OR: 6.31 [2.53–22.1]; p < 0.001), with perfect sensitivity (100 %), moderate specificity (62 %), and an AUC of 0.88 [0.78–0.98]. Haptoglobin was also significantly associated (OR: 1.03 [1.01–1.04]; p = 0.003; AUC: 0.80 [0.66–0.94]).

Markers of microbial translocation and immune activation also showed significant associations. sCD14 had an OR of 1.00 [1.00–1.00]; p = 0.003 with AUC 0.80 [0.67–0.93], while LBP (OR: 1.01 [1.00–1.02]; p = 0.024) and EndoCAb (OR: 1.02 [1.01–1.03]; p = 0.001) were also demonstrated discriminatory ability, with AUCs of 0.72 and 0.84, respectively.

Gut epithelial damage markers, iFABP and zonulin, showed the strongest associations with progression status. iFABP had an OR of 1.04 [1.02–1.08]; p < 0.001, with both perfect sensitivity (100 %) and a strong AUC of 0.93 [0.86–1.00]. Zonulin similarly showed a strong association (OR: 2.33 [1.53–4.92]; p = 0.003), with an AUC of 0.94 [0.88–1.00] and 100 % sensitivity. IGRA status did not reach statistical significance (OR: 2.85 [0.80–10.8]; p = 0.11), and its discriminatory capacity was limited (AUC: 0.63 [0.47–0.78]). In summary, inflammatory and gut barrier dysfunction markers, particularly CRP, SAP, iFABP, and zonulin, demonstrated strong biomarkers associated with progression risk.

Table 4 A
Multiple logistic regression.

Characteristic	OR [CI] (p-value)	Sensitivity	Specificity	AUC [CI] (p-value)
iFABP (pg/ml)	1.04 [0.99–1.16] (0.21)	0.93	1	0.99 [0.97–1]
CRP (pg/ml)	1.3 [0.86–2.9] (0.21)			
Zonulin (ng/ml)	2.23 [1.21–8.6] (0.07)			

Note: Random forest analysis was done to identify biomarkers that were most relevant for differences in progressors and non-progressors.

Table 4 B
Exploratory performance characteristics of key biomarkers associated with TB progression

Exploratory performance estimates for the three biomarkers with the strongest group differences—iFABP, CRP, and zonulin—are summarized in Table 4B. AUC values are presented with 95 % confidence intervals, while sensitivity and specificity represent exploratory point estimates derived from ROC-based thresholds (Youden Index).

Biomarker	OR [95 % CI] (p-value)	Sensitivity	Specificity	AUC [95 % CI]
iFABP (pg/ml)	1.04 [0.99–1.16] (0.21)	1.00	0.79	0.93 [0.86–1.00]
CRP (pg/ml)	1.3 [0.86–2.9] (0.21)	0.87	0.86	0.94 [0.87–1.00]
Zonulin (ng/ml)	2.23 [1.21–8.6] (0.07)	1.00	0.79	0.94 [0.88–1.00]

Note: Sensitivity and specificity values reflect dataset-derived thresholds using the Youden Index and should be interpreted as exploratory due to small sample size. AUCs are presented with 95 % confidence intervals.

LTBI to active TB is crucial.

In our cohort, TST and IGRA results showed limited discriminatory ability for TB progression. IGRA positivity was higher among progressors (60 %) than non-progressors (34 %), but this difference was not statistically significant, consistent with previous findings that these tests primarily reflect immunological sensitization rather than progression risk. Similarly, TST positivity did not distinguish individuals who later developed active TB from those who remained disease-free. These observations underscore the constrained utility of traditional immunological tests and highlight the relevance of plasma biomarkers—including CRP, iFABP, and zonulin—which demonstrated stronger exploratory discriminatory performance in our analysis.

