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► **To cite this version:**

Sébastien Bommart, Jérémy Charriot, Nicolas Nagot, Hélène Vernhet-Kovacsik, Marie Revel, et al..
Differentiating between active and latent tuberculosis with chest computed tomography. Diagnostic
and Interventional Imaging, In press, 10.1016/j.diii.2021.05.011 . hal-03274653

HAL Id: hal-03274653

<https://hal.science/hal-03274653>

Submitted on 30 Jun 2021

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Differentiating between active and latent tuberculosis with chest computed tomography

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ARTICLE INFO

Keywords:
Tuberculosis
Latent tuberculosis
Multidetector computed tomography
Interferon-gamma release tests

ABSTRACT

Purpose: The purpose of this study was to evaluate the capabilities of chest computed tomography (CT) in distinguishing between active and latent tuberculosis in patients positive for interferon-gamma release assay (IGRA) testing, and to compare the performance of CT with that of quantitative IGRA testing in a low incidence setting.

Materials and methods: Patients with latent or active tuberculosis defined by an IGRA positive test were retrospectively recruited. Sensitivity, specificity and accuracy were determined for CT variables and quantitative IGRA results. Final diagnosis of active tuberculosis was based on clinical data and microbiological culture. Univariable and multivariable analyses were performed using logistic regression model to identify CT variables associated with the diagnosis of active tuberculosis.

Results: A total of 92 patients with positive IGRA results who underwent CT examination were included. There were 54 men and 38 women with a mean age of 53.5 ± 18 (SD) years (range: 40–68 years). Of them, 22 patients (24%) had positive *Mycobacterium tuberculosis* culture and 70 (76%) had latent tuberculosis. Among CT variables, consolidation had the greatest sensitivity (77%; 95%CI: 60–95%) and “tree-in-bud” the greatest specificity (97%; 95% CI: 93–100%) for the diagnosis of active tuberculosis. At univariable analysis “tree-in-bud”, splenic calcification and non-calcified lung nodules were the significant variables independently associated with active tuberculosis. At multivariable analysis, the adjusted odds ratio of “tree-in-bud” was 42.91 (95% CI: 5.62–327.42). Using an optimal threshold of 51 spots, quantitative IGRA yielded 64% sensitivity (95% CI: 44–84%) and 61% specificity (95% CI: 50–73%) for the diagnosis of active tuberculosis.

Conclusions: In a low incidence setting, chest CT, especially when “tree-in-bud” pattern is present, is superior to quantitative IGRA testing to identify patients with active tuberculosis among those with positive IGRA testing.

Abbreviations: CI, Confidence interval; CT, Computed tomography; HR, Hazard ratio; IGRA, Interferon-gamma release assay; SD, Standard deviation; WHO, World health organization.

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1. Introduction

Although chest X-ray examination remains the only recommended imaging modality in the management of tuberculosis according to current guidelines [1], chest computed tomography (CT) can be useful for assessing differential diagnosis in symptomatic patients. Chest CT is also useful in the investigation of contact subjects of known patients with tuberculosis and in

immunocompromised patients because it is more sensitive than chest X-ray [2,3].

However, the interpretation of chest CT abnormalities in patients with a history of tuberculosis is challenging, especially when no prior CT examination is available, and accurate criteria are needed to distinguish active tuberculosis from sequelae. The question is even more complex when considering the concept of latent tuberculosis. The WHO-definition of latent tuberculosis is based on the existence of a specific immune response with an absence of clinical signs. Chest X ray is included within the “clinical signs” cited by the WHO, contrary to CT whose role remains controversial as a diagnostic tool for tuberculosis diagnosis [4].

