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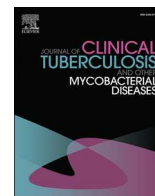
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Abnormalities suggestive of latent tuberculosis infection on chest radiography; how specific are they?



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ABSTRACT

Background: Several radiological features have been reported in association with latent tuberculosis infection (LTBI) but it has not been studied which are specific. The aim of this study was to evaluate allegedly characteristic abnormalities on chest radiography (CXR) in patients with LTBI compared to uninfected controls.

Methods: From 236 patients tested with QuantiFERON-TB Gold In-Tube (QFT), the CXR was re-evaluated in a blinded fashion for fibrotic scarring, (non-)calcified nodules and pleural thickening. LTBI was defined as presence of a positive QFT result and/or positive tuberculin skin test result stratified by Bacille Calmette-Guérin-vaccination status.

Results: Any predefined abnormality of LTBI was observed in 116/236 (49.2%) patients, the frequency not being different between groups. However, the specificity for LTBI of a fibrotic scar ≥ 2 cm² was 100% [95% CI: 92.0%–100%] and of a calcified nodule ≥ 1.5 mm was 95.7% [95% CI: 85.2%–99.5%]. The frequency of non-calcified nodules and pleural thickening did not differ between groups.

Conclusion: Only a fibrotic scar ≥ 2 cm² and/or a calcified nodule ≥ 1.5 mm were significantly associated with LTBI. This finding is clinically relevant mainly in patients who are at significant risk of TB reactivation and in whom indirect diagnostic tests may be unreliable.

1. Introduction

Adequate screening for latent tuberculosis (TB) infection (LTBI) has become increasingly important in low TB-endemic countries such as The Netherlands, particularly due to a growing number of immigrants coming from high TB-endemic countries [1] and increasing use of immunosuppressive therapies [2]. For the diagnosis of LTBI the World Health Organisation (WHO) recommends using either the tuberculin skin test (TST) or interferon-gamma release assays (IGRA). In case of a positive TST or IGRA (either QuantiFERON Gold[®] or T-SPOT.TB[®] test) result, chest radiography (CXR) is indicated to evaluate for possible signs of active (subclinical) TB, followed by initiation of treatment for LTBI [3]. According to the Dutch national guideline regarding screening for LTBI before initiating immunosuppressive therapy, a CXR is always indicated regardless of immunological results [4]. From the literature it

is known that certain allegedly characteristic abnormalities on CXR, such as (calcified) nodule(s), pleural thickening and/or fibrotic lesions, may be present in case of a prior *Mycobacterium tuberculosis* (*Mtb*) infection [5, 6]. Thus, the CXR could have additional value for LTBI screening. However, there are no validated criteria for interpretation of such abnormal findings on a CXR.

Both TST and IGRA, being dependent on the patient's immune system, can be false negative or indeterminate in patients with chronic diseases and/or immunosuppressed individuals [7, 8]. An advantage of the CXR is that abnormalities due to past infection are independent of the immune status. In previous studies, the prevalence of any of the mentioned radiological signs in individuals with LTBI ranged from 6.1% in a low TB-endemic area to 63.0% in a high TB-endemic area [9, 10], suggesting that repeated infections and/or higher infection burden may be associated with more detectable radiological lesions. Specific