This study evaluated acute-phase proteins and microbial translocation markers as predictors of TB progression. Elevated levels of these biomarkers, reflecting systemic inflammation and immune activation,

were significantly associated with progression to active TB. Notably, CRP demonstrated high sensitivity (93 %) but moderate specificity (60 %) in distinguishing individuals who developed active TB from those who did not [16,25]. CRP has been proposed as a simple point-of-care diagnostic tool for pulmonary TB [26–28]. CRP is an effective screening tool that can enhance the accuracy of tuberculosis diagnosis in people living with HIV [16,29–31]. Additionally, acute-phase proteins such as α-2-M, Hp, and SAP have been identified as promising biomarkers for TB diagnosis [31,32]. These proteins have also been reliable baseline predictors for treatment failure in pulmonary TB [14]. Our study confirms that all four of these acute-phase proteins are elevated in TB progressors compared to non-progressors, reinforcing their potential role as valuable biomarkers in TB prognosis.

In comparison to the study by Dunik et al., which found CRP to be a valuable marker for TB risk stratification with varying predictive accuracy based on threshold levels [33], our exploratory model highlighted that while CRP alone had useful discriminatory ability, the combination of CRP, iFABP, and zonulin demonstrated superior performance in distinguishing progressors from non-progressors. Although PPV and NPV values are influenced by prevalence assumptions in case–control designs and should be interpreted cautiously, the observed biomarker trends suggest that a multi-marker panel may enhance identification of individuals at elevated risk of progression. These associations require validation in larger, independent cohorts. Thus, while CRP remains a valuable tool, our findings suggest that incorporating iFABP and zonulin may enhance the ability to identify individuals who are more likely to progress, although these associations require validation in larger cohorts.

Beyond acute-phase proteins, microbial translocation markers—including LPS, sCD14, and LBP—were associated with increased risk of TB progression. Microbial translocation, often due to compromised mucosal integrity, allows bacterial components like LPS to enter circulation without overt bacteremia [34,35]. Elevated LPS levels have been reported in TB patients with advanced pulmonary disease [35]. while sCD14, an LPS co-receptor, is elevated in TB, particularly in individuals with HIV co-infection [9,36]. Our group has previously shown increased sCD14 in TB patients with coexisting diabetes, suggesting heightened immune activation. LBP, another acute-phase reactant, has also been implicated in chronic immune activation in TB-HIV co-infection [37]. Together, these findings indicate exploratory associations between MTMs and TB progression.

iFABP, a cytoplasmic protein released during enterocyte injury [38]. and zonulin, a physiological regulator of epithelial barrier integrity [38,39], were also elevated in progressors. In individuals with LTBI and HIV co-infection, increased iFABP and sCD14 indicate ongoing intestinal damage [39]. Elevated plasma Zonulin levels have also been associated with asthma and immune activation [40]. In our cohort, significantly higher levels of iFABP, EndoCAb, and zonulin were observed among progressors, suggesting a potential link between intestinal barrier disruption and TB progression risk.

Increased intestinal permeability and microbial translocation are consistent with elevated iFABP and zonulin, which indicate tight-junction dysregulation and enterocyte injury, respectively. Such barrier disruption may permit translocation of bacterial products (e.g., LPS), leading to systemic innate immune activation, monocyte/macrophage priming, and heightened inflammatory cytokine responses that may impair the containment of *M. tuberculosis* (Vancamelbeke M, Expert Rev Gastroenterol Hepatol. 2017; Derikx JP, PLoS One. 2008; Brenchley JM, Nat Med. 2006). Recent research on the gut–lung axis further illustrates how intestinal dysbiosis and altered microbial metabolites can influence pulmonary immunity and TB outcomes (Alvarado-Peña N, Front Immunol. 2023; Enjeti S, Front Microbiol. 2023; Budden KF, J Bacteriol. 2021). Our findings align with this emerging concept, suggesting that gut barrier dysfunction and microbiota-driven immune activation may contribute to progression from latent to active TB, warranting further mechanistic investigation.

