Diagnostic Accuracy of Chest Radiography for the Diagnosis of Tuberculosis (TB) and Its Role in the Detection of Latent TB Infection: a Systematic Review

Riccardo Piccazzo, Francesco Paparo, and Giacomo Garlaschi

ABSTRACT. In this systematic review we evaluate the role of chest radiography (CXR) in the diagnostic flow chart for tuberculosis (TB) infection, focusing on latent TB infection (LTBI) in patients requiring medical treatment with biological drugs. In recent findings, patients scheduled for immunomodulatory therapy with biologic drugs are a group at risk of TB reactivation and, in such patients, detection of LTBI is of great importance. CXR for diagnosis of pulmonary TB has good sensitivity, but poor specificity. Radiographic diagnosis of active disease can only be reliably made on the basis of temporal evolution of pulmonary lesions. *In vivo* tuberculin skin test and *ex vivo* interferon-γ release assays are designed to identify development of an adaptive immune response, but not necessarily LTBI. Computed tomography (CT) is able to distinguish active from inactive disease. CT is considered a complementary imaging modality to CXR in the screening procedure to detect past and LTBI infection in specific subgroups of patients who have increased risk for TB reactivation, including those scheduled for medical treatment with biological drugs. (J Rheumatol Suppl. 2014 May; 91:32–40; doi:10.3899/jrheum.140100)

Key Indexing Terms:
CHEST RADIOGRAPHY
TUBERCULOSIS
LATENT TUBERCULOSIS INFECTION
BIOLOGICS

Pulmonary tuberculosis (TB) remains a common worldwide infection that produces high mortality and morbidity, especially in developing countries[1,2]. Latent TB infection (LTBI) is defined as a state of persistent infection, in the absence of clinical symptoms of active disease[3,4]. When clinically manifest illness is present, the term TB, without further qualifications, is used to designate the disease[4]. Given these definitions, both LTBI and TB may be considered different moments in a continual pathological process, and both conditions are usually distinguished on the basis of the presence (TB) or absence (LTBI) of clinical, laboratory, and chest radiography (CXR) findings[3].

Control of TB infection relies on the identification and preventive treatment of individuals who are latently infected by *Mycobacterium tuberculosis* (Mtb)[5]. The diagnostic tests used to identify individuals with LTBI are the *in vivo* tuberculin skin test (TST) and the *ex vivo* interferon-γ release assays (IGRA); both are designed to identify an adaptive immune response against (but not necessarily a latent infection with) Mtb. The problem of LTBI screening has become more and more relevant in recent years because of the introduction of immunomodulatory biologic drugs in clinical practice[6,7], especially in the field of rheumatic diseases. In fact, tumor necrosis factor-α (TNF-α) antagonists can be the cause of either *de novo* TB infection or reactivation of LTBI. Therefore, different surveillance agencies for disease control and prevention have issued recommendations to ensure the detection and treatment of LTBI before TNF-α antagonist initiation[8,9,10].

This systematic review focuses on the role and value of CXR in TB diagnosis and screening for LTBI detection in patients who undergo medical treatment with biological drugs. The main objective of this work was to give evidence-based answers to relevant clinical issues regarding the value of diagnostic imaging in the screening for LTBI.

Methods

A systematic review of the medical literature was performed by searching PubMed up to January 2013, with no time limits, using the following MeSH terms as keywords in variable associations: "chest" or "thoracic" + "radiography" or "radiograph" or "x-rays" + "post primary tuberculosis" or "postprimary tuberculosis" or "post-primary tuberculosis" or "latent tuberculosis" or "tuberculosis reactivation." "Chest" or "thoracic" + "radiography" or "radiograph" or "x-rays" + "tumor necrosis factor-alpha" or "tumor necrosis

From the School of Radiology, University of Genoa; Unit of Radiology, Department of Diagnostic Imaging, E.O. Galliera Hospital; and Department of Health Sciences (DISSAL), Section of Radiology, University Hospital IRCCS San Martino-IST National Institute for Cancer, Genoa, Italy.

R. Piccazzo, MD, School of Radiology, University of Genoa; F. Paparo, MD, Unit of Radiology, Department of Diagnostic Imaging, E.O. Galliera Hospital; G. Garlaschi, MD, Professor, School of Radiology, University of Genoa; and Department of Health Sciences (DISSAL), Section of Radiology, University Hospital IRCCS San Martino-IST National Institute for Cancer.

Address correspondence to Prof. Garlaschi, Department of Health Sciences (DISSAL), Section of Radiology, University Hospital IRCCS San Martino-IST National Institute for Cancer, Via Pastore 1, 16132 Genoa, Italy. E-mail: giacomo.garlaschi@fastwebnet.it

factor-alpha antagonists" or "biologics" were used as additional keywords. A manual search of the references of the retrieved articles was performed. Articles in languages other than English or Italian were excluded. We included only original papers dealing with latent and post-primary TB imaging and diagnosis, with particular attention to those related to TB reactivation in patients under treatment with biologics.

Results

A total of 1111 papers were retrieved (Figure 1). A large number (936 articles) were initially excluded on the basis of the title or abstract, i.e., considered not pertinent. The remaining were analyzed according to the close relevance of their title or abstract. This method led us to read 157 articles, and at the end of the review process, 67 papers were selected. All included papers were in English. The remaining 90 articles were excluded because they were not pertinent or not focused on our topic.

What is the Current Role of CXR in the Screening for LTBI?

