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Characteristics of culture-negative subclinical pulmonary tuberculosis: a single-center observation

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ABSTRACT

Background: Little is known about culture-negative subclinical pulmonary tuberculosis (TB), and its diagnosis remains challenging. Therefore, this study aimed to identify the characteristics and the extent of disease associated with culture-negative subclinical pulmonary TB.

Methods: This retrospective cohort study was conducted on immunocompetent individuals with subclinical pulmonary TB at a university hospital in Thailand from January 2014 to December 2019. Subclinical pulmonary TB was diagnosed based on the presence of radiographic abnormalities consistent with TB in the absence of TB symptoms. All subjects demonstrated significant improvement or resolution of radiographic abnormalities following the completion of treatment. At least two negative sputum cultures were needed to fulfill the definition of culture-negative pulmonary TB. Data were analyzed using univariate and multiple logistic regression analyses to determine the characteristics of those with culture-negative subclinical pulmonary TB compared to culture-positive ones.

Results: Out of the 106 individuals identified with subclinical pulmonary TB, 84 met the criteria for inclusion in the analysis. The study found lower radiographic extent and increasing age were key attributes of culture-negative subclinical pulmonary TB. The odds ratios (95% confidence interval) were 7.18 (1.76 to 29.35) and 1.07 (1.01 to 1.13), respectively. They tend to have lower rates of bilateral involvement in both chest x-ray (8.5% vs. 32.0%, p=0.006) and computed tomography (15.4% vs. 42.9%, p=0.035). However, no other specific radiographic findings were identified.

Conclusions: People with culture-negative subclinical pulmonary TB were likely to have less radiographic severity, reflecting early disease. Nevertheless, no radiographic patterns, except for unilaterality, were related to culture-negative subclinical pulmonary TB.

Key words: Mycobacterium infections; Tuberculosis; Asymptomatic diseases; Radiography.

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Data availability statement: The authors declare that the data supporting the findings of this study are available within the article.

Conflict of interest: The authors have no conflicts of interest to declare.

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Introduction

Tuberculosis (TB) remains a major public health concern worldwide [1]. Early TB detection to interrupt *Mycobacterium tuberculosis* (Mtb) transmission is a cornerstone for TB control [2]. Historically, TB was categorized into binary stages, including latent infection and active disease. Nevertheless, it has recently been conceptualized as a spectrum of disease stages, including latent TB infection, subclinical (i.e., asymptomatic) TB disease, and clinical or active (i.e., symptomatic) TB disease [3]. A better understanding of this emerging trajectory is needed to end the global TB epidemic.

Subclinical TB is considered an early-stage disease prior to the development of active TB [3]. This is supported by the evidence that subclinical pulmonary TB tends to be less severe than active pulmonary TB, as demonstrated by lower rates of multiple pulmonary lesions [4,5]. Previous studies showed that the prevalence of the subclinical disease among individuals with pulmonary TB varied from 18% to 68%, with a vast proportion of smear and culture positivity [4-6]. Moreover, owing to the lack of noticeable symptoms, subclinical pulmonary TB is less likely to be detected by symptom-based or passive case-finding [7]. As a result, they can by far pose a risk of transmission, especially through unrecognizable respiratory symptoms such as unrelated cough [8]. A recent analysis in Vietnam also demonstrated that people with subclinical pulmonary TB are able to spread through household contact [9]. Noteworthily, a retrospective study in Canada found that approximately three-quarters of pulmonary TB patients were identified through active case-finding [10].

The TB epidemic is still ongoing in Thailand, as classified among the thirty nations with the highest TB burden, with an incidence of 155 per 100,000 population in 2022 [1]. Studies on healthcare workers in university hospitals in Bangkok, Thailand, have revealed even more overall TB incidences of 164 to 200 per 100,000 persons based on data between 2011 and 2020 [11,12]. Notably, a substantial proportion of these cases (up to 44%) were identified as subclinical and detected through routine health checks [11,12]. Similarly, cross-sectional research conducted at a university hospital in Bangkok found that nearly half of patients with co-infection of COVID-19 and microbiologically confirmed TB did not have symptoms consistent with TB [13]. As a result, these findings emphasize the intensification of an active case-finding strategy by vigilant screening for subclinical TB. This also aligns with the Thailand Operational Plan to End Tuberculosis (2023-2027) [14] and appears vital in efforts to combat TB, especially in high TB burden countries.

