COMPARISON OF HIGH RESOLUTION COMPUTED TOMOGRAPHY FINDINGS OF THORAX BETWEEN SMEAR NEGATIVE PULMONARY TUBERCULOSIS AND NON-PULMONARY TUBERCULOSIS AMONG PATIENTS WITH SUSPECTED PULMONARY TUBERCULOSIS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

DR. YAP TECK CHONG

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR MASTER OF MEDICINE (RADIOLOGY)

UNIVERSITI SAINS MALAYSIA

2022

COMPARISON OF HIGH RESOLUTION COMPUTED TOMOGRAPHY FINDINGS OF THORAX BETWEEN SMEAR NEGATIVE PULMONARY TUBERCULOSIS AND NON-PULMONARY TUBERCULOSIS AMONG PATIENTS WITH SUSPECTED PULMONARY TUBERCULOSIS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

DR. YAP TECK CHONG

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR MASTER OF MEDICINE (RADIOLOGY)

UNIVERSITI SAINS MALAYSIA

2022

ACKNOWLEDGEMENT

The completion of this undertaking could not have been possible without the participation, cooperation and assistance from so many parties whose names may not all be enumerated. Their assistance is sincerely appreciated and gratefully acknowledged. At this opportunity, I would also like to express my deep and utmost gratitude, particularly to the following groups of people;

1. Dr Wan Aireene Wan Ahmed, my supervisor, who had assisted and provided priceless scientific guidance and advice throughout the period of this study.
2. Dr. Nurashikin Mohammad and Dr Mohd Jazman bin Che Rahim, my co-supervisors, who had been supportive and encouraging during the progress of this study.
3. Professor Dr. Mohd Shafie Abdullah, Associate Professor Dr. Mohd Ezane Aziz, Associate Professor Dr. Juhara Haron, Dr. Khairil Amir Sayuti, Dr. Chandran Nadarajan, Dr. Ahmad Hadif Zaidin Samsudin, Dr. Nur Asma Sapiai, and Dr. Nasibah Mohamad (Lecturers cum Radiologists), all of whom directly or indirectly had contributed their ideas and comments to help me complete this study.
4. Radiographers, colleagues, and all the other staff in the Department of Radiology, Hospital USM.

TABLE OF CONTENT

LIST OF FIGURES

LIST OF TABLE

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

AFB	Acid Fast Bacilli
C&S	Culture and Sensitivity
CPG	Clinical Practice Guidelines
CT	Computed Tomography
CXR	Chest radiograph
ESR	Erythrocyte Sedimentation Rate
Hb	Hemoglobin
HRCT	High Resolution Computed Tomography
LIS	Laboratory Information System
MDR	Multidrug-resistant
MTB	Mycobacterium Tuberculosis
PACS	Picture Archive and Communication System
PCR	Polymerase Chain Reaction
PTB	Pulmonary Tuberculosis
RIS	Radiology Information System
RN	Registration Number
TB	Tuberculosis
TCA	To Come Again
WBC	White Cell Count
WHO	World health organization

ABSTRAK

Latar belakang: Tuberkulosis pulmonari merupakan masalah perubatan di seluruh dunia. Diagnosa smer kahak negatif PTB adalah satu cabaran. Keupayaan tomografi berkomputer beresolusi tinggi (HRCT) dalam mendiagnosis PTB masih dalam perbincangan dan penyiasatan dalam situasi smer kahak negatif. Disebabkan ini, kajian ini dijalankan untuk menentukan keputusan HRCT dalam mendiagnosis peringkat awal aktif smer-negatif PTB dan untuk mengkaji keputusan HRCT dalam mendiagnoskan smer-negatif PTB.

Metod: Kajian keratan lintang dijalankan di Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia ke atas 22 pesakit yang smer kahaknya negatif, dan telah menjalani HRCT paru paru. Keputusan HRCT dalam smer-negatif PTB telah dikumpul dan dihuraikan menggunakan statistik deskriptif, kiraan (n) dan peratusan (%); dan perbandingan HRCT antara smer-negatif PTB dengan bukan PTB dianalisis dengan menggunakan kaedah korelasi Pearson.

Keputusan: ”Tree-in-bud” menunjukkan perkaitan yang signifikan dengan smer-negatif PTB, dengan nilai *p* 0.046. Dan “tree-in-bud” yang berada di S5 (segmen medial) paru-paru kanan dan S3 (segmen depan) paru-paru kiri, dengan nilai p 0.025 masing-masing, menunjukkan perkaitan yang signifikan dengan smer-negatif PTB.

Kesimpulan: “Tree-in-bud” yang merupakan peringkat awal aktif smer-negatif PTB, menunjukkan perkaitan yang signifikan dengan smer-negatif PTB, dan dapat dikesani dalam HRCT. Disebabkan ini, HRCT boleh digunakan sebagai cara alternatif untuk

mengesankan pesakit berisiko yang lebih tinggi di kalangan mereka yang disyaki mempunyai aktif PTB dalam latar belakang smear-negatif kahak.

