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Systematic review

Acute phase proteins and IP-10 as triage tests for the diagnosis of tuberculosis: systematic review and meta-analysis

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ABSTRACT

Objectives: We examined the data reported in studies for diagnostic purposes and to discuss whether their intended use could be extended to triage, as rule-in or rule-out tests to select individuals who should undergo further confirmatory tests.
Methods: We searched Scopus, PubMed and Web of Science with the terms 'acute phase proteins,' 'IP-10,' 'tuberculosis,' 'screening' and 'diagnosis,' extracted the sensitivity and specificity of the biomarkers and explored methodologic differences to explain performance variations. Summary estimates were calculated using random-effects models for overall pooled accuracy. The hierarchical summary receiver operating characteristic model was used for meta-analysis.
Results: We identified 14, four and one studies for C-reactive protein (CRP), interferon γ–induced protein 10 (IP-10) and alpha-1-acid glycoprotein (AGP). The pooled CRP sensitivity/specificity (95% confidence interval) was 89% (80–96) and 57% (36–65). Sensitivity/specificity were higher in high-tuberculosis-burden countries (90%/64%), HIV-infected individuals (91%/61%) and community-based studies (90%/62%). IP-10 sensitivity/specificity in TB vs. non-TB studies was 85%/63% and in TB and HIV coinfected vs. other lung conditions 94%/21%. However, IP-10 studies included diverse populations and a high risk of bias, resulting in very low-quality evidence. AGP had 86%/93% sensitivity/specificity.
Conclusions: Few studies have evaluated CRP, IP-10 and AGP for the triage of symptomatic patients. Their high sensitivity and moderate specificity warrant further prospective studies exploring whether their combined use could optimize performance. **V.S. Santos, Clin Microbiol Infect 2019;25:169**

Introduction

Tuberculosis (TB) causes an estimated 1.7 million deaths and 10.4 million incident cases per year [1]. Despite its public health burden, nearly one third of the estimated cases are missed by national surveillance systems, suggesting that many cases fail to reach

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the health services. TB mortality is higher in patients with a late diagnosis, advanced disease stages and coinfection with HIV, and strategies which increase case detection and reach an early diagnosis are integral to the global strategy for the control of TB [2].

One of the major problems for the management of TB is the inefficiency of the diagnostic cascade. Diagnostic investigations are usually triggered after a patient has had cough for two or more weeks; however, the tests used are unsuitable for rapid and large-scale screening. The most frequently used tests, smear microscopy and Xpert MTB/RIF (*Mycobacterium tuberculosis* complex/resistance to rifampin), are highly specific. However, smear microscopy has low sensitivity and is technically unsuitable as a screening tool, and Xpert MTB/RIF and X-rays require an infrastructure that is rarely available at peripheral diagnostic centres. It is recognized that diagnostic algorithms could be improved with the use of triage tests that select patients requiring further confirmatory tests and exclude patients unlikely to have TB [3]. The World Health Organization has included, among the high-priority target product profiles for TB diagnosis, a non–sputum-based triage test, which, under ideal conditions, would require sensitivity ≥95% and specificity >75% [4]. However, early promising prototypes for triage, such as a β-lactamase C assay [5], failed to reach the production stages, and the pipeline for these tests has very few candidates [6].

Serum levels of acute phase proteins (APPs) and cytokines are increased in individuals with TB. Among these, C-reactive protein (CRP) is often used in clinical practise as an adjuvant test for diagnosis (especially in children) [7], and interferon γ–induced protein 10 (IP-10) may have potential to monitor treatment responses to anti-TB therapy [7–9]. Despite their frequent use for diagnosis, they are rarely used as triage tests, and their use for these different purposes require different performance characteristics. Cutoffs or thresholds for a test for diagnostic purposes are defined to achieve a high accuracy and use the best combination of sensitivity and specificity, whereas triage tests require high sensitivity in order to identify as many cases as possible, often at the expense of lower specificity.

There is renewed interest to explore whether APPs and cytokines could be used as triage tests for TB. As few studies have considered using APPs and IP-10 for screening purposes, we examined the data reported in studies for diagnostic purposes and assessed whether their intended use could be extended to triage, as rule-in or rule-out tests to select individuals who should undergo further confirmatory tests.

Methods

This study was conducted following the Cochrane Collaboration's Diagnosis Test Accuracy Working Group protocol. Institutional review board approval and informed consent were not required for this systematic review and meta-analysis. A study protocol was designed *a priori* and was registered in the PROSPERO database (registration CRD42018087015). We reported our findings according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

Search strategy and selection criteria

We performed a systematic review using Scopus, PubMed and Web of Science databases to identify studies published without language restriction up to 14 October 2017. We used the search terms 'acute phase proteins,' 'IP-10,' 'tuberculosis,' 'screening,' 'diagnosis' and related terms. The full search strategy is described in the Supplementary Appendix. Two independent review authors (VSS and KK) screened the title and abstract for relevance, and a third review author (LEC) was consulted to resolve disagreements. Articles considered to have original material were obtained and assessed in detail, and the references cited in these publications were searched to identify further publications.

