Treatment outcomes and risk factors of extra-pulmonary tuberculosis in patients with co-morbidities

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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 EPTB and their treatment outcomes.

Methods: A retrospective study was conducted to recognize the epidemiology facts of EPTB. Individual data for EPTB patients were collected from TB registers, laboratory TB registers, treatment cards and TB medical personal files into a standardized study questionnaire. Crude (COR) and adjusted odds ratios (AOR) and 95% confidence intervals (CI) were determined to assess the risk factors for EPTB and unsuccessful treatment outcomes.

Results: There were 1222 EPTB patients presenting 13.1% of all TB cases during 2006–2008. Pleural effusion and lymph node TB were the most frequent types and accounted for 45.1% of all EPTB cases among study participants. Treatment success rate was 67.6%. The best treatment completion rates were found in children ≤15 years (0.478 [0.231–1.028]; p = 0.05). On multivariate analysis, age group 56–65 years (1.658 [1.157–2.376]; P = 0.006), relapse cases (7.078 [1.585–31.613]; P = 0.010), EPTB-DM (1.773 [1.165–2.698]; P = 0.008), patients with no formal (2.266 [1.254–4.095]; P = 0.001) and secondary level of education (1.889 [1.085–3.288]; P = 0.025) were recorded as statistically positive significant risk factors for unsuccessful treatment outcomes. Patients at the risk of EPTB were more likely to be females (1.524 [1.311–1.746]; P < 0.001), Malays (1.251 [1.056–1.482]; P = 0.010) and Indians (1.450 [1.142–1.842]; P = 0.002), TB-HIV (3.215 [2.347–4.405]; P < 0.001), EPDM-HIV (4.361 [1.657–11.474]; P = 0.003), EPTB-HIV-HEP (4.083 [2.785–5.987]; P < 0.001), those living in urban areas (1.272 [1.109–1.459]; P = 0.001) and no formal education (1.361 [1.018–1.820]; P = 0.037).

Conclusion: The findings of this study extend the knowledge of EPTB epidemiology and highlight the need for improved EPTB detection in Malaysia, especially in subpopulations with high risk for EPTB and unsuccessful treatment outcomes.

Keywords: Extra-pulmonary TB, Co-morbidities, Risk factors, Treatment outcomes
Background
TB is the ninth foremost reason of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS [1]. Overall, a relatively small proportion (5–15%) of the people infected with Mycobacterium tuberculosis (MTB) will develop TB disease during their lifetime. However, the probability of developing TB disease is much higher among people infected with HIV, and also higher among people affected by risk factors such as under-nutrition, diabetes, smoking and alcohol consumption [1].

Pulmonary TB (PTB), the most common type of TB, has the great epidemiological significance due to its extremely contagious nature [2]. The proportion of patients with extra-pulmonary TB (EPTB) relative to those with PTB varies among countries and depends on associated diseases, geographical, social, ethnic and economic parameters [3, 4]. EPTB is defined according to WHO classification criteria as an infection by MTB which affects tissues and organs outside the pulmonary parenchyma. It represents between 20 and 25% of all TB cases [5].

In the early 1940s and 1950s, TB was graded as the main reason of death in Malaysia. Realizing its seriousness, the Malaysian government launched its National TB Control Program (NTP) in 1961 [6]. With regards to the type of TB, of 25,739 reported TB cases in Malaysia during 2016, 22,135 (86%) were PTB cases while 3604 (14%) were EPTB [1]. The most common forms of EPTB seen in Malaysia are TB lymphadenitis, bone/joint TB and miliary TB [6]. From 1990 to 2016, the number of TB-HIV co-infection reported nationwide has increased from 6 to 3396 cases [7]. EPTB involvement tends to increase in frequency if the immune system is compromised [2]. Diabetes Mellitus (DM) has been identified as a risk factor for TB [8–10]. Although immune deficiency also occurs with diabetes, but little is known about the epidemiological or clinical relationship between diabetes and EPTB. However, we hypothesized that infectious and immune-compromised conditions increased frequency and severity of EPTB. The current study was conducted with the aim to evaluate the clinical characteristics and treatment outcomes of patients with EPTB. Furthermore, we were interested to identify the risk factors of EPTB on socio-demographic, co-morbidities and clinical basis.

