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# CT in the detection of latent tuberculosis: a systematic review

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AIM: To evaluate the use of computed tomography (CT) and low-dose CT in the detection of latent tuberculosis (TB).

MATERIALS AND METHODS: A systematic search of literature in adherence with the PRISMA guidelines was carried out. Quality assessment of the included studies was conducted.

RESULTS: The search strategy identified a total of 4,621 studies. Sixteen studies were considered eligible and included in the review. There was high heterogeneity among all studies. CT was identified as much more sensitive for the detection of latent TB in all studies despite chest radiography often being recommended in guidelines to assess patients for latent TB. Low-dose CT showed promising results in four of the studies; however, these results were limited due to small sample sizes.

CONCLUSION: CT is much superior to chest radiography consistently identifying additional cases of latent TB. There are limited high-quality publications available using low-dose CT but findings thus far suggest low-dose CT could be used as an alternative to standard-dose CT for the detection of latent TB. It is recommended that a randomised controlled trial investigating low-dose CT should be carried out.



## Introduction

Tuberculosis (TB) continues to be one of the top 10 causes of death worldwide,[1] caused by *Mycobacterium tuberculosis*. Latent tuberculosis infection (LTBI) is an immune response against *M. tuberculosis* without clinical manifestations or radiological evidence of active TB.[1,2] Approximately 22.5% of the global population (1.78 billion) are said to have LTBI.[3,4] This chronic inactive infection is controlled by the cellular immunity of the infected person. Detection of LTBI is crucial as the risk is that it might become active TB. This risk is heightened in particular groups, including young children, immunodeficient patients, individuals with a high-risk of exposure, recently infected individuals, and intravenous drug users.[5–8] LTBI is a term that includes latent TB and previous (inactive)TB.

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Although the incidence of active TB has declined recently in most high-income countries, the prevalence of LTBI has remained stable.[2] Despite the historic decline, the incidence of active TB has reversed in the UK in the last 30 years and has become an area of concern for public health with the increase predominantly among the foreign born people in the UK.[9] Appropriate screening therefore remains important because of the rising number of people travelling from high endemic areas and also because of the increasing use of immunosuppressive therapies.[10] The magnitude of the reactivation of TB risk varies among high-risk categories; however, early diagnosis of LTBI may prevent the development of active TB.[11,12] A systematic approach to managing LTBI in cohorts at high-risk reactivation is a critical component of the World Health Organization (WHO) End TB Strategy.[13,14] Consequently, many countries have introduced LTBI control programmes targeting high-risk groups and screening to identify those with LTBI as well as TB.[15] Nonetheless, the WHO has expressed concerns over the effect of COVID-19 on TB prevention control programmes, noting a sharp decrease in TB notifications in 2020.[1] Regardless, there is consensus that screening for LTBI is indicated in high-risk groups but little consensus on how this screening is done.

There is no reference standard test for the diagnosis of LTBI. The diagnosis is commonly based on immune response against *M. tuberculosis* antigens using the tuberculin skin test (TST) or the more recent *M. tuberculosis*-specific interferon-gamma release assays (IGRA)[13,16] commercially available as Quantiferon-TB (Qiagen, Hilden, Germany) and T.Spot TB (Oxford Immunotec, Abington, UK); however, neither can differentiate between active TB and LTBI, which is problematic for establishing appropriate treatments.[8] Consequently, differentiation often relies on additional radiological assessments to increase diagnostic sensitivity.

Clinical practice guidelines regarding LTBI are inconsistent in their recommendations.[11] The National Institute for Health and Care Excellence (NICE) guidelines recommend carrying out TST followed by IGRA and additional work-up with chest radiography (CR).[17] The findings of each test dictating the next test required. All of the international guidelines deem an individual at risk if either TST or IGRA are positive.[18] CR is usually recommended as part of the screening process in addition to immunological tests.[5,11,13,14] Despite this, CR lacks diagnostic accuracy with limited sensitivity for the detection of LTBI.[11,19] A recent meta-analysis reported that the sensitivity of a CR for detection of LTBI is as low as 15%.[20] CR has limited value for LTBI diagnosis in high-risk individuals[21] and in patients with other underlying diseases.[22] Therefore, there is a risk of undertreating TB due to the insensitivity of a CR and overtreating LTBI due to the lack of specificity of TST and IGRA.