Kata kunci: Smer negatif tuberkulosi pulmonari, tomografi berkomputer beresolusi tinggi, "tree-in-bud"

ABSTRACT

Background: Pulmonary tuberculosis (PTB) has been around for over 100 years since it was first discovered. Despite its long existence, medical practitioners still found it challenging to diagnose sputum smear negative PTB. The ability of high resolution computed tomography (HRCT) in diagnosing PTB is still under discussion and investigation in the sputum smear-negative setting. Thus, this study was conducted to determine the HRCT findings in diagnosing early stage of active smear negative PTB and to study specific HRCT findings in diagnosing smear negative PTB.

Methods: A cross-sectional study was conducted in Hospital Universiti Sains Malaysia (USM), Kota Bharu, Kelantan, Malaysia on 22 patients whose sputum smears were negative, and had undergone HRCT thorax. HRCT findings were collected and described using descriptive statistic, count (n) and percentage (%); and comparative HRCT findings between smear negative PTB versus non-PTB was analysed using the Pearson chi-square test.

Results: The tree-in-bud appearance showed a significant association with smear negative PTB, with p-value of 0.046. And this main findings of tree-in-bud appearance showed significant association with smear negative PTB at S5 (medial segment) of right middle lobe and S3 (anterior segment) of left upper lobe, with p-value of 0.025 on both sides.

Conclusion: Tree-in-bud appearance which indicates the early stage of active PTB, had shown significant association with smear negative PTB, and can be detected in HRCT.

Hence, HRCT could be used as an alternative method to detect active PTB in the background of sputum smear-negative setting among higher risk patients.

Keywords: Smear negative pulmonary tuberculosis, high resolution computed tomography, tree-in-bud appearance.

CHAPTER 1: BACKGROUND

1.1 Introduction

Tuberculosis (TB) continues to dominate the global medical scene despite concerted effort and investment put in by countries for more than 20 years. The causative agent for TB is Mycobacterium Tuberculosis (MTB). It is one of the top ten causes of mortality and a leading cause of death from a single infectious agent. A total of 1.5 million people died from TB and estimated 10 million people were infected with TB in 2018 (WHO, 2019). In Malaysia, the incidence of pulmonary tuberculosis reported is 92 per 100,000 in 2019, which is the intermediate range when compared to the rest of the world (World Health Organization, 2017; Chan *et al.*, 2019; Avoi and Liaw, 2021).

MTB is a causative agent, which is spread via air-borne droplets particles when a person with TB coughs, sneezes, talks, or sings. However, not everyone who inhales these droplets develops TB. This is due to the fact that these people have good immune system – alveolar macrophage, to protect them from developing TB.

Tuberculosis can be classified into – pulmonary and extra-pulmonary. Pulmonary tuberculosis (PTB) can be further classified into smear positive and negative. PTB is suspected when the suggestive clinical history of predominantly prolonged cough, fever and constitutional symptoms are present. It is then confirmed with sputum smear for acid-fast bacilli (AFB), mycobacterium culture and sensitivity (MTB C&S), and supportive imaging particularly chest radiograph.

The common practice to determine if a patient has PTB is simple and straightforward. Proper guideline mentions that only one of the sputum samples is needed to show positive smear result to diagnose PTB. (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2002; Yon Ju Ryu, 2013). However, for those patients whose sputum samples show the negative result in the direct smear method, the PTB diagnosis is confirmed by obtaining a positive mycobacterium colony on culture media (Lowenstein-Jensen culture media), which is the gold standard of diagnosis (Chan, Sun and Hoheisel, 1990; Yon Ju Ryu, 2013). However, there are limitations to this culture method as it can take between 4 to 12 weeks before a patient is diagnosed as having PTB and a delay in initiating anti-TB therapy for patients with smear negative PTB.

In order to prevent the progress of the disease and reduce the infection rate, there are two ways that can be performed. First is using the rapid diagnostic method, the clinicians also have the option of using nucleic acid amplification test (NAAT) which detects DNA sequence specific for MTB called GeneXpert MTB/RIF®. However, this method lacks the sensitivity in diagnosing smear negative PTB with results ranging from 60% to 80%.

The second is to use another diagnostic method that can help in making the presumptive diagnosis of PTB more accurately. An alternative approach is using high resolution computer tomography (HRCT) thorax which is a better tool to diagnose patients with smear negative PTB (Naseem, Saeed and Khan, 2008; Lee *et al.*, 2010; Nakanishi *et al.*, 2010; Yon Ju Ryu, 2013; Çalişkan *et al.*, 2014). However, HRCT is not a routine practice to diagnose PTB patients in Malaysian Hospitals. Hence, this study is

conducted to determine the HRCT findings in diagnosing early stage of active smear negative PTB and to study specific HRCT findings in diagnosing smear negative PTB.

1.2 Objectives

1.2.1 General Objective

To study HRCT findings in early stage of smear negative PTB.

1.2.2 Specific Objectives

1. To determine HRCT findings that can be used in diagnosing smear negative PTB.
2. To compare the finding between smear negative PTB and other diseases (non-PTB) which presented with PTB-like symptoms.