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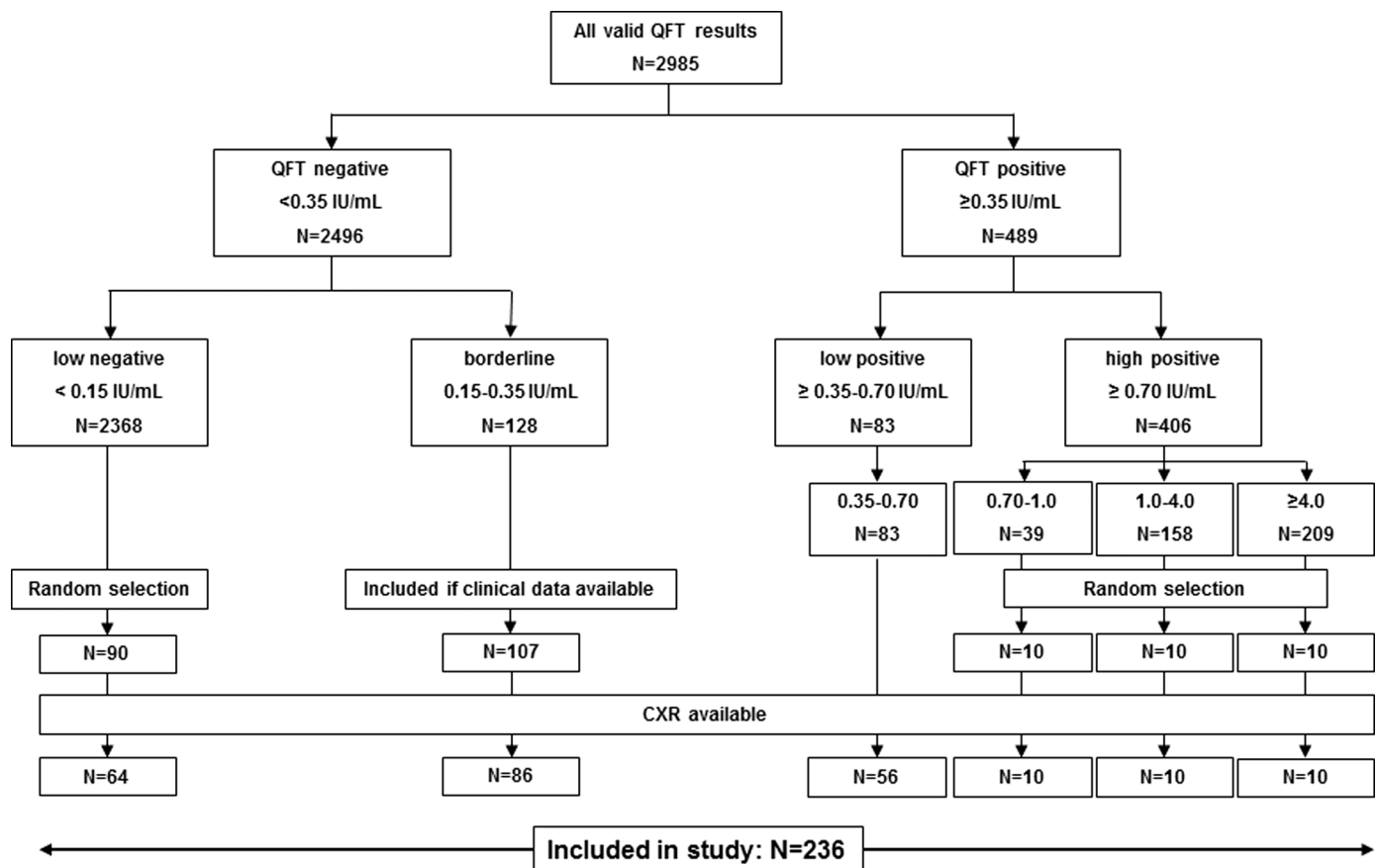


Fig. 1. Overview of all included patients

NOTE. The selection of patients is described in detail in a previous publication [15].

Abbreviations: QFT: QuantiFERON-TB Gold In-Tube; CXR: chest radiography.

radiological signs such as non-calcified nodules and fibrotic lesions have been associated with a high risk of progression to active TB [5, 11, 12]. Most studies that assessed radiological signs of LTBI, however, lacked a control group of uninfected individuals. Three studies that did include a control group only referred to 'radiological abnormalities' but did not describe which lesions were assessed, nor were the radiologists blinded to the infection status of the study participants [11, 13, 14]. Thus, all past studies had a high risk of bias.

The aims of the present study were to assess the sensitivity and specificity of abnormalities previously reported as being suggestive for LTBI on CXR in individuals with or without LTBI. LTBI diagnosis was based on a positive QuantiFERON TB Gold In-tube® (QFT) and/or TST. The radiological assessment was performed in a blinded fashion, in the sense that the reader was blinded to the QFT and TST results and the diagnosis.

2. Methods

2.1. Setting

All CXRs were performed at either Leiden University Medical Center (LUMC), which is a tertiary care teaching hospital, the occupational health service (OHS) or at the regional municipal health service (MHS). The protocol of this retrospective observational study using anonymised data was evaluated by the Medical Ethics Committee of LUMC and waived from the requirement of informed consent (protocol G16.105).

2.2. Study design

Data were retrieved between October 2016 and June 2018.

Collected data included demographics, immigration status, Bacille Calmette-Guérin (BCG)-vaccination status, and, if available, relevant comorbidities, risk factors, reported TB contact, past TB, QFT results, TST results if available and microbiological results.

