Diagnostic accuracy of C-reactive protein for active pulmonary tuberculosis: a meta-analysis

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SUMMARY

SETTING: Systematic screening for active pulmonary tuberculosis (PTB) is recommended for high-risk populations, including people living with the human immunodeficiency virus (PLHIV); however, currently recommended TB screening tools are inadequate for most high-burden settings.

OBJECTIVE: To determine whether C-reactive protein (CRP) possesses the necessary test characteristics to screen individuals for active PTB.

DESIGN: We performed a systematic review and meta-analysis of studies evaluating the diagnostic accuracy of CRP (10 mg/l cut-off point) for culture-positive PTB. Pooled diagnostic accuracy estimates were generated using random-effects meta-analysis for out-patients and in-patients, and for pre-specified subgroups based on HIV status and test indication.

RESULTS: We identified nine unique studies enrolling 1793 adults from out-patient (five studies, 1121 patients) and in-patient settings (five studies, 672 patients), 72% of whom had confirmed HIV infection. Among out-patients, CRP had high sensitivity (93%, 95% CI 88–98) and moderate specificity (60%, 95% CI 40–75) for active PTB. Specificity was lowest among in-patients (21%, 95% CI 6–52) and highest among out-patients undergoing TB screening (range 58–81%). There was no difference in summary estimates by HIV status.

CONCLUSION: CRP, which is available as a simple, inexpensive and point-of-care test, can be used to screen PLHIV presenting for routine HIV/AIDS (acquired immune-deficiency syndrome) care for active TB.

KEY WORDS: TB screening; systematic TB screening; symptom screen; systematic review; HIV

Despite substantial investments in global tuberculosis (TB) control, TB incidence remains high, with over 10 million new cases in 2015 alone.1 Because high-risk groups such as people living with the human immunodeficiency virus (PLHIV) shoulder a disproportionately heavy burden of TB,1 the World Health Organization (WHO) recommends systematic screening (provider-initiated screening, regardless of symptoms) of all PLHIV.2 However, the lack of an accurate yet simple TB screening tool is a key barrier to the implementation of systematic screening. A good screening test for TB should have ≥90% sensitivity and ≥70% specificity for active TB.3 The high sensitivity requirement minimizes the proportion of TB patients missed by screening, whereas the moderately high specificity requirement limits referrals for more costly confirmatory testing such as Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) and/or culture to patients with a high likelihood of having TB. A test with these characteristics that is also low-cost and which can be performed by frontline health workers has been ranked among the highest priority needs for TB diagnostics.3

Currently recommended TB screening tools such as symptom-based screening (cough ≥2 weeks in people without HIV or any of the four symptoms suggestive of TB in PLHIV) and chest X-ray (CXR) are inadequate.2 A symptom-based approach requires a priori knowledge of the patient’s HIV status to be sufficiently sensitive, and has poor specificity for active TB, particularly among PLHIV (specificity range 5–61%).4–8 Although CXR is sufficiently sensitive and has high specificity,8,9 it requires costly infrastructure and trained interpreters. To facilitate the scale-up of WHO TB screening guidelines, there is an urgent need to identify an accurate screening tool that is practical for use in lower-level health centers, where most patients present for care.

C-reactive protein (CRP) is an acute-phase reactant whose levels rise in response to interleukin (IL) 6-mediated pyogenic infections such as active TB. Previous studies have consistently shown that CRP
has high sensitivity for TB\textsuperscript{10–15} and that TB-associated increases in CRP levels are independent of HIV status.\textsuperscript{11} In addition, CRP can be measured from capillary blood using a low-cost (US$2–8 per test) point-of-care (POC) assay. To determine whether CRP is an adequate screening test for pulmonary TB (PTB), we performed a systematic review and meta-analysis to determine the diagnostic accuracy of CRP for active PTB in two clinical settings: out-patient and in-patient. For each setting, our objective was to assess the diagnostic accuracy of CRP among: 1) patients undergoing TB screening vs. TB diagnosis (i.e., active vs. passive case finding); and 2) patients with and without HIV infection.

**STUDY POPULATION AND METHODS**

We utilized a standardized protocol as recommended by the Cochrane Collaboration’s Diagnostic Test Accuracy Working Group,\textsuperscript{16} and reported our findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses.\textsuperscript{17}

**Search strategy and selection criteria**

We performed an online search to identify all studies that measured blood CRP levels from patients undergoing screening or evaluation for active TB. We searched PubMed, Embase, the Cochrane Library, and Web of Science databases for relevant studies published on or before 31 January 2014; we updated our search to identify additional studies published through 31 January 2015 (see Appendix Table A.1 for search criteria).\textsuperscript{*} To minimize the impact of potential publication bias, we also performed an online search of abstracts presented at the annual World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease after 2004.