We included studies that met the following conditions. First, the study used quantitative laboratory-based and/or point-of-care assays to measure levels of at least one of APP (α-1-anti–chymotrypsin, α-1-anti–trypsin, α-2-macroglobulin, alpha-1-acid glycoprotein (AGP), ceruloplasmin, complement factors, CRP, factor VIII, ferritin, fibrinogen, haptoglobin, hepcidin, mannan-binding lectin, orosomucoid, plasminogen activator inhibitor 1, prothrombin, serum amyloid A, serum amyloid P component and von Willebrand factor) or unstimulated IP-10 as an index test. We included unstimulated IP-10 because there is an extensive number of publications reporting its potential use for diagnosis. Second, the study enroled symptomatic patients suspected of having active pulmonary TB, of whom a proportion was confirmed as having pulmonary TB and another proportion as having other lung disease. Third, patients had confirmed pulmonary TB based on solid and/or liquid sputum *M. tuberculosis* culture as the reference standard. Finally, it reported cases in absolute numbers of true-positive, false-positive, false-negative and true-negative results or these data were derivable from the published results. Articles were included regardless of age (adults or children) or whether subjects had coinfections (e.g. HIV).

We excluded studies that only reported stimulated IP-10 values, but the authors of these studies were asked to provide the non-stimulated baseline results if available (e.g. the nil values of the QuantiFERON assay) to prepare additional receiver operating curves for meta-analysis. Studies that focused on latent *M. tuberculosis* infections, those that tested patients after initiation of treatment and those that used samples other than blood (e.g. pulmonary biopsy samples or pleural exudates) as well as case–control studies were excluded.

Data extraction and bias assessment

We predefined tables for data extraction, which were piloted in ten articles. The information extracted included author, country, study design, clinical setting (hospital or community) participant characteristics, case definition for TB diagnosis, markers included, method of detection and the threshold used for each marker. We extracted the absolute numbers of true-positive, false-positive, false-negative and true-negative test results from the paper or through (re)calculations of the sensitivity and specificity based on the authors' diagnostic classification of the participants and sample size of the study. If a study presented multiple cutoff values for an index test and as consequence reported multiple pairs of sensitivity and specificity, the data with the best combined estimates for sensitivity and specificity were extracted. Countries were classified according to the World Health Organization burden of TB classification [1] to describe the epidemiologic context. The quality of studies and the risk of bias were assessed by two independent reviewer authors using the QUADAS-2 guidelines (Supplementary Materials). We used RevMan 5.3 software (Cochrane Collaboration) to generate the graphs on the risk of bias.

Statistical analysis

We used the sensitivity and specificity of the markers reported by the author or (re)calculated them from the data presented. For diagnostic performance of CRP, we fitted the hierarchical summary receiver operating characteristic (HSROC) model proposed by Rutter and Gatsonis [10], which takes into account correlation between sensitivity and specificity across studies while also allowing for variation in test performance among studies through the inclusion

of random effects. We expected that the methods for measuring the markers and the cutoffs would vary across studies and thus investigated potential methodologic and assay differences to interpret variations in performance. An exploratory analysis to investigate potential factors of heterogeneity was performed by visual inspection of HSROC curves. Metaregression was conducted by adding these factors as covariates to the hierarchical model [11]. The characteristics explored were the World Health Organization TB burden classification of the country where the study took place (high burden vs. others), HIV status (positive vs. negative), clinical settings (hospitalized vs. community) and method for CRP quantification. Publication bias was examined using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks *et al.* [12].

For IP-10, because few studies were available, the diagnostic performance was analysed by modelling the trade-off between sensitivity and specificity using the Moses summary receiver operating characteristic regression [13,14].

For all analyses, two-sided $p < 0.05$ values were considered statistically significant. Statistical analyses were performed by the R 2.10.13 statistical programming language (R Core Team, 2013) and Stata 14 (StataCorp).

Results

The search strategy identified 891 records. After screening titles and abstracts, 104 full-text articles were assessed for eligibility and 19 were included (Fig. 1). CRP was reported in 14 studies [15–28],