The World Health Organization once estimated that about one-third of the world's population had been infected by Mtb, with 8.7 million new cases of infection in 2011[1]. A complete diagnostic evaluation for TB infection should include medical history, physical examination, CXR, TST, serologic test (IGRA), microbiologic smears, and cultures. The gold standard for the diagnosis of TB is obtained by culturing Mtb from a specimen taken from the patient[11,12,13], but owing to the slow-growth of this aerobic, non-motile, non-spore-forming rod[11,14], diagnosis usually takes a long time. Worldwide clinical trials and post-marketing surveillance data have demonstrated an increased incidence of TB infection associated with anti-TNF-α agents[10,15,16,17]. The majority of these cases are presumed to result from a reactivation of an LTBI, while the rate of new infections is unknown. So, several studies have suggested screening patients for LTBI before anti-TNF-α therapy[18,19], but it is currently not possible to identify the presence of living bacilli in subjects thought to have LTBI[4,20,21,22,23,24,25]. Different screening programs for LTBI detection in patients scheduled for medical treatment with biologics include as the first step the case history, TB risk factor assessment, and physical examination. CXR is used in conjunction with TST or IGRA, but its position in the screening procedure may vary among different guidelines and recommendations. The American College of Rheumatology panel and the National Psoriasis Foundation recommend screening to identify LTBI in patients with rheumatoid arthritis (RA) and psoriatic diseases who are scheduled for therapy with biologic agents, indicating TST

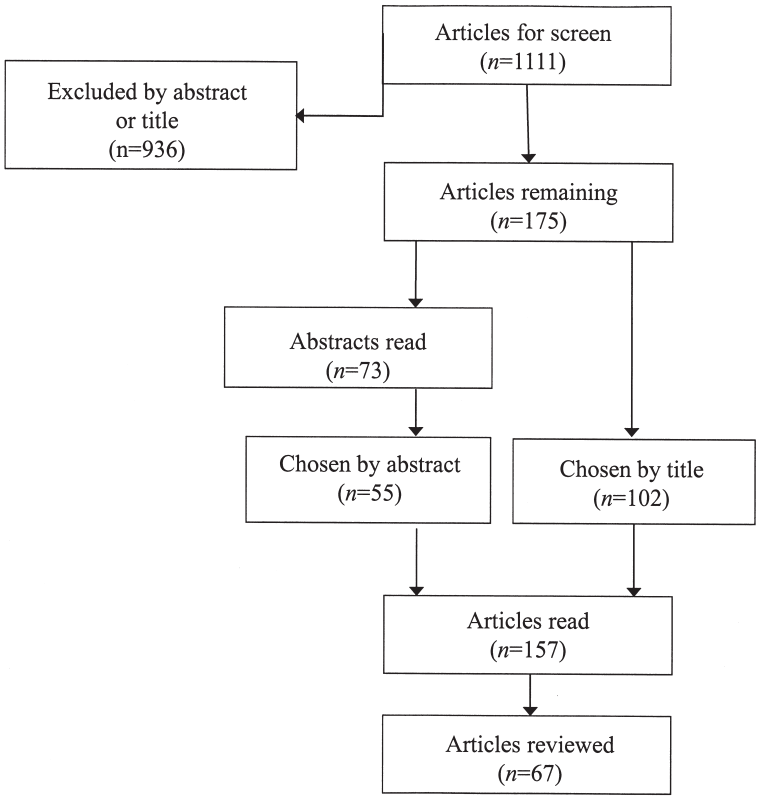

Figure 1. Flowchart of the articles selected for review.

and IGRA as the first screening tests. CXR is considered in the case of positive TST/IGRA[26,27]. Other scientific societies suggest that CXR should be considered as the first step of the screening process[8,9,28,29]. CXR is useful when TST results are unreliable, reading of the skin test is impractical, or the risk of transmission of undiagnosed cases is high, as occurs in institutional settings (jails, hospitals, longterm care facilities)[30,31]. It must be remembered that patients with RA could have an attenuated response to TST[32,33,34,35]. In addition, the diagnosis of TB can be elusive, and symptomatic, culture-positive pulmonary TB with a normal CXR is not uncommon[36].

What is the Diagnostic Performance of CXR in the Detection of TB Infection?

CXR screening for TB/LTBI in high-risk populations may demonstrate findings consistent with prior and/or active infection[37]. Apart from fibrous scarring of the lung parenchyma, there are specific CXR patterns indicative of prior and/or current TB infection. A Ghon lesion is a calcified tuberculous caseating granuloma that represents the sequelae of primary TB infection. Ranke complex is the combination of a Ghon focus with enlarged or calcified hilar/mediastinal lymph nodes; Simon foci are apical nodules, often calcified, that result from hematogenous seeding at the time of initial infection[11,37,38,39]. When examining a CXR it is important to identify findings suggestive of active TB infection, bearing in mind their differential diagnosis with other conditions: areas of parenchymal consolidation should be distinguished from tumors and other infections (e.g., mycetomas); mediastinal lymph node enlargement has to be correlated with corresponding parenchymal changes or contextualized within systemic diseases such as infections, hematopoietic disorders, lymphomas, sarcoidosis; cavitations should be distinguished from tumors, abscesses, and parasitic infections[11,39] (Table 1). TB can sometimes present with consolidation in the lower lung fields and, when compared to the cases involving the upper lobes, it produces less cavitation and residual fibrotic changes, but more parenchymal atelectasis[40,41].

Table 1. Most common tuberculosis (TB) findings on chest radiography.

TB Chest Radiography Findings
Primary disease
Lymphadenopathy (83–96%, decreases with age)
Parenchymal opacities (on the same side as nodal enlargement; 78–84%)
Obstructive atelectasis (by adjacent enlarged nodes, especially in children)
Pleural effusion (29–38%)
Post-primary disease
Cavitations (40–45%)
Parenchymal opacities situated in the apical and posterior segments of the upper lobes (83–85%) and the superior segment of the lower lobes (11–14%)
Pleural effusion (18%)
Tuberculomas (round or oval, sharply marginated lesions, 0.5–4.0 cm)
Hilar and mediastinal lymphadenopathy (5%)
Endobronchial involvement (2–4%)

According to a joint statement issued by the American Thoracic Society and the US Centers for Disease Control and Prevention, subjects infected with Mtb, as evidenced by a positive TST, should be classified starting from clinical, radiographic, and bacteriologic findings into one of the following categories: (a) TB infection, no disease; (b) TB infection, clinically active; (c) TB infection, clinically inactive[37]. CXR has a high negative predictive value for the presence of active TB. In the adult immunocompetent population, the frequency of false negative examinations is about 1%, increasing to 7%–15% in individuals seropositive for human immunodeficiency virus (HIV)[20,42]. The detection of any abnormality (parenchymal, lymph nodal, or pleural), with or without associated calcification, cannot give precise information on disease activity on a single screening CXR. Temporal evolution is the only variable that allows a radiographic differentiation between active and inactive disease[43]. Lack of radiographic change over a time interval of 4 to 6 months generally indicates inactive disease[37]. However, given that longterm stability of radiographic findings may occasionally be associated with culture-positive disease, Miller and MacGregor underline that such findings should be described as "radiographically stable" rather than "inactive"[44].

