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Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals (Review)

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[Diagnostic Test Accuracy Review]

Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals

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ABSTRACT

Background

Accurate diagnosis of tuberculosis in people living with HIV is difficult. HIV-positive individuals have higher rates of extrapulmonary tuberculosis and the diagnosis of tuberculosis is often limited to imaging results. Ultrasound is such an imaging test that is widely used as a diagnostic tool (including point-of-care) in people suspected of having abdominal tuberculosis or disseminated tuberculosis with abdominal involvement.

Objectives

To determine the diagnostic accuracy of abdominal ultrasound for detecting abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals.

To investigate potential sources of heterogeneity in test accuracy, including clinical setting, ultrasound training level, and type of reference standard.

Search methods

We searched for publications in any language up to 4 April 2019 in the following databases: MEDLINE, Embase, BIOSIS, Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index- Science (CPCI-S), and also ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform to identify ongoing trials.

Selection criteria

We included cross-sectional, cohort, and diagnostic case-control studies (prospective and retrospective) that compared the result of the index test (abdominal ultrasound) with one of the reference standards. We only included studies that allowed for extraction of numbers of true positives (TPs), true negatives (TNs), false positives (FPs), and false negatives (FNs). Participants were HIV-positive individuals

aged 15 years and older. A higher-quality reference standard was the bacteriological confirmation of *Mycobacterium tuberculosis* from any clinical specimen, and a lower-quality reference standard was a clinical diagnosis of tuberculosis without microbiological confirmation. We excluded genitourinary tuberculosis.

Data collection and analysis

For each study, two review authors independently extracted data using a standardized form. We assessed the quality of studies using a tailored Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. We used the bivariate model to estimate pooled sensitivity and specificity. When studies were few we simplified the bivariate model to separate univariate random-effects logistic regression models for sensitivity and specificity. We explored the influence of the type of reference standard on the accuracy estimates by conducting separate analyses for each type of reference standard. We assessed the certainty of the evidence using the GRADE approach.

Main results

We included 11 studies. The risks of bias and concern about applicability were often high or unclear in all domains. We included six studies in the main analyses of any abnormal finding on abdominal ultrasound; five studies reported only individual lesions.

The six studies of any abnormal finding were cross-sectional or cohort studies. Five of these (83%) were conducted in low- or middle-income countries, and one in a high-income country. The proportion of participants on antiretroviral therapy was none (1 study), fewer then 50% (4 studies), more than 50% (1 study), and not reported (5 studies). The first main analysis, studies using a higher-quality reference standard (bacteriological confirmation), had a pooled sensitivity of 63% (95% confidence interval (CI) 43% to 79%; 5 studies, 368 participants; very low-certainty evidence) and a pooled specificity of 68% (95% CI 42% to 87%; 5 studies, 511 participants; very low-certainty evidence). If the results were to be applied to a hypothetical cohort of 1000 people with HIV where 200 (20%) have tuberculosis then:

- About 382 individuals would have an ultrasound result indicating tuberculosis; of these, 256 (67%) would be incorrectly classified as having tuberculosis (false positives).

- Of the 618 individuals with a result indicating that tuberculosis is not present, 74 (12%) would be incorrectly classified as not having tuberculosis (false negatives).

In the second main analysis involving studies using a lower-quality reference standard (clinical diagnosis), the pooled sensitivity was 68% (95% CI 45% to 85%; 4 studies, 195 participants; very low-certainty evidence) and the pooled specificity was 73% (95% CI 41% to 91%; 4 studies, 202 participants; very low-certainty evidence).

Authors' conclusions

In HIV-positive individuals thought to have abdominal tuberculosis or disseminated tuberculosis with abdominal involvement, abdominal ultrasound appears to have 63% sensitivity and 68% specificity when tuberculosis was bacteriologically confirmed. These estimates are based on data that is limited, varied, and low-certainty.

The low sensitivity of abdominal ultrasound means clinicians should not use a negative test result to rule out the disease, but rather consider the result in combination with other diagnostic strategies (including clinical signs, chest x-ray, lateral flow urine lipoarabinomannan assay (LF-LAM), and Xpert MTB/RIF). Research incorporating the test into tuberculosis diagnostic algorithms will help in delineating more precisely its value in diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement.

26 September 2019

Up to date

All studies incorporated from most recent search

All studies identified during the most recent search (4 Apr, 2019) have been incorporated in the review, and one ongoing study identified

PLAIN LANGUAGE SUMMARY

Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in people with HIV

Why is improving tuberculosis diagnosis in people with HIV important?

Diagnosing active tuberculosis in people living with HIV is challenging. People with advanced immunosuppression have high rates of extrapulmonary tuberculosis (tuberculosis outside the lungs).

What is the aim of this review?

The aim of this review is to find out how accurate an ultrasound examination of the abdomen (abdominal ultrasound) is for diagnosing tuberculosis in people with HIV suspected of having tuberculosis in the abdomen or widespread tuberculosis (disseminated tuberculosis) involving the abdomen.

What was studied in the review?

Abdominal ultrasound can be done after other tests (e.g. the chest x-ray did not indicate tuberculosis) or it can be done before other tests in people suspected of having tuberculosis. This review focuses on situations where other tests are not available.

What are the main results in this review?

We found 11 studies, but only six were relevant for the main analyses. The six studies were divided into two groups. In the first group tuberculosis was diagnosed by identifying the organism causing tuberculosis from any specimen (microbiological confirmation). For the second group, tuberculosis was diagnosed when healthcare personnel suspected tuberculosis and started anti-tuberculosis treatment, but without identifying the organism (clinical diagnosis). Three studies provided results for both groups.

The review included five studies (a total of 879 participants) with microbiological confirmation. The results showed that if abdominal ultrasound were to be used in a group of 1000 people with HIV where 200 (20%) have tuberculosis then:

- About 382 individuals would have an ultrasound result indicating tuberculosis; of these, 256 (67%) would be incorrectly classified as having tuberculosis (false positives).

- Of the 618 individuals with a result indicating that tuberculosis is not present, 74 (12%) would be incorrectly classified as not having tuberculosis (false negatives).

How reliable are the results of the studies in this review?

Microbiological confirmation is likely to be a reliable method for deciding whether people really have tuberculosis; clinical diagnosis is likely to be less trustworthy. We found problems in both groups with how studies were conducted. Decreasing the number of false positive results may make abdominal ultrasound appear more accurate than it is. Numbers shown are an average across studies. As estimates from individual studies varied, we cannot be sure that abdominal ultrasound will always produce these results. Not enough people have been studied for us to be confident about the results.

Who do the results of the review apply to?

Studies included in the main analyses were done in Cambodia, India, South Africa, South Sudan, Spain, and Tanzania. Reasons for including people differed between the studies. Four studies used trained radiologists (specialists) or sonographers; two used doctors trained in ultrasound (non-specialists), and two included people without any suspicion of tuberculosis. Across the studies, the percentage of people with a final diagnosis of tuberculosis ranged from 18% to 64%.

What are the implications of this review?

If the test is used to rule in the disease in the absence of other evidence, then, the chance of diagnosing someone with tuberculosis when they actually do not have it is high. Chances of missing a diagnosis of tuberculosis when the test is positive are lower, but a negative test alone is probably insufficient to rule out the disease. These findings should be considered when deciding whether or not to use abdominal ultrasound to test for tuberculosis involving the abdomen and how to interpret the results in the context of other clinical and diagnostic test information.

How up-to-date is this review?

The review authors searched for studies up to 4 April 2019.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings for abdominal ultrasound (any abnormality)

Review question: Should abdominal ultrasound be used to diagnose abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals?

Patient or population: HIV-positive individuals

Setting: Healthcare facility

Index test: Abdominal ultrasound

Reference standard: We considered two reference standards. The higher-quality reference standard was bacteriological confirmation of *M tuberculosis* (any clinical specimen including (i) at least one specimen culture positive for *M tuberculosis*, (ii) microscopic identification of acid-fast bacilli on stained sputum smears, lymph node aspirate, or any other specimen; or iii) Xpert MTB/RIF positive). The lower-quality reference standard was clinical diagnosis of TB without microbiological confirmation (including cases diagnosed on the basis of: i) suggestive histology (necrotizing granulomatous inflammation), ii) x-ray abnormalities, iii) extrapulmonary cases without laboratory confirmation, and iv) anti-tuberculosis therapy initiated by a healthcare practitioner for cases with a high suspicion of tuberculosis).

Threshold: Any abnormality found on abdominal ultrasound

Study design: Cross-sectional and cohort

Limitations: A small number of studies and participants were included in the analyses. Risks of bias were generally high in the patient selection domain

Test result	Number of results per 1000 HIV-positive individuals tested (95% CI)			Number of studies	Number of participants	Certainty of the evidence (GRADE)
	Prevalence 10%	Prevalence 20%	Prevalence 40%			
Bacteriological confirmation as reference standard: pooled sensitivity = 63% (95% CI 43% to 79%) and pooled specificity = 68% (95% CI 42% to 87%)						
True positives (participants correctly classified as having tuberculosis)	**63** (43 to 79)	**126** (86 to 158)	**252** (172 to 316)	5	368	⊕⊖⊖⊖ **VERY LOW** a,b,c,d
False negatives (participants incorrectly classified as not having tuberculosis)	**37** (21 to 57)	**74** (42 to 114)	**148** (84 to 228)			
True negatives (participants correctly classified as not having tuberculosis)	**612** (378 to 783)	**544** (336 to 696)	**408** (252 to 522)	5	511	⊕⊖⊖⊖ **VERY LOW** b,c,e,f
False positives (participants incorrectly classified as having tuberculosis)	**288** (117 to 522)	**256** (104 to 464)	**192** (78 to 348)			

Abbreviations: CI: confidence interval

GRADE certainty of evidence (GRADEpro GDT 2015; Schünemann 2016)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

The table displays normalized frequencies within a hypothetical cohort of 1000 people at three different tuberculosis prevalences (pre-test probabilities): 10%, 20% and 40%. We selected prevalence values based on the range of prevalence observed across the included studies. We estimated confidence intervals based on those around the point estimates for pooled sensitivity and specificity.

Explanations

[a]Risk of bias: We rated one study at high risk for participant selection since it excluded people unable to produce sputum (Griesel 2019-h). We downgraded the certainty of the evidence by one level.

[b]Indirectness: We deemed three studies to be of high concern for applicability for receiving ultrasound in a tertiary care (referral) centre (Ndege 2019-h; Sculier 2010-h Weber 2018-h). Two studies only included asymptomatic HIV-positive participants (Bobbio 2019-l; Sculier 2010-h). We downgraded the certainty of the evidence by two levels.

[c]Inconsistency: Point estimates were substantially different between studies. We could not explain this variability and we downgraded the certainty of the evidence by one level.

[d]Imprecision:Three studies had a wide 95% CI for true positives and false negatives (Dominguez-Castellano 1998-h; Sculier 2010-h; Weber 2018-h). We downgraded the certainty of the evidence by one level.

[e]Risk of bias: All studies used a higher-quality reference standard. We did not downgrade the certainty of the evidence.

[f]Imprecision: Two studies had a wide 95% CI for true negatives and false positives (Dominguez-Castellano 1998-h; Weber 2018-h). We downgraded the certainty of the evidence by one level.

BACKGROUND

Target condition being diagnosed

Tuberculosis is caused by the bacillus *Mycobacterium tuberculosis.* Although it usually affects the lungs (pulmonary tuberculosis), it can also spread to other body sites (extrapulmonary tuberculosis) (WHO 2018).

An estimated 10 million people were diagnosed with tuberculosis in 2017, and 1.6 million people died from tuberculosis (WHO 2018). Resource-limited countries are the most affected; for example, the African region of the World Health Organization (WHO) had the second highest estimated number of incident cases (2.5 million), but the highest incidence rate (237 versus 133 globally) and mortality rate (HIV-positive: 24 versus 4.0 globally; HIV-negative: 39 versus 17 globally) per 100,000 people (WHO 2018).

The probability of developing tuberculosis is higher among people living with HIV. Approximately 920,000 people diagnosed worldwide with tuberculosis in 2017 were HIV-positive (WHO 2018), with HIV prevalence among incident tuberculosis cases in the African region at 27% (WHO 2018).

The worldwide case detection rate in 2016 was only an estimated 61% (WHO 2017), reflecting a mixture of under-reporting of detected cases and underdiagnosis of tuberculosis. The low detection rate possibly relates to delays in diagnosis, which could be from problems with tuberculosis diagnostic tests (accuracy and availability), the negative influence of HIV infection on the performance of diagnostic tests, and HIV co-infection and the opportunistic conditions that complicate it (Palmieri 2002; Dawson 2010; Padmapriyadarsini 2011; Horne 2019; WHO 2017). Other factors might be weaknesses in health systems and broader social and economic influences (for example, undernourishment, poverty) on the tuberculosis epidemic (WHO 2017). The diagnosis of active tuberculosis in HIV-positive people with advanced immunosuppression is challenging due to more atypical clinical presentations; other opportunistic pulmonary infections with similar presentations; a high proportion of negative sputum smears; and high rates of extrapulmonary tuberculosis (Sharma 2005). This is illustrated by autopsy studies, which indicate a very high proportion of tuberculosis in HIV-positive adults (32% to 47%); almost half (46%) of adult tuberculosis cases remained undiagnosed before death (Gupta 2015).

An estimated 14% of the 6.4 million incident tuberculosis cases in 2017 were extrapulmonary tuberculosis (WHO 2018). In people with HIV-associated tuberculosis, extrapulmonary tuberculosis accounts for up to 50% of all tuberculosis cases (Sharma 2004b; Kingkaew 2009; Namme 2013), and is often disseminated (two or more non-contiguous sites simultaneously infected) (Sharma 2005). Any anatomical site can be involved, but the commonest sites are the lymph nodes, pleura, meninges, and the abdominal cavity (Sharma 2005). Many terms are used in the literature to describe tuberculosis in the abdominal cavity. For the purposes of this Cochrane Review, we use the terms abdominal tuberculosis or disseminated tuberculosis with abdominal involvement, excluding genitourinary tuberculosis. Many abdominal structures can be affected in abdominal tuberculosis or disseminated tuberculosis with abdominal involvement, including involvement of the gastrointestinal tract, peritoneum, omentum, mesentery, intra-abdominal lymph nodes, and solid organs (liver, spleen, pancreas) (Sharma 2004b). People often present with non-specific symptoms and signs, and a high index of suspicion is therefore needed for early diagnosis and timely management. It mimics a large number of medical and surgical conditions, including malignant neoplasms, inflammatory bowel disease, chronic liver disease, and other gastrointestinal infections (Jadvar 1997).

Index test(s)

Many HIV-positive people with low CD4 counts have abdominal tuberculosis or disseminated tuberculosis with abdominal involvement. As sputum smears are frequently negative in HIV-associated tuberculosis, it is common clinical practice, supported by WHO guidelines, to reach a tuberculosis diagnosis on the basis of imaging results and clinical case definitions (Wilson 2006; WHO 2016). Ultrasound is such an imaging test that can be used as a diagnostic tool (Heller 2010a; Heller 2010b; Patel 2011; Giordani 2013; Sharma 2017), although the only WHO recommendation refers to the use of ultrasound to diagnose pericardial effusions (WHO 2006). Ultrasound uses sound waves to produce images of structures and organs within the body, and has traditionally been performed by trained specialists in dedicated radiology departments. However, the numerous advantages of ultrasound (e.g. rapidly performed, portable, non-invasive, repeatable, etc.) have led to many physicians in different specialties adopting ultrasound (Adhikari 2014). The use of ultrasound by trained medical professionals (non-radiologists) is particularly relevant in resource-limited settings. Computed tomography (CT) or magnetic resonance imaging (MRI) is expensive, mostly only available in tertiary-level settings, and require specially-trained personnel to perform and report these examinations. Many low-income and middle-income countries have a high tuberculosis burden (WHO 2018), but without widespread access to specialists and tertiary-level imaging. However, ultrasound machines are mostly accessible and their use by non-radiologists would be of great value.

