THE CORRELATION OF SEVERITY OF BRONCHIECTASIS BASED ON MODIFIED REIFF CT SCORING WITH CLINICAL OUTCOMES.

DR NUR SALSABILA MOHD ROSLI

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE (RADIOLOGY)

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMNS

BTS	British thoracic society
COPD	chronic obstructive pulmonary disease
CT	Computed tomography
CXR	Chest radiograph
HRCT	High-resolution computed tomography
HUSM	Hospital Universiti Sains Malaysia
HRPZ(II)	Hospital Raja Perempuan Zainab II
kV	kilovolt
mAs	miliamperes
MJMS	Malaysian journal of medical sciences
PACS	Picture Archiving and Communication System
WHO	world health organization

ABSTRAK

Objektif: Untuk menentukan corak morfologi bronchiectasis dan korelasi tahap keterukan penyakit berdasarkan penilaian Modified Reiff CT di kalangan pesakit bronchiectasis dewasa dengan hasil klinikal.

Metodologi: Pesakit dengan penemuan positif dalam HRCT thoraks dikenal pasti daripada sistem PACS, Jabatan Radiologi, HUSM. Kriteria subjek adalah pesakit berusia 18 tahun ke atas dan disahkan kes bronchiectasis oleh HRCT thoraks scan. Setiap imej HRCT thoraks dikaji semula dan skor di berikan berdasarkan kepada sistem scor Reiff. Rekod perubatan pesakit dikaji semula dan bilangan tanda-tanda dan bilangan kemasukan ke hospital yang berkaitan dengan masalah pernafasan telah dikira.

Keputusan: Jumlah pesakit adalah 90 orang (n=90) dengan usia purata 57.97 tahun (45.6% lelaki, 54.4% wanita). Jenis bronchiectasis adalah tiub 40%, varises 16.7%, sista di 12.2% dan jenis campuran 31.1%. Penilaian keparahan penyakit; bilangan tanda-tanda menunjukkan hubungan yang lemah dan positif dengan skor Reiff diubahsuai, p-nilai 0.014. Bilangan hospitalisasi tidak menunjukkan statistik yang signifikan dengan p-nilai 0.189.

Kesimpulan: Dalam kajian ini, perubahan morfologi bronchiectasis pada HRCT thorax menggunakan Modified Reiff skor mungkin menjadi prediktor untuk bilangan keterukan tetapi bukan mampu meramal bilangan kemasukan ke hospital.

Kata kunci: *Bronchiectasis, thorax HRCT, Reiff Score Modified, exacerbation*

ABSTRACT

Objective: To determine the morphologic patterns of bronchiectasis and the correlation of disease severity based on Modified Reiff CT scoring among adult bronchiectasis patients with clinical outcomes.

Methodology: Patients with positive HRCT thorax finding were traced retrospectively from the PACS system, Department of Radiology, HUSM. The inclusion criteria are patient aged 18 years old and above and confirmed cases of bronchiectasis by HRCT thorax scan. Each HRCT thorax image reviewed and scored using modified Reiff. Patient medical records reviewed and number of exacerbation and number of hospitalization related to the respiratory problem were calculated.

Results: Total of patients are 90 (n=90) , with mean age of 57.97 years (45.6% male, 54.4% female). Types of bronchiectasis were tubular in 40%, varicose in 16.7%, cystic in 12.2% and mix types 31.1%. Disease severity assessment; number of exacerbation showed weak and positive relationship with modified Reiff score, p-value of 0.014. Number of hospitalization show no statistical significant with p-value of 0.189.

Conclusions: In this study, morphological changes of bronchiectasis on HRCT thorax using modified Reiff may become predictor for the number of exacerbation but not a predictor for the number of hospitalization.

Keywords: *Bronchiectasis, HRCT thorax, Modified Reiff Score, exacerbation.*

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION.

Bronchiectasis is a chronic lung illness occurs due to irreversible dilatation of bronchial tree from destruction of the elastic and muscular components of their walls, usually secondary to recurrent or severe infections. Abnormal shape of bronchi and bronchiole cause reduction in internal pressure and this impairs clearance of mucoid and mucopurulent secretions. This condition usually occur secondary to other illness and there is a broad range of pathological processes that needs to be identified, including primary disorders of bronchial structure, disease of mucus clearance, infectious causes and inflammatory disorders, Dähnert (2011). However, in majority of cases no cause could be found and half of the identified causes are due to post infectious. Common symptoms of this disease include chronic cough, mucopurulent sputum production, haemoptysis, dyspnea and tiredness.