CXR has been used for over a century to diagnose pulmonary TB; however, it is limited by modest specificity with a high interobserver variability in radiological reports[35,46]. Different studies aimed to determine the sensitivity and specificity of CXR findings for the diagnosis of TB (Figure 2). Cohen, *et al* found a sensitivity of 73–79% and a specificity of 60–63% in a high-risk population[47]. Similar results were found by den Boon, *et al,* who compared the diagnostic value of typical TB symptoms (cough, sputum production, fever, weight loss, night sweats, hemoptysis, anorexia, and dyspnea) versus chest radiography in a TB prevalence survey. The presence of any abnormalities on CXR had the highest sensitivity for detecting subjects with bacteriologically positive TB (0.97, 95% CI 0.90–1.00), while the specificity for any detectable abnormalities was 0.67 (95% CI 0.64–0.70)[48]. For peculiar findings, such as miliary TB, it is possible to reach sensitivity values ranging from 59 to 69%, and specificity from 97 to 100%[49]. The detection of enlarged lymph nodes in children has a sensitivity of 67% and a specificity of 59%. Performing an additional lateral view of the chest, the sensitivity increased by 1.8%, and specificity by 2.5%[50]. A correct diagnosis of pulmonary TB on CXR is dependent on the reader's expertise, because the technique of CXR interpretation is currently not well standardized[45,46]. In this regard, several authors have attempted to introduce

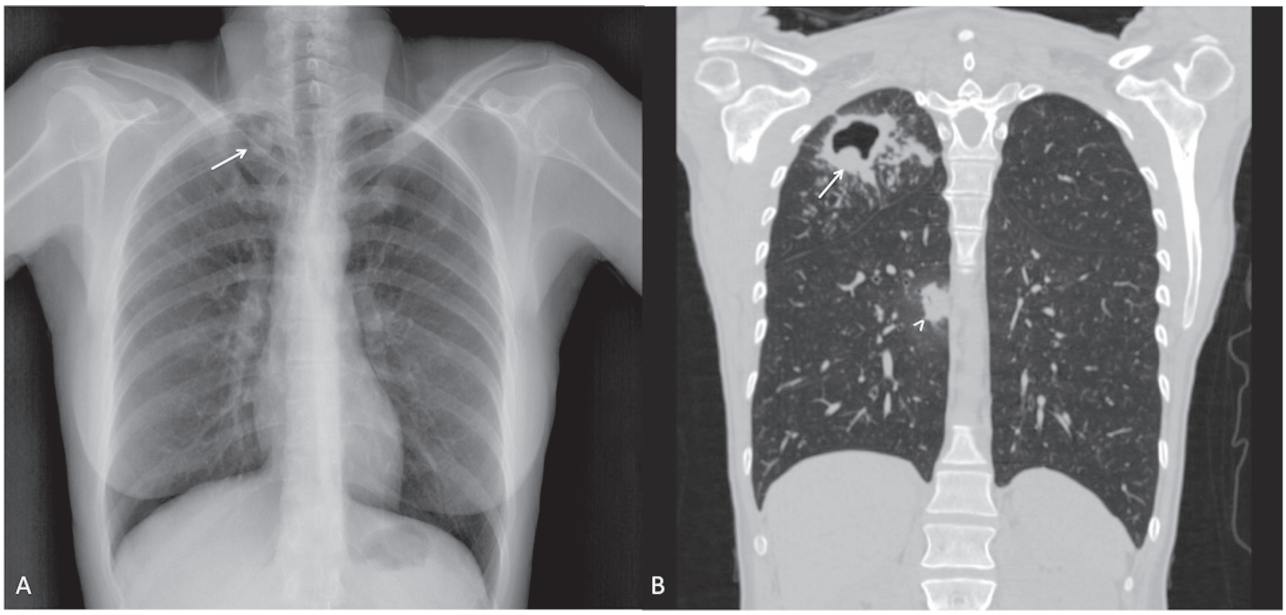

Figure 2. Tubercular cavity. Posteroanterior chest radiography (A) and computerized tomography reformatted image on the coronal plane (B). Panel A shows an irregularly round opacity at the apex of the right lung (arrow). Panel B demonstrates that the lesion in the apical lung parenchyma is a tubercular cavity (arrow). A smaller focus of parenchymal consolidation, which was not detectable on chest radiography, is appreciable in panel B in correspondence to the paravertebral portion of the mid-lung field (arrowhead).

standardized scoring systems that would increase CXR sensitivity and specificity. Results of a recent metaanalysis indicate that none of the scoring systems that have been proposed from 1899 to 2012 was based on the exclusive use of imaging findings. In fact, only the multimodal integration of clinical, laboratory, and imaging data allows to improve the diagnostic performance of CXR, reaching an overall sensitivity and specificity of 96% and 46%, respectively[45]. A simplified scoring system has been recently proposed, including 4 easy-to-recognize features on CXR: upper lobe opacities, cavities, unilateral pleural effusion, and mediastinal/hilar lymphadenopathy[51]. The authors obtained a high negative predictive value (91.5%, 95% CI 87.1–94.7), but a low positive predictive value (49.4%, 95% CI 42.9–55.9). Eisenberg and Pollock assessed the frequency and spectrum of abnormalities on routine screening of CXR in the preemployment evaluation of healthcare workers with positive TST, finding that CXR is of low yield in the detection of active TB or increased LTBI reactivation risk, and provided no assistance in deciding which individuals to prioritize for LTBI treatment[52].