Abdominal ultrasound (an ultrasound examination evaluating the abdominal cavity) may be useful in HIV-positive people with suspected abdominal tuberculosis or disseminated tuberculosis with abdominal involvement. Ultrasound techniques to diagnosis HIV-associated tuberculosis are easily learned by non-radiologists and quick to perform (less than 10 minutes) (Heller 2010a). The ultrasound findings are non-specific, and various other diseases may present with the same features. For example, intra-abdominal lymphadenopathy can be due to other infections (for example, cryptococcosis, histoplasmosis); lymphomas (non-Hodgkin's lymphoma and Hodgkin's lymphoma); and Kaposi's sarcoma (Martin-Bates 1993).

Clinical pathway

Any structure or organ in the abdominal cavity (for example, gastrointestinal tract, pancreatobiliary system, peritoneum, and lymph nodes) can be affected by tuberculosis disease. The presentation varies considerably and depends on the specific organ involved (Sharma 2017); other diseases are also often mimicked (Sharma 2004a). Common presenting symptoms are abdominal pain, anorexia, bowel disturbances, fever, and weight loss. The clinical examination often reveals abdominal tenderness, ascites, and solid organ enlargement (for example, hepatomegaly, splenomegaly, or hepatosplenomegaly) (Ibrahim 2005; Mandal 2011; Sharma 2017).

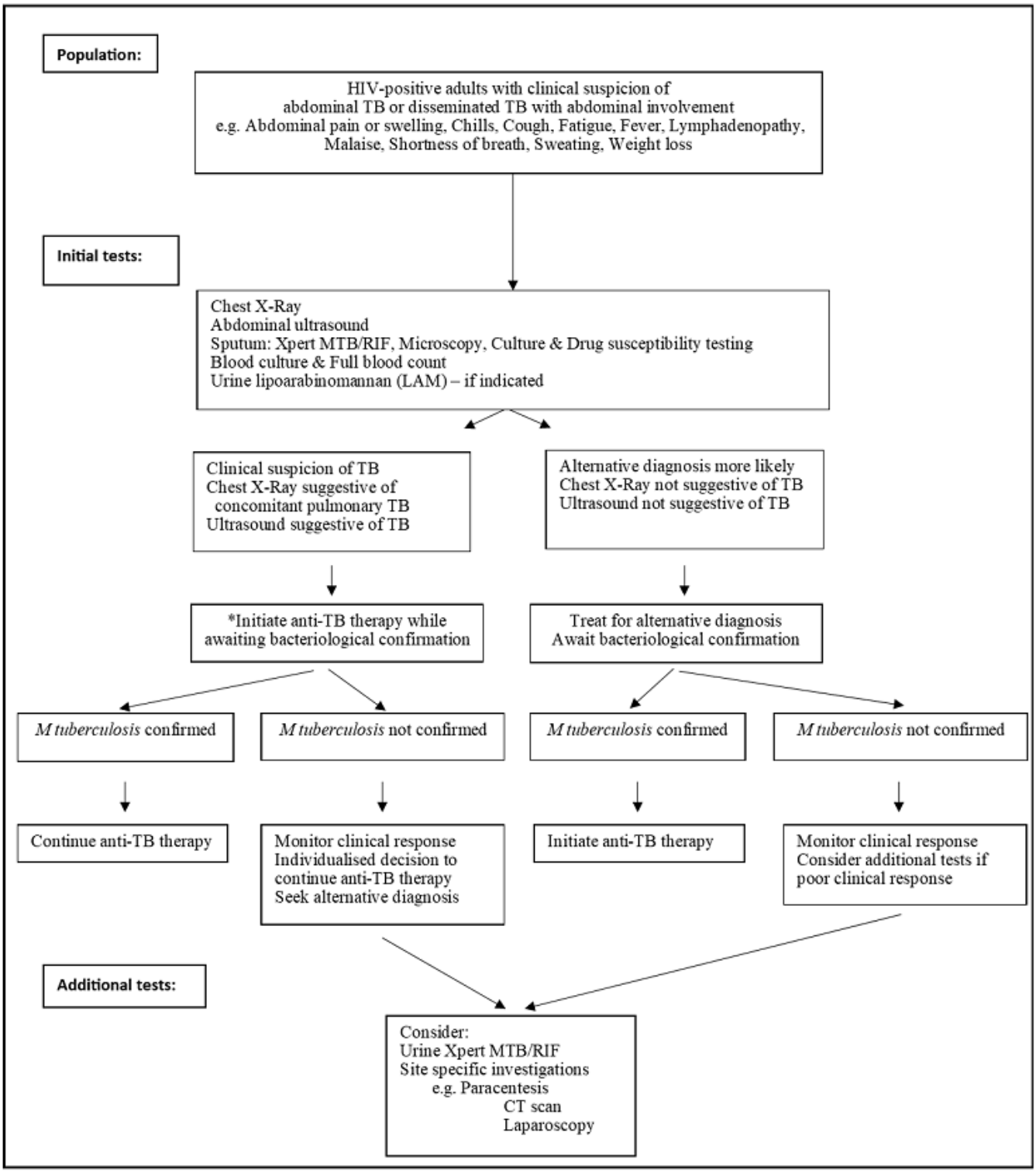
Essential diagnostic tests for individuals who are suspected of having abdominal tuberculosis or disseminated tuberculosis with abdominal involvement include a chest x-ray, sputum evaluation (if able to produce) for bacteriological confirmation of tuberculosis disease (smear or culture or Xpert MTB/RIF), and blood cultures (WHO 2013b). Urine specimens remain a convenient clinical sample for the diagnosis of tuberculosis. Although conventional tuberculosis diagnostics applied to urine specimens have limited clinical utility, the use of urinary lipoarabinomannan (LAM) has been recommended by the WHO in HIV-positive adults with advanced immunosuppression (CD4 cell count of 100 cells/µL or less) or in HIV-positive adults who are seriously ill (respiratory rate above 30/min, temperature above 39 °C, heart rate above 120/min and unable to walk unaided), regardless of their CD4 cell count (WHO 2015; Shah 2016). These tests are usually done in the primary care setting and higher.

Abdominal ultrasound has become part of the initial diagnostic work-up in adults living with HIV where abdominal tuberculosis or disseminated tuberculosis with abdominal involvement is suspected (especially in those with a low CD4 count), despite the lack of robust evidence of validity from large studies (NICE 2016). The diagnostic pathway might vary in different settings if there are ultrasound findings suggestive of tuberculosis. In resource-limited settings this might be enough evidence to initiate anti-tuberculosis treatment, but in high-resource settings it would prompt site-specific investigations which could include CT scan, paracentesis, laparoscopy, fine needle aspiration, or stool examination.

A presumptive diagnosis of abdominal tuberculosis or disseminated tuberculosis with abdominal involvement can be made in the setting of known active pulmonary tuberculosis, although fewer than half of chest radiographs are compatible with active or healed tuberculosis (Chow 2002). However, data are lacking in HIV-positive individuals.

WHO recommends immediate initiation of anti-tuberculosis therapy in people living with HIV who have clinical features of disseminated tuberculosis (WHO 2016). Bacteriological confirmation of tuberculosis from any specimen remains important, but treatment should not be delayed until results become available (Figure 1). People started on anti-tuberculosis therapy without bacteriological confirmation should be assessed after one month to evaluate the clinical response to treatment. They should be re-assessed and an alternative diagnosis sought if there is no clinical improvement.

Figure 1. Diagnostic workup of HIV-positive individuals with suspected abdominal tuberculosis or disseminated tuberculosis with abdominal involvement



HIV: Human Immunodeficiency Virus; TB: Tuberculosis

* In high resource settings, this would most likely prompt additional site-specific investigations (additional tests) and not immediate initiation of treatment

Role of index test(s)

Abdominal ultrasound is often combined with existing tests such as chest x-ray, haemoglobin, etc. to reach a diagnosis of abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in clinical practice. However, all the existing tests that could inform a confirmed diagnosis may not always be available.

Alternative test(s)

Ascitic fluid analysis suggestive of abdominal tuberculosis or disseminated tuberculosis with abdominal involvement includes a leukocyte count of 150 to 4000 cells/mL, which consists predominantly of lymphocytes (Sharma 2004a; Sanai 2005). The ascitic fluid is usually an exudate with the protein content greater than 30 g/L and the serum-ascites albumin gradient (SAAG) less than 11 g/L (Sharma 2004a; Sanai 2005). Adenosine deaminase activity (ADA) of ascitic fluid (> 39 IU/L) is also suggestive of abdominal tuberculosis (Riquelme 2006), while the ascites to blood glucose ratio is usually less than 0.96 (Wilkins 1984). Acid-fast bacilli (AFB) smear and culture of ascitic fluid also have disappointingly low yields (Chow 2003), while Xpert MTB/RIF for peritoneal tuberculosis using peritoneal fluid has a pooled sensitivity of 59% (credible interval (CrI) 45 to 74) and a pooled specificity of 98% (CrI 96 to 99) (Kohli 2018).

Different imaging modalities can be useful to diagnose abdominal tuberculosis or disseminated tuberculosis with abdominal involvement. Abdominal x-rays are of very limited value, but can assist with the diagnosis of intestinal obstruction and perforation (Debi 2014). CT features include thickening of the peritoneum, omentum, and bowel wall; lymph nodes (especially if these have hypodense centres due to caseous necrosis); and ascites with strands, debris, and fine septations (Sharma 2004a; Lee 2012). The excellent soft tissue resolution and multiplanar acquisition of MRI have resulted in it being used to evaluate solid organs and lymphadenopathy (Joshi 2014). However, CT and especially MRI are expensive and access is very limited in resource-limited settings. Barium studies may be useful for intrinsic bowel abnormalities such as strictures, fistulae, and erosions (Sharma 2004a; Debi 2014).

Colonoscopy with biopsy is a useful non-operative diagnostic procedure to obtain material for histology and culture (Kim 1998). Mucosal nodules and transverse ulcers in the bowel are very suggestive of tuberculosis, with definitive results obtained from tissue sent for polymerase chain reaction (PCR), Ziehl-Neelsen stain, and culture (Kim 1998; Sharma 2004a). Laparoscopy is useful in two ways: (i) it allows visual inspection of the peritoneum; and (ii) it permits specimens for histology, AFB stain, and culture to be obtained. However, imaging modalities as described above provide a safer, less invasive and less expensive alternative, but may be less specific since they are unable to provide a definitive microbiological diagnosis (Sanai 2005).

Most studies relating to the diagnosis of tuberculosis were done in HIV-negative people and the true diagnostic accuracy of the above tests in those living with HIV remains uncertain. Expanded clinical case definitions were developed to diagnose smear-negative tuberculosis in HIV-positive people living in resource-limited settings (Wilson 2006), including abdominal tuberculosis or disseminated tuberculosis with abdominal involvement (Wilson 2006; WHO 2016). For example, a person presenting with symptoms and signs suggestive of abdominal tuberculosis or disseminated tuberculosis with abdominal involvement can be started on anti-tuberculosis treatment if the ascitic fluid consists of a lymphocytic exudate along with either a fever of 38 °C or more on two occasions or drenching sweats for more than two weeks (Wilson 2006). In this study, the positive predictive value for abdominal lymph nodes diagnosed by ultrasound was 94% (Wilson 2006). Augmented by the use of objective criteria to monitor response to treatment within the first eight weeks, this approach has reasonable diagnostic accuracy (Wilson 2006).

Rationale

Multiple studies of various quality and designs have looked at the use of abdominal ultrasound as a diagnostic tool for abdominal tuberculosis or disseminated tuberculosis with abdominal involvement, with varying sensitivity, specificity, and predictive values for diagnosing tuberculosis (Monill-Serra 1997-l; Mugala 2006; Sinkala 2009-l; Sculier 2010-h; Patel 2011). Abdominal ultrasound may be used alone, in combination with existing tests (chest radiograph, full blood count), or as an add-on following negative results from existing tests (smear microscopy, sputum Xpert MTB/RIF, sputum culture, chest radiograph). The role of abdominal ultrasound as an add-on test is an important clinical question because it may reflect the way that abdominal ultrasound is used in practice, especially in resource-limited settings. However, after a scoping search, we did not find any studies that have evaluated the accuracy of ultrasound as an add-on test or in combination with other tests.

OBJECTIVES

To determine the diagnostic accuracy of abdominal ultrasound for detecting abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals.

Secondary objectives

To investigate potential sources of heterogeneity in test accuracy, including clinical setting, ultrasound training level, and type of reference standard.

METHODS

Criteria for considering studies for this review

Types of studies

We included cross-sectional, cohort, or diagnostic case-control studies (prospective and retrospective) that compared the result of the index test (abdominal ultrasound) with one of the reference standards (see Reference standards). Case-control studies may overestimate sensitivity and specificity, but we include them because we anticipated identifying few relevant studies. We only included studies in which the study authors reported the numbers of true positives (TPs), true negatives (TNs), false positives (FPs), and false negatives (FNs), or where we were able to derive the data from reported statistics. We also wrote to all study authors where data were missing. We excluded descriptive studies (for example, case series).

Participants

We included all HIV-positive individuals (aged 15 years and older) with a clinical suspicion of abdominal tuberculosis or disseminated tuberculosis with abdominal involvement (excluding

genitourinary tuberculosis), who were investigated using an abdominal ultrasound examination. We also considered studies that included confirmed cases of abdominal tuberculosis and controls. We did not place any restrictions on setting. Although abdominal ultrasound can be used to evaluate children, microbiological confirmation of tuberculosis is far more difficult than in adults, and so we excluded children where possible.

Index tests

We included studies that evaluated the accuracy of abdominal ultrasound. We did not place any restrictions on the type of ultrasound machine used or the qualification of the person performing the ultrasound, but recorded these data. A positive result was an ultrasound scan with abnormal findings suggestive of abdominal tuberculosis or disseminated tuberculosis with abdominal involvement, including, but not limited to, free abdominal fluid, abdominal lymph nodes, hepatic lesions, and splenic lesions. A negative result was an ultrasound scan with no abnormal findings.

Target conditions

Active disease due to *M tuberculosis* – either abdominal tuberculosis or disseminated tuberculosis with abdominal involvement.

Reference standards

We used a hierarchy of reference standards. The reference standard diagnosis typically relates to microbiological confirmation (microscopy or culture), although histopathological characteristics strongly support a diagnosis of active tuberculosis in clinically and epidemiologically appropriate settings. Xpert MTB/RIF assay (an automated nucleic acid amplification test) can also identify *M tuberculosis.* A clinical diagnosis of tuberculosis is sometimes used in the absence of confirmative tests, for example, probable tuberculosis can be defined as the clinical picture of tuberculosis without objective diagnostic tuberculosis criteria and treated for tuberculosis by the attending physician. Although this approach is clinically useful, it is very subjective as it relies on the clinical gestalt of the treating physician. We therefore viewed it as a lower-quality reference standard.