Chest CT is more accurate than CR,[3] but is associated with much higher radiation doses. CT is often considered a supplementary technique to CR for screening high-risk individuals[23] and is sometimes used for serial screening in high endemic regions.[24,25] Given the associated high radiation doses, there has been a range of dose-reduction strategies trialled. The most successful are iterative reconstruction algorithms, which allow substantial reductions in radiation dose by removing image noise and artefacts.[26] These have led to the development of low-dose (LDCT) or ultra-low-dose CT (ULDCT) protocols, which are already accepted in clinical practice for lung nodule follow-up and in lung cancer screening programmes.[27] Low radiation doses in the thorax have been reported to deliver doses similar to conventional chest radiography, which are 0.05–0.24 mSv.[27]

The primary aim of this review was to evaluate the use of CT to detect radiological abnormalities suggestive of LTBI and evaluate its use as part of a screening protocol. A secondary aim is to identify if LDCT could be used as an alternative to standard-dose CT to do this.

## Materials and methods

As a systematic review was carried out no ethical approval was required. A systematic search of the literature was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews.[28] The Population, Intervention, Comparison, Outcomes and Study design tool[29] was the framework used to formulate the eligibility criteria (Table 1). The search terms “latent tuberculosis” and “computed tomography” and “screening” and “biologic therapies” with their synonyms, acronyms, and spelling alternatives were generated.

An extensive literature search was performed using PubMed, Scopus, Web of Science and Embase databases to identify relevant English language literature. Over 10 years from 1 September 2011 to 1 September 2021. This

**Table 1**
PICOS elements for eligibility criteria.

| | |
|---|---|
| Population | All studies reporting diagnosis or changes on CT suggestive of LTBI, which include individuals ≥16 years of age, with suspected latent TB infection and have had an IGRA/TST and/or a chest radiography performed<br>All studies which include individuals ≥16 years of age who are undergoing screening for latent TB and have had a CT thorax and an IGRA/TST and/or a chest radiography performed |
| Intervention | CT/low-dose CT/ultra-low-dose CT |
| Comparison | CR and IGRA/TST or IGRA/TST or CR |
| Outcomes | Detection rate of LTBI using CT or LDCT or ULDCT, detection rate of radiological abnormalities suggestive of LTBI using CT or LDCT or ULDCT |
| Study Design | All studies with the exception of case reports and case studies |

CT, computed tomography; LTBI, latent tuberculosis infection; CR, chest radiography; IGRA, (*M. tuberculosis*-specific) interferon-gamma release assay; TST, tuberculin skin test specific LDCT, low-dose CT; ULDCT, ultra-low dose CT.

timeframe was considered appropriate due to the technical developments in multidetector CT.

*Selection process*

All identified records were screened on title and abstract, the remaining studies were assessed for eligibility. Full texts were obtained for abstracts that met the selection criteria. Reference lists of retrieved studies were also reviewed for relevant studies.

*Quality assessment*

The quality assessment of each of the included studies was conducted using a Critical Appraisal Skills Programme (CASP).[30] When the validity of results, clarity of results, and the clinical relevance of results were absent or unclear, they were excluded from the review. Internal validity of the studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool (QUADAS-2)[31] to determine bias in four critical domains patient selection, index test(s), reference standard, and flow and timing. For this review, any study containing high or unclear risk of bias in all four domains was eliminated.

A data extraction form was developed and was used on studies that met the reviewers' inclusion criteria. Data extracted included study design, clinical history, diagnostic methods, radiological imaging for LTBI diagnosis. These headings were used for thematic analysis (Electronic Supplementary Material Table S1).

## Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig 1) summarises the search results and the review process. The search strategy identified 4,621 studies, 4,385 after removal of duplicates. The titles and abstracts were screened, and 4,266 were removed. A full-text review was completed on the remaining 119 studies. Sixteen of these studies were considered eligible for inclusion. These 16 potential studies were appraised for inclusion using the modified QUADAS-2 ROB tool,[31] and none were considered "high risk" or "unclear risk" in all of the domains (Table 2). The 16 studies were also appraised using the CASP diagnostic checklist,[30] which did not identify any low-quality studies (Table 2).

