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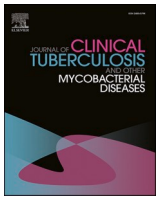

A systematic review of potential screening biomarkers for active TB disease

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ABSTRACT

Introduction: The standard TB Four Symptom Screen does not meet the World Health Organization (WHO) ideal screening criteria for having greater than 90% sensitivity to identify active TB disease, regardless of HIV status. To identify novel screening biomarkers for active TB, we performed a systematic review of any cohort or case-control study reporting associations between screening biomarkers and active TB disease.
Methods: We searched PubMed and Embase for articles published before October 10, 2021. We included studies from high or medium tuberculosis burden countries. We excluded articles focusing on C-reactive protein and lipoarabinomannan. For all included biomarkers, we calculated sensitivity, specificity and 95% confidence intervals, and assessed study quality using a tool adapted from the QUADAS-2 risk of bias.
Results: From 8,062 abstracts screened, we included 79 articles. The articles described 302 unique biomarkers, including host antibodies, host proteins, TB antigens, microRNAs, whole blood gene PCRs, and combinations of biomarkers. Of these, 23 biomarkers had sensitivity greater than 90% and specificity greater than 70%, meeting WHO criteria for an ideal screening test. Among the eleven biomarkers described in people living with HIV, only one had a sensitivity greater than 90% and specificity greater than 70% for active TB.
Conclusion: Further evaluation of biomarkers of active TB should be pursued to accelerate identification of TB disease.

1. Introduction

Tuberculosis (TB) has surpassed HIV globally as the leading infectious cause of death, with approximately 1.51 million deaths worldwide in 2020 [1]. One major barrier to eradicating TB is that the standard screening tools for active TB have limited sensitivity, particularly among people living with HIV (PLHIV). Currently, the World Health Organization (WHO) recommends screening using the Four Symptom Screen (fevers, cough, night sweats, weight loss) either in isolation or in combination with chest radiographs and other screening tests [2]. However, Four Symptom Screen has an estimated sensitivity of 60–80% depending on the population studied [3]. The sensitivity of symptom-based TB screening also varies based on HIV status, from as low as 51% in people taking ART, to 89% in ART-naïve individuals [2,4]. The WHO has called for increasing support for biomarker research and development in the END TB strategy [5].

TB screening tools identify people with high likelihood of active TB. These stand in contrast to diagnostic tools, which confirm active TB disease. The WHO have described an ideal TB screening tool as having greater than 90% sensitivity and 70% specificity regardless of HIV status [2]. Existing reviews on TB screening have described the test characteristics of symptom screening algorithms [4], C-reactive protein (CRP) [6], urine lipoarabinomannan (LAM) [7], and sputum Xpert MTB/RIF and Xpert Ultra [8]. Urine LAM proved to have very poor sensitivity [7,9]. CRP has also been proposed as a screening tool, however a meta-analysis demonstrated that while CRP may be more sensitive than symptom screening [6], the sensitivity is still lower than the 90% threshold set by the WHO for a TB screening test [2]. Previous systematic reviews of other TB biomarkers have focused on TB diagnostics in cohorts of patients presenting with TB symptoms rather than true alternatives to TB symptom screening [10,11].

Since improved screening tools will be imperative to ending the TB pandemic, we sought to characterize the existing literature regarding screening biomarkers for active tuberculosis to further guide research and development of novel TB screening tools.

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2. Methods

2.1. Search strategy and study selection

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12], we searched PubMed and Embase for articles published since database inception through October 10, 2021. Keywords for our search included tuberculosis, screening, and a list of countries with high or medium burden of tuberculosis according to the WHO [13]. The full search protocol is available in the included online supplement. We registered our review with the PROSPERO database, with registration number CRD42021149957. In part due to delays in processing due the COVID-19 pandemic, our registration was not complete until after the initial article search.

We extracted results from each database search to Covidence.org [14]. We removed duplicate search results, and two authors (JW and CP) independently reviewed titles and abstracts, discussing disagreements prior to making a final decision. The same authors then conducted full-text review, and again discussed disagreements prior to making final decisions. Excluded full-text articles were categorized based on reason for exclusion. The authors performed data extraction on the included articles using a standardized form.

Using a pre-specified format adapted from the QUADAS-2 risk of bias tool [15], the authors independently assessed risk of bias and study applicability and again reviewed disagreements prior to making a final decision.

