Interleukin-18 as an Immunological Biomarker in Latent and Active Tuberculosis: A Systematic Literature Review (2016-2026)

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Abstract. The persistence of tuberculosis (TB) remains a global health concern; approximately a quarter of the population carries a latent TB infection (LTBI), with 5-10% advancing to active disease. Current assays, like interferon-gamma release assays and tuberculin skin tests, cannot reliably differentiate contained latent infection from clinically active tuberculosis (ATB). Interleukin-18 (IL-18), a pro-inflammatory cytokine driving host immune responses to Mycobacterium tuberculosis, has emerged as a promising candidate to distinguish TB stages. This systematic review synthesizes the diagnostic effectiveness of IL-18 in differentiating LTBI from ATB. A PRISMA-compliant literature search in Google Scholar and PubMed (2016–2026) screened 664 initial records, including 13 quantitative studies in the final synthesis. Evidence reveals standalone IL-18 demonstrates weak-to-moderate diagnostic accuracy (AUC 0.71–0.83) for differentiating ATB from LTBI, falling short of WHO target profiles for independent triage tests. However, diagnostic precision improves substantially within multi-biomarker panels. Concentration trends indicate significantly higher IL-18 levels in ATB compared to LTBI across serum, plasma, and antigen-stimulated samples. Crucially, this trend is context-dependent: it correlates strongly with disease severity and reverses entirely in extrapulmonary manifestations like tuberculous lymphadenitis, where IL-18 is suppressed at the infection site. Additionally, longitudinal data show IL-18 levels reliably normalize following successful anti-tuberculosis therapy. While IL-18 is insufficient as a standalone rapid test, it acts as a dynamic, context-sensitive biomarker that provides significant clinical value when integrated into multi-analyte diagnostic panels and used for longitudinal treatment monitoring.

Keywords: Interleukin-18, Tuberculosis, Active, Latent, Biomarker.

1 Introduction

Tuberculosis (TB) remains the leading cause of death from a single infectious agent worldwide: the World Health Organization's most recent Global Tuberculosis Report estimates that 10.7 million people fell ill with TB and 1.23 million died of the disease in 2024 alone [1]. A large fraction of the world's population — historically

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approximated as one-third but re-estimated at closer to one-quarter once demographic change and declining transmission are accounted for — carries an asymptomatic, latent Mycobacterium tuberculosis (M.tb) infection (LTBI) [2].

Although host immunity contains bacterial replication in these individuals, it rarely achieves sterilizing clearance; progression risk is highest in the first one to two years after infection but persists over a lifetime [2]. Between 5% and 10% of people with LTBI will progress to active tuberculosis (ATB) if untreated, and this untreated reservoir is considered a major source of new active-disease transmission and a principal obstacle to the WHO End TB Strategy's elimination targets [3].

A central and unresolved problem in TB control is the inability of currently available immunological tests to reliably distinguish LTBI from ATB. Interferon-gamma release assays (IGRAs) such as QuantiFERON-TB Gold and the tuberculin skin test can identify M.tb sensitization with reasonable accuracy — a 2023 evidence synthesis conducted for the US Preventive Services Task Force reported pooled IGRA sensitivities in the range of 79–83% and specificities of 95–99% for detecting infection [4]. However, neither test can differentiate a contained, latent infection from clinically active disease, nor can either be used with confidence to monitor treatment response.

This diagnostic gap is especially consequential because it limits clinicians' ability to prioritize preventive therapy for those at highest risk of progression, and it delays detection of paucibacillary or extrapulmonary disease forms that evade sputum-based diagnostics. Interleukin-18 (IL-18) has attracted growing interest as a candidate biomarker in this context. Originally described as an "interferon-gamma-inducing factor," IL-18 is a member of the IL-1 cytokine family produced by monocytes, macrophages, dendritic cells, and epithelial cells as an inactive precursor requiring caspase-1 cleavage, and it drives natural killer (NK) cell cytotoxicity and Th1 polarization [5]. IL-18 bioactivity is tightly regulated by a natural antagonist, IL-18 binding protein (IL-18BP), and by its functional receptor complex (IL-18R), such that the net inflammatory effect of IL-18 signalling depends on the balance among ligand, receptor, and inhibitor rather than on IL-18 concentration alone [5].

Studies published over the last decade have examined IL-18 across a widening range of biological compartments from serum to antigen-stimulated blood cells, and even excised lymph node tissue in extrapulmonary disease. These studies also span across diverse patient populations, including pulmonary and extrapulmonary (lymphadenitis) TB, community-acquired pneumonia, symptomatic non-TB respiratory illness, and LTBI cohorts. Several of these studies have incorporated IL-18 into multi-analyte diagnostic panels together with markers such as IL-33, IL-1β, IL-1RA, IL-6, IL-8, VEGF, IL-18BP, and IP-10, reporting improved discriminatory performance compared with IL-18 measured in isolation [6–10].