All included studies evaluated high-risk individuals. There was high heterogeneity in the literature with variations in the combination of diagnostic tools used to diagnose LTBI. There was variation in the groups of participants investigated between high-risk participants undergoing immunosuppressive therapy, close contact with a person with TB, and participants working in high endemic regions. The retrospective studies, in particular, were often ambiguous on clinical histories such as BCG (Bacillus Calmette–Guérin) vaccination and also lacked detail on the diagnostic methods being reviewed, e.g., methodology (Electronic Supplementary Material Table S1). Variation exists across all studies between the use of TST, IGRA, CR, and CT for the diagnosis of LTBI (Table 2). The criteria implemented to determine positivity for each test within a screening protocol varied in many of the studies included. These variations included radiological appearances of LTBI and the cut-off points to determine immunological test positivity.

*Radiological imaging for the diagnosis of LTBI*

CT was used as the reference standard in only one study.[32] Four publications[21,22,24,32] included CT as part of a screening protocol for all patients and three used CT for most of its participants. Tannus *et al.* carried out CT in 34/37 participants,[33] Lee *et al.* used LDCT in six out of seven participants[25] and 104/107 participants in Allwood *et al.* underwent both CT and CR[34] as the authors attempted to identify the optimal approach between structured questionnaires, CT, and CR for ruling out previous pulmonary TB. The remaining nine studies[6,8,35–41] reported CT as either an additional screening tool, as part of routine practice,[6] or for a reason other than screening for LTBI, e.g., metastatic work-up.[39]

The typical radiological appearances suggestive of LTBI on CT (Table 3) varied in the literature, with many listing pleural thickening, interstitial granuloma, fibrotic scarring, nodules, or lymphadenopathy as the predominant appearances.[6,21,22,24,32–34,36–40] Examples of some typical appearances can be seen in Fig 2. The remaining four studies[8,25,35,41] provided detail on the radiological appearances of active TB but provided no detail on the radiological appearances suggestive of LTBI[8,41] when no radiological signs of active TB were classified. Yoon *et al.* employed serial LDCT findings to determine diagnosis in patients with some non-calcified nodules disappearing in two contacts.[40]

CRs were not included as part of the screening protocol in five of the studies[24,32,33,38,40] while eight[8,21,22,25,35,36,39,41] carried out CR on all participants. In the remaining three studies, CRs were carried out in addition to or instead of CT.[6,34,37] Seven studies compared CT and CR, with CT frequently identifying findings suggestive of LTBI, which were not identified by CR[6,8,21,22,34,35,39] (Electronic Supplementary Material Table S1). Examples of this can be seen in Fig 3. Tannus-Silva *et al.* found that CT identified a higher number of positive results (52.9% positivity) than immunological tests demonstrating 36.8% positivity for T.SPOT-TB. and 13.5% for TST.[33]

*Low-dose CT*

Four of the 16 studies used LDCT for the diagnosis of LTBI.[24,25,34,40] The largest of these studies by He *et al.* provided insufficient detail to confirm whether the acquisition parameters that were used equated to low dose. The exposure parameters tube voltage and tube current were provided but tube rotation time was omitted.[24] No dose estimations were provided.

Allwood *et al.* describe using LDCT but provided no detail on imaging parameters.[34]