2.2. Eligibility criteria

We included cross-sectional, retrospective, and prospective cohort studies, randomized controlled trials, and case-control studies. We included case-control studies that described biomarker performance among TB cases and controls. We excluded qualitative studies, systematic reviews, and non-peer reviewed abstracts. For non-case control studies, we excluded studies where the population of interest included only tuberculosis suspects, or participants who had already screened positive using the Four Symptom Screen. Using WHO definitions [13] we included any paper reporting data from a high or medium TB burden country.

Our primary exposures of interest were screening biomarkers for tuberculosis. We included any study of a population being screened for active TB disease that reported a biomarker, sensitivity and specificity for active TB disease, or reported raw numbers allowing for the calculation of sensitivity, specificity and 95% confidence intervals. We excluded studies that only included a cohort suspected to have active TB disease based on symptoms or other prior screening. Given the existing published literature, we excluded urine and serum lipoarabinomannan (LAM) and C-reactive protein (CRP), unless used as part of a composite screening tool utilizing multiple biomarkers (e.g. LAM and hemoglobin) [6,9]. We also excluded papers describing the use of sputum Xpert TB/RIF (Cephid) or sputum Xpert Ultra as screening tests. We excluded papers that used biomarkers typically used to screen for latent tuberculosis, including interferon gamma release assays (IGRA) or tuberculin skin tests (TST).

Our primary outcome of interest was active TB disease. We defined active tuberculosis as participants who had infections confirmed by sputum culture, smear, GeneXpert, clinical diagnosis, or response to anti-tuberculosis therapy. We recorded the method of tuberculosis diagnosis when reported. When papers reported multiple methods of tuberculosis diagnosis, we pooled outcomes. We recorded the total number of biomarkers tested, and we extracted any biomarker with a sensitivity greater than 75%. We stratified biomarkers by those meeting WHO criteria for a TB screening test (sensitivity greater than 90%, specificity greater than 70%), and those not meeting criteria.

2.3. Statistical analysis

When not reported, we calculated sensitivity, specificity, and 95% confidence intervals for each reported biomarker. We planned to conduct pooled meta-analysis for individual biomarkers, however, there was not sufficient data to do so.

We assessed study quality and applicability concerns using a pre-specified tool adapted from the QUADAS-2 risk of bias tool. The full evaluation tool is described In Online Supplement 2. In evaluating study quality, we assigned sputum culture and sputum GeneXpert as being associated with a low risk of bias, and any other method of TB diagnosis as associated with a high risk of bias.

3. Results

3.1. Search results

Our search returned 8444 articles for review. After removing duplicates, two authors (JW and CP) screened the 8062 remaining abstracts (Fig. 1. 7158 titles were excluded at the title/abstract level, leaving 481 articles for full-text review. We included 79 studies for full data extraction and review [16–94].

3.2. Characteristics of the included studies

The full characteristics of the 79 included studies are described in Online Supplement 3. Ten of the included studies were cohort studies; the remaining 69 studies were case-control studies. The sample size ranged from 129 to 3123 participants among cohort studies, and from 40 to 1813 participants among the case-control studies. 33 studies (45.2%) were located in China. Other countries with multiple included studies were India (12), South Africa (9), Brazil (6), and Pakistan (4). Two studies each were located in Ethiopia, Peru, Tunisia, Uganda, and Vietnam. One study each was located in Turkey, Guinea-Bissau, Singapore, Thailand, Gambia, and Mozambique. Four studies included data from multiple countries.

3.2.1. Outcomes

The ten included cohort studies described eleven unique biomarkers. The 69 included case-control studies described 291 unique biomarkers. The most common type of biomarker reported was host antibody, or combination of multiple host antibodies. This included both existing TB antibody test kits and novel antibody tests. Other types of commonly reported biomarkers included host proteins, TB proteins, and microRNAs.

Of the total 302 described biomarkers, 23 met the WHO criteria of sensitivity greater than 90% and specificity greater than 70% (Table 1. This included nine antibody tests (Fig. 2A and fourteen non-antibody tests (Fig. 2B. Sixteen of these tests included a single biomarker, while seven included a combination of biomarkers. Only one of the ten included cohort studies described a biomarker meeting WHO criteria, which was a single TB gene PCR [25].

Another 78 biomarkers did not meet WHO criteria, but had a reported sensitivity of greater than 75%. Their sensitivities, specificities, and 95% confidence intervals are described in Online Supplement 5. These included 35 antibody tests, five microRNAs, four small RNAs, five Gene PCR tests, four TB proteins, ten host lipids, eight host proteins, two synthetic peptides, two host cells, and one exhaled nitric oxygen breath test.