1.3 Research Questions and Hypothesis

Question 1:

What are the common HRCT findings in smear negative PTB patients?

Hypothesis:

Cavities, centrilobular nodules, consolidation, ground-glass opacities, lobular consolidation, lymph node enlargement, micronodules, nodules, tree-in-bud appearance, pleural effusion, and presence of the main lesion in lung segments (S1, S2, and S6) as shown in Table 1.

Question 2:

What findings from HRCT can be used specifically in diagnosing smear negative PTB?

Hypothesis:

Nodules, lobular consolidation, tree-in-bud appearance, and presence of the main lesion in lung segments (S1, S2, and S6).

CHAPTER 2: LITERATURE REVIEW

2.1 Pulmonary Tuberculosis

2.1.1 Epidemiology of pulmonary tuberculosis

Pulmonary tuberculosis (PTB) continues to dominate the medical world, even after twenty years. Yearly cases reported to World Health Organisation (WHO) show no signs of declining (Tozkoparan *et al.*, 2005; Ors *et al.*, 2007). A total of 1.5 million people died from TB and estimated 10 million people were infected with TB in 2018 (WHO, 2019). In Malaysia, the incidence of pulmonary tuberculosis reached 92 per 100,000 in 2015, which is an intermediate incidence in the world (World Health Organization, 2017; Chan *et al.*, 2019). Diagnosis of tuberculosis is based on clinical, radiological, and bacteriological evidence.

MTB is an air-borne causative agent, which is transmitted via air-borne droplet nuclei when a person with pulmonary tuberculosis coughs, sneezes, talks, or even sings. When the droplets are inhaled into the lungs, usually it will be ingested by alveolar macrophages, which is known as microbicidal power. However, if the macrophage is unable to destroy the MTB, then the bacteria will multiply within its intracellular environment and then burst, causing this cycle to continuously happen inside the body. More often, immune-compromised patients are more prone to contact MTB (Feng *et al.*, 2013).

2.1.2 Diagnostic methods

There are few tests available to help clinicians with TB diagnosis, however, they are varied in terms of specificities and sensitivities. One of the commonly used, is the Tuberculin skin test, i.e Mantoux test. This test is usually employed for paediatric cases. In government hospitals all over Malaysia, the test is carried out by using 2 tuberculin units (T.U.) in 0.1ml of prepared solution. The results of skin changes will be obtained at 72 hours. The diameter of induration will be measured. Diameter of 10mm or more in children or adults is considered positive. Diameter of 15mm or more in a child is considered significant and may indicate recent infection. Diameter of less than 10mm is considered negative, but this cannot rule out a diagnosis of PTB (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2002).

The next diagnostic method is sputum direct smear for acid-fast bacilli (AFB), by using the Ziehl-Neelson method (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2002; Yon Ju Ryu, 2013). However, this direct microscopic method only shows high specificity, but low or variable sensitivity (20-80%) (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2002). Three sputum specimens, preferably early morning specimens, are usually collected for diagnosis. Despite that, this method has its limitation in terms of sensitivity.

Besides the above, the gold standard for PTB diagnosis is culture. The culture method is the most common method in confirming the diagnosis. The culture method is carried out using solid media, Lowenstein-Jensen slope, broth or egg-based media. For patients with difficulty in sputum expectoration, bronchoscopic aspiration or bronchoalveolar lavage can be used to obtain samples (Chan, Sun and Hoheisel, 1990;

Yon Ju Ryu, 2013). Despite this method being widely used, it also has limitations, which is the time taken to get the results. Usually, it would require 4 to 8 weeks before a patient can be properly diagnosed (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2002; Lee *et al.*, 2010; Yon Ju Ryu, 2013).

Another latest method worth mentioning is the GeneXpert MTB/RIF®. This method is especially useful to detect MTB and multidrug-resistant (MDR) TB by PCR amplification of the rifampicin resistance-determining region (RRDR) of the MTB *rpoB* gene (Blakemore *et al.*, 2010; Weyer *et al.*, 2013). At present, this method is used to overcome the long waiting period of MTB C&S as a standard of care. This procedure takes less than 2 hours to detect MTB. It is a fully automated, closed real-time PCR system, requiring basic laboratory infrastructure, operation skills of biosafety precaution. Based on the research done, the specificity of this procedure is 99% for most of the cases. Like the two previously mentioned methods, it has its limitation in detecting smear negative PTB with sensitivity ranging from 67% to 82% (Boehme *et al.*, 2011; Theron *et al.*, 2013; Weyer *et al.*, 2013; KR *et al.*, 2014).

Common clinical presentations which suggest PTB includes chronic cough (more than 2 weeks), haemoptysis, loss of appetite and weight, fever, and night sweat. Uncommon symptoms include dyspnoea, chest pain, and hoarseness of voice (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2002; Nakanishi *et al.*, 2010). Patients with clinical symptoms mentioned earlier will be screened for PTB, especially patients with a combination of 2 or more of the clinical presentations.

