LUNG ULTRASOUND PATTERN IN PULMONARY TUBERCULOSIS

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LIST OF ABBREVIATIONS

HUSM : Hospital Universiti Sains Malaysia

HRPZ II : Hospital Raja Perempuan Zainab II

HKL : Hospital Kuala Lumpur

IPR : Institut Perubatan Respiratori

NMRR : National Medical Research Register

JEPeM: Human Research Ethics Committee of Universiti Sains Malaysia

PTB : Pulmonary Tuberculosis

TB : Tuberculosis

AFB : Acid-fast bacilli

MTB PCR : Mycobacterium Tuberculosis Polymerase Chain Reaction

Gene Xpert® MTB/RIF : Gene Xpert® Mycobacterium Tuberculosis Resistance to Rifampicin

CT : Computed Tomography

ABSTRAK

Latar Belakang

Penyakit batuk kering adalah penyakit berjangkit yang boleh membawa maut. Terdapat pelbagai cabaran dalam menghasilkan diagnosis kerana kaedah sedia ada melalui ujian makmal dan sinaran X-ray dada mempunyai tahap pengenalpastian yang rendah. Ini mengakibatkan proses diagnosis tergendala, dan lebih ramai populasi terdedah kepada penyakit ini. Kajian kami ini bermatlamat untuk meningkatkan tahap ketepatan diagnosis dengan penggunaan ultrabunyi dada untuk digabungkan dengan kaedah diagnosis sedia ada. Kami cuba mencari karakter ultrabunyi yang unik untuk penyakit ini dan membandingkan keputusannya dengan X-ray dada.

Tatacara

Kajian prospektif ini melibatkan beberapa pusat rawatan penyakit batuk kering. Pesakit mestilah berumur 18 tahun ke atas dan positif ujian makmal untuk penyakit batuk kering. Ultrabunyi dada dilakukan menggunakan ‘probe’ berbentuk cembung pada 14 sektor dada yang merangkumi bahagian hadapan, tepi dan belakang. Karakter yang diperhatikan pada ruang ‘pleura’, di bawah ‘pleura’ dan ‘subkostal’ digambarkan. Karakter yang dilihat direkodkan dan dibandingkan dengan X-ray dada pesakit.

Keputusan

Seramai 141 pesakit telah terlibat dalam kajian ini dari tempoh Januari 2019 hingga Februari 2020. Sektor yang paling tinggi mencatatkan rekod penemuan ialah R1a iaitu seramai 92 (65.4%) pesakit, diikuti sektor R1b seramai 88 (62.4%) pesakit. Zon paling

tinggi dicatatkan ialah zon tengah kanan sebanyak 112 (79.4%). Karakter yang paling kerap ditemui ialah ketidaksamaan lapisan ‘pleura’ dalam 139 (98.6%) pesakit dan konsolidasi di bawah ‘pleura’ dalam 125 (88.7%) pesakit. Dari segi perbandingan dengan X-ray dada, ultrabunyi mempunyai tahap persetujuan yang sederhana sama dan merekodkan keputusan yang lebih tinggi berbanding X-ray dada. Terdapat tahap persetujuan Kappa yang sederhana antara ultrabunyi dada dan X-ray dada diperhatikan di semua zon dengan julat nilai dari 0.46 hingga 0.59, dengan kepekaan yang lebih tinggi diperhatikan bagi ultrabunyi dada.

Kesimpulan

Karekter ultrabunyi dada yang diperhatikan adalah selari dengan patologi penyakit batuk kering yang melibatkan sektor sebelah kanan dan atas bahagian dada. Ultrabunyi dada menunjukkan tahap pengenalpastian yang lebih tinggi berbanding X-ray dada terutamanya zon tengah kanan dan zon bawah kanan.

Tajaan

Tiada tajaan yang diterima untuk kajian ini.

ABSTRACT

Background

Pulmonary tuberculosis is a lethal transmissible airborne disease. There are various challenges in establishing diagnosis due to the low sensitivity of conventional bacteriological confirmation and limited accessibility to chest X-ray. These challenges result in a delay of diagnosis, risking more populations being infected, resulting in overall poor control of the disease. We aim to increase the diagnostic accuracy by introducing the usage of lung ultrasound in combination with current diagnostic modalities. We describe common lung ultrasound pattern seen in pulmonary tuberculosis and measure its agreement with the routine screening imaging, that is chest X-ray.

Methods

A multicenter prospective cross-sectional study was conducted among confirmed pulmonary tuberculosis patients aged above 18 years old. Lung ultrasound was performed using a convex probe covering 14 lung sectors that covered the anterior, lateral and posterior aspect of the lung. The pattern observed in pleura, subpleural and subcostal space were described. The findings were also being compared with chest X-ray to find the agreement between the two imaging modalities.