Despite this expanding body of evidence, findings on the direction, magnitude, and diagnostic value of IL-18 across the LTBI–ATB spectrum remain inconsistent, and no synthesis has yet consolidated this literature into a coherent assessment of IL-18's utility as an immunological biomarker. This review therefore aims to systematically synthesize the available evidence (2016–2026) on IL-18 as an immunological biomarker capable of differentiating LTBI from ATB, addressing two specific questions: (1) what is the diagnostic accuracy of IL-18 for differentiating LTBI from

ATB, and (2) how do IL-18 concentrations across plasma, serum, or stimulated PBMC/whole-blood supernatants compared between individuals with LTBI and those with ATB.

2 Methods

2.1 Search Strategy

A systematic literature search was conducted to identify studies evaluating interleukin-18 as a biomarker for distinguishing latent tuberculosis infection (LTBI) from active tuberculosis (ATB). The search was restricted to publications from 2016 to 2026 to capture the most recent evidence on IL-18 diagnostic utility. Two electronic databases were searched: Google Scholar and PubMed. The search strategy employed two complementary query strings designed to maximize retrieval of relevant studies while maintaining specificity for the research questions

For Google Scholar, the following search queries were executed: **"IL-18" OR "interleukin-18" "tuberculosis" "active" "latent" biomarker** For PubMed, the search queries were structured as follows: **("interleukin-18"[tiab] OR "interleukin 18"[tiab]**
OR "IL-18"[tiab] OR "IL18"[tiab]
OR "Interleukin-18"[MeSH Terms]) AND("tuberculosis"[MeSH Terms]
OR "tuberculosis"[tiab]
OR "Mycobacterium tuberculosis"[tiab]
OR "M. tuberculosis"[tiab]) OR "Latent TB Infection" OR "Active TB Infection"

Both queries incorporated Boolean operators to combine key concepts: IL-18 terminology, tuberculosis infection states, and diagnostic performance indicators. The PubMed queries utilized field tags to restrict search terms to title and abstract fields, enhancing precision. All searches were limited to the publication date range of January 1, 2016, through December 31, 2026. No language restrictions were applied during the initial search phase.The systematic search yielded a total of 664 records. Google Scholar contributed 200 records, while PubMed contributed 464 records. These records were exported for subsequent screening and eligibility assessment according to predefined inclusion and exclusion criteria.

2.2 Eligibility Criteria

Study selection was guided by six predefined criteria, comprising three inclusion criteria and three exclusion criteria. Each criterion was applied systematically during abstract and full-text screening phases to ensure retrieval of studies directly relevant to IL-18 as a biomarker for differentiating active tuberculosis from latent tuberculosis infection.

Inclusion Criteria.

Criterion 1: TB Population Differentiation. Studies were required to include human participants with confirmed diagnoses of either active tuberculosis (ATB) or latent tuberculosis infection (LTBI). Confirmation could be established through any recognized diagnostic method, including microbiological culture, molecular testing, clinical evaluation, tuberculin skin testing, or interferon-gamma release assays.
Criterion 2: IL-18 Biomarker Measurement. Studies must have measured interleukin-18. Measurement methods included enzyme-linked immunosorbent assay, multiplex bead-based immunoassays, single-molecule arrays, or other validated quantitative platforms.
Criterion 3: Comparative Diagnostic Data. Studies were required to provide either direct comparison of IL-18 levels between ATB and LTBI groups or diagnostic accuracy metrics relevant to distinguishing TB infection states without comorbidity.

Exclusion Criteria

Criterion 4: Non-Human. Studies conducted exclusively in animal models or cell lines studies were excluded.
Criterion 5: Irrelevant Clinical Focus. Studies not primarily focused on non-diagnostic or differentiation were excluded. This included studies examining tuberculosis-associated comorbidities without infection state differentiation, or comparisons limited to ATB versus healthy controls or other respiratory diseases without LTBI representation.
Criterion 6: Incomplete Quantitative Reporting. Studies lacking quantitative IL-18 data were excluded.

2.3 Study Selection

The systematic search yielded 664 records across two databases: 464 from PubMed and 200 from Google Scholar. Following deduplication, 29 duplicate records were removed, leaving 635 unique records for title and abstract screening. At the title and abstract screening stage, 600 records were excluded based on predefined eligibility criteria. These exclusions reflected studies that did not meet the core requirement of measuring serum or plasma IL-18 protein levels in human participants with both ATB and LTBI for comparative diagnostic evaluation.