3.2.2. People living with HIV

Among both cohort and case-control studies, twelve studies included only PLWH, or included subgroup analyses of PLWH, describing eleven unique biomarkers. These included anemia (serum hemoglobin $<$ 12 mg/dl) [31,76], absolute neutrophil count [30], serum neopterin [21], serum anti-mycolic acid IgG antibody [51], a combination of anti-6, 27,

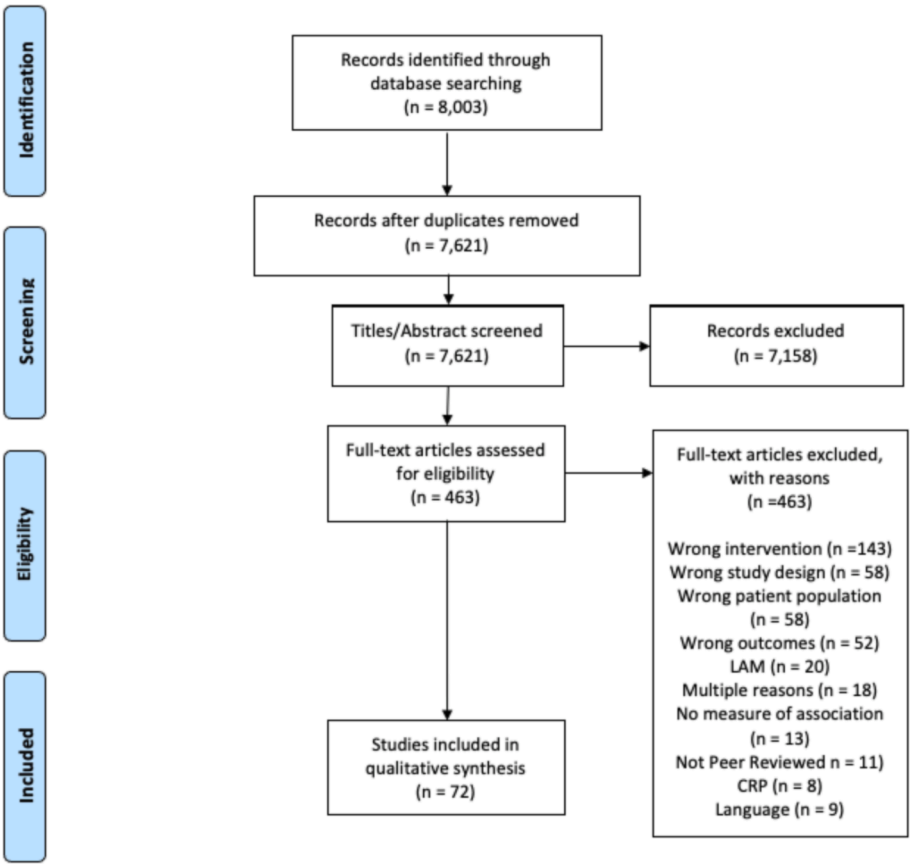


Fig. 1. PRISMA Diagram.

30, and 38 kDa Tb antigen IgG antibodies [52], serum Mycodot assay [28], three serum gene PCR tests [87,92,95], and a combinations of three TB antigens [79].

Of these, three biomarkers met the WHO criteria, including the RISK6 genomic score, TB Gene IS 6110 PCR, and a combination of five TB antigens including 6, 27, 30, 38 and 64 kDa antigens (Table 2. An additional four biomarkers had sensitivity greater than 90% but low specificity. These included combination of three antigens, Rv0934-P38, Ag85A, and Rv2031-HSPX [79], serum neopterin [21], anti-mycolic acid IgG [51], Xpert-MTB-HR-Prototype [92].

3.3. Assessment of risk of bias and applicability

A summary of the risk of bias and applicability concerns is described in Fig. 3, with full results for each study available in Online Supplement 4. Risk of bias generally high due to the large proportion of case-control studies included. Additionally, few studies described blinding procedures for those interpreting index tests, and few studies specified the time between gold-standard testing and obtaining samples for the index test. In 38 studies, TB was diagnosed by sputum culture, GeneXpert, or biopsy (in the case of extra-pulmonary disease. Other methods used to diagnose TB in the other 41 studies included sputum smear, chest radiograph, clinical symptoms, and response to anti-TB therapy.