As sputum smear microscopy is not sensitive enough, bacterial culture remains the gold standard for confirmation of *Mycobacterium tuberculosis* infection, although final results may take up to 12 weeks. During this phase, differentiating between latent and active tuberculosis infection is challenging and is likely to delay the start of specific care or lead to prolonged unnecessary airborne precautions. Although other biomarkers, such as interferon-gamma release assay (IGRA) add important information in well-identified situations such as contact with an active tuberculosis patient or before immunosuppression, positivity of IGRA testing alone is insufficient to justify specific treatment, especially in low incidence countries [5,6]. Sputum nucleic acid amplification tests are used as additional and/or alternative test when culture is not available [7,8]. Neither test provides a definitive diagnosis, but they could replace the microscopic smear as the first-line diagnostic test in areas with an intermediate tuberculosis burden. [9].

Until now, chest CT criteria is only used to describe latent and active tuberculosis [10–14]. Patterns of disease activity in tuberculosis have been highlighted and compared to tuberculosis culture but no study evaluated the diagnostic performance of chest CT to distinguish between active and latent tuberculosis in patients with a positive IGRA testing.

The purpose of this study was to evaluate the capabilities of chest CT in distinguishing between active and latent tuberculosis in patients with IGRA positive tests, and to compare the performance of CT with that of quantitative IGRA.

2. Materials and methods

2.1. Study design and population

Our institutional review board (AFSSAPS 2010-A00422-37, Sud-Méditerranée) approved this study and written informed consent was obtained from all participants. CT examinations of patients with clinically suspected chest tuberculosis and positive IGRA results who were recruited between December 2008 and October 2012 were retrospectively analyzed. Inclusion and exclusion criteria are given in Table 1. Chest CT was performed either to help chest X-ray interpretation or performed because of unspecific symptoms such as cough, fever or expectoration. Only patients with positive IGRA testing (*i.e.*, >7 spots/100000) were included. Fig. 1 describes the study flow chart of patients. Smear cultures were concomitantly initiated on three consecutive days and processed according to best standards. In some patients broncho-alveolar lavage and bronchial aspirates were also sampled and processed for tuberculosis-culture.

2.2. CT protocol

Chest CT examinations were performed with or without contrast media injection in the supine position using various multidetector CT scanners. Images were acquired in our department using a lightspeed[®] VCT unit (General Electric Healthcare) at 120 kV

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Male or female	Age < 18 years
Age > 18 years	Asymptomatic patient or no clinical information available
Clinically suspected tuberculosis ('or' should be read between each item)	
Persistent cough > 2 weeks	
Fever	
Hemoptysis	
Nocturnal sweats	
Loss of weight, anorexia	
Asthenia	
Contact with a subject definitively diagnosed with active tuberculosis	
All consecutive patients who underwent IGRA in our institution between Dec 2008 and oct 2012	IGRA test failed or below the quality control standards
Chest CT examination of acceptable quality	Incomplete chest CT examination CT image thickness > 1.25 mm or non-contiguous slices
Affiliated to the French health coverage	Not protected by law Deprived of liberty

CT indicates computed tomography. IGRA indicates Interferon-gamma release assay.

with automated tube current modulation and a maximal tube current set at 300 mA, 0.5s tube rotation; 64 × 0.6 mm collimation and 0.9 increment. Images were reconstructed with a 512 matrix, 0.625 mm and 1.25 mm reconstruction slice thicknesses using a high and standard frequency kernel. Acquisition field-of-view ranged from 320- to 380 mm depending on patient habitus.

2.3. Quantitative IGRA test

Immune reactivity to *Mycobacterium tuberculosis* was tested using the ELISA assay, T-spot tuberculosis (Oxford Immunotec Ld.) which reveals the specific interferon-gamma production in response to stimulation by specific mycobacterial proteins.