Computed tomography (CT) is a corroborative imaging modality to study TB[53,54,55,56,57,58,59]. It helps to distinguish between active and inactive disease[34], and is more sensitive than CXR in the detection of both localized and disseminated disease and mediastinal lymphadenopathy[11,60,61,62]. Woodring, *et al* said that the first CXR diagnosis of TB is correct in only 49% of cases (i.e., 34% of primary TB and 59% of TB reactivation)[11,39]. Chest CT can effectively detect 80% of patients with active TB and 89% of those with inactive TB[34]. CT is very useful when there is a disagreement between clinical and radiological findings and/or when imaging findings are equivocal or inconclusive[11,63]. Subjects with normal or equivocal CXR may have findings indicative of active TB on chest CT[35,64] (Figure 3). Lew, *et al*[3] showed that no diagnostic test has a 100% sensitivity for TB diagnosis, suggesting a combined diagnostic approach including TST, CXR, IGRA, and CT[65].

Findings suggestive of active TB were detected by CT in 17 (32.7%) of the 52 subjects with a high probability of infection (30 subjects who were IGRA-positive and 22 subjects in whom the TST induration size was ≥ 20 mm). Collectively, among 21 (1.1%) patients with TB, all were TST-positive, 12 (57.1%) were IGRA-positive, and active TB was diagnosed by CT, but not by CXR, in 11 subjects[3].

When compared to the conventional approach with TST and CXR, the combined use of IGRA and chest CT in TST-positives may be more effective in differentiating between active TB, LTBI, and non-infected subjects in a contact investigation[3]. On the other hand, as commented by Marais, *et al*[66], the use of chest CT for screening of asymptomatic contacts is not safe because it leads to overdiagnosis of "active TB," exposing patients to high radiation doses and undermining confidence in existing screening tools[67,68,69]. Introduction of CT is considered only in certain groups of individuals at high risk for TB reactivation, such as immunocompromised patients[3,63,70]. A more effective detection of active TB would prevent the prescription of

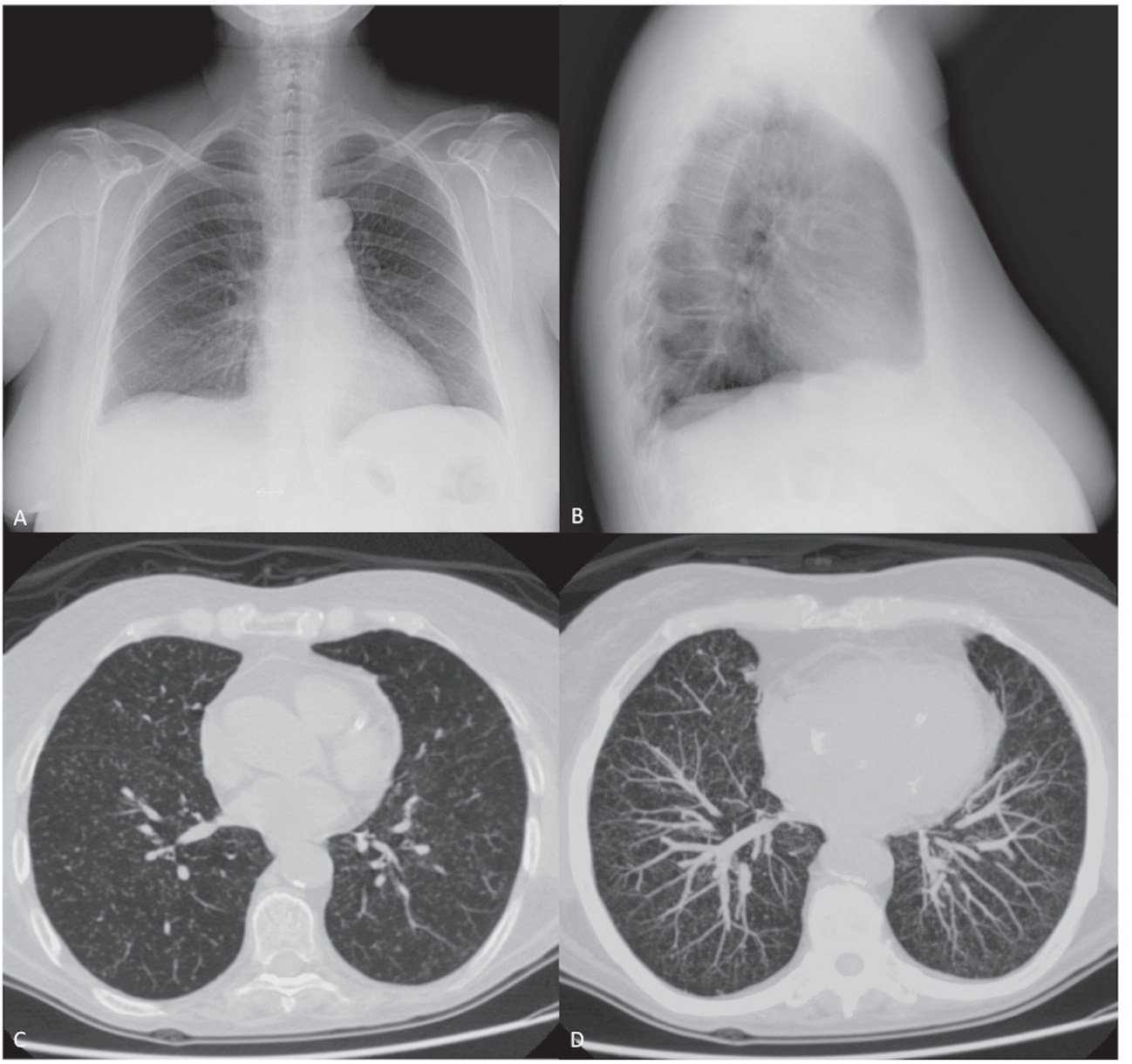

Figure 3. Miliary tuberculosis from hematogenous seeding. Posteroanterior (A) and lateral (B) chest radiographs. Panel A demonstrates peribronchovascular interstitial thickening with a micronodular appearance. Computerized tomography (CT) image on the axial plane (C) shows multiple micronodules disseminated in both lungs, and the reconstructed CT image with maximum intensity projection technique clearly demonstrates their centrilobular location (D).