2.3. Study participants

The study population has been previously described in a study which was focused on evaluation of QFT results near the cut-off [15]. The study population consists of 90 randomly selected individuals with a low-negative QFT result (< 0.15 IU/ml), 107 subjects with a borderline (0.15–0.35 IU/ml), 83 with a low positive (0.35–0.70 IU/ml) and a random selection of 30 patients with a high-positive (≥ 0.70 IU/ml) QFT result. Excluded were individuals < 18 years old and those in whom no CXR had been performed. A flow diagram of the study population is shown in Fig. 1.

2.4. Classification criteria for LTBI

Patients were considered *Mtb* infected in case of a positive QFT result (≥ 0.35 IU/ml) and/or positive TST, defined as induration ≥ 15 mm irrespective of BCG-vaccination status or ≥ 10 mm in BCG unvaccinated individuals or those vaccinated up to one year of age. *Mtb* infection was considered possible in case of a borderline QFT result (0.15–0.35 IU/ml) in association with a negative TST result, if performed, or with no TST performed. In a separate analysis, the criteria for LTBI were broadened to include immunological proof and/or all available evidence for an infection with *Mtb* including history and microbiological results.

Table 1
Characteristics of the study population.

Characteristics	Leiden University Medical Center N = 179	Municipal or occupational health services N = 57	All N = 236	p value
Age (y)	51.7 ± 19.4	39.7 ± 14.0	48.8 ± 18.9	< 0.001
Sex (male)	87/179 (48.6%)	24/57 (42.1%)	111/236 (47.0%)	0.39
Immigrant	79/179 (44.1%)	33/57 (57.9%)	112/236 (47.5%)	0.07
Sub-Saharan Africa	11/79 (13.9%)	6/33 (18.2%)	17/112 (15.2%)	
North Africa	14/79 (17.7%)	4/33 (12.1%)	18/112 (16.1%)	
Asia/Indonesia	35/79 (44.3%)	8/33 (24.2%)	43/112 (38.4%)	
Middle and S. America	10/79 (12.7%)	1/33 (3.0%)	11/112 (9.8%)	
Eastern-Europe/Russia	1/79 (1.3%)	0/33 (0%)	1/112 (0.9%)	
Other	8/79 (10.1%)	14/33 (42.4%)	22/112 (19.6%)	
Originating from a high TB-endemic country ^a	43/179 (24.0%)	11/57 (19.3%)	54/236 (22.9%)	0.46
Travel to TB-endemic country	65/159 (40.9%)	25/50 (50.0%)	90/209 (43.1%)	0.26
Reported past active TB treated	5/179 (2.8%)	0/57 (0%)	5/236 (2.1%)	0.34
Reported contact with active TB	4/5 (80.0%)	0/0 (0%)	4/5 (80.0%)	
Professional risk	26/179 (14.5%)	38/57 (66.7%)	64/236 (27.1%)	< 0.001
Immunocompromised	32/179 (17.9%)	13/57 (22.8%)	45/236 (19.1%)	0.41
BCG-vaccinated	54/179 (30.2%)	1/57 (1.8%)	55/236 (23.3%)	< 0.001
TST performed	73/179 (40.8%)	37/57 (64.9%)	110/236 (46.6%)	0.001
TST ≥ 10 mm	87/179 (61.7%)	54/57 (94.7%)	141/236 (59.7%)	< 0.001
QFT-GIT	53/87 (60.9%)	47/54 (87.0%)	100/141 (70.9%)	< 0.001
< 0.15 IU/ml	52/179 (29.1%)	12/57 (21.1%)	64/236 (27.1%)	0.41
0.15–0.35 IU/ml	63/179 (35.2%)	20/57 (35.1%)	83/236 (35.2%)	
≥ 0.35 IU/ml	64/179 (35.8%)	25/57 (43.9%)	89/236 (37.7%)	
LTBI (based on TST & IGRA ^b)				0.006
No	42/179 (23.5%)	4/57 (7.0%)	46/236 (19.5%)	
Possible	52/179 (29.1%)	3/57 (5.3%)	55/236 (23.3%)	
Yes	85/179 (47.5%)	50/57 (87.7%)	135/236 (57.2%)	
Any prespecified abnormality on CXR	96/179 (53.6%)	20/57 (35.1%)	116/236 (49.2%)	0.015

Continuous variables are displayed as mean ± SD, categorical values are displayed as numerator over denominator (%).