2.4. Image analysis

CT examinations were randomly assigned and read on a workstation (ADW 4.6, GE healthcare) by two readers (S.B., A.B.) with 8- and 10-year experience in chest imaging respectively, blinded to the results of IGRA and clinical data. Images were reviewed using a lung (width 1600 Hounsfield unit [HU]; center -600 HU) and a mediastinal window setting (width 440 HU; center 40 HU). The readers had to report the presence of one or more abnormalities, among the following items defined according to the Fleischner society glossary terms [15]. These included: (i), randomly distributed calcified and non-calcified nodules (nodules fulfilling intra pulmonary lymph node criteria (*i.e.*, sub pleural or perifissural location, triangular shape [<1 cm in size were not considered here]) (Fig. 2) [10]; (ii), centrilobular nodules [10,14]; (iii), branching linear opacities (“tree-in-bud” pattern) [10,14]; (iv), cavities; (v), consolidations [11,12]; (vi), localized fibrosis [10]; (vii), pleural [11] or (viii), pericardial effusions [11]; (ix), enlarged mediastinal lymph nodes (*i.e.*, > 10 mm short axis) [10]; (x), splenic [16] or (xi), hepatic calcified nodules [16]. Spatial distribution in the ten right and left segments of the Boyden classification was also determined for each sign. The two readers used a structured report including a description for each abnormality of the pre-defined list. When discordant reading was obtained, a consensus opinion was reached by the two readers during a final reading session. The results of the consensus reading were used for further analysis.

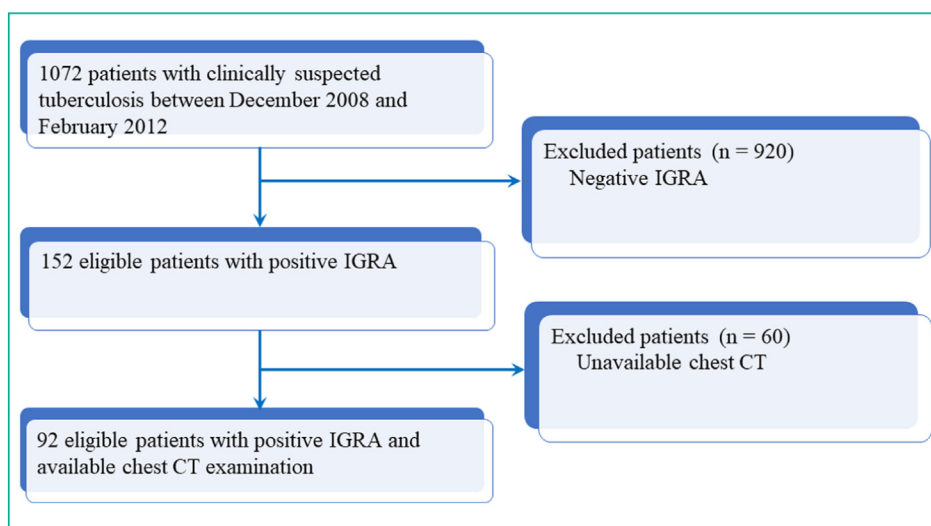


Fig. 1. Flowchart shows patient inclusion in the study. CT indicates computed tomography; IGRA indicates interferon-gamma release assay.