4. Discussion

In this review, we summarized the extensive literature describing biomarkers for TB screening. We identified 23 biomarkers that met the WHO criteria of a sensitivity greater than 90% and specificity greater than 70%. These biomarkers may be promising candidates towards developing a novel screening tool that can outperform standard TB symptom screening. However, many of the biomarkers are described in early phase studies with low quality evidence; more data are needed to definitively evaluate these biomarkers as effective screening tools.

Previous literature describing novel TB screening biomarkers has focused on CRP, LAM, and sputum Xpert MTB/RIF and Xpert Ultra [6,8–9]. These tests have good potential as screening tools as they are inexpensive and easily implemented at the point of care, making them an easy replacement or complement to community-based symptom screening. Unfortunately, urine LAM has proven to have inadequate sensitivity to be used as a screening tool [7]. CRP has relatively low specificity but may still have a role to play in community-based screening [6]. Both sputum Xpert tests have high specificity, but low sensitivity when used as primary screening test rather than their typical use as a diagnostic test [96]. Their reliance on participants' capacity to produce a sputum sample at the time of testing likely limits their sensitivity as a screening test. This review expands the existing conversation on TB biomarkers by identifying novel screening tools. While we were unable to identify a single biomarker with enough evidence to recommend implementation currently, there are a number of promising targets, including host and pathogen proteins as well as genetic tests.

Identifying screening tools for PLWH remains a WHO priority given the high prevalence and mortality of tuberculosis among PLWH. Unfortunately, the paucity of studies in Table 2 demonstrates that relatively few biomarkers with promising test characteristics exist for PLWH. However, many of the gene PCR tests included in this review show promise as further screening tests, particularly among PLWH. When tested in a cohort containing only PLWH, the RISK6 genomic score had a sensitivity of 90.50% and specificity of 72.5% [95], while another study found TB Gene IS 6110 PCR had a sensitivity of 96.2% in a cohort with an HIV prevalence of 87.6% [25]. Another study of PLWH described a novel gene signature with sensitivity greater than 90% and specificity greater than 70%, but did not report exact sensitivity and specificity and thus was not included in this review [97]. Additionally, one study

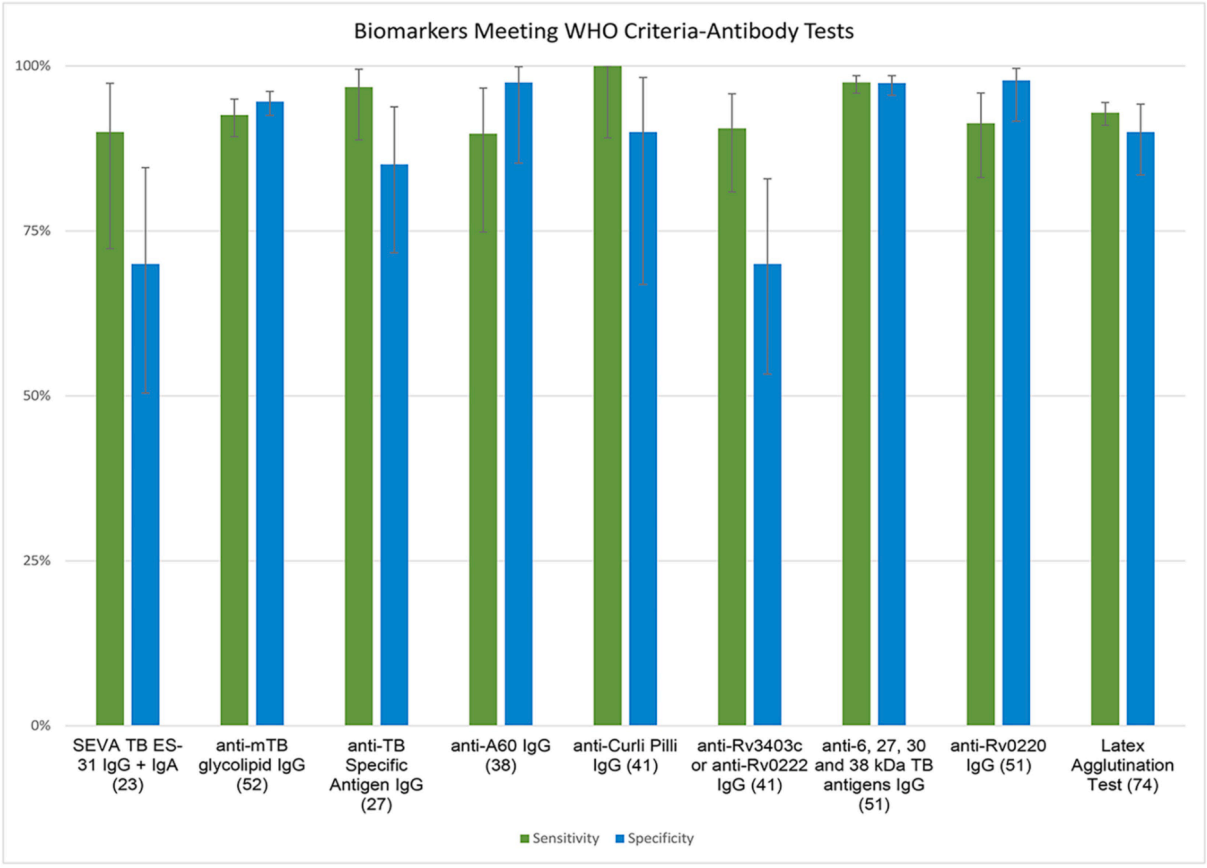
Table 1
Biomarkers meeting WHO Sensitivity (>90%) and Specificity (>70%) Criteria.