Abbreviations: TB: tuberculosis; BCG: Bacille Calmette-Guérin; TST: tuberculin skin test; QFT-GIT: QuantiFERON-TB Gold In-Tube; LTBI: latent tuberculosis infection; IGRA: interferon-gamma release assays; CXR: chest radiography.

^a Defined as country with TB incidence ≥ 50 cases of active tuberculosis/100,000 inhabitants.

^b As explained in the methods.

2.5. Radiography

Because the routine evaluation of the CXR investigations had often not primarily been focused on identification of characteristics of possible LTBI, all CXR were re-assessed by an expert thoracic radiologist (LK, who has > 20 years of experience in CXR evaluation). The radiologist was blinded to all data except for age and clinical history of lung diseases, and thus unaware of QFT and TST results and final clinical diagnosis. All CXRs, both posteroanterior and lateral, were evaluated for signs compatible with prior TB, being fibrous scarring (including size and presence of volume loss), pleural thickening, calcified nodules (including calcified lymph nodes) with size and number, and non-calcified nodules. STROBE guidelines for reporting observational studies were followed [16].

2.6. Statistical analysis

Differences between categorical data were evaluated with chi square tests or Fisher's Exact Probability Test if appropriate. Sensitivity and specificity of abnormalities considered suggestive for LTBI on CXR were calculated. Continuous data were compared between groups using one-way ANOVA or nonparametrically with Mann-Whitney U or Kruskal-Wallis test as appropriate. Using two-sided testing, differences were considered significant at $p < 0.05$. Statistical analysis was performed using IBM SPSS Statistics version 23 and GraphPad Prism 7.

3. Results

3.1. Study population

Of 293 selected patients, no CXR was available for 57 individuals. In

the remaining 236 the CXR was reassessed. The characteristics of all 236 included individuals are shown in Table 1. Roughly 75% originated from the hospital setting, the remaining 25% from the MHS/OHS. Patients from the hospital setting were significantly older, more often immunocompromised and had a higher frequency of TB-related abnormalities on CXR. Patients from the MHS/OHS were more frequently BCG vaccinated, TST positive and more often reported TB contact. The proportion of patients with LTBI was significantly higher in those originating from the MHS/OHS.

3.2. Comparison between patients with LTBI and uninfected individuals

Patients classified as having LTBI were compared to those with possible LTBI (as based on only a borderline QFT result) and to those considered uninfected (Table 2). Any prespecified abnormality on CXR was observed in 116/236 (49.2%) of all included persons, in similar frequencies among patients with LTBI, possible LTBI or no LTBI. Pleural thickening was the most prevalent abnormality (24.2%), but not different between groups. Fibrotic scarring, both with and without volume loss was even significantly more often observed in individuals without LTBI. However, a fibrotic scar ≥ 2 cm² was observed in 27 patients, all of whom were diagnosed with LTBI or possible LTBI ($p = 0.003$). At least one calcified nodule ≥ 1.5 mm was observed in 25 patients, of whom 23 (92.0% [95% CI: 74%–99%]) were diagnosed with LTBI or possible LTBI ($p = 0.002$). Examples of a fibrotic scar ≥ 2 cm² without and with a calcified nodule ≥ 1.5 mm are shown in Figs. 2 and 3, respectively. Both features were very specific but not sensitive for LTBI (Table 3). Thus, positive findings were informative but absence of such lesions does not exclude LTBI. Four individuals had both a fibrotic scar ≥ 2 cm² and a calcified nodule ≥ 1.5 mm, all of whom were diagnosed with either LTBI or possible LTBI. The frequency of non-calcified

Table 2
Radiological characteristics stratified by *Mtb* infection status.