Findings

A total of 141 patients were recruited between January 2019 and February 2020. The most frequent sector with findings was R1a seen in 92 (65.4%) patients, followed by R1b seen in 88 (62.4%) patients. The most common zone with finding was right middle zone observed in 112 (79.4%) patients. Pleural irregularity and subpleural consolidation were observed in 139 (98.6%) and 125 (88.7%), respectively. There was a moderate Kappa

agreement between lung ultrasound and chest X-ray observed in all zones with a value ranging from 0.46 to 0.59, with higher sensitivity observed for lung ultrasound.

Conclusion

The lung ultrasound pattern observed is in line with pulmonary tuberculosis pathology, which involved the right upper and middle sector of the lung parenchyma. Lung ultrasound showed higher sensitivity compared to chest X-ray especially when involving right middle zone and right lower zone.

Funding

No grants were received for this study.

CHAPTER 1: INTRODUCTION

1·0 INTRODUCTION

Pulmonary tuberculosis (PTB) is an airborne disease caused by *Mycobacterium tuberculosis*. It is a global threat, with up to 8 million numbers of cases per year.[1] In developing countries, particularly Southeast Asia and Africa, it is a significant cause of morbidity and mortality.[2]

In Malaysia, the number of tuberculosis cases continues to rise over the years. In 2017 alone, the incidence was 90 per 100,000 population.[1] Figure 1a below shows the rising trend as depicted from the year 2000 to 2016 from WHO Country Tuberculosis Profile 2017;

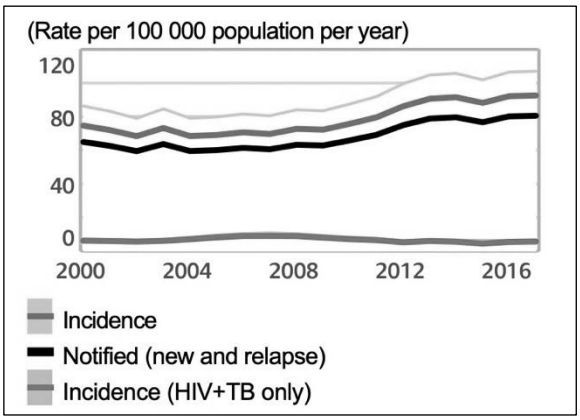

Figure 1a: Incidence of TB cases in Malaysia from 2000 to 2016 (World Health Organization Tuberculosis Country Profile. 2017)

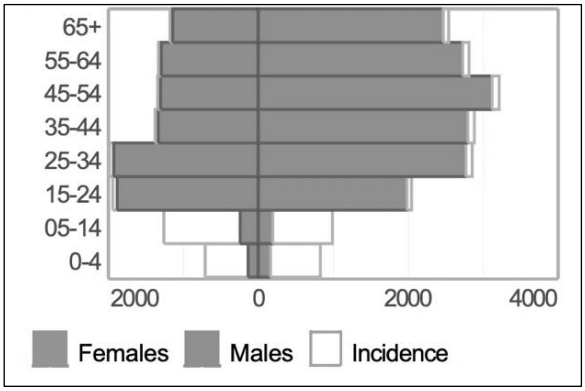

Figure 1b: Notified cases by age group and sex in Malaysia for 2017 (World Health Organization Tuberculosis Country Profile. 2017)

As shown in Figure 1b, the most common age group falls between 15-64 years old with male predominance.[1]Among the states, Sabah was reported to have the highest prevalence, followed by Selangor and Sarawak. Meanwhile, Kelantan was reported to have the highest prevalence in comparison with other east coast states in the country (Table 1c).

States	Total Case	TB Notification Rate (per 100,000 population)	TB Death	TB Mortality Rate (per 100,000 population)
Johor	2409	67.8	135	3.8
Kedah	1279	61.7	142	6.8
Kelantan	1233	71.8	93	5.4
Melaka	513	58.8	39	4.5
NS	667	60.7	60	5.5
Pahang	936	57.7	80	4.9
Perak	1657	66.9	162	6.5
Perlis	130	52.8	14	5.7
PP	1283	77.1	132	7.9
Sabah	4464	126.0	264	7.4
Sarawak	2575	97.7	195	7.4
Selangor	4429	75.4	255	4.3
Terengganu	710	61.6	58	5.0
WPKL	1819	98.0	58	3.1
Labuan	116	119.8	9	9.3
MALAYSIA	**24220**	**79.4**	**1696**	**5.5**