The primary (higher-quality) reference standard was bacteriological confirmation of any clinical specimen including (i) at least one specimen culture positive for *M tuberculosis*, (ii) microscopic identification of AFB on stained sputum smears, lymph node aspirate, or any other specimen; or iii) Xpert MTB/RIF positive (WHO 2013a). We considered a positive result on any of these tests as a positive result for the microbiological (higher-quality) reference standard and a tuberculosis case, since not all of the tests might have been performed or might have a positive result. The reference standard for culture was either solid or liquid culture for *M tuberculosis* complex (Lawn 2011). The sensitivity of smear microscopy can be increased by examining more than one sample, using fluorescence microscopy, and using physical and chemical sputum processing techniques including centrifugation, sedimentation, and bleach (Steingart 2006a; Steingart 2006b). We therefore included studies that used any of these techniques.

The secondary (lower-quality) reference standard was clinical diagnosis of tuberculosis without microbiological confirmation. A clinically diagnosed tuberculosis case is one that has been diagnosed with active tuberculosis by a healthcare practitioner and where anti-tuberculosis therapy has subsequently been initiated. This definition lacks bacteriological confirmation but includes cases diagnosed on the basis of suggestive histology (necrotizing granulomatous inflammation), x-ray abnormalities, and extrapulmonary cases without laboratory confirmation (WHO 2017). Using clinical diagnosis as a reference standard could potentially bias test accuracy because abdominal ultrasound is often used to inform the clinical decision to treat for tuberculosis (incorporation bias). We included these studies, as incorporation bias had a small effect in diagnostic accuracy estimates (Rutjes 2006), and we used an adapted version of the revised tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2).

Search methods for identification of studies

Electronic searches

Vittoria Lutje (VL), the Information Specialist for the Cochrane Infectious Diseases Group (CIDG), performed literature searches up to 4 April 2019, without language restrictions. She searched MEDLINE (PubMed, 1946 to 4 April 2019); Embase (Ovid, 1947 to 4 April 2019); Biosis (Web of Science, 1926 to 4 April 2019); Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), both 1900 to 4 April 2019, and Conference Proceedings Citation Index- Science (CPCI-S), 1990 to 4 April 2019, (all three in the Web of Science). She also searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/) for trials in progress. The search terms and strategy are reported in Appendix 1.

Searching other resources

We examined the reference lists of relevant reviews and studies; and searched websites of the WHO, the Stop TB Partnership, and the National Institute of Allergy and Infectious Diseases (NIAID). We also performed forward citation searching of relevant articles using the PubMed ‘related articles' feature, Google Scholar, and ISI citation indices. We also contacted study authors for additional information if we deemed it necessary.

Data collection and analysis

Selection of studies

Two review authors (DJvH and RG) independently judged study eligibility by examining the title and abstract of each article identified by the literature search and excluded obviously irrelevant studies. We obtained the full-text article if either review author considered the abstract to be potentially eligible. The two review authors independently assessed each full-text article against the predefined inclusion and exclusion criteria, as stated in the ‘Criteria for considering studies for this review' section. The two review authors resolved any disagreements by discussion. If the review authors could not reach consensus, a third review author (GrM) made the final decision. We maintained a list of all articles excluded after full-text assessment and their reasons for exclusion in the ‘Characteristics of excluded studies' table. The study selection process is also illustrated using a PRISMA flow diagram.

Data extraction and management

We developed a standardized data extraction form before two review authors (DJvH and RG) independently extracted data. The extracted data were:

1. Details of study: first author, publication year, journal, study design, inclusion/exclusion criteria
2. Characteristics of study population: age, gender, estimated tuberculosis prevalence in study setting; estimated HIV prevalence in study setting, antiretroviral therapy (ART) status
3. Reference standard: bacteriological, clinical
4. Index test: general (abdominal ultrasound normal or abnormal), specific (individual findings on ultrasound), training level of person performing the ultrasound, additional tests (and their results)
5. Details of outcome: number of indeterminate, missing or unavailable test results, number of TP, TN, FP, and FN results

We resolved any discrepancies in data extraction by discussion, and a third review author (GrM) had the final say.

Assessment of methodological quality

We used the revised tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) to assess the risks of bias and applicability of included studies (Whiting 2011). We tailored the tool to the context of the review, as shown in Appendix 2. Two review authors (DJvH and RG) independently assessed methodological quality using the tailored QUADAS-2 tool. We resolved any disagreements through consensus or by consulting a third review author (EAO). We present the results in graphs, text, and the 'Characteristics of included studies' table.

Statistical analysis and data synthesis

In our primary meta-analyses, we used the individual participant as the unit of analysis (that is, any abnormal finding versus none) and not individual ultrasound findings. Clinically, it is also useful to know the accuracy of individual ultrasound findings, as it is plausible that some findings are better indicators of tuberculosis than others. We therefore determined the accuracy of individual ultrasound findings in secondary analyses.

We only included studies that reported test thresholds to enable us to construct 2 x 2 tables and also to select an appropriate method of meta-analysis. Studies used different criteria to determine the positivity of ultrasound. For example, studies may define an ultrasound scan as positive based on the presence of any abnormal abdominal finding including (but not limited to) organ enlargement, the presence or number of hepatic or splenic lesions, or the presence or size of abdominal nodes. For the primary analysis we thus defined the threshold as the presence or absence of any abnormal lesion. In order to produce clinically meaningful results, we conducted two separate sets of primary meta-analyses by estimating the pooled sensitivity and specificity for each type of reference standard (higher quality and lower quality).

For the secondary analyses (individual lesion as unit of analysis), we did not estimate the pooled sensitivity and specificity because some studies did not report thresholds and those that did used different thresholds. We only report the range of sensitivity and specificity.

We used the number of TPs, FPs, FNs, and TNs to construct 2 x 2 tables using the criteria specified in the studies. We plotted the estimates of sensitivity and specificity from the included studies on forest plots using Review Manager 5 software (Review Manager 2014).

We used the bivariate model (Chu 2006) to estimate pooled sensitivity and specificity at common thresholds. We fitted the models using the xtmelogit command in Stata version 15.0 (StataCorp, College Station, TX, USA).

Investigations of heterogeneity

Potential sources of heterogeneity included the type of reference standard (higher quality versus lower quality), clinical setting (any setting versus tertiary/referral hospital), and ultrasound training level (radiologist versus non-radiologist). We stratified the primary analysis by the type of reference standard. Due to the small number of included studies and sample sizes we did not investigate other sources of heterogeneity.

Sensitivity analyses

We did not perform sensitivity analyses because of the small number of included studies.

Assessment of reporting bias

We did not carry out a formal assessment of publication bias.

Assessment of the certainty of the evidence

We used the GRADE approach (Schünemann 2016) and GRADEpro Guideline Development Tool (GDT) software (GRADEpro GDT 2015) to assess the certainty of the evidence (also called the quality of the evidence). We rated the certainty of the evidence as either high (not downgraded), moderate (downgraded by one level), low (downgraded by two levels), or very low (downgraded by more than two levels) for five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. For each domain, the certainty of evidence started as high if there were high-quality observational studies (cross-sectional or cohort studies) that enrolled participants with diagnostic uncertainty. We used our judgement to classify the reason for downgrading as either serious (downgraded by one level) or very serious (downgraded by two levels).

Two review authors (DJvH and RG) discussed judgements and applied GRADE in the following way.

Risk of bias: we used the tailored QUADAS-2 to assess risks of bias.

Indirectness: we used the tailored QUADAS-2 for concerns of applicability and evaluated the studies for important differences between the populations studied (for example, age) and the setting. We made judgements on whether the differences were sufficient to lower our certainty in the results.

Inconsistency: we downgraded the certainty of the evidence for unexplained inconsistency in sensitivity and specificity estimates.

Imprecision: we considered a point estimate to be substantially different if it would alter a clinical decision. We considered the width of the CI, and whether a different clinical decision would be made if the lower or upper boundary of the CI represented the truth. We also made judgements on the imprecision of projected ranges for TP, FN, TN, and FP for a given prevalence of tuberculosis.

Publication bias: as recommended, we did not downgrade the certainty of evidence for publication bias for the following reasons (Schünemann in press). We did not detect studies done for-profit interest. Included studies had small sample sizes and accuracy

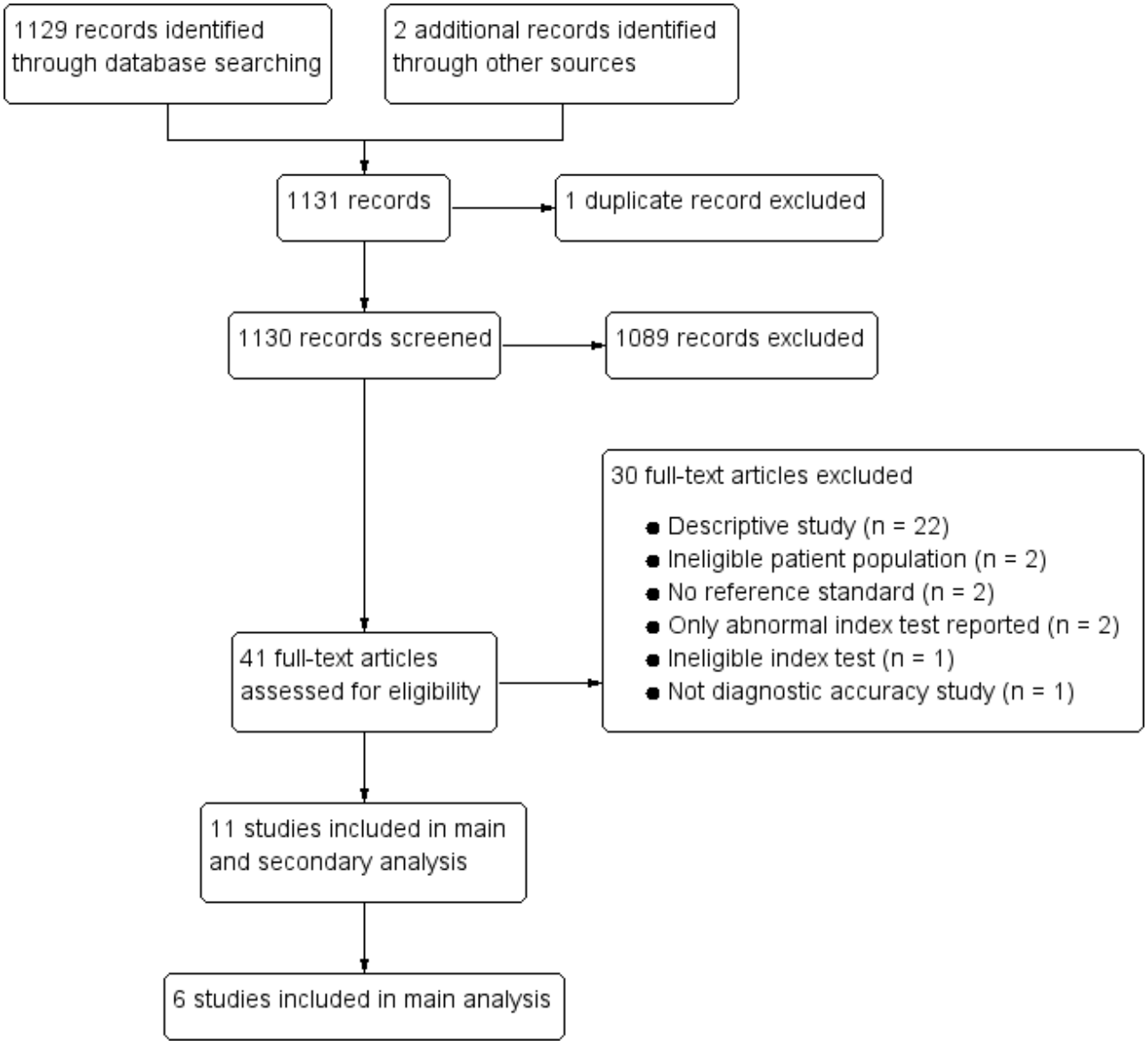
estimates were low and imprecise. We did an extensive search in electronic databases and grey literature and did not identify completed studies that were unpublished. We only identified one ongoing study, the results of which are not yet registered in the Pan African Clinical Trials Registry (Trial ID: PACTR201712002829221) (PACTR201712002829221).

RESULTS

Results of the search

Our search yielded 1129 records. We identified two additional studies through contact with experts. After we removed one duplicate, we had 1130 records. We excluded 1089 records based on a review of title, abstract, or both. We retrieved 41 full-text articles and excluded 30 studies for the following reasons: descriptive study (22 studies); ineligible participant population (2 studies); no reference standard reported (2 studies); ineligible index test evaluated (1 study); only abnormal index test reported (2 studies); and not a diagnostic accuracy study (1 study). We therefore include 11 unique studies in this review (Barreiros 2008-h; Bobbio 2019-l; Dominguez-Castellano 1998-h; Griesel 2019-h; Kaneria 2009-l; Monill-Serra 1997-l; Ndege 2019-h; O'Keefe 1998-h; Sculier 2010-h; Sinkala 2009-l; Weber 2018-h). We listed the excluded studies and reasons for their exclusion in the Characteristics of excluded studies section. Figure 2 shows the flow of studies through the screening process.

Figure 2. Study flow diagram.