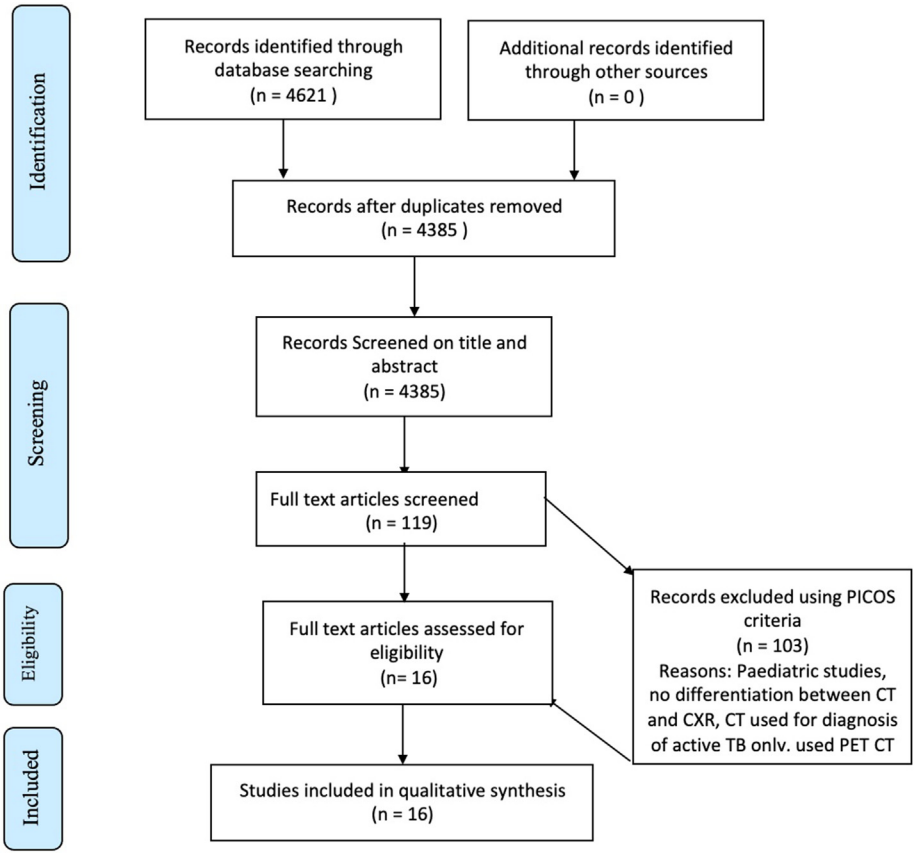


**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic Flowchart.

Lee *et al.*[25] and Yoon *et al.*[40] did provide a detailed breakdown of parameters and protocols used, and they estimated effective doses per CT scan of 0.19–0.25 mSv and 0.13 ± 0.03 mSv, respectively. Both of these studies were comparable in the dose estimates as they used a similar conversion factor of 0.0145 to estimate effective doses. A limitation of these studies however is the small number of participants ($n$=6)[25] and ($n$=17)[40] who underwent LDCT.

### *Screening for LTBI*

Seven of the studies investigated screening among close contacts and healthcare workers.[8,24,25,35,36,40,41] Yoshiyama *et al.*[35] followed-up screening with participants for 2 years. In the remaining studies[8,24,25,36,40,41] participants were either not followed up for 2 years or it was unclear.

He *et al.* recommended replacing CR with CT as a cost-effective option in screening for TB.[24] Allwood *et al.*[34] felt CT was financially justified in certain circumstances such as TB vaccine research, in advance of commencing immunosuppressive therapy, pre-transplant, and in cases where there was a risk of reactivation; however, Saidenberg-Kermanac'h *et al.* argued this might not be financially justified due to only one out of 60 inflammatory rheumatic disease patients in their study diagnosed with LTBI using CT.[21]

## Discussion

This systematic review demonstrates that CT is useful for detecting radiological abnormalities suggestive of LTBI and justifies its use as part of a screening protocol. There are limited high-quality publications available using LDCT for the detection of LTBI but findings thus far suggest LDCT could be used as an alternative to standard-dose CT for the detection of LTBI. It has also been recognised that there are substantial methodological limitations in this review with some studies limited by including only a small number of participants, and in addition, most studies either did not use a reference standard or CT was itself part of the reference standard. Some of the studies patients were selected to undergo CT based on the results of other tests, which were themselves part of a reference standard. This however is a limitation of the absence of a true reference standard for the diagnosis of LTBI. A more appropriate study design would be to compare LDCT, CR, immunological tests, and the patients' backgrounds.

It is important to recognise that it is not merely a matter of the sensitivity of CT for detecting lung lesions in LTBI, but that complex questions exist around screening for LTBI.[8] The only way to improve the sensitivity is to implement a screening protocol with tests demonstrated to be useful.[23] All studies in this review included a combination of tests

**Table 2**
QUADAS 2 tool, ROB tool and CASP diagnostic checklist and methods of assessment for the detection of latent tuberculosis infection (LTBI).