Methods
Study design and data collection
A retrospective study was conducted in four states of Malaysia from 2006 to 2008. Data on socio-demographic, clinical, histopathological, microbiological and other laboratory variables of EPTB cases were collected from TB registers, treatment cards and TB medical personal files using standard data collection tool. Patients in whom the site of infection was confined to lungs were considered as PTB while infection extended to other organs or tissues outside lungs were considered as EPTB. Patients who had both PTB and EPTB involvements were excluded from the analysis of EPTB based on WHO sample selection policy [11]. The sites of infection were as lymph nodes, gastrointestinal system, spinal, meningitis pleural effusion, miliary and bones/joints. All other sites of infection were considered as part of a seventh group identified as “other rare forms” (including urogenital, eyes, ear, breast etc.) for convenience. Statistical analysis the diagnosis of EPTB was done following Clinical Practice Guidelines [12], which is consistent with the WHO’s diagnostic criteria [13]. 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 [12].

Study location
The study was carried out in selected hospitals and prisons located in four states of Malaysia (Penang, Sabah, Sarawak, and Selangor). The states of Penang, Sabah and Sarawak were selected for the present study based on previous literature report of TB burden. The prevalence of TB in Malaysia was highest in Sabah followed by Sarawak and Penang [6]. The state of Selangor was also considered for the present study as it has two big prisons at national level in Malaysia.

Data analysis
The whole data collection form was assigned a serial number to ensure the traceability. Coding of the responses was carried out and the data was entered into the computer and analysed by using statistical package for SPSS for Windows version 16.0 (SPSS, Inc., Chicago, IL, USA). Logistic regression model was used to analyze the predictors for EPTB and unsuccessful treatment outcomes. However, p value was used to calculate significance of co-morbidities among different variables. Factors found significant in univariate analysis, were finally included in multivariate logistic regression to estimate the odds ratios (ORs) with their 95% confidence intervals (CIs). A p value < 0.05 was considered statistically significant.

Results
Proportion, socio-demographic and baseline clinical characteristics
Proportion of EPTB registered in four states of Malaysia during study time period is shown in Table 1. Patients with EPTB constituted about 13.1% of all TB cases, with
higher prevalence in Selangor than other three states. Socio-demographic and clinical characteristics of patients are shown in Table 2. The study cohort included 778 (63.7%) males and 444 (36.3%) females. Of the 1222 cases included in the present study, age group 26–35 years constituted the highest cases (24.2%) and least numbers were recorded for ≤15 years old (4.5%). In terms of residence, higher proportions of EPTB were observed in the urban areas (67%). The results showed that there was a significant difference \( p < 0.001 \) in the incidence of EPTB among different races. The Malays seemed to be highly affected with a number of 389 (31.8%) cases followed by the Chinese (23.9%).

Around, 330 (27%) of cases had acid fast bacilli smear positive and 687 (56.2%) culture positive. However, 360 patients (29.5%) were diagnosed via pathology alone and 43 (3.5%) were confirmed on polymerase chain reaction (PCR). Among the culture confirmed EPTB cases, 1.5% of patients were resistant to single first line drugs. On baseline 4 patients were recorded resistant to isoniazid and 4 for streptomycin whereas 1 each for rifampicin and ethambutol. Of HIV co-infection, 139 patients were receiving Highly Active Antiretroviral Therapy (HAART). For EPTB patients with DM, 152 were getting oral hypoglycemic agents plus insulin.

**Frequency distribution of EPTB**

Of 9335 all TB cases registered during the study time period, 1222 had EPTB. Lymph node 324 (26.5%) and Pleural effusion 227 (18.6%) TB were the most frequent types of all EPTB cases among study participants (Table 2). The proportions of different types of EPTB varied with statistically significant difference observed among gender \( p = 0.03 \), age groups \( p < 0.001 \), different ethnic groups \( p < 0.001 \), co-morbidities \( p < 0.001 \), and smokers \( p < 0.001 \) (Table 2).