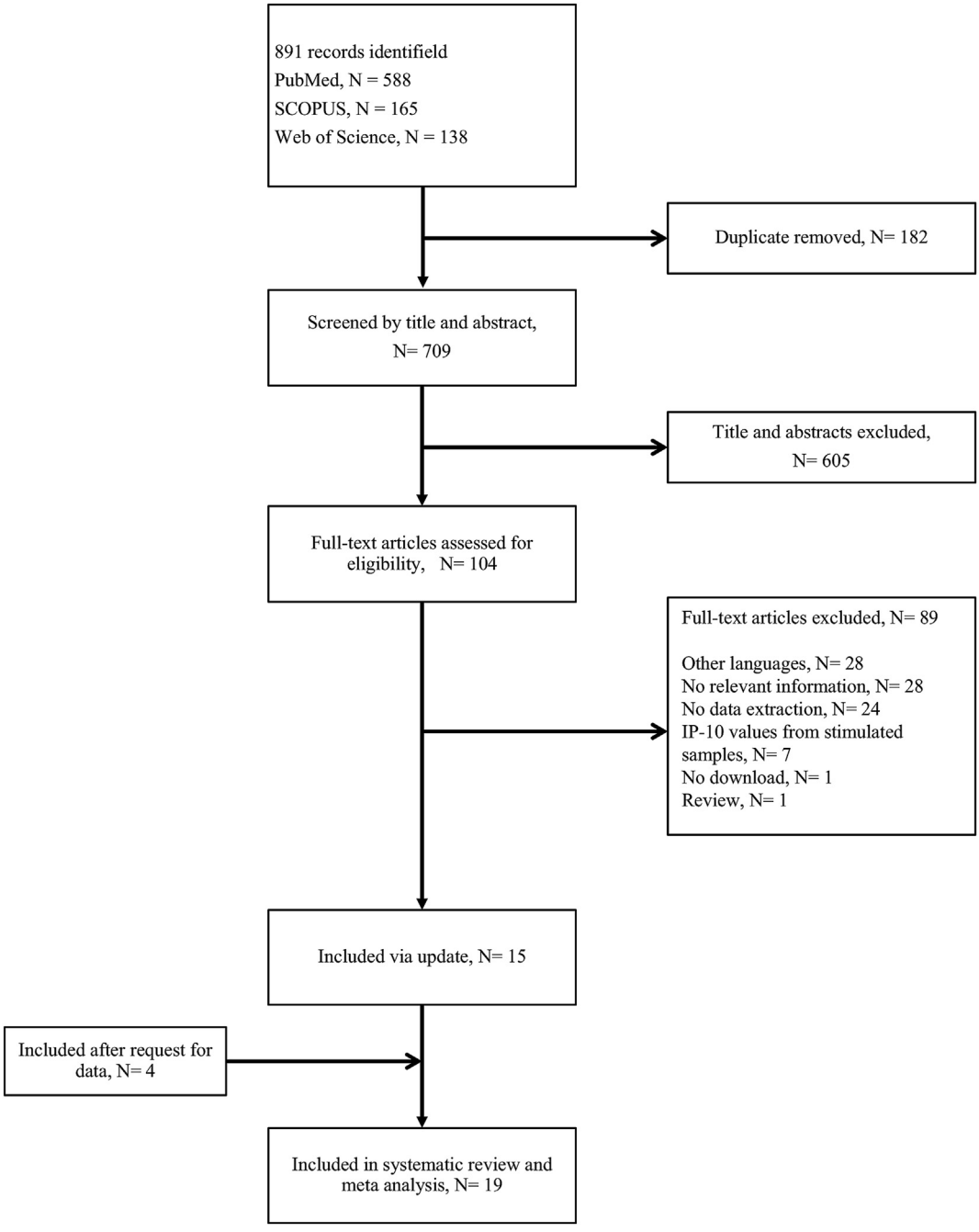

Fig. 1. Flow diagram of study selection.

IP-10 in four [29–32] and AGP [33] in one. Table 1 summarizes the main characteristics of each study.

C-reactive protein

Six of the 14 studies reporting CRP sensitivity and specificity included only HIV-infected [16,19,24,26–28], four only HIV-uninfected [17,21,23,25] and two both HIV-infected and HIV-uninfected [20,22] patients; in two studies the HIV status was not described [15,18]. Nine studies were conducted in high-TB-burden countries [15,16,20,22,24–28]. Nine studies enroled patients in community settings [15,17,18,22,24–28] and five enroled hospitalized patients [16,19–21,23]. All studies focused on adults. Most studies used a 10 mg/dL cutoff point (Table 1).

The quality of the studies and the risk of bias are shown Supplementary Figs. S1 and S2. The QUADAS-2 tool showed that the studies that enroled patients in the community had a lower risk of bias than studies enrolling hospitalized patients. Most studies enrolling community individuals were designed to evaluate the diagnostic accuracy of CRP for TB and enroled a representative spectrum of patients, whereas hospital studies did not provide sufficient information to determine the patient selection method and had unclear blinding for the interpretation of results, which are potential sources of bias.

The overall (95% confidence interval (CI)) pooled sensitivity of CRP was 89% (80–96) with a pooled (95% CI) specificity of 57% (36–65) (Table 2). The positive and negative likelihood ratios (95% CI) were 1.91 (1.42–2.56) and 0.21 (0.10–0.43), respectively (Supplementary Tables S1 and S2). The summary diagnostic odds ratio (95% CI) was 8.27 (3.40–20.00) (Supplementary Table S3). The HSROC curve for CRP is shown in Fig. 2. Table 3 describes the subgroup analysis. CRP had a higher pooled sensitivity and specificity (95% CI) in countries with high TB burden (90% (82–92) and 64% (53–75)), in HIV-infected patients (91% (85–93) and 61% (32–71)) and in community patients (90% (85–93) and 62% (51–73), respectively).

