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ORIGINAL ARTICLE

Incidence of Post Tuberculosis Chronic Obstructive Pulmonary Disease in a Tertiary Centre In Malaysia

ANDREA BYL[1] FAISAL AH[1], CHONG GY[1], SYED ZULKIFLI SZ[2]

[1]Respiratory Unit, Department of Medicine, [2]Department of Paediatric, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia

ABSTRAK

Tuberkulosis (TB) paru-paru dan penyakit "Chronic Obstructive Pulmonary Disease" (COPD) adalah punca utama kematian dan morbiditi di Malaysia. Di Malaysia, jumlah kes TB semakin meningkat dan terdapat 500,000 rakyat Malaysia yang didiagnosa dengan COPD pada tahun 2016. Sejumlah besar pesakit TB mendapat "COPD" pada jangka panjang. Jangkitan TB yang lepas telah terbukti menyumbang kepada etiologi COPD. Kami menjalankan kajian keratan rentas selama satu tahun yang melibatkan pesakit dewasa di klinik pesakit luar di Pusat Perubatan Universiti Kebangsaan Malaysia (UKMMC) yang mempunyai sejarah TB paru-paru 3 tahun sebelum kajian. Pesakit yang dikecualikan adalah pesakit asma, COPD, penyakit paru-paru interstitial dan bronchiectasis. Obstruksi aliran udara ditakrifkan sebagai nisbah FEV1: FVC <0.70. Soal Selidik Ujian COPD (CAT) telah digunakan. Lapan puluh dua pesakit telah direkrut dengan umur median 52.5 tahun (IQR 36-62). Pesakit lelaki seramai 56.1% dengan 29 (35.4%) perokok. Lapan belas (22%) mempunyai masalah aliran udara di mana enam (33%) dari subjek ini adalah perokok. Empat belas (17%) mempunyai "restrictive pattern" dan 50 (61%) mempunyai spirometri normal. Lima subjek (22.22%) mempunyai "mild obstruction", 7 (44.44%) "moderate obstruction", dan 6 (33.33%) mempunyai "severe obstruction". Terdapat korelasi positif antara keabnormalan sinar-x dada dan umur dengan obstruksi aliran udara (P<0.05). Corak spirometri yang tidak normal didapati dalam 39% subjek. Post TB-COPD insiden adalah 22% pada mereka yang tamat rawatan TB. Terdapat kaitan antara penemuan radiografi dada yang tidak normal dengan halangan aliran udara dalam subjek dengan sejarah PTB.

Kata kunci: jangkitan tuberkulosis paru-paru, obstruksi aliran udara, penyakit paru-paru obstruktif kronik

Address for correspondence and reprint requests: Mohamed Faisal Abdul Hamid. Respiratory Unit, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-91456018 Email: faisal.hamid@ppukm.ukm.edu.my

ABSTRACT

Pulmonary tuberculosis (PTB) and chronic obstructive pulmonary disease (COPD) are important causes of mortality and morbidity in Malaysia. The number of tuberculosis (TB) cases in Malaysia appears to be increasing and there were 500,000 Malaysians diagnosed with COPD in 2016. A substantial number of PTB patients go on to develop post tubular airway disease. Past infection with TB has been shown to contribute to the aetiology of COPD. We conducted a one year cross-sectional study in outpatient setting involving adult subjects in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) with a history of pulmonary tuberculosis three years prior to the study. We excluded subjects with bronchial asthma, COPD, interstitial lung disease and bronchiectasis. Airflow obstruction was defined as FEV_1: FVC ratio <0.70. The COPD Assessment Test (CAT) questionnaire was used. Eighty-two subjects were recruited with a median age of 52.5 years (IQR 36-62). Male predominance (56.1%) with 29 (35.4%) smokers. Eighteen (22%) subjects had airflow obstruction. Six (33%) out of these subjects were smokers. Fourteen(17%) had restrictive pattern and 50 (61%) had normal spirometry results. Five subjects (22.22%) had mild obstruction, 7 (44.44%) moderate obstruction, and 6 (33.33%) had severe obstruction. There was a positive correlation between chest X-ray abnormalities and age with airflow obstruction (P<0.05). Abnormal spirometry pattern was found in 39% of subjects. Post TB-COPD incidence was 22% in those who completed TB treatment. There appeared to be an association between abnormal chest radiograph findings with airflow obstruction in subjects with history of PTB.

