

# A retrospective study on Tuberculous Lymphadenitis; A retrospective finding from multicenters referral hospitals

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## Research article

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# Abstract

**Background** Extra-pulmonary tuberculosis (EPTB) represents about 14% of all cases of tuberculosis (TB) in Malaysia. The aims of the study include evaluation of socio-demographic factors, clinical manifestations, co-morbidities among patients with Tuberculous Lymphadenitis and their treatment outcomes.

**Methods** The retrospective study was conducted from 2006 to 2008. Data on socio-demographic along with histopathological results were collected. Signs and symptoms were also recorded from TB registers, treatment cards and TB medical personal files using standard data collection tool. Among multiple variables significant factors identified by univariate analysis, were included in multivariate logistic regression to estimate the odds ratios (ORs) with the 95% confidence intervals (CIs). The statistically significant p value was considered as  $< 0.05$ .

**Results** There were 348 (57%) males and on the other hand 262 (43%) females which shows almost equal incidence rate of Lymphadenitis in both genders. Mean age was found as  $34.3 \pm 14.6$  years were majorly reported with positive diagnosis. 196 (32.1%) Malay was found with Tuberculous lymphadenitis followed by Chinese population of 148 (24.3%). Geographically from 386 (63.3%) urban population were found positive for lymphadenitis and over 224 (36.7%) of rural region. treatment outcome was observed 444 (72.8%) with successful treatment. WHO states the types of treatment failures and accordingly 85 (13.9%) patients were continued with the therapy that can be due to non-compliance or relapse of Tb. Among unsuccessful outcomes 194 patients of age group 26 -35 years, 65 (33.5%) were reported and 38 (29.7%) patients out of 128 between 16 – 25 years. Blood results showed erythrocyte sedimentation rate greater than 10 in 280 (45.9%) patients. Therefore, among 280 there were 115 (41.1%) patients found to have unsuccessful treatment showing strong association with p-value of  $<0.001$ .

**Conclusion** Finding signifies that effect of weight loss on poor treatment outcomes` and active screening measures for patients with comorbidities are therefore recommended in patients with Tb lymphadenitis along with improvements in the diagnosis and early management of co-morbidities complications. As young age group were found to have poor or unsuccessful treatment outcomes and required aggressive strategy together with educating patients can further increase the treatment success rate.

## Background

Infectious diseases are one of the major causes of health burden and among that Tuberculosis is a disease caused by mycobacteria belonging to the Mycobacterium tuberculosis complex. A small group of people gets affected by Mycobacterium africanum, Mycobacterium. canetti, Mycobacterium. caprae, Mycobacterium. microti, and Mycobacterium. Pinnipedii [1]. Mycobacterium. bovis was previously a major cause of human disease, but its relative importance has considerably declined as for an estimate 1.4% incident TB cases were reported in 2016.[2] Despite of many new updated and advanced diagnostic and treatment techniques are available an estimate of ten (10) million incident TB patients were reported

globally in 2017 [3]. The most communal consequence is a subclinical (latent), asymptomatic infection. Whether one can achieve a spontaneous or drug-induced complete eradication of latent infection from the host is unclear, [3] but latent infection is typically kept under control through a cell-mediated immune response, preventing the activation of infection into disease. Histopathological damages of an uncontrolled infection are responsible for clinical signs and symptoms of TB disease.[4] TB typically affects the lungs but, in up to a third of patients, can also affect other sites.[5] It is not practically possible to identify *M. tuberculosis* strains present in the body in patients latently infected.[3]

In Malaysia the early 1940s and 1950s was the era when Tuberculosis was one of the major diseases causing death in the region. Understanding the situation the Malaysian government launched its health controlling body named as National TB Control Program in 1961 [6]. According to the recent extensive research performed in Malaysia, 25,739 reported TB cases were observed during 2016 among those 22,135 (86%) were Pulmonary TB cases and on the other hand 3604 (14%) were extra pulmonary TB [6]. The most common forms of EPTB seen in Malaysia are TB lymphadenitis and bone/joint TB [7]. However, in Malaysia there has been an increase in the prevalence of non-communicable diseases, such as DM. Based on the National Health Morbidity Survey (NHMS) in 2015, the prevalence of DM increased from 11.6% in 2006 to 17.5% in 2015. (Institute for Public Health, 2015)