To investigate the potential sources for heterogeneity, we conducted a metaregression analysis using the country TB burden, HIV status, clinical settings and CRP assays. Of these, the most important source of heterogeneity was the clinical setting (Table 4). We also explored the performance for CRP among HIV-infected patients from high-TB-burden countries. The pooled (95% CI) sensitivity for this group was 92% (89–94), with a pooled (95% CI) specificity of 66% (64–68).

No publication bias and high symmetry of the included studies were proved by Deeks's funnel plot asymmetry test (p 0.73; Fig. 3).

IP-10

Unstimulated IP-10 values were obtained from four studies [29–32] (Table 1). One study included HIV-uninfected individuals [29], two included both HIV-uninfected and HIV-infected patients [30,32] and in one the HIV status was unknown [31]. Three studies [29–31] were conducted in adults and only one in children [32]. All studies used culture-positive sputum samples as the reference standard for the confirmation of cases. There was a wide variation in the kits and thresholds used, and many studies did not report the cutoffs selected, which precluded further analysis.

Most of the studies did not enrol a representative spectrum of patients or failed to provide satisfactory information to determine the patient selection methods. Furthermore, the unblinded interpretation of results, the lack of a prespecified cutoff thresholds and the different assays used were common sources of potential bias (Supplementary Figs. S6 and S7).

Because the studies included a wide range of populations (often without matched groups), it was not possible to estimate pooled sensitivity and specificity across the studies. The performance of unstimulated IP-10 test is thus presented for each group in Table 5. The pooled (95% CI) sensitivity and specificity to diagnose TB was 85% (77–92) and 63% (54–71), respectively. Studies comparing patients with TB and HIV coinfection and patients with other lung diseases had an estimated sensitivity (95% CI) of 94% (80–99) and specificity of 21% (14–29). Summary diagnostic odds ratios (95% CI) were as follows: TB vs. non-TB, 13.19 (2.28–76.27); TB HIV positive vs. non-TB HIV positive, 3.11 (0.79–12.26).

Alpha-1-acid glycoprotein

Only one study [33] reporting data for AGP was included. This study enroled 21 patients with TB and 27 patients with bacterial pneumonia. The sensitivity and specificity (95% CI) were 86% (64–95) and 93% (75–98), respectively.

There were no studies describing the combined use of CRP with IP-10 or AGP to explore whether using two or more of these markers would result in a higher sensitivity.

Discussion

It is estimated that nearly 4.1 million TB cases are missed annually worldwide [1], and increasing the accessibility of diagnostic and treatment services is essential for its effective control. Although sensitive and specific molecular diagnostics, such as Xpert MTB/RIF, are now available, these tests require well-established laboratory facilities and are relatively expensive for low-income countries. Although national programmes are attempting to increase the use of Xpert MTB/RIF as the first test for diagnosis of presumptive TB, patients attending primary health centres are mostly screened using smear microscopy or need to travel or have their samples transported to laboratories with Xpert MTB/RIF facilities. The goal of an accessible and efficient quality diagnosis therefore remains elusive and is one of the largest barriers for TB control.

Improved diagnostic algorithms able to triage patients to select individuals with a high or low probability of TB could optimize the use of limited resources of national programmes. These approaches should be able to identify (rule in) individuals with a high risk of TB and rule out those who, despite their symptoms, have a low likelihood of TB. Triage approaches also need to be simple and rapid, without the need of complex platforms to facilitate implementation in low-resource settings.

Here we reviewed the potential of established APPs currently used as adjunct assays for the diagnosis of TB. APPs are proteins whose plasma concentrations increase or decrease rapidly as an innate response to injury or local inflammation. CRP, for example, binds to bacterial and fungal cell walls and to phosphocholine in the surface of damaged human cells, and a high concentration suggests the presence of bacterial infections. Although their stimulation in response to a wide range of inflammatory processes would result in a low specificity, their high sensitivity and the maintenance of response integrity, even in individuals of young age or immunodeficient as a result of severe malnutrition or HIV, have resulted in their frequent use for the diagnosis and management of infection. Paradoxically, although APPs are included in many diagnostic algorithms for TB, especially in children, these markers are usually used in parallel with other tests, and testing is rarely reported in a stepwise cascade for triage. This is a major limitation, as markers used for diagnosis are used in parallel with other tests, while screening tests are usually cascaded, with an emphasis on