Chest radiograph remains as a primary radiological method to rule out PTB, however, chest radiograph shows its sensitivity in detecting active PTB, but is limited in specificity (Tozkoparan *et al.*, 2005; Yon Ju Ryu, 2013; Çalişkan *et al.*, 2014). Many 'obvious' manifestations shown in chest radiographs, such as cavitation, consolidation/cavitary opacities in apical and posterior segments of upper lobes, as well as in the superior segment of lower lobes, combined with the given clinical history of the patient may lead to the diagnosis of PTB (Yon Ju Ryu, 2013). Chest radiograph is a preferred method for follow up on the patients to assess the progress of the disease.

2.2 Smear Negative Pulmonary Tuberculosis

In view of the low sensitivity of the smear method of AFB, patients with suspected PTB whose sputum smear shows AFB negative always cause a medical issue in clinical practice. For smear negative PTB patients, culture remains as an essential method for the final diagnosis of PTB (Tozkoparan *et al.*, 2005; Lee *et al.*, 2010; Nakanishi *et al.*, 2010; Yon Ju Ryu, 2013). In order to prevent the progress of the disease and reduce the infectious rate, prompt initiation of anti-tuberculous (anti-TB) therapy for PTB is an important issue for clinicians. Patients with suspected PTB whose sputum smears for AFB are negative cause the clinicians to have some difficulty with the initiation of anti-tuberculous (anti-TB), particularly in the older patients and patients with chronic liver disease, as we know the side effect of anti-TB is drug-induced hepatitis (Tozkoparan *et al.*, 2005, Ramappa and Aithal, 2013).

The following criteria are particularly used to diagnose smear-negative PTB; (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2002; Yon Ju Ryu, 2013)

1. Patients with at least three sputum smear examinations that are negative of AFB, and with radiographic abnormalities consistent with PTB, determined by a doctor followed by a decision to treat patients with a full-focussed of anti-TB.
2. Patients whose initial sputum smears were negative, with sputum culture which is positive for *Mycobacterium Tuberculosis (MTB).*

2.3 High Resolution Computed Tomography (HRCT)

HRCT is a radiological method which is particularly used in evaluating lung parenchyma changes. The use of HRTC allows clinicians to detect lung parenchyma changes. Also, HRTC can provide more accurate image results as compared to conventional CT and chest radiographs (Swensen, Aughenbaugh and Brown, 1989; Kazerooni, 2001; Dalal and Hansell, 2006; Sundaram, Chughtai and Kazerooni, 2010).

In addition, HRCT is also an alternative method when the chest radiographs show normal or inconclusive findings (Yon Ju Ryu, 2013). Besides that, HRTC can also provide more accurate findings that are suggestive of PTB (Nakanishi *et al.*, 2010; Shaarrawy *et al.*, 2013). HRCT findings like tree-in-bud appearance, lobular consolidation, larger nodule, and main lesions in segment 1, segment 2, and segment 6, are highly suspicious of PTB (Naseem, Saeed and Khan, 2008; Nakanishi *et al.*, 2010; Shaarrawy *et al.*, 2013). And a combination of few HRCT findings can increase the accuracy in terms of specificity and sensitivity (Nakanishi *et al.*, 2010; Shaarrawy *et al.*, 2013). The typical locations of lung parenchymal involvement in PTB are usually at the

apical segment of the right upper lobe, the posterior segment of the right upper lobe, the apicoposterior segment of the left upper lobe, and the superior segment of both lower lobes (Nakanishi *et al.*, 2010; Shaarrawy *et al.*, 2013).

Endo-bronchial infection and bronchogenic spread indicate the early stage or active phase of the disease, findings include clustered micronodules, centrilobular nodules, and tree-in-buds branching opacities are identified in CT (Bhalla *et al.*, 2015). The findings in the early infectious stage are only about 20% detected in chest radiographs. Thus, HRCT can be served as an alternative method to detect these subtle findings which are hardly defined or seen when using chest radiograph.