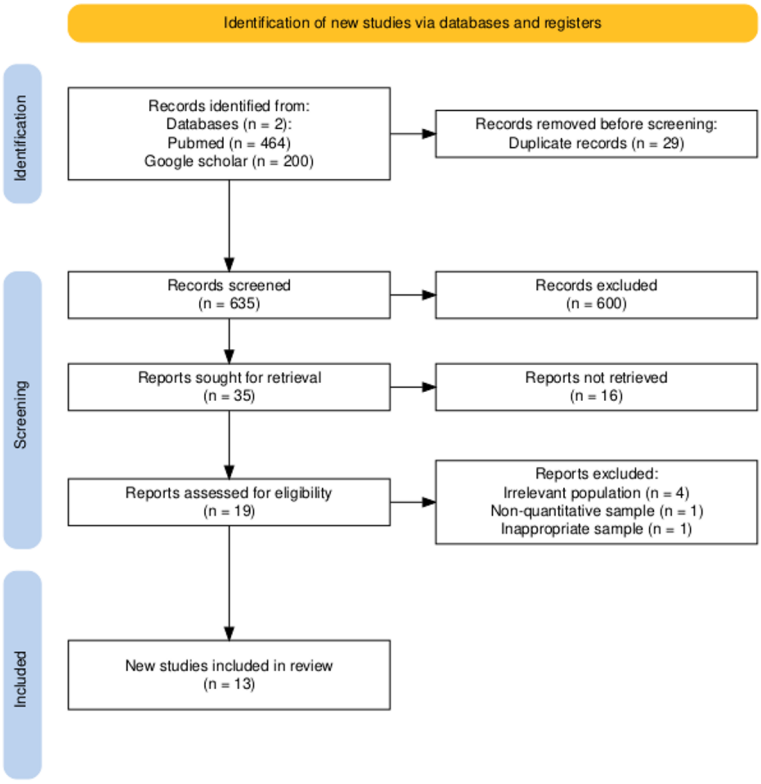


Fig. 1. Prism Diagram Flow for Systematic Literature Search [11].

The remaining 35 articles advanced to full-text assessment. During full-text screening, 16 articles failed to be retrieved leaving 19 studies for eligibility assessment. Six additional articles were excluded due to several eligibility mismatches. Four studies focused on the irrelevant population, failing to satisfy the criterion requiring direct ATB versus LTBI comparison. The second excluded study presented IL-18 measurements as genetic polymorphism, rendering the data unsuitable for quantitative synthesis. Lastly the excluded study was related to inappropriate sample use which is CSF sample. These exclusions ensured that only studies providing robust, directly relevant evidence with complete quantitative reporting were retained.

The final synthesis included 13 studies that met all eligibility criteria at the stringent full-text threshold. All included studies provided quantitative data enabling comparison of IL-18 levels between ATB and LTBI groups.

3 Results and Discussion

3.1 Study Characteristic

This systematic literature review identified 13 studies published between 2016 and 2026 that examined interleukin-18 (IL-18) in the context of tuberculosis (TB) diagnosis, disease stratification, or treatment monitoring [6–10, 12–19]. The included studies enrolled participants from at least eleven countries across four continents: Poland, India, China, Brazil, Tanzania, the Philippines, Vietnam, South Africa, and Peru, South Africa and France. Most studies included in this review use prospective observational cohort's design. Three of the studies make extra observations by using longitudinal cohorts with serial post-treatment sampling [15–17]. One study even used randomized controlled trials with paired pre/post sampling [19], and another study has two-phase discovery-plus-validation study design [6].

Study populations ranged from small, tightly defined discovery cohorts of 11–20 participants [8, 15, 17] to large-scale cohorts exceeding 700 pooled samples [6]. The comparator groups varied across studies, affecting how each study answers the review's two research questions. Seven of the thirteen studies compared LTBI (or a latent-infection subgroup) to active disease. Methodologically, the included studies employed a variety of immunoassay platforms to quantify IL-18 and various specimen types. Enzyme-linked immunosorbent assay (ELISA) was the most frequently used technique [6, 7, 12, 13, 16–18]. IL-18 was assessed at baseline (unstimulated) and after stimulation with M.tb-specific antigens (purified protein derivative, ESAT-6, CFP-10, or QFT/TruCulture antigen tubes) in nine of the thirteen studies [6–9, 13, 16–19]. A structured overview of study-level characteristics is presented in Table 1.

Table 1. Characteristics of included studies.