The diagnosis of culture-negative subclinical pulmonary TB is particularly slippery. It has been proposed that culture-negative disease is the very early disease stage that later progresses to culture-positive disease, which may contribute to a higher risk of transmission [8]. Still, the data supporting this statement has yet to be explored. Previous studies on culture-negative pulmonary TB have not solely included those asymptomatic and most presented symptoms [15,16]. Distinguishing its characteristics would extend the understanding of natural history and help enhance the detection rate, implicating a more efficient TB control strategy. We hypothesized that those with culture-negative subclinical pulmonary TB had less

extensive disease than those with culture-positive disease. Therefore, the aim of this study was to determine the characteristics and the extent of radiographic abnormalities associated with culture-negative subclinical pulmonary TB.

Methods

Study design and population

This retrospective cohort study was conducted at a 2,000-bed university hospital in Bangkok, Thailand. We reviewed the medical records of all consecutive pulmonary TB-diagnosed patients registered at the health checkup clinic between January 2014 and December 2019. The health check-up clinic operates within the Department of Preventive and Social Medicine at our institute. It serves as a primary facility providing health maintenance services to both outpatients and hospital employees. Additionally, the clinic offers other relevant health check services, such as pre-employment examinations. As part of its standard practice, the clinic routinely conducts screening chest x-rays (CXR) during health assessments.

Those with abnormal screening CXR were referred to two qualified pulmonologists, each with 23 and 25 years of experience, respectively. All individuals with pulmonary TB or suspicion of having pulmonary TB were routinely asked to provide three initial cough-up sputum specimens for microbiological studies. The local National Tuberculosis Control Program Guideline recommended that at least two sputum specimens, including spot and collected morning sputum, should be acquired [17]. Further, those with an equivocal diagnosis of pulmonary TB underwent chest computed tomography (CT) to ensure the diagnosis before or at the time of anti-TB treatment initiation. The pulmonologists regularly recorded all presented symptoms among all patients.

The study included subjects diagnosed with pulmonary TB who met all the following: age 18 years and over, had no symptoms suggestive of TB, and had a significant improvement of radiographic abnormalities after anti-TB treatment completion. Subjects lost to follow up were excluded. Two physicians independently screened the subjects' eligibility, ensuring the observed abnormalities were TB-related. Disagreements were subsequently resolved through a consensus discussion. Specifically, the follow up radiological assessments were conducted in accordance with the Thai National TB Control Program Guideline [17], which recommends evaluations at 2- and 6-months post-treatment initiation. The standard treatment regimen for pulmonary TB typically comprises an initial two months of the intensive phase of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) and the subsequent continuation phase of four months of INH and RIF.

Definitions

Subclinical pulmonary TB was defined as the absence of symptoms suggestive of TB while demonstrating radiographic abnormalities consistent with TB. TB-related symptoms include chest symptoms such as cough, hemoptysis, dyspnea, and chest pain, as well as constitutional symptoms such as fever, weight loss, malaise, and night sweats, irrespective of duration. In terms of radiographic features, CXR findings highly suggestive of pulmonary TB include the presence of air-space nodules/clustered nodules or consolidation predominantly in the upper or mid lung zones. In addition, cavities with surrounding consolidation are commonly observed in those with pulmonary TB [18].

A diagnosis of culture-negative pulmonary TB requires at least two separate sputum specimens with negative results for Mtb cultures. This definition is founded on the principle that TB patients may exhibit radiographic evidence of the disease without symptoms or positive microbiological findings [8]. In contrast, culture-positive pulmonary TB was diagnosed when the initial sputum specimens yielded a positive Mtb culture result.

Following the completion of a full course of anti-TB treatment, all cases exhibited significant radiographic improvement or the resolution of radiographic abnormalities when compared to the initial images. This differentiation increased the certainty that the observed changes were distinct from any pre-existing chest radiographic abnormalities.

Data collection

Covariates collected were as follows: demographics and comorbidities (age, sex, smoking status, diabetes mellitus [DM], previous pulmonary TB, being a hospital employee); the radiographic extent of pulmonary lesions (CXR severity grade, CT severity score); CXR findings (patchy opacities, reticulonodular opacities, nodules, cavitation, enlarged hilar shadow, and bilateral involvement); chest CT findings (consolidation, tree-in-bud pattern, ground glass opacities [GGO], nodules, mass, cavitation, adenopathy, bronchiectasis, calcified nodules, calcified lymph node, upper lobe involvement, bilateral involvement, and multilobar involvement [2 lobes or more]).

