A Retrospective Study on Tuberculous Lymphadenitis: A Finding from Multicenter Referral Hospitals

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Background: Extrapulmonary tuberculosis represents about 14% of all cases of tuberculosis (TB) in Malaysia. The aim of the study includes the evaluation of sociodemographic factors, clinical manifestations, comorbidities among patients with tuberculous lymphadenitis and their treatment outcomes. Methods: The retrospective study was conducted from 2006 to 2008. Data on sociodemographic along with histopathological results were collected. The signs and symptoms were also recorded from TB registers, treatment cards, and TB medical personal files using the standard data collection tool. Among multiple variables, the significant factors identified by univariate analysis were included in the multivariate logistic regression to estimate the odds ratios with the 95% confidence intervals. The statistically significant P value was considered <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. The age group was observed from 2 to 83 years old. Therefore, the age group between 26 and 35 years showed 194 (31.8%) patients diagnosed with lymphadenitis and followed by 16–25 years (21%). The mean age was found as 34.3 ± 14.6 years were majorly reported with positive diagnosis. One hundred and ninety-six (32.1%) Malay population were found with tuberculous lymphadenitis followed by the Chinese population of 148 (24.3%). The other prominent races were Pilipino, Indonesians, and other expatriates. Geographically, patients were from 386 (63.3%) urban population were found positive for lymphadenitis and over 224 (36.7%) population of the rural region. The treatment outcome was observed 444 (72.8%) with successful treatment. The World Health Organization states the types of treatment failures, and accordingly, 85 (13.9%) patients were continued with the therapy that can be due to noncompliance or relapse of TB. Among the unsuccessful outcomes, 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. Blood test results showed erythrocyte sedimentation rate >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 < 0.001. Conclusion: The 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 tuberculous lymphadenitis along with improvements in the diagnosis and early management of comorbidities complications. As young age group was found to have poor or unsuccessful treatment outcomes and required aggressive strategy together with educating patients can further increase the treatment success rate.

**Keywords:** Comorbidities, extrapulmonary tuberculosis, risk factors, treatment outcomes

complex. A small group of people gets affected by *Mycobacterium africanum*, *Mycobacterium canetti*, *Mycobacterium caprae*, *Mycobacterium microti*, and *Mycobacterium pinnipedii*. 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. Despite many new updated and advanced diagnostic and treatment techniques are available an estimate of ten million incident TB patients were reported globally in 2017. 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, 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 the clinical signs and symptoms of TB disease. TB typically affects the lungs but, in up to a third of patients, can also affects other sites. It is not practically possible to identify *M. tuberculosis* strains present in the body in patients latently infected.

In Malaysia, the early 1940s and 1950s was the era when TB 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. 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 extrapulmonary TB. The most common forms of extrapulmonary TB (EPTB) seen in Malaysia include TB lymphadenitis and bone/joint TB. However, in Malaysia, there has been an increase in the prevalence of noncommunicable 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.

**Study design and data collection**

The protocol of the study was approved by the Clinical Research Centers of Ministry of Health-Malaysia and authorities from four states of Malaysia National Medical Research Registry KKM/NIHSEC/08/0804/P67-177. Informed consent was given and signed by the subjects before performing needle biopsy test for the investigation which is a standard protocol performed before biopsy which must have been done when patient arrived. The retrospective study was conducted from 2006 to 2008. Data on sociodemographic along with histopathological results were collected. The signs and symptoms were also recorded from TB registers, treatment cards, and TB medical personal files using the standard data collection tool which was self-designed and experts supervision. Patients were identified on the basis of site of infection. If the patient had infection confined to lungs were considered pulmonary TB whereas, those patients which had infection at other organs or tissues outside lungs were considered as extrapulmonary TB. Based on the WHO sample selection policy, patients who had both PTB and EPTB infections were excluded from the analysis. The sites of infection for extrapulmonary TB were lymph nodes, and apart from that, all other sites were not included in the study. Successful treatment refers to the complete 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 2008 originated by the Health Ministry of Malaysia.

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.

**Study Location**

Multiple state hospitals were used for investigation, namely (Penang, Selangor, Sabah, and Sarawak). Selection of hospitals was only tertiary care hospitals where TB referral cases are received from each state from KKM (Local government clinics, Klinik Kesihatan Malaysia) 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.
Data analysis

Complete data were assigned a unique identification serial number to ensure the traceability of each data collection form. Data were coded into the computer for the analysis and result interpretation and generation and analysis was performed by using the Statistical Package for the Social Sciences software Windows version 24.0.0 (SPSS, Inc., Chicago, IL, USA). To analyze the predictors of extrapulmonary TB specifically lymphadenitis treatment outcomes univariate analysis was used to identify the importance of risk factors through Chi-square test for the categorical variables and independent sample t-test/Mann–Whitney U-test for the continuous data. The significant factors identified by the univariate analysis were included in the 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. If F value is available, then 20.05 will be considered statistically significant.

RESULTS

Sociodemographic characteristics

Among the four states of Malaysia during the study, data of 610 patients were collected which showed tuberculous lymphadenitis. As shown in Table 1, there were 348 (57%) males, and on the other hand, 262 (43%) females which show almost equal incidence rate of lymphadenitis in both genders. The age group was observed from 2 to 83 years old. Therefore, the age groups between 26 and 35 years showed 194 (31.8%) patients diagnosed with lymphadenitis and followed by 16–25 years (21%). The mean age was found as 34.3 ± 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 the 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 the urban and rural background, but 386 (63.3%) urban population were found positive for lymphadenitis over 224 (36.7%) population of the rural region.