Study	Country	Study Design	Groups compared, n (per group)
Abhimanyu et al., 2016	*India*	*Prospective, discovery + validation cohorts*	*LNTB vs. PTB vs. HC vs. LAP; LNTB 50–65 (pooled), PTB 30–84, HC 20–84*
Kathamuthu et al., 2017a (Cytokine)	*India*	*Prospective, paired systemic/antigen-stimulated sampling, pre/post-treatment*	*TBL (extrapulmonary ATB) vs. LTBI; TBL 31, LTBI 31*
Kathamuthu et al., 2017b (Clin Vaccine Immunol)	*India*	*Prospective, paired whole-blood/lymph-node sampling, pre/post-treatment*	*TBL vs. PTB (both active disease); plus paired whole blood vs. lymph node within TBL; TBL 14, PTB 14*

Study	Country	Study Design	Groups compared, n (per group)
Vinhaes et al., 2019	*China (cohort); Brazil/USA (coordination)*	*Prospective, longitudinal (baseline, 2, 8, 24 weeks of ATT)*	*PTB vs. EPTB vs. HC (no LTBI arm); PTB 94, EPTB 50, HC 11*
Wawrocki et al., 2019 (PLOS ONE)	*Poland*	*Prospective observational, cross-sectional, with classification/ML modelling*	*ATB vs. LTBI vs. HC; ATB 95, LTBI 52, HC 91*
Ahmad et al., 2019	*Tanzania, Philippines (discovery); Vietnam, South Africa, Peru (validation)*	*Two-phase discovery + blinded validation*	*ATB vs. OTD (small latent-TB subgroup in validation); Discovery: ATB 199, OTD 188; Validation: ATB 160, OTD 138, Latent 19*
He et al., 2020	*China*	*Prospective, preliminary + independent validation cohorts*	*TB vs. LTBI vs. HD; Preliminary 30/30/30, Validation 30/30/30*
Wawrocki et al., 2020a (Pathogens)	*Poland*	*Prospective observational*	*ATB vs. LTB vs. Control; ATB 51, LTB 24, Control 22*
Wawrocki et al., 2020b (Saudi J Biol Sci)	*Poland*	*Prospective observational*	*ATB (M/MTB + advanced) vs. CAP; TB 89 (M/MTB 50, ATB 39), CAP 35*
Cao et al., 2021	*China*	*Randomized controlled trial (preventive treatment), longitudinal*	*Treated LTBI vs. untreated LTBI (pre/post); Treated 63, Untreated 32*
Duffy et al., 2021	*South Africa (discovery + replicatio*	*Prospective observational, discovery + independent replication*	*ATB vs. LTBI; Discovery: ATB 25, LTBI 25; Replication: ATB 51, LTBI 9*

Study	Country	Study Design	Groups compared, n (per group)
	n), France		
Zhao et al., 2025 (Infection)	*China*	*Prospective, cross-sectional*	*ATB vs. LTBI vs. HC; ATB 16, LTBI 12, HC 20*
Sobrinho et al., 2026	*Brazil*	*Screening + independent validation cohorts*	*TB vs. SR non-TB (no LTBI arm); Screening: TB 20, SR 20; Validation: TB 21, SR 33*

3.2 Evidence Synthesis-IL-18 Diagnosis Accuracy

Formal diagnostic accuracy metrics for IL-18 that expressed as area under the receiver operating characteristic curve (AUC), sensitivity, and specificity were reported in six of the thirteen studies. Wawrocki et al. reported that serum total IL-18 alone yielded a modest AUC of 0.635 (95% CI 0.544–0.720) for discriminating all TB (mild/moderate and advanced) from CAP, with a sensitivity of 91.0% but a specificity of only 40.0% at the optimal cut-off (281.40 pg/mL) [13]. Moreover, when restricted to advanced ATB versus CAP, the AUC improved slightly to 0.685 (95% CI 0.567–0.787). A different trend is shown in IL-18 measured with antigen-stimulated QuantiFERON supernatants which performed poorly with AUC 0.576. In this study, IL-18 diagnosis accuracy was consistently outperformed by IL-18 binding protein (IL-18BP; AUC 0.678) and IP-10 (AUC 0.686) in the same cohort [13].

Abhimanyu et al. similarly found that serum IL-18 alone achieved an AUC of only 0.583 (95% CI 0.470–0.696) for classifying tubercular lymphadenitis against pulmonary TB and healthy controls. However, since this study includes multiple biomarkers and it has a pre-specified relevance threshold of AUC > 0.65, IL-18 was consequently excluded from the final three-analyte biosignature for differentiating tubercular lymphadenitis [12]. Wawrocki et al. now provides the most direct and best-powered standalone accuracy estimate for IL-18 identified in this review [7].