Radiologic assessment

This study selected chest images prior and closest to the date of initiation of treatment. One radiologist and one pulmonologist (with experience of 20 and 25 years, respectively) reviewed and interpreted all images. Any discrepancies were settled by mutual consensus. The extent of the disease was quantified by using the scoring systems adapted from the previous studies [19,20]. Although originally developed for idiopathic pulmonary fibrosis, this CT severity scoring method was utilized in the present study due to the lack of validated systems for pulmonary TB on CT images, to our knowledge. Additionally, its clinical relevance in assessing pulmonary lesion involvement has been demonstrated through its correlation with histopathology sections [20]. The radiologic assessments are followings:

1. CXR severity grading: the lung fields were divided into six zones. Grade 1 for the involvement of one zone without cavitation; grade 2 for two or three zones, or one zone with cavitation; grade 3 for more than three zones regardless of cavitation.
2. Chest CT severity scores: each lobe was graded according to a percentage of the affected area with a score of 0 to 5; 0 for no involvement; 1 for <5% of a lobe; 2 for 5%-25% of a lobe; 3 for 26%-49% of a lobe; 4 for 50%-75% of a lobe; 5 for >75% of a lobe. Hence, the total possible score ranges from 0 to 25.

Laboratory processing

A 2-5 ml sputum specimen characterized by its mucoid and viscous nature was collected. The specimen was delivered within the standardized containers to the laboratory as soon as possible after collection. If immediate delivery was not possible, it was refrigerated at a temperature of 4 to 8 °C for a maximum duration of 7 days. Importantly, the TB laboratory at our institute, which is responsible for TB diagnostic tests, is certified in compliance with ISO15189:2012 and ISO15190:2020 standards. Internal audits and external quality control checks are conducted annually for every test.

Mtb culture was conducted using either solid media, such as Löwenstein-Jensen (LJ) medium, or liquid media, such as MGIT 960 tubes (Becton Dickinson, Buenos Aires, Argentina). When using LJ medium, 200 µl of the decontaminated sample was inoculated, and TB growth was monitored weekly. A negative result was concluded if no growth was observed after 60 days. Meanwhile, when using MGIT 960 tubes, 500 µl of the decontaminated sample was inoculated, and growth was monitored daily. A negative result was determined if no growth was observed after 42 days. In cases of suspected TB based on positive culture results, confirmation was achieved through acid-fast bacilli (AFB) staining and MPT64 antigen testing.

Statistical analysis

Characteristics, extent, and radiographic findings were compared between culture-negative and culture-positive groups. Continuous variables were shown as means with standard deviations (SD) or medians with interquartile ranges (IQR). Categorical variables were shown as counts with percentages. The t-test or Mann-Whitney U test was used for continuous data, depending on the data distribution. The Chi-square or Fisher's exact test was used for categorical data, as appropriate. Subsequently, variables related to demographics and comorbidities, and radiographic extent, with a $p<0.15$, were entered in the multiple logistic regression. Odds ratios (ORs) with 95% confidence intervals (95% CIs) for having culture-negative subclinical pulmonary TB were calculated, compared to culture-positive subclinical pulmonary TB. A two-sided p below 0.05 was

considered statistically significant. All analyses were performed using IBM SPSS Statistics (version 18, IBM Corp., Armonk, NY, USA).

Results

During the six-year period, 106 individuals with subclinical pulmonary TB were identified, all of whom were identified through screening CXR during routine checkups. Out of these, a total of 84 subjects met the criteria for the main analysis (Figure 1). The age ranged from 18 to 61 years, with a median of 31 years. The proportion of culture positivity was 29.8% (25/84). No subjects known to have human immunodeficiency virus (HIV) infection or severely immunosuppressed states were identified. Regarding the radiographic extent, most had a relatively low severity disease; 83.3% had grade 1 CXR severity, and CT severity scores ranged from 1 to 14 with a median of 2. Patchy opacities were the most frequent CXR findings (67.9%), followed by reticulonodular opacities (36.9%). A tree-in-bud pattern and nodules were the most common CT patterns, contributing 92.5% and 58.5%, respectively. In addition, a miliary pattern was not detected in any subject. Figure 2 and Figure 3 reveal pre- and post-treatment chest images of two patients with culture-positive and culture-negative subclinical pulmonary TB.