Bronchiectasis is under diagnosed and for this reason the exact prevalence of bronchiectasis is unknown. However, it is reported that incidence has decreased in developed countries with declining incidence of pulmonary tuberculosis, advancement of immunization and effective antibiotic treatment. According to the World Health Organization (WHO) in Global Burden of Disease Study 2015, lower respiratory infections remained the most deadly communicable disease, causing 3.2 million deaths worldwide and this give them at third rank of top ten causes of death. In Malaysia, common causes of bronchiectasis are chronic obstructive pulmonary disease (COPD) and post infection especially secondary to pulmonary tuberculosis. Chronic obstructive

pulmonary disease also claimed 3.2 million lives in 2015 worldwide. It is estimated that about 500,000 Malaysians have COPD and many of them are suffering in silence, Ban *et al.* (2012). The lack of awareness of the disease contributes to late diagnosis of COPD and this disorder is one of the leading disease that causing bronchiectasis. COPD is ranked fifth in terms of disease burden and this is reflected in hospital admission rates for COPD attack.

When we discussed regarding bronchiectasis severity, there are two components that we are looking for. First were the imaging features that we can assess the severity based on radiological changes. There are few scoring systems were developed to study on this and one of the most well-known were scoring systems described by Reiff *et al.* (1995) and Bhalla *et al.* (1991). But this scoring system was not correlated with the clinical condition of the patient.

The second component is the clinical condition of the bronchiectasis patient. Two studies by Martinez-Garcia *et al.* (2013) and Chalmers *et al.* (2014) had looked at these. They had combined the pathological state and clinical assessment in assessing the bronchiectasis severity. However, their assessment only focused on lung function test and microbiological finding. For radiological assessment, they only looked at the number of segment involved.

So, both radiology scores might not be applicable at the initial stage of diagnosis of bronchiectasis since a lung function test is not usually performed to all of the bronchiectasis patients during the initial follow-up. Sputum culture is not routinely sent for analysis for those patients who are managed as an outpatient in our clinical setting.

High-resolution computed tomography (HRCT) thorax is a noninvasive gold standard in diagnosing bronchiectasis. Besides confidently providing structural information about the diseased lung, it plays an important role in the detection, diagnosis and follow-up of many lung diseases. It is also very helpful in predicting prognosis of the disease. This can be done by studying the correlation between radiological information and clinical assessment from multiple aspects.

Therefore, the purpose of this study was to evaluate the morphologic changes in bronchiectasis lung in correlation with patient clinical condition among study population in Hospital Universiti Sains Malaysia, Kubang Kerian. Therefore, it is hoped that HRTC thorax will not only have diagnostic value but at the same time provide predictive value of disease progression to the clinician in order to initiate appropriate management for the patient.

CHAPTER 2: LITERATURE REVIEW

The incidence of bronchiectasis is generally not well documented and is underestimated in the developed and developing countries. However, the prevalence is likely to be relatively high as bronchiectasis is a chronic condition, and the case ascertainment is increasing with the wider availability of computed tomography (CT) scanning. A study in United Kingdom, Quint *et al.* (2012) has looked at database for a period of 7 years from 2004 until 2011. They found that overall incidence increased overtime; 2004 incidence 18/100,000 years at risk and in 2011 the incidence was 32/100,000 person years at risk. The prevalence also increased in trend, was higher in older age groups and was higher in women than in men. Another study by the same author Quint *et al.* (2016) also looked at the incidence, prevalence, and mortality of bronchiectasis among the United Kingdom population. They focused on the database from 1st January 2004 until 31st December 2013. Most of their bronchiectasis patients were diagnosed at a secondary care setting and HRCT thorax was performed. In this study, the increase in trend of the incidence and prevalence as well as mortality among bronchiectasis patients was almost similar to the initial study.