We included studies that measured serum, plasma or whole blood CRP levels in children and adults undergoing PTB evaluation for symptoms suggestive of active PTB or high-risk (e.g., PLHIV) individuals undergoing TB screening. We included only studies that used mycobacterial culture on solid and/or liquid media for one or more specimens from each patient as a reference standard. We excluded 1) non-English language studies; 2) animal studies; 3) case series/case reports, case-control studies, review articles and letters to the editor; 4) studies evaluating only extra-pulmonary TB as the target condition; 5) studies that measured CRP level using a non-quantitative assay; 6) studies recruiting only patients with comorbid conditions that are themselves associated with increased CRP levels (e.g., inflammatory bowel disease); and 7) studies with <5 active PTB cases.

Three reviewers (CY, LHC, SMP) independently screened the citations for relevance, reviewed full-text articles for eligibility, and resolved disagreements by consensus. The reviewers used a standardized form to extract epidemiological, demographic and clinical data from individual studies (see Appendix Figure A.1).

**Index tests**

Eligible studies used quantitative laboratory-based and/or POC assays to measure CRP levels and utilized various CRP cut-off points. To standardize the assessment of diagnostic accuracy, we selected a priori a well-established CRP cut-off point of 10 mg/l; large-scale epidemiological studies have found CRP levels $\geq 10$ mg/l to be clinically significant because such levels are suggestive of ongoing pyogenic infection and/or another pathologic systemic inflammatory process.\textsuperscript{18,19} We contacted study authors via e-mail to obtain additional information for studies that did not present sufficient data to allow us to extract data using a CRP cut-off of $\geq 10$ mg/l. We excluded studies whose authors did not provide the necessary information.

**Reference standard**

Only studies that used solid and/or liquid sputum mycobacterial culture results as the reference standard were included. For studies using both culture results and clinical criteria to classify TB status, we asked the study authors to provide data using only culture as the reference standard.

**Assessment of study quality**

The quality of each study included was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, a validated tool for diagnostic accuracy studies.\textsuperscript{20} To address potential conflicts of interest, we also reported whether private industries had any involvement with study design or conduct.

**Statistical analysis**

We calculated individual study estimates of sensitivity, specificity, and their 95% confidence intervals (CIs). We adopted a pre-specified approach to account for expected heterogeneity. Briefly, because test accuracy depends largely on the spectrum of clinical disease severity in a study population, the data were synthesized separately for out-patient and in-patient studies. Subgroup analyses were also performed to determine CRP sensitivity and specificity for diagnosis-seeking vs. screening populations and for HIV-infected vs. non-infected patients. Heterogeneity of all the analyses was assessed visually using forest plots and statistically using $\chi^2$ and $I^2$ tests. We then calculated pooled sensitivity and specificity estimates using random-effects modeling

\textsuperscript{*} The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000009/art00012
(hierarchical summary receiver operating characteristic [HSROC] models), which provides more conservative estimates than fixed-effects modeling if heterogeneity is a concern.\(^{21,22}\) Pooled estimates were calculated when \( \geq 4 \) studies, each with \( \geq 10 \) patients, were available in any subgroup; individual study estimates were reported when \(<4\) studies were available. We performed secondary analyses that excluded studies reporting industry involvement.

All analyses were performed using Stata v13 (StataCorp, College Station, TX, USA); forest plots were generated using Review Manager 5 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

**RESULTS**

**Search results**

Our initial search identified 1198 citations published on or before 31 January 2014, including 16 conference abstracts (Figure 1). An updated search (up to 31 January 2015) identified no additional eligible studies. Of 13 full-text articles and one abstract identified as eligible for this review, four were excluded (see Appendix Table A.2 for reasons for exclusion).\(^{23–27}\) One study evaluated two CRP assays (POC vs. laboratory-based immunoturbidometric) within the same study population and found no differences in their diagnostic accuracy for PTB.\(^{27}\) To avoid underestimating heterogeneity, we included accuracy data obtained from only the POC assay. A final total of eight articles\(^{6,13,14,15,27–30}\) and one abstract,\(^{31}\) all of which enrolled only adults, were included.