inappropriate LTBI treatment and the subsequent development of drug resistance[3]. Lee, *et al* evaluated the advantages of chest CT in a TB outbreak investigation in the South Korean army. Lesions indicative of active TB were detected in 18 participants (21%), including 9 without any lesion on CXR and positive results in either TST or IGRA. The authors conclude that CT can be helpful for differentiating active TB from LTBI. Otherwise this diagnostic tool should be carefully considered, taking into account its risk and cost[71,72]. Other authors commented on the article by Lee, *et al,* suggesting that chest CT leads to a significantly higher radiation dose than CXR[73], and to higher costs. They underlined that the use of CT as a screening test during TB outbreak investigations is not justified[74,75], but it could only be performed in symptomatic patients[76], and in certain high-risk groups[75]. The importance of identifying LTBI has become even greater since TNF-α antagonists have been introduced in routine clinical practice for the treatment of RA and other inflammatory rheumatologic disorders[17,77,78]. Tannus Silva, *et al* evaluated the advantages of CT as a screening tool for LTBI detection in patients with RA[59]. CT showed changes compatible with LTBI in 52.9% of patients,

including 8 of the 11 patients with negative TST and IGRA. These results underline the importance of a combined use of different diagnostic modalities for an effective detection of LTBI.

What About "Atypical" Patterns and Peculiar Conditions?

Since the 1950s the incidence of TB infection in industrialized countries has decreased markedly. However, in recent years this trend has started to reverse because of changing population characteristics, such as an influx of immigrants from high-incidence areas and the wide diffusion of the HIV[79,80,81,82,83]. In comparison to the past, it mainly affects younger adults who belong to certain groups[8], such as immunocompromised patients. These patients may present with "atypical" or "unusual" patterns on CXR (i.e., solitary pleural effusion, miliary pattern, lesions in the lung bases, solitary mediastinal or hilar lymphadenopathies)[79,84,85]. HIV-associated pulmonary TB has CXR patterns that are dependent on the level of immunosuppression[37,86,87].

Correlating CXR and CD4 T lymphocyte levels, a significantly higher prevalence of mediastinal and/or hilar lymphadenopathy and a lower prevalence of cavitation were identified in patients with a CD4 T lymphocyte count of less than 200/mm^3. With the worsening of immunosuppression, a higher incidence has been reported of miliary pattern, extrapulmonary disease, and atypical presentation[88,89]. CT evaluation of pulmonary TB in HIV-seropositive patients with normal CXR usually demonstrates subtle abnormalities[37,89], and some authors have identified some specific CT patterns such as multiple parenchymal nodules, tuberculoma, and lymphadenopathy[89]. Lymphadenopathy can present on CT images with a central low attenuation area and peripheral enhancement, as for example in immunocompetent patients[90]. HIV-seropositive patients had a lower prevalence of localized parenchymal disease and a higher prevalence of disseminated disease at CT[88,89].

When a child has positive TST, normal CXR, and no symptoms, the child is considered to have LTBI. When the findings are positive TST, pathological CXR, and symptoms, the child is considered to have TB. In a child in whom previous contact with TB is certain, the presence of positive TST and pathological CXR with or without symptoms suggests a diagnosis of TB. On the basis of indirect signs of low specificity, symptoms, CXR, and TST, the diagnosis of primary TB is difficult to achieve[60,91,92]. In this context, the correct interpretation of CXR is a crucial requirement, and chest CT is recommended if CXR is equivocal[93]. An abnormal thoracic CT occurs in 92.8% of children with positive TST and negative CXR. So, Garrido, *et al* suggested that, in children younger than 4 years with positive TST and normal CXR, it would be advisable to perform CT[67,94]. A recent study on post-liver transplantation patients demonstrated that a pretransplant chest CT scan is more useful to show LTBI than a CXR in a TB endemic country. An increased risk for pulmonary TB is associated with findings such as a "tree-in-bud" appearance (indicative of endobronchial spread), lobular consolidation, and large nodules on CT scans[95,96].

In subgroups of individuals with a high probability of infection, the combined use of TST, IGRA, CXR, and CT is effective in differentiating between active TB, LTBI, and uninfected subjects. The usefulness of chest CT among immunocompromised patients should be further investigated[3].

Statement

CXR must be performed after positive TST/IGRA. Because patients undergoing medical treatment with biologics are a group at high risk for TB reactivation, CT may be indicated when faced with a positive TST/IGRA and inconclusive CXR findings.

The role of CXR in the detection of LTB1 can be summarized as follows:

- Chest radiography for the diagnosis of pulmonary TB has good sensitivity but poor specificity
- Radiographic diagnosis of active disease can only be reliably made on the basis of temporal evolution of pulmonary lesions
- The radiographic diagnosis of TB can be elusive, and symptomatic, culture-positive pulmonary TB with a normal CXR is not uncommon
- In specific subgroups of patients, including candidates for anti-TNF-α treatment, the combined approach based on immunological tests, CXR, and CT could be very useful for LTBI detection