**EPTB and co-morbidities**

Out of 1222 EPTB patients, 525 (43%) were recorded with co-morbidities. Chi-square analysis of categorical variables of the study participants showed a significant difference in males and females, distribution of age, races, residence, patient categories, marital status, education and employment between EPTB and co-morbidities groups (Table 3). Among the co-morbidities, HIV and DM contributed to the highest cases and almost at the equal rate. Overall, higher proportions of all co-morbidities were seen among males than females and patients aged 35 years or older. Numbers of EPTB with diabetes mellitus (EPTB-DM), EPTB with human immunodeficiency virus (EPTB-HIV) and EPTB and hepatitis (EPTB-HEP) cases were frequently seen among 35–55 years age whereas the co-morbidities became more complex with increasing age. Patients from the rural areas were significantly had increased proportions of HIV related comorbidities. Moreover, patients with CD4+ lymphocyte cell counts <100 had 37.3% lymph node TB, 18.6% cases of miliary and pleural TB each. We further confirmed that of total deaths among known CD4+ lymphocyte count, 55% occurred in patients with <100 counts. Other diseases which patients already had at the baseline include hypertension (3%), ischemic heart disease (1%), renal failure (2%), lung carcinoma (0.2%), lung fibrosis (0.2%), liver cirrhosis (0.2%), hypertension and COPD (0.2%), ischemic heart disease+ renal failure+ hypertension (0.4%) (Table 3).

**Treatment outcomes**

Around, 67.6% (826/1222) patients successfully completed treatment. Treatment outcomes in relation to socio-demographic characteristics and co-morbidities are shown in Table 4. There were no statistically significant differences seen with regard to treatment outcomes among males and females, residency, ethnicity, alcohol habit and employment on univariate analysis (Table 4).

On multivariate analysis (Table 4), age group 56–65 years \( (1.658 [1.157–2.376]; p = 0.006) \), relapse cases \( (7.078 [1.585–31.613]; p = 0.010) \), EPTB-DM \( (1.773 [1.165–2.698]; p = 0.008) \), patients with no formal \( (2.266 [1.254–4.095]; p = 0.001) \) and secondary level of education \( (1.889 [1.085–3.288]; p = 0.025) \) were recorded as statistically positive significant risk factors for unsuccessful treatment outcomes. Comparing the proportion of default and deaths among different types of EPTB, significantly higher were reported in meningitis and miliary TB (Fig. 1).