## Methods

### Study design and data collection

The protocol of study was approved by the Clinical Research Centers of Ministry of Health- Malaysia and authorities from four states of Malaysia. Informed consent was given and signed by the subjects before performing needle biopsy test for the investigation. The retrospective study was conducted from 2006 to 2008. Data on socio-demographic along with histopathological results were collected. Signs and symptoms were also recorded from TB registers, treatment cards and TB medical personal files using standard data collection tool. Patients were identified on the basis of site of infection. If the patient had infection confined to lungs were considered as pulmonary TB whereas, those Patients which had infection at other organs or tissues outside lungs were considered as extra pulmonary TB. Based on the WHO sample selection policy patients who had both PTB and EPTB infections were excluded from the analysis [8]. The sites of infection for extra pulmonary TB were Lymph nodes and apart from that all other sites were not included in the study. Successful treatment refers to the completion of TB therapy and no more positive diagnostic results. Unsuccessful or treatment failure represents the reoccurrence of infection or morbidity of patients. The treatment of patients completed TB regime according to the Clinical Practice Guidelines originated by Health Ministry of Malaysia [9].

Treatment success refers to the patients who were cured and have completed TB treatment. Completed TB treatment was defined as any patient who had completed a TB regime based on the Clinical Practice Guidelines created by Malaysia Ministry of Health [9].

Study Location:

Multiple state hospitals were used for investigation namely (Penang, Selangor, Sabah and Sarawak). The study was mainly performed in both regions of Malaysia, states of western Malaysia also known as Peninsular Malaysia along with the Eastern states known as Malaysia Timur. Eastern states were chosen because Sabah and Sarawak are reported to have the most number of TB cases in Malaysia, Penang and Selangor states were considered for its densely populated multiracial and expatriate population [10].

### Study data analysis

Complete data was assigned a unique identification serial number to ensure the traceability of each data collection form. Data was coded into the computer for analysis and result interpretation and generation and analysis was performed by using statistical package for SPSS for Windows version 24.0.0 (SPSS, Inc., Chicago, IL, USA). To analyze the predictors of extra pulmonary TB specifically Lymphadenitis treatment outcomes univariate analysis was used to identify the importance of risk factors through Chi square test for categorical variables and independent sample t-test/ Mann Whitney U Test for continuous data. Significant factors identified by univariate analysis, were included in multivariate logistic regression to estimate the odds ratios (ORs) of unsuccessful treatment outcome of the Lymphadenitis TB with the 95% confidence intervals (CIs). The statistically significant p value was considered as < 0.05.

## Results

### Socio-demographic characteristics:

Among the four states of Malaysia during the study, data of 610 patients was collected which showed Tuberculous lymphadenitis. As shown in Table 1. There were 348 (57%) males and on the other hand 262 (43%) females which shows almost equal incidence rate of Lymphadenitis in both genders. The age group was observed from 2–83 years old. Therefore, the age groups between 26–35 years showed 194 (31.8%) patients diagnosed with lymphadenitis and followed by 16–25 years (21%). Mean age was found as  $34.3 \pm 14.6$  years were majorly reported with positive diagnosis. Malaysia being a multi-racial country and consisting of numerous expatriates working or residing, 196 (32.1%) Malay population was found with Tuberculous lymphadenitis followed by Chinese population of 148 (24.3%). The other prominent races were Pilipino, Indonesians and other expatriates. As mentioned in Table 1. Geographically patients were from both urban and rural background but 386 (63.3%) urban population were found positive for lymphadenitis over 224 (36.7%) population of rural region.