Characteristics	No LTBI N = 46	Possible LTBI (borderline QFT only) N = 55	LTBI N = 135	All N = 236	p value
Age (y)	49.0 ± 19.7	51.0 ± 21.2	47.8 ± 17.7	48.8 ± 18.9	0.55
Sex (male)	25/46 (54.3%)	31/55 (56.4%)	55/135 (40.7%)	111/236 (47.0%)	0.08
Immigrant	13/46 (28.3%)	24/55 (43.6%)	75/135 (55.6%)	112/236 (47.5%)	0.005
BCG	13/46 (28.3%)	22/55 (40.0%)	75/135 (55.6%)	110/236 (46.6%)	0.003
Immunocompromised	11/46 (23.9%)	15/55 (27.3%)	29/135 (21.5%)	55/236 (23.3%)	0.69
Reported past active TB treated	1/46 (2.2%)	2/55 (3.6%)	2/135 (1.5%)	5/236 (2.1%)	0.70
Reported contact with active TB	0/1 (0%)	2/2 (100%)	2/2 (100%)	4/5 (80%)	
Reported pulmonary diseases nonTB	6/46 (13.0%)	11/55 (20.0%)	47/135 (34.8%)	64/236 (27.1%)	0.007
Past pulmonary diseases nonTB	13/43 (30.2%)	6/26 (18.8%)	11/56 (19.6%)	30/131 (22.9%)	0.38
COPD/emphysema	0/13 (0%)	0/6 (0%)	4/11 (36.4%)	4/30 (13.3%)	
pneumonia nonTB	6/13 (46.2%)	3/6 (50.0%)	5/11 (45.5%)	14/30 (46.7%)	
other	7/13 (53.8%)	3/6 (50.0%)	2/11 (18.2%)	12/30 (40.0%)	
Prespecified signs of latent TB on CXR	28/46 (60.9%)	23/55 (41.8%)	65/135 (48.1%)	116/236 (49.2%)	0.15
Fibrotic scar any size	13/46 (28.3%)	15/55 (27.3%)	19/135 (14.1%)	47/236 (19.9%)	0.034
Fibrotic scar ≥ 2 cm ²	0/44 (0%)	12/54 (22.2%)	15/135 (11.1%)	27/233 (11.6%) ^a	0.003
Fibrotic scar any size with volume loss	11/46 (23.9%)	9/55 (16.4%)	13/135 (9.6%)	33/236 (14.0%)	0.046
Calcified nodules	8/46 (17.4%)	9/55 (16.4%)	18/135 (13.3%)	35/236 (14.8%)	0.75
Size of largest nodule					0.053
< 1.5 mm	6/8 (75.0%)	0/9 (0%)	4/18 (22.2%)	10/35 (28.6%)	
≥ 1.5 mm	2/8 (25.0%)	9/9 (100%)	14/18 (77.8%)	25/35 (71.4%)	0.002
1.5–3 mm	1/8 (12.5%)	4/9 (44.4%)	6/18 (33.3%)	11/35 (31.4%)	
3–10 mm	1/8 (12.5%)	4/9 (44.4%)	6/18 (33.3%)	11/35 (31.4%)	
≥ 10 mm	0/8 (0%)	1/9 (11.1%)	2/18 (11.1%)	3/35 (8.6%)	
Number					0.72
1	5/8 (62.5%)	5/9 (55.6%)	11/18 (61.1%)	21/35 (60.0%)	
2–5	2/8 (25.0%)	4/9 (44.4%)	4/18 (22.2%)	10/35 (28.6%)	
> 5	1/8 (12.5%)	0/9 (0%)	3/18 (16.7%)	4/35 (11.4%)	
Non-calcified nodule	3/46 (6.5%)	2/55 (3.6%)	10/135 (7.4%)	15/236 (6.4%)	0.71
Pleural thickening	12/46 (26.1%)	8/55 (14.5%)	37/135 (27.4%)	57/236 (24.2%)	0.16

Continuous variables are displayed as mean ± SD, categorical values are displayed as numerator over denominator (%).

Abbreviations: LTBI: latent tuberculosis infection; QFT: QuantiFERON-TB Gold In-Tube; BCG: Bacille Calmette-Guérin; TB: tuberculosis; COPD: chronic obstructive pulmonary disease.

^a The size of the fibrotic scar could not be assessed reliably in three cases due to other acute pathology (N = 2) or pre-existent familial pulmonary fibrosis (N = 1).