Our results can be contextualized within the World Health Organization's (WHO) 2017 Target Product Profile (TPP) for TB progression diagnostics, which emphasizes the need for sensitive, specific, and implementable tools, particularly in high-burden settings [41]. Several WHO-endorsed and candidate TB risk signatures—such as RISK6, COR, and other transcriptomic panels—primarily rely on interferon-stimulated gene expression to identify individuals at short-term risk of progression (Penn-Nicholson A, Lancet Respir Med. 2020; Warsinske HC, Nat Commun. 2018; Scriba TJ, Nat Rev Immunol. 2021). These transcriptomic tests require specialized laboratory capacity and may be affected by intercurrent infections, limiting their widespread implementation. By comparison, CRP, iFABP, and zonulin are simple plasma-based biomarkers reflecting inflammatory and gut-barrier biology not captured by current transcriptomic signatures. While exploratory, the observed discriminatory differences suggest that these biomarkers may complement existing gene-expression signatures. Larger validation studies are required to directly compare and integrate biomarker modalities.

5. Limitations

This study has several limitations. The small sample size and variability in progression timelines may limit generalizability. Only 5 of the 15 progressors were culture-confirmed, and the remainder were classified as probable cases based on clinical and radiological criteria, introducing some diagnostic uncertainty. Six individuals progressed within four months of enrollment, raising the possibility that elevated biomarkers reflected incipient disease; however, sensitivity analyses excluding these early cases demonstrated similar trends, suggesting that associations were not solely driven by subclinical disease. Because biomarkers were measured only at baseline, temporal dynamics could not be assessed. Longitudinal profiling will be necessary to determine whether biomarker elevations precede progression or reflect early disease activity. We did not evaluate biomarker associations with bacterial load, which may provide additional insight. No household contacts received TB preventive therapy, aligning with eligibility guidelines at the time. Sensitivity and specificity estimates were derived from dataset-based thresholds and should be interpreted cautiously given the small sample size. The study included only adults, limiting applicability to children and older adults, who have distinct immunological risk profiles. Finally, fully adjusted multivariable models were not feasible due to limited events; therefore, residual confounding cannot be excluded. Validation in larger cohorts will be required to establish independent associations and translational relevance.

6. Conclusion

Our findings add to the growing evidence supporting plasma-based biomarkers for identifying individuals at increased risk of progressing from latent TB infection (LTBI) to active disease. Among the biomarkers evaluated, CRP, iFABP, and zonulin consistently demonstrated strong discriminatory performance across both Random Forest and logistic regression analyses, highlighting their potential utility for TB risk stratification and early intervention.

Validation in larger and more diverse cohorts will be essential to assess the generalizability of these exploratory findings. Such studies could help inform the development of rapid, point-of-care diagnostic tools to enable earlier preventive therapy. Longitudinal analyses may further clarify the temporal dynamics of these biomarkers and their relevance to TB transmission and vaccine responsiveness. Overall, by advancing non–sputum-based biomarker research, this study provides a foundation for improving TB diagnosis and management, particularly in high-burden settings.

CRediT authorship contribution statement

Anuradha Rajamanickam: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Evangeline Ann Daniel:** Methodology, Investigation. **Nikhil Gupte:** Formal analysis, Data curation. **Kannan Thiruvengadam:** Formal analysis, Data curation. **Padmapriyadarsini Chandrasekaran:** Supervision, Resources, Project administration, Investigation, Funding acquisition. **Sathyamurthi Pattabiraman:** Methodology, Investigation. **Brindha Bhanu:** Methodology, Investigation. **Amsaveni Sivaprakasam:** Supervision, Project administration, Investigation. **Mandar Paradkar:** Visualization, Supervision, Resources, Investigation. **Vandana Kulkarni:** Visualization, Supervision, Resources, Project administration. **Rajesh Karyakarte:** Visualization, Supervision, Resources, Project administration, Investigation. **Vidya Mave:** Visualization, Supervision, Resources, Project administration, Investigation. **Amita Gupta:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Investigation, Funding acquisition. **Luke Elizabeth Hanna:** Visualization, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition. **Subash Babu:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Ethics statement

This study was approved by the Institutional Review Boards and Ethics Committees of Johns Hopkins University (JHU), USA; Byramjee Jeejeebhoy Government Medical College (BJGMC), Pune, India; and the ICMR-National Institute for Research in Tuberculosis (ICMR-NIRT), Chennai, India (ICMR-NIRT-NIRT-ICE-2020-021), and was conducted in accordance with ethical guidelines. Written informed consent/assent was obtained from all the recruited study participants.