Keywords: airway obstruction, chronic obstructive pulmonary disease, pulmonary tuberculosis

INTRODUCTION

Tuberculosis (TB) and chronic obstructive pulmonary disease (COPD) are among the world's ten most prevalent diseases. The main burden of tuberculosis in developing countries is in the form of Pulmonary tuberculosis (PTB). In Malaysia, TB was the second most common notified communicable disease in 2001. In Malaysia, PTB was found to be more common (83.1%) compared to with extra pulmonary tuberculosis (11.1%) (Elamin et al. 2004). Drug resistance and the growing number of HIV-PTB coinfection makes eradication of tuberculosis challenging (Siti et al. 2018).

COPD is a progressive airflow limitation that is not fully reversible. COPD has a high prevalence in Asia Pacific countries with up to 20% requiring hospitalisation (Lim et al. 2015). COPD can occur as a sequelae of PTB and is a recognised risk factor for COPD (Rabe et al. 2007; Menezes

et al. 2005). It is thought to be caused by immunological mechanisms resulting in a reversible or irreversible airflow obstruction, mixed defects or as pure restrictive defects (Elkington & Friedland 2006). Changes seen include a lower forced vital capacity (FVC) and post bronchodilator forced expiratory volume in 1 second (FEV1) (Lee & Chang 2003). A longer interval post completion of anti-TB treatment appears to increase the chance of developing COPD with the relative risk of 20% at 5 years and 41% at 10 years post anti-tuberculosis treatment (Bhome et al. 2012).

In Malaysia, post-TB respiratory morbidity is common and constitutes a significant subgroup of chronic lung disease subjects presenting to outpatient departments (Lim et al. 2015). Recognizing post-TB COPD and assessing the extent of airflow obstruction severity may improve and stratify the management, depending on the natural course of this disease which has not been well elucidated. The objective of this study was to determine the incidence of post-TB COPD in subjects who had completed TB treatment at local settings.

MATERIALS AND METHODS

This was a cross-sectional study, conducted from June 2018 to February 2019 in the respiratory clinic University Kebangsaan Malaysia Medical Centre (UKMMC). We included subjects aged 18 years and above with a history of smear positive and smear negative PTB treated in the 3 years prior to the study who had completed at least 6 months of TB treatment. Subjects with sputum positive were considered to have completed TB treatment when their sputum converted. Sputum negative patients were considered to have completed treatment when they had clinical and radiological improvement. We excluded subjects that were diagnosed with asthma or COPD, interstitial lung disease, bronchiectasis and those where spirometry was contraindicated i.e.; recent eye or abdominal surgery and history of pneumonectomy or lobectomy.

Spirometry test was done using SpiroUSB carefusion spirometer by trained technicians. Subjects were asked to blow out for 6 seconds according to the American Thoracic

Table 1: Demographic characteristics of study participants (n=82)

Demographic Characteristic	Frequency, n (%)
Gender	
Male	46 (56.1)
Female	36 (43.9)
Age Groups (years)	
18-35	19 (23.2)
36-50	18 (22.0)
51-65	34 (41.5)
66-80	11 (13.4)
Median (IQR)	52.5 (36, 62)
Ethnic	
Malay	49 (59.8)
Chinese	27 (32.9)
Indian	4 (4.9)
Other	2 (2.4)
Weight, mean (sd) kg	62.69 ± 16.45
Height, mean (sd) cm	161.54 ± 8.69
BMI, median (IQR)	23.2 (20.25,25.82)