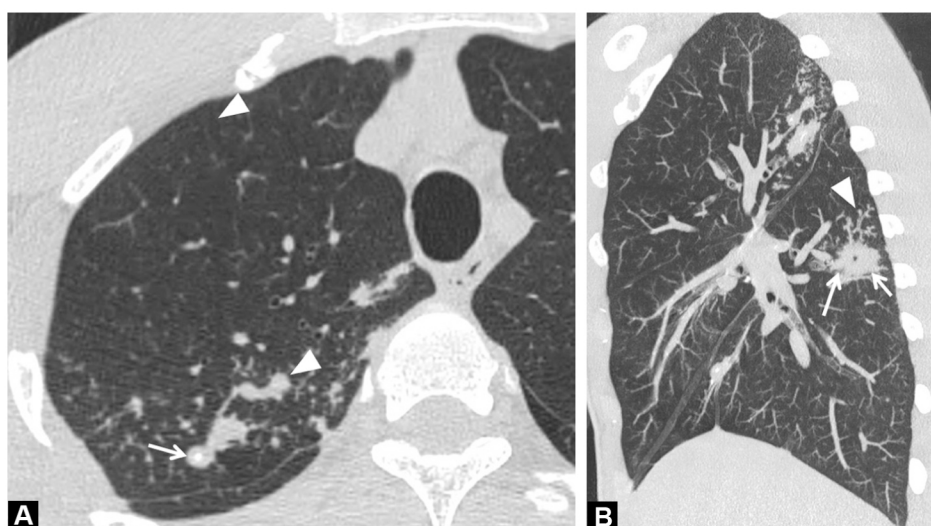


Fig. 2. 26-year-old man with active tuberculosis and positive for interferon- γ release assay (IGRA) (T spot number: 125/250 000). A, CT image of the chest in the axial plane shows calcified (arrow) and non-calcified (arrowhead) nodules in the right upper lobe. B, CT image of the chest in sagittal plane and maximum intensity projection shows a mass (arrow) with a small cavity and micronodules (arrowheads) displaying the "tree in bud" pattern.

2.5. Standard of reference

CT findings were compared to quantitative IGRA results (number of interferon- γ producing cells also called T-spot) and final diagnoses for active tuberculosis were established using clinical data and microbiological culture.

Immune reactivity to *Mycobacterium tuberculosis* (IGRA testing) was tested using the ELISA assay, T-spot tuberculosis (Oxford Immunotec Ltd.) which reveals the specific interferon- γ production in response to stimulation by specific mycobacterial proteins.

Latent tuberculosis infection was defined by an IGRA positive test and an absence of tuberculosis-culture positivity at 12 weeks after sample gathering, or absence of clinical symptoms at twelve months follow-up. Active tuberculosis infection was defined by a positive IGRA test and a positive tuberculosis culture.

2.6. Statistical analysis

All analyses were performed using SAS version 6.1 (SAS Institute). Qualitative data were reported as raw numbers, proportions

and percentages. Quadratic kappa (κ) coefficients were calculated to assess interobserver agreement between the two readers before the final consensus reading and reported with their 95% confidence intervals (CIs) [17]. The threshold of the number of T-spots to differentiate between patients with active tuberculosis and those with latent tuberculosis was determined using the Youden index. Quantitative variables in patients with active tuberculosis were compared to those in patients with latent tuberculosis using the Mann-Whitney test. The frequency and location of each CT sign in active and latent tuberculosis were compared using the Chi² test. The *P*-values were adjusted using the Holm-Bonferroni method. The corresponding sensitivities, specificities and accuracies were calculated along with their 95% CIs.

To identify CT variables associated with the diagnosis of active tuberculosis, categorical variables were entered into univariable analysis using a conditional logistic regression model. To take into account confounders, multivariable analysis was performed using a logistic regression model with forward stepwise selection of covariables and adjusted for age. Correlations between all variables were searched for. In case of a strong correlation between two variables,

Table 2
Inter-observer agreement for chest CT variables.

Variable	Observer 1	Observer 2	Kappa	95% CI
Centrilobular nodules	16 (16/92; 17.4%)	5 (5/92; 5.4%)	0.32	0.06–0.58
Tree-in-bud	11(11/92; 11.9%)	26 (26/92; 40.2%)	0.51	0.31–0.71
Cavity	8 (8/92; 8.7%)	12 (12/92; 13%)	0.66	0.41–0.91
Consolidation	37 (37/92; 40.2%)	37 (37/92; 40.2%)	0.68	0.53–0.83
Non-calcified nodule	36 (36/92; 39.1%)	35 (35/92; 38%)	0.51	0.33–0.69
Calcified nodule	40 (40/92; 43.5%)	26 (26/92; 28.3%)	0.53	0.36–0.70
Pleural effusion	14 (14/92; 15.2%)	17 (17/92; 18.5%)	0.88	0.75–1
Pericardial effusion	5 (5/92; 5.4%)	8 (8/92; 8.7%)	0.75	0.48–1
Hepatic calcified nodules	10 (10/92; 10.9%)	13 (13/92; 14.1%)	0.65	0.42–0.89
Splenic calcified nodules	5 (5/92; 5.4%)	7 (7/92; 7.6%)	0.64	0.32–0.97
Enlarged mediastinal lymph node	21 (21/92; 22.8%)	38 (38/92; 41.3%)	0.43	0.25–0.61

Data are expressed as raw numbers; numbers in parentheses are proportions followed by percentages.