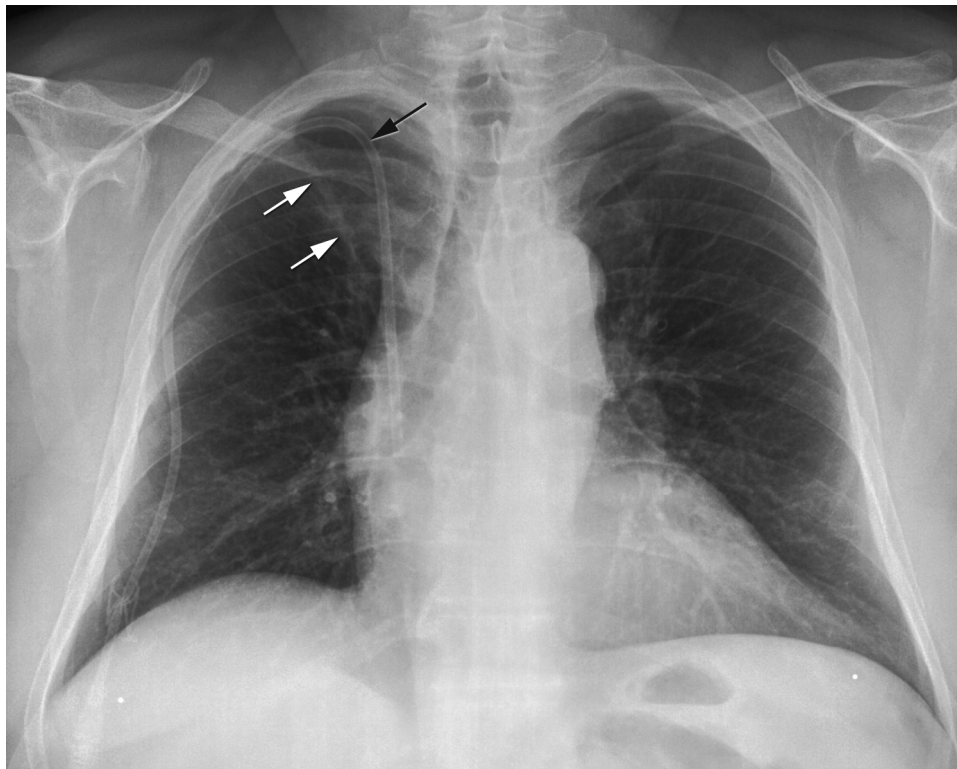


Fig. 2. Fibrotic scar ≥ 2 cm²
Posteroanterior chest X-ray of a 52-year old Turkish man with diabetes mellitus and on hemodialysis. Central line in dialysis patient (black arrow). Fibrotic scar larger than 2 cm² in the right upper lobe (white arrows).

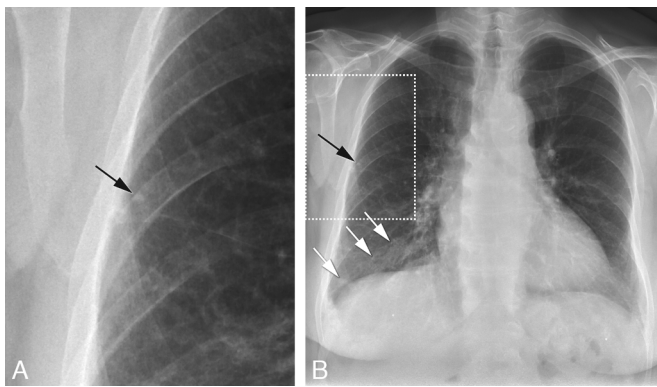


Fig. 3. Fibrotic scar $\geq 2 \text{ cm}^2$ with a calcified nodule $\geq 1.5 \text{ mm}$ 78-year old female with diabetes mellitus and auto-immune disease on immunosuppression. Zoomed-in part (a) of posteroanterior chest X-ray (b) showing small 3 mm sized calcified nodule (black arrow in a, b). Fibrotic scar larger than 2 cm^2 in the right lower lobe (white arrows, b).

nodules did not differ between groups. If the criteria for LTBI were broadened including microbiological results and a positive history of latent or active TB, the results were not different.

3.3. Assessment by QFT or TST result

Individuals were also compared by QFT and TST result (Tables S1 and S2). Patients with a positive, borderline or negative QFT result were similar with regard to the presence of most abnormalities on CXR, except for a fibrotic scar $\geq 2 \text{ cm}^2$ which was more often observed in patients with a borderline or positive QFT result ($p = 0.01$). If one or more calcified nodules were present ($N = 35$), then presence of a calcified nodule $\geq 1.5 \text{ mm}$ was strongly associated with a borderline or positive QFT result ($p = 0.008$). No significant differences in radiological abnormalities were observed between individuals with a positive or negative TST result.

4. Discussion

In this study, 236 CXRs of patients in whom a QFT had been performed for various reasons were re-evaluated for prespecified lesions by a radiologist who was unaware of corresponding IGRA and TST result and final clinical diagnosis. Presence of a fibrotic scar $\geq 2 \text{ cm}^2$ and/or a calcified nodule $\geq 1.5 \text{ mm}$ were specific for LTBI or possible LTBI. In our study, all other abnormalities on CXR that have previously been reported to be characteristic of LTBI occurred in similar frequencies in patients with or without LTBI.