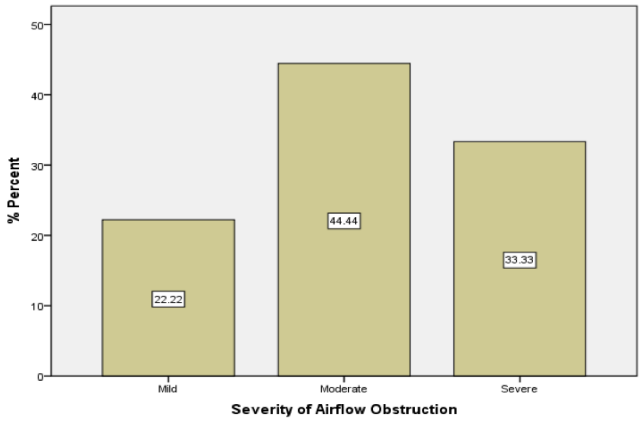

Figure 1: Distribution of subjects by severity of airflow obstruction according to GOLD criteria

Society (ATS) criteria. A minimum of three attempts were recorded and only considered if the variation between two best readings was <5%. Pre and post bronchodilator (ipratropium bromide 500 mcg + salbutamol 2.5 mg) were recorded. We excluded subjects with significant post bronchodilator reversibility (more than 12%). Spirometry values were recorded as FVC, FEV1 and FEV1/FVC. Subjects with positive airflow obstruction proceeded to answer the CAT questionnaire. Chest radiograph findings were reviewed and recorded. Statistical analysis was performed using Statistical Package for Social Science (SPSS) version 19. Frequencies and percentages were generated for categorical data. For continuous data the means and standard deviations or median and interquartile ranges were reported. Categorical variables were analysed using Pearson Chi-square. Continuous data were analysed using Kruskal-Wallis test.

RESULTS

A total of 105 subjects were screened, 10 declined to participate, 5 defaulted spirometry appointment and 8 were excluded because of poor spirometry technique and positive reversibility. A total of 82 subjects were recruited with male predominance 56.1% (Table 1). The Malays were the largest ethnic group (59.8%), the median age was 52.5 (IQR 36,62) and median body mass index (BMI) 23.2 (IQR 20.25, 25.82).

Majority of subjects were sputum negative (70.7%), 64.6% were life-long non-smokers and 30.5% had a history of diabetes. The median FEV1 was 2.165L. Most subjects had completed TB treatment less than a year (39%), followed by 1-2 years (32.9%) and 2-3 years (28%).

The incidence of post-TB airflow obstruction was 22%, with 17% of subjects having restriction pattern and 61% normal spirometry. Of the total subjects who had obstructive defect on spirometry, 44.44% had moderate

Table 2: Association between subjects' characteristics and post-TB airflow obstruction

Parameters	Normal	Spirometry Pattern, n (%)		p-value
		Obstruction	Restrictive	
Gender				
Male	28(56)	11(61.1)	7(50)	0.628
Female	22(44)	7(38.9)	7(50)	
Ethnicity	32(64)	8(44.4)	9(64.3)	
Malay	13(26)	10(55.6)	4(28.6)	0.326
Chinese	3(6)	0 (0)	1(7.1)	
Indian	2(4)	0 (0)	0 (0)	
Other	49.5	61.5	59.5	
Age, median (IQR)	(35.75,57)	(43,65.5)	(37.50,64.25)	*0.016
Smoker				
Yes	18(36)	6(33.3)	5(35.7)	0.979
No	32(64)	12(66.7)	9(64.3)	
Sputum status				
Positive	14(28)	4(22.2)	6(42.9)	0.423
Negative	36(72)	14(77.8)	8(57.1)	
Duration Post Treatment				
2-3 years	12(24)	6(33.3)	5(35.7)	0.833
1-2 years	17(34)	5(27.8)	5(35.7)	
Less than 1year	21(42)	7(38.9)	4(28.6)	
Diabetes				
Yes	13(26)	4(22.2)	8(57.1)	0.056
No	37(74)	14(77.8)	6(42.9)	
Median FEV1 (L),(IQR)	2.29 (1.86,2.72)	1.53 (0.88,2,36)	1.80 (1.23,2.16)	*0.006

obstruction, 33.33% had severe obstruction and 22.22% had mild obstruction (Figure 1).