Table 1c: Total TB case, notification rate, TB death and TB Mortality according to states in 2015 (National Strategic Plan for Tuberculosis Control. 2016-2020: p. 6)

PTB infection starts when mycobacteria reach the alveoli. Alveolar macrophages will phagocytize these mycobacteria, causing interaction with T lymphocytes which then cause further differentiation of macrophages to epithelioid histiocytes.[7] Both lymphocytes and epithelioid histiocytes would then form small clusters, called a granuloma. Within the granuloma, CD4 T lymphocytes secrete cytokines which stimulate macrophage to kill the bacteria.[8] The bacteria can either be eliminated or remains dormant, to cause a latent

infection. Because of this mechanism too, the central part of the granuloma will form as necrosis.

Ghon focus is the description of the primary site of infection. It may undergo healing or enlarges as the disease progresses. If it heals, a visible scar will be formed, which is dense and calcified. The spread of this primary infection to adjacent lymph nodes will result in the formation of Ranke complex.[9]

1·1 PROBLEM STATEMENT

According to the World Health Organization (WHO), the definition of a tuberculosis case is either by bacteriologically confirmed method or through clinical diagnosis. A bacteriologically confirmed case is when a biological specimen is positive by either smear microscopy, culture or WHO-approved rapid diagnosis test (such as Xpert® MTB/RIF).[5] A clinically-diagnosed tuberculosis case is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active tuberculosis by a clinician or other medical practitioner who has decided to give the patient a full course of tuberculosis treatment. This includes cases diagnosed based on chest X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation.[5]

In Malaysia, the current Malaysian Clinical Practice Guideline on Management of Tuberculosis 3rd edition follows these definitions. However, most of the diagnoses made were based on a clinical definition rather than bacteriological.[3] This is based on the fact that bacteriological tests will take some time to yield results, and the faster rapid presumptive test available (acid-fast bacilli sputum staining) is less sensitive, hovering around 40-75% only.[3] Clinical diagnosis depends on collective judgement based on history, physical examination and imaging modality, mostly utilising chest X-ray.

The diagnostic dilemma arises when the chest X-ray showed normal findings or showed findings not typical of tuberculosis pattern. This study intends to explore pattern observed from lung ultrasound and compared it with chest X-ray, with an attempt to offer it as an aiding imaging modality to assist clinicians' decision.

1·2 LITERATURE REVIEW

The earlier literature on pulmonary tuberculosis imaging focused on the chest X-ray findings to assist pulmonary tuberculosis diagnosis. However, it was shown that some cases were missed due to normal X-ray findings. The subsequent update extensively described the roles of computed tomography (CT) scan to fill in the gap.[9,10,11] CT scan has higher sensitivity and specificity[3], however, it is costly and may not be available at all settings. The use of other imaging modalities apart from chest X-ray and CT scan has not been described in the present literature.

In the emergency department and most health clinics setting in Malaysia, ultrasound is an available bedside imaging tool used widely to confirm pulmonary findings. The current lung ultrasound literature described non-specific lung ultrasound findings[6]. For example, a general description of how consolidation would appear on lung ultrasound was described. However, whether different causes of lung consolidation would exhibit different patterns or combinations of pattern owing to their unique pathology were unknown.

We intend to see whether any studies describe a specific pattern of pulmonary tuberculosis on lung ultrasound. A systematic review of studies on chest ultrasound in thoracic tuberculosis revealed 12 studies in five main areas; detection of pleural effusion, assessing residual pleural thickening, assisting trans-thoracic needle biopsy, and assessing mediastinal lymphadenopathies and detection of pulmonary involvement in military TB.[27] From this review, there was no study apart from a single case report that analyzes the parenchymal ultrasound pattern in pulmonary tuberculosis. Apart from that, none of the trials listed in the review compared chest ultrasound with other imaging modalities.[27]

Our other literature searches revealed one small study entitled ‘Chest ultrasound findings in pulmonary tuberculosis’ by Agostinis P. et al.[12] In this study, a group of known pulmonary tuberculosis patient underwent lung ultrasound and the findings were described. It was found that subpleural nodule was the most frequent finding. However, due to the small sample size, the p-value was not significant. There was also no further description of other pattern observed other than this one new finding.