In the univariable analysis, subjects with culture-negative subclinical pulmonary TB were slightly older (35 years vs. 26 years, p=0.047). Moreover, they also had a lower degree in the extent shown by a higher proportion of grade 1 CXR severity (89.8% vs. 68.0%, p=0.014). After analyzing the multiple logistic regression, significant variables associated with culture-negative subclinical pulmonary TB remained an increasing age (OR 1.07; 95% CI 1.01 to 1.13) and grade 1 CXR severity (OR 7.18; 95% CI 1.76 to 29.35) (Table 1).

Most radiographic patterns between the two groups did not statistically differ (Table 2), predominant with patchy opacities and tree-in-bud patterns in CXR and chest CT, respectively. However, the culture-negative group had lower rates of bilateral pulmonary involvement in both CXR (8.5% vs. 32.0%, p=0.006) and chest CT (15.4% vs. 42.9%, p=0.035). Although statistical significance was not achieved, multilobar involvement in the chest CT tended to be more commonly found in the culture-positive group (23.1% vs. 50.0%, p=0.060).

Discussion

Consistent with the hypothesis, the present study showed that culture-negative subclinical pulmonary TB had significantly milder radiographic grading and

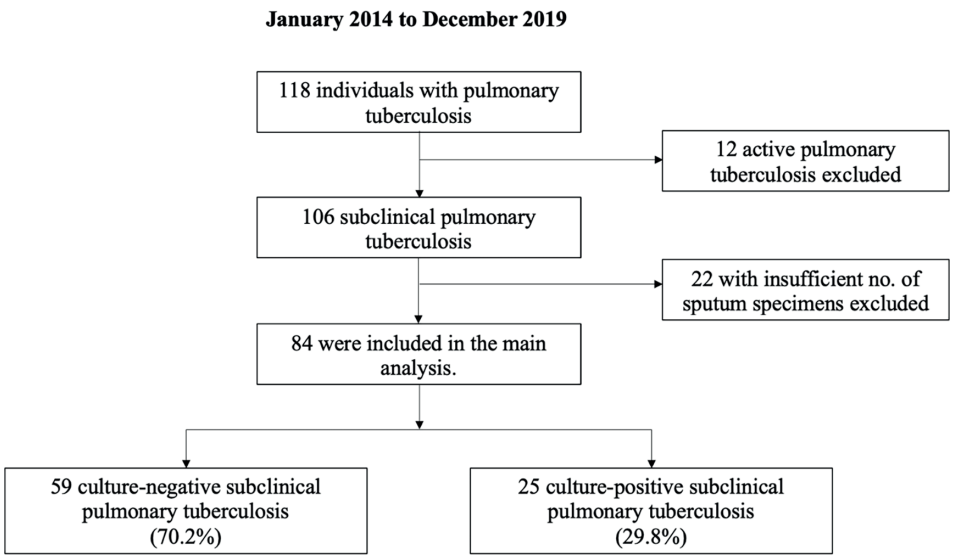

Figure 1. Flow Diagram of the Study.