There was no significant correlation between airflow obstruction with gender, ethnicity, smoking history, sputum status, duration of PTB treatment completion and diabetes (Table 2). There was positive correlation between age and airflow obstruction (P<0.05) (Table 3).

Airflow obstruction in this study was defined as FEV1/FVC <70%. There was positive correlation between airflow obstruction and radiograph findings (Table 4). There was a total of 25.3% chest radiograph with cavitation, 35.4% with consolidation, 15.2% normal, 11.4% pleural effusion and 12.7% reticulonodular pattern.

There were 22.2% sputum positive and 77.8% sputum negative subjects with airflow obstruction. However, there was no correlation between severity of airflow obstruction with sputum status (Table 5).

There were 33.3% subjects with smoking history and 66.7% non-

Table 3: Association between subjects' age and spirometry pattern

	Spirometry Pattern	Mean Rank	p-value
Age	Normal	31.05	*0.016
	Obstruction	44.08	

smoker with airflow obstruction. There was no correlation between severity of airflow obstruction with smoking status (Table 5).

In the obstructive group, there were 61.1% subjects with CAT score <5 and 38.9% with CAT score 6-10. There was no correlation between severity of airflow obstruction with CAT score (Table 5). There was also no significant correlation between BMI and spirometry pattern.

DISCUSSION

Tuberculosis can cause severe irreversible damage to the lungs. Studies have shown airflow obstruction to be a common complication in previously treated PTB patients. To the best of our knowledge this is the first published study in Malaysia evaluating the characteristics of TB-associated COPD.

In this study, we had slightly more males (56.1%) compared to females. Almost half of the subjects resided within Klang Valley. There were 59.8% Malays, 32.9% Chinese, 4.9% Indians and 2.4% grouped as "others". The median age of the subjects was 52.5 years (IQR 36-62). The median age was slightly higher compared to another Malaysian TB study (Elamin et al. 2004). In the PLATINO study, a large proportion of their patients were 60 years and above (Menezes et al. 2005).

Obesity was reported to be associated with a lower risk of active pulmonary tuberculosis especially in the older population (Leung et al. 2007). In 2015, the national health and morbidity survey showed that slightly more than half the Malaysian adults (51.2%) were obese or overweight (Chan et al. 2017). The median BMI of the study population was 23.3kg/m^2 which is normal following the Asia Pacific guidelines.

In this study population, more than half (70.7%) were sputum negative with 19 subjects had culture positive and 11 subjects with TB PCR positive in this group. While there are alternative methods to collect sputum samples such as bronchoalveolar lavage, gastric washing and sputum induction, these are not done routinely in our hospital. This may explain the low sputum positivity in our study.

More than half of the subjects

Table 4: Association between abnormal chest X-ray and post-TB airflow obstruction

Abnormal Chest Radiograph	Airflow Obstruction, n(%)	
Yes	18(100)	49(76.6)
No	0(0)	15(24.4)
p = 0.034		

Table 5. Association between severity of airflow obstruction and sputum, smoking and CAT status.

