

# Pre-existing chronic medical illnesses and follow up status among active pulmonary tuberculosis cases in a district population

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## ABSTRACT

**Introduction:** The knowledge of pre-existing medical illnesses and their follow up status among active pulmonary tuberculosis (PTB) subjects can help in tuberculosis (TB) control programme. The aims of our study were to examine: the prevalence of pre-existing chronic medical illnesses, the follow up status of known pre-existing co-morbid and to distinguish between diagnosed and undiagnosed pre-existing tuberculosis related chronic medical illnesses among our active PTB subjects.

**Methods:** We conducted a retrospective review of demographic and clinical data of active PTB subjects that were diagnosed between January 2015 and June 2017 in the district of Manjung, Perak, Malaysia. Among the 302 TB clinical notes reviewed, 253 patients were included. Subjects below the age of 18 years and whose follow up centres for their medical illnesses that were located outside of Manjung were excluded. Demographic and clinical data were collected using pre-tested data collection form by trained investigators. The data was analysed using SPSS Version 20.0.

**Results:** We identified diabetes mellitus as the most prevalent pre-existing co-morbid (77 cases) and almost 90% (68 cases) of these diabetic subjects were diagnosed prior to active PTB diagnosis. This was followed by Human Immunodeficiency Virus and Hepatitis C infection which accounted for 12.0% (30 cases) of the study populations. Among 132 subjects who had pre-existing chronic medical illnesses, only 74 subjects (29%) were under regular follow up at healthcare facilities in Manjung prior to PTB diagnosis.

**Conclusion:** Overall, our research provides evidence on the existence of wide variation of clinical background among active PTB subjects.

## KEY WORDS:

*Active Pulmonary Tuberculosis, Follow-up Status, Pre-existing Chronic Medical Illnesses*

## INTRODUCTION

Globally tuberculosis (TB) is a major health concern and it is one of the top ten causes of mortality worldwide. World Health Organization has declared a vision to progress towards tuberculosis elimination. The goals are to achieve a 90 % reduction in tuberculosis incidence rate from 2015 to 2035 and to fully eliminate TB by 2050.<sup>1</sup> In order to achieve these goals, tuberculosis control efforts must be expedited and new strategies be implemented, especially in Malaysia that has an intermediate burden of TB, with reported incidence rate of near 92 cases per 100 000 populations.<sup>2</sup>

It is well known that coexisting chronic medical illnesses weakens the host immune system and increases the susceptibility of individuals in progressing to active tuberculosis.<sup>3-8</sup> Despite intensification of efforts in controlling TB among high risk groups, a significant number of our Malaysian pulmonary tuberculosis (PTB) cases were detected late in the moderate to advance stages of the disease.<sup>9</sup> This situation calls for an urgent need to review and improve the efficacy of current screening strategies.

Thus there is a need for a review to improve the efficacy of current screening strategies in detecting active PTB.<sup>10</sup> It is well known that diabetes mellitus is the leading risk factor in active disease.<sup>4,7,11,12</sup> This imposes great challenges to Malaysia in the effort to control TB in view of the increasing number of diabetic populations.<sup>13-15</sup>

Our knowledge on the local prevalence rate of pre-existing co-morbidities among PTB subjects were largely based on data published before 2014.<sup>16</sup> With this in mind, we undertook this research in the district of Manjung, Perak, Malaysia. The district has a population size of 258 000 with an annual TB incidence rate of near 60 cases per 100 000 populations. Additionally, the district is ethnically diverse which follows our national demographics of mainly Malays followed by Chinese, Indian and other minor ethnic groups. There are 2 public hospitals, 2 private hospitals and many health clinics. Treatment for TB is readily accessible from either hospitals or health clinics.

The aim of this research was to evaluate the prevalence of pre-existing chronic medical illnesses among active pulmonary tuberculosis subjects and the follow up status among active PTB subjects with known pre-existing co-morbidities prior diagnosis. We aimed to distinguish between the diagnosed and undiagnosed pre-existing tuberculosis related chronic medical diseases.

## MATERIALS AND METHODS

### Overview

This was a retrospective study of all active PTB cases which were diagnosed and registered in Manjung from January 2015 till June 2017 in all the health facilities that provided TB treatment and treatment for other pre-existing chronic medical illness.

### Data Collection Techniques

We identified all active PTB cases diagnosed through our online tuberculosis registration system. Only subjects aged 18 years and above were included, and excluded those with missing medical records or those whose follow up centres located outside of Manjung.

Trained investigators reviewed the TB records in the respective health facilities that provided treatment for tuberculosis. Demographic data, clinical data and centres of follow up for pre-existing chronic medical diseases were collected.