Table 3
Comparison of CT findings for categorical criteria between 22 patients with active tuberculosis and 70 patients with latent tuberculosis.

Variable	Group 1Active TB (n = 22)	Group 2Latent TB (n = 70)	P value ^a
Centrilobular nodules	10 (10/22; 45%)	6 (6/70; 8.6%)	0.002
“Tree-in-bud”	9 (9/22; 40.9%)	2 (2/70; 2.9%)	0.002
Cavity	5 (5/22; 22.7%)	3 (3/70; 4.3%)	0.234
Consolidation	17 (17/22; 77.3%)	20 (20/70; 28.6%)	0.002
Non-calcified nodule	14 (14/22; 64%)	22 (22/70; 32%)	0.126
Calcified nodule	11 (11/22; 52%)	29 (29/70; 42%)	> 0.999
Pleural effusion	4 (4/22; 19%)	10 (10/70; 14%)	> 0.999
Pericardial effusion	2 (2/22; 9.5%)	3 (3/70; 4.3%)	> 0.999
Hepatic calcified nodules	1 (1/22; 4.7%)	9 (9/70; 12.8%)	> 0.999
Splenic calcified nodules	3 (3/22; 15%)	2 (2/70; 2.8%)	0.876
Enlarged mediastinal lymph node	7 (7/22; 33%)	14 (14/70; 20%)	> 0.999

TB indicates tuberculosis. Bold indicates significant *P* value. Numbers are raw numbers; numbers in parentheses are proportions followed by percentages.

^a Corresponding to the Holm adjusted *P* value.

one or other variables was included in the multivariable model. All tests were two-tailed and statistical significance was set at a *P*-value < 0.05.

Significant chest CT variables in the multivariable model were further compared between upper and lower lung segments (numbers 1, 2, 3 and 6 versus others) using the Fisher exact test.

3. Results

3.1. Patient characteristics

The final cohort study consisted of 92 patients with positive IGRA who underwent chest CT. There were 54 men and 38 women with a mean age of 53.5 ± 18 (SD) years (range: 40–68 years). Among them, 22 patients (13 men, 9 women; mean age, 40.5 ± 19 [SD] years; age range: 29–53 years) had active tuberculosis. Seventy patients (41 men, 29 women; mean age, 57.0 ± 24 [SD] years; age range: 42–70 years) were considered having latent tuberculosis infection. The diagnosis of latent tuberculosis was based on negative 12-week culture results and a 12-month negative clinical follow-up.

3.2. Description of CT patterns and quantitative IGRA in latent and active tuberculosis

Inter-observer agreement ranged from fair to almost perfect (Table 2). Kappa values obtained for centrilobular nodules was 0.32 (95% CI: 0.06–0.58) and 0.88 (95% CI: 0.75–1) for pleural effusion.

On CT, centrilobular nodules (*P* = 0.002), “tree-in-bud” pattern (*P* = 0.002) as well as consolidation (*P* = 0.002) were more frequently observed in patients with active tuberculosis than in those with latent tuberculosis. Table 3 shows the distribution of CT findings for the two groups of patients.

The sensitivity, specificity and accuracy of each CT variable for the diagnosis of active tuberculosis are reported in Table 4.

Alveolar consolidation showed greatest sensitivity for the diagnosis of active tuberculosis (77%; 17/22; 95% CI: 60–95%) followed by non-calcified lung nodules (64%; 14/22; 95% CI: 43–84%). Specificity of “tree-in-bud” for the diagnosis of active tuberculosis ranked first as well as splenic calcified nodules (97%; 68/70; 95% CI: 93–100% for both), followed by cavities (96%; 67/70; 95% CI: 0.91–1.00).