2.4 Conceptual framework

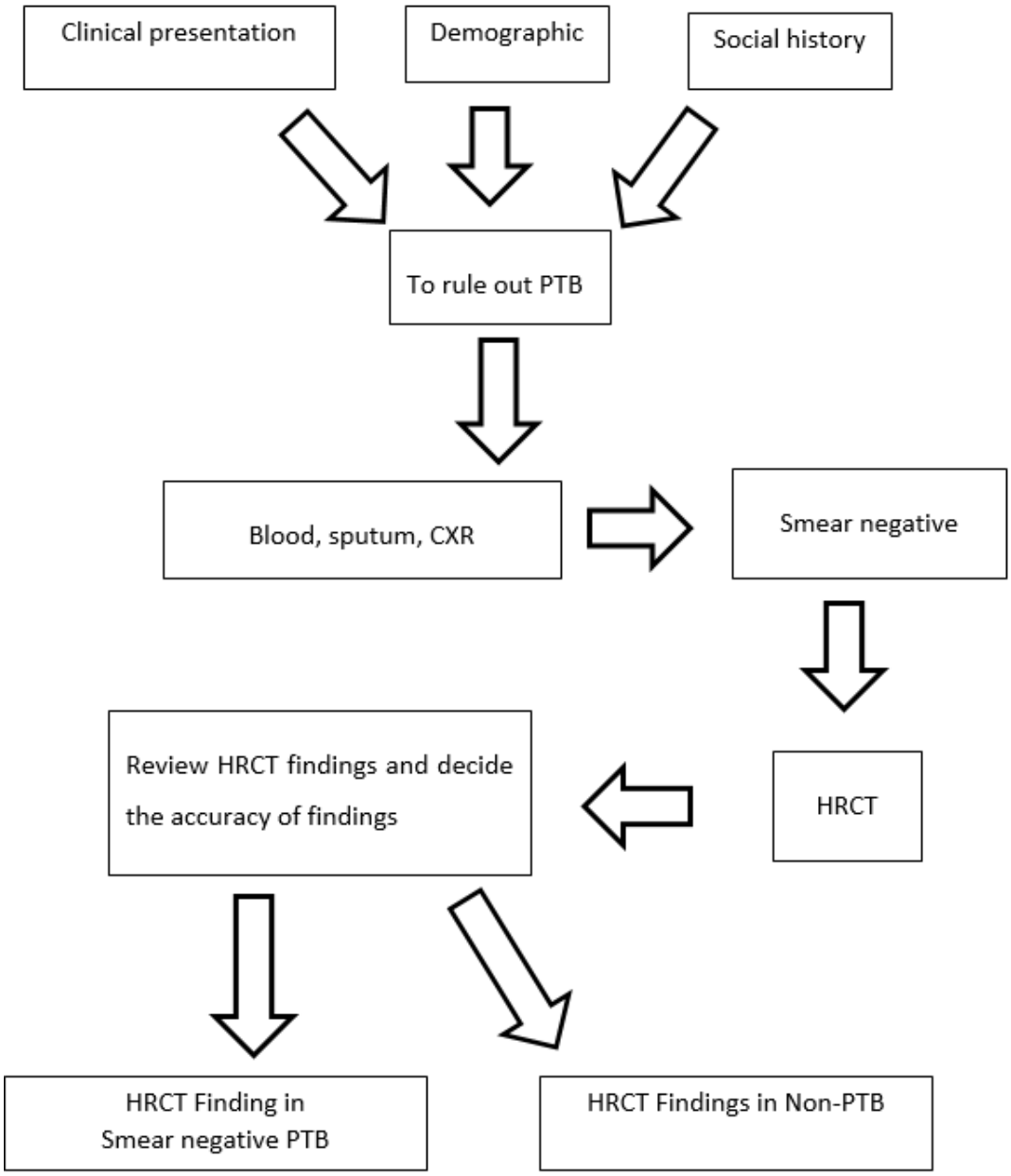


Figure 1: Conceptual framework

2.5 Problem Statement and Rationale of Study

Research and studies have shown that sputum culture is the best available method to confirm PTB, however, its long duration is a major limitation. Direct smear of AFB and chest radiograph are the primary diagnostic methods used in diagnosis of PTB, however, both show low sensitivity and low specificity. It can be challenging for clinicians to decide for smear negative PTB while waiting for the culture result, which usually takes about 4 to 8 weeks. Although GeneXpert MTB/RIF® can be used to detect MTB, however, the sensitivity in smear negative cases is varied, ranging from 67% to 82%.

As a result of the limitations mentioned above, this study aims to use HRCT findings in assisting the diagnosis of smear negative PTB. The outcome of this study might help clinicians prior to anti-TB initiation. HRCT thorax can be an ancillary tool to diagnose smear negative PTB early in order to prevent the progress of the disease and subsequently reduce the rate of infection.

CHAPTER 3: METHODOLOGY

3.1 Study Design

This was a cross-sectional study which was conducted in Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia for a period of 23 months, from 1st January 2020 to 31st November 2021.

3.2 Sample Population

i. Reference population – Subjects who are suspected to have PTB.

ii. Source population – Subjects who are suspected to have PTB and referred to Hospital USM to rule out PTB.

iii. Target population – Subjects who are suspected to have PTB and planned for HRCT after being seen by a clinician in Hospital USM.

iv. Sampling frame – Subjects who are suspected to have PTB and fulfilled the inclusion and exclusion criteria to proceed with HRCT.

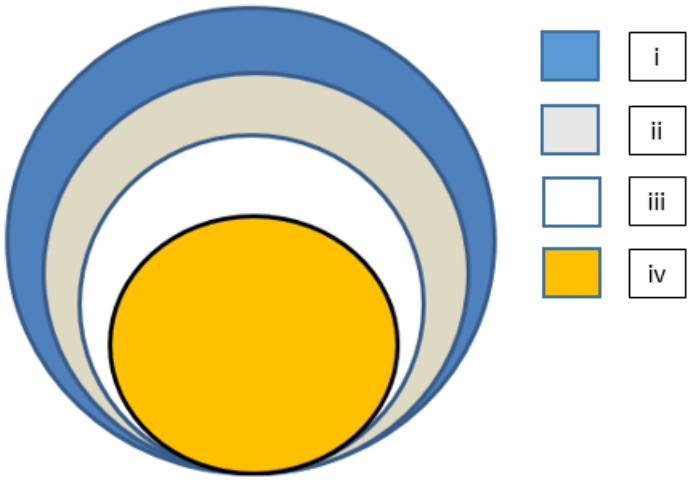


Figure 2: Study population

3.3 Sample Size Calculation

Objective 1

A study was done previously by Nakanishi et al., (2010), comparing HRCT findings in PTB. The sample size is calculated using the "Sample Size Calculator for Estimation of Single Proportion", which is a computer software created by Najib, MY (2015).