Three studies were conducted in low-income countries, three in lower-middle-income countries, two in upper-middle-income countries, and three in high-income countries. We noted poor reporting on the estimated prevalence of tuberculosis and HIV in study setting, qualification of sonographer and setting in which ultrasound was performed. Studies used different criteria to determine the positivity of ultrasound (see Characteristics of

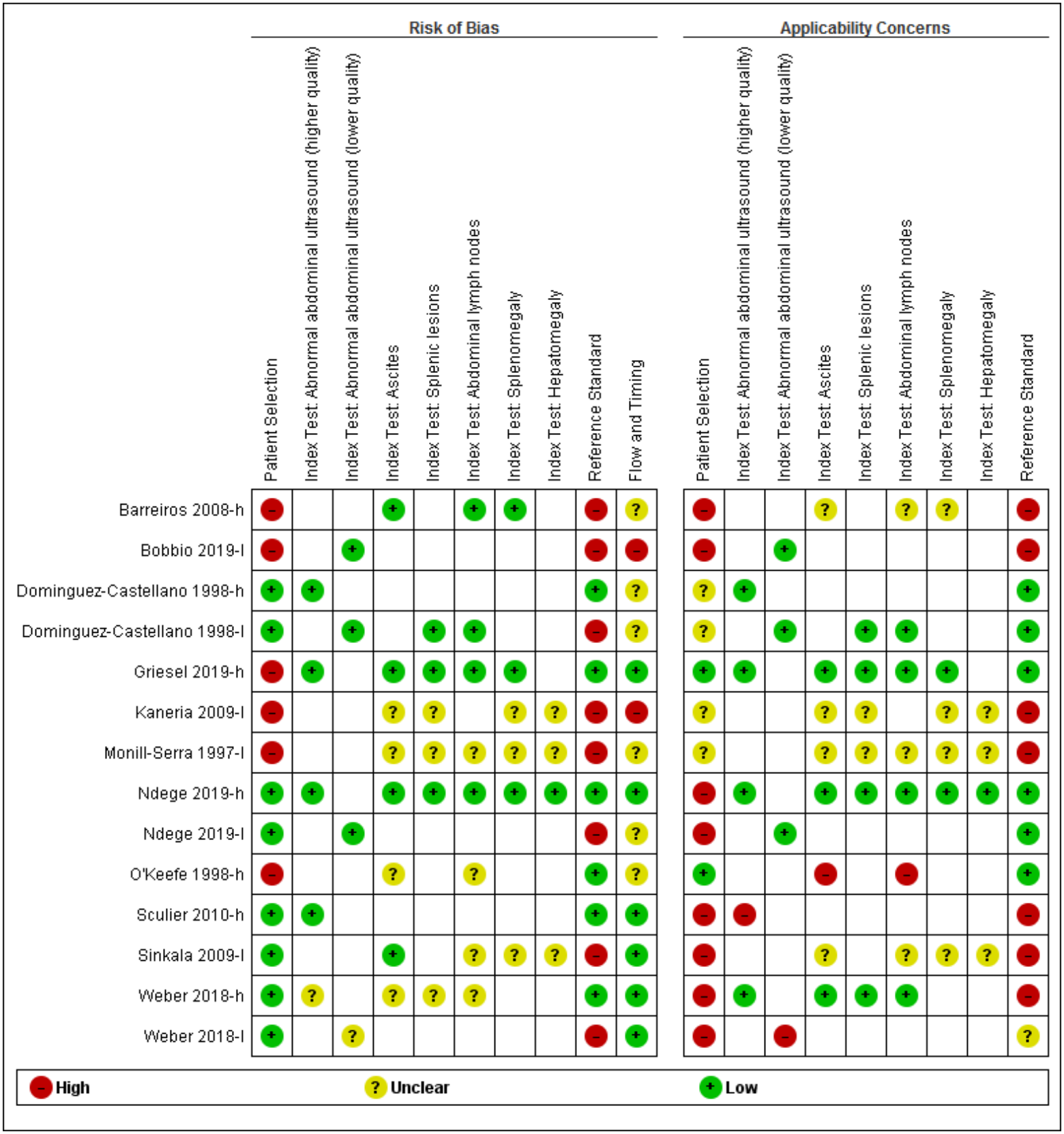
included studies section). Key findings of included studies are presented in Table 1 and Table 2.

We contacted the authors of all 11 studies, of whom five responded. We received unpublished data from four studies (Weber 2018-h; Bobbio 2019-l; Griesel 2019-h; Ndege 2019-h), and one study clarified the qualification of the sonographer (O'Keefe 1998-h).

Methodological quality of included studies

We present the results of the methodological assessment of the 11 studies in Figure 3. The results are reported below separately for studies included in the primary analyses (any abnormal finding) and those included in the secondary analyses (individual lesions). Studies that used a higher-quality reference standard are indicated with the suffix ‘h' and studies that used a lower-quality reference standard are indicated with the suffix ‘l'.

Figure 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study. Suffix (h) indicates higher quality reference standard; suffix (l) indicates lower quality reference standard.



Studies of any abnormal finding included in primary analyses

Six studies with a higher-level reference standard contributed data (Figure 3). One study was considered to be at high risk of bias in the patient selection domain since it excluded people unable to produce sputum (Griesel 2019-h). Concerns about applicability (i.e. are there concerns that the included participants do not match the review question?) were deemed high in four studies, since they included asymptomatic people (Sculier 2010-h; Bobbio 2019-l) or were conducted in a referral or tertiary setting (Sculier 2010-h; Weber 2018-h; Bobbio 2019-l; Ndege 2019-h). One study was deemed of unclear concern as the setting in which the ultrasound was done was not reported (Dominguez-Castellano 1998-h). In the index test domain, we considered one study to be at unclear risk of bias because, although the study did specify thresholds for positivity, the test was sometimes interpreted with knowledge of the results of the reference standard (Weber 2018-h). We considered the conduct and interpretation of the index test to be of high concern for applicability in one study where the ultrasound was performed by a trained radiologist (Sculier 2010-h). In the reference standard domain, all studies used a higher-quality reference standard (microbiological confirmation). We regarded two studies as being of high concern for applicability, as neither study speciated mycobacteria isolated in culture (Sculier 2010-h; Weber 2018-h). For the flow and timing domain, we considered one study to be at unclear risk of bias because the study did not report the interval between the index test and the reference standard, and it was unclear if all participants received the same reference standard (Dominguez-Castellano 1998-h).

For the main analyses (abnormal versus normal ultrasound examination), four studies with a lower-level reference standard contributed data (Figure 3). We considered one study to be at high risk of bias in the patient selection domain because it did not enrol participants consecutively or randomly (Bobbio 2019-l). Concerns about applicability (i.e. are there concerns that the included participants do not match the review question?) were deemed high in three studies since they included asymptomatic participants (Bobbio 2019-l), or the study was conducted in a referral or tertiary setting (Weber 2018-l; Bobbio 2019-l; Ndege 2019-l). We rated one study at unclear concern as the setting in which the ultrasound was done was not reported (Dominguez-Castellano 1998-l). In the index test domain, we considered one study to be at unclear risk of bias because the index test was sometimes interpreted with knowledge of the results of the reference standard (Weber 2018-l). In the reference standard domain, we considered all studies to be at high risk of bias because the studies included a lower-quality reference standard (clinical diagnosis) (Dominguez-Castellano 1998-l; Weber 2018-l; Bobbio 2019-l; Ndege 2019-l). We rated one study at unclear concern for applicability since it is unclear whether all clinically diagnosed participants improved on anti-tuberculosis treatment (Weber 2018-l). In terms of the flow and timing domain, we considered one study to be at unclear risk of bias because the study did not report the interval between the index test and the reference standard, and it was unclear if all participants received the same reference standard (Dominguez-Castellano 1998-l). We judged one study to be at high risk of bias because not all participants received a reference standard and not all participants received the same reference standard (Bobbio 2019-l).

Studies of individual lesions included in secondary analyses

Nine studies contributed data (Figure 3). In the patient selection domain, we deemed five studies (56%) to be at high risk of bias because: i) three studies used a case-control design (Monill-Serra 1997-l; Barreiros 2008-h Kaneria 2009-l); ii) one study excluded patients with a CD4 cell count of 200 or more (O'Keefe 1998-h); and iii) one study excluded patients unable to produce sputum (Griesel 2019-h). For applicability, we judged four studies (44%) to be at high concern since one study included HIV-negative participants (Barreiros 2008-h), and the ultrasound examination was performed in a tertiary or referral centre in three studies (Sinkala 2009-l; Weber 2018-h; Ndege 2019-h). We rated three studies at unclear concern as the setting in which the ultrasound was done was not reported (Monill-Serra 1997-l; Dominguez-Castellano 1998-l; Kaneria 2009-l). In the index test domain we judged five studies (56%) to be at unclear risk of bias because four studies did not specify (or it was unclear) whether index test results were interpreted without knowledge of the results of the reference standard (Monill-Serra 1997-l; O'Keefe 1998-h; Kaneria 2009-l; Weber 2018-h), and three studies did not report prespecified thresholds (O'Keefe 1998-h; Kaneria 2009-l; Sinkala 2009-l). We considered the conduct and interpretation of the index test to be of high concern for applicability in one study where the ultrasound was performed by a trained radiologist (O'Keefe 1998-h); we rated four studies at unclear concern since we were not able to make a decision on the qualification of the person performing the index tests (Monill-Serra 1997-l; Barreiros 2008-h; Kaneria 2009-l; Sinkala 2009-l). Five studies (56%) used a lower-quality reference standard and were deemed at high risk of bias in the reference standard domain (Monill-Serra 1997-l; Dominguez-Castellano 1998-l; Barreiros 2008-h; Kaneria 2009-l; Sinkala 2009-l). We rated five studies at high concern for applicability for the reference standard since mycobacteria isolated in culture were not speciated (Monill-Serra 1997-l; Barreiros 2008-h; Kaneria 2009-l; Sinkala 2009-l; Weber 2018-h). For the flow and timing domain, we considered one study to be at high risk of bias because not all participants received a reference standard and not all participants received the same reference standard (Kaneria 2009-l). Four studies were deemed to be at unclear risk of bias since: i) three studies did not report the interval between the index test and the reference standard, and it was unclear if all participants received the same reference standard (Monill-Serra 1997-l; Dominguez-Castellano 1998-l; Barreiros 2008-h); and ii) one study did not report the interval between the index test and the reference standard, and not all participants received the same reference standard (O'Keefe 1998-h).

Findings

For the diagnostic accuracy of abdominal ultrasound (main and secondary analyses), the 11 studies included 1319 participants. The median number of participants in the studies was 100 (interquartile range (IQR) 58 to 134). The proportion of tuberculosis cases in the non-case-control studies ranged from 17.5% (Sculier 2010-h) to 71.0% (Sinkala 2009-l), median 40.6% (IQR 27.5 to 53.7). Table 1 present key characteristics for each of the 11 studies. Three studies used a case-control design (Monill-Serra 1997-l; Barreiros 2008-h; Kaneria 2009-l) and eight studies used cross-sectional or cohort design (Dominguez-Castellano 1998-h; O'Keefe 1998-h; Sinkala 2009-l; Sculier 2010-h; Weber 2018-h; Bobbio 2019-l; Griesel 2019-h; Ndege 2019-h). Eight studies (73%) were conducted in low-income or middle-income countries, while the remaining three

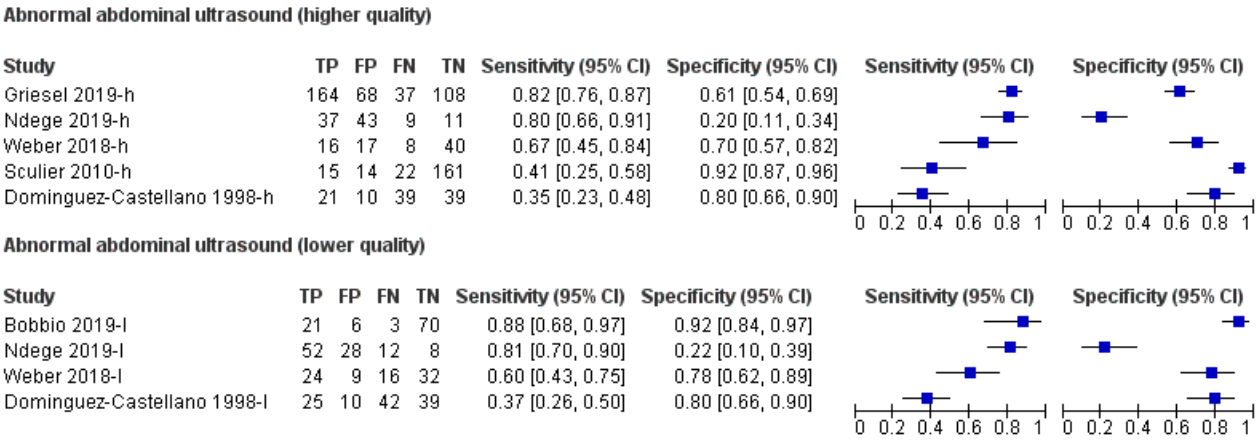
studies were conducted in high-income countries. Results of the primary and secondary analyses are summarized in Table 3.

I. Any abnormal abdominal ultrasound finding for tuberculosis detection

We included six of the 11 studies in the primary analyses (Dominguez-Castellano 1998-h; Dominguez-Castellano 1998-l; Sculier 2010-h; Weber 2018-h; Weber 2018-l; Bobbio 2019-l; Griesel 2019-h; Ndege 2019-h; Ndege 2019-l); three studies provided data for each type of reference standard.

Five studies (879 participants) used a higher-quality reference standard (Dominguez-Castellano 1998-h; Sculier 2010-h; Weber 2018-h; Griesel 2019-h; Ndege 2019-h). Study estimates of sensitivity and specificity ranged from 35% to 82% and from 20% to 92%. The pooled sensitivity and specificity were 63% (95% CI 43% to 79%) and 68% (95% CI 42% to 87%), respectively (Figure 4).

Figure 4. Forest plot of abdominal ultrasound for detecting abdominal TB or disseminated TB with abdominal involvement. TP = true positive; FP = false positive; FN = false negative; TN = true negative. Suffix (h) indicates higher quality reference standard; suffix (l) indicates lower quality reference standard.



Four studies (397 participants) used a lower-quality reference standard (Dominguez-Castellano 1998-l; Weber 2018-l; Bobbio 2019-l; Ndege 2019-l). Sensitivity estimates ranged from 37% to 88% and specificity estimates ranged from 22% to 92% (Figure 4). The pooled sensitivity and specificity were 68% (95% CI 45% to 85%) and 73% (95% CI 41% to 91%), respectively.

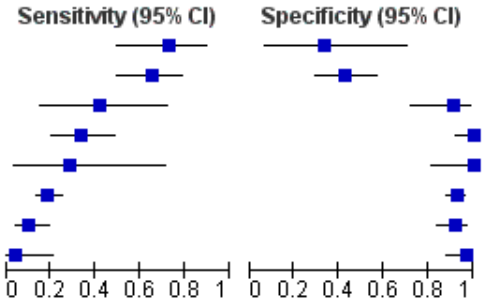
II. Splenic lesions on abdominal ultrasound for tuberculosis detection

We included six studies involving 916 participants, of whom 477 had tuberculosis (Monill-Serra 1997-l; Dominguez-Castellano 1998-l; Kaneria 2009-l; Weber 2018-h; Griesel 2019-h; Ndege 2019-h). Sensitivity estimates were very heterogeneous and ranged from 13% to 62%. Specificity estimates were less heterogeneous and ranged from 86% to 100% (Figure 5).

Figure 5. Forest plot of individual findings on ultrasound for detecting abdominal TB or disseminated TB with abdominal involvement. TP = true positive; FP = false positive; FN = false negative; TN = true negative. Suffix (h) indicates higher quality reference standard; suffix (l) indicates lower quality reference standard.