Table 1  
Demographic profile of patients (N = 610).

| Parameter                  | N (%)         |
|----------------------------|---------------|
| Sex ratio (M: F) 1.33: 1   | N = 610 n (%) |
| Range of age (2–83 years)  |               |
| Mean age 34.3 ± 14.6 years |               |
| Gender                     |               |
| Male                       | 348 (57.0)    |
| Female                     | 262 (43.0)    |
| Race                       |               |
| Malay                      | 196 (32.1)    |
| Chinese                    | 148 (24.3)    |
| Indian                     | 52 (8.5)      |
| Sabahan                    | 98 (16.1)     |
| Sarawakian                 | 48 (7.9)      |
| Indonesian                 | 33 (5.4)      |
| Pilipino                   | 21 (3.4)      |
| Others                     | 14 (2.3)      |
| Age Group                  |               |
| ≤ 15 years                 | 45 (7.4)      |
| 16–25 years                | 128 (21.0)    |
| 26–35 years                | 194 (31.8)    |
| 36–45 years                | 86 (14.1)     |
| 46–55 years                | 82 (13.4)     |
| 56–65 years                | 57 (9.3)      |
| ≥ 66 years                 | 18 (3.0)      |
| Geographical location      |               |
| Urban area                 | 386 (63.3)    |
| Rural area                 | 224 (36.7)    |

Lymphadenitis and co-morbidities/ risk factors with major symptoms:

Table number 2 explains the total of 610 lymphadenitis patients were observed but 287 (47%) found to have co-morbidities such as Diabetes Mellitus, HIV and Hepatitis etc. DM is a major risk factor for TB and specifically extra pulmonary TB but only 83 (13.6%) patients were having DM previously diagnosed. Apart from that HIV which is another major risk factor for Lymphadenitis TB shows 150 (24.6%) patients positive. Regarding the Hepatitis both type B virus and type C virus were monitored and the data shows 43 (7%) and 24 (3.9%) patients diagnosed, moreover 2 (0.3%) out of total were found to have both types of hepatitis simultaneously. Regarding the social habits which lead to increased risk of TB, 48 (7.9%) patients were drinking alcohol and 195 (32%) patients were active smokers which exacerbate the symptoms of TB.

Table 2  
Co-Morbidities and social habits  
of the study population

| Parameter         | N (%)      |
|-------------------|------------|
| Diabetes Mellitus |            |
| Yes               | 83 (13.6)  |
| No                | 527 (86.4) |
| HIV               |            |
| Yes               | 150 (24.6) |
| No                | 460 (75.4) |
| Hepatitis         |            |
| HBV               | 43 (7.0)   |
| HCV               | 24 (3.9)   |
| HBV + HCV         | 2 (0.3)    |
| Drinks alcohol    |            |
| Yes               | 48 (7.9)   |
| No                | 546 (89.5) |
| Unknown           | 16 (2.6)   |
| Smokes            |            |
| Yes               | 195 (32.0) |
| No                | 339 (55.6) |
| Unknown           | 76 (12.5)  |

Apart from that as mentioned in table number 3 there were few common symptoms reported among patients. The most common symptom of infection which leads to hyperthermia known as fever was found in 477 (78.2%) patients followed by sputum 326 (53.4%) and cough 299 (49%). Cough and sputum formation leads to inflammation of bronchioles which causes shortness of breath and it was observed in 252 (41.3%) patients. Furthermore, 301 (49.3%) patients were found to experience loss of appetite, Therefore. It was found to have weight loss in 257 (42.1%) patients.

Table 3

Symptoms reported by patients with tuberculous lymphadenitis (N = 610).

| Sign/Symptom        | N (%)      |
|---------------------|------------|
| Fever               | 477 (78.2) |
| Cough               | 299 (49.0) |
| Sputum              | 326 (53.4) |
| Hemoptysis          | 143 (23.4) |
| Weight loss         | 257 (42.1) |
| Loss of appetite    | 301 (49.3) |
| Shortness of breath | 252 (41.3) |
| Night sweating      | 230 (37.7) |

Laboratory test findings and treatment outcomes:

As stated in Table number 4 treatment outcome was observed 444 (72.8%) with successful treatment. WHO states the types of treatment failures and accordingly 85 (13.9%) patients were continued with the therapy that can be due to non-compliance or relapse of Tuberculosis. Apart from that 27 (4.4%) were expired during the treatment but only 36 (5.9%) were defaulters of treatment as they did not show up for drug administration to hospital and 18 (3%) were transferred to other hospitals during the treatment course. Among the unsuccessful outcomes it was noted that from 194 patients of age group 26–35 years, 65 (33.5%) were reported and 38 (29.7%) patients out of 128 between ages of 16–25 years. As mentioned in table number 5 significant association was observed between unsuccessful treatment and Intravenous drug users (drug abuse) with 0.005 p-value. Among 31 IV drug users 20 (64.5%) patients were reported to have unsuccessful treatment. Therefore, patients were observed to have loss of appetite as one of the main symptoms so strong association was found between appetite and loss of weight among 257 patients who lost weight during the treatment 115 (44.7%) experienced treatment failure. The most important and reliable radiological test was found to be chest X-ray as 366 (60%) lymphadenitis patients were showing lesions in the chest, on the other hand 215 (35.2%) showed clear chest. Strong correlation was observed as p-value < 0.001 was identified among patients who were having chest lesions 142 (38.8%) were found to have unsuccessful treatment outcome. Only half of the patients showed sputum as a symptom therefore, AFB (Acid fast bacilli) for the culture test showed 327 (53.6%) positive results. Similarly 224 (36.7%) were reported positive for AFB (acid fast bacilli, direct smear). Another method of diagnosis used is the fine needle biopsy testing which gives precise information. There were 238 (39%) Lymphadenitis patients showing positive results but also there were 234 (38.4%) patients that gave unknown results that can be due to improper technique or sample error. Blood test results showed erythrocyte sedimentation rate greater than 10 in 280 (45.9%) patients. Therefore, among 280 there were

115 (41.1%) patients were found to have unsuccessful treatment showing very strong association with p-value of  $< 0.001$ .

Table 4

Laboratory test results and treatment outcomes (N = 610).

| <b>Parameter</b>              | <b>N (%)</b> |
|-------------------------------|--------------|
| Chest x-ray                   |              |
| Showing lesion                | 366 (60.0)   |
| Clear                         | 215 (35.2)   |
| Unknown                       | 29 (4.8)     |
| Sputum for AFB (direct smear) |              |
| Positive                      | 224 (36.7)   |
| Negative                      | 365 (59.8)   |
| Unknown                       | 21 (3.4)     |
| Sputum for AFB (culture)      |              |
| Positive                      | 327 (53.6)   |
| Negative                      | 50 (8.2)     |
| Unknown                       | 233 (38.2)   |
| Pleural biopsy                |              |
| Positive                      | 238 (39.0)   |
| Negative                      | 138 (22.6)   |
| Unknown                       | 234 (38.4)   |
| ESR (mm/h)                    |              |
| > 10                          | 280 (45.9)   |
| < 10                          | 73 (12.0)    |
| Unknown                       | 257 (42.1)   |
| Treatment outcomes            |              |
| Successfully treated          | 444 (72.8)   |
| Patient defaulter             | 36 (5.9)     |
| Transferred out               | 18 (3.0)     |
| Patient expired               | 27 (4.4)     |
| Treatment continue            | 85 (13.9)    |

| Parameter  | N (%) |
|--|-------|
| AFB, Acid-fast bacilli; ESR, Erythrocyte sedimentation rate. |       |

Table 5

Multivariate analysis of the predictors of unsuccessfully treated tuberculous lymphadenitis (N = 610).

| Variable   | Unsuccessful treatment, n (%) | Adjusted OR [95% CI]  | P-value |
|--|-------------------------------|-----------------------|---------|
| Age group*   |                               |                       |         |
| 16–25 years  | 38/128 (29.7)                 | 4.119 [1.138–14.914]  | 0.031   |
| 26–35 years  | 65/194 (33.5)                 | 3.710 [1.054–13.059]  | 0.041   |
| IV drug users  | 20/31 (64.5)                  | 3.640 [1.464–9.054]   | 0.005   |
| Hemoptysis   | 30/143 (21.0)                 | 0.429 [0.239–0.768]   | 0.004   |
| Weight loss  | 115/257 (44.7)                | 2.549 [1.342–4.839]   | 0.004   |
| Lesion on chest x-ray  | 142/366 (38.8)                | 20.850 [7.699–56.464] | 0.000   |
| Positive sputum culture  | 94/327 (28.7)                 | 0.133 [0.056–0.320]   | 0.000   |
| ESR > 10 mm/h  | 115/280 (41.1)                | 6.359 [2.446–16.530]  | 0.000   |
| Only significant values are provided in the table<br>* reference category: age ≤ 15 years<br>Constant = -5.032<br>Backward LR method was applied<br>Classification table 86.1% correctly classified<br>CI, Confidence interval; ESR, Erythrocyte sedimentation rate. |                               |                       |         |