We contacted the subjects via phone calls if information regarding their previous follow up centres for pre-existing medical diseases was unavailable in tuberculosis clinical notes. During the calls, we explained this study in detail. Subjects were informed that their participation was voluntary. Their refusal to disclose information regarding their previous follow up centres would not affect their right to seek and treatment with us. Subjects were required to answer only one question about their follow up centre for their pre-existing chronic medical disease prior to diagnosis of PTB and this was expected to take less than 1 minute.

After determining the status of pre-existing chronic medical illnesses, trained investigators then visited health facilities in Manjung which provided treatment for the pre-existing chronic medical illnesses. Investigators reviewed the clinical notes to determine the follow up status of the subject. All data was collected using a pre-tested data collection form. We defined the term "follow up" as an incidence that an individual health facility visited for his scheduled appointment within the last 6 months for his chronic medical disease prior to the diagnosis of active pulmonary tuberculosis. On the other hand, we defined "Default of follow up" as any incidence of being absence from his last scheduled appointment within the last 6 months prior to the diagnoses of active PTB.

### Sampling Size & Sampling Method

The minimum sample size required was 183. This figure was arrived at by using Epi Info Version 7.2 software, by setting the population size at 350, expected frequency (proportion) at 50%, acceptable margin of error at 5% and confidence

level at 95%. Investigators decided to include data of all patients that fulfilled the inclusion criteria as well as not meeting any of the exclusion criteria from January 2015 till June 2017.

### Data Analysis

The data was entered into Statistical Package for the Social Science (SPSS) Version 20 for analysis. The demographic and clinical data were presented descriptively as number (percentage).

The prevalence rate of pre-existing chronic medical diseases among active PTB subjects was calculated using the number pre-existing chronic medical disease cases as the numerator, and the total number of active TB subjects as the denominator. The follow up centres were presented in pie chart. The overall follow up status of active PTB subjects in the past 6 months prior to PTB diagnosis were presented in pie of pie chart. The percentage of PTB patients who were under regular follow up was calculated using the number of patients under regular follow up as nominator, and the total number of PTB cases as denominator. The denominator has excluded those patients with (i) unidentifiable follow up centre, (ii) follow up centre located outside Manjung and (iii) known follow up centre but record at follow up centre was untraceable.

## RESULTS

### Demographic And Clinical Characteristics Of Pulmonary Tuberculosis Subjects

We reviewed a total of 302 TB clinical notes. Of these patients, 253 patients who had fulfilled all the inclusion criteria without meeting any of the exclusion criteria were included. Their median age was 44 years (IQR: 31, 59) with 64.4% of them being males. Majority of them were Malays (60.9%) while 7.5% of them were foreigners. The prevalence of PTB cases with pre-existing chronic medical diseases was 52.2%. The most common co-morbidity was diabetes mellitus (DM) with 30.5% of the PTB patients having diagnosed or undiagnosed DM prior to PTB diagnosis. This was followed by HIV (6.0%), hepatitis C (6.0%), chronic kidney disease (2.4%), chronic obstructive pulmonary disease (2.4%) and hepatitis B (1.6%), either diagnosed or undiagnosed prior to PTB diagnosis. Percentage of PTB cases with diseases known to be risk factors of PTB (with or without other concurrent diseases not known to be risk factors of PTB) was 42.3%. The above data is shown in Table I.

Among 132 patients with pre-existing chronic medical illnesses prior to PTB diagnosis, 92 (69.7%) had confirmed follow up centres.

Majority of PTB subjects were attending either government hospitals or health clinics for follow up for their chronic medical illnesses.

Overall follow up status of all 253 patients in the past 6 months prior to PTB diagnosis is presented in Figure 2. For calculation of the percentage of PTB patients who were under regular follow up, the denominator (241) has excluded those patients with (i) unidentifiable follow up centre, (ii) follow up

Table I: Demographic and Clinical Characteristics of Subjects (n=253)