Biomarker	Study	Country	Sensitivity (95% CI)	Specificity (95% CI)	People with TB (Total Participants)	Risk of Bias
		Host Antibodies				
anti-TB Specific Antigen IgG	Jiao 2015 [27]	China	96.8% (88.8–99.5%)	85.1% (71.7–93.8)	62 (109)	High
anti-A60 IgG	Meena 2002 [38]	India	89.7% (75.0–97.0%)	97.5% (85.3–99.9%)	39 (79)	High
anti-6, 27, 30 and 38 kDa IgG	Tiwari 2013 [52]	India	97.5% (95.9%-98.5%)	97.4% (95.6–98.5%)	538 (1179)	High
anti-Rv0220 IgG	You 2017 [67]	China	91.3% (83.1–95.9%)	97.8% (91.6–99.6%)	92 (184)	High
Anti-Curli Pilli IgG	Naidoo 2017 [42]	South Africa	100.0% (89.0–100.0%)	90.0% (67.0–98.0%)	40 (60)	High
Anti-Rv3403c and anti-Rv0222 IgG	Naidoo 2017 [42]	South Africa	90.5% (80.9–95.8%)	70.0% (53.3%-82.9%)	40 (60)	High
SEVA TB ES-31 IgG and IgA	Gupta 2002 [24]	India	90.0% (72.3–97.4%)	70.0% (50.4–84.6%)	60 (30)	High
Anti-MTB glycolipid IgG	Tiwari 2005 [53]	India	92.6% (89.3–95.0%)	94.6% (92.5–96.1%)	364 (1031)	High
Latex Agglutination Test	Bhaskar 2003 [72]	India	92.9% (91.0–94.5%)	90.0% (83.5–94.2%)	918 (1058)	Low
		Host Protein				
Protein Z + Amyloid A + C4 Binding Protein Beta Subunit	Jiang 2017 [26]	China	97.6% (92.2–99.1%)	95.5% (86.4–98.8%)	136 (202)	High
Phosphatidylcholine (12:0/22:2)	Han 2020 [78]	China	91.2% (75.2–97.7%)	76.5% (65.8–84.7%)	119 (34)	High
APOCII, CD5L, and RBP4	Xu 2014 [64]	China	93.4% (84.7–97.6%)	92.9% (81.9–97.7%)	76 (132)	High
I-309, MIG, IL-8, 38KDa, 32KDa, 14-16KDa, and Ag85B	Chen 2015 [19]	China	91.0% (81.8–96.0%)	90.8% (84.1–94.9%)	60 (208)	High
		TB Proteins				
Ribokinase	Luo 2019 [36]	China	90.0% (81.4–91.8%)	86.0% (76.2–91.8%)	90 (180)	High
Rv2970c	Gupta 2016 [23]	India	98.6% (94.9–99.5%)	98.2% (93.6–99.5%)	140 (250)	High
Rv2145c	Gupta 2016 [23]	India	97.9% (93.9–100.0%)	100% (96.6–100.0%)	140 (250)	High
Rv1827	Gupta 2016 [23]	India	97.1% (92.9–97.3%)	93.6% (87.4–96.9%)	140 (250)	High
Rv1437	Gupta 2016 [23]	India	92.7% (87.3–93.6%)	89.1% (81.9–93.6%)	140 (250)	High
PstS1, Rv0831c, FbpA, EspB, BfrB, HspX, and Ssb	Burbelo 2015 [94]	Thailand	90.0% (77.5–100.0%)	100.0% (88.6–100.0%)	56 (94)	High
		MicroRNAs and TB Gene PCRs				
TB Gene IS 6110 PCR	Hira 2010 [25]	India	96.2% (85.7–99.33%)	87.0% (77.0–93.3%)	52 (129)	Low
Combination of 6 microRNAs	Zhang 2013 [73]	China	95.0% (89.0%-98.3%)	92.1% (83.8–96.5%)	108 (196)	High
RISK6 Gene PCR	Penn-Nicholson 2020 [95]	South Africa	90.2% (77.8–96.3%)	93.4% (83.3–97.9%)	93 (194)	High
RISK6 Gene PCR	Bayaa 2021 [90]	Georgia, Madagascar, Lebanon, Bangladesh	90.1% (84.4–94.8%)	80.3% (68.8–88.4%)	71 (212)	High