**Out-patients**

**Study quality**

Five studies enrolled patients from the out-patient setting,\(^{6,13,15,27,31}\) including one that enrolled patients from both the out-patient and in-patient setting.\(^{13}\) Figure 2 describes the risk of bias and applicability concerns for each out-patient study. Most studies were designed to evaluate the diagnostic accuracy of CRP for PTB.\(^{6,15,27,31}\) Two studies enrolled a representative spectrum of patients,\(^{6,31}\) whereas three studies restricted enrollment to patients with a high probability of PTB (e.g., symptomatic patients with suspected smear-negative PTB).\(^{13,15,27}\) All studies selected patients either consecutively or by random sampling.\(^{6,13,15,27,31}\) Most studies reported that PTB status was assessed without knowledge of CRP results.\(^{6,15,27,31}\) All studies acknowledged industry involvement,\(^{6,13,15,27,31}\) including two that received donated POC CRP assays from the manufacturer.\(^{27,31}\)

**Study characteristics**

The five out-patient studies enrolled 1121 outpatients, 313 (28%) of whom had PTB (Appendix Table A.3). All studies were conducted in high TB-HIV burden countries and involved a total of 1006 patients (90%) with confirmed HIV infection,\(^{6,13,15,27,31}\) including four studies that restricted enrollment to HIV-infected individuals.\(^{6,13,27,31}\) Two studies \((n = 767)\) evaluated CRP as a screening test among patients with advanced HIV/AIDS (acquired immune-deficiency syndrome) initiating antiretroviral therapy.\(^{6,31}\) The remaining three studies evaluated CRP as a diagnostic test among patients self-reporting symptoms suggestive of TB.\(^{13,15,27}\) The proportion of PTB cases in the studies included was lowest (10%) for screening studies\(^{31}\) and highest (80%) for diagnostic studies.\(^{13}\)

**Sensitivity and specificity**

There was significant heterogeneity in specificity (range 33–81%; \( P^2 = 93\% \), \( P < 0.001 \)) but not sensitivity (range 81–97%; \( P^2 = 53\% \), \( P = 0.07 \)) estimates across studies (Figure 3A). The pooled sensitivity of CRP was 93% (95%CI 88–98), and pooled specificity was 60% (95%CI 46–75; Figure 3B).

**Subgroup analyses**

Sensitivity ranged from 81% to 85% and specificity from 58% to 81% in the two studies that evaluated CRP in the context of TB screening.\(^{6,31}\) As expected, sensitivity was higher (range 96–97%) and specificity lower (range 33–73%) in the three studies that enrolled patients self-reporting symptoms suggestive of PTB.\(^{13,15,27}\) Among HIV-infected out-patients, pooled sensitivity (93%, 95%CI 88–98; \( P^2 = 53 \), \( P = 0.08 \)) and pooled specificity (61%, 95%CI 45–77; \( P^2 = 94\% \), \( P < 0.001 \)) estimates were nearly identical to the overall estimates (Appendix Figure A.2A and B). Sensitivity was 100% (95%CI 63–100) and specificity was 85% (95%CI 55–98) among 21 non-HIV-infected out-patients enrolled in one study.\(^{15}\)

**In-patients**

**Study quality**

In general, the five studies enrolling hospitalized patients were judged to have higher and/or unclear risk of bias and greater concerns for applicability for all domains (Appendix Figure A.3).\(^{13,14,28–30}\) Most studies did not enroll a representative spectrum of patients,\(^{13,28–30}\) and did not provide sufficient information to determine the patient selection method.\(^{28–30}\)

Although all studies used culture as the reference standard for TB,\(^{13,14,28–30}\) none explicitly stated that researchers assessing TB status were blinded to CRP results. Industry involvement was unknown for three studies.\(^{28–30}\)

**Study characteristics**

Of the 5 studies that enrolled 672 hospitalized patients, 2 were conducted in high TB-HIV burden countries\(^{13,28}\) and 3 were conducted in countries with low-to-intermediate TB burden (Appendix Table
A.3, 14, 29, 30 Overall, 185 patients (28%) had PTB. Four studies included 289 in-patients (43%) with confirmed HIV infection, 13, 14, 28, 30 including two studies that restricted enrollment to HIV-infected individuals. 13, 14 All studies enrolled only patients self-reporting symptoms suggestive of TB.

Sensitivity and specificity
There was significant heterogeneity in sensitivity (range 56–96%; $I^2 = 80\%$, $P = 0.001$) and specificity (range 0–67%; $I^2 = 95\%$, $P < 0.0001$) estimates across studies (Appendix Figure A.4). The pooled sensitivity of CRP was 78% (95% CI 58–90) and pooled specificity was 21% (95% CI 6–52).