In Malaysia, specific incidence and prevalence of bronchiectasis were not well studied and documented. However, based on the one of the major causes of bronchiectasis which is chronic obstructive pulmonary disease (COPD), the prevalence and burden of COPD are expected to constantly increase in the coming decades due to continued exposure to its risk factors like cigarette smoking, changing in age and time of death. This directly indicates that morbidity and mortality related to this disease will continue to rise. In United States, morbidity caused by COPD is 4%, making COPD the

fourth leading cause of death, exceeded only by heart attacks, cancer and stroke. So internationally, there is variation in death rates possibly reflecting smoking behavior, type and processing of tobacco, pollution, climate, respiratory management and genetic factors (Hurd, 2000). Establishing the healthcare burden is essential for allocation of healthcare resources and improving patient care..

There are several features of bronchiectasis on plain radiograph which are tram-track opacities, cystic changes with or without air-fluid levels, increased linear marking, crowding of bronchovascular marking and sometimes pulmonary vasculature appears ill-defined (Gudbjerg, 1955). A study by Van Der Bruggen-Bogaarts *et al.* (1996) prospectively they compared chest radiograph finding with HRCT thorax on 84 patients. They found that a significant linear relationship between the severity of bronchiectasis at HRCT and abnormalities as seen on the chest radiograph ($r=0.62$, $p=0.001$). They also found that chest radiograph showed high sensitivity of 87.8% with a rather low specificity, 74%. This was comparable with a study by Cooke *et al.* (1987). In their study of 27 patients, three radiologists were asked to assess the presence or absence of bronchiectasis. They found a sensitivity of the chest radiograph compared with bronchography of only 37% with a specificity of 95%. Even though chest x-rays are usually abnormal, but are inadequate in the diagnosis or quantification of bronchiectasis (Collins and Stern, 2008).

Naidich *et al.* (1982) has described types and CT signs of bronchiectasis based on HRCT thorax in 6 patients. These include signet rings and tramline for cylindrical/tubular type, presence of string of pearls for varicose type and clusters of rounded cyst and distended bronchi and some with air-fluid levels within for cystic type. Distended bronchi must be distinguished from emphysematous blebs, which generally have no definable wall thickness and no accompanying vessels. It was concluded that CT should have a role in establishing the presence and anatomic extent of bronchiectasis. Other non-specific feature that can be found associated with this condition is mucoid impaction or so called "finger in glove". However this sign was also seen in other various conditions of obstructive or non-obstructive causes as stated in the recent review by Martinez *et al.* (2008).

There are well described three morphological types of bronchiectasis; tubular, varicose and cystic types (Weissleder *et al.*, 2011) and (Naidich *et al.*, 2007). Several articles also described in detail the morphology of bronchiectasis appearance on HRCT and how to differentiate these condition from other lung pathology (McGuinness *et al.* (1993), Cartier *et al.* (1999) and Cantin *et al.* (2009)).

Technological advancement in CT and rapid development of therapeutic options in bronchiectasis has allowed CT scan to be used as the monitoring tool. Multiple CT scoring were developed and established in providing an approach to qualifying disease and enabling structure-function relationships (Aziz *et al.*, 2007). CT findings provide the

morphologic information about the disease and a scoring system was developed to offer a reliable way to monitor disease status and progression of disease radiologically. Thus, CT scan may provide a reasonable tool to assess treatment interventions.

One of the most well-known first scoring systems was Bhalla scoring system (Bhalla *et al.*, 1991). Bhalla scoring system has nine components to assess and the score was given based on the severity of peribronchial thickening, the extent of bronchiectasis, the extent of mucous plugs, the presence of abscesses or sacculations, bronchial generations affected, the number of bullae, the extent of emphysema and presence of collapse or consolidation. A study had found that Bhalla scoring system was more sensitive than pulmonary function test in detecting initial morphological changes (Cademartiri *et al.*, 2008). Bhalla scoring system is currently used for evaluation of cystic fibrosis bronchiectasis. However, there are many more CT scoring systems have been developed mainly modified, for cystic fibrosis type of bronchiectasis. A study by Jong and Tiddens (2007) showed that the inter-observer agreement for five established scoring systems- Castile, Bhalla, Hebich, Santamaria and Brody score were good with intraclass coefficients ranging from 0.74 to 0.97. To date, it has not been determined which scoring systems is the most superior in detecting clinical relevant changes.