| QUADAS 2: Risk of bias | | | | | CASP: quality assessment | | | Methods of assessment |
|---|---|---|---|---|---|---|---|---|
| Study name | Patient selection | Index test | Reference standard | Flow and timing | Are the results of the study Valid? | What are the results? | Will the results help locally? | LTBI diagnostic methods/criteria LTBI |
| Agarwal *et al.*, 2018 | ✓ | ? | ? | ? | ? | ? | Yes | Patient history + TST/IGRA/CXR/CT |
| Fujikawa *et al.*, 2014 | ✓ | ✓ | ? | ? | Yes | Yes | Yes | Patient history + IGRA + CXR ± CT |
| Allwood *et al.*, 2015 | ✓ | ✓ | X | ? | No | Yes | Yes | 2 Questionnaires on patient history + CXR + hi-res LDCT |
| Maeda *et al.*, 2011 | ✓ | ? | ? | ✓ | Yes | ? | Yes | Patient history + CT ± TST/IGRA |
| Uzorka *et al.*, 2020 | ✓ | ? | ? | X | No | Yes | Yes | Patient history/TST/IGRA ± CXR ± CT |
| Guirao Arrabal *et al.*, 2016 | ✓ | ✓ | X | X | No | Yes | Yes | Patient history + CT + CXR ± TST |
| Lyu *et al.*, 2011 | ? | ✓ | ? | X | ? | ? | Yes | Patient history + CXR ± CT |
| He *et al.*, 2017 | ✓ | ✓ | ? | ? | ? | ? | Yes | Patient history + LDCT |
| Lee *et al.*, 2017 | ✓ | ✓ | ? | ✓ | Yes | No | Yes | Patient history + CXR + TST ± IGRA + ULDCT |
| Hirama *et al.*, 2011 | ✓ | ? | ? | ? | Yes | No | Yes | Patient history + IGRA + CXR, ± CT |
| Targowski *et al.*, 2014 | ✓ | ✓ | ? | ✓ | Yes | Yes | Yes | Patient history + CXR + TST + IGRA ± CT |
| Yoshiyama *et al.*, 2019 | ✓ | X | ✓ | ✓ | ? | No | Yes | Patient history + IGRA + CXR ± CT |
| Song *et al.*, 2017 | ✓ | ? | ? | ? | Yes | Yes | Yes | Patient history + IGRA ± CT |
| Yoon *et al.*, 2020 | ✓ | ✓ | X | ? | Yes | ? | Yes | Patient history + TSPOT.TB + QFT-GIT + LDCT chest |
| Tannus Silva *et al.*, 2012 | ✓ | ✓ | ? | ? | Yes | ? | Yes | Patient history + TST ± IGRA ± hi-res CT chest |
| Saidenberg-Kermanac'h *et al.*, 2012 | ✓ | ✓ | ? | ? | Yes | Yes | Yes | Patient history + CXR + TST ± IGRA ± CT |

Interferon-gamma release assays (IGRA) are available commercially as Quantiferon-TB (Gold In tube, QFT-GIT and Gold Plus, QFT-Plus; Qiagen, Hilden, Germany) and T.Spot TB (Oxford Immunotec, Abington, UK).
✓, Low risk; X, high risk; ?, unclear; TST, tuberculin skin test; IGRA, *M. tuberculosis*-specific interferon-gamma release assay; CXR, chest radiography; CT, computed tomography; hi-res, high resolution; LDCT, low dose CT.

or the development of active TB as the reference standard except for Maeda *et al.*,[32] who used CT as the reference standard. As CT is not 100% sensitive,[42] this study[32] may have classified TB disease incorrectly, potentially resulting in inaccurate findings. The other studies demonstrated great variation in the accuracy of TST, IGRA, and CR for LTBI diagnosis. Due to the retrospective nature of half of the studies reviewed, selection bias cannot be excluded as CT was generally carried out on individuals with a higher risk of having the disease.

Many CT examinations in the review were interpreted by only one radiologist; however, CT as part of a protocol is prone to reader variability, as highlighted by Yoshiyama *et al.*[35] They re-evaluated previous CT findings in 205 contacts, which revealed four contacts who had been judged as having LTBI initially but were later judged as having active TB at re-evaluation. Allwood *et al.* identified that low inter-reader agreement often limits subjective radiological evaluation.[34] Given the low sensitivity and specificity of CT in some studies, consideration should be given to the interpretation process of CT examinations. Six of the included studies blinded the assessors to the results of other tests[8,21,24,33,34,39] (Electronic Supplementary Material Table S1), which may have disadvantaged them compared to standard practice where they are presented with all of the clinical information to make a report. Seven of the studies did not provide any detail on the blinding of assessors.[6,22,25,32,37,40,41]