	Airflow Obstruction, n (%)			Total	p value
	Mild	Moderate	Severe		
Sputum					
Positive	1 (25)	1 (25)	2 (50)	4 (22.2)	*p=0.643*
Negative	3 (21.4)	7 (50)	4 (28.6)	14 (77.8)	
Smoking					
Yes	0 (0)	3 (50)	3 (50)	6 (33.3)	*p=0.245*
No	4 (33.3)	5 (41.75)	3 (25)	12 (66.7)	
CAT score					
0-5	2 (11.1)	7(38.9)	2 (11.1)	11 (61.1)	*p=0.105*
6-10	2 (11.1)	1(5.6)	4 (22.2)	7 (38.9)	

(64.6%) were non-smokers. Smoking has also been listed as a risk factor for development of PTB (Malaysia CPG Tuberculosis 2012). As ours was a face to face interview, the smoking history was self-reported and may not be reliable.

More than half the study population (69.5%) was non-diabetic. We did not collect data for the other comorbidities nor did we have the mean HbA1c in these patients. Our study subjects with obstructive airway as demonstrated by spirometry went on to complete the CAT 8-item questionnaire. The range of CAT scores is from 0-40. In this study, 61% scored 5 and below. While there is no target score, a lower score indicates a lower impact of disease.

The median FEV_1 was 2.165L, keeping in line with the low CAT score obtained. Duration from completion of TB treatment were equally divided with 39% less than 1 year, 32.9% 1-2 years and 28% 2-3 years from completion.

Majority of subjects (60.98%) had a normal spirometry. Twenty-two percent had an obstructive airflow obstruction and 17% of subjects had a restriction pattern. Of the total subjects who had obstructive defect on spirometry, 44.44% had moderate obstruction, 33.33% had severe obstruction and 22.22% had mild obstruction. TB can cause extensive damage to one or both lungs and the sequelae of damage are heterogenous. A patient may present with mixed pathologies and a wide range of pulmonary lung function defects, as shown in our study. This variability may be related to different host-pathogen interaction.

Our study did not show a significant correlation between airflow obstruction with gender, ethnicity, smoking history, sputum status, duration of PTB treatment completion and diabetes. Our study population did show a positive correlation between age and airflow obstruction ($P<0.05$). Thirteen subjects (72%) who developed airflow obstruction were above the age of 50. We postulated that aging with history of PTB infection would have a higher impact on airflow obstruction. Post infectious female TB

patients tend to present at a younger age and were reported to have higher prevalence of airflow obstruction (Buist et al. 2007). A population based study reported up to 30.7% subjects with airflow obstruction (Menezes et al. 2005) while others reported airflow obstruction of 28% and 24%, respectively (Plit et al. 1998; Ramos et al. 2006). The age group studied were different in these studies compared to ours. The BOLD study found only 5.3% of COPD subjects with history of PTB (Schirnhofer et al. 2007). Our youngest subject was an 18-year-old female. She was diagnosed with smear positive PTB and had cavitation on chest X-ray. Her spirometry test showed restrictive pattern. Our oldest subject was a 75-year-old male non-smoker with smear negative PTB and normal spirometry.

This study showed a incidence of post-tuberculous airflow obstruction of 22%. Reports from previous studies had shown prevalence ranging from 24 to 55%. (Menezes et al. 2005; Plit et al. 1998; Ramos et al. 2006; Baig et al. 2010). Most of the studies with high prevalence were occupational cohorts and population base which had a high prevalence of lung diseases (Allwood et al. 2013). The result from this study was comparable with other published studies (Plit et al. 1998; Ramos et al. 2006).

Our spirometry results showed 22% subjects with obstructive defect and 17% restriction pattern. A study in India involving 500 subjects without smoking history showed 32% obstructive defect and 22% restrictive pattern. In their study, males were predominant 56% with mean age of 48±9 years (Patil et al. 2018). The difference in the result may be due to a higher biomass and air pollution compared to our subjects.

The distribution of subjects according to severity of airflow obstruction showed that 22.22% had mild obstruction, 44.44% had moderate obstruction and 33.33% had severe obstruction. A study from Pakistan showed a higher percentage of subjects with severe obstruction (69.2%) (Baig et al. 2010). This difference may be explained by the different study population i.e. predominantly hospitalised subjects with chronic exertional dyspnoea against recruited stable subjects from clinic with less symptoms i.e. shortness of breath, cough and sputum production and corresponded with lower CAT scoring used in the present study.