For assessment of non-cystic fibrosis bronchiectasis, Modified Reiff score was chosen because of its simplicity and more practical to daily clinical work. This scoring system assesses the number of lobes involved with lingula segment considered to be a

separate lobe and the severity of bronchial dilatation in comparison to the adjacent vessel (0=no bronchiectasis; 1= 1-2 times; 2= 2-3 times; 3= >three times), in other word tubular type=1 point, varicose type=2 point and cystic type=3 point. The maximum score is 18 and the minimum score is 1 (Reiff *et al.*, 1995). Ninety three consecutive HRCT thorax were assessed by chest physician and radiologist in which two scoring systems (Modified Reiff and Bhalla Score) were correlated with sputum microbiology and FEV1% as outcome (Mandal *et al.*, 2013). They found that, Modified Reiff score correlated well with the more complicated Bhalla score with p-value of <0.001. In conclusion, Modified Reiff score was a simplified score and will be easier for clinicians to use in clinical practice.

An international derivation and validation study of the bronchiectasis severity index by Chalmers *et al.* (2014) has identified independent predictors of hospitalization and mortality in bronchiectasis patient. Predictors for future hospitalization were prior hospital admission, FEV_1 <30% predicted, *Pseudomonas aeruginosa* colonization, colonization with other pathogenic organisms and three or more lung lobes involved on HRCT thorax. Whereas, independent predictors of mortality were older age, low $FEV_{1,}$ lower body mass index, prior hospitalization and three or more exacerbation in the year before their study. An outcome of this study, bronchiectasis severity was classified as mild, moderate and severe. Each has its own morbidity and mortality prediction. In mild bronchiectasis, 1 year outcomes: 0 - 2.8 % mortality rate, 0 - 3.4 % hospitalisation rate; 4 year outcomes: 0 - 5.3 % mortality rate, 0 - 9.2 % hospitalisation rate. In moderate bronchiectasis, 1 year outcomes: 0.8 - 4.8 % mortality rate, 1.0 - 7.2 % hospitalisation

rate; 4 year outcomes: 4 % - 11.3 % mortality rate, 9.9 - 19.4 % hospitalisation rate. In severe bronchiectasis 1 year outcomes: 7.6 % - 10.5 % mortality rate, 16.7 - 52.6 % hospitalisation rate; 4 year outcomes: 9.9 - 29.2 % mortality, 41.2 - 80.4 % hospitalisation rate.

A study by Martinez-Garcia *et al.* (2013) had come out with a score as assessment of severity tool for non-cystic fibrosis bronchiectasis. FACED score consists of five variables; FEV_1, age, chronic colonization by *Pseudomonas aeruginosa*, number of lobe involved and dyspnea. These two scores, Bronchiectasis Severity Index and FACED score later on were compared by Minov *et al.* (2015) and they found similar results regarding the assessment of severity of bronchiectasis for both scores.

A study by Cademartiri *et al.* (2008) has showed that CT score significantly changed between the scans obtained in a mean interval of 36.5 months, whereas functional pulmonary test result did not, suggesting that CT is more sensitive than function tests for detecting small changes. This finding able to highlight that CT scoring system is a good predictive tool in managing bronchiectasis patient.

Therefore, the purpose of this study was to evaluate the morphologic changes in bronchiectasis lung correlating with patient clinical condition. Number of exacerbation

and number of hospitalization were justified as indicators of patient's clinical condition among study population in Hospital Universiti Sains Malaysia, Kubang Kerian.

CHAPTER 3: OBJECTIVE

3.1 OBJECTIVES

3.1.1 GENERAL OBJECTIVE:

To determine the morphological patterns of bronchiectasis and the correlation of disease severity based on Modified Reiff CT scoring among adult bronchiectasis patients with clinical outcomes.

3.1.2 SPECIFIC OBJECTIVES:

1. To determine the morphologic patterns of bronchiectasis among those diagnosed with bronchiectasis.

2. To determine the disease severity based on Modified Reiff CT scoring.

3. To correlate the Modified Reiff CT scoring with number of exacerbations and number of hospitalization as clinical outcomes.

CHAPTER 4: METHODOLOGY

4.1 STUDY DESIGN:

This is a retrospective cohort study which was conducted at Hospital Universiti Sains Malaysia. Data collection started from May 2016 until March 2018

4.2 POPULATION AND SAMPLE

4.2.1 Reference population

Patients who have diagnose with bronchiectasis.

4.2.2 Source population

All adult subjects from outpatient and inpatient who had HRCT thorax performed at Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan from 1st January 2010 until 31st December 2016.

4.2.3 Sampling method

Convenience sampling was performed to all HRCT thorax cases which were performed from 1st January 2010 until 31st December 2016. A total of approximately 200 cases of HRCT thorax performed within this 6 years of duration.