## Discussion

There are multiple studies performed on Pulmonary and extra pulmonary Tuberculosis but with numerous important limitations with either gives up biased data or lack of adequate sample size to conclude. Therefore, to best of our know knowledge there is the pioneer study in Malaysia explaining the epidemiological characteristics along with the clinical outcomes either successful or unsuccessful according to the WHO guidelines with the diagnostic approach chosen for the specific Tubercular lymphadenitis patients.

Among multiple races and expatriates available in different states of Malaysia, Malays were found to have higher risk of lymphadenitis TB. Similar results were published in previous studies performed in Malaysia, as the population of Malays is higher than others and rate of relapse of diseases is also considered higher in Malay race.

A similar study performed on the extra-pulmonary TB shows that Patients at the risk of EPTB were more likely to be females [11], Contrary to that current study shows that Males were more in number 348 (57%). The higher number of males can be due to the age factor as mostly males were belonging to the mean age group of 34.3 which has proved to have a higher risk of Lymphadenitis. Since the study shows the patients between the age of 18 to 35 years were found to have most diagnosed with lymphadenitis compared to other age groups despite of gender. Similar results were reported by an Egyptian study performed prospectively on extra-pulmonary Tb patients, which states  $34.8 \pm 12.5$  years as the mean age diagnosed with Tuberculosis [12]. Another recent study was performed in Penang General Hospital on Tuberculous Lymphadenitis patients also states that average mean age is  $36.4 \pm 12.87$  among the active Tuberculosis patients[13]

There was strong association found in the research as those who were using other intravenous drugs for addiction or abuse were found to have unsuccessful treatment outcomes. Most of the unsuccessful treatment outcome was reported among the IV drug users which lead to weight loss as well among the tuberculous lymphadenitis patients. A similar study performed in Kota Bahru Malaysia also reported the similar reasons for unsuccessful treatments leading to TB load in Malaysian population in 2011 [14]. Similarly another similar study performed prospectively on the TB lymphadenitis patients concluded the weight loss as a factor for loss of appetite leading to unsuccessful treatments which can be due to other confounding factors such as non-compliance or Intra venous drug abuse [15]

There are multiple risk factors associated with Tuberculosis but current research showed contradictory results in relation to extra pulmonary TB lymphadenitis. Diabetes, Human Immuno deficiency virus and Hepatitis were studied and it shows no statistically significant result to any of the risk factors. Recently study performed in North-East Peninsular Malaysia on the mortality among the Tb and HIV co-morbid patients reported strong relationship on the unsuccessful treatment outcomes of TB and a major risk factor for extra-pulmonary Tb [16]. Present study findings shows only few patients were found to have diabetes which is less than 15 percent of the total diagnosed population with Tb lymphadenitis. Therefore there is no direct risk association found in the study which is contradictory to some of the other researches performed to evaluate the treatment outcomes in relation to risk factors such as Diabetes etc. A review was performed on DM and TB risk analysis shows that 41 TB drug trials 12 were reported DM as comorbidity among the study participants and there was reports of DM to be found higher in drug-resistant-TB [17]. Similarly a cross sectional study performed in Manjung district of Malaysia reported that the commonest comorbidity was diabetes mellitus (DM) with majority of cases of the PTB patients having diagnosed or undiagnosed DM prior to PTB diagnosis, followed by Human Immunodeficiency Virus (HIV) and Hepatitis C infection which accounted for the study populations [18]