Table 1
Characteristic of included studies

Topic	Study	Country	Study design	Status HIV	Setting	Study subjects	Tuberculosis definition	Non-TB definition	Detection method	Threshold
Alpha-1-acid glycoprotein	Fassbender (1995) [33]	Germany	Cross-sectional	Unknown	Community	21 confirmed TB, 27 non-TB and 36 healthy controls	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	Immunoelect -rophoresis (immunoaffinity)	Not provided
C-reactive protein	Lin (1986) [15]	China	Cross-sectional	Unknown	Community	18 confirmed TB, 26 non-TB, 12 healed TB and 31 healthy controls	Confirmed TB based on clinical features, X-ray of chest, smear or culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	Nephelometry	7 μg/mL
	Wilson (2006) [16]	South Africa	Cohort	Positive	Hospital	59 confirmed TB and 15 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: adults who were initially suspected of active TB, but who ended up had other disease	Immunoturbidimetry	10 mg/L
	Choi (2007) [17]	South Korea	Cross-sectional	Negative	Community	46 confirmed TB and 67 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	Immunoturbidimetry	11.2 mg/L
	Kang (2009) [18]	South Korea	Prospective	Unknown	Community	30 confirmed TB and 57 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	Immunoturbidimetry	12.5 mg/L
	Sage (2010) [19]	United Kingdom	Prospective	Positive	Hospital	28 confirmed TB and 219 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	ELISA	10 mg/L
	Bandyopadhyay (2011) [20]	India	Cohort	Negative/ positive	Hospital	9 confirmed TB and 43 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	Immunoturbidimetry	10 mg/L
	Lee (2011) [21]	South Korea	Prospective	Negative	Hospital	82 confirmed TB and 190 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	Immunoturbidimetry	10 mg/L
	Wilson (2011) [22]	South Africa	Prospective	Negative/ positive	Community	135 confirmed TB and 115 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: adults who were initially suspected of active TB, but who ended up had other disease	immunoturbidimetry/ spectrophotometry	10 mg/L
	Cho (2012) [23]	South Korea	Prospective	Negative	Hospital	40 confirmed TB and 33 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	Immunoturbidimetry	10 mg/L
	Lawn (2013) [24]	South Africa	Cohort	Positive	Community	81 confirmed TB and 415 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	ELISA	5 mg/L
	Niu (2013) [25]	China	Cross-sectional	Negative	Community	78 confirmed TB and 113 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	immune scatter turbidimetry	15.2 mg/mL
	Drain (2014) [26]	South Africa	Prospective	Positive	Community	45 confirmed TB and 47 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up not having TB	Immunometric semi-quantitative assay/ spectrophotometry	8 mg/L
	Yoon (2014) [27]	Uganda	Prospective	Positive	Community	27 confirmed TB and 244 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up not having TB	ELISA	10 mg/L
	Yoon (2017) [28]	Uganda	Prospective	Positive	Community	163 confirmed TB and 1014 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up not having TB	ELISA	10 mg/L
IP-10	Hong (2012) [29]	South Korea	Cross-sectional	Negative	Hospital/ community	46 confirmed TB, 22 LTBI and 32 health controls	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	ELISA	119 pg/mL
	Vanini (2012) [30]	Italy	Prospective	Negative/ positive	Community	58 confirmed TB and 137 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of PTB, but who ended up had other disease	ELISA	Not provided
	Yang (2014) [31]	China	Cross-sectional	Unknown	Hospital/ community	123 confirmed TB patients, 91 non-TB patients, 33 LTBI patients and 36 health controls	Confirmed TB based on positive culture from sputum	Non-TB patients: sick adults who were initially suspected of active TB, but who ended up had other disease	ELISA	Not provided
	Petrone (2015) [32]	Uganda	Cross-sectional	Negative/ positive	Hospital/ community	32 confirmed TB patients, 79 non-TB patients	Confirmed TB based on positive culture from sputum	Non-TB patients: sick children who were initially suspected of PTB, but who ended up had other disease	ELISA	209.1 pg/mL

ELISA, enzyme-linked immunosorbent assay; IP-10, interferon γ–induced protein 10; LTBI, latent tuberculosis infection; PTB, pulmonary tuberculosis; TB, tuberculosis.

Table 2
Diagnostic performance of C-reactive protein for diagnosis of tuberculosis

Source	Test result (*n*)				Sensitivity, % (95% CI)	Specificity, % (95% CI)
	Truly positive	Falsely positive	Falsely negative	Truly negative		
Lin (1986) [15]	15	6	3	20	89 (65–99)	77 (57–91)
Wilson (2006) [16]	57	10	2	5	97 (88–100)	33 (12–62)
Choi (2007) [17]	44	39	2	28	96 (85–99)	42 (30–54)
Kang (2009) [18]	30	28	0	29	100 (88–100)	51 (37–64)
Sage (2010) [19]	25	171	3	48	89 (72–98)	22 (17–28)
Bandyopadhyay (2011) [20]	5	14	4	29	56 (21–86)	67 (51–81)
Lee (2011) [21]	67	175	15	15	82 (72–89)	8 (4–13)
Wilson (2011) [22]	128	27	7	88	95 (90–98)	77 (68–84)
Cho (2012) [23]	23	20	17	13	58 (41–73)	39 (23–58)
Lawn (2013) [24]	73	233	8	182	90 (81–96)	44 (39–49)
Niu (2013) [25]	64	14	14	21	82 (72–90)	60 (42–76)
Drain (2014) [26]	44	22	1	26	98 (88–100)	54 (39–69)
Yoon (2014) [27]	22	47	5	197	81 (62–94)	81 (75–85)
Yoon (2017) [28]	145	283	18	731	89 (83–93)	72 (69–75)
Summary estimates	—	—	—	—	89 (80–96)	57 (36–65)

CI, confidence interval.

high sensitivity for selection of patients who should undergo more specific tests for confirmation.