described a 3-gene score with sensitivity of 90.9% in a cohort with low HIV prevalence [60], and another described 7-gene signature with a sensitivity of 89.7%, but did not report HIV prevalence. Regional variation in TB genomics has the potential to limit the external validity of gene-based screening. Thus, further studies should validate these results in other cohorts. However, previous studies have shown sputum GeneXpert MTB/RIF (Cephid) testing is feasible as a mobile screening tool [96], which could serve as a model for how to turn novel gene signatures into a point-of-care PCR test.

While our results focus exclusively on screening tests for active tuberculosis disease, defining active tuberculosis is difficult, and may impact the validity of individual screening tests. Gold standard methods for TB diagnosis rely on the participant producing sputum, which likely limits their sensitivity. Additionally, the definition of screening for active tuberculosis in our review excludes incipient TB. Recent publications highlight that some screening tests may have value in this setting [77], and may be an important tool in improving overall screening strategies. We also did not define standard time to tuberculosis diagnosis for confirmed cases, but instead used each individual studies' case definition, resulting in significant heterogeneity. Finally, because the WHO Target Product Profile for a screening test is defined by sensitivity and specificity [5], we only reported these two metrics for included biomarkers. Positive and negative predictive value may also be valuable metrics by which to consider screening tests, particularly in high-burden settings. For example, the RISK11 gene signature test did not meet WHO criteria based on sensitivity (86.5% vs. 90%), but had a negative predictive value of 99.8% (99.4–100).

Our review is limited by the generally low quality of evidence, as demonstrated by our quality analysis. Most of the studies included were case control, portending a high risk of bias. This could be because these studies were intended as early phase trials, examining prospects for larger cohort studies, rather than because studies themselves were performed poorly. We included case control studies to broaden the scope of our review and include biomarkers that may be in early phases of testing. However, case control studies are unable to accurately describe screening test characteristics, as they require the uses of a mix of cases and controls, rather than a population being screened. While the included case control studies describe test characteristics that can be