IGRA sensitivity for active tuberculosis was 64% (14/22; 95% CI: 44–84%) and specificity 61% (43/70; 95% CI: 50–73%) using an optimal threshold of 51 spots.

At multivariable logistic regression analysis (Table 5), the presence of tree-in-bud (OR, 25.5; 95% CI: 4.9–132.8) (*P* < 0.001), non-calcified nodules (OR, 3.7; 95% CI: 1.3–10) (*P* = 0.012), lymph nodes enlargement (OR, 3.66; 95% CI: 1.34–10.01) (*P* = 0.17) and splenic calcified nodules (OR, 5.9; 95% CI: 0.9–38.2) (*P* = 0.062) were independently associated with active tuberculosis. Adjusted for age, OR of tree-in-bud in the multivariate analysis was 42.91 (95% CI: 5.62–327.42).

The location of non-calcified nodules and tree-in-bud in the upper lung (segments 1, 2, 3 and 6 vs. others) did not improve the diagnosis of disease activity (*P* = 0.19 and *P* = 0.189, respectively).

4. Discussion

In this study, the performance of chest CT in discriminating between latent and active tuberculosis in a population positively screened by IGRA was investigated and then compared to the discriminative value of the quantitative IGRA. Our results show that “tree-in-bud” and non-calcified nodules on CT significantly and better diagnose active tuberculosis than quantitative IGRA.

Despite advances in health care, *Mycobacterium tuberculosis* infection remains a major public health burden, worsened in the past decade by increased levels of immunosuppression in the population and antibiotic resistance [18]. The WHO does not recommend chest CT or IGRA test to assess tuberculosis in endemic countries.

Table 4
Sensitivity, specificity and accuracy of each CT variables for the diagnosis of active tuberculosis vs. latent tuberculosis.

Variable	TN	TP	FN	FP	Sensitivity	Specificity	Accuracy
Centrilobular nodules	64	10	12	6	45 (10/22) [25–66]	91 (64/70) [85–98]	80 (74/92) [72–88]
“Tree in bud”	68	9	13	2	41 (9/22) [20–61]	97 (68/70) [93–100]	84 (77/92) [76–91]
Cavity	67	5	19	3	23 (5/22) [5–40]	96 (67/70) [91–100]	78 (72/92) [70–87]
Consolidation	50	17	5	20	77 (17/22) [60–95]	71 (50/70) [61–82]	73 (67/92) [64–82]
Non-calcified nodules	48	14	8	22	64 (14/22) [43–84]	69 (48/70) [58–79]	67 (62/92) [58–77]
Calcified nodules	41	11	11	29	50 (11/22) [29–71]	59 (41/70) [47–70]	56 (52/92) [46–66]
Pleural effusion	60	4	18	10	18 (4/22) [2–34]	0.86 (60/70) [77–94]	70 (64/92) [60–79]
Pericardial effusion	67	2	20	3	9 (2/22) [3–21]	96 (67/70) [91–100]	75 (69/92) [66–84]
Hepatic calcified nodules	61	1	21	9	4 (1/22) [4–13]	87 (61/70) [79–95]	67 (62/92) [58–77]
Splenic calcified nodules	68	3	19	2	14 (3/22) [1–28]	97 (68/70) [93–100]	77 (71/92) [69–86]
Enlarged mediastinal lymph nodes	56	7	15	14	32 (7/22) [12–51]	80 (56/70) [71–89]	68 (63/92) [59–78]

TP: true positive; FP: false positive; FN: false negative; TN: true negative. Data are expressed as raw numbers; numbers in parentheses are proportions followed by 95% exact confidence intervals in brackets.

Table 5
Multivariable analysis for chest CT signs associated with active tuberculosis.