Table 3
Specific findings associated with latent tuberculosis infection.

	LTBI or possible LTBI N = 189	No LTBI N = 44	
Fibrotic scar $\geq 2 \text{ cm}^2$	27	0	Positive predictive value: 100% Negative predictive value: 21.4% (95% CI: 20.4%–22.4%)
No fibrotic scar $\geq 2 \text{ cm}^2$	162	44	
	Sensitivity: 14.3% (95% CI: 9.6%–20.1%)		Specificity: 100% (95% CI: 92.0%–100%)
	LTBI or possible LTBI N = 190	No LTBI N = 46	
Calcified nodule $\geq 1.5 \text{ mm}$	23	2 ^a	Positive predictive value: 92.0% (95% CI: 73.8%–97.9%) Negative predictive value: 20.9% (95% CI: 19.6%–22.2%)
No calcified nodule $\geq 1.5 \text{ mm}$	167	44	
	sensitivity: 12.1% (95% CI: 7.8%–17.6%)		specificity: 95.7% (95% CI: 85.2%–99.5%)

Abbreviations: LTBI: latent tuberculosis infection; CI: confidence interval.

^a In both cases no tuberculin skin test had been performed.

It is plausible that a fibrotic scar $\geq 2 \text{ cm}^2$ and/or a calcified nodule $\geq 1.5 \text{ mm}$ on CXR were specific for LTBI because these lesions reflect the result of the *Mtb*-host interaction during infection in the lung. After inhalation, *Mtb* is phagocytosed by alveolar macrophages. At the site of infection, a granuloma is formed through interaction between infected macrophages, neutrophils, B cells and T cells [17]. In case of a non-progressor, the immune response will contain bacillary growth, which eventually can result in the development of fibrotic tissue in or around the granuloma [18, 19]. This fibrotic tissue is sometimes visible on CXR and can be (partly) calcified. The size of granulomas varies depending on the extent of granulomatous inflammatory response before the containment is achieved. A calcified granuloma at the initial place of infection in the lung is named a Ghon focus, while this lesion in combination with an ipsilateral calcified hilar node is named a Ranke complex [17, 19]. Nevertheless, both a fibrotic scar and a calcified nodule have an extensive differential diagnosis, and may be present in e.g. granulomatous diseases such as sarcoidosis, bacterial or other pulmonary infections or interstitial lung diseases [12], and/or occupational lung diseases such as silicosis or pneumoconiosis, or may represent metastasis [19].

Although not pathognomonic, our data suggest that a fibrotic scar and/or a calcified nodule in combination with an increased *a priori* risk, e.g. due to *Mtb*-exposure or history of TB or LTBI, is highly suggestive of TB infection. This finding can be of added value in patients in whom it is important not to miss LTBI because of a very high risk of TB re-activation and in whom the TST and IGRA may be unreliable as a result of an impaired immune status. Only two previous studies evaluated the difference between a fibrotic scar larger or smaller than 2 cm^2 , but both lacked uninfected controls. In the first study among TST positive healthcare workers, a fibrotic scar $\geq 2 \text{ cm}^2$ was associated with a positive QFT [10]. In the second study among TST positive untreated individuals, it was associated with a higher risk of development of active TB [20]. To our knowledge, our study is the first to identify calcified nodules or calcified nodules $\geq 1.5 \text{ mm}$ as being specific for LTBI.

Roughly 50% of all included patients in our study had any pre-specified abnormality on CXR considered previously associated with LTBI. Previous studies specifically aimed at assessing radiological abnormalities in individuals with or without LTBI reported a prevalence of any suggestive lesion between 4.1% and 67.9% [9, 10, 21–24]. This large range was probably related to the setting and the type of lesions that were assessed in these studies. In our cohort, the prevalence of certain radiological abnormalities was higher than reported in the literature, with the exception of calcified nodules. Five previous studies assessed the frequency of predefined abnormalities on CXR [9, 10, 22, 24, 25]. In these studies, the prevalence of fibrotic scarring, calcified nodules, non-calcified nodules, and pleural thickening varied from 0% to 3.0%, 1.8% to 59.8%, 0% to 3.0%, and 0.3% to 2.7%, respectively.