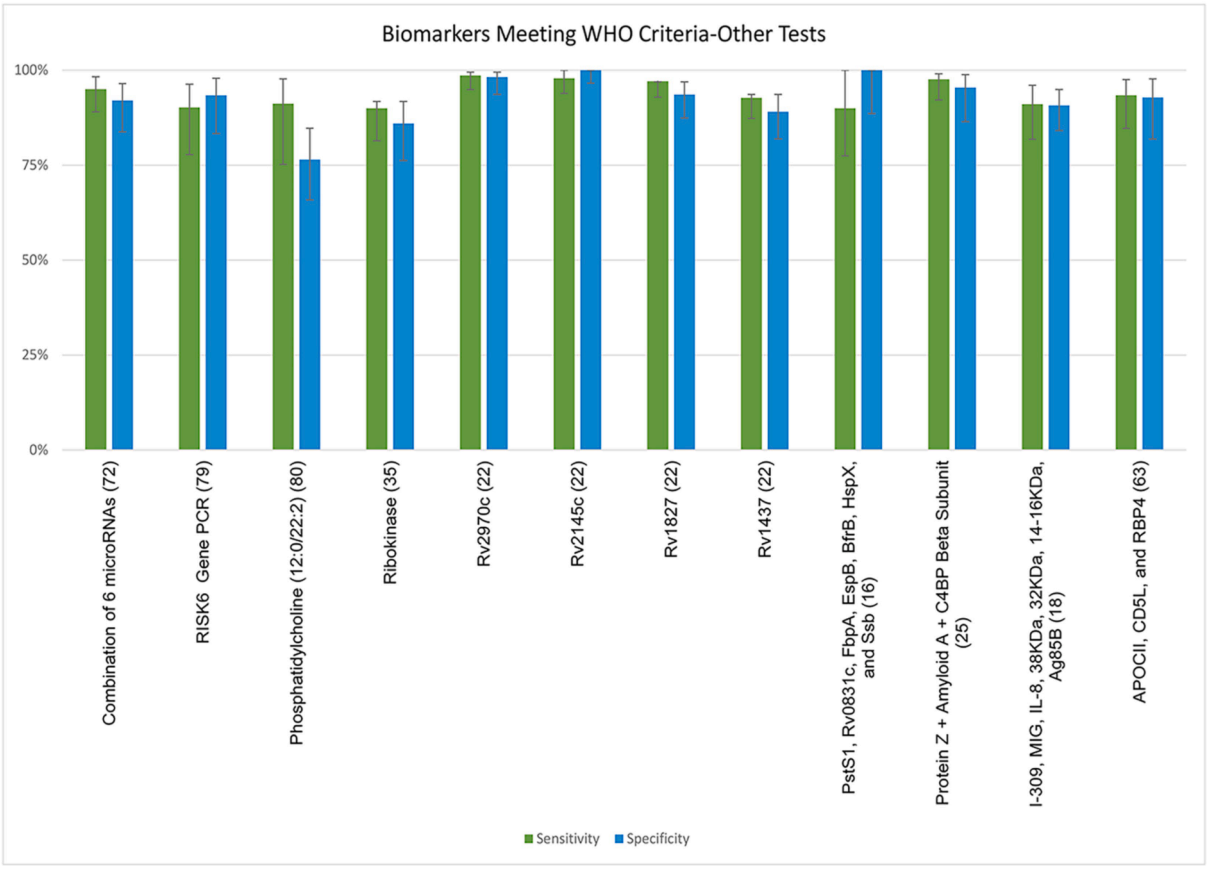


Fig. 2. Sensitivity, specificity and 95% confidence intervals for tests meeting WHO Criteria.

Table 2
Biomarkers described in People Living with HIV meeting WHO Criteria.

Author	Biomarker	Sensitivity (95% CI)	Specificity (95% CI)	People with TB (Total Participants)	Biomarker Type
Tiwari 2013 [52]	Combination of 5 TB antigens: 6, 27, 30, 38 and 64 kDa	99.2% (95.2–100%)	98.3% (89.9–99.9%)	130 (190)	Combination of TB antigens
Penn-Nicholson 2020 [77]	RISK6 Genomic Score	90.5% (76.0–97.0%)	72.5% (56.3–84.6%)	40 (82)	TB Gene PCR
Hira 2010 [25]	TB Gene IS 6110 PCR	95.83% (84.6–99.3%)	84.61% (73.1–92.0%)	48 (113)	TB Gene PCR