Characteristics	n (%)
<b>Age in years, median (IQR)</b>	44 (IQR: 31, 59)
<b>Gender</b>	
Male	163 (64.4%)
Female	90 (35.6%)
<b>Ethnicity</b>	
Malay	154 (60.9%)
Chinese	48 (19.0%)
Indian	22 (8.7%)
Other ethnicities in Malaysia	10 (4.0%)
Foreigners	19 (7.5%)
<b>Pre-existing chronic medical diseases prior to PTB diagnosis</b>	
Yes, subjects with diseases known to be risk factors of PTB	107 (42.3%)
Yes, subjects with only diseases not known to be risk factors of PTB*	25 (9.9%)
No pre-existing diseases	121 (47.8%)
<b>PRE-EXISTING CHRONIC MEDICAL DISEASES PRIOR TO PTB DIAGNOSIS</b>	
<b>Diabetes Mellitus (DM)</b>	
Diagnosed	68 (26.9%)
Undiagnosed	9 (3.6%)
No	176 (69.6%)
<b>Human Immunodeficiency Virus (HIV)</b>	
Diagnosed	10 (4.0%)
Undiagnosed	5 (2.0%)
No	238 (94.1%)
<b>Hepatitis C</b>	
Diagnosed	8 (3.2%)
Undiagnosed	7 (2.8%)
No	238 (94.1%)
<b>Chronic Kidney Disease (CKD)</b>	
Diagnosed	6 (2.4%)
Undiagnosed	0 (0%)
No	247 (97.6%)
<b>Chronic Obstructive Pulmonary Disease (COPD)</b>	
Diagnosed	6 (2.4%)
Undiagnosed	0 (0%)
No	247 (97.6%)
<b>Malignancy</b>	
Diagnosed	2 (0.8%)
Undiagnosed	0 (0%)
No	251 (99.2%)
<b>Hepatitis B</b>	
Diagnosed	1 (0.4%)
Undiagnosed	3 (1.2%)
No	249 (98.4%)
<b>End Stage Renal Failure (ESRF)</b>	
Diagnosed	1 (0.4%)
Undiagnosed	0 (0%)
No	252 (99.6%)
<b>Systemic Lupus Erythematosus (SLE)</b>	
Diagnosed	1 (0.4%)
Undiagnosed	0 (0%)
No	252 (99.6%)
<b>Chronic Liver Disease</b>	
Diagnosed	1 (0.4%)
Undiagnosed	0 (0%)
No	252 (99.6%)

\*Diseases not known to be risk factors of PTB collected: Asthma, gout, hypertension, ischaemic heart disease, cerebrovascular accident, dyslipidaemia, epilepsy, aplastic anaemia, gastritis, congestive heart failure, hypothyroidism, atrial fibrillation, renal tubular acidosis and neurofibromatosis.

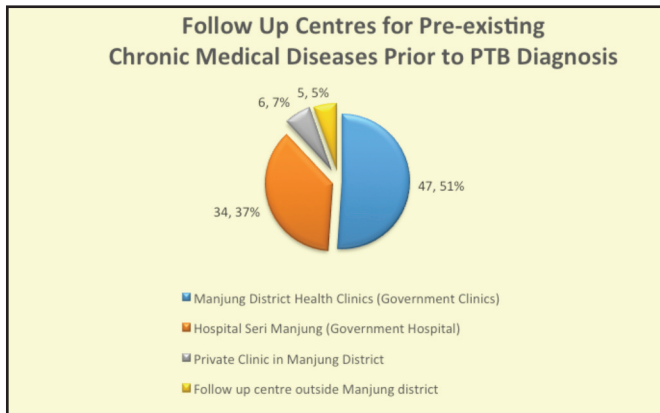


Fig. 1: Follow up centres for pre-existing chronic medical diseases prior to pulmonary tuberculosis diagnosis.

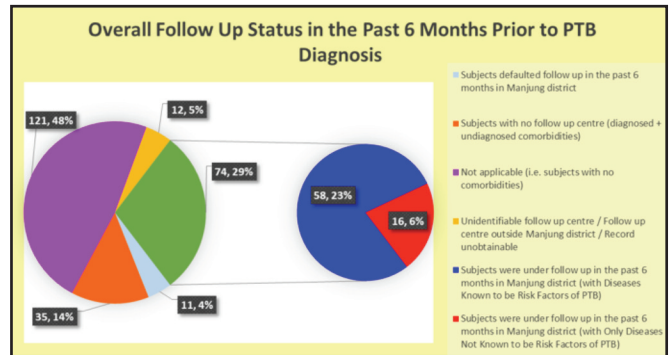


Fig. 2: Overall follow up status in the past 6 months prior to pulmonary tuberculosis diagnosis.

centre outside Manjung and (iii) known follow up centre, but record at follow up centre was untraceable. Among these 241 PTB patients, less than one third (30.7%) were under regular follow up at healthcare facilities in Manjung.

**DISCUSSION**

Active case detection, or screening for active PTB has been intensified in recent years with the primary objective of ensuring that active PTB cases are detected early to allow prompt treatment as well as to reduce ongoing TB transmissions. Unpublished data about the TB service from the state of Perak revealed that a total 3730 individuals under regular health care follow up in Manjung who had pre-existing TB related risk factors were screened for TB by means of chest radiography regardless of symptoms in the year 2016. However, only 21 cases (0.56%) were detected to be positive for PTB. This poor screening results compelled us to determine the prevalence rate of TB related co-morbidities and their follow up status prior to pulmonary tuberculosis among PTB patients.