Subgroup analyses
No study evaluated CRP as a screening tool for PTB among hospitalized patients. Three of the four studies that enrolled PLHIV included ≥10 in-patients with confirmed HIV infection. Individual study estimates of CRP sensitivity among 287 HIV-infected in-patients were high (range 89–100%), whereas CRP specificity estimates were low (range 0–40%, Appendix Figure A.5A). 13, 14, 28 Three studies enrolled 384 non-HIV-infected in-patients. Individual study estimates of CRP sensitivity (range 43–82%) and specificity (range 8–76%) among non-HIV-infected in-patients exhibited substantial variability (Appendix Figure A.5B). 28–30

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Figure 1 Flowchart of studies describing the process by which eligible studies were identified. We included 1) studies enrolling children and/or adults undergoing PTB evaluation for symptoms suggestive of active PTB or high-risk individuals (e.g., HIV-infected individuals) undergoing TB screening; 2) studies that measured CRP levels from serum, plasma, or whole blood; and 3) studies that used mycobacterial culture on solid and/or liquid media for one or more specimens from each patient as a reference standard. We excluded 1) non-English language studies; 2) animal studies; 3) case reports/case series, case-control studies, review articles, and letters to the editor; 4) studies evaluating only extra-pulmonary TB as the target condition; 5) studies that measured CRP using a non-quantitative assay; 6) studies recruiting only patients with comorbidity conditions that are themselves associated with elevated CRP levels (e.g., inflammatory bowel disease); and 7) studies with <5 active PTB cases. CRP = C-reactive protein; PTB = pulmonary tuberculosis; HIV = human immunodeficiency virus.
DISCUSSION

Systematic screening of PLHIV and other high-risk populations for active TB is a key aspect of the WHO’s TB elimination strategy. However, current screening tools for key high-risk groups have inadequate test characteristics (e.g., symptom-based screening) or have high cost and infrastructure requirements (e.g., CXR). In this systematic review, we found that CRP, which can be measured by frontline health care workers using a simple and inexpensive (US$2–8 per test) POC assay, has similar sensitivity to and better specificity than that reported for symptom-based screening, particularly among PLHIV. POC CRP testing can therefore be used as a screening tool to improve the efficiency and lower the cost of intensified case finding (TB screening followed by confirmatory TB testing) among PLHIV, relative to current options.

The WHO’s target product profile for a TB screening test states that sensitivity should be ≥90% and specificity ≥70%. A recent modeling study concluded that there is no ‘ideal’ TB screening algorithm that meets these criteria across all populations and settings. Several systematic reviews have shown that symptom-based screening is more sensi-
tive (range 84–90%) in patients with HIV infection than in those without, thereby limiting its general applicability.\textsuperscript{4,5} In addition, specificity is poor (range 5–61\%) among PLHIV, particularly in sub-Saharan Africa.\textsuperscript{4–5} CXR either alone or after symptom screening has better and more consistent performance characteristics,\textsuperscript{8,34} but is not routinely available and requires trained personnel to interpret results. To implement WHO systematic screening and intensified case finding guidelines, there is thus an urgent need for a low-cost, simple and accurate TB screening test.

The findings from this systematic review suggest that CRP has strong potential to facilitate systematic screening of high-risk groups presenting for routine care. In the out-patient context—where most systematic screening would take place—we found that the pooled sensitivity of CRP for active PTB was 93\%. Moreover, results were consistent across studies and similar for patients with and those without HIV infection. CRP can therefore be expected to meet or exceed the minimum sensitivity threshold recommended for a TB screening test in most contexts. Pooled specificity, however, was 60\%, with significant heterogeneity (range 33–81\%; $I^2 = 93\%$). Although the pooled specificity of CRP is lower than the recommended threshold for a TB screening test, three of the five studies evaluated CRP in the context of TB diagnosis (specificity range 33–73\%)\textsuperscript{13,15,27} rather than TB screening (specificity range 58–81\%).\textsuperscript{6,31} Because patients self-presenting with TB symptoms have a higher prevalence of pyogenic infections or other systemic inflammatory conditions mimicking TB, the specificity of CRP for active PTB can be expected to be lower in this population than in populations undergoing provider-initiated TB screening, such as PLHIV presenting for routine HIV/AIDS care. Among in-patient studies in which the prevalence of diseases mimicking TB is high, we found that the pooled specificity of CRP was only 21\%. At the other extreme, healthy out-patient populations, such as those used to establish CRP cut-off points, have few individuals with CRP levels $\geq 10$ mg/l, as the prevalence of pyogenic infections and other systemic inflammatory conditions is low. When viewed within this context, CRP specificity in populations targeted for systematic screening is likely to be higher than the pooled value of 60\% that we report here.