Another literature by Heller T et al. described the ultrasound findings specific in HIV-associated tuberculosis patient, with the development of FASH (Focused Assessment with Sonography for HIV-associated TB) protocol.[28] However, this protocol only depicted the extrapulmonary ultrasound findings and did not include any specific lungs pattern.[28] Hunter L. et al. performed an extended FASH to include all lung parenchyma. However, their findings only pertain to military tuberculosis, which was frequently seen in HIV-associated tuberculosis cases.[30]

With regards to a different manifestation of pulmonary tuberculosis in different age groups, Buonsenso D. et al. showed that adult cases usually manifest broader and more extensive area of a parenchymal lesion, which makes it easier to be detected by ultrasound.[29] Whereas in paediatric age group, hilar lymph nodal disease, which was the hallmark of paediatric tuberculosis, are more challenging to be seen due to interposition of air between the probe and hilar lymph nodes.[29] The pleural changes are also rare to be seen with only 20% of cases, contributing to the low specificity of lung ultrasound findings in paediatric group.[29]

Based on our literature review, there are limited studies that described lung ultrasound pattern of pulmonary tuberculosis in extensive details. The study by Agostinis P. et al. [12] is closer to

our intention, and thus we think of adapting it with some modifications and a significant number of samples to find whether pulmonary tuberculosis exhibit any specific pattern on lung ultrasound. Our study intends to find whether the pattern observed is parallel with the existing chest X-ray or CT scan, as we aim to propose incorporating lung ultrasound as additional imaging modality to assist diagnosis. Apart from that, should a specific pattern be observed from this study, we hope this could impact other studies about lung ultrasound pattern for other lung pathologies.

1·3 STUDY JUSTIFICATION AND BENEFIT OF THIS STUDY

Chest X-ray could be normal in up to 15% of patients.[3] Computed tomography (CT) is the next useful imaging, especially in case of normal chest X-ray as it yields higher sensitivity and specificity.[3] However, it is costly, and might result in a delay of diagnosis and thus starting the appropriate treatment.

Ultrasound is a bedside clinical tool which is quick, usually accessible at primary care setting (Klinik Kesihatan) and also first liners (Emergency Department). If ultrasound could reveal PTB imaging comparable to chest X-ray and CT thorax, it could perhaps assist these first liners to come with diagnosis at initial encounter accurately.

Lung ultrasound studies currently describe general findings of lung pathologies, without further delineating possible specific pattern observed for different type of lung pathologies. This study is aimed to provide a necessary foundation for this unexplored field, starting with pulmonary tuberculosis.

The immense benefit of this study is for the first-line healthcare practitioners who might be having a dilemma in accurately diagnosing pulmonary tuberculosis. However, this study is the first phase of this intention as we would like to explore first whether this specific pattern does exist. The more specific study on ultrasound sensitivity and specificity is intended in the next phase, at another different setting as that requires its comparison with other lung pathologies, namely lung fibrosis, lung carcinoma and so on.

1·4 RESEARCH QUESTIONS

(i) Does pulmonary tuberculosis exhibit any specific lung findings on ultrasound?

(ii) Would the ultrasound findings in pulmonary tuberculosis be similar to the chest X-ray or CT thorax findings?

1·5 OBJECTIVES

1·5·1 General objective:

To explore the lung ultrasound pattern of pulmonary tuberculosis

1·5·2 Specific objectives:

(i) To identify the most common lung sector with findings in pulmonary tuberculosis using lung ultrasound

(ii) To explore specific lung ultrasound pattern observed in pulmonary tuberculosis

(iii) To find the agreement between ultrasound findings with chest X-ray or CT thorax