In a cohort of 95 ATB, 52 LTBI, and 91 healthy-control participants, ROC analysis of serum IL-18 yielded an AUC of 0.76 (95% CI 0.75–0.77) for the LTBI-versus-ATB contrast specifically, alongside an AUC of 0.71 (95% CI 0.65–0.77) for LTBI-versus-healthy-control and 0.76 (95% CI 0.76–0.77) for ATB-versus-healthy-control. IL-18 measured in QFT-stimulated supernatant performed similarly for LTBI-versus-ATB (AUC 0.71, 95% CI 0.69–0.72). However, IL-18 alone was consistently outperformed by combined models, a full logistic-regression panel of all measured proteins achieved an AUC of 0.79 (95% CI 0.73–0.80) for LTBI-versus-ATB in serum. Lastly, complex co-expression of IL-18BP with IL-37, IP-10, and IFN-γ was identified as the single highest-performing discriminative biomarker set for active disease overall [7].

Zhao et al. similarly reports standalone accuracy data for IL-18 in a smaller (n=16 ATB, 12 LTBI, 20 HC) but well-designed cross-sectional Chinese cohort [8]. Unstimulated (baseline) IL-18 alone achieved an AUC of 0.807 (p=0.006), with 75% sensitivity and 75% specificity at a cut-off of 20.10 pg/mL for distinguishing ATB from

LTBI. When the ESAT-6/CFP10-stimulated value was expressed as a net response, IL-18 alone achieved an AUC of 0.828 (p=0.003), with 91.7% sensitivity and 87.5% specificity at a cut-off of 17.29 pg/mL. IL-18 alone was again outperformed by IL-33 in the same cohort (baseline AUC 0.763; stimulated AUC 0.927; net-response AUC 0.849). The authors also tested two-marker combinations using a simple decision-tree model, with two different marker pairs and value types: combining IL-18 and IL-33 correctly classified 24 of 28 subjects (sensitivity 91.67%, specificity 81.25%, accuracy 85.71%) [8].

Ahmad et al. reported full diagnostic accuracy statistics for a panel including IL-18 that was validated against a cohort containing a latent-TB subgroup [6]. IL-18 was one of four proteins (IL-6, IL-8, IL-18, and vascular endothelial growth factor) selected by machine learning from an initial panel of candidate analytes. The combined four-protein signature achieved an AUC of 0.87 (86% sensitivity, 65% specificity) in the discovery cohort. The same panel achieved AUC of 0.80 (80% sensitivity, 65% specificity) in an independent, blinded, validation cohort for distinguishing ATB from other TB-like diseases. In the validation cohort's latent-TB subgroup (n=19) showed IL-18 concentrations (mean 321 pg/mL) intermediate between OTD (606–618 pg/mL) and ATB (1065–1450 pg/mL), consistent with the direction reported elsewhere [6].

Sobrinho et al. provides recent, ELISA-validated standalone accuracy data for IL-18, although the comparator was symptomatic respiratory (SR) non-TB illness rather than LTBI [10]. In an initial Luminex screening cohort, IL-18 alone achieved an AUC of 0.82 (linear discriminant analysis; 65% sensitivity, 82% specificity). Meanwhile, in an independent ELISA validation cohort (21 TB, 33 SR non-TB), IL-18 alone achieved an AUC of 0.72 (57% sensitivity, 85% specificity, 74% accuracy), figures that are numerically similar to the LTBI-versus-ATB AUCs reported by Wawrocki et al. and Zhao et al., despite the different comparator population [7, 8].

Lastly, study from Duffy et al., which offers the most direct head-to-head LTBI-versus-ATB design after Wawrocki et al. study, identified IL-18 as one of 12 proteins significantly differentially expressed between the two groups following Mycobacterium tuberculosis (M.tb)-antigen stimulation [18]. But there is no AUC analysis for IL-18 diagnostic accuracy assessment. Taken together, the evidence that standalone IL-18 accuracy for a direct, comparator-appropriate LTBI-versus-ATB distinction is now reported in two independent cohorts, at AUCs of approximately 0.71–0.83 depending on specimen and stimulation condition. This places IL-18 in a weak-to-moderate accuracy range on its own, below the WHO target product profile threshold generally sought for a stand-alone triage test.

3.3 Evidence Synthesis- IL-18 concentrations across multiple sample types in LTBI versus ATB

Across the seven studies enabling a direct Latent Tuberculosis Infection (LTBI)-versus-active Tuberculosis (ATB) comparison, the direction of the IL-18 difference was reasonably, though not universally, consistent: IL-18 tended to be higher in ATB than in LTBI, particularly under antigen-stimulated conditions and in serum/plasma matrices, but this pattern was substantially qualified by the specific active-disease

phenotype under study, the stimulation condition used, and by anatomical compartment.