Our systematic review had several potential limitations. First, heterogeneity was substantial for the out-patient pooled specificity estimate (significant heterogeneity for the out-patient pooled sensitivity estimate was not observed). We used empirical random effects weighting and excluded all studies contributing $<5$ TB cases to minimize heterogeneity. Second, our systematic review included only nine studies evaluating CRP accuracy with respect to PTB, only two of which evaluated CRP as a TB screening test.\textsuperscript{6,31} Additional good-quality studies that enroll populations targeted for systematic screening are clearly needed to confirm the conclusions from this systematic review, but our analysis of data from the out-patient and in-patient contexts provides the justification needed to move forward with such studies. Third, four of the five out-patient studies included in our systematic review were conducted in South Africa, potentially limiting the generalizability of our findings to other settings. Last, as with all systematic reviews, there is a possibility of publication bias.

**CONCLUSIONS**

CRP shows considerable promise as a tool to facilitate systematic TB screening of HIV-infected adults. It has similar sensitivity and higher specificity than symptom-based screening, and is simpler and less resource-intensive to implement than CXR. However, to support policy recommendations, additional well-designed studies that enroll children and high-risk populations targeted for systematic screening, such as household contacts, current/former silica workers, and prisoners,\textsuperscript{2} are needed. Future studies should evaluate whether the diagnostic accuracy of CRP-based TB screening may be further improved when used in combination with CXR and/or other promising biomarkers. In addition to diagnostic accuracy, such studies should also assess the impact of POC CRP-based TB screening on the timing of TB diagnosis and treatment, the proportion of eligible patients who initiate preventive treatment, and health system- and patient-related costs relative to current TB screening options.

**Acknowledgements**

The authors thank J Luke Davis, P Nahid and G Rutherford for providing thoughtful feedback for earlier versions of the manuscript/analysis and G Won for assistance in searching for and obtaining relevant articles.

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An earlier version of this analysis was presented at the 45th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease, Barcelona, Spain, 1 November 2014.

Conflicts of interest: none declared.

**References**


APPENDIX

Table A.1  Search terms

<table>
<thead>
<tr>
<th>Online database</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>tuberculosis AND (c reactive protein OR CRP) AND English[la] NOT case reports[pt] NOT (animals[mh] NOT humans[mh])</td>
</tr>
<tr>
<td>Embase</td>
<td>‘tuberculosis’/mj OR ‘lung tuberculosis’/exp/mj OR tuberculosis:ab,ti AND (‘c reactive protein’ OR crp:ab,ti) AND (english):lm NOT ([animals]:lm NOT ([humans]:lm OR ‘patient’:exp)) NOT ‘case report’:de</td>
</tr>
<tr>
<td>Web of Science</td>
<td>TS = (tuberculosis) #1 AND #2 (TS = (‘c reactive protein’ OR CRP) AND Language = (English)) AND (#4 AND TS = (‘case report’ OR ‘case reports’ OR ‘report of a case’)) AND Databases = SCI-EXPANDED, SSCI, A&amp;HCI Timespan = All years (#4 NOT #5) AND Language = (English)</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>tuberculosis:ti,ab,kw and ‘c reactive protein’ or CRP:ti,ab,kw (Word variations have been searched)</td>
</tr>
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</table>

Table A.2  Characteristics of excluded studies among all studies in which additional data were requested from the corresponding author to determine final eligibility*

<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Country</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agranoff, 200623</td>
<td>Uganda, The Gambia Austria</td>
<td>Did not provide accuracy data</td>
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<tr>
<td>Ratzinger, 201224</td>
<td>Austria</td>
<td>Reference standard not satisfied; additional data provided by the author did not limit TB diagnosis to culture-positive TB</td>
</tr>
<tr>
<td>Shi, 201325</td>
<td>China</td>
<td>Did not provide accuracy data</td>
</tr>
<tr>
<td>Tintinger, 201226</td>
<td>South Africa</td>
<td>Reference standard not satisfied; additional data provided by the author did not limit TB diagnosis to culture-positive TB</td>
</tr>
</tbody>
</table>

* All corresponding authors were contacted via e-mail.