The screening of TB among HIV-infected individuals is also particularly challenging. A recent systematic review of CRP for the screening of TB in patients with HIV, however, reported unexpectedly good results in this high-risk group [34].

Furthermore, although many studies have investigated IP-10 expression as a specific response to the *in vitro* stimulation of white blood cells to specific TB antigens, few studies have reported its use in its steady, unstimulated concentrations. Altered serum and/or tissue expression of IP-10 has been associated with inflammatory diseases, including organ-specific or systemic autoimmune diseases [35], neurologic disorders [36], vascular diseases [37,38] and viral and bacterial infections [39]. One previous meta-analysis [40] reported a pooled sensitivity and specificity of 73% and 82% for the diagnosis of TB. However, this study included data of both stimulated and unstimulated IP-10 in patients with pleural effusions and compared patients with TB and healthy controls, which limited its interpretation. In the current study, we focused on nonstimulated (in the absence of in vitro TB antigens) IP-10 in patients with pulmonary TB and requested data sets from investigators to conduct a reanalysis with a triage perspective. Although the number of studies is small, CRP and IP-10 seem to have high sensitivity and moderate specificity as triage markers in patients with symptoms suggestive of active TB. Our data resulted in a CRP pooled sensitivity and specificity of 89% and 57%, while the pooled sensitivity and specificity for IP-10 were 85% and 63%. Despite their low/moderate specificity, these performances would make them strong candidates for triage because although they miss the target product profiles, their performance could potentially be improved by calculating optimal screening cutoffs in prospectively enroled patients. Several semiquantitative CRP tests are also available in the market, and their use as point-of-care devices for screening would increase the capacity of the health services to diagnose larger number of patients. IP-10 studies in turn were judged to have a high risk of bias and high concern about applicability. Furthermore, the IP-10 studies included were considered to have a high risk of bias, and thus the quality of evidence is very low at this stage.

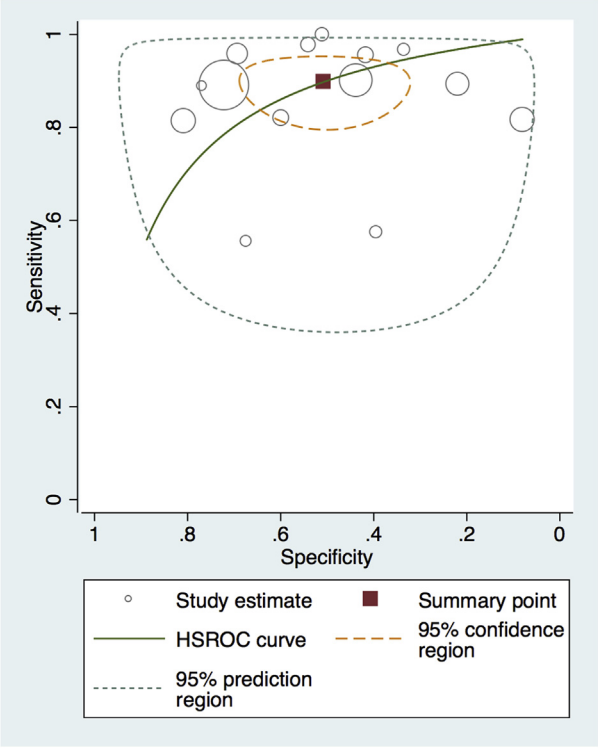

Fig. 2. Diagnostic accuracy of C-reactive protein test.

Our findings therefore should be treated with caution as we faced important limitations. As expected, the performance of the markers varied with the burden of TB across settings, with a higher sensitivity and specificity in high-burden countries. The higher sensitivity in these settings may reflect the late presentation of patients to health services and the higher frequency of comorbidities, such as HIV, malaria and bacterial coinfections. The higher specificity may reflect the location used to enrol study participants, as most studies were based on TB diagnostic services, where the proportion of patients with TB would be higher than in general clinical services. Some studies also did not provide sufficient information to determine the patient selection method, with unclear blinding, and some studies used inappropriate patient exclusions with potential to introduce bias. Furthermore, although there was no limitation for patient age in the search, most the articles limited their analyses to adults, which fixed the interpretations of our findings to this age group. As much as possible, data included comparisons between patients with and without a diagnosis of TB. Our findings therefore reflect the investigator-selected cutoffs, usually decided retrospectively by observing the data, which