The greatest deterioration of pulmonary function had been reported at 1.5 year after the completion of the treatment (Chung et al. 2011). In this study, almost one third of subjects were 2 years post completion and most (38.9%) subjects with treatment completion of less than a year. However, there was no significant correlation between year of tuberculosis treatment completion and airflow obstruction spirometry pattern. As we did not have the spirometry results pre-TB infection, we were unable to see the decline post treatment.

Individuals with diabetes mellitus (DM) have been reported to have three times the risk of developing TB (Jeon & Murray 2008). If this is true, there will be a larger impact on post

TB-COPD as the global prevalence of DM among adults has increased by 20% in less than 30 years (Danaei et al 2011). Twenty-five subjects (30.5%) in our study had diabetes with 10 (40%) of them being smear positive. About one third of the diabetes subjects had suffered from diabetes 10 year or more with suboptimal Hba1c control on insulin treatment. However, there was no significant correlation between diabetes and airflow obstruction in this study.

There was no significant correlation between BMI and spirometry pattern in this study. Low BMI has been shown to be associated with host susceptibility to active TB infection and delays in recovery (Falagas & Kompoti 2006). A study in Hong Kong found obesity to be associated with a lower risk of active pulmonary tuberculosis in older population (Leung et al. 2007). However, a population-based study in Korea showed that a BMI of >30kg/m^2 did not reduced risk of TB in young female and subjects with diabetes comorbid (Kim et al. 2018). Ten subjects (3 sputum positive) were underweight with BMI <18.5 and 10 (4 sputum positive) were obese with BMI >30. Those with airflow obstruction had a lower median BMI of 21.8 (IQR 20.47, 25.70). Study from China showed a higher prevalence of COPD (21.1% vs. 7.5%) when the subjects are underweight (Zhou et al. 2013).

The risk of COPD has been found to increase with radiological extent of damage from TB (Ramos et al. 2006). Most earlier studies reported that even minimal scar changes of lung infiltration were associated with development of post TB-airflow obstruction (Kim et al. 2006). In this study, we found comparable result, where all subjects with airflow obstruction had an abnormal chest radiograph at presentation ($p<0.05$).

Both post TB-COPD and smoking-related COPD are not well defined. Smoking related COPD generally occurs in patient more than 40 years-old. In this study, 4 subjects below the age of 40 had obstructive airway disease. Only 1 out of the 4 subjects was a smoker with smoking history of less than 10 packed years. We postulate the lung function abnormality was related to the TB infection.

Smear positive disease appears to be an important predictor of pulmonary function deterioration after the completion of pulmonary TB treatment (Chung et al. 2011). In this study, we did not find any association between sputum status and development of post-TB COPD. A majority of the study subjects were smear negative (72.75%).

A Korean study reported the FEV_1 decline of 20 ml per year in a TB destroyed lung and was association with high mortality (Rhee et al. 2013). Another study reported a FEV_1 improvement in subjects who had received long acting anti-muscarinic (LAMA) inhaler treatment for more than a year (Kim et al. 2018).

The main limitation of the present study was the sample size. Large population-based study would be more useful to represent the overall incidence. Study sample size in the present study remained small due to the limited time frame as well as the stipulated exclusion criteria. This

study also did not look further into the possibility of small airway disease or endobronchial disease post-PTB recovery.

CONCLUSION

In conclusion, slightly more than one third (39%) of our subjects had an abnormal spirometry pattern. Majority of the subjects (77.78%) had moderate to severe obstructive pattern. Post-TB-COPD incidence was 22% in those who had completed at least 6 months of PTB treatment. There appeared to be an association between abnormal chest radiograph findings with airflow obstruction in subjects with history of PTB.

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