Of 139 patients who were on HAART, 111 (79.9%) successfully completed the treatment while the remaining 28 (20.1%) had unsuccessful treatment outcomes. Nevertheless, statistically significant association was observed between DM and treatment outcomes for EPTB-DM patients. When death and default cases were compared among the different co-morbidities, maximum death cases were observed for EPTB-DM-HEP followed by EPTB-DM-HIV. However, higher proportions of default were seen among patients with EPTB-DM (Fig. 2).
| Variables        | Total n = 1222 (%) | Lymph node n = 324 (%) | Pleural effusion n = 227 (%) | Meningitis n = 122 (%) | Miliary n = 113 (%) | Bones n = 116 (%) | Gastro-intestinal n = 105 (%) | Spinal n = 93 (%) | Others n = 122 (%) |
|------------------|--------------------|------------------------|------------------------------|------------------------|-----------------|----------------|-------------------------------|----------------|-----------------|
| **Gender**       |                    |                        |                              |                        |                 |                 |                               |                 |                 |
| Male             | 778 (63.7%)        | 214 (27.5%)            | 155 (19.9%)                  | 75 (6.6%)              | 83 (10.7%)      | 72 (9.3%)       | 55 (7.1%)                     | 61 (7.8%)   | 63 (8.1%)       |
| Female           | 444 (36.3%)        | 110 (24.8%)            | 72 (16.2%)                   | 47 (10.6%)             | 30 (6.8%)       | 44 (9.9%)       | 50 (11.3%)                    | 32 (7.2%)   | 59 (13.3%)      |
| **Age (years)**  |                    |                        |                              |                        |                 |                 |                               |                 |                 |
| ≤ 15             | 55 (4.5%)          | 14 (25.5%)             | 7 (12.7%)                    | 7 (12.7%)              | 2 (3.6%)        | 0               | 11 (20%)                     | 4 (7.3%)    | 10 (18.2%)      |
| 16–25            | 177 (14.5%)        | 50 (28.2%)             | 28 (15.8%)                   | 13 (7.3%)              | 13 (7.3%)       | 21 (11.9%)      | 26 (14.7%)                    | 4 (2.3%)    | 22 (12.4%)      |
| 26–35            | 296 (24.2%)        | 118 (39.9%)            | 33 (11.1%)                   | 28 (9.5%)              | 30 (10.1%)      | 34 (11.5%)      | 17 (5.7%)                     | 10 (3.4%)   | 26 (8.8%)       |
| 36–45            | 224 (18.3%)        | 54 (24.1%)             | 42 (18.8%)                   | 25 (11.2%)             | 21 (9.4%)       | 23 (10.3%)      | 16 (7.1%)                     | 28 (12.9%)  | 15 (6.7%)       |
| 46–55            | 233 (19.1%)        | 46 (19.7%)             | 47 (20.2%)                   | 20 (8.6%)              | 23 (9.9%)       | 23 (9.9%)       | 24 (10.3%)                    | 27 (11.6%)  | 23 (9.9%)       |
| 56–65            | 170 (13.9%)        | 36 (21.2%)             | 46 (27.1%)                   | 23 (13.5%)             | 15 (8.8%)       | 11 (6.5%)       | 9 (5.3%)                      | 14 (8.2%)   | 16 (9.4%)       |
| ≥ 66             | 67 (5.5%)          | 6 (9%)                 | 24 (35.8%)                   | 6 (9%)                 | 9 (13.4%)       | 4 (6%)          | 2 (3%)                        | 6 (9%)      | 10 (14.9%)      |
| **Race**         |                    |                        |                              |                        |                 |                 |                               |                 |                 |
| Malay            | 389 (31.8%)        | 132 (33.9%)            | 62 (15.9%)                   | 26 (6.7%)              | 34 (8.7%)       | 39 (10%)        | 31 (8%)                       | 31 (8%)     | 34 (8.7%)       |
| Chinese          | 292 (23.9%)        | 78 (27.6%)             | 61 (20.9%)                   | 26 (8.9%)              | 26 (8.9%)       | 29 (9.9%)       | 24 (8.2%)                     | 23 (7.9%)   | 25 (8.6%)       |
| Indian           | 128 (10.5%)        | 34 (26.6%)             | 30 (23.4%)                   | 6 (4.7%)               | 16 (12.5%)      | 10 (78%)        | 12 (94%)                      | 10 (7.8%)   | 10 (7.8%)       |
| Immigrants Indian| 63 (5.2%)          | 13 (20.6%)             | 16 (25.4%)                   | 7 (11.1%)              | 7 (11.1%)       | 7 (11.1%)       | 5 (79%)                       | 4 (63%)     | 4 (63%)         |
| Immigrants Indonesian | 45 (3.7%)   | 4 (8.9%)               | 6 (13.3%)                    | 11 (244%)              | 2 (4.4%)        | 2 (4.4%)        | 8 (178%)                      | 3 (67%)     | 9 (143%)        |
| Sarawakian       | 87 (7.1%)          | 15 (17.2%)             | 25 (28.7%)                   | 3 (3.4%)               | 2 (2.3%)        | 12 (138%)       | 2 (3%)                        | 7 (8%)      | 21 (24%)        |