$$n = \left(\frac{Z}{\Delta}\right)^2 * P(1-P)$$

Z = 1 – alpha/2

Parameter	**P (%)**	**Estimated Sample Size**	**Corrected Sample Size**
Cavity	26	74	83
Centrilobular nodules	86	47	53
Consolidation	9	32	36
Ground-glass opacities	9	32	36
Lobular Consolidation	55	96	107
Lymph node enlargement	9	32	36
Micronodules	0	0	0
Nodules	85	49	55
Tree-in-buds	45	96	107

Pleural effusion	15	49	55
Main lesion at S1, S2, S6	91	32	36

*P = Percentage in smear negative patient

*Precision of estimation = 10%

*Drop out – 10%

Sample Size Calculator for Estimation of Single Proportion	
Instruction: Enter values in green cells Read output in gray cells	
Level of confidence (%)	95.0%
Population proportion, P (%)=	45.00%
Precision of estimation, (%)=	10.00%
Sample size calculated, n =	96
Anticipated dropout rate, % =	10.0%
Corrected sample size, n_c =	107
If finite population,	
Population size	
Corrected sample size after FPC	

Objective 2

Similar comparison study was done by Nakanishi et al., (2010). The sample size is calculated using the "Sample Size Calculator for Estimation of Two Independent Proportion", which is a computer software created by Najib, MY (2015) using the formula below:

$$n = \left(\frac{m+1}{2m}\right)\frac{(P_1(1-P_1)+P_0(1-P_0))}{(P_1-P_0)^2}\left(Z_{(1-\frac{\alpha}{\tau})}+Z_{(1-\beta}\right)^2$$

Parameter	**P0 (%)**	**P1 (%)**	**Estimated Sample Size**	**Corrected Sample Size**	**Total sample size (x 2)**
Centrilobular nodules	57	86	35	39	78
Lobular Consolidation	20	55	27	30	60
Micronodules	29	0	20	23	46
Nodules	57	85	38	43	86
Tree-in-buds	10	45	22	25	50
Main lesion at S1, S2, S6.	57	91	23	26	52

*P0 - control group

*P1 - smear negative PTB patient.

Drop out – 10%

Sample Size Calculator for Two Independent Proportion	
Instruction: Enter values in green cells Read output in gray cells	
Proportion in control group, Po=	57.00%
Estimated proportion in cases, P1=	85.000%
Type I error, α =	5.0%
Number of tail, τ =	2
Type II error, β =	20.0%
(power of study =)	80.00%
Ratio between control to case, m =	1
Sample size calculated, n =	38
Sample size for control =	38
Sample size for case =	38
Total sample size =	76
Anticipated dropout rate =	10.0%
Corrected sample size, n_c =	43
Sample size for control =	43
Sample size for case =	43
Total sample size =	86

Based on sample size calculation for both objectives 1 and 2, the highest sample size required was 107.

3.4 Sampling Method

No sampling method was applied. All eligible patients that fulfilled the inclusion criteria were enrolled in the study.

3.5 Inclusion Criteria

i. All subjects who were diagnosed by the primary team of Hospital USM as clinically smear negative PTB.
ii. Subjects who had not yet started on anti-TB or patients who had just started anti-TB (within 1 week).
iii. Subjects with sputum smear negative but GeneXpert positive.

3.6 Exclusion Criteria

i. Subjects who had started anti-TB for more than 1 week.
ii. Subjects with miliary pattern chest radiograph.
iii. Subjects who had poor sputum sampling.
iv. Subjects with smear positive PTB.
v. Subjects who had been diagnosed with any malignancy or interstitial lung disease.

3.7 Research Tools

1. CT Siemens Somatom Definition AS 128-slice was used for images acquisition.

   Protocol for image acquisition:

	CT Siemen
kVp	140
Effective mAs	110
Scan time	± 3.98s
Rotation time	0.5s
Pitch	1.2
Slice thickness	1mm
Direction	Craniocaudal
Kernal - Lung - Mediastinal	 B70f B26f

   *Total radiation of mSv – depends on CTDI vol and DLP

2. Picture archive and communication system (PACS) in Hospital USM (GE Healthcare, PACS Universal Viewer Version 6.0). All images will be displayed on a monitor at the pulmonary window level setting (level, -550HU; width 1600HU)
3. Socio-demographic data and clinical history from respiratory team.
4. Blood results, sputum AFB, and sputum culture results from Laboratory Information System (LIS) RESULTs application.
5. GeneXpert MTB/RFI result will be provided by the respiratory team if available.
6. Data collection sheet