1·6 CONCEPTUAL FRAMEWORK

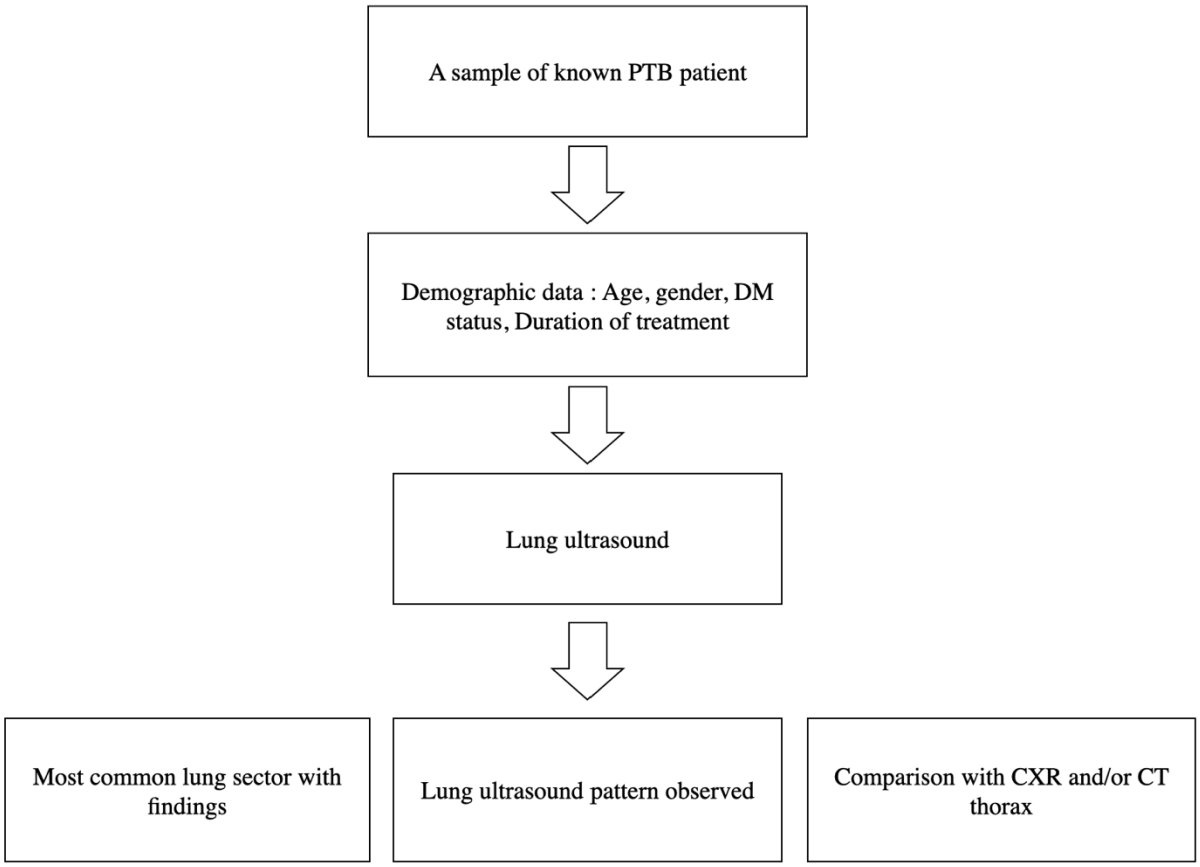

Figure 1d: Conceptual framework of study

CHAPTER 2 : STUDY PROTOCOL

2·0 STUDY DESIGN

(i) Study design

This is a comparative, cross-sectional, observational study.

(ii) Study duration

The study was performed from January 2019 to February 2020. The duration of ultrasound performed for each patient was 15 minutes.

(iii) Study area

This is a multi-centre study involving :

a. Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan
b. Hospital Raja Perempuan Zainab II (HRPZ II), Kota Bharu, Kelantan
c. Institut Perubatan Respiratori (IPR), Kuala Lumpur

(iv) Study population

a. Reference population: Pulmonary tuberculosis patient in Kelantan and Kuala Lumpur
b. Source population: Pulmonary tuberculosis patient under HUSM, HRPZ II, Kota Bharu and HKL and IPR in Kuala Lumpur follow up
c. Study participants: Pulmonary tuberculosis patient under chest clinic of HUSM, HRPZ II and IPR Kuala Lumpur follow up, at best within two weeks of commencement of treatment
    1) Inclusion criteria

- All pulmonary tuberculosis patients diagnosed with bacteriological confirmation (either sputum AFB, sputum MTB culture, Gene Xpert® or MTB PCR) at best within two weeks of commencement of treatment, or within intensive phase (2 months of treatment)
- Age above 18 years old

2) Exclusion criteria
   - Patients with extrapulmonary tuberculosis without pulmonary involvement
   - Patients refused to be involved
   - Patients with concurrent pneumonia / heart failure / lung carcinoma/ lung fibrosis
3) Withdrawal criteria
   - Patients with scarce diagnosis in the beginning (either pulmonary tuberculosis or other pathologies), in which subsequent investigations and physician decision is not pulmonary tuberculosis
   - Withdrawal rate anticipated: 10-20%

2·1 SAMPLING

Sampling Size Calculation

(i) For the first specific objective: To identify the most common site of PTB

The sample size needed is 93. A study by Curvo-Semedo L.et al.l shows 41% of active tuberculosis have apical findings on chest radiograph[19]. Using single proportion formula

to estimate the sample size, with P of 0·41, confidence interval 95% and precision of 0·1, n (sample size);

$$n = [1{\cdot}96/0{\cdot}1]^2 \times 0{\cdot}41 \times (1- 0{\cdot}41)$$

$$= 93$$

(ii) For the second specific objective: To explore specific lung ultrasound features in pulmonary tuberculosis