| Sabahian         | 189 (15.5%)        | 36 (19%)               | 18 (9.5%)                    | 42 (22.2%)             | 26 (138%)       | 16 (8.5%)       | 21 (111%)                    | 13 (69%)    | 17 (9%)         |
| Others           | 29 (2.4%)          | 12 (41.4%)             | 9 (31%)                      | 1 (3.4%)               | 0               | 1 (3.4%)        | 2 (65%)                       | 2 (69%)     | 2 (69%)         |
| **Residence**    |                    |                        |                              |                        |                 |                 |                               |                 |                 |
| Urban            | 819 (67%)          | 194 (23.7%)            | 177 (21.6%)                  | 77 (9.4%)              | 66 (8.1%)       | 81 (10%)        | 75 (9.2%)                     | 56 (68%)    | 93 (11.4%)      |
| Rural            | 403 (33%)          | 130 (32.3%)            | 50 (12.4%)                   | 45 (11.2%)             | 47 (11.7%)      | 35 (8.7%)       | 30 (7.4%)                     | 37 (9.2%)   | 29 (7.2%)       |
| **Patient category** |                |                        |                              |                        |                 |                 |                               |                 |                 |
| Unknown          | 23 (1.9%)          | 5 (21.7%)              | 7 (30.4%)                    | 0                     | 4 (17.4%)       | 3 (13%)         | 0                             | 1 (43)       | 3 (13)          |
| New              | 1131 (92.6%)       | 304 (26.9%)            | 206 (18.2%)                  | 115 (10.2%)            | 103 (91%)       | 110 (9.7%)      | 95 (84%)                      | 86 (76%)    | 112 (9.9%)      |
| Relapse          | 68 (5.6%)          | 15 (22.1%)             | 14 (20.6%)                   | 7 (10.3%)              | 6 (8.8%)        | 3 (4.6%)        | 10 (14.7%)                    | 6 (8.8%)    | 7 (10.3%)       |
| **Co-morbidity** |                    |                        |                              |                        |                 |                 |                               |                 |                 |
| Only TB          | 697 (57%)          | 165 (23.7%)            | 111 (15.9%)                  | 70 (10%)               | 75 (10.8%)      | 74 (10.6%)      | 68 (9.8%)                     | 50 (7.2%)   | 84 (12.1%)      |
| TB-DM            | 180 (14.7%)        | 40 (22.2%)             | 61 (33.9%)                   | 16 (8.9%)              | 7 (3.9%)        | 10 (5.6%)       | 17 (9.4%)                     | 13 (7.2%)   | 16 (8.9%)       |
| TB-HIV           | 188 (15.4%)        | 70 (37.2%)             | 22 (11.7%)                   | 20 (10.6%)             | 18 (9.6%)       | 23 (12.2%)      | 11 (5.9%)                     | 9 (48)      | 15 (8)          |
| TB-Hep           | 60 (4.9%)          | 9 (15%)                | 16 (26.7%)                   | 6 (10%)                | 4 (6.3)         | 3 (5)           | 3 (5)                         | 15 (25%)    | 4 (47)          |
| TB-DM-HIV        | 7 (0.6%)           | 3 (42.9%)              | 2 (28.6%)                    | 1 (143%)               | 0               | 0               | 0                             | 0           | 1 (143%)        |
| Variables                      | Total n = 1222 (%) | Lymph node n = 324 (%) | Pleural effusion n = 227 (%) | Meningitis n = 122 (%) | Milliary n = 113 (%) | Bone n = 116 (%) | Gastro-intestinal n = 105 (%) | Spinal n = 93 (%) | Others n = 122 (%) |
|-------------------------------|---------------------|------------------------|-----------------------------|-----------------------|---------------------|----------------|-------------------------------|----------------|-------------------|
| TB-DM                         | 11 (0.9)            | 1 (9.1)                | 2 (18.2)                    | 2 (18.2)              | 1 (9.1)             | 0              | 4 (36.4)                     | 1 (9.1)        | 0                 |
| TB-HIV                        | 79 (6.5)            | 36 (45.6)              | 13 (16.5)                   | 7 (8.9)               | 8 (10.1)            | 6 (7.8)        | 2 (2.5)                      | 5 (6.3)        | 2 (2.5)           |
| Smoking habit                 |                     |                        |                             |                       |                     |                |                               |                |                   |
| Ex-smoker                     | 166 (1.3)           | 28 (16.9)              | 33 (19.9)                   | 12 (7.2)              | 24 (14.5)           | 12 (7.2)       | 27 (16.3)                    | 7 (42)         | 23 (13.9)         |
| No                            | 647 (52.9)          | 180 (27.8)             | 114 (17.6)                  | 62 (9.6)              | 57 (8.8)            | 56 (8.7)       | 58 (7)                       | 50 (7.7)       | 70 (10.8)         |