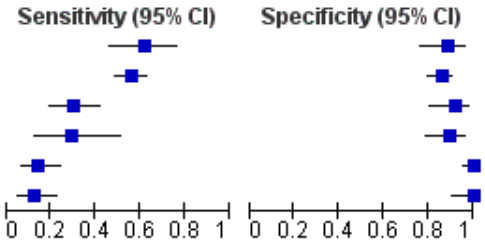
Ascites

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sinkala 2009-l	16	6	6	3	0.73 [0.50, 0.89]	0.33 [0.07, 0.70]
Ndege 2019-h	30	31	16	23	0.65 [0.50, 0.79]	0.43 [0.29, 0.57]
O'Keefe 1998-h	5	2	7	21	0.42 [0.15, 0.72]	0.91 [0.72, 0.99]
Kaneria 2009-l	15	0	30	45	0.33 [0.20, 0.49]	1.00 [0.92, 1.00]
Barreiros 2008-h	2	0	5	18	0.29 [0.04, 0.71]	1.00 [0.81, 1.00]
Griesel 2019-h	38	13	163	163	0.19 [0.14, 0.25]	0.93 [0.88, 0.96]
Monill-Serra 1997-l	8	6	68	70	0.11 [0.05, 0.20]	0.92 [0.84, 0.97]
Weber 2018-h	1	2	23	55	0.04 [0.00, 0.21]	0.96 [0.88, 1.00]



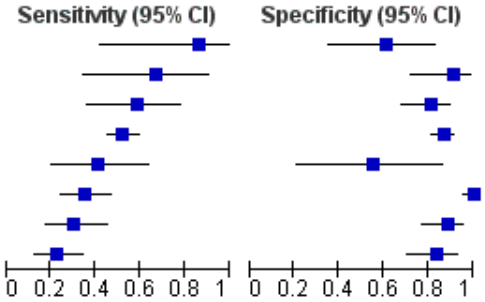
Splenic lesions

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kaneria 2009-l	28	5	17	40	0.62 [0.47, 0.76]	0.89 [0.76, 0.96]
Griesel 2019-h	113	25	88	151	0.56 [0.49, 0.63]	0.86 [0.80, 0.91]
Dominguez-Castellano 1998-l	20	4	47	45	0.30 [0.19, 0.42]	0.92 [0.80, 0.98]
Weber 2018-h	7	6	17	51	0.29 [0.13, 0.51]	0.89 [0.78, 0.96]
Monill-Serra 1997-l	11	0	65	76	0.14 [0.07, 0.24]	1.00 [0.95, 1.00]
Ndege 2019-h	8	0	56	36	0.13 [0.06, 0.23]	1.00 [0.90, 1.00]



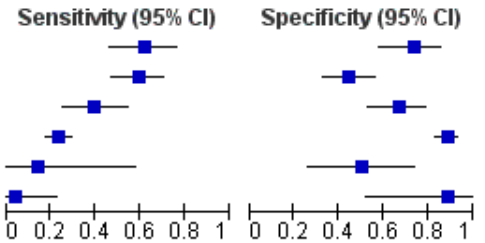
Abdominal lymph nodes

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barreiros 2008-h	6	7	1	11	0.86 [0.42, 1.00]	0.61 [0.36, 0.83]
O'Keefe 1998-h	8	2	4	21	0.67 [0.35, 0.90]	0.91 [0.72, 0.99]
Weber 2018-h	14	11	10	46	0.58 [0.37, 0.78]	0.81 [0.68, 0.90]
Griesel 2019-h	105	23	96	153	0.52 [0.45, 0.59]	0.87 [0.81, 0.92]
Sinkala 2009-l	9	4	13	5	0.41 [0.21, 0.64]	0.56 [0.21, 0.86]
Monill-Serra 1997-l	27	0	49	76	0.36 [0.25, 0.47]	1.00 [0.95, 1.00]
Ndege 2019-h	14	6	32	48	0.30 [0.18, 0.46]	0.89 [0.77, 0.96]
Dominguez-Castellano 1998-l	15	8	52	41	0.22 [0.13, 0.34]	0.84 [0.70, 0.93]



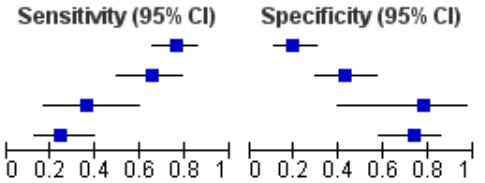
Splenomegaly

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kaneria 2009-l	28	12	17	33	0.62 [0.47, 0.76]	0.73 [0.58, 0.85]
Monill-Serra 1997-l	45	42	31	34	0.59 [0.47, 0.70]	0.45 [0.33, 0.57]
Ndege 2019-h	18	18	28	36	0.39 [0.25, 0.55]	0.67 [0.53, 0.79]
Griesel 2019-h	47	20	154	156	0.23 [0.18, 0.30]	0.89 [0.83, 0.93]
Barreiros 2008-h	1	9	6	9	0.14 [0.00, 0.58]	0.50 [0.26, 0.74]
Sinkala 2009-l	1	1	21	8	0.05 [0.00, 0.23]	0.89 [0.52, 1.00]



Hepatomegaly

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Monill-Serra 1997-l	58	61	18	15	0.76 [0.65, 0.85]	0.20 [0.11, 0.30]
Ndege 2019-h	30	31	16	23	0.65 [0.50, 0.79]	0.43 [0.29, 0.57]
Sinkala 2009-l	8	2	14	7	0.36 [0.17, 0.59]	0.78 [0.40, 0.97]
Kaneria 2009-l	11	12	34	33	0.24 [0.13, 0.40]	0.73 [0.58, 0.85]



III. Intra-abdominal lymph nodes on abdominal ultrasound for tuberculosis detection

Eight studies involving 917 participants (included 455 tuberculosis cases) reported on intra-abdominal lymph nodes on abdominal ultrasound (Monill-Serra 1997-l; Dominguez-Castellano 1998-l; O'Keefe 1998-h; Barreiros 2008-h; Sinkala 2009-l; Weber 2018-h; Griesel 2019-h; Ndege 2019-h). The sensitivities ranged from 22% to 86% and specificities from 56% to 100% (Figure 5).

IV. Ascites on abdominal ultrasound for tuberculosis detection

We included eight studies involving 891 participants, of whom 433 had tuberculosis (Monill-Serra 1997-l; O'Keefe 1998-h; Barreiros 2008-h; Kaneria 2009-l; Sinkala 2009-l; Weber 2018-h; Griesel 2019-h; Ndege 2019-h). Sensitivity and specificity estimates were very heterogeneous and ranged from 4% to 73% and from 33% to 100% respectively (Figure 5).

V. Splenomegaly

Six studies (775 participants, 397 tuberculosis cases) reported splenomegaly (Monill-Serra 1997-l; Barreiros 2008-h; Kaneria 2009-l; Sinkala 2009-l; Griesel 2019-h; Ndege 2019-h). Estimates were very heterogeneous and ranged from 5% to 62% for sensitivity and 45% to 89% for specificity (Figure 5).

VI. Hepatomegaly

Four studies (373 participants, of whom 189 had tuberculosis) were included for hepatomegaly. The sensitivity ranged from 24% to 76% and specificity from 20% to 78% (Figure 5).

Investigations of heterogeneity

We did not investigate heterogeneity, due to limited data.

DISCUSSION

This systematic review of the diagnostic accuracy of abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals summarizes the current literature and includes 11 studies. Six studies reported on abdominal ultrasound with any abnormal finding, and nine studies reported on individual ultrasound findings. Studies were conducted in low-, middle- and high-income countries. Five studies were performed in referral or tertiary-level healthcare facilities, and in four studies the ultrasound examinations were performed by radiologists.

Summary of main results

We have summarized the main results in Summary of findings 1. An abdominal ultrasound with any abnormal finding had a pooled sensitivity of 63% (95% CI 43% to 79%) and a pooled specificity of 68% (95% CI 42% to 87%) when bacteriological confirmation was used as the (higher-quality) reference standard. The pooled sensitivity was 68% (95% CI 45% to 85%) and the pooled specificity was 73% (95% CI 41% to 91%) when the reference standard was clinical diagnosis without microbiological confirmation (lower-quality reference standard).

The sensitivity of abdominal ultrasound is of concern, due to the high chance of missing tuberculosis cases (high false negative rate). This means that HIV-positive individuals who have tuberculosis may be wrongly classified as not having tuberculosis, with a delay in initiating appropriate treatment. Ultrasound examination is operator-dependent and subjective, with the possibility of missing subtle signs. Ultrasound also evaluates anatomical changes, and abnormalities might not occur in individuals with advanced immunosuppression.

The effect of the type of reference standard used is reflected in the improvement in both the sensitivity and specificity in the lower-quality reference standard group. The primary concern with a lower-quality reference standard (clinical diagnosis) is that clinicians may overdiagnose tuberculosis for fear of missing or delaying a diagnosis that could result in excess morbidity and mortality, particularly among HIV-postive adults. This would result in an overestimation of the diagnostic accuracy of abdominal ultrasound, as fewer false positive and negative results would occur. In addition, in studies where abdominal ultrasound is part of the reference standard, incorporation bias would further result in an overestimation of diagnostic accuracy.

The estimates of sensitivity for the primary and secondary analyses were low and very heterogeneous. This means that a negative abdominal ultrasound should not be used to rule out abdominal tuberculosis or disseminated tuberculosis with abdominal involvement.

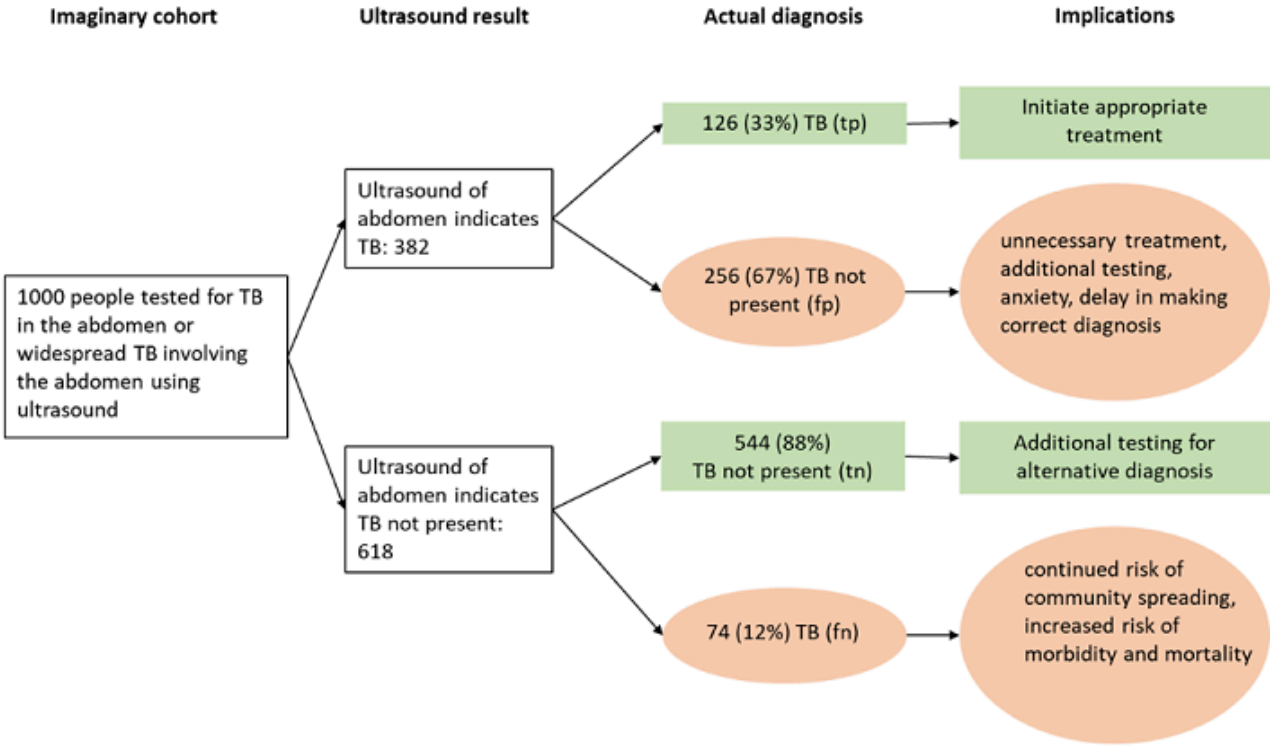
Specificity estimates were very heterogeneous, especially for hepatomegaly and splenomegaly.

Application of the main meta-analytic findings to a hypothetical cohort

The main findings of the review were illustrated by applying the results to a hypothetical cohort of 1000 HIV-positive individuals thought to have tuberculosis. We presented different scenarios where the tuberculosis prevalence varies from 10% to 20% to 40%. The consequences of false positive results are probably unnecessary initiation of treatment, additional testing with subsequent morbidity, patient anxiety, and possible delay in further diagnostic evaluation. The consequences of false negative results are the continued risk of community transmission of tuberculosis and an increased risk of patient morbidity and mortality.

If the pooled estimates (from using a higher-quality reference standard) for an abdominal ultrasound with any abnormal finding are applied to a hypothetical cohort of 1000 HIV-positive individuals where 100 (10%) of them actually have tuberculosis, abdominal ultrasound would be expected to miss 37 tuberculosis cases and falsely diagnose 288 people as tuberculosis cases (Summary of findings 1). For a prevalence of 20% (200 tuberculosis cases), 74 tuberculosis cases will be missed and 256 people will be falsely diagnosed as having tuberculosis (Figure 6) while for a prevalence of 40% (400 tuberculosis cases), 148 tuberculosis cases will be missed and 192 people will be falsely diagnosed as having tuberculosis (Summary of findings 1).

Figure 6. Flow diagram summarizing the main results in hypothetical cohort with TB prevalence 20%



tp: true positive – test is positive (indicates TB) and patient has TB
fp: false positive – test is positive (indicates TB) but patient does not have TB
tn: true negative – test is negative (indicates TB not present) and patient dies not have TB
Fn: false negative – test is negative (indicates TB not present) but patient has TB

Strengths and weaknesses of the review

The findings in this review are based on comprehensive literature searches, strict inclusion criteria, and standardized data extraction. The search included studies published in all languages and we corresponded with study authors to obtain additional and unpublished data. However, as diagnostic accuracy studies are poorly indexed, we acknowledge that we may have missed some studies despite the comprehensive search.

The main limitations of the review were the small number of studies and participants included in the analyses. The results were very heterogeneous with a high false negative rate, and should therefore be interpreted with caution. The high risks of bias in the patient selection domain and the reference standard domain further weaken our confidence in the results. A further limitation in the reference standard was the use of microscopic identification of acid-fast bacilli on stained sputum smears. Although smear positivity has high specificity in high tuberculosis prevalence settings, it is not a perfect reference standard as smear will also detect non-tuberculous mycobacteria, which are found in a higher proportion in low-prevalence tuberculosis settings.

Applicability of findings to the review question

We had high concern about the applicability of the included studies to our review question. We foresee that in clinical practice abdominal ultrasound to diagnose abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals would be most beneficial when performed by non-radiologists in non-tertiary endemic settings. Most studies were performed in tertiary settings with trained radiologists or sonographers performing the ultrasound examination, and it is possible that the accuracy of abdominal ultrasound may be lower when performed in a different setting or by less experienced users. The predictive values of any diagnostic test are influenced by disease prevalence, so the inclusion of studies performed in low tuberculosis-burden countries would have decreased the positive predictive value of abdominal ultrasound. Two studies included HIV-positive participants without a clinical suspicion of tuberculosis. In these studies, abdominal ultrasound has been used as a screening test and not a diagnostic test. This will further affect the diagnostic accuracy of abdominal ultrasound and increase the risk of inappropriate additional testing and initiation of anti-tuberculous treatment. Studies were carried out under research conditions, and it is possible that the diagnostic accuracy of abdominal ultrasound might be lower in routine practice.

AUTHORS' CONCLUSIONS

Implications for practice

Abdominal ultrasound had a sensitivity of 63% among HIV-positive individuals suspected of having abdominal tuberculosis or disseminated tuberculosis with abdominal involvement. The high false negative rate suggests that ultrasound cannot be relied on alone for the diagnosis of tuberculosis. The specificity of 68% of any abnormal finding on abdominal ultrasound further indicates

that care must be taken to not use abdominal ultrasound alone to rule in tuberculosis, as the false positive rate is high. The presence of individual findings such as ascites, splenic lesions and intra-abdominal lymphadenopathy had a higher specificity as evidenced by the range of study estimates, and, if proven in large prospective studies, might be a useful indicator for tuberculosis involving the abdomen. In light of our review findings, the intended role for ultrasound is to be used with other tests, such as lateral flow urine lipoarabinomannan assay (LF-LAM), chest x-ray and Xpert MTB/RIF or Xpert Ultra, to confirm the diagnosis of abdominal tuberculosis or disseminated tuberculosis with abdominal involvement.