TB = tuberculosis.
<table>
<thead>
<tr>
<th>First author, year, reference</th>
<th>Country</th>
<th>Study population</th>
<th>Total patients, n (% HIV+%)</th>
<th>Active TB n (%)</th>
<th>CRP test/manufacturer, assay type</th>
<th>Reference standard</th>
<th>Industry involvement*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Out-patient pulmonary TB</strong></td>
<td></td>
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<tr>
<td>TB screening</td>
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<tr>
<td>Lawn, 2013^6</td>
<td>South Africa</td>
<td>Out-patients initiating ART</td>
<td>496 (100)</td>
<td>81 (16)</td>
<td>Quantikine/R&amp;D Systems, ELISA</td>
<td>MGIT</td>
<td>Kit donation</td>
</tr>
<tr>
<td>Yoon, 2014^7</td>
<td>Uganda</td>
<td>Out-patients initiating ART</td>
<td>271 (100)</td>
<td>27 (10)</td>
<td>iCHROMA/Boditech, Sandwich immunoassay†</td>
<td>MGIT</td>
<td>Kit donation</td>
</tr>
<tr>
<td>TB diagnosis</td>
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<tr>
<td>Drain, 2014^27</td>
<td>South Africa</td>
<td>Out-patients with TB symptoms and negative sputum AFB smears</td>
<td>76 (100)</td>
<td>30 (39)</td>
<td>NycoCard/Axis-Shield, Sandwich immunoassay†</td>
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<td>Kit donation</td>
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<td>Wilson, 2006^13</td>
<td>South Africa</td>
<td>Out-patients with TB symptoms and negative sputum AFB smears or unable to produce sputum</td>
<td>74 (100)</td>
<td>59 (80)</td>
<td>Synchron CX7/Beckman Coulter, immunoturbidometry</td>
<td>LJ and MGIT</td>
<td>Funding</td>
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<td>Wilson, 2011^15</td>
<td>South Africa</td>
<td>Out-patients with TB symptoms and negative sputum AFB smears or unable to produce sputum</td>
<td>204 (44)</td>
<td>116 (57)</td>
<td>Olympus AU640/Olympus, immunoturbidometry</td>
<td>Dimension RXL/Dade-Behring, immunoturbidometry</td>
<td>MGIT</td>
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<td><strong>In-patient pulmonary TB</strong></td>
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<tr>
<td>Bandyopadhyay, 2011^28</td>
<td>India</td>
<td>In-patients with fever of unknown origin§</td>
<td>52 (23)</td>
<td>9 (17)</td>
<td>Not provided/Abbott, immunoturbidometry</td>
<td>Sputum and/or BAL culture¶</td>
<td>Unclear</td>
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<tr>
<td>Cho, 2012^30</td>
<td>South Korea</td>
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<td>73 (3)</td>
<td>40 (55)</td>
<td>Not provided, immunoturbidometry</td>
<td>Sputum and/or BAL culture¶ or positive NAAT</td>
<td>Unclear</td>
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<tr>
<td>Lee, 2011^19</td>
<td>South Korea</td>
<td>In-patients with TB symptoms</td>
<td>272 (0)</td>
<td>82 (30)</td>
<td>CRPL3/Roche Diagnostics, immunoturbidometry</td>
<td>Sputum and/or BAL culture¶</td>
<td>None</td>
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<td>Sage, 2010^14</td>
<td>United Kingdom</td>
<td>In-patients with TB symptoms</td>
<td>247 (100)</td>
<td>28 (11)</td>
<td>Not provided</td>
<td>Sputum and/or BAL culture¶</td>
<td>Unclear</td>
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<tr>
<td>Wilson, 2006^13</td>
<td>South Africa</td>
<td>In-patients with TB symptoms and negative sputum AFB smears or unable to produce sputum</td>
<td>28 (100)</td>
<td>26 (93)</td>
<td>Synchron CX7/Beckman Coulter, immunoturbidometry</td>
<td>LJ and MGIT</td>
<td>Funding</td>
</tr>
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</table>

* Determined after reviewing the author’s conflict of interest statement and included kit donation (free and/or discounted test materials) and funding. If a conflict of interest statement was not available with the published article, industry involvement was described as “unclear.”
† Measured using a point-of-care assay.
‡ Study utilized two CRP assays during the study period; study participants had CRP levels measured with one assay only.
§ Defined as: 1) temperature ≥ 38.3°C on several occasions, 2) fever lasting ≥ 3 weeks, 3) failure to reach a diagnosis despite three out-patient visits or 3 days in the hospital without elucidation of a cause or 1 week of ambulatory investigation.
¶ Solid and/or liquid culture not specified.
HIV = human immunodeficiency virus; TB = tuberculosis; CRP = C-reactive protein; ART = antiretroviral therapy; ELISA = enzyme-linked immunosorbent assay; MGIT = Mycobacteria Growth Indicator Tube; LJ = Löwenstein-Jensen; AFB = acid-fast bacilli; BAL = bronchoalveolar lavage; NAAT = nucleic acid amplification test.
**DATA EXTRACTION FORM**