Variable	OR [95% CI]	P value	Adjusted OR [95% CI]	P value
Centrilobular nodules	9.70 [2.93–32.11]	<0.001		
Tree-in-bud	25.50 [4.90–132.84]	<0.001	42.91 [5.62–327.42]	<0.001
Cavity	6.57 [1.43–30.24]	0.016		
Consolidation	8.50 [2.76–26.15]	<0.001		
Non-calcified nodule	3.66 [1.34–10.01]	0.012	5.16 [1.09–24.33]	0.034
Calcified nodules	1.52 [0.57–4.05]	0.405		
Pleural effusion	1.41 [0.39–5.07]	0.597		
Pericardial effusion	2.32 [0.36–14.88]	0.376		
Hepatic calcified nodules	0.3 [0.04–2.95]	0.335		
Splenic calcified nodules	5.91 [0.91–38.22]	0.062	14.49 [1.30–162.09]	0.044
Enlarged mediastinal lymph node	2.17 [0.72–6.53]	0.170	2.05 [0.44–9.49]	0.361

OR: odds ratio. 95% CI=95% exact confidence interval. Bold indicates significant P value.

Nonetheless, the diagnosis of tuberculosis can be challenging in low prevalence areas such as in Europe or in the USA and induces important consequences on clinical outcomes. Chest X-ray is advocated by the WHO as a diagnostic tool but some abnormalities such as “tree-in-bud” pattern may be missed [19]. Although the use of chest CT for the diagnosis of tuberculosis is still controversial, it is clearly indicated in most clinical situations where tuberculosis is uncertain. Moreover, CT can also help for lung lesions sampling for tuberculosis culture using percutaneous biopsy in doubtful situations [20].

Tree-in-bud is a frequent lung lesion pattern. Bronchiolar obstruction and alveolar filling are thought to explain this phenomenon. Hatipoğlu et al. also reported a relationship between “tree-in-bud” on CT and active tuberculosis [10]. “Tree-in-bud” has also been described as a frequent manifestation of lung infection and small airway diseases [21,22]. This sign had a greater specificity in our study for the diagnosis of active tuberculosis than quantitative IGRA test.

Unlike Yeh et al. who developed a CT scoring system to discriminate between tuberculosis infection and other pulmonary lesions, upper zone involvement was not identified as a finding associated with active tuberculosis in this study [12]. This can be explained by the fact that tuberculosis infection was not compared to other causes of parenchymal diseases. The comparison in this study was only made between active and latent tuberculosis, which can both occur simultaneously in the same lung segments.

Our study has limitations. First, this retrospective analysis from a single cohort included only 92 patients with latent or active tuberculosis. The sample size of some CT patterns such as lymph node enlargement or extra thoracic calcification suggestive of granuloma could limit the conclusions regarding these signs. Additionally, CT protocol, and especially low dose protocol may also influence imaging presentation, so that our findings should be confirmed from a validation cohort using standardized CT parameters [23,24].

In conclusion, the results of this study highlight the added value of chest CT to the diagnosis of active tuberculosis in patients with positive IGRA showing that a “tree-in-bud” pattern has greater specificity for disease activity than quantitative IGRA testing. These findings should however be confirmed in a prospective validation cohort to improve the early detection of active tuberculosis in IGRA positive populations.

Human rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

Institutional ethic committee approval was obtained. Written informed consent was obtained from the patients. The authors

declare that this report does not contain any personal information that could lead to the identification of the patients. The authors also confirm that the personal details of the patients have been removed.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

CRedit authorship contribution statement

Sébastien Bommart: investigation, writing, writing - review & editing original draft preparation, visualization. Jérémy Charriot: writing - review & editing original draft preparation, visualization. Nicolas Nagot: methodology, formal analysis, data curation. Héléne Vernhet-Kovacsik: writing - review & editing. Marie Pierre Revel: writing - review & editing original draft preparation. Clement Boissin: investigation. Arnaud Bourdin: conceptualization, writing - review & editing original draft preparation, visualization. Edouard Tuillon: investigation, supervision, validation.

Disclosure of interest

The authors declare that they have no competing interest.

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