Implications for research

Future studies that evaluate the diagnostic accuracy of abdominal ultrasound in HIV-positive people should use a robust reference standard with speciation to ensure that tuberculosis is correctly diagnosed. Larger, prospective, well-designed studies that recruit a representative sample of participants are also needed. The role of abdominal ultrasound in addition to existing diagnostic strategies (e.g. chest x-ray, LF-LAM, Xpert MTB/RIF) needs to be evaluated, as well as its incorporation into tuberculosis diagnostic algorithms.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barreiros 2008-h

Study characteristics	
Patient sampling	Case-control design

Barreiros 2008-h *(Continued)*

Patient characteristics and setting	Country: Germany Setting: Not reported High tuberculosis burden country: No High HIV-associated tuberculosis burden country: No Sample size: 7 cases (of these 3 HIV-negative); 18 controls (of these 9 HIV-negative) Median age (range): Cases 41 (27 - 66); Controls 36 (21 - 69) Gender proportion (M:F): Cases 3:4; Controls 11:7 Proportion on antiretroviral therapy (ART): Not reported
Index tests	Sonographer qualification: Not reported Threshold(s): • Thickened bowel wall: > 5 mm; • Intramural abscess: thickened hypervascular bowel wall > 8 mm with non-vascularized, oval-shaped, intramural mass-like lesions; • Extramural abscess: Circumscribed hypoechoic or echo-free fluid collections > 10 mm next to fistula; • Lymph nodes: Longitudinal diameter > 20 mm; • Splenomegaly: > 13.5 cm
Target condition and reference standard(s)	Target condition: Intestinal tuberculosis Confirmation of active tuberculosis: "…based on clinical, endoscopic, histologic, radiologic and operative findings including microbiology (in all) and polymerase chain reaction (PCR) (in 5 patients) of biopsies taken during endoscopy."
Flow and timing	
Comparative	
Notes	Second control group of healthy persons not included 4 cases and 9 controls were HIV-positive Cases had pulmonary tuberculosis only (randomly selected) Reference standard results not delineated

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		

Barreiros 2008-h *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		High	**High**
DOMAIN 2: Index Test Ascites			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test Abdominal lymph nodes			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test Splenomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Was incorporation bias avoided?	Yes		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Unclear	

Bobbio 2019-l

Study characteristics			
Patient sampling	Cross-sectional design		
Patient characteristics and setting	Country: South Sudan Setting: Referral hospital High tuberculosis burden country: No High HIV-associated tuberculosis burden country: No Sample size: 100 Median age (range): Not available (only categories available) Gender proportion (M:F): 48:52 Proportion on antiretroviral therapy (ART): 3%		
Index tests	Sonographer qualification: Clinician trained in ultrasound Threshold(s): At least one of • Pericardial effusion; • Periportal/para-aortic lymph nodes (> 1.5 cm in diameter); • Focal splenic lesions; • Pleural effusion or consolidation of lung; • Ascites without alternative explanation; • Focal liver lesion		
Target condition and reference standard(s)	Target condition: Disseminated tuberculosis Confirmation of active tuberculosis: Acid-fast bacilli sputum smears, ultrasound, clinical diagnosis		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	**High**

Bobbio 2019-l *(Continued)*

DOMAIN 2: Index Test Abnormal abdominal ultrasound (lower quality)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was incorporation bias avoided?	No		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	No		
		High	

Dominguez-Castellano 1998-h

Study characteristics	
Patient sampling	Prospective cross-sectional
Patient characteristics and setting	Country: Spain Setting: Not reported High tuberculosis burden country: No High HIV-associated tuberculosis burden country: No Sample size:116 Age: 31.56 ± 4.68 years (mean ± SD) Gender proportion: Not reported Proportion on antiretroviral therapy (ART): Not reported
Index tests	Sonographer qualification: “Medical sonographer”

Dominguez-Castellano 1998-h *(Continued)*

	Threshold(s): • Multiple splenic focal lesions: hypoechoic, < 10 mm diameter, poorly-defined / irregular borders, homogeneous distribution; • Abdominal adenopathy: hypo or isoechoic, between 1 and 3 cm, around hepatic hilum, spleen, aorta or celiac trunk; • Hypo or hyperechoic focal liver lesions
Target condition and reference standard(s)	Target condition: Pulmonary tuberculosis, Extra-pulmonary tuberculosis and disseminated tuberculosis (with or without abdominal involvement) Confirmation of active tuberculosis: Smear microscopy, Lowenstein culture
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test Abnormal abdominal ultrasound (higher quality)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was incorporation bias avoided?	Yes		
		Low	**Low**

Dominguez-Castellano 1998-h *(Continued)*

DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Yes
Did all patients received a reference standard?	Yes
	Unclear

Dominguez-Castellano 1998-l

Study characteristics	
Patient sampling	Prospective cross-sectional
Patient characteristics and setting	Country: Spain Setting: Not reported High tuberculosis burden country: No High HIV-associated tuberculosis burden country: No Sample size:116 Age: 31.56 ± 4.68 years (mean ± SD) Gender proportion: Not reported Proportion on antiretroviral therapy (ART): Not reported
Index tests	Sonographer qualification: “Medical sonographer” Threshold(s): • Multiple splenic focal lesions: hypoechoic, < 10 mm diameter, poorly-defined / irregular borders, homogeneous distribution; • Abdominal adenopathy: hypo or isoechoic, between 1 cm and 3 cm, around hepatic hilum, spleen, aorta or celiac trunk; • Hypo or hyperechoic focal liver lesions
Target condition and reference standard(s)	Target condition: Pulmonary tuberculosis, extra-pulmonary tuberculosis and disseminated tuberculosis (with or without abdominal involvement) Confirmation of active tuberculosis: Compatible with clinical and radiography findings with improvement to anti-tuberculosis treatment
Flow and timing	

Dominguez-Castellano 1998-I *(Continued)*

Comparative
Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test Abnormal abdominal ultrasound (lower quality)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Splenic lesions			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Abdominal lymph nodes			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was incorporation bias avoided?	Unclear		

Dominguez-Castellano 1998-l *(Continued)*

		High	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Unclear	

Griesel 2019-h

Study characteristics	
Patient sampling	Prospective cross-sectional
Patient characteristics and setting	Country: South Africa Setting: Secondary-level hospitals High tuberculosis burden country: Yes High HIV-associated tuberculosis burden country: Yes Sample size: 377 Age: Median (IQR) tuberculosis cases: 35 (30 - 41); Non-tuberculosis controls: 36 (30 - 42) Gender proportion (M:F) tuberculosis cases: 64:137; Non-tuberculosis controls: 64:112 Proportion on antiretroviral therapy (ART): tuberculosis cases: 59/201 (29%); Non-tuberculosis controls: 61/176 (35%)
Index tests	Sonographer qualification: Trained sonographers Threshold(s): • Lymph nodes (long-axis length: any and ≥ 10 mm in diameter); • Splenic hypoechoic lesions; • Spleen enlargement ≥ 110 mm; • Any one of abdominal, pleural, or pericardial effusions
Target condition and reference standard(s)	Target condition: Tuberculosis Confirmation of active tuberculosis: Positive culture for *M tuberculosis*

Griesel 2019-h *(Continued)*

Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	**Low**
DOMAIN 2: Index Test Abnormal abdominal ultrasound (higher quality)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Ascites			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Splenic lesions			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Abdominal lymph nodes			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

Griesel 2019-h *(Continued)*

DOMAIN 2: Index Test Splenomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was incorporation bias avoided?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Low	

Kaneria 2009-l

Study characteristics	
Patient sampling	Case-control
Patient characteristics and setting	Country: India Setting: Not reported High tuberculosis burden country: Yes High HIV-associated tuberculosis burden country: Yes Sample size: 90 Age: Mean (range) Cases: Male 36.4 (24 - 60), Female 33.41 (25 - 60); Controls: Male 39.46 (24 - 60), Female 38.71 (25 - 61) Gender proportion: M:F Cases: 31:14; Controls: 30:15

Kaneria 2009-I *(Continued)*

	Proportion on antiretroviral therapy (ART): Cases: 7/45 (15.6%); Controls: 15/30 (50%)
Index tests	Sonographer qualification: Not reported Threshold(s): Not reported
Target condition and reference standard(s)	Target condition: Pulmonary tuberculosis, extra-pulmonary tuberculosis and disseminated tuberculosis (with or without abdominal involvement) Confirmation of active tuberculosis: Microscopic identification of AFB and compatible clinical findings
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Yes		
		High	**Unclear**
DOMAIN 2: Index Test Ascites			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		Unclear	**Unclear**
DOMAIN 2: Index Test Splenic lesions			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		Unclear	**Unclear**
DOMAIN 2: Index Test Splenomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		

Kaneria 2009-l *(Continued)*

If a threshold was used, was it pre-specified?	No		
		Unclear	**Unclear**
DOMAIN 2: Index Test Hepatomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Was incorporation bias avoided?	Unclear		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	No		
		High	

Monill-Serra 1997-l

Study characteristics	
Patient sampling	Case-control
Patient characteristics and setting	Country: Spain Setting: Not reported High tuberculosis burden country: No High HIV-associated tuberculosis burden country: No Sample size: 152 Age: Cases: Mean 30; Range 20 - 49; Controls: Not reported

Monill-Serra 1997-I *(Continued)*

	Gender proportion: M:F Cases: 56:20; Controls: Not reported Proportion on antiretroviral therapy (ART): Not reported
Index tests	Sonographer qualification: Not reported Threshold(s): • Lymph nodes > 1.5 cm; • Splenomegaly long axis > 12 cm or subjective impression; • Hypoechoic splenic lesions 0.5 cm to 1.0 cm (Not prespecified)
Target condition and reference standard(s)	Target condition: Disseminated tuberculosis (with or without abdominal involvement) Confirmation of active tuberculosis: Microbiological (culture) or histopathological examination
Flow and timing	
Comparative	
Notes	Controls were HIV-positive with no associated neoplastic illness or opportunistic infection

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	No		
		High	**Unclear**
DOMAIN 2: Index Test Ascites			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test Splenic lesions			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		

Monill-Serra 1997-l *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test Abdominal lymph nodes			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test Splenomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test Hepatomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was incorporation bias avoided?	Yes		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Unclear	

Ndege 2019-h

Study characteristics	
Patient sampling	Prospective cohort
Patient characteristics and setting	Country: Tanzania Setting: Referral hospital High tuberculosis burden country: Yes High HIV-associated tuberculosis burden country: Yes Sample size: 100 (original study size including HIV-negative n = 191) Age: Median 38 years; IQR 32 - 44 years Gender proportion: M:F 47:53 Proportion on antiretroviral therapy (ART): 56%
Index tests	Sonographer qualification: Board-certified sonographers Threshold(s): • Original FASH: pleural or pericardial effusion, ascites, abdominal lymph nodes > 1.5 cm, hypoechogenic lesions in the liver or spleen, ileum wall thickening > 4 mm or destructed ileum wall architecture; • Splenomegaly > 140 mm in long axis; • Hepatomegaly ≥ 2 cm below costal margin; • Pleural or pericardial fibrin strands in presence of effusion
Target condition and reference standard(s)	Confirmed tuberculosis was defined as ≥ 1 positive microbiological result from any site confirmed by Xpert MTB/RIF assay and/or bacteriologic culture (growth of *M tuberculosis*) in sputum, pleural fluid, ascites, cerebrospinal fluid, urine or lymph node aspirate
Flow and timing	
Comparative	
Notes	

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Ndege 2019-h *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**
DOMAIN 2: Index Test Abnormal abdominal ultrasound (higher quality)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Ascites			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Splenic lesions			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Abdominal lymph nodes			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Splenomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Hepatomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Ndege 2019-h *(Continued)*

		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was incorporation bias avoided?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Low	

Ndege 2019-l

Study characteristics	
Patient sampling	Prospective cohort
Patient characteristics and setting	Country: Tanzania Setting: Referral hospital High tuberculosis burden country: Yes High HIV-associated tuberculosis burden country: Yes Sample size: 100 (original study size including HIV-negative n = 191) Age: Median 38 years; IQR 32 - 44 years Gender proportion: M:F 47:53 Proportion on antiretroviral therapy (ART): 56%
Index tests	Sonographer qualification: Board-certified sonographers Threshold(s): • Original FASH: pleural or pericardial effusion, ascites, abdominal lymph nodes > 1.5 cm, hypoechogenic lesions in the liver or spleen, ileum wall thickening > 4 mm or destructed ileum wall architecture; • Splenomegaly > 140 mm in long axis; • Hepatomegaly ≥ 2 cm below costal margin;

Ndege 2019-I *(Continued)*

	• Pleural or pericardial fibrin strands in presence of effusion
Target condition and reference standard(s)	Confirmed tuberculosis was defined as ≥ 1 positive microbiological result from any site confirmed by Xpert MTB/RIF assay and/or bacteriologic culture (growth of *M tuberculosis*) in sputum, pleural fluid, ascites, cerebrospinal fluid, urine or lymph node aspirate. In addition, the identification of acid-fast bacilli in sputum by another health centre, or adenosine deaminase (ADA) ≥ 40 U/ml in pleural fluid, ≥ 35 U/ml in pericardial fluid and ≥ 30 U/ml in ascitic fluid were accepted as microbiological confirmation. Probable tuberculosis was defined as negative microbiological tests in a participant in whom anti-tuberculosis therapy (prescribed based on clinical suspicion or on chest x-ray) in the absence of an alternative diagnosis led to a resolution of clinical signs and symptoms, radiographic and sonographic signs, and to an increase in body weight documented 2 months after start of anti-tuberculosis treatment
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**
DOMAIN 2: Index Test Abnormal abdominal ultrasound (lower quality)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was incorporation bias avoided?	Unclear		

Ndege 2019-l *(Continued)*

		High	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Unclear	

O'Keefe 1998-h

Study characteristics	
Patient sampling	Prospective cross-sectional
Patient characteristics and setting	Country: South Africa Setting: Non-tertiary setting High tuberculosis burden country: Yes High HIV-associated tuberculosis burden country: Yes Sample size: 35 (original study size n = 44) Age: Mean 32.9; Range 18.4 - 53.3 Gender proportion: M:F 26:18 Proportion on antiretroviral therapy (ART): 0/44 (0%)
Index tests	Sonographer qualification: Radiologist Threshold(s): Not reported
Target condition and reference standard(s)	Target condition: Disseminated tuberculosis with abdominal involvement) Confirmation of active tuberculosis: Microbiological (culture) or postmortem evidence
Flow and timing	
Comparative	
Notes	Only 35/44 had ultrasound examination
Methodological quality	

O'Keefe 1998-h *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	**Low**
DOMAIN 2: Index Test Ascites			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		Unclear	**High**
DOMAIN 2: Index Test Abdominal lymph nodes			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was incorporation bias avoided?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Unclear	