3.8 Operational Definition

Smear positive PTB (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2002)

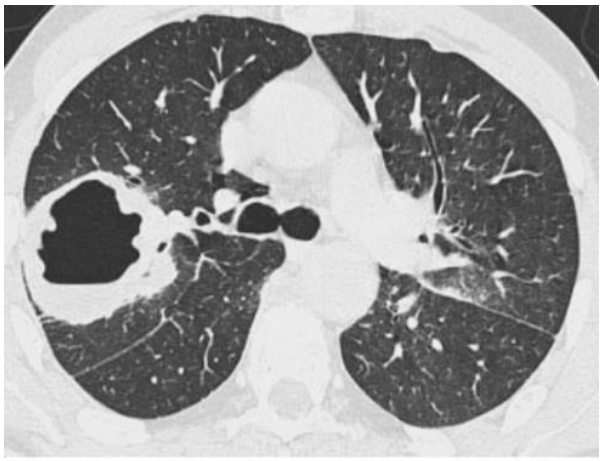
I. Patient with at least two initial sputum smear examinations (direct smear microscopy) positive for AFB
II. Patients with one sputum smear examination positive for AFB and radiographic abnormalities consistent with active PTB as determined by the treating doctor.
III. Patient with at least one sputum smear examination positive for AFB and sputum culture positive for MTB.

Smear negative PTB (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2002)

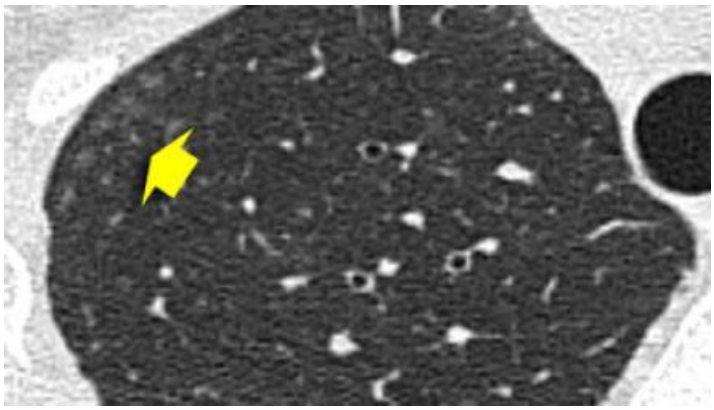
I. Patients with at least three sputum smear examinations which are negative of AFB, and with radiographic abnormalities consistent with PTB, determined by a doctor followed by a decision to treat the patient fully focussed on anti-TB.
II. Patients whose initial sputum smears were negative, and who had sputum culture showed positive for *Mycobacterium Tuberculosis (MTB).*

HRCT findings (Hansell et al.</i>, 2008)

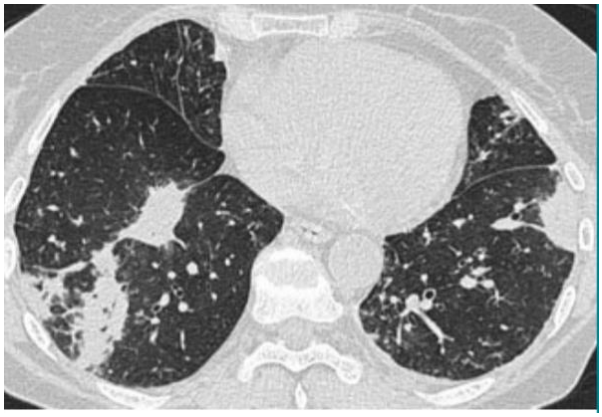
a. Cavities: A gas-filled space, seen as a lucency or low-attenuation area, within pulmonary consolidation, a mass, or a nodule.



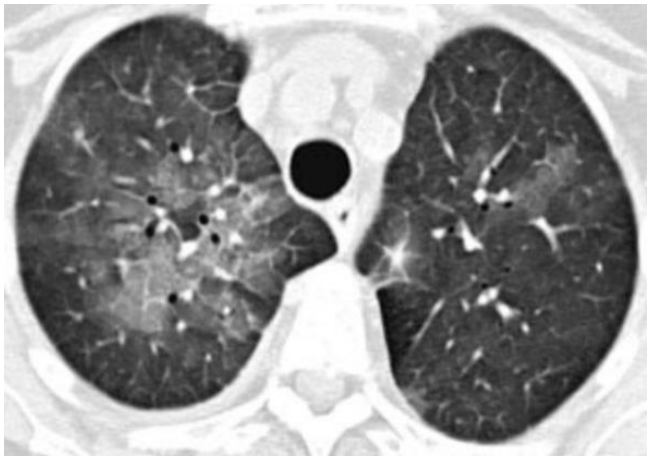
b. Centrilobular nodules: nodules at the region of the bronchiolovascular core of a secondary pulmonary lobule, most obvious within 1cm of the pleural surface.