Furthermore, there is a heavy burden placed on the public health facilities in Malaysia, as evidenced by the fact that almost all our subjects with underlying chronic medical illnesses were on follow up in public health facilities. This burden is estimated to rise further in future in view of the soaring number of patients with chronic medical co-morbid and rising cost of healthcare.<sup>17-19</sup> Hence, a targeted and cost effective TB screening system should be in place to ensure that the limited resources within the public health service are used justifiably and at the same time allowing delivery of good quality health service.<sup>10</sup>

We identified DM as the most prevalent co-morbid among PTB subjects, which was followed by clinical groups with HIV infection and chronic viral hepatitis infection. Our results concur with other studies which were published previously.<sup>6,8,11,14,20</sup> The prevalence rate of DM among active PTB in our study was 30.5 % and it was higher than our national DM rate from Malaysian National Health Morbidity Survey 2015 which was reported as 17.5%.<sup>15</sup> This indicates that DM is a risk factor for developing PTB. Further study and

analysis are needed to identify high risk groups among the diabetics as the number of diabetics is high and increasing.<sup>13</sup> Indiscriminate screening has failed to yield high number of PTB cases in Perak in 2016.

It is also noteworthy that the majority of DM was already diagnosed prior to PTB diagnosis. In contrast, chronic viral hepatitis and HIV cases were mainly undiagnosed and therefore not under regular healthcare surveillance. This was likely attributable to the nature of the diseases among HIV or viral hepatitis subjects who are mainly asymptomatic in the early stage. Therefore, efforts to screen pulmonary cases for DM, HIV and viral hepatitis should be continued in view of the notable prevalence rate of these diseases among active PTB populations to allow continuum of care as well as curtail the ongoing transmissions of such infectious diseases.<sup>5,21,22</sup>

There is no retrievable evidence on follow up status among active PTB subjects with underlying chronic medical co-morbid prior to the PTB diagnosis. Knowledge about the follow up status of at-risk populations is vital as it would influence the screening outcome among population at risk in healthcare facilities. Based on our study, we confirmed that approximately one third of our active PTB subjects had contact with healthcare professional at least once in the past 6 months prior to the diagnosis of TB during their follow up. Self-presentation of an individual to health facility offers an opportunity for detection of a potentially undiagnosed or unrecognized PTB. Therefore, we recommend that tuberculosis symptoms to be actively noted regardless of the reason of clinic visit for populations with tuberculosis related comorbid. Interview for TB symptoms and risk profile assessment for TB should be conducted first, followed by diagnostic tuberculosis test such as sputum examination and radiography if the suspicion of active TB infection is high.<sup>10,23</sup>

Yet, focusing on active case finding within healthcare facilities alone is still probably going to miss a large proportion of individuals with active PTB in view of virtually half (48 %) of our active pulmonary tuberculosis subjects did not have pre-existing chronic medical illnesses and less than one third of them had healthcare contact in the last 6 months prior to PTB diagnosis. The wide variation in the clinical

backgrounds among active PTB subjects presents challenges in screening and controlling it. We recommend future research to analyse the non-clinical aspects of such group of subjects, such as their socioeconomic status, residences and accessibility to health care facility. This then would allow focused active case finding among the sub-population with similar profiles and identify outbreak within localities. This is important because community-wide active case finding in country with moderate burden of TB like Malaysia is unlikely to be cost-effective.<sup>10</sup>

At the same time, passive case detection should be continued and strengthened in the community to complement active case finding in early detection of active PTB subjects. Although passive case finding was not as effective as active case finding, it still plays a significant role in ensuring early diagnosis of the disease, improve individual patient outcomes, and limit ongoing transmission.<sup>10</sup> Measures such as periodic health education about tuberculosis symptoms, widespread distribution of patient education materials and early clinic attendance in the presence of tuberculosis symptoms should be encouraged. Similarly, regular tuberculosis update should be organized for healthcare providers to enhance their expertise in tuberculosis management.

The strength of this research lies in being the first research to determine the status of TB related co-morbid and their follow up status among active PTB, with special focus on TB related co-morbid. This result will lend itself well to the Public Health Authority in planning a well-covered TB control programme.

One of the limitations in this study was the small sample of subjects as we only examined the population in a district. This could lead to an underestimation of the exact burden of TB related medical illnesses on the disease. Besides, there were missing medical records of patients that could not be reviewed due to the unavailability of electronic medical records in the healthcare facilities.

## CONCLUSION

Overall, DM was the most prevalent co-morbid among active PTB subjects. Yet, majority of the PTB subjects did not have pre-existing TB related medical co-morbid and were not under healthcare facilities regular follow up prior to PTB diagnoses. Active screening targeting individuals under healthcare follow up will at best detect only one third to total active PTB subjects. We recommend a targeted and systematic TB control programme case focusing on both at risk populations under healthcare follow up as well as the community at large.

## ETHICAL APPROVAL

This study was registered with National Medical Research register (NMRR) and approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH). NMRR ID: NMRR-17-1052-36174

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