Table 3
Subgroup analysis for diagnosis performance of CRP for diagnosis of TB

Subgroup	No. of studies	Sensitivity, % (95% CI)	Specificity, % (95% CI)
TB burden			
High-burden countries	9	90 (82–92)	64 (53–75)
Other countries	5	86 (69–81)	28 (15–48)
HIV status			
Unknown	2	90 (54–99)	63 (36–85)
Infected	6	91 (85–93)	61 (32–71)
Uninfected	4	81 (65–90)	32 (12–63)
Uninfected/infected	2	83 (27–98)	73 (65–81)
Clinical setting			
Community	9	90 (85–93)	62 (51–73)
Hospital	5	80 (61–91)	51 (37–64)
CRP quantification method			
Nephelometry	1	83 (59–95)	77 (57–89)
Immunoturbidimetry	9	88 (78–94)	46 (29–65)
ELISA	4	88 (84–91)	55 (31–77)

CI, confidence interval, CRP, C-reactive protein, ELISA, enzyme-linked immunosorbent assay, TB, tuberculosis.

Table 4
Metaregression analysis for potential sources of heterogeneity

Variable	Sensitivity			Specificity		
	Coefficient (95% CI)	Standard error	p	Coefficient (95% CI)	Standard error	p
WHO TB burden						
High-burden country	Reference					
Other country	1.686 (0.140 to 3.232)	0.789	0.033	−0.750 (−2.104 to 0.605)	0.691	0.278
HIV status						
Unknown	Reference					
Uninfected	−1.020 (−4.171 to 2.132)	1.608	0.526	−0.366 (−1.841 to 1.110)	0.753	0.627
Infected	1.360 (−2.414 to 5.134)	1.926	0.480	−0.617 (−2.641 to 1.407)	1.033	0.550
Uninfected/infected	−0.127 (−4.428 to 4.173)	2.194	0.954	1.149 (−1.748 to 4.046)	1.478	0.437
Clinical setting						
Community	Reference					
Hospital	−2.074 (−3.574 to −0.574)	0.765	0.007	−1.205 (−2.455 to 0.045)	0.638	0.059
Community/hospital	−0.434 (−2.890 to 2.022)	1.253	0.729	−0.860 (−2.635 to 0.915)	0.906	0.342
CRP quantification method						
Nephelometry	Reference					
ELISA	−0.899 (−4.905 to 3.107)	2.044	0.660	0.107 (−2.399 to 2.613)	1.279	0.933
Immunoturbidimetry	0.815 (−2.627 to 4.258)	1.756	0.643	−0.420 (−2.566 to 1.727)	1.095	0.702
Intercept	1.609 (0.347 to 2.872)	0.644	0.012	1.204 (−0.088 to 2.496)	0.659	0.068

CI, confidence interval, CRP, C-reactive protein, ELISA, enzyme-linked immunosorbent assay, TB, tuberculosis, WHO, World Health Organization.

limited our ability to establish an appropriate threshold for screening across the studies. Other APPs, such as AGP, should also be explored. Although this biomarker could have similar potential as CRP for triage, we could only find one publication that met the inclusion criteria.

The results of these studies can be modelled in a scenario where CRP assays were to be used in a high-TB-prevalence setting in a group of 1000 individuals with symptoms compatible with TB, where 200 (20%) are typically expected to have a positive TB culture (confirmed TB). In this scenario, the CRP test would be followed by a confirmatory test (e.g. Xpert MTB/RIF) with an estimated 75% sensitivity and 98% specificity. In this scenario, an estimated 468 participants will have a positive CRP result (180 truly positive and 288 falsely positive) and 562 would have negative CRP (512 truly negative and 50 falsely negative). The follow-on Xpert MTB/RIF test among the 468 patients with positive CRP would correctly identify 135 patients with confirmed TB and six patients with false-positive results. The combination of CRP followed by Xpert MTB/RIF would then yield 926 patients (92.6%) correctly classified, of which 135 would have confirmed TB and 794 would not have confirmed TB (negative culture). In contrast, testing the same population with the routine Xpert MTB/RIF as the first test would result in 150 of 200 patients with TB being classified as having TB and 784 of 800 participants correctly classified as not having TB (culture negative). This would result in 934 patients (93.4%) correctly classified, of whom 150 would have confirmed TB and 784 would not have confirmed TB (negative culture). Although the difference between the two approaches is not statistically significant, the screening test would result in significant gains by rapidly identifying 562 patients with a very low likelihood of having TB, facilitating earlier clinical management decisions and avoiding having to wait for Xpert MTB/RIF test results and multiple visits.

Further prospective studies are needed to establish the optimal assays and thresholds for CRP and/or unstimulated IP-10 for TB screening and whether their combined use could increase their performance. Future studies should enrol prospectively consecutive patients with signs and symptoms of presumptive TB undergoing a differential diagnosis. In conclusion, CRP is a promising marker as a triage test to identify individuals with TB, while the evidence available for IP-10 is of very low quality. Further prospective studies are warranted for both markers.