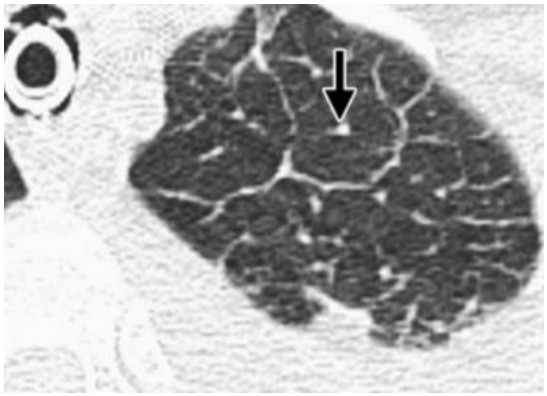
c. Consolidation: refers to an exudate or other product of disease that replaced alveolar air, rendering the lung solid.

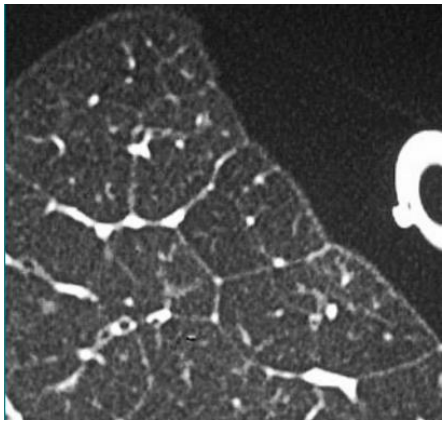


d. Ground-glass opacities: appears as hazy increased opacity of lung, with preservation of bronchial and vascular margins.

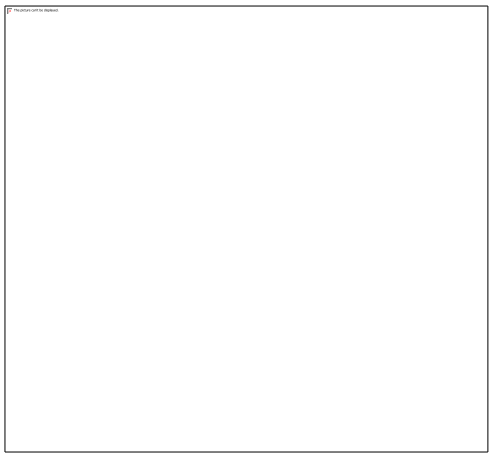


e. Lobular consolidation: consolidative changes involving the lobular core structures, which are the central structures in secondary pulmonary lobules and consist of a centrilobular artery and bronchiole.



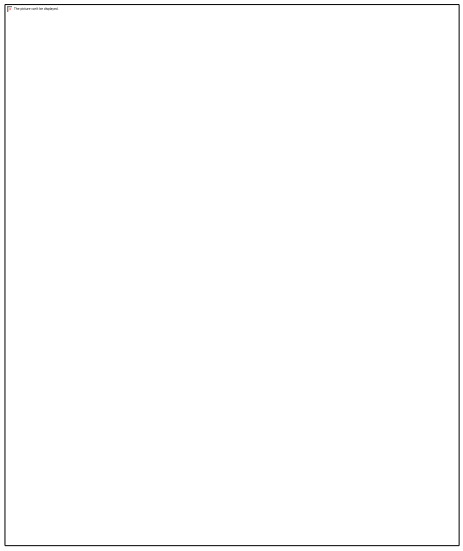


f. Lymph node enlargement: more than 1cm in mediastinal nodes, and more than 3mm for most hilar nodes.

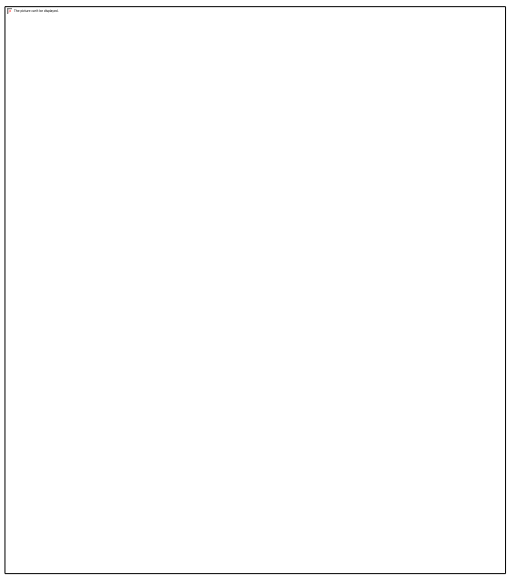


g. Micronodules: discrete, small, round, focal opacities, which are recommended used in nodules less than 3mm in diameter.

h. Nodules: rounded or irregular opacities, well or poorly defined, measuring less than 3cm in diameter.



i. Tree-in-bud appearance: represents centrilobular branching structures that resemble a budding tree. Usually reflecting a spectrum of endo-or peribronchiolar disorders.



j. Pleural effusion: Excess fluid in the pleural cavity (a space in between the parietal and visceral pleura).

k. Presence of a main lesion in lung segments (S1, S2, and S6)