Sculier 2010-h

Study characteristics			
Patient sampling	Prospective cross-sectional		
Patient characteristics and setting	Country: Cambodia Setting: “not-for-profit referral hospital” High tuberculosis burden country: Yes High HIV-associated tuberculosis burden country: No Sample size: 212 Age: Median (IQR) 34 (29 - 41.5) years (included participants < 18 years) Gender proportion: M 40%, F 60% Proportion on antiretroviral therapy (ART): Not reported		
Index tests	Sonographer qualification: “Trained radiologist” Threshold(s): • Any lymph nodes ≥ 1.2 cm; • Ascites; • Hepatomegaly; • Splenomegaly; • Hepatic or splenic hypoechoic lesions with or without organ enlargement		
Target condition and reference standard(s)	Target condition: Disseminated tuberculosis (with or without abdominal involvement) Confirmation of active tuberculosis: Culture		
Flow and timing			
Comparative			
Notes	Substudy		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**

Sculier 2010-h *(Continued)*

DOMAIN 2: Index Test Abnormal abdominal ultrasound (higher quality)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was incorporation bias avoided?	Yes		
		Low	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Low	

Sinkala 2009-l

Study characteristics	
Patient sampling	Prospective cross-sectional
Patient characteristics and setting	Country: Zambia Setting: “secondary and tertiary care hospital” High tuberculosis burden country: Yes High HIV-associated tuberculosis burden country: Yes Sample size: 31 Age: Mean (SD) All: 33.4 (8.3) years (in text: mean 33.1 range 18 - 54); tuberculosis: 30.7 (6.9); No tuberculosis: 39.8 (8) Gender proportion: M:F All: 8:23; tuberculosis: 7:15; No tuberculosis: 1:8 Proportion on antiretroviral therapy (ART): Not reported

Sinkala 2009-I *(Continued)*

Index tests	Sonographer qualification: Not reported Threshold(s): Not reported
Target condition and reference standard(s)	Target condition: Abdominal tuberculosis Confirmation of active tuberculosis: "…definitive diagnosis of tuberculosis was made by demonstration of *M tuberculosis* infection via positive bacteriological culture and/or granulomatous inflammation on histopathological examination with positive Ziehl-Neelsen (ZN) staining on microscopy. A presumptive diagnosis of tuberculosis was made when granulomatous inflammation was seen on microscopy, or when visual inspection on laparoscopy was consistent with tuberculosis and the patient's clinical response to anti-tuberculous treatment was good. Laparoscopic features felt to be consistent with tuberculosis for the purpose of making a presumptive diagnosis were the presence of tubercles, fibro adhesive peritonitis, or caseating lymphadenopathy."
Flow and timing	
Comparative	
Notes	Ultrasound used as part of inclusion and exclusion criteria (selection bias)

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**
DOMAIN 2: Index Test Ascites			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Low	**Unclear**
DOMAIN 2: Index Test Abdominal lymph nodes			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Unclear	**Unclear**

Sinkala 2009-l *(Continued)*

DOMAIN 2: Index Test Splenomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Unclear	**Unclear**
DOMAIN 2: Index Test Hepatomegaly			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was incorporation bias avoided?	Yes		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Low	

Weber 2018-h

Study characteristics	
Patient sampling	Prospective controlled cohort
Patient characteristics and setting	Country: India Setting: Tertiary setting High tuberculosis burden country: Yes High HIV-associated tuberculosis burden country: Yes

Weber 2018-h *(Continued)*

	Sample size: 81 (original study size including HIV-negative n = 425) Age: Overall median (IQR) 43 (31.5 - 55); HIV only 43 (38 - 48) (included participants < 18 years) Gender proportion: Overall: M 328/425 (77%); HIV-positive M 56/81 (69%) Proportion on antiretroviral therapy (ART): 29/81 (35.8%)
Index tests	Sonographer qualification: Clinician trained in the study's ultrasound protocol but without formal ultrasound training Threshold(s): • FASH: at least 1 of pericardial or pleural effusion, focal liver or splenic lesions, or abdominal lymphadenopathy; • Pericardial effusion: qualitative assessment; • Focal liver lesions: Size 2 mm to 15 mm; multiple in appearance; • Focal splenic lesions: Size 2 mm to 15 mm; multiple in appearance; • Abdominal lymphadenopathy: Max diameter at least 15 mm
Target condition and reference standard(s)	Target condition: Pulmonary tuberculosis and extra-pulmonary tuberculosis Confirmation of active tuberculosis: "…'confirmed tuberculosis' (i.e., positive fluorescent microscopy, polymerase chain reaction, or tuberculosis culture)…"
Flow and timing	
Comparative	
Notes	Includes patients ≥ 16 years "…therapeutic and diagnostic management was fully the responsibility of the attending hospital doctor." Additional info received from authors

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**
DOMAIN 2: Index Test Abnormal abdominal ultrasound (higher quality)			
Were the index test results interpreted without knowledge of the results of the reference standard?	No		

Weber 2018-h *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test Ascites			
Were the index test results interpreted without knowledge of the results of the reference standard?	No		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test Splenic lesions			
Were the index test results interpreted without knowledge of the results of the reference standard?	No		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test Abdominal lymph nodes			
Were the index test results interpreted without knowledge of the results of the reference standard?	No		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was incorporation bias avoided?	Yes		
		Low	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Low	

Weber 2018-I

Study characteristics	
Patient sampling	Prospective controlled cohort
Patient characteristics and setting	Country: India Setting: Tertiary setting High tuberculosis burden country: Yes High HIV-associated tuberculosis burden country: Yes Sample size: 81 (original study size including HIV-negative n = 425) Age: Overall median (IQR) 43 (31.5 - 55); HIV only 43 (38 - 48) (included participants < 18 years) Gender proportion: Overall: M 328/425 (77%); HIV-positive M 56/81 (69%) Proportion on antiretroviral therapy (ART): 29/81 (35.8%)
Index tests	Sonographer qualification: Clinician trained in the study's ultrasound protocol but without formal ultrasound training Threshold(s): • FASH: at least 1 of pericardial or pleural effusion, focal liver or splenic lesions, or abdominal lymphadenopathy; • Pericardial effusion: qualitative assessment; • Focal liver lesions: Size 2 mm to 15 mm; multiple in appearance; • Focal splenic lesions: Size 2 mm to 15 mm; multiple in appearance; • Abdominal lymphadenopathy: Max diameter at least 15 mm
Target condition and reference standard(s)	Target condition: Pulmonary tuberculosis and extra-pulmonary tuberculosis Confirmation of active tuberculosis: "…'clinical tuberculosis' (no microbiological confirmation, but clinical tuberculosis diagnosis and tuberculosis treatment initiated)…"
Flow and timing	
Comparative	
Notes	Includes patients ≥ 16 years "…therapeutic and diagnostic management was fully the responsibility of the attending hospital doctor." Additional info received from authors

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Weber 2018-l *(Continued)*

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**
DOMAIN 2: Index Test Abnormal abdominal ultrasound (lower quality)			
Were the index test results interpreted without knowledge of the results of the reference standard?	No		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Was incorporation bias avoided?	No		
		High	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
Did all patients received a reference standard?	Yes		
		Low	

Suffix (h) indicates higher-quality reference standard; suffix (l) indicates lower-quality reference standard

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abiri 1985	Descriptive study
Agarwal 2010	No reference standard
Akinkuolie 2008	Descriptive study

Study	Reason for exclusion
Aubry 1994	Descriptive study
Barthwal 2005	Descriptive study
Batra 2000	Descriptive study
Chen 2009	Descriptive study
Clarke 2007	Descriptive study
Emby 2002	Descriptive study
Feng 2016	Ineligible index test
Giordani 2013	Descriptive study
Heller 2010a	Descriptive study
Heller 2013	Descriptive study
Heller 2017	Descriptive study
Ibrahim 2005	Descriptive study
Jain 1995	Ineligible patient population
Kedar 1994	Descriptive study
Landoni 2002	Descriptive study
Ouedraogo 2016	Only abnormal index test reported
Patel 2011	Only abnormal index test reported
Porcel-Martin 1998	Descriptive study
Sheikh 1999	Descriptive study
Solomon 1998	Not a diagnostic accuracy study
Soriano 1991	Descriptive study
Spalgais 2013	Descriptive study
Spalgais 2017	No reference standard
Tarantino 2003	Descriptive study
Tarantino 2004	Descriptive study
Tshibwabwa 2000	Ineligible patient population
Wafai 2017	Descriptive study

Characteristics of ongoing studies *[ordered by study ID]*

PACTR201712002829221

Trial name or title	Ultrasound in managing tuberculosis: A randomized controlled two-center study
Target condition and reference standard(s)	Target condition: Extrapulmonary tuberculosis Reference standard: Not stipulated
Index and comparator tests	Index test: eFASH (extended focused assessment with sonography for HIV and tuberculosis) and a management algorithm Comparator group: Standard of care (Management according to the decision of the treating physician)
Starting date	September 2018
Contact information	mrohacek@ihi.or.tz
Notes	

D A T A

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Abnormal abdominal ultrasound (higher quality)	5	879
2 Abnormal abdominal ultrasound (lower quality)	4	397
3 Ascites	8	891
4 Splenic lesions	6	916
5 Abdominal lymph nodes	8	917
6 Splenomegaly	6	775
7 Hepatomegaly	4	373

Test 1. Abnormal abdominal ultrasound (higher quality).

Test 2. Abnormal abdominal ultrasound (lower quality).

Test 3. Ascites.

Test 4. Splenic lesions.

Test 5. Abdominal lymph nodes.

Test 6. Splenomegaly.

Test 7. Hepatomegaly.

ADDITIONAL TABLES

Table 1. Key findings of included studies

Author (publication year)	Study design	Country	Clinical setting	Target condition definition	Qualification of person performing index test	Sample size	Tuberculosis proportion in study
Barreiros 2008-h	Case-control	Germany	Not reported	Gastro-intestinal tuberculosis	Not reported	25[a] (7 cases, 18 pulmonary tuberculosis controls)	-
Bobbio 2019-l	Cross-sectional	South Sudan	Referral hospital	Extra-pulmonary tuberculosis	Trained non-radiologist	100	24%
Dominguez-Castellano 1998-h; Dominguez-Castellano 1998-l	Cross-sectional	Spain	Not reported	Extra-pulmonary tuberculosis	Sonographer	116	55% (higher) 58% (lower)
Griesel 2019-h	Cross-sectional	South Africa	Non-tertiary hospital	Culture-positive tuberculosis	Sonographer	377	53%
Kaneria 2009-l	Case-control	India	Not reported	Pulmonary tuberculosis, extra-pulmonary tuberculosis, disseminated tuberculosis	Not reported	90 (45 cases, 45 HIV-positive controls without any pathology)	-
Monill-Serra 1997-l	Case-control	Spain	Not reported	Disseminated tuberculosis	Not reported	152 (76 cases, 76 HIV-positive controls without any pathology)	-
Ndege 2019-h; Ndege 2019-l	Cohort	Tanzania	Referral hospital	Pulmonary tuberculosis, extra-pulmonary tuberculosis, disseminated tuberculosis	Board-certified sonographers	100 (191 original study sample)	46% (higher) 64% (lower)
O'Keefe 1998-h	Cross-sectional	South Africa	Non-tertiary hospital	Disseminated tuberculosis	Radiologist	35 (44 original study sample)	34%
Sculier 2010-h	Cross-sectional	Cambodia	Referral hospital	Disseminated tuberculosis	Radiologist	212	18%
Sinkala 2009-l	Cross-sectional	Zambia	Tertiary hospital	Abdominal tuberculosis	Not reported	31	71%
Weber 2018-h; Weber 2018-l	Cohort	India	Tertiary hospital	Disseminated tuberculosis	Trained non-radiologist	81 (425 original study sample)	30% (higher)

Table 1. Key findings of included studies *(Continued)*

						49% (lower)	

[a]Includes five HIV-negative participants.
Suffix (h) indicates higher-quality reference standard; suffix (l) indicates lower-quality reference standard.

Table 2. Indext test threshold and reference standard of included studies

Author (publication year)	Index test variable included (threshold)	Reference standard quality and definition
Barreiros 2008-h	Ascites (any) Lymphadenopathy (abdominal and perihepatic nodes with longitudinal diameter > 20 mm) Splenomegaly (> 135 mm)	Lower: Clinical, endoscopic, histologic, radiologic and operative findings including microbiology and polymerase chain reaction of biopsies taken during endoscopy
Bobbio 2019-l	Any abnormality (Presence of ≥ 1: i) pericardial effusion, ii) periportal/para-aortic lymph nodes (> 15 mm diameter), iii) focal splenic lesions, iv) pleural effusion or consolidation of the lung, v) ascites without alternative explanation)	Lower: Sputum microscopy OR clinical reasons OR Focused Assessment with Sonography in HIV-associated tuberculosis (FASH)
Dominguez-Castellano 1998-h; Dominguez-Castellano 1998-l	Any abnormality (presence of ≥ 1: i) multiple hypoechoic splenic lesions (< 10 mm), ii) any abdominal adenopathy, iii) hypo- or hyperechoic liver lesions)	Higher: Microscopy OR culture Lower: Microscopy OR culture OR clinical or radiographic indications and response to treatment
Griesel 2019-h	Any abnormality (presence of ≥ 1: i) abdominal lymph nodes (any size), ii) splenic hypoechoic lesions, iii) splenomegaly (≥ 110 mm), iv) any one of abdominal, pleural, or pericardial effusions) Ascites (any) Lymphadenopathy (any size) Splenic lesions (hypoechoic) Splenomegaly (≥ 110 mm)	Higher: Positive culture for *M tuberculosis* from any site
Kaneria 2009-l	Ascites (any) Hepatomegaly (not defined) Lymphadenopathy (diameter > 15 mm) Splenic lesions (multiple, hypoechoic, 5 mm to 10 mm diameter) Splenomegaly (not defined)	Lower: Lymphocytic predominance and elevated adenosine deaminase (ADA) levels in pleural or ascitic fluid OR granulomatous lymphadenitis and acid-fast bacilli in lymph node OR sputum microscopy
Monill-Serra 1997-l	Ascites (any) Hepatomegaly (not defined) Lymphadenopathy (> 15 mm diameter) Splenic lesions (hypoechoic nodes) Splenomegaly (long axis > 120 mm or subjective impression)	Lower: Blood culture positive for *M tuberculosis* OR medullary bone or liver biopsy with granulomatous inflammation or culture positive for *M tuberculosis* OR microbiological or histopathological confirmation in ≥ 2 non-contiguous extra-pulmonary sites
Ndege 2019-h; Ndege 2019-l	Any abnormality (presence of ≥ 1: i) pleural or pericardial effusion, ii) ascites, iii) abdominal lymph nodes > 15 mm, iv) hypoechogenic lesions in the liver or spleen, v) ileum wall thickening > 4 mm or destructed ileum wall architecture) Ascites (any) Hepatomegaly (not defined)	Higher: Xpert MTB/RIF assay and/or bacteriologic culture (growth of *M tuberculosis*) Lower: Positive Xpert MTB/RIF assay and/or bacteriologic culture (growth of *M tuberculosis*) OR acid-fast bacilli in sputum OR raised adenosine deaminase (ADA) levels in pleural, pericardial or ascitic fluid OR negative microbiological

Table 2. Indext test threshold and reference standard of included studies *(Continued)*