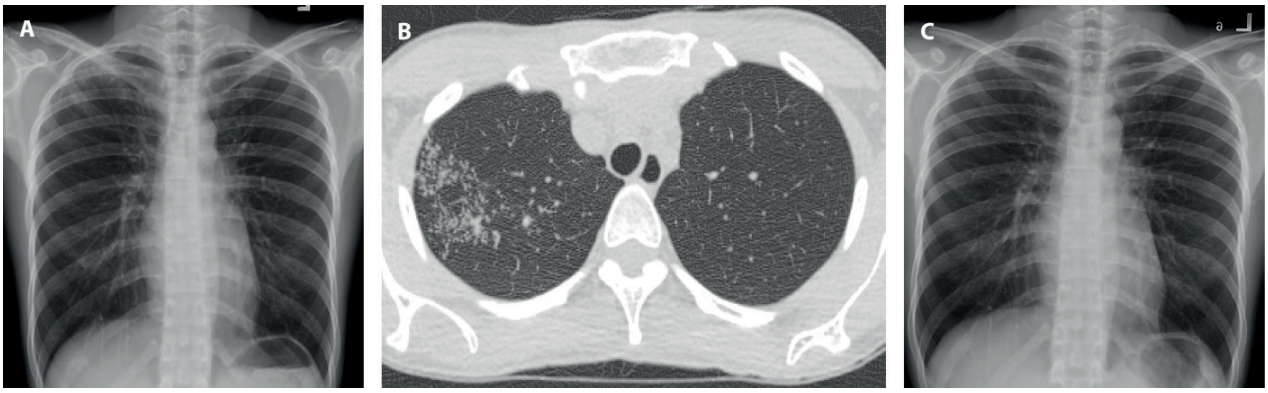

Figure 2. A-C) Pre- and post-treatment chest images of a 26-year-old female with culture-positive subclinical pulmonary TB. A) Pre-treatment chest radiograph shows reticulonodular opacities at the right apical lung. B) Axial CT image in lung window performed 1 month after A. reveals multiple centrilobular nodules with tree-in-bud pattern in the apical segment of the right upper lobe. C) Post-treatment chest radiograph (7 months after A.) shows resolution of the abnormalities of the right apical lung.

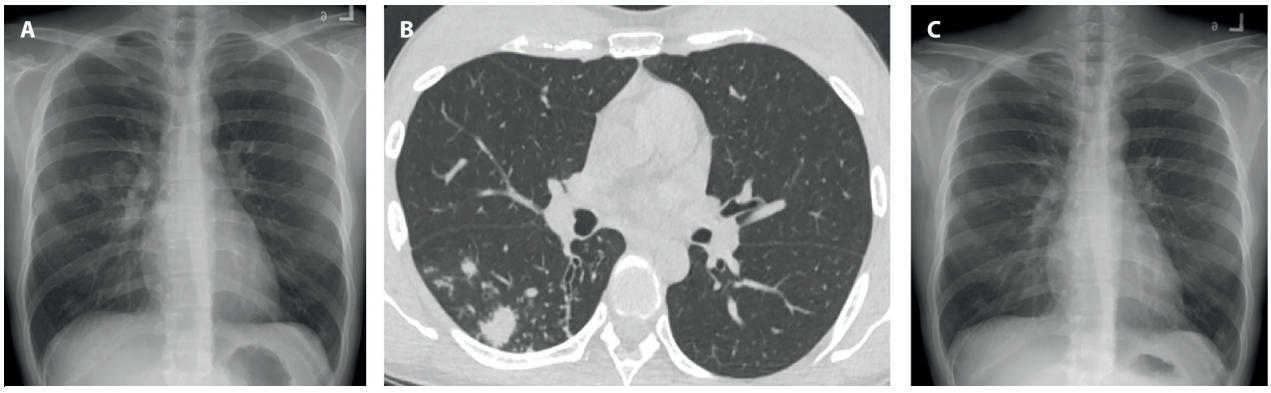

Figure 3. A-C) Pre- and post-treatment chest images of a 32-year-old female with culture-negative subclinical pulmonary TB. A) Pre-treatment chest radiograph shows patchy nodular opacities at the right middle lung zone. B) Axial CT image in lung window performed on the same date as A. reveals solid pulmonary nodules with adjacent centrilobular and tree-in-bud opacities in the superior segment of the right lower lobe as well as bronchial wall thickening and bronchiectasis. C) Post-treatment chest radiograph (10 months after A.) shows resolution of the abnormalities with minimal residual fibrosis at the right middle lung zone.

less frequent bilateral patterns. However, the study did not find other radiographic patterns specific to the culture-negative disease.

This study found that grade 1 CXR severity was strongly related to culture-negative subclinical pulmonary TB, indicating that they were likely to have less extent of the disease than those with culture-positive subclinical pulmonary TB. This aligns with the statement that Mtb may be contained within granuloma in the early stage, resulting in minimal pathology and a lack of symptoms [8]. Interestingly, prior studies also found that individuals with culture-negative pulmonary TB had fewer cavitary lesions than culture-positive ones, reflecting less extensive tissue damage [15,16]. However, the present study revealed a few such lesions exclusively in the culture-negative group, though not statistically significant due to their rarity. Still, the overall evidence suggests that culture-negative subclinical pulmonary TB might represent an earlier stage of TB disease compared to culture-positive cases.