Funding

The work was supported in whole or in part with Federal funds from the Government of India' s (GOI) Department of Biotechnology (DBT), the Indian Council of Medical Research (ICMR), the United States National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Office of AIDS Research (OAR), and distributed in part by CRDF Global (A.G and P.C) [grant USB1-31149-XX-13]. This work is also funded by CRDF Global RePORT India Consortium Supplemental Funding (L.E.H) [grant OISE-17-62911-1]. The contents of this publication are solely the responsibility of the authors and do not represent the official views of the DBT, the ICMR, the NIH, or CRDF Global. This work was also funded in part by the Division of Intramural Research, NIAID, NIH (S.B).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank NIRT Director for the constant support throughout the study. We also thank the NIRT-ICER staff for the technical support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tube.2025.102720.

Data availability

All data generated or analyzed during this study are included in this published article.

References

[1] WHO. Global tuberculosis report 2024. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.
[2] Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. Bmj 2018;362:k2738. https://doi.org/10.1136/bmj.k2738.
[3] Forecasting the effects of smoking prevalence scenarios on years of life lost and life expectancy from 2022 to 2050: a systematic analysis for the global burden of disease study 2021. Lancet Public Health 2024;9:e729–44. https://doi.org/10.1016/s2468-2667(24)00166-x.
[4] Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, Metcalfe JZ, Cattamanchi A, Dowdy DW, Dheda K, Banaei N. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev 2014;27:3–20. https://doi.org/10.1128/cmr.00034-13.
[5] Scordo JM, Aguillón-Durán GP, Ayala D, Quirino-Cerrillo AP, Rodríguez-Reyna E, Joya-Ayala M, Mora-Guzmán F, Ledezma-Campos E, Villafañez A, Schlesinger LS, Torrelles JB, Turner J, Restrepo BI. Interferon gamma release assays for detection of latent Mycobacterium tuberculosis in older Hispanic people. Int J Infect Dis 2021;111:85–91. https://doi.org/10.1016/j.ijid.2021.08.014.
[6] Floyd K, Glaziou P, Zumla A, Raviglione M. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the end TB era. Lancet Respir Med 2018;6:299–314. https://doi.org/10.1016/s2213-2600(18)30057-2.
[7] Godoy P. Guidelines on controlling latent tuberculosis infection to support tuberculosis elimination. Rev Esp Sanid Penit 2021;23:28–36. https://doi.org/10.18176/resp.00028.
[8] Zhuang L, Yang L, Li L, Ye Z, Gong W. Mycobacterium tuberculosis: immune response, biomarkers, and therapeutic intervention. MedComm 2020;2024(5):e419. https://doi.org/10.1002/mco2.419.
[9] Toossi Z, Funderburg NT, Sirdeshmuk S, Whalen CC, Nanteza MW, Johnson DF, Mayanja-Kizza H, Hirsch CS. Systemic immune activation and microbial translocation in dual HIV/tuberculosis-infected subjects. J Infect Dis 2013;207:1841–9. https://doi.org/10.1093/infdis/jit092.
[10] Kumar NP, Moideen K, Viswanathan V, Sivakumar S, Ahamed SF, Ponnuraja C, Hissar S, Kornfeld H, Babu S. Heightened microbial translocation is a prognostic biomarker of recurrent tuberculosis. Clin Infect Dis 2022;75:1820–6. https://doi.org/10.1093/cid/ciac236.
[11] Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006;12:1365–71. https://doi.org/10.1038/nm1511.
[12] Sandler NG, Koh C, Roque A, Eccleston JL, Siegel RB, Demino M, Kleiner DE, Deeks SG, Liang TJ, Heller T, Douek DC. Host response to translocated microbial products predicts outcomes of patients with HBV or HCV infection. Gastroenterology 2011;141:1220–30. https://doi.org/10.1053/j.gastro.2011.06.063. 1230.e1221-1223.
[13] Rajamanickam A, Munisankar S, Bhootra Y, Dolla C, Nutman TB, Babu S. Microbial translocation associated with an acute-phase response and elevations in MMP-1, HO-1, and proinflammatory cytokines in Strongyloides stercoralis infection. Infect Immun 2017;85. https://doi.org/10.1128/iai.00772-16.
[14] Kumar NP, Moideen K, Nancy A, Viswanathan V, Thiruvengadam K, Sivakumar S, Hissar S, Kornfeld H, Babu S. Acute phase proteins are baseline predictors of tuberculosis treatment failure. Front Immunol 2021;12:731878. https://doi.org/10.3389/fimmu.2021.731878.
[15] Leboueny M, Maloupazoa Siawaya AC, Bouanga LDJ, Mvoundza Ndjindji O, Mveang Nzoghe A, Djoba Siawaya JF. Changes of C-reactive protein and procalcitonin after four weeks of treatment in patients with pulmonary TB. J Clin Tuberc Other Mycobact Dis 2023;31:100348. https://doi.org/10.1016/j.jctube.2023.100348.
[16] Ruperez M, Shanaube K, Mureithi L, Wapamesa C, Burnett MJ, Kosloff B, de Haas P, Hayes R, Fidler S, Gachie T, Schaap A, Floyd S, Klinkenberg E, Ayles H. Use of point-of-care C-reactive protein testing for screening of tuberculosis in the community in high-burden settings: a prospective, cross-sectional study in Zambia and South Africa. Lancet Glob Health 2023;11:e704–14. https://doi.org/10.1016/s2214-109x(23)00113-4.
[17] Organization WH. Global tuberculosis report 2025. 2025.
[18] Padhi A, Agarwal A, Bhise M, Chaudhary A, Joshi K, Katoch CDS. Progress and challenges in achieving tuberculosis elimination in India by 2025: a systematic review and meta-analysis. PLoS One 2024;19:e0301060. https://doi.org/10.1371/journal.pone.0301060.
[19] Gupte A, Padmapriyadarsini C, Mave V, Kadam D, Suryavanshi N, Shivakumar SV, Kohli R, Gupte N, Thiruvengadam K, Kagal A, Meshram S, Bharadwaj R, Khadse S, Ramachandran G, Hanna LE, Pradhan N, Gomathy NS, DeLuca A, Gupta A, Swaminathan S. Cohort for tuberculosis research by the Indo-US medical partnership (CTRIUMPH): protocol for a multicentric prospective observational study. BMJ Open 2016;6:e010542. https://doi.org/10.1136/bmjopen-2015-010542.