Wawrocki et al. provided the largest and most statistically robust confirmation of the "higher-in-ATB" direction identified in this review. Serum total IL-18 was significantly higher in ATB (median 568.1 pg/mL, IQR 371.9–980.3) than in LTBI (median 261.6 pg/mL, IQR 109.3–492.3) or healthy controls (median 283.1 pg/mL) ($p < 0.001$). Antigen-stimulated IL-18 in QFT supernatant was likewise significantly higher in ATB (median 765.5 pg/mL) than in LTBI (445.7 pg/mL) or healthy controls (397.5 pg/mL) ($p < 0.001$ for both). Interestingly, IL-18 levels remained similar among ATB patients regardless of QFT or tuberculin skin test positivity, suggesting a pathway distinct from IGRA reactivity [7].

Zhao et al. independently confirmed the same direction in a Chinese cohort using a different antigen-stimulation platform (LEGENDplex) [8]. IL-18 was one of five cytokines (alongside IL-8, IL-33, MCP-1, and MIG) with the highest baseline (unstimulated) secretion in ATB, significantly higher than in LTBI and healthy controls [8]. However, at the molecular level, a study by Wawrocki et al. found no statistically significant difference in IL-18 mRNA expression between the ATB and LTBI groups. Conversely, they observed significantly lower IL-18R mRNA expression in LTBI compared with both ATB and control groups ($p < 0.001$ for both comparisons). These findings suggest that immune homeostasis in latent infection may be maintained through a receptor-level mechanism rather than through ligand expression [14].

Findings from studies without a true LTBI arm nuance this picture in ways relevant to interpreting the broader IL-18 literature. Wawrocki et al. comparing ATB with community acquired pneumonia (CAP), found that serum total IL-18 was significantly higher in advanced ATB than CAP ($p = 0.01$). However, the concentrations in mild/moderate TB were statistically indistinguishable from CAP (553.9 vs. 530.6 pg/mL), indicating that elevated IL-18 in active disease may depend on disease severity or bacillary burden rather than being a uniform feature of ATB [13].

Antigen stimulation reveals distinct immune profiles by highlighting cytokine concentration differences between ATB and LTBI. Duffy et al. demonstrated that the diagnostic utility of IL-18 is highly dependent on the stimulation condition. While M.tb-antigen stimulation produces significantly higher IL-18 responses in ATB, the use of live Bacillus Calmette-Guérin (BCG) reverses this trend for most cytokines. However, IL-18 remains uniquely elevated in ATB [18]. Supporting this diagnostic value, He et al. confirmed a graded, linear increase in ESAT6-stimulated IL-18 across healthy, LTBI, and ATB cohorts, establishing a consistent ATB > LTBI > healthy donor ordering that parallels IFN-γ behavior [9]. This finding matched to IL-18 levels ordering reported other studies [6–8].

Kathamuthu et al. from Chennai, India, nuance the higher IL-18 in ATB pattern by focusing on tuberculous lymphadenitis (TBL), an extrapulmonary manifestation, rather than isolated pulmonary TB [16, 17]. In Kathamuthu study (n=31 per arm), IL-18 was significantly lower in TBL than LTBI across unstimulated plasma (124.3 vs. 174.0 pg/mL), antigen-stimulated whole blood (188.9 vs. 254.8 pg/mL), and mitogen stimulation (178.6 vs. 286.0 pg/mL) [16]. IL-1β showed a parallel reduction, while other Type 1 and Type 17 cytokines did not differ significantly.

Meanwhile another Kathamuthu et al. paper (n=14 per arm), extended these findings [17]. First, IL-18 and IL-1β were significantly lower in TBL than in active pulmonary TB at baseline and following PPD, ESAT-6, and CFP-10 whole-blood stimulation, despite TBL patients showing higher IFN-γ, TNF-α, and IL-17. Second, within TBL patients, IL-18 and IL-1β were significantly lower in antigen-stimulated lymph node culture than in paired whole blood, indicating that suppression is greatest at the site of infection. These studies demonstrate that the direction of IL-18 differences depends heavily on clinical phenotype and anatomical site rather than infection stage alone, a trajectory reversed by treatment [17].

Following six months of standard antituberculosis treatment, baseline IL-18 and IL-1β concentrations in TBL individuals rose significantly across conditions [16]. In contrast to unstimulated serum, M.tb-antigen-stimulated IL-18 in QFT supernatants showed no significant differences across groups. Similarly, preventive LTBI treatment did not significantly alter mycobacteria-specific antigen-induced IL-18 ($p = 0.075$), despite significant changes in twelve other cytokines, including IL-8, IL-1RA, and IFN-α2 [14, 19].