4.2.4 INCLUSION CRITERIA:

1. Age, 18 years old and above.

2. Positive finding of bronchiectasis by HRCT thorax.

4.2.5 EXCLUSION CRITERIA:

1. Underlying cystic fibrosis.
2. Active mycobacterial disease (including active nontuberous mycobacteria (NTM)).
3. History of previous lung resections.
4. No other major parenchymal lung disease e.g lung malignancy, lung metastasis.
5. Suboptimal image due to cardiorespiratory motion artifact.
6. Missing images from PACS.
7. Non-traceable medical record.

4.3 SAMPLE SIZE CALCULATION:

Sample size is calculated using sample size calculator (Version 2.0). Available from **http://wnarifin.github.io,** http://www.medic.usm.my/biostat/articles/118-sample-size-calculator.html

For objective 1:

The sample size calculation using single proportion. (Chalmers *et al.*, 2014)

Proportion(p)=8.6%

Precision=5.0%

Confident level, alpha =0.05.

Drop-out=10%

Sample size: 121

For objective 2:

The sample size calculation using single proportion. (Quint *et al.*, 2016)

Proportion(p)=5%

Precision=5.0%

Confident level, alpha =0.05.

Drop-out=10%

Sample size: 73

For objective 3:

The sample size calculation using two means comparison (independent).

SD =4.8. (Stretton *et al.*, 2012)

Precision=3.48

Power of study is 0.8,

Confident level, alpha is 0.05

Drop out 10%

Sample size=34

The largest sample size is n= 121 patients (from objective 1).

After adding 10% estimated missing data, we get; n=121 + (0.1 x 121) =133.

Therefore, a total patient to be sampled is 133 patients.

4.4 MATERIALS AND METHOD

4.4.1 Research Tools:

1. CT Scanner: Siemens SOMATOM sensation 64; Siemens AG, Munich, Germany. HRCT thorax protocol: Patient was in supine position: Images were acquired during breath holding at full inspiration. Scanning anatomical coverage was from lung apices through the diaphragm to include both adrenal glands in craniocaudal direction. Non contrasted study.

The parameters include: 100-120kVp, 100-150mAs (dependent on patient habitus); rotation time 0.5s, average acquisition time: 8-10 sec, detector collimation: 64 x 0.6mm, section thickness 1mm, pitch 0.8cm.

Reconstruction parameters: Images were reconstructed into a bone algorithm, 1mm in slice thickness, 10mm reconstruction spacing, B80f kernel and image were obtained by using standard lung window settings (window level,-500 HU; window width,1000-1500 HU).

2. Picture Achieve and Communication System (PACS) in HUSM (PACS universal viewer version 5.0 SP6). PACS is a computerized system means of replacing the roles of conventional radiological film. Radiological images are acquired, stored, transmitted, and displayed digitally creating a filmless clinical environment. Once the image has been acquired onto PACS it cannot be lost, stolen or misfiled. It will available all the time for viewing anywhere in the hospital.

3. Diagnostic 2 mega pixel monitors (Barco).

This is multi-modality diagnostic display monitor by BARCO which all images from PACS were reviewed. There were 2 types monitor BARCO available. Barco MDNC-3421 with resolution of 2048 x 1536 and Barco MDNG-6121 with resolution 2096 x 2800.

4.4.2 Operational Definition

a) Bronchiectasis is abnormal and persistent dilatation of the smaller bronchi mainly the segmental or sub-segmental bronchi. At HRCT, the characteristic of bronchiectasis included the following findings:

i) Bronchus visualized within 1 cm of pleural surface

ii) Lack of tapering of bronchi"tram-track"sign

iii) Internal bronchial diameter larger than the diameter of the accompanying pulmonary artery, (diameter of bronchus should measure approximately <1 times that adjacent pulmonary artery branch)" signet-ring"sign.