**Table 3**
Typical computed tomography (CT) appearances suggestive of latent tuberculosis (TB) infection.

| CT appearances suggestive of latent TB |
|---|
| Granuloma |
| Calcified lymph nodes |
| Stable fibronodular changes |
| Fibrotic scarring |
| Calcified nodules in the apical and upper regions |
| Pleural thickening |

It was also apparent that radiographic appearances suggestive of LTBI differed between studies (Electronic Supplementary Material Table S1). CT appearances depend on the stage of TB described, with LTBI often detected by another diagnostic method but confirmed by the absence of radiological features indicative of active disease.[8,35,41] Calcified granulomas or lymph nodes indicate LTBI when they are the only radiographic findings. Inactive TB appears radiographically as stable fibronodular changes, scarring, and nodular opacities in apical and upper lung regions.[3,24] Broadly the literature defined LTBI as a blanket term without differentiating latent and inactive TB. Variations in radiographic appearances and reader variability are important to consider as this could modify the accuracy of CT causing a conflation of CT findings for the diagnosis of LTBI.

The Centres for Disease Control and Prevention have recommended that all healthcare workers have baseline TB screening[43] and those with known exposure or with

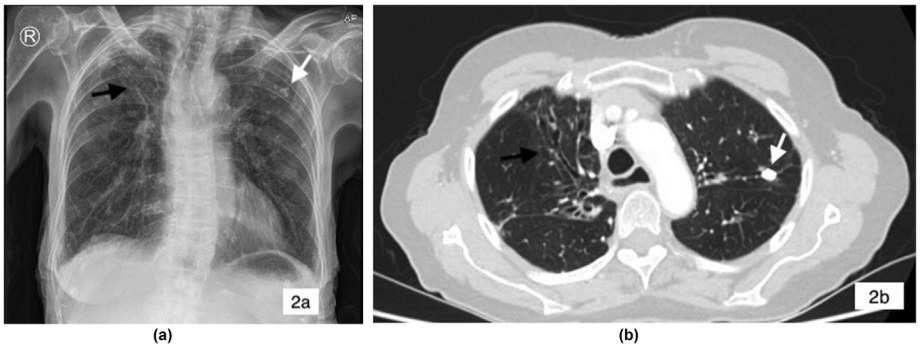


**Figure 2** Plain radiographic and CT features of LTBI. (a) Chest radiograph shows right apical fibrotic scarring, fibronodular change, and volume loss, with questionable upper lobe bronchiectasis (black arrow). There are left upper lobe granulomata (white arrows). (b) Conventional-dose chest CT more clearly demonstrates volume loss in the right upper lobe with cicatricial bronchiectasis (black arrow). Calcified granulomata are seen more clearly in the left upper lobe.

evidence of ongoing TB transmission should undergo serial TB screening.[43] TB granuloma is the greatest indicator of primary and post-primary TB.[44] An indication of progression to active disease is the progression of parenchymal abnormalities on follow-up.[25] Individuals who have been in contact with active TB within 2 years are considered high-risk for the progression from LTBI to active TB[12,39]; however, in six of the studies it was either unclear or participants were not followed up for 2 years.[8,24,25,36,40,41] The stability of imaging findings in a screening protocol is a key consideration, highlighting the benefit of serial CT. Yoon *et al.* observed radiological changes in their repeated LDCTs. Healthcare workers are at high risk of TB,[45] He *et al.* recommended annual LDCT examinations screening healthcare workers working in TB specialist hospitals.[24]

CT has superior sensitivity to CR for detecting minimal changes in lung diseases and helps differentiate active and inactive TB disease.[24,46–48] As far back as 1996, Lee *et al.* demonstrated that CT can effectively detect and determine disease activity in 80% of those with active TB and 89% of those with LTBI.[47] This review revealed many CT lesions associated with past TB that were not identified on CR.[6,8,21,22,34,35,39,48,49] Uzorka *et al.* identified lesions on CT in 70% of participants compared to 22.7% revealed by CR.[6] Using only CT, Maeda *et al.* classified past infection and non-infection in a group of rheumatic patients.[32] The addition of CT increases the sensitivity and specificity of TB detection and is a useful additional imaging method for the study of LTBI.[24,25] No diagnostic test used to diagnose LTBI is 100% sensitive, but sensitivity improves significantly with CT used as part of a screening protocol.[35] Despite these findings, CT is not routinely recommended in international guidelines due to the associated radiation doses.