Longitudinal data confirms that anti-tuberculous therapy normalizes circulating IL-18 toward an intermediate, non-diseased set-point, with the direction of change depending on the initial disease process [15]. In pulmonary TB patients with high baseline levels, plasma IL-18 decreased significantly within two weeks and remained reduced through 24 weeks [15]. In extrapulmonary (pleural) TB, this reduction occurred more slowly, reaching significance at week 24. This downward trend mirrors the upward normalization observed in IL-18-suppressed TBL cohorts [16, 17].

In summary, five of seven studies comparing LTBI and active disease found higher IL-18 concentrations in ATB across three geographic cohorts and multiple specimens, including Polish serum and QFT supernatant, Chinese stimulated whole blood, South African stimulated plasma, and a multinational plasma cohort [6–9, 18]. A sixth cohort showed a similar, non-significant mRNA trend [14]. However, this elevation was not universal: it reversed under BCG stimulation; IL-18 did not significantly discriminate against QFT supernatants in two Polish and Chinese studies [13, 19]. Moreover this trend inverted entirely, showing lower IL-18 in active disease especially at the infection site in two Chennai studies evaluating tuberculous lymphadenitis rather than pulmonary TB [16, 17]. Longitudinal data indicate that successful therapy returns IL-18 to a standard, non-diseased range, whether initial levels were elevated or suppressed [15].

4 Conclusion

In conclusion, current evidence indicates that interleukin-18 (IL-18) possesses weak-to-moderate accuracy as a standalone diagnostic biomarker for differentiating active tuberculosis (ATB) from latent tuberculosis infection (LTBI), falling short of World Health Organization targets for independent triage tests. However, its true diagnostic potential is realized when integrated into multi-analyte biosignatures alongside complementary markers such as IL-33, IP-10, IL-18BP, and IFN-γ. Moreover, literature also shows that IL-18 can be highly context-dependent, in which this marker

strongly correlates pulmonary TB severity, but reverses entirely in extrapulmonary manifestations. Despite these phenotypic variations, IL-18 is highly effective for longitudinal treatment monitoring, as successful antituberculosis therapy reliably returns its circulating levels to a non-diseased baseline. Ultimately, while IL-18 cannot be recommended as a solitary rapid diagnostic tool, it remains a dynamic and valuable biomarker for comprehensive TB management when incorporated into diagnostic panels and used to track patient recover

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References

1. Global tuberculosis report 2025. World Health Organization (2025).
2. Houben, R.M.G.J., Dodd, P.J.: The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLOS Med. 13, e1002152 (2016).
3. Uplekar, M., Weil, D., Lonnroth, K., Jaramillo, E., Lienhardt, C., Dias, H.M., Falzon, D., Floyd, K., Gargioni, G., Getahun, H., Gilpin, C., Glaziou, P., Grzemska, M., Mirzayev, F., Nakatani, H., Raviglione, M.: WHO's new End TB Strategy. The Lancet. 385, 1799–1801 (2015).
4. Jonas, D.E., Riley, S., Lee, L., Coffey, C., Wang, S.-H., Asher, G.N., Berry, A., Williams, N., Balio, C., Voisin, C.E., Kahwati, L.: Introduction. In: Screening for Latent Tuberculosis Infection in Adults: An Evidence Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality (US) (2023).
5. Dinarello, C., Novick, D., Kim, S., Kaplanski, G.: Interleukin-18 and IL-18 Binding Protein. Front. Immunol. 4, (2013).
6. Ahmad, Xie, Pyle, Suarez, Broger, Steinberg, Ame, Lucero, Szucs, MacMullan, Berven, Dutta, Sanvictores, Tallo, Bencher, Eisinger, Dhingra, Deb, Ali, Mehta, Fawzi, Riley, Sazawal, Premji, Black, Murray, Rodriguez, Carr, Walt, Gillette: A rapid triage test for active pulmonary tuberculosis in adult patients with persistent cough. Sci. Transl. Med. (2019).
7. Wawrocki, S., Seweryn, M., Kielnierowski, G., Rudnicka, W., Włodarczyk, M., Druszczy\' nska, M.: IL-18/IL-37/IP-10 signalling complex as a potential biomarker for discriminating active and latent TB. PLOS ONE. (2019).
8. Zhao, H., Chen, Z., Lowrie, D.B., Hu, Z., Lu, S., Fan, X.: The blood biomarker combination IL-8/IL-33 and IL-18/IL-33 distinguish between active tuberculosis and latent infection. (2025).
9. He, J., Fan, Y., Shen, D., Yu, M., Shi, L., Ding, S., Li, L.: Characterization of cytokine profile to distinguish latent tuberculosis from active tuberculosis and healthy controls. Cytokine. (2020).
10. Sobrinho, C.P., Ara\' ujo, L.E., Meira, R.L., Horta, T. a, Cerqueira, S. ania M.A., Oliveira, F. avia M. ilia F., Petrilli, J. essica D., Arruda, S. ergio, Queiroz, A.: Novel Plasma Biomarkers for the Diagnosis of Pulmonary Tuberculosis. Tuberculosis. (2026).