The sample size needed is 93. A study by Agostinis P. et al. shows that 42% of pulmonary tuberculosis patients exhibit subpleural nodule with consolidation on lung ultrasound[12]. Using single proportion formula to estimate the sample size, with P of 0·42, confidence interval 95% and precision of 0·1, n (sample size);

$$n = [1{\cdot}96/0{\cdot}1]^2 \times 0{\cdot}42 \times (1-0{\cdot}42)$$

$$= 93$$

(iii)For the third specific objective To find the agreement between ultrasound findings with chest X-ray or CT thorax

The sample size needed is 156. The sample size was calculated using 'Kappa size' package in R software to find the Kappa agreement (agreement between ultrasound with CXR or CT scan). The agreement for consolidation, pleural effusion and subpleural nodule was assumed to be 0·85, 0·65 and 0·5 respectively;

a. Consolidation

The expected Kappa = 0·89 (based on a study by Lichtenstein DA et al., the Kappa coefficient between ultrasound and chest X-ray in detecting consolidation is 0·89 meaning a strong level of agreement)[23]. The proportion of positive findings = 0·44 (based on Hatipoglu ON et al., 44% of pulmonary tuberculosis patient have a positive finding of consolidation)[24]

b. Pleural effusion

The expected Kappa = 0·64 (based on a study by Mattison LE et al., the Kappa coefficient between ultrasound and chest Xray in detecting pleural effusion is 0·64 meaning moderate level of agreement)[25]

The proportion of positive findings = 0·25 (based on Zhai et al., 25% of pulmonary tuberculosis patient have a positive finding of pleural effusion)[26]

c. Subpleural nodule

The expected Kappa = no study/literature on this yet

The proportion of positive findings = 0·96 (based on Agostinis P et al., 96% of pulmonary tuberculosis patient have a positive finding of subpleural nodule)[12]

The lower Kappa agreement was set at 0·75, 0·55 and 0·4 respectively. The upper Kappa agreement was set at missing to allow for a one-sided test. The number raters equal 2 (ultrasound vs chest X-ray or CT) and type 1 error at 5%.

The sample size needed is 141, and with 10% oversampled, the number needed is 156 patients.

Sampling Method & Subject Recruitment

With the sample size calculation shown above, the sample size needed is 156 to include all three specific objectives. The sampling method will be convenience sampling.

2·2 OPERATIONAL DEFINITION

(i) This study is a cross-sectional comparative study

(ii) Tools

The ultrasound machine used is the mobile ultrasound model Logic V2 GE. The probe used is a convex probe, with frequency of 4-5 MHz (medium frequency transducer). The reasons for using medium frequency transducer are;

a. The most universal transducer in any setting (district, clinics, interdepartmental)
b. Wider field of view. Thus in case of a consolidation, a definitive border could be visualized
c. Depth could be tailored for obese patients with thick chest wall

Should a more detailed description of the finding needed, the probe may be changed to linear probe, which has a higher frequency and could provide better spatial resolution.

(iii) Area scanned

There are several methods of dividing the areas for lung ultrasound. We adopted the 12-area division which is based on anatomical landmark[15]. This consists of two anterior, two lateral, and two posteriors for both side of the lung:

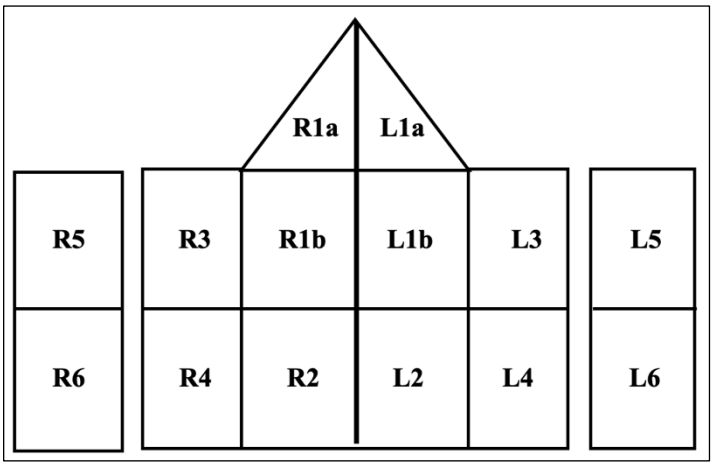

Figure 2e : Area to be scanned

Chest	Sector	Boundaries	Anatomical/study significance
Anterior	R1 or LI (anterior upper)	Upper: clavicle; lower: 4th rib; medial: sternal edge; lateral: defined by LUS image of lung; beyond this border are contents of the axilla and clavipectoral triangle	• Horizontal fissure is in line with the 4th rib; therefore, this zone contains the upper lobe of the lung
	R2 or L2 (anterior lower)	Upper: 4th rib; lower: variable, depending on body habitus and defined by curtain sign in LUS and appearance of abdominal contents;liver on the right side, bowel and spleen on the left; medial: sternal edge; lateral: anterior axillary line	• The 6th rib approximates the inferior most part of the lung and anterior insertion of diaphragm (not seen in normal LUS with curtain sign). Beyond the 6th rib is the potential space: costophrenic recess • This sector contains mainly the middle lobe; on the left lung, lingular lobe; with a small portion of the lower lobe on the lateral side • The sector on the left hemithorax is very small due to the position of the heart; no sector in cardiomegaly states
	Rs or Ls supraclavicular fossa	Triangle formed by the clavicle, lower parts of sternomastoid and trapezius	• Optional study area for the following: first rib; apical pneumothorax; pulmonary tuberculosis
Lateral	R3 or L3 lateral axilla	Upper: axilla; lower: the axis of the 4th rib; anterior: anterior axillary line; posterior: posterior axillary line	• This sector contains primarily the upper lobe of the lung with a small portion of the lower lobe
	R4 or L4 lateral lower	Upper: the axis of the 4th rib; lower: variable, depending on body habitus. Defined by curtain sign in LUS; anterior: anterior axillary line; posterior: posterior axillary line	• This sector contains primarily the lower lobe of the lung
Posterior	R5 or L5 posterior upper	Upper: defined by LUS image of the lung; medial: thoracic spine; lateral: medial border of scapula; lower: level of the inferior angle of the scapula	• This sector contains the upper lobe and lower lobe of the lung in almost equal proportion
	R6 or L6 posterior lower	Upper: level of the inferior angle of the scapula; medial: thoracic spine Lateral: posterior axillary line; lower: defined by curtain sign in LUS and appearance of abdominal contents ; liver on the right side; bowel and spleen on the left	• This sector contains primarily the lower lobe of the lung

Table 2f : Detailed anatomical landmark. (Lee FCY. Lung ultrasound-a primary survey of the acutely dyspneic patient. *J Intensive Care Med*. 2016, p: 3)

Should any abnormality detected, these will follow through:

a. The sub-specific site/s will be further delineated on the collection sheet

   This would apply specifically to R1 and L1, which would be further divided to R1a, R1b and L1a, L1b respectively. Anatomically, R1a extend from Rs region down to the second rib (thus focusing on apical region), and R1b from the second rib to the fourth rib. The L1a and L1b would be the same for the left side.

b. The specific description of the findings, which is according to the evidence-based recommendations[6] ;

   A. Consolidation: Echo-poor region or one with tissue-like echotexture[6]

      1. Subpleural consolidation : consolidation confined to pleura, uniformly hypoechoic with borders so well defined and irregular that it appears as if it were torn out from the surrounding normal parenchyma (‘shred sign’).[6,18]

      2. Subcostal consolidation : consolidation that extend to the costal region, borders may not be so well defined

   B. B lines: Discrete laser-like vertical hyperechoic reverberation artifacts that arise from the pleural line (previously described as ‘comet-tails’), extend to the bottom of the screen without fading and move synchronously with lung sliding.

   C. Pleural effusion: A usually anechoic space between parietal and visceral pleura. Could present as complex (echoic) in case suggestive of exudative or haemorrhage, which is further categorized into septated or non-septated.

(iv) Ultrasound image review protocol

The image interpretation done by the operator is validated by two certified instructors of WINFOCUS (World Interactive Network Focused on Critical Ultrasound). On the other hand, the chest X-ray images were interpreted by a radiologist who was blinded to the lung ultrasound images. Both lung ultrasound and chest X-ray images are then compared.

2·3 DATA COLLECTION

(i) Setting

The operator will be on the right side of the patient. Patient will be lying supine or semi-supine initially to scan the anterior and lateral part. Then, the patient will sit with his/her back turned to the operator for scanning of the posterior areas. The estimated duration of scan per patient is 15-20 minutes.

(ii) Image collection and interpretation

The ultrasound will be performed by the principal investigator. Images recorded are to be interpreted by supervisors who are certified instructors of WINFOCUS (World Interactive Network Focused on Critical Ultrasound). Standardization of interpretation is ensured as both supervisors will be looking into the images for consensus on the interpretation.

(ii) Data handling and storage

Images will be stored in secured computer database which is password protected. It will be stored in an independent removable hard disc, only accessible to the principal investigator and her team. This hard disk is stored in a dedicated ultrasound room in USM which is locked. The study data will be destroyed five years after final publication based on an international standard. For paper-based data, USM provides secure shredded service for its destruction.