[20] Ren W, Ma Z, Li Q, Liu R, Ma L, Yao C, Shang Y, Zhang X, Gao M, Li S, Pang Y. Antigen-specific chemokine profiles as biomarkers for detecting Mycobacterium tuberculosis infection. Front Immunol 2024;15:1359555. https://doi.org/10.3389/fimmu.2024.1359555.

[21] Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, Den Boon S, Borroto Gutierrez SM, Bruchfeld J, Burhan E, Cavalcante S, Cedillos R, Chaisson R, Chee CB, Chesire L, Corbett E, Dara M, Denholm J, de Vries G, Falzon D, Ford N, Gale-Rowe M, Gilpin C, Girardi E, Go UY, Govindasamy D, A DG, Grzemska M, Harris R, Horsburgh Jr CR, Ismayilov A, Jaramillo E, Kik S, Kranzer K, Lienhardt C, LoBue P, Lönnroth K, Marks G, Menzies D, Migliori GB, Mosca D, Mukadi YD, Mwinga A, Nelson L, Nishikiori N, Oordt-Speets A, Rangaka MX, Reis A, Rotz L, Sandgren A, Sañé Schepisi M, Schünemann HJ, Sharma SK, Sotgiu G, Stagg HR, Sterling TR, Tayeb T, Uplekar M, van der Werf MJ, Vandevelde W, van Kessel F, van't Hoog A, Varma JK, Vezhnina N, Voniatis C, Vonk Noordegraaf-Schouten M, Weil D, Weyer K, Wilkinson RJ, Yoshiyama T, Zellweger JP, Raviglione M. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J 2015;46:1563–76. https://doi.org/10.1183/13993003.01245-2015.