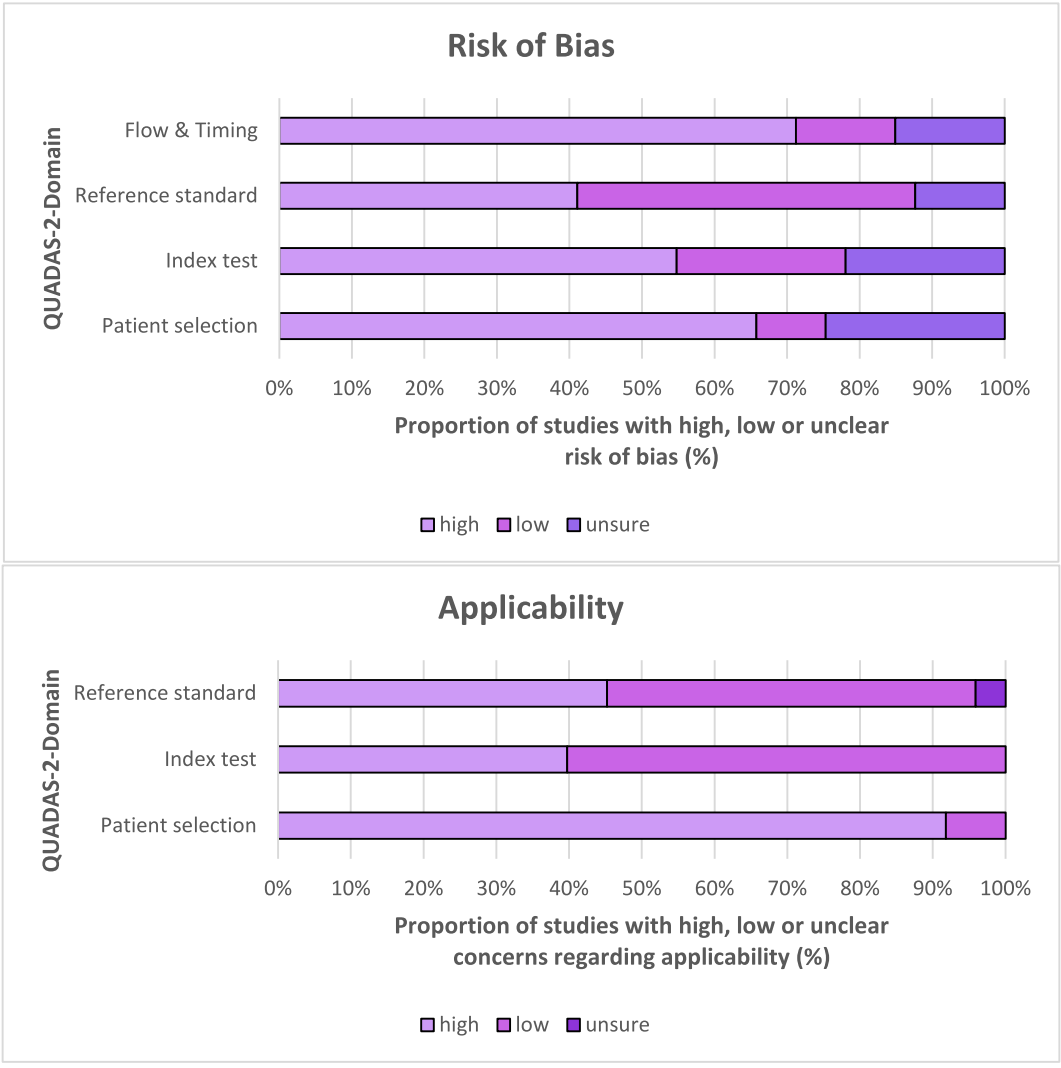


Fig. 3. Risk of Bias and Applicability Concerns for all included studies.

applied against the WHO criteria for a screening test, these studies may have been designed to evaluate the potential of biomarkers as diagnostic tests. Of the few included cohort studies, only one described a biomarker that met WHO criteria. Many of the biomarkers showing promise in case control studies may not hold up to the scrutiny of more rigorous cohort studies and randomized controlled trials. Additionally, many of the included studies did not use gold-standard methods for diagnosing TB, instead using methods with poor sensitivity (sputum smear), poor specificity (clinical presentation), or both. Few studies reported study flow procedures like blinding and timing of sample acquisition, limiting our ability to fully assess their quality.

We chose to only include studies located in countries with a high or medium prevalence of tuberculosis in order to capture settings that would most benefit from improved TB screening tools. This decision limits the applicability of our findings to low-burden countries. A majority of the included studies were located in China (31 of 72) or India (12 of 72). In contrast, only 13 of 72 studies were located in sub-Saharan Africa, seven of which were in South Africa. Of the 23 biomarkers identified meeting WHO criteria, only 3 were described in sub-Saharan Africa, all in South Africa. One of the 23 biomarkers was described in Thailand. Sub-Saharan Africa is more strongly represented among the studies describing PLWH, consistent with the global burden of TB/HIV co-infection. The over-representation of Chinese and Indian studies in our sample suggests our results may not be applicable to sub-Saharan Africa, where largest burden of tuberculosis currently exists. Prior to implementation, biomarkers would need to be validated in sub-Saharan

Africa, both to account for regional variations in TB epidemiology and genomics, but also for a larger burden of TB-HIV co-infection.

While effective screening remains a key part of eradicating TB, current screening tools are inadequately specific, and do not meet the WHO threshold of 90% sensitivity. We described the existing literature on TB screening tools and identified many biomarkers that are candidates for further study. In particular, host response genetic PCR tests may be good screening tools both among PLWH and people without HIV. These candidate biomarkers should be further tested in rigorous, diverse, high-quality cohort studies to better characterize their potential as screening biomarkers for TB.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2021.100284.

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