Concerns may arise regarding the adequacy of sputa in subclinical TB patients. However, this study adhered to standardized collection procedures and provided patients with proper instructions, as detailed previously. Furthermore, the TB laboratory at our

Table 1. Univariable and multivariable analyses of factors associated with culture-negative subclinical pulmonary tuberculosis.

	Total (N=84)	Culture-negative (N=59)	Culture-positive (N=25)	P	Multivariable analysis	
					AOR (95% CI)	P
Age (years)	31 (25,38.5)	35 (28,40)	26 (24,30)	0.047†	1.07 (1.01-1.13)¶	0.022
Male sex	19 (22.6)	16 (27.1)	3 (12.0)	0.162‡	-	-
Diabetes	2 (2.4)	-	2 (8.0)	0.086‡	-	-
Previous pulmonary TB	2 (2.4)	2 (3.4)	-	1.000‡	-	-
Smoking status						
Never-smokers	76 (90.5)	53 (89.8)	23 (92.0)	1.000‡	-	-
Ever-smokers	8 (9.5)	6 (10.2)	2 (8.0)			
Being hospital employee	71 (84.5)	51 (86.4)	20 (28.2)	0.456§	-	-
CXR severity grading						
Grade 1	70 (83.3)	53 (89.8)	17 (68.0)	0.014§	7.18 (1.76-29.35)	0.006
Grade 2 and 3	14 (16.7)	6 (10.2)	8 (32.0)		Reference	
No. of CT performed	53 (63.1)	39 (66.1)	14 (56.0)	0.380§	-	-
CT severity score	2 (2,3)	2 (2,3)	2 (2,4)	0.186†	-	-

AOR, adjusted odds ratio; 95% CI, 95% confidence interval. †Data were shown as median (Q1,Q3); P was obtained from the Mann-Whitney U test. ‡Data were shown as n (%); P was obtained from the Fisher's exact test. §Data were shown as n (%); P was obtained from the Chi-square test. ¶For an increase by 1 year.

Table 2. Radiologic features of culture-negative subclinical pulmonary tuberculosis.

CXR findings	**Total (N=84)**	**Culture-negative (N=59)**	**Culture-positive (N=25)**	**P**
Patchy opacities	57 (67.9)	41 (69.5)	16 (64.0)	0.622‡
Reticulonodular opacities	31 (36.9)	19 (32.2)	12 (48.0)	0.170‡
Nodules	4 (4.8)	2 (3.4)	2 (8.0)	0.579†
Cavitation	1 (1.2)	1 (1.7)	-	1.000†
Enlarged hilar shadow	1 (1.2)	1 (1.7)	-	1.000†
Bilateral involvement	13 (15.5)	5 (8.5)	8 (32.0)	0.006‡,*
Chest CT findings	**Total (N=53)**	**Culture-negative (N=39)**	**Culture-positive (N=14)**	**P**
Consolidation	13 (24.5)	9 (23.1)	4 (28.6)	0.725†
Tree-in-bud pattern	49 (92.5)	35 (89.7)	14 (100.0)	0.563†
Ground glass opacities	1 (1.9)	-	1 (7.1)	0.269†
Nodules	31 (58.5)	25 (64.1)	6 (42.9)	0.166†
Mass	1 (1.9)	1 (2.6)	-	1.000†
Cavitation	2 (3.8)	2 (5.1)	-	1.000†
Adenopathy	5 (9.4)	3 (7.7)	2 (14.3)	0.599†
Bronchiectasis	7 (13.2)	5 (12.8)	2 (14.3)	1.000†
Calcified nodules	14 (26.4)	9 (23.1)	5 (35.7)	0.358‡
Calcified lymph node	5 (9.4)	3 (7.9)	2 (14.3)	0.599†
Upper lobe involvement	46 (86.8)	35 (89.7)	11 (78.6)	0.364†
Bilateral involvement	12 (22.6)	6 (15.4)	6 (42.9)	0.035‡,*
Multilobar involvement	16 (30.2)	9 (23.1)	7 (50.0)	0.060‡

*†Data were shown as n (%); P was obtained from the Fisher's exact test. ‡Data were shown as n (%); P was obtained from the Chi-square test. *Statistically significant.*

institute upholds rigorous standards undergoing internal audits and external quality control checks to ensure optimal performance. Correspondingly, the observation of milder radiographic severity in culture-negative disease implies potentially lower bacterial loads, which in turn supports the accuracy of the culture results.