[22] Goletti D, Delogu G, Matteelli A, Migliori GB. The role of IGRA in the diagnosis of tuberculosis infection, differentiating from active tuberculosis, and decision making for initiating treatment or preventive therapy of tuberculosis infection. Int J Infect Dis 2022;124(Suppl 1):S12–s19. https://doi.org/10.1016/j.ijid.2022.02.047.

[23] da Costa C, Benn CS, Nyirenda T, Mpabalwani E, Grewal HMS, Ahmed R, Kapata N, Nyasulu PS, Maeurer M, Hui DS, Goletti D, Zumla A. Perspectives on development and advancement of new tuberculosis vaccines. Int J Infect Dis 2024;141s:106987. https://doi.org/10.1016/j.ijid.2024.106987.

[24] Kobashi Y. Current status and future landscape of diagnosing tuberculosis infection. Respir Investig 2023;61:563–78. https://doi.org/10.1016/j.resinv.2023.04.010.

[25] Yoon C, Chaisson LH, Patel SM, Allen IE, Drain PK, Wilson D, Cattamanchi A. Diagnostic accuracy of C-reactive protein for active pulmonary tuberculosis: a meta-analysis. Int J Tuberc Lung Dis 2017;21:1013–9. https://doi.org/10.5588/ijtld.17.0078.

[26] Soedarsono S, Subiantoro MC. Changes of CRP serum levels in pulmonary TB patients with AFB smear-positive sputum before and two months after receiving anti-tuberculosis drug treatment. Indian J Tubercul 2019;66:134–8. https://doi.org/10.1016/j.ijtb.2018.07.007.

[27] Bosman S, Ayakaka I, Muhairwe J, Kamele M, van Heerden A, Madonsela T, Labhardt ND, Sommer G, Bremerich J, Zoller T, Murphy K, van Ginneken B, Keter AK, Jacobs BKM, Bresser M, Signorell A, Glass TR, Lynen L, Reither K. Evaluation of C-Reactive protein and computer-aided analysis of chest X-rays as tuberculosis triage tests at health facilities in Lesotho and South Africa. Clin Infect Dis 2024;79:1293–302. https://doi.org/10.1093/cid/ciae378.

[28] Cox SR, Erisa KC, Kitonsa PJ, Nalutaaya A, Nantale M, Kayondo F, Mukiibi J, Mukiibi M, Nakasolya O, Dowdy DW, Katamba A, Kendall EA. Accuracy of C-Reactive protein for tuberculosis detection in general-population screening and ambulatory-care triage in Uganda. Ann Am Thorac Soc 2024;21:875–83. https://doi.org/10.1513/AnnalsATS.202308-752OC.

[29] Reeve BWP, Ndlangalavu G, Mishra H, Palmer Z, Tshivhula H, Rockman L, Naidoo S, Mbu DL, Naidoo CC, Derendinger B, Walzl G, Malherbe ST, van Helden PD, Semitala FC, Yoon C, Gupta RK, Noursadeghi M, Warren RM, Theron G. Point-of-care C-reactive protein and Xpert MTB/RIF ultra for tuberculosis screening and diagnosis in unselected antiretroviral therapy initiators: a prospective, cross-sectional, diagnostic accuracy study. Lancet Glob Health 2024;12:e793–803. https://doi.org/10.1016/s2214-109x(24)00052-4.

[30] Saripalli A, Ramapuram J. C-Reactive protein as a screening test for tuberculosis in people living with HIV in southern India: a cross-sectional, observational study. J Clin Med 2022;11. https://doi.org/10.3390/jcm11133566.

[31] Gaeddert M, Glaser K, Chendi BH, Sultanli A, Koeppel L, MacLean EL, Broger T, Denkinger CM. Host blood protein biomarkers to screen for tuberculosis disease: a systematic review and meta-analysis. J Clin Microbiol 2024;62:e0078624. https://doi.org/10.1128/jcm.00786-24.