	Lymphadenopathy (> 15 mm diameter) Splenomegaly (not defined)	tests and improvement 2 months after start of anti-tuberculosis treatment
O'Keefe 1998-h	Ascites (any) Lymphadenopathy (not defined)	Higher: Positive mycobacterial blood or bone marrow cultures OR positive mycobacterial cultures from 2 or more other sites OR post mortem evidence
Sculier 2010-h	Any abnormality (presence of ≥ 1: i) any lymph nodes ≥ 12 mm, ii) ascites, iii) hepatomegaly, iv) splenomegaly, v) hepatic or splenic hypoechoic lesions with or without organ enlargement)	Higher: Positive culture for *M tuberculosis* from any site
Sinkala 2009-l	Ascites (any) Hepatomegaly (not defined) Lymphadenopathy (not defined) Splenomegaly (not defined)	Lower: Positive bacteriological culture OR granulomatous inflammation with positive Ziehl-Neelsen (ZN) staining on microscopy OR granulomatous inflammation on microscopy OR visual inspection on laparoscopy consistent with tuberculosis (presence of tubercles, fibro-adhesive peritonitis, or caseating lymphadenopathy) and favourable response to anti-tuberculous treatment
Weber 2018-h; Weber 2018-l	Any abnormality (presence of ≥ 1: i) pericardial or pleural effusion, ii) focal liver or splenic lesions, iii) abdominal lymphadenopathy) Ascites (any) Hepatomegaly (not defined) Lymphadenopathy (≥ 15 mm diameter) Splenic lesions (multiple, hypoechoic, 2 mm to 5 mm diameter)	Higher: Positive fluorescent microscopy, polymerase chain reaction, or tuberculosis culture Lower: Microbiological confirmation (fluorescent microscopy, polymerase chain reaction, culture) OR clinical diagnosis and anti-tuberculous treatment initiated

Suffix (h) indicates higher quality reference standard; suffix (l) indicates lower quality reference standard

Table 3. Summary estimates of sensitivity and specificity for any abnormality and individual abdominal ultrasound findings

Abdominal ultrasound finding	Number of studies	Number of participants (tuberculosis-cases)	Pooled sensitivity (95% CI) %	Pooled specificity (95% CI) %	Range of sensitivity %	Range of specificity %
Any abnormality (higher-quality reference standard)	5	879 (368)	63 (43 to 79)	68 (72 to 87)	35 to 82	20 to 92
Any abnormality (lower-quality reference standard)	4	397 (149)	68 (45 to 85)	73 (41 to 91)	37 to 88	22 to 92
Splenic lesions	6	916 (477)	Not calculated	Not calculated	13 to 62	86 to 100

Table 3. Summary estimates of sensitivity and specificity for any abnormality and individual abdominal ultrasound findings *(Continued)*

Intra-abdominal lymph nodes	8	917 (455)	Not calculated	Not calculated	22 to 86	56 to 100
Ascites	8	891 (433)	Not calculated	Not calculated	4 to 73	33 to 100
Splenomegaly	6	775 (397	Not calculated	Not calculated	5 to 62	45 to 89
Hepatomegaly	4	373 (189)	Not calculated	Not calculated	24 to 76	20 to 78

APPENDICES

Appendix 1. Search strategy

Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946 to Present>

1 extrapulmonary tuberculosis.mp.

2 Peritonitis, Tuberculous/ or Tuberculosis, Gastrointestinal/ or Tuberculosis, Hepatic/

3 abdominal tuberculosis.mp.

4 Tuberculosis, Hepatic/ or liver tuberculosis.mp. or gastric tuberculosis.mp. or intestinal tuberculosis.mp.

5 Tuberculosis, Miliary/

6 disseminated tuberculosis.mp.

7 1 or 2 or 3 or 4 or 5 or 6

8 HIV infection.mp. or HIV Infections/

9 exp HIV/

10 human immunodeficiency virus.mp.

11 Acquired Immunodeficiency Syndrome/ or acquired immunodeficiency syndrome.mp.

12 (acquired immun* and deficiency syndrome).mp.

13 ((HIV* adj2 (people or person* or patient*)) or PLHIV).mp.

14 8 or 9 or 10 or 11 or 12 or 13

15 7 and 14

16 Radiography, Abdominal/

17 X-Ray Diffraction/ or x-ray*.mp.

18 (ultrasound or barium).mp.

19 Tomography, X-Ray Computed/

20 (comput* adj2 tomograph*).mp.

21 Magnetic Resonance Imaging/

22 (MRI or CAT).mp.

23 Ultrasonography/ or ultrasonograph*.mp.

24 Bacteriological Techniques/ or Sputum/ or sputum specimen.mp.

25 liquid culture system.mp.

26 Xpert MTB*.mp.

27 Genotype MTBDR*.mp.

28 (lipoarabinomannan or LAM or LF-LAM).mp.

29 QuantiFERON-TB-Gold.mp. or Tuberculin Test/ or tuberculin.mp.

30 Diagnostic Imaging/ or Point-of-Care Systems/

31 (Laparotomy or laparoscopy or fine needle aspiration).mp.

32 CD4 Lymphocyte Count/

33 Ascites/diagnosis or Ascites/microbiology or Paracentesis/ or Laparoscopy/

34 colonoscopy.mp. or Colonoscopy/

35 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36 15 and 35

Embase 1947-Present, updated daily

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1 tuberculosis.mp. or tuberculosis/

2 (Abdominal or gastroenteric or gastrointestinal or intestinal or hepatic or liver or splenic).mp.

3 1 and 2

4 abdominal tuberculosis/

5 miliary tuberculosis/

6 HIV infection.mp. or Human immunodeficiency virus infection/

7 human immunodeficiency virus.mp.

8 acquired immune deficiency syndrome/

9 ((HIV* adj2 (people or person* or patient*)) or PLHIV).mp.

10 6 or 7 or 8 or 9

11 abdominal ultrasound.mp.

12 X ray/ or radiography/ or X ray*.mp.

13 (ultrasound or barium).mp.

14 (comput* adj2 tomograph*).mp.

15 Magnetic Resonance.mp. or nuclear magnetic resonance/

16 Ultrasonography.mp. or echography/

17 sputum analysis/ or sputum cytodiagnosis/ or sputum culture/

18 microbiological examination/

19 liquid culture/

20 (Xpert MTB* or Genotype MTBDR*).mp.

21 (lipoarabinomannan or LAM or LF-LAM).mp.

22 (QuantiFERON-TB-Gold or Tuberculin Test).mp.

23 "point of care system"/

24 (Laparotomy or laparoscopy).mp

25 ascites fluid analysis/ or ascites/ or ascites fluid cytology/

26 colonoscopy/

27 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28 3 and 10 and 27

BIOSIS Previews

You searched for: **TOPIC:** ("liver tuberculosis" or "gastric tuberculosis" or "intestinal tuberculosis" or "abdominal tuberculosis".) *AND* **TOPIC:** (HIV or AIDS or "acquired immunodeficiency syndrome") *AND* **TOPIC:** (ultrasound or ultrasonography or scan or "Magnetic Resonance Imaging" or MRI or tomography)

Timespan: All years. **Indexes:** BIOSIS Previews.

Web of Science Core Collection

You searched for: **TOPIC:** ("liver tuberculosis" or "gastric tuberculosis" or "intestinal tuberculosis" or "abdominal tuberculosis") *AND* **TOPIC:** (HIV or AIDS or "acquired immunodeficiency syndrome") *AND* **TOPIC:** (ultrasound or ultrasonography or scan or "Magnetic Resonance Imaging" or MRI or tomography)

Timespan: All years. **Indexes:** SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH

ClinicalTrials.gov and WHO ICTRP

tuberculosis and ultrasound, tuberculosis and ultrasonography, tuberculosis and MRI

Appendix 2. QUADAS-2 tool tailored to the context of the review

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	**Methods of patient selection**	**How index test was conducted and reported**	**How reference standard was conducted and reported**	**Describe patients that did not receive and time interval between index test or reference standard**
Signalling questions (yes, no, or unclear)	Consecutive or random sample of patients? • Yes if the study reported consecutive enrolment or random sampling of patients. • No if patients were purposefully selected, for example based on previous test results (other tests or reference standard). • Unclear if the study did not explicitly state consecutive enrolment or random sampling, and it was unclear how patients were sampled.	Index test results interpreted without knowledge of the results of reference standard? • Yes if it is apparent that ultrasound (and test combinations) results were interpreted without knowledge of reference standard results. • No if results of ultrasound (and test combinations) were interpreted with knowledge of the reference standard results.	Reference standard likely to correctly classify the target condition? • Yes if the higher quality reference standard was used (that is, culture, microscopic identification of acid-fast bacilli, or Xpert MTB/RIF). • No if the lower quality reference standard was used (that is, not coupled with any mentioned in higher quality reference).	Was there an appropriate interval between index test and reference standard? • Yes if abdominal ultrasound and the reference standard(s) (samples taken or clinical diagnosis made) were performed at the same time or if the time interval is less than one week. • No if the time period between ultrasound and the reference standard is more than one week.

(Continued)

	• Unclear if insufficient information on how ultrasound (and test combinations) was interpreted.	• Unclear if insufficient information on the reference standard(s) used.	• Unclear if insufficient or no information on the time interval.
Was a case-control design avoided? • Yes if a case-control design was not used. • No if patients with known disease (cases) and patients without the disease (controls) were clearly enrolled (such that participants are unrepresentative of the spectrum of patients seen in clinical practice). • Unclear if the study design used was not clearly reported.	Pre-specified threshold used? • Yes if the study states the use of one, pre-specified, cut-off value, for example, "abdominal lymph nodes greater than 10 mm in the shortest diameter were deemed as a positive result". • No if multiple cut-off values were evaluated and an optimal one (based on maximising test accuracy) was subsequently chosen. • Unclear if a cut-off was used but was not reported, or only one cut-off value was reported, but was not explicitly pre-specified in the study.	Reference standard results interpreted without knowledge of the results of index test? • Yes if results of the reference standard are interpreted without knowledge of ultrasound results. However, the clinical reference standard may incorporate ultrasound. • No if results of the reference standard were interpreted with knowledge of ultrasound results • Unclear if there is insufficient information on whether or not the reference standard results were interpreted with knowledge of ultrasound results	Did all patients receive a reference standard? • Yes if all participants received a reference standard. • No if one or more participants did not receive a reference standard. • Unclear if there is insufficient information to determine whether or not all patients received a reference standard.
Did the study avoid inappropriate exclusions? • Yes if no patients were excluded after inclusion in the study. • No if specific populations were excluded (for example, pregnant patients, elderly), or patients with high CD4 counts were excluded because of low clinical suspicion of TB. • Unclear if unreported or insufficient information given to make a decision.		Was incorporation bias avoided (inclusion of index test as part of the reference standard)? • Yes if abdominal ultrasound was not used as part of the reference standard. • No if abdominal ultrasound formed part of the reference standard. • Unclear if insufficient information given to make a decision.	Did all patients receive the same reference standard? • Yes if study participants received the same reference standard (regardless of ultrasound result). • No if participants did not receive the same reference standard. • Unclear if there is insufficient information to determine whether or not all patients received the same reference standard.
			Were all patients included in the analysis? • Yes if all participants recruited into the study were included in the analysis. • No if some participants recruited into the study

(Continued)

				were excluded in the analysis. • Unclear if unreported or insufficient information given to make a decision.
Risk of bias[a](high, low, or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation has introduced bias?	Could the patient flow have introduced bias?
Applicability concerns (high, low, or unclear)	Are there concerns that the included patients do not match the review question? • High if participants received ultrasound in a tertiary care (referral) centre or if asymptomatic HIV-positive participants included. • Low if participants received ultrasound in any setting, or if HIV-positive individuals with presumptive abdominal tuberculosis or disseminated tuberculosis with abdominal involvement included. • Unclear if insufficient information to make a decision.	Are there concerns that the index test, its conduct, or interpretation differs from the review question? • High if, for example, specially trained radiologists performed the ultrasound. • Low if non-radiologists performed the ultrasounds. • Unclear if insufficient information to make a decision.	Are there concerns that the target condition as defined by the reference standard does not match the review question? • High if studies did not speciate mycobacteria isolated in culture or clinically diagnosed TB cases were not followed up to evaluate treatment response. • Low if studies did speciate mycobacteria isolated in culture or clinically diagnosed TB cases improved on anti-TB therapy. • Unclear if insufficient information to make a decision.	Not applicable

Abbreviations: TB: tuberculosis

[a]**Grading criteria for 'Risk of bias' assessment**

- If all signalling questions for a domain are answered 'yes' then we will judge the risk of bias to be 'low'.
- If any signalling question is answered 'no' this will flag the potential for bias and we will judge risk of bias with a senior review author.
- If all signalling questions or most of them were answered 'no', then we will judge the risk of bias as 'high'.
- We will assign the 'unclear' category when the study authors report insufficient data to permit a judgment.

CONTRIBUTIONS OF AUTHORS

Daniël J van Hoving and Eleanor A Ochodo wrote the protocol with input from Yemisi Takwoingi, Rulan Griesel, Graeme Meintjes, and Gary Maartens. Daniël J van Hoving and Rulan Griesel reviewed articles for inclusion and extracted data. Discrepancies were resolved by Graeme Meintjes. Eleanor A Ochodo analysed the data with input from Yemisi Takwoingi. Daniël J van Hoving and Eleanor A Ochodo interpreted the analyses and drafted the manuscript. Graeme Meintjes, Gary Maartens and Yemisi Takwoingi provided critical revisions to the manuscript. All review authors read and approved the final manuscript draft.

DECLARATIONS OF INTEREST

Daniël J van Hoving has no conflicts of interest to declare.

Graeme Meintjes has no conflicts of interest to declare.

Yemisi Takwoingi has no conflicts of interest to declare.

Rulan Griesel has no conflicts of interest to declare.

Gary Maartens has no conflicts of interest to declare.

Eleanor A Ochodo has no conflicts of interest to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We amended the protocol title from *Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive adults* to *Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals*.

Our review differed from the Cochrane protocol in several ways (Van Hoving 2017). In the protocol we stated a secondary objective to determine the diagnostic accuracy of combinations of abdominal ultrasound and existing tests (chest radiograph, full blood count) for detecting abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals. However, we could not find any study that evaluated abdominal ultrasound as an add-on test or in combination with other tests, and we therefore did not report on this.

The MEDION database is not active anymore and has not been searched.

In the protocol, we stated that we would have one primary meta-analysis at individual patient level. However we decided to have two sets of primary meta-analyses; one with 2 x 2 tables generated with a higher-quality reference standard and the other with a lower-quality reference standard. As stated in the analysis section, some studies produced two data points (with higher-quality and lower-quality reference standards). Because we did not want to lose information by only selecting one data point for each study and also to produce meaningful results, we present two sets of meta-analyses. We used Stata instead of SAS for all analyses.

Due to insufficient data we did not investigate all potential sources of heterogeneity as stated in the protocol (including clinical setting, and ultrasound training level).

We defined adults in the protocol as participants aged 18 years or older. Two studies included participants under 18 years (older than 15 years) (Sculier 2010-h; Weber 2018-h; Weber 2018-l). We included the studies as i) the number of paediatric cases was low, ii) many countries manage 15-year-old patients as adults, and iii) the results would be valuable for policy making. However, we have downgraded the certainty of the evidence for applicability concerns due to indirectness.

We judged publication bias using three criteria: for-profit interest, only studies detected that produce precise estimates of high accuracy despite small sample size, and knowledge about studies that were conducted but are not published.

INDEX TERMS

Medical Subject Headings (MeSH)

AIDS-Related Opportunistic Infections [*diagnostic imaging]; HIV Infections [*complications]; Randomized Controlled Trials as Topic; Tuberculosis [*diagnostic imaging]; Ultrasonography [*methods]

MeSH check words

Humans