Increasing age is the other factor related to culture-negative subclinical pulmonary TB in this study. The average age of the culture-negative group was higher than the culture-positive group. However, this may not be clinically important and the explanation for this association has been unclear. Most studies that compared culture-negative and culture-positive pulmonary TB did not show a remarkable association between age and culture positivity [15,16,21]. Hence, the relationship between age and culture positivity needs to be clarified, particularly in subclinical disease.

Regarding the radiographic characteristics, the study demonstrated that subjects with culture-negative subclinical pulmonary TB had lower rates of bilateral pulmonary involvement. Again, this displays the progression of the disease from the culture-negative to culture-positive stages and corresponds with our results on the extent of TB lesions discussed earlier. In addition, multilobar involvement in chest CT was less frequent in the culture-negative group; however, the difference failed to reach statistical significance. Likewise, median CT severity scores were similar between the two groups. Such findings might be due to a small proportion of subjects that received CT scanning. It is also worth noting that prior research did not find differences in laterality and multilobar involvement proportions between culture-negative and culture-positive cases [21], of which the inclusion of symptomatic participants might attenuate the result.

In the present study, other radiologic patterns in both imaging modalities, namely CXR and CT, were indistinguishable between the two groups. In the same way, a study in Thailand found that there were no radiographic manifestations specific to smear-negative TB [22]. Meanwhile, a Korean study demonstrated that patchy opacities predicted positive mycobacterial culture (OR 2.14; 95% CI 1.19 to 3.83) [21]. Nevertheless, neither restricted the participants to only subclinical cases. Noteworthily, findings consistent with previous TB, including bronchiectasis, calcified nodules, and calcified lymph nodes, support that spontaneous regression occurs as part of the TB spectrum depicted by Drain and colleagues [3]. From a biological aspect, mycobacterial burden and immune activities play a role in cycling through the emerging TB stages [3].

Importantly, treating TB disease earlier will accelerate TB control at the population level. Establishing a diagnosis of subclinical pulmonary TB without microbiological confirmation is a clinical dilemma. Alternative diagnoses must always be considered in such cases [23]. A study comparing CXR and CT features of subclinical pulmonary TB also underscored that undetectable TB-related pulmonary lesions by CXR were major [24]. Therefore, we proposed leveraging a CT scan could aid the diagnosis in this clinical situation where available. A low-dose CT (LDCT) scan is a useful option as it performs well in detecting pulmonary TB with the advantage of lower radiation compared to conventional CT [25]. According to a study in China, the sensitivity and positive predictive value of using LDCT alone to diagnose pulmonary TB among healthcare workers were 100% and 86.4%, respectively [25]. Based on our facility's pricing, an LDCT scan of the chest costs approximately 6,050 Thai Baht or 165 USD per scan. Of note, the clinical decisions in this study, conducted in the context of a high TB burden country, were rooted in the pre-test probability of TB, alongside the diagnostic information provided by CT findings, which were highly suggestive of TB. This approach strengthened the accuracy of the diagnostic methods utilized.

To our knowledge, this is one of the first studies exclusively conducted on subclinical pulmonary TB cases comparing culture-negative and culture-positive diseases. In addition, the subjects were initially referred from the health checkups. As a result, they provided us with essential information on the very early stage of TB disease.

Several limitations due to the retrospective nature of this study should be considered. First, the study was conducted at a single center with a small sample size, causing decreased robustness and generalizability. Nonetheless, the study presents novel insights into the subclinical disease, serving as a notion for subsequent research. Second, approximately 40% of the participants did not undergo a chest CT scan, resulting

in insufficient power to detect the difference in CT findings accordingly. Even so, this reflects the normal practice that not all cases receive or require a CT scan, such as people who cannot access such investigation and whose CXR findings are typical for pulmonary TB. Third, the study design might not have captured all potential health and comorbidity variables. However, the focus on subjects from health checkup clinics suggests they were generally immunocompetent and healthy. Furthermore, the study accounted for diabetes, a well-established risk factor for TB progression. Replication studies are still crucial.

Conclusions

In conclusion, the authors believe that the present study adds evidence to the knowledge of the earlier stage of TB. To bring about widespread TB elimination, an active case-finding approach in settings with high TB prevalence and advocacy to enhance clinicians' awareness about subclinical, bacteriologically negative pulmonary TB are warranted.

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