Radiation doses in CT can be significantly reduced with LDCT or ULDCT, and although LDCT/ULDCT are used to enable the detection of subtle lung disease in common practice they are not ubiquitous. Traditionally, there is a lack of definition between LDCT and ULDCT, which is compounded in this review due to a lack of detail on image acquisition parameters and radiation doses. LDCT or ULDCT can significantly reduce doses compared to conventional-dose CT and, if shown to have equal diagnostic accuracy, could be used for the screening of LTBI. Three of the included studies demonstrated promising results using LDCT to screen for LTBI[24,25,40] despite some lacking detail for reproducible protocols. LDCT/ULDCT appearances suggestive of LTBI

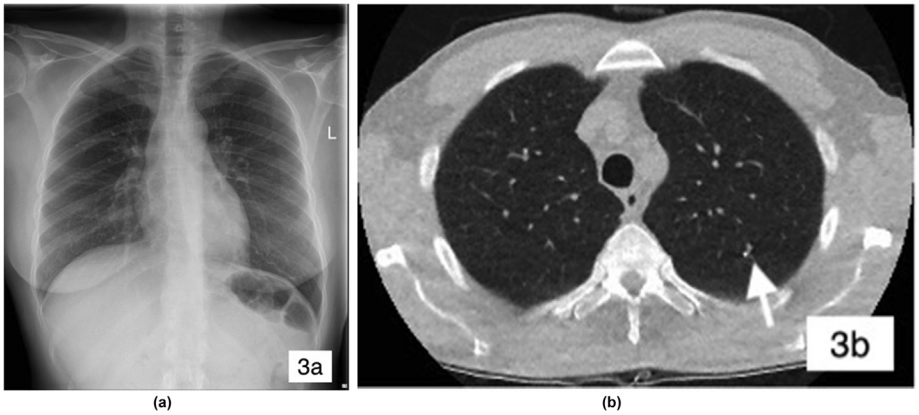


**Figure 3** LDCT has increased sensitivity for calcified granulomata. This is a non-specific finding but can be useful in the correct clinical context. (a) Normal chest radiograph|. Calcified granuloma not seen. (b) Unenhanced LDCT of the chest (DLP 6.0 mGy.cm) shows a tiny 1 mm left upper lobe calcified granuloma (white arrow).

identified in corroboration with other screening methods should be implemented to provide an appropriate diagnosis with minimal risk of disease progression.

Like all of the other diagnostic tests used for diagnosing LTBI, CT has suboptimal sensitivity and may fail to identify all patients at risk of reactivation; however, it remains superior to a CR for identifying possible subclinical or latent disease, in order to appropriately refer patients for suitable microbiologic testing. Given its increased sensitivity, the introduction of CT, in particular LDCT, should be considered as a supplementary screening method instead of CR with the possibility of increased sensitivity for the detection of LTBI disease in patients with a positive immunological test, in particular in patients where the prior probability of asymptomatic TB disease is higher.

In conclusion, given the absence of a reference standard, CT is a corroborative method for diagnosing LTBI. CT will detect many lesions that may be due to LTBI and should be used as part of the diagnostic work-up in high-risk patients with positive immunological tests in advance of commencing immunosuppressive therapies.

As the sensitivity of CT is much greater than CR, the efficacy of LDCT needs to be considered. This work demonstrates the need for a high-quality prospective clinical trial comparing LDCT/ULDCT to CR to determine its accuracy and associated radiation doses in high-risk individuals. With the recommendation for CT comes the necessity to balance true treatment, overtreatment, and harm of radiation, and further work should investigate this. CT is often considered financially expensive; however, the findings from CT often avoid costly hospital stays or interventional surgeries, both of which increase the risks of iatrogenic errors.[50] Given the differing opinions in relation to cost effectiveness between three of the studies,[21,24,34] cost and risk versus effectiveness also should be monitored and reviewed.[51]

## Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Niamh Moore reports was provided by University College Cork.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2023.04.014.

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