Transparency declaration

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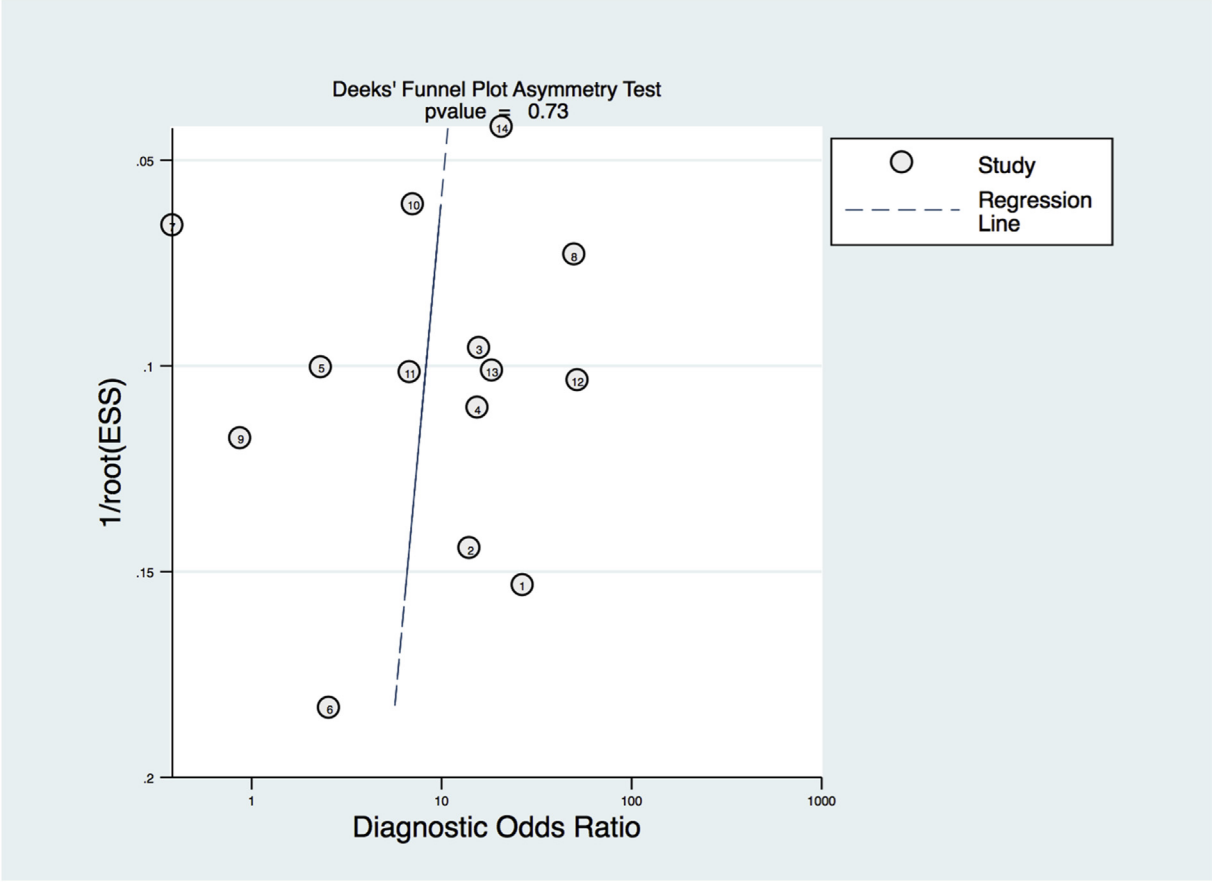

Fig. 3. Deeks's funnel plot to analyse likelihood of publication bias.

Table 5
Diagnostic performance of IP-10 for diagnosis of TB

Source	Test result (*n*)				Sensitivity, % (95% CI)	Specificity, % (95% CI)
	Truly positive	Falsely positive	Falsely negative	Truly negative		
TB vs. non-TB						
Hong (2012)[29]	21	10	3	12	0.88 (0.67–0.95)	0.55 (0.34–0.73)
Yang (2014)[31]	41	3	5	30	0.89 (0.81–0.95)	0.91 (0.75–0.97)
Petrone (2015)[32]	25	37	7	42	0.78 (0.61–0.89)	0.53 (0.43–0.64)
Summary estimates	—	—	—	—	0.85 (0.77–0.92)	0.63 (0.54–0.71)
TB HIV positive vs. non-TB HIV positive						
Vanini (2012)[30]	19	76	2	21	0.91 (0.69–0.98)	0.22 (0.15–0.31)
Petrone (2015)[32]	13	15	0	3	0.96 (0.62–0.99)	0.20 (0.07–0.42)
Summary estimates	—	—	—	—	0.94 (0.80–0.99)	0.21 (0.14–0.29)

CI, confidence interval; IP-10, interferon γ–induced protein 10; TB, tuberculosis.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2018.07.017.

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