This study has revealed some strong association between the risk factors and treatment outcomes. One of few reasons is weight loss or lower BMI which showed unsuccessful treatment outcome in the present study. Recently another study was performed in Yemen on multi drug resistant Tuberculosis and their analysis revealed that a baseline body weight of  $\leq 40$  kg was found to have lower successful treatment rate [19]. Another study performed in Pakistan shows that patient with baseline body weight of  $< 40$  kg

were at significantly greater risk of developing death and treatment failure [20]. Similar positive association between low body weight and unfavorable treatment outcomes have been reported by studies conducted elsewhere [21, 22, 23]. Poor absorption from GI tract is one of the main reasons of sub-therapeutic serum concentration of anti-TB drugs. Lower body weight or BMI is believed to be a contributing factor for lower serum drug levels in TB patients [24]. It not only reduces the gastrointestinal absorption of drugs but also increase the renal clearance of free drugs, subsequently resulting in sub-therapeutic drug levels and poor treatment outcomes. Moreover, inadequate dosing of drugs in underweight patients could be another cause of sub-therapeutic serum drug concentration and high incidence of death and treatment failure in these patients [24]. Age is another important factor which defines the physical condition as well as metabolic level of an individual. This study reported that younger age group between 16–35 years were found to have unsuccessful treatment outcomes which may be due to no follow up or any confounding factors. In Yemen a study was performed among general population and it shows homelessness, male gender and age  $\geq 25$  years were the risk factors reported for poor treatment outcomes [25]. Furthermore, in Netherlands recently a study showed predictors for mortality were aged 74–84 years (OR, 5.58; 95% CI 3.10–10.03) or  $\geq 85$  years which is contradictory to current study results as these were not specific to lymphadenitis Tuberculosis[26]. Another study performed in Malaysia states that the mean age of unsuccessful treatments was  $34.6 \pm 10.55$  years and among them 68.9% were females [27]. Moreover, Factors associated with death were older age, HIV positivity and not receiving directly observed therapy (DOTS) as it is important for health care professionals to be aware of these increased risks and for authorities to implement protective measures [27]. Current study shows younger age group are more associated with unfavorable treatment outcomes which shows that for Tb lymphadenitis younger age should be considered for followed up and intensive therapy to prevent mortality and have higher rate of successful treatment in Malaysia.

## Limitations

This study has some limitations for its retrospective nature. We could not assess whether patients who completed treatment increased their weight. Beside this, documentation of diabetes, hepatitis and HIV was likely to be incomplete.

## Conclusions

With continuous growing trend, Tb Lymphadenitis is a grave concern to public health in Malaysia for mainly affecting nationals. High prevalence of EPTB-DM, EPTB-HIV and EPTB-HEP is found in Malaysia. In the present study signifies the fact that these patients are at high risk of developing lymphadenitis. Effect of weight loss on poor treatment outcomes` and active screening measures for patients with comorbidities are therefore recommended in patients with Tb lymphadenitis along with improvements in the diagnosis and early management of co-morbidities complications. As young age group were found to have poor or unsuccessful treatment outcomes and required aggressive strategy together with educating patients can further increase the treatment success rate. Age as a risk factor in young group should be considered for intensive therapy and early diagnosis.

## Abbreviations

AOR: Adjusted odds ratio; CI: Confidence intervals; COR: Crude odds ratio; DM: Diabetes Mellitus; EPTB: Extra-pulmonary tuberculosis; HAART: Highly Active Antiretroviral Therapy; MTB: Mycobacterium tuberculosis; NIMR: National Institute for Medical Research, London; NTP: National TB Control Program; PCR: Polymerase Chain Reaction; PTB: Pulmonary tuberculosis; TB: Tuberculosis; WHO: World Health Organization

## Declarations

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### Funding

None.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

Amer Hayat Khan and Syed Ghouse Mohiuddin conceptualized the study and analysis. Amer Hayat Khan and Muhammad Shahid Iqbal provided oversight and collection of the data. Orwa Albitar and Siti Maisharah conducted the analysis. Syed Ghouse Mohiuddin drafted the manuscript, and all authors provided revisions. All authors have read and approved the manuscript.

### Ethics approval and consent to participate

Ethical clearance was obtained from the Clinical Research Centre (CRC) Penang General Hospital. Permission to proceed with the study protocol and access the raw data was obtained from the state level relevant authorities. Research approval was also taken from prison authorities and Ministry of Health, Malaysia prior to the study. Data was de-identified and consent was waived due to retrospective nature of study.

### Consent for publication

Not applicable.

### Competing interests

Amer Hayat Khan is an editorial manager. The authors declare that they have no competing interests.

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