However, none of these studies included uninfected controls, precluding conclusions with regard to the specificity of these lesions. The differences in the prevalence rates for each abnormality between our study and earlier literature could be caused by several characteristics of our study population and the method of assessment. Firstly, nearly 20% of all patients in our study had a history of pulmonary disease, even more in the group without LTBI, which could account for various non-TB related lesions on CXR that look similar to those due to past *Mtb* infection. Secondly, except for one study [25], earlier literature described a population that consisted of asymptomatic patients screened for occupational purposes, whereas patients in our study were screened for different reasons such as possible active TB, or detecting LTBI in case of eligibility for immunosuppressive therapy. Finally, the mean age of our population was at least 10 years higher than that of patients in previous studies, resulting in a higher chance of having other unreported pulmonary conditions reflected in various lesions on CXR.

That the frequency of most predefined lesions on the CXR in individuals with and without LTBI was similar is in line with the results of several previous studies [13, 26–30], most of which specified the lesions considered suggestive for LTBI [13, 26, 27, 29, 30], although only one was specifically aimed at finding abnormalities on CXR [13], and the radiologist was blinded in only two studies [27, 30]. In other studies, however, predefined lesions considered suggestive for LTBI were observed significantly more frequently in patients with LTBI than in uninfected controls [11, 23, 27, 29, 31]. The assessment by the radiologist was blinded in four of these studies [11, 23, 27, 31]. However, only one study was specifically aimed to find LTBI-related abnormalities on CXR [23]. Studies in which the radiologist is aware of immunological results prior to evaluating a CXR are subject to potential observer bias, as a radiologist can be more inclined to register minor abnormalities in patients with a positive TST or IGRA result. The strength of our study was that the radiologist was blinded to all immunological results and final clinical diagnosis. The lack of a second observer was a limitation, but a previous study demonstrated high inter-observer agreement between radiologists [10].

Another limitation of our study was that the study population included a disproportionately large number of individuals with a QFT result around the cut-off (0.15–0.70 IU/ml) and only a limited number of patients with a high positive QFT, as participants had been selected with the focus on borderline QFT results [15]. Therefore, it would be useful to repeat our study in a population reflecting the natural distribution of QFT results. Inclusion of more patients with a high positive QFT is expected to result in more pronounced differences between groups and may reveal additional lesions specific for LTBI. Interestingly, the presence of a fibrotic scar ≥ 2 cm² and/or a calcified nodule ≥ 1.5 mm on CXR was found as often in individuals with possible LTBI (borderline QFT result with negative or no TST) as in those with LTBI. This corroborates the findings from previous studies in which it was demonstrated that most borderline QFT results reflect infection with *Mtb* as opposed to random assay variability [15, 32, 33].

In general, finding abnormalities of LTBI on a CXR can occur in three different settings. First, if a CXR is made to assess for possible active TB after a positive TST or IGRA result during screening for LTBI. Here, findings suggestive for LTBI have no added value since preventive therapy is guided by the positive immune test. A second setting is when lesions on CXR suspect for possible LTBI can be an incidental finding in patient in whom CXR is made for other purposes. If the patient is or will be at risk of TB reactivation, e.g. as a result of immunosuppressive therapy, treatment of LTBI may be indicated. The third situation, in which CXR can be of particular value, is when patients are screened for LTBI because of (planned) immunosuppression with drugs such as TNF antagonists or those used for prevention of rejection after organ transplantation, and in whom a suppressed or waned immune response can result in false negative TST or IGRA results [8, 34, 35]. Importantly, negative IGRA results include borderline QFT results and it has previously been demonstrated that the majority of individuals with a

borderline QFT are actually infected with *Mtb*, which is highly relevant if immunosuppression is planned [15, 32, 33]. A case of disseminated TB during treatment with infliximab, and who in retrospect had a borderline QFT result, illustrates that the sensitivity of screening methods in this setting can be improved [36]. Nevertheless, the CXR has suboptimal sensitivity for LTBI, even for calcified nodules [37]. In that regard, computed tomography (CT) had a higher sensitivity and a high concordance rate with IGRA results [6, 38]. Because CT findings carry the risk of more false positive results it is of utmost importance to better define which lesions on CT are specific for TB infection. Computer-aided detection of active pulmonary TB on CXR has been studied [39, 40]. Thus far this has not yet been done for detection of LTBI, but this could be considered if the highly specific lesions observed in our study can be confirmed.

5. Conclusion

In conclusion, a fibrotic scar ≥ 2 cm² and/or a calcified nodule ≥ 1.5 mm on CXR were specifically associated with prior TB infection. Finding such lesions is clinically relevant in patients who are at high risk of TB reactivation and in whom results of TST and IGRA may be false negative.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jctube.2019.01.004.

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