REFERENCES

1. World Health Organization. Global tuberculosis report, 2012. [Internet. Accessed January 22, 2014.] Available from: www.who.int/tb/publications/global_report/gtbr12_main.pdf
2. Gordin FM, Masur H. Current approaches to tuberculosis in the United States. JAMA 2012;308:283-9.
3. Lew WJ, Jung YJ, Song JW, Jang YM, Kim HJ, Oh YM, et al. Combined use of QuantiFERON-TB Gold assay and chest computed tomography in a tuberculosis outbreak. Int J Tuberc Lung Dis 2009;13:633-9.
4. Mack U, Migliori GB, Sester M, Rieder HL, Ehlers S, Goletti D, et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur Respir J 2009;33:956-73.
5. Bothamley GH, Ditiu L, Migliori GB, Lange C, TBNET contributors. Active case finding of tuberculosis in Europe: a Tuberculosis Network European Trials Group (TBNET) survey. Eur Respir J 2008;32:1023-30.
6. Papay P, Eser A, Winkler S, Frantal S, Primas C, Miehsler W, et al. Factors impacting the results of interferon-gamma release assay and tuberculin skin test in routine screening for latent tuberculosis in patients with inflammatory bowel diseases. Inflamm Bowel Dis 2011;17:84-90.
7. Teh BW, Street AC, McBryde ES, Denholm JT. Miliary tuberculosis following negative latent tuberculosis infection screening prior to tumor necrosis factor-alpha antagonists:

implications for management? J Rheumatol 2012;39:1297-8.
8. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. Thorax 2005;60:800-5.
9. Fonseca JE, Lucas H, Canhão H, Duarte R, Santos MJ, Villar M, et al. Recommendations for the diagnosis and treatment of latent tuberculosis and active tuberculosis in inflammatory joint diseases candidates for therapy with tumor necrosis factor alpha inhibitors: March 2008 update. Acta Reumatol Port 2008;33:77-85.
10. Lioté H, Lioté F. Role for interferon-gamma release assays in latent tuberculosis screening before TNF-alpha antagonist therapy. Joint Bone Spine 2011;78:352-7.
11. Jeong YJ, Lee KS. Pulmonary tuberculosis: up-to-date imaging and management. AJR Am J Roentgenol 2008;191:834-44.
12. LoBue PA, Enarson DA, Thoen TC. Tuberculosis in humans and its epidemiology, diagnosis and treatment in the United States. Int J Tuberc Lung Dis 2010;14:1226-32.
13. Schluger NW. The diagnosis of tuberculosis: what's old, what's new. Semin Respir Infect 2003;18:241-8.
14. Marais BJ, Parker SK, Verver S, van Rie A, Warren RM. Primary and postprimary or reactivation tuberculosis: time to revise confusing terminology? AJR Am J Roentgenol 2009;192:W198; author reply W199-200.
15. Balato N, Di Costanzo L, Ayala F, Balato A, Sanduzzi A, Bocchino M. Psoriatic disease and tuberculosis nowadays. Clin Dev Immunol 2012;2012:747204.
16. Whitworth HS, Scott M, Connell DW, Dongés B, Lalvani A. IGRAs — the gateway to T cell based TB diagnosis. Methods 2013;61:52-62.
17. Ringrose JS, Sanche SE, Taylor-Gjevre RM. Detecting latent tuberculosis infection during anti-tumor necrosis factor therapy. Clin Exp Rheumatol 2011;29:790-4.
18. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis 2003;3:148-55.
19. Keystone EC, Papp KA, Wobeser W. Challenges in diagnosing latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. J Rheumatol 2011;38:1234-43.
20. Sánchez-Moya AI, Dauden E. Incidence of tuberculosis infection in psoriatic patients on anti-TNF therapy: report of a case series with 144 patients. J Eur Acad Dermatol Venereol 2011;25:730-3.
21. Shovman O, Anouk M, Vinnitsky N, Arad U, Paran D, Litinsky I, et al. QuantiFERON-TB Gold in the identification of latent tuberculosis infection in rheumatoid arthritis: a pilot study. Int J Tuberc Lung Dis 2009;13:1427-32.
22. Jeong YJ, Yoon S, Koo HK, Lim HJ, Lee JS, Lee SM, et al. Positive tuberculin skin test or interferon-gamma release assay in patients with radiographic lesion suggesting old healed tuberculosis. J Korean Med Sci 2012;27:761-6.
23. Laffitte E, Janssens JP, Roux-Lombard P, Thielen AM, Barde C, Marazza G, et al. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-gamma release assay vs. tuberculin skin test. Br J Dermatol 2009;161:797-800.
24. Seyhan EC, Sökücü S, Altin S, Günlüoğlu G, Trablus S, Yilmaz D, et al. Comparison of the QuantiFERON-TB Gold In-Tube test with the tuberculin skin test for detecting latent tuberculosis infection in hemodialysis patients. Transpl Infect Dis 2010;12:98-105.
25. European Centre for Disease Prevention and Control. Use of interferon-gamma release assays in support of TB diagnosis. Stockholm: ECDC; 2011.
26. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.
27. Doherty SD, Van Voorhees A, Lebwohl MG, Korman NJ, Young MS, Hsu S. National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. J Am Acad Dermatol 2008;59:209-17.
28. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol 2009;161:987-1019.
29. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler D, et al. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. Br J Dermatol 2005;153:486-97.
30. Lee KS, Hwang JW, Chung MP, Kim H, Kwon OJ. Utility of CT in the evaluation of pulmonary tuberculosis in patients without AIDS. Chest 1996;110:977-84.
31. Delacourt C, Mani TM, Bonnerot V, de Blic J, Sayeg N, Lallemand D, et al. Computed tomography with normal chest radiograph in tuberculous infection. Arch Dis Child 1993;69:430-2.
32. Provenzano G, Ferranti MC, Simon G. Tb screening and anti-TNF-alpha treatment. Thorax 2005;60:612–5.
33. Ponce de León D, Acevedo-Vazquez E, Sanches-Torres A, Cucho M, Alfaro J, Perich R, et al. Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with high prevalence of tuberculosis. Ann Rheum Dis 2005;64:1360-1.
34. Malaviya AN, Kapoor S, Garg S, Rawat R, Shankar S, Nagpal S, et al. Preventing tuberculosis flare in patients with inflammatory rheumatic diseases receiving tumor necrosis factor-alpha inhibitors in India. An audit report. J Rheumatol 2009;36:1414-20.
35. Linh NN, Marks GB, Crawford AB. Radiographic predictors of subsequent reactivation of tuberculosis. Int J Tuberc Lung Dis 2007;11:1136-42.
36. Marciniuk DD, McNab BD, Martin WT, Hoeppner VH. Detection of pulmonary tuberculosis in patients with a normal chest radiograph. Chest 1999;115:445-52.
37. Leung AN. Pulmonary tuberculosis: the essentials. Radiology 1999;210:307-22.
38. Jones BE, Ryu R, Yang Z, Cave MD, Pogoda JM, Otaya M, et al. Chest radiographic findings in patients with tuberculosis with recent or remote infection. Am J Respir Crit Care Med 1997;156:1270-3.
39. Woodring JH, Vandiviere HM, Fried AM, Dillon ML, Williams TD, Melvin IG. Update: the radiographic features of pulmonary tuberculosis. AJR Am J Roentgenol 1986;146:497-506.
40. Wang JY, Hsueh PR, Lee CH, Chang HC, Lee LN, Liaw YS, et al. Recognising tuberculosis in the lower lung field: an age- and sex-matched controlled study. Int J Tuberc Lung Dis 2006; 10:578-84.
41. Choyke PL, Sostman HD, Curtis AM, Ravin CE, Chen JT, Godwin JD, et al. Adult-onset pulmonary tuberculosis. Radiology 1983;148:357-62.
42. Greenberg SD, Frager D, Suster B, Walker S, Stavropoulos C, Rothpearl A. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). Radiology 1994;193:115-9.
43. McAdams HP, Erasmus J, Winter JA. Radiologic manifestations of pulmonary tuberculosis. Radiol Clin North Am 1995;33:655-78.
44. Miller WT, MacGregor RR. Tuberculosis: frequency of unusual radiographic findings. AJR 1978;130:867–5.
45. Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D, Steingart KR. Scoring systems using chest radiographic features for the