Three morphological patterns of bronchiectasis, adapted from (Cantin *et al.*, 2009):

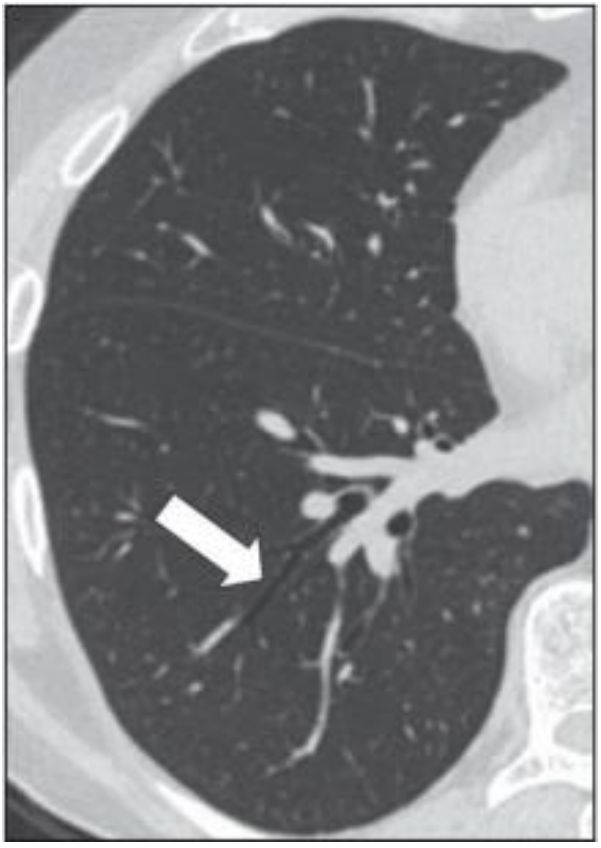

Figure 1: Type 1 of bronchiectasis

Tubular/ cylindrical bronchiectasis: bronchi have a uniform calibre, do not taper and have parallel walls.

Figure 2: Type 2 of bronchiectasis.

Varicose bronchiectasis: beaded appearances where dilated bronchi have interspersed sites of relative narrowing.

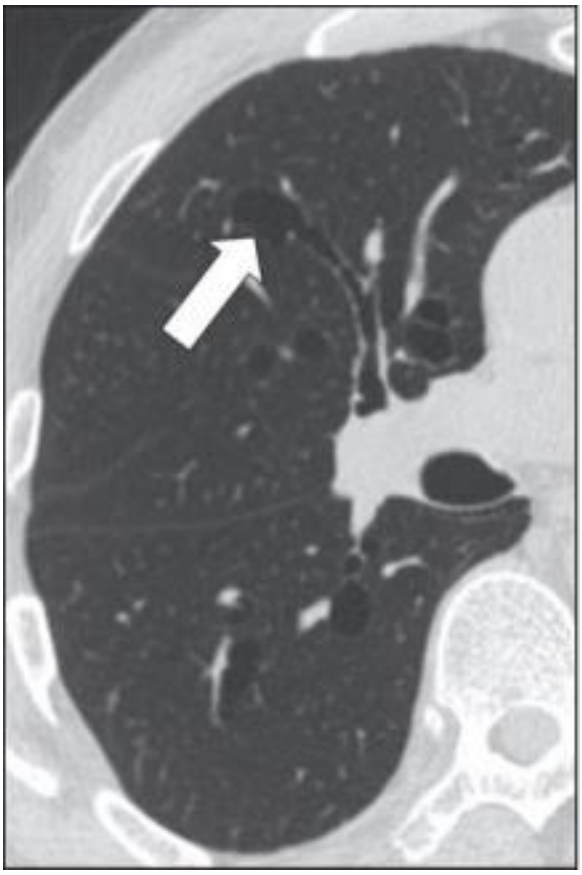

Figure 3: Type 3 of bronchiectasis.

Cystic bronchiectasis: cyst-like bronchi that extend to the pleural surface.

b) Modified Reiff score: Radiological severity of bronchiectasis was assessed using a modified Reiff score, which assesses the number of lobes involved (with the lingula segment considered to be a separate lobe) and the morphological changes (tubular=1, varicose=2, and cystic=3). The maximum score is 18 and minimum score is 1. Each lobe was assessed for the morphological type of bronchiectasis. When there were 2 types of morphology within one lobe, a higher score of morphology was taken as final. We just looked at the types of morphology and not the number of morphology within each lobe of the lung.

Table 1: Modified Rieff score:

	Right lung	Left lung
Upper lobe		
Middle/Lingular lobe		
Lower lobe		

Total point;

0-4 points: Low score

5-8 points: Intermediate score

9 or more points: High score.

References: Reiff *et al.* (1995),Chalmers *et al.* (2014).