Record ID

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**ELIGIBILITY**

Title

---

Authors

---

Journal

---

Year

---

Eligible

- No
- Yes

Eligibility notes

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**STUDY CHARACTERISTICS**

Country

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Country level TB burden

- Low burden
- Medium burden
- High burden

Study design

- RCT
- Cohort
- Cross-sectional
- Case-control
- Other

Participant selection

- Consecutive
- Convenience
- Random
- Other

Study setting

- Outpatient
- Inpatient
- Both outpatient and inpatient

Industry involvement (check all that apply)

- No
- Yes, funding
- Yes, kit donation
- Yes, other

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**Figure A.1** Standardized data extraction form for individual studies. TB = tuberculosis; RCT = randomized controlled trial; CRP = C-reactive protein; HIV = human immunodeficiency virus.
### STUDY POPULATION CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with CRP levels available</td>
<td></td>
</tr>
<tr>
<td>Number of adults</td>
<td></td>
</tr>
<tr>
<td>Number of children</td>
<td></td>
</tr>
<tr>
<td>Number of outpatients</td>
<td></td>
</tr>
<tr>
<td>Number of inpatients</td>
<td></td>
</tr>
<tr>
<td>Number of patients with confirmed HIV infection</td>
<td></td>
</tr>
<tr>
<td>Number of patients without HIV</td>
<td></td>
</tr>
<tr>
<td>Number of patients undergoing TB screening</td>
<td></td>
</tr>
<tr>
<td>Number of patients with suspected TB undergoing TB</td>
<td></td>
</tr>
<tr>
<td>evaluation</td>
<td></td>
</tr>
<tr>
<td>Additional comments</td>
<td></td>
</tr>
</tbody>
</table>

### INDEX TEST CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
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</thead>
<tbody>
<tr>
<td>CRP assay used</td>
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</tr>
<tr>
<td>CRP manufacturer</td>
<td></td>
</tr>
<tr>
<td>Specimen used for CRP testing</td>
<td>Serum, Plasma, Whole blood</td>
</tr>
<tr>
<td>Was CRP cut-point specified?</td>
<td>No, Yes, 10 mg/L cut-point was used, Yes, different cut-point was used</td>
</tr>
<tr>
<td>Additional comments</td>
<td></td>
</tr>
</tbody>
</table>

### COMPARISON TEST(S) CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum mycobacterial culture used as the reference standard</td>
<td>No, Yes</td>
</tr>
<tr>
<td>Type of mycobacterial culture</td>
<td>Solid, Liquid</td>
</tr>
<tr>
<td>Number of cultures performed per patient</td>
<td>1, 2, 3 or more</td>
</tr>
<tr>
<td>Other TB tests performed (check all that apply)</td>
<td>Smear microscopy, Xpert MTB/RIF, Nucleic acid amplification testing, Other</td>
</tr>
<tr>
<td>Additional comments</td>
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</tr>
<tr>
<td>OUTCOMES</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Total number of patients evaluated for active pulmonary TB</td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td></td>
</tr>
<tr>
<td>False positives</td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td></td>
</tr>
<tr>
<td>False negatives</td>
<td></td>
</tr>
<tr>
<td>Total number of patients diagnosed with culture-confirmed TB</td>
<td></td>
</tr>
<tr>
<td>Additional comments</td>
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</tr>
</tbody>
</table>
Figure A.2  Diagnostic accuracy of CRP for PTB among out-patients with confirmed HIV infection. A) Forest plot of individual out-patient study estimates of sensitivity and specificity for people with confirmed HIV infection. B) HSROC plot of out-patient studies restricted to patients with confirmed HIV infection. Individual and pooled sensitivity and specificity estimates as a hierarchical summary receiver-operating curve. * CRP evaluated as a screening test for tuberculosis. ^ CRP evaluated as a diagnostic test for symptomatic patients undergoing tuberculosis evaluation. Pooled sensitivity 93% (95%CI 88–98); test for heterogeneity $I^2 = 53$, $P = 0.08$. Pooled specificity 61% (95%CI 45–77); test for heterogeneity $I^2 = 94$, $P < 0.001$. TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative; CI = confidence interval; HSROC = hierarchical summary receiver operating characteristic; CRP = C-reactive protein; PTB = pulmonary tuberculosis.

Figure A.3  In-patient pulmonary tuberculosis study quality using the Quality Assessment of Diagnostic Studies (QUADAS-2) tool. The Figure summarizes the risk of bias and applicability concerns for all in-patient studies included in this systematic review/meta-analysis.
Figure A.4  Diagnostic accuracy of CRP for PTB among in-patients. Forest plot of individual in-patient study estimates of sensitivity and specificity. Pooled sensitivity 78% (95%CI 58–90); test for heterogeneity $I^2 = 80\%$, $P = 0.001$. Pooled specificity 21% (95%CI 6–52); test for heterogeneity $I^2 = 95\%$, $P < 0.0001$. TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative; CI = confidence interval; CRP = C-reactive protein; PTB = pulmonary tuberculosis.