11. Haddaway, N.R., Page, M.J., Pritchard, C.C., McGuinness, L.A.: PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. Campbell Syst. Rev. 18, e1230 (2022).
12. Abhimanyu, Bose, M., Varma-Basil, M., Jain, A., Sethi, T., Tiwari, P.K., Agrawal, A., Banavaliker, J.N., Bhowmick, K.T.: Establishment of Elevated Serum Levels of IL-10, IL-8 and TNF-β as Potential Peripheral Blood Biomarkers in Tubercular Lymphadenitis: A Prospective Observational Cohort Study. PLOS ONE. 11, e0145576 (2016).
13. Wawrocki, S., Seweryn, M., Kielnierowski, G., Rudnicka, W., Druszczynska, M.: IL-18 and related function proteins associated with tuberculosis severity and screening for active TB among patients with non-mycobacterial community-acquired pneumonia (CAP). Saudi J. Biol. Sci. 27, 3035–3045 (2020).
14. Wawrocki, S., Kielnierowski, G., Rudnicka, W., Seweryn, M., Druszczy\' nska, M.: Interleukin-18, functional IL-18 receptor and IL-18 binding protein expression in active and latent tuberculosis. Pathogenetics. (2020).
15. Vinhaes, C.L., Oliveira-de-Souza, D., Silveira-Mattos, P.S., Nogueira, B., Shi, R., Wei, W., Yuan, X., Zhang, G., Cai, Y., Barry, C.E., Via, L.E., Fukutani, K.F., Andrade, B.B., Mayer-Barber, K.D.: Changes in Inflammatory Protein and Lipid Mediator Profiles Persist After Antitubercular Treatment of Pulmonary and Extrapulmonary Tuberculosis: A Prospective Cohort Study. Cytokine. 123, 154759 (2019).
16. Kathamuthu, G.R., Moideen, K., Bhaskaran, D., Sekar, G., Sridhar, R., Vidyajayanthi, B., Gajendraraj, G., Babu, S.: Reduced systemic and mycobacterial antigen-stimulated concentrations of IL-1β and IL-18 in tuberculous lymphadenitis. Cytokine. 90, 66–72 (2017).
17. Kathamuthu, G.R., Moideen, K., Baskaran, D., Banurekha, V.V., Nair, D., Sekar, G., Sridhar, R., Vidyajayanthi, B., Gajendraraj, G., Parandhaman, D.K., Srinivasan, A., Babu, S.: Tuberculous Lymphadenitis Is Associated with Enhanced Baseline and Antigen-Specific Induction of Type 1 and Type 17 Cytokines and Reduced Interleukin-1β (IL-1β) and IL-18 at the Site of Infection. Clin. Vaccine Immunol. CVI. 24, e00045-17 (2017).
18. .Duffy, D., Nemes, E., Llibre, A., Rouilly, V., Musvosvi, M., Smith, N. ia, Filander, E., Africa, H., Mabwe, S., Jaxa, L., Charbit, B., Mulenga, H., Tameris, M., Walzl, G., Malherbe, S.T., Thomas, S. ephanie, Hatherill, M., Bilek, N., Scriba, T.J., Albert, M.L., Abel, L., Alcover, A. es, Aschard, H., Astrom, K., Bousso, P., Bruhns, P., Cumano, A., Demangel, C., Deriano, L., Santo, J.P.D., Dromer, F., Eberl, G. erard, Enninga, J., Fellay, J., Gelpi, O., Gomperts-Boneca, I., Hasan, M., Hercberg, S., Lantz, O., Leclerc, C., Mouquet, H., Patin, E., Pellegrini, S., Pol, S., Rausell, A., Rogge, L., Sakuntabhai, A., Schwartz, O., Schwikowski, B., Shorte, S.L., Soumelis, V., Tangy, F. ed\' eric, Tartour, E., Toubert, A., Touvier, M., Ungeheuer, M.-N. elle, Quintana-Murci, L.: Immune Profiling Enables Stratification of Patients With Active Tuberculosis Disease or Mycobacterium tuberculosis Infection. Clin. Infect. Dis. (2021).
19. Cao, X., Xin, H., Zhang, H., Liu, J., Pan, S., Du, Y., Feng, B., Quan, Z., Guan, L., Shen, F., Liu, Z., Wang, D., Zhang, B., Guan, X., Yan, J., Jin, Q., Gao, L.: The association between mycobacteria-specific antigen-induced cytokines and host response to latent tuberculosis infection treatment in a Chinese population. Front. Microbiol. (2021).

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