[32] Pavan Kumar N, Anuradha R, Andrade BB, Suresh N, Ganesh R, Shankar J, Kumaraswami V, Nutman TB, Babu S. Circulating biomarkers of pulmonary and extrapulmonary tuberculosis in children. Clin Vaccine Immunol 2013;20:704–11. https://doi.org/10.1128/cvi.00038-13.

[33] Dupnik K, Rivera VR, Dorvil N, Duffus Y, Akbarnejad H, Gao Y, Liu J, Apollon A, Dumont E, Riviere C, Severe P, Lavoile K, Duran Mendicuti MA, Pierre S, Rouzier V, Walsh KF, Byrne AL, Joseph P, Cremieux PY, Pape JW, Koenig SP. Potential utility of C-reactive protein for tuberculosis risk stratification among patients with non-meningitic symptoms at HIV diagnosis in Low- and middle-income countries. Open Forum Infect Dis 2024;11. https://doi.org/10.1093/ofid/ofae356. ofae356.

[34] Brenchley JM, Douek DC. Microbial translocation across the GI tract. Annu Rev Immunol 2012;30:149–73. https://doi.org/10.1146/annurev-immunol-020711-075001.

[35] Gallucci G, Santucci N, Díaz A, Bongiovanni B, Bértola D, Gardeñez W, Rassetto M, Bay ML, Bottasso O, D'Attilio L. Increased levels of circulating LPS during tuberculosis prevails in patients with advanced pulmonary involvement. PLoS One 2021;16:e0257214. https://doi.org/10.1371/journal.pone.0257214.

[36] Temu TM, Polyak SJ, Wanjalla CN, Mandela NA, Dabee S, Mogaka JN, Masyuko S, Longernecker C, Shakil S, Chohan B, Page ST, Lacourse SM, Gitura B, Crothers K, Oyugi J, Jaspan H, Farquhar C, Zifodya JS. Latent tuberculosis is associated with heightened levels of pro-and anti-inflammatory cytokines among Kenyan men and women living with HIV on long-term antiretroviral therapy. Aids 2023;37:1065–75. https://doi.org/10.1097/qad.0000000000003523.

[37] Pillay K, Lewis L, Rambaran S, Yende-Zuma N, Archary D, Gengiah S, Govender D, Hassan-Moosa R, Samsunder N, Abdool Karim SS, McKinnon LR, Padayatchi N, Naidoo K, Sivro A. Plasma biomarkers of risk of tuberculosis recurrence in HIV Co-Infected patients from South Africa. Front Immunol 2021;12:631094. https://doi.org/10.3389/fimmu.2021.631094.

[38] Kokesova A, Coufal S, Frybova B, Kverka M, Rygl M. The intestinal fatty acid-binding protein as a marker for intestinal damage in gastroschisis. PLoS One 2019;14:e0210797. https://doi.org/10.1371/journal.pone.0210797.

[39] Vinnard C, Ravimohan S, Tamuhla N, Pasipanodya J, Srivastava S, Modongo C, Zetola NM, Weissman D, Gumbo T, Bisson GP. Markers of gut dysfunction do not explain low rifampicin bioavailability in HIV-associated TB. J Antimicrob Chemother 2017;72:2020–7. https://doi.org/10.1093/jac/dkx111.

[40] Kim NY, Shin E, Byeon SJ, Hong SJ, Kang SH, Lee T, Kim TB, Choi JH. Serum Zonulin is a biomarker for severe asthma. Allergy Asthma Immunol Res 2023;15:526–35. https://doi.org/10.4168/aair.2023.15.4.526.

[41] WHOWRnWHTcM. Consensus meeting report: development of a target product profile (TPP) and a framework for evaluation for a test for predicting progression from tuberculosis infection to active disease . Report no. WHO/HTM/TB/2017.18 2018 [cited 2019 Mar 22]. Available from: http://www.who.int/iris/handle/10665/259176.