Figure A.5  Diagnostic accuracy of CRP for pulmonary tuberculosis among in-patients stratified by HIV status. A) HIV-positive in-patients; B) HIV-negative in-patients. TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative; CI = confidence interval; CRP = C-reactive protein; HIV = human immunodeficiency virus.
CONTEXTE : Le dépistage systématique de la tuberculose pulmonaire (TBP) active est recommandé pour les populations à risque élevé, notamment les personnes vivant avec le virus de l'immunodéficience humaine (PVVIH). Cependant, les outils de dépistage de la TB actuellement recommandés ne sont pas suffisants pour la majorité des zones très lourdement touchées.

OBJECTIF : Déterminer si la protéine C-réactive (CRP) possède les caractéristiques nécessaires pour dépister les individus à la recherche d'une TBP active.

SCHEMA : Nous avons réalisé une revue systématique et un méta-analyse des études évaluant la précision diagnostique de la CRP (seuil de 10 mg/l) pour la TBP à culture positive. Des estimations regroupées de précision diagnostique ont été générées par un ménata-analyse à effets aléatoires pour les patients externes et hospitalisés et pour des sous-groupes définis à l'avance, basés sur le statut VIH et l'indication du test.

RESULTATS : Nous avons identifié neuf études uniques enrollant 1793 adultes externes (cinq études, 1121 patients) et hospitalisés (cinq études, 672 patients), dont 72% avaient une infection à VIH confirmée. Parmi les patients externes, la CRP a eu une sensibilité élevée (93%, IC95% 88–98) et une spécificité modérée (60%, IC95% 40–75) pour la TBP active. La spécificité a été la plus basse parmi les patients hospitalisés (21%, IC95% 6–52) et la plus élevée parmi les patients externes bénéficiant d’un dépistage de TB (fourchette 58–81%). Il n’y a pas eu de différence dans les estimations en fonction du statut VIH.

CONCLUSION : La CRP, qui est disponible en tant que test simple, peu coûteux et faisable sur place, peut être utilisée pour dépister la TB active parmi les PLVIH se présentant pour une prise en charge de routine du VIH/SIDA (syndrome d’immunodéficience acquise).

RESUMEN

MARCO DE REFERENCIA: Se recomienda practicar la detección sistemática de la tuberculosis pulmonar (TBP) activa en las personas con alto riesgo de contraer la TB, incluidas las personas infectadas por el virus de la inmunodeficiencia humana (PVVIH), sin embargo, los instrumentos de cribado de la TB que se recomiendan en la actualidad son inadecuados en la mayor parte de entornos con alta carga de morbilidad.

OBJETIVO: Determinar si las características de la determinación de la proteína C-reactiva (CRP) son suficientes con el fin de practicar la detección sistemática de la TBP activa.

MÉTODOS: Se llevó a cabo una revisión sistemática con metanálisis de los estudios que evaluaban la exactitud diagnóstica de la CRP (umbral 10 mg/l) para la TBP con cultivo positivo. Se generaron estimaciones combinadas de la exactitud diagnóstica mediante un metanálisis de efectos aleatorios en pacientes ambulatorios y pacientes hospitalizados y en subgrupos predeterminados en función del estado frente al VIH y la indicación de la prueba.

RESULTADOS: Se encontraron nueve estudios únicos que incluían 1793 adultos de ámbitos ambulatorios (cinco estudios con 1121 pacientes) e intrahospitalarios (cinco estudios con 672 pacientes), de los cuales el 72% presentaba infección confirmada por el VIH. En los pacientes ambulatorios, la CRP exhibió una alta sensibilidad (93%; IC95% 88–98) y moderada especificidad (60%; IC95% 40–75) para la TBP activa. La especificidad más baja se observó en los pacientes hospitalizados (21%; IC95% 6–52) y la más alta en los pacientes ambulatorios en quienes se practicaba la detección sistemática de la TB (intervalo 58–81%). No se observó ninguna diferencia en las estimaciones combinadas según el estado frente al VIH.

CONCLUSIÓN: La determinación de la CRP—disponible como una prueba en el punto de atención, sencilla y de bajo costo—se puede utilizar en la detección sistemática de la TBP de las PVVIH que acuden a los servicios de atención corriente de la infección por el VIH/SIDA (síndrome de inmunodeficiencia adquirida).