Lymphadenitis and comorbidities/risk factors with major symptoms

Table 2 explains the total of 610 lymphadenitis patients were observed, but 287 (47%) found to have comorbidities such as diabetes mellitus (DM), human immunodeficiency virus (HIV), and hepatitis. DM is a major risk factor for TB and specifically extrapulmonary 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

| Table 1: Demographic profile of patients (n=610) |
| Parameter | n (%) |
| Sex ratio (male: female) | 1.33:1 |
| Range of age (years) | 2-83 |
| Mean age (years) | 34.3±14.6 |
| 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 (years) | |
| ≤15 | 45 (7.4) |
| 16-25 | 128 (21.0) |
| 26-35 | 194 (31.8) |
| 36-45 | 86 (14.1) |
| 46-55 | 82 (13.4) |
| 56-65 | 57 (9.3) |
| ≥66 | 18 (3.0) |
| Geographical location | |
| Urban area | 386 (63.3) |
| Rural area | 224 (36.7) |

| Table 2: Comorbidities 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) |

HBV: Hepatitis B virus, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus
150 (24.6%) patients positive. Regarding the hepatitis, both type B virus and type C virus were monitored, and the data show 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.

Apart from that as mentioned in Table 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 the 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.

**Laboratory test findings and treatment outcomes**

As shown in Table 4, treatment outcome was observed 444 (72.8%) with successful treatment. The WHO states the types of treatment failures, and accordingly, 85 (13.9%) patients were continued with the therapy that can be due to noncompliance or relapse of TB. Apart from that 27 (4.4%) were expired during the treatment, but only 36 (5.9%) were defaulter of treatment as they did not show up for the 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 to 35 years, 65 (33.5%) were reported and 38 (29.7%) patients out of 128 between the age group of 16 and 25 years. As mentioned in Table 5, significant association was observed between unsuccessful treatment and intravenous (IV) 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 < 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, acid-fast bacilli (AFB) for the culture test showed 327 (53.6%) positive results. Similarly, 224 (36.7%) were reported positive for AFB (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 >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 < 0.001.

### 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) |

### Table 4: Laboratory test results and treatment outcomes (n=610)

| Parameter                          | n (%)  |
|------------------------------------|--------|
| 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                           | 138 (22.6) |
| Unknown                            | 234 (38.4) |
| 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) |

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     |
|----------------------------------|------------------------------|----------------------|-------|
| Age group (years)                |                              |                      |       |
| 16-25                            | 38/128 (29.7)                | 4.119 (1.138-14.914) | 0.031 |
| 26-35                            | 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)| 0.001 |
| Positive sputum culture          | 94/327 (28.7)                | 0.133 (0.056-0.320)  | 0.001 |
| ESR >10 (mm/h)                   | 115/280 (41.1)               | 6.359 (2.446-16.530) | 0.001 |

Only significant values are provided in the table, constant=−5.032, backward LR method was applied, classification table 86.1% correctly classified. CI: Confidence interval, ESR: Erythrocyte sedimentation rate, OR: Odds ratio, LR: Likelihood ratio.

### Discussion

There are multiple studies performed on pulmonary and extrapulmonary TB but with numerous important limitations with either gives up biased data or lack of adequate sample size to conclude. Therefore, to the best of our 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 the 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 Malys is higher than others and rate of relapse of diseases is also considered higher in Malay race due to lower economic and social conditions.

A similar study performed on the extrapulmonary TB shows that patients at the risk of EPTB were more likely to be females. 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 and 35 years were found to have most diagnosed with lymphadenitis compared to other age groups despite gender. Similar results were reported by an Egyptian study performed prospectively on extra-pulmonary Tb patients, which states 34.8 ± 12.5 years as the mean age diagnosed with TB. Another recent study was performed in Penang General Hospital on tuberculous lymphadenitis patients also states that average mean age is 36.4 ± 12.87 among the active TB patients.

There was strong association found in the research as those who were using other IV 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. 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 noncompliance or Intra venous drug abuse.

There are multiple risk factors associated with TB, but current research showed contradictory results in relation to extrapulmonary TB lymphadenitis. Diabetes, human immunodeficiency 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 comorbid patients reported strong relationship on the unsuccessful treatment outcomes of TB and a major risk factor for extrapulmonary TB. The present study findings show only few patients were found to have diabetes which is <15% of the total diagnosed population with tuberculous 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. 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. Similarly, a cross-sectional study performed in Manjung district of Malaysia reported that the most common comorbidity was DM with majority of cases of the PTB patients having diagnosed or undiagnosed DM prior to PTB.
This study has revealed some strong association between the risk factors and treatment outcomes. One of few reasons is weight loss or lower body mass index (BMI) which showed unsuccessful treatment outcome in the present study. Recently, another study was performed in Yemen on multidrug-resistant Tb and their analysis revealed that a baseline body weight of ≤40 kg was found to have lower successful treatment rate. 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. Similar positive association between low body weight and unfavorable treatment outcomes has been reported by studies conducted elsewhere. Poor absorption from gastrointestinal (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. It not only reduces the gastrointestinal absorption of drugs but also increases 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. 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 and 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 ≥25 years were the risk factors reported for poor treatment outcomes. 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 ≥85 years which is contradictory to current study results as these were not specific to lymphadenitis TB. Another study performed in Malaysia states that the mean age of unsuccessful treatments was 34.6 ± 10.55 years and among them 68.9% were females. 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. The current study shows that younger age group is more associated with unfavorable treatment outcomes which shows that for tuberculous 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 were likely to be incomplete.

**Conclusions**

With continuous growing trend, tuberculous lymphadenitis is a grave concern to public health in Malaysia for mainly affecting nationals. A 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 comorbidities 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.

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**Conflicts of interest**

There are no conflicts of interest.

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