diagnosis of pulmonary tuberculosis in adults: A systematic review. Eur Respir J 2013;42:480-94.
46. Sakurada S, Hang NT, Ishizuka N, Toyota E, Hung le D, Chuc PT, et al. Inter-rater agreement in the assessment of abnormal chest X-ray findings for tuberculosis between two Asian countries. BMC Infect Dis 2012;12:31.
47. Cohen R, Muzaffar S, Capellan J, Azar H, Chinikamwala M. The validity of classic symptoms and chest radiographic configuration in predicting pulmonary tuberculosis. Chest 1996;109:420-3.
48. den Boon S, White NW, van Lill SW, Borgdorff MW, Verver S, Lombard CJ, et al. An evaluation of symptom and chest radiographic screening in tuberculosis prevalence surveys. Int J Tuberc Lung Dis 2006;10:876-82.
49. Kwong JS, Carignan S, Kang EY, Müller NL, FitzGerald JM. Miliary tuberculosis: diagnostic accuracy of chest radiography. Chest 1996;110:339-42.
50. Swingler GH, du Toit G, Andronikou S, van der Merwe L, Zar HJ. Diagnostic accuracy of chest radiography in detecting mediastinal lymphadenopathy in suspected pulmonary tuberculosis. Arch Dis Child 2005;90:1153-6.
51. Pinto LM, Dheda K, Theron G, Allwood B, Calligaro G, van Zyl-Smit R, et al. Development of a simple reliable radiographic scoring system to aid the diagnosis of pulmonary tuberculosis. PLoS One 2013;8:e54235.
52. Eisenberg RL, Pollock NR. Low yield of chest radiography in a large tuberculosis screening program. Radiology 2010; 256:998-1004.
53. Im JG, Itoh H, Han MC. CT of pulmonary tuberculosis. Semin Ultrasound CT MR 1995;16:420-34.
54. Lee JY, Lee KS, Jung KJ, Han J, Kwon OJ, Kim J, et al. Pulmonary tuberculosis: CT and pathologic correlation. J Comput Assist Tomogr 2000;24:691-8.
55. Poey C, Verhaegen F, Giron J, Lavayssiere J, Fajadet P, Duparc B. High resolution chest CT in tuberculosis: evolutive patterns and signs of activity. J Comput Assist Tomogr 1997;21:601-7.
56. Pamuk ON, Yesil Y, Donmez S, Unlü E, Köker IH, Cakir N. The results of purified protein derivative test in ankylosing spondylitis patients: clinical features, HRCT results and relationship with TNF-blocker usage. Rheumatol Int 2008;29:179-83.
57. Yoon JY, Lee IJ, Im HJ, Lee K, Lee Y, Bae SH. CT findings in apical versus basal involvement of pulmonary tuberculosis. Diagn Interv Radiol 2013;19:85-90.
58. Lee KS, Im JG. CT in adults with tuberculosis of the chest: characteristic findings and role in management. AJR Am J Roentgenol 1995;164:1361-7.
59. Tannus Silva DG, Silva BD, Torres PP, Santana PJ Jr, Junqueira-Kipnis AP, Fouad Rabahi M. Latent tuberculosis in rheumatoid arthritis: evaluating cellular response and high-resolution computed tomography. Arch Bronconeumol 2012;48:144-9.
60. Pediatric Tuberculosis Collaborative Group. Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents. Pediatrics 2004;14:1175-201.
61. Im JG, Itoh H, Shim YS, Lee JH, Ahn J, Han MC, et al. Pulmonary tuberculosis: CT findings — early active disease and sequential change with antituberculous therapy. Radiology 1993;186:653-60.
62. Hulnick DH, Naidich DP, McCauley DI. Pleural tuberculosis evaluated by computed tomography. Radiology 1983;149:759-65.
63. Beigelman C, Sellami D, Brauner M. CT of parenchymal and bronchial tuberculosis. Eur Radiol 2000;10:699-709.
64. Gottridge JA, Meyer BR, Schwartz NS, Lesser RS. The nonutility of chest roentgenographic examination in asymptomatic patients with positive tuberculin test results. Arch Intern Med 1989;149:1660-2.
65. Maeda T, Banno S, Maeda S, Naniwa T, Hayami Y, Watanabe M, et al. Comparison of QuantiFERON-TB Gold and the tuberculin skin test for detecting previous tuberculosis infection evaluated by chest CT findings in Japanese rheumatoid arthritis patients. J Infect Chemother 2011;17:842-8.
66. Marais BJ, Schaaf HS, Gie RP, Donald PR. TB contact screening: which way to go? Int J Tuberc Lung Dis 2009;13:1576-7; author reply 1577-8.
67. Brody AS, Frush DP, Huda W, Brent RL. Radiation risk to children from computed tomography. Pediatrics 2007;120:677-82.
68. Brenner DJ, Hall EJ. Computed tomography — an increasing source of radiation exposure. N Engl J Med 2007;357:2277-84.
69. Bach PB, Jett JR, Pastorino U, Tockman MS, Swensen SJ, Begg CB. Computed tomography screening and lung cancer outcomes. JAMA 2007;297:953-61.
70. Casarini M, Ameglio F, Alemanno L, Zangrilli P, Mattia P, Paone G, et al. Cytokine levels correlate with a radiologic score in active pulmonary tuberculosis. Am J Respir Crit Care Med 1999; 159:143-8.
71. Lee SW, Jang YS, Park CM, Kang HY, Koh WJ, Yim JJ, et al. The role of chest CT scanning in TB outbreak investigation. Chest 2010;137:1057-64.
72. Hirama T, Hagiwara K, Kanazawa M. Tuberculosis screening programme using the QuantiFERON-TB Gold test and chest computed tomography for healthcare workers accidentally exposed to patients with tuberculosis. J Hosp Infect 2011;77:257-62.
73. Schluger NW. CT scanning for evaluating contacts of TB patients: ready for prime time? Chest 2010;137:1011-3.
74. Joekes E, Davies G, Mwandumba HC, Squire SB. Insufficient evidence for chest CT scan in TB outbreak investigation. Chest 2010;138:234-5.
75. Marais BJ. On the role of chest CT scanning in a TB outbreak investigation. Chest 2011;139:229.
76. Bhuniya S, De P. Questions in the role of chest CT scanning in TB outbreak investigation. Chest 2010;138:1522-3.
77. Hernandez C, Cetner AS, Jordan JE. Tuberculosis in the age of biologic therapy. J Am Acad Dermatol 2008;59:363-79.
78. Hanta I, Ozbek S, Kuleci S, Kocabas A. The evaluation of latent tuberculosis in rheumatologic diseases for anti-TNF therapy: experience with 192 patients. Clin Rheumatol 2008;27:1083-6.
79. Graham S, Das GK, Hidvegi RJ, Hanson R, Kosiuk J, Al ZK, et al. Chest radiograph abnormalities associated with tuberculosis: reproducibility and yield of active cases. Int J Tuberc Lung Dis 2002;6:137-42.
80. Miller WT. Tuberculosis in the 1990's. Radiol Clin North Am 1994;32:649-61.
81. Lee KS, Song KS, Lim TH, Kim PN, Kim IY, Lee BH. Adult-onset pulmonary tuberculosis: findings on chest radiographs and CT scans. AJR Am J Roentgenol 1993;160:753-8.
82. Wittram C, Weisbrod GL. Mycobacterium avium complex lung disease in immunocompetent patients: radiography-CT correlation. Br J Radiol 2002;75:340-4.
83. Pai M, O'Brien R. New diagnostics for latent and active tuberculosis: state of the art and future prospects. Semin Respir Crit Care Med 2008;29:560-8.
84. Van den Brande P, Dockx S, Valck B, Demedts M. Pulmonary tuberculosis in the adult in a low prevalence area: is the radiological presentation changing? Int J Tuberc Lung Dis 1998;2:904-8.
85. Curvo-Semedo L, Teixeira L, Caseiro-Alves F. Tuberculosis of the chest. Eur J Radiol 2005;55:158-72.
86. Garcia GF, Moura AS, Ferreira CS, Rocha MO. Clinical and radiographic features of HIV-related pulmonary tuberculosis according to the level of immunosuppression. Rev Soc Bras Med Trop 2007;40:622-6.
87. Pitchenik AE, Rubinson HA. The radiographic appearance of