(iii)Time gap of ultrasound with chest X-ray or CT thorax date

With regards to the time gap between ultrasound and chest X-ray or CT thorax, the investigating team will evaluate the radiological imaging within 2 weeks. However according to literature, this gap could go up to 2 months, as the earliest chest X-ray changes only took place after 2 months of intensive therapy[20] (presumably the treatment started at the point chest X-ray were first made). This is based on the fact that tuberculosis is a slowly progressive disease that would take some time to show radiological changes following antituberculosis treatment.

c. Data collection forms :

Demographic		
1. Study ID		
2. Age		
3. Gender	Male	Female
4. Diabetes mellitus	Yes	No
PTB background		
5. PTB diagnosis	Bacteriological If yes ; Sputum AFB stain Sputum MTB culture MTB PCR Gene Xpert®	Clinical If yes ; CXR CT thorax Histology
6. Date of diagnosis		
7. Date of treatment started / duration		
Imaging data		
8. Date of ultrasound		
9. Ultrasound finding		

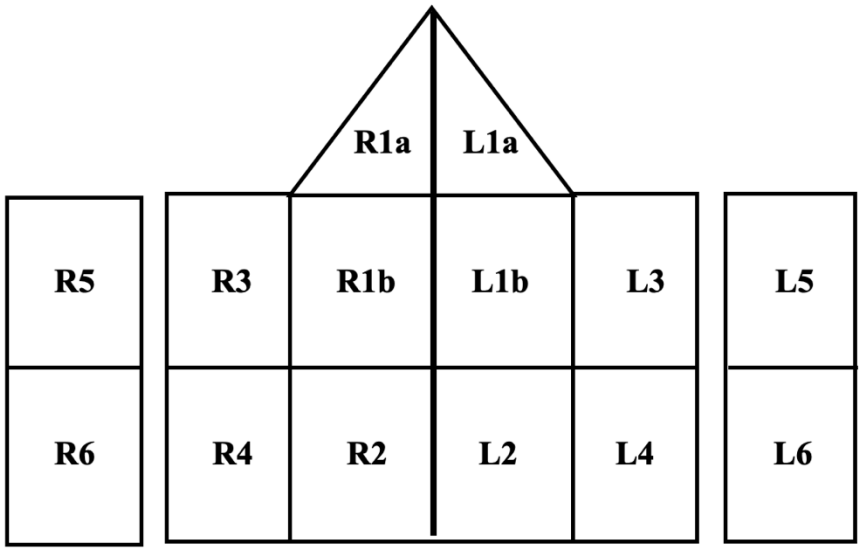

Table 2g: Data Collection Form 1

A second form (shown below) will be filled up separately from the time ultrasound being carried out, consisting of chest X-ray or CT thorax reports.

1. Subject ID	
2. CXR date	
3. CXR findings/ report	
4. CT thorax date	
5. CT thorax findings/ report	

Table 2h : Data Collection Form 2

2·4 DATA ENTRY AND ANALYSIS

2·4·1 Variables

(i) Universal variables :

a. Identifier: ID 00117

b. Patient's demography: Gender age, diabetes mellitus status

(ii) Time variables :

a. Date of diagnosis made

b. Date of treatment started / Duration of treatment

c. Date of chest X-ray performed

d. Date of CT scan performed

e. Date of ultrasound performed

(iii) Independent variables :

a. Patient's diagnostic determinant:

- Bacteriologically confirmed : Sputum AFB staining/ culture /PCR/Gene Xpert®
- Clinically diagnosed: CXR / CT thorax/histology result

b. Chest X-ray report

c. CT thorax report

(iv) Dependent variables :

a. The most common lung sectors with findings

b. Lung ultrasound pattern observed

c. Comparability of ultrasound finding with chest X-ray and or computed tomography (CT) scan

2·4·2 Data entry and analysis

Data will be entered and analyzed using Statistical Package for Social Science (SPSS) version 22·0. Descriptive statistics will be used to summaries the socio-demographic characteristics of subjects. Numerical data will be presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data will be presented as frequency (percentage). For the third objective, Kappa coefficient agreement will be applied.

2·4·3 Dummy tables

Characteristics	n	%
Gender		
Male		
Female		
Age		
Mean		
Range		
Age group		
Young (18-60)		
Old (>60)		
DM		
Yes		
No		
Bacteriological confirmation		
Sputum AFB		
Sputum MTB culture		
MTB PCR		
Gene Xpert		
Duration of treatment		
≤ 2 weeks		
> 2-8 weeks		

Table 2i: Socio-demographic and clinical characteristics of *n of PTB patients under HUSM, HRPZ II and IPR follow up