Host blood biomarkers for the diagnosis of childhood tuberculosis: A systematic review and meta-analysis

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Background

New diagnostic tests are needed in childhood tuberculosis (TB) as respiratory **culture sensitivity is only 24-60%.**[1,2]

Host blood biomarkers (proteins, mRNA, miRNA, etc.) have shown promise for diagnosing TB disease in adults.[3]

World Health Organization **(WHO) target product profile** (TPP) criteria for new non-sputum point-of-care tests for TB diagnosis are: **sensitivity ≥65%, specificity >98%.**[4]

Objectives: 1) Identify host blood biomarkers which diagnose TB disease in children, and 2) Summarize biomarker diagnostic accuracy.

Please scan for our **PROSPERO protocol:**

Methods

Population: Children <15 years old with TB disease (microbiologically & clinically diagnosed) compared to TB infection, healthy controls, and/or other clinical conditions.

Index tests: Any host biomarker measured in blood (*in vitro* antigen-stimulated markers and antibodies were excluded).

Reference standards: Culture, NAAT, and clinical diagnosis.

Outcomes: sensitivity, specificity, and AUC with 95% CI.

Search strategy: MEDLINE, Embase, SCOPUS, Cochrane, WHO Global Index Medicus, and ClinicalTrials.gov searched from inception through January 17, 2025.

Risk of bias: QUADAS-2/QUADAS-C tools.

Meta-analysis: hierarchical summary ROC model (random-effects) performed when 2x2 tables reported in ≥4 studies.

Results

Studies: search yielded (n=2,794) → included (n=50) → preliminary analysis (n=36): case-control (n=17, 47.2%), cohort (n=16, 44.4%), cross-sectional (n=3, 8.3%).

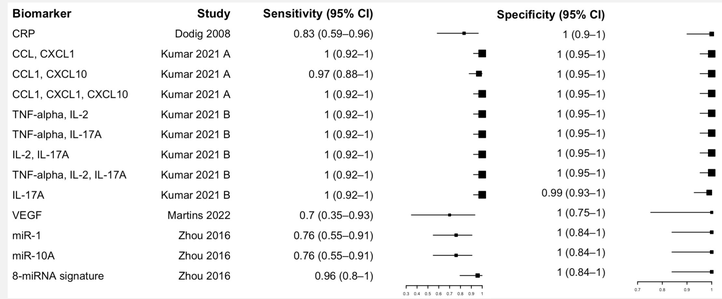
Biomarker classes reported (n studies): cytokine/protein (n=20), mRNA (n=8), miRNA (n=4), metabolites (n=3), enzyme activity (n=1), PBMC (n=1), lncRNA (n=1).

WHO TPP criteria: met by 8 biosignatures and 5 individual biomarkers (Fig. 1).

Risk of bias: 24 (66.7%) studies were at high risk of bias in 1 or more domains of QUADAS-2/QUADAS-C, mostly in patient selection domain due to case-control design.

Meta-analysis: C-reactive protein (CRP) and interferon-gamma inducible protein 10 (IP-10) were reported in ≥4 studies and underwent meta-analysis (Fig. 2 & 3).

Figure 1: Forest plots of diagnostic accuracy for biomarkers that met WHO Target Product Profile criteria (sens. ≥65%, spec. >98%).



Biomarker	Study	Sensitivity (95% CI)	Specificity (95% CI)
CRP	Dodig 2008	0.83 (0.59–0.96)	1 (0.9–1)
CCL, CXCL1	Kumar 2021 A	1 (0.92–1)	1 (0.95–1)
CCL1, CXCL10	Kumar 2021 A	0.97 (0.88–1)	1 (0.95–1)
CCL1, CXCL1, CXCL10	Kumar 2021 A	1 (0.92–1)	1 (0.95–1)
TNF-alpha, IL-2	Kumar 2021 B	1 (0.92–1)	1 (0.95–1)
TNF-alpha, IL-17A	Kumar 2021 B	1 (0.92–1)	1 (0.95–1)
IL-2, IL-17A	Kumar 2021 B	1 (0.92–1)	1 (0.95–1)
TNF-alpha, IL-2, IL-17A	Kumar 2021 B	1 (0.92–1)	1 (0.95–1)
IL-17A	Kumar 2021 B	1 (0.92–1)	0.99 (0.93–1)
VEGF	Martins 2022	0.7 (0.35–0.93)	1 (0.75–1)
miR-1	Zhou 2016	0.76 (0.55–0.91)	1 (0.84–1)
miR-10A	Zhou 2016	0.76 (0.55–0.91)	1 (0.84–1)
8-miRNA signature	Zhou 2016	0.96 (0.8–1)	1 (0.84–1)

Figure 2: Summary ROC plot of CRP; meta-analysis of 9 studies.

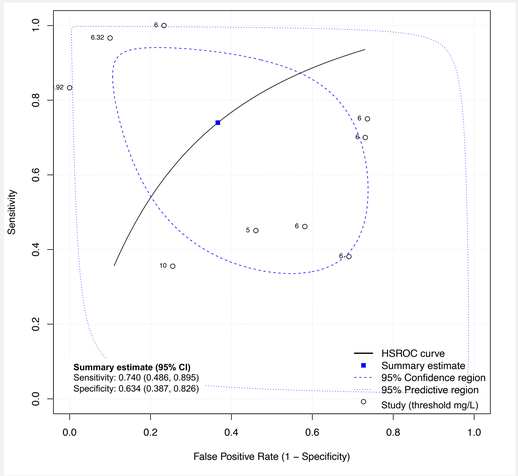
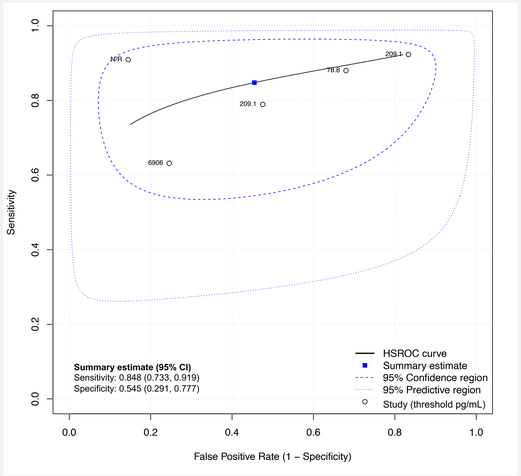


Figure 3: Summary ROC plot of IP-10, meta-analysis of 5 studies.



Discussion

Cytokines and miRNAs, individually and as biosignatures, were identified that **met WHO TPP criteria** for diagnostic accuracy.

In meta-analysis, **CRP and IP-10 met WHO TPP for sensitivity** (74% and 84.8% respectively), but **not specificity** (63.4% and 54.5% respectively).

Our results differ from meta-analyses in adults: CRP more accurate (sensitivity 85%, specificity 67%),[5] IP-10 less sensitive but more specific (sensitivity 75%, specificity 74%) in adults.[6]

Limitations: between-study heterogeneity (ref. standards, comparators, thresholds), most studies at high risk of bias, case-control studies may overestimate accuracy.

Further research needed: certain cytokines and miRNAs show promise for childhood TB diagnosis but warrant further investigation before being incorporated into diagnostic algorithms.

References

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