tuberculosis in patients with the acquired immune deficiency syndrome (AIDS) and pre-AIDS. Am Rev Respir Dis 1985;131:393-6.
88. Kawooya VK, Kawooya M, Okwera A. Radiographic appearances of pulmonary tuberculosis in HIV-1 seropositive and seronegative adult patients. East Afr Med J 2000;77:303-7.
89. Leung AN, Brauner MW, Gamsu G, Mlika-Cabanne N, Ben Romdhane H, Carette MF, et al. Pulmonary tuberculosis: comparison of CT findings in HIV-seropositive and HIV-seronegative patients. Radiology 1996;198:687-91.
90. Pastores SM, Naidich DP, Aranda CP, McGuinness G, Rom WN. Intrathoracic adenopathy associated with pulmonary tuberculosis in patients with human immunodeficiency virus infection. Chest 1993;103:1433-7.
91. Agrons GA, Markowitz RI, Kramer SS. Pulmonary tuberculosis in children. Semin Roentgenol 1993;28:158-72.
92. Connell TG, Zar HJ, Nicol MP. Advances in the diagnosis of pulmonary tuberculosis in HIV-infected and HIV-uninfected children. J Infect Dis 2011;204 Suppl 4:S1151-8.
93. Fonseca-Santos J. Tuberculosis in children. Eur J Radiol 2005;55:202-8.
94. Garrido JB, Alías Hernández I, Bonillo Perales A, Rubí Ruiz T, González Jiménez Y, González-Ripoll Garzón M, et al. Usefulness of thoracic CT to diagnose tuberculosis disease in patients younger than 4 years of age. Pediatr Pulmonol 2012;47:895-902.
95. Lyu J, Lee SG, Hwang S, Lee SO, Cho OH, Chae EJ, et al. Chest computed tomography is more likely to show latent tuberculosis foci than simple chest radiography in liver transplant candidates. Liver Transpl 2011;17:963-8.
96. Nakanishi M, Demura Y, Ameshima S, Kosaka N, Chiba Y, Nishikawa S, et al. Utility of high-resolution computed tomography for predicting risk of sputum smear-negative pulmonary tuberculosis. Eur J Radiol 2010;73:545-50.