| Yes                           | 409 (33.5)          | 116 (28.4)             | 80 (19.6)                   | 48 (11.7)             | 32 (7.8)            | 48 (11.7)       | 20 (43.9)                    | 36 (8.8)       | 29 (7.1)          |
| Drinking Habit                |                     |                        |                             |                       |                     |                |                               |                |                   |
| Unknown                       | 12 (1)              | 2 (16.7)               | 2 (16.7)                    | 0                     | 0                   | 1 (8.3)        | 1 (8.3)                      | 4 (33.3)       |                   |
| No                            | 1094 (89.5)         | 291 (27)               | 207 (18.9)                  | 110 (10.1)            | 96 (8.8)            | 105 (9.6)       | 97 (8.9)                     | 78 (7.1)       | 110 (10.1)        |
| Yes                           | 116 (9.5)           | 31 (26.7)              | 18 (15.5)                   | 10 (8.6)              | 17 (14.7)           | 11 (9.5)       | 7 (6)                        | 14 (12.1)      | 8 (6.9)           |
| MAR^a                         |                     |                        |                             |                       |                     |                |                               |                |                   |
| Unknown                       | 23 (1.9)            | 7 (30.4)               | 7 (30.4)                    | 1 (43)                | 3 (13)              | 4 (13)         | 1 (43)                       | 1 (43)         | 1 (43)            |
| No                            | 1113 (91)           | 301 (27)               | 205 (18.4)                  | 105 (9.4)             | 100 (9)             | 111 (10)       | 96 (8.6)                     | 86 (7.8)       | 109 (9.8)         |
| Yes                           | 86 (7.1)            | 16 (18.6)              | 15 (17.4)                   | 16 (18.6)             | 10 (11.6)           | 4 (4.7)        | 7 (8.1)                      | 6 (7)          | 12 (14)           |
| Marital status                |                     |                        |                             |                       |                     |                |                               |                |                   |
| Unknown                       | 22 (1.8)            | 4 (18.2)               | 6 (27.3)                    | 2 (9.1)               | 5 (22.7)            | 2 (9.1)        | 0                            | 0              | 3 (13.6)          |
| Married                       | 539 (44.1)          | 99 (26.9)              | 72 (19.6)                   | 35 (9.5)              | 46 (12.5)           | 32 (8.7)       | 35 (9.5)                     | 17 (4.6)       | 32 (8.7)          |
| Unmarried                     | 832 (68.1)          | 221 (26.8)             | 149 (17.9)                  | 85 (10.2)             | 62 (7.5)            | 82 (9.9)       | 70 (8.4)                     | 76 (9.1)       | 87 (10.5)         |
| Education                     |                     |                        |                             |                       |                     |                |                               |                |                   |
| Unknown                       | 876 (71.7)          | 224 (25.8)             | 162 (18.5)                  | 97 (11.1)             | 84 (9.6)            | 78 (8.9)       | 80 (9.1)                     | 63 (7.2)       | 88 (10)           |
| Primary                       | 111 (9.1)           | 40 (36)                | 13 (11.7)                   | 7 (6.3)               | 9 (8.1)             | 13 (11.7)      | 8 (7.2)                      | 7 (6.3)        | 14 (12.6)         |
| Secondary                     | 84 (6.9)            | 17 (20.2)              | 22 (26.2)                   | 8 (9.5)               | 6 (7.1)             | 8 (9.5)        | 10 (11.9)                    | 5 (6)          | 8 (9.5)           |
| College                       | 42 (3.4)            | 23 (54.8)              | 7 (16.7)                    | 0                    | 1 (2.4)             | 1 (2.4)        | 2 (48)                       | 5 (11.9)       | 3 (7.1)           |
| University                    | 8 (0.7)             | 1 (12.5)               | 3 (37.5)                    | 0                    | 1 (12.5)            | 0              | 0                            | 1 (12.5)       | 2 (23)            |
| Diploma                       | 20 (1.6)            | 5 (25)                 | 1 (5)                       | 0                    | 10 (50)             | 1 (5)          | 3 (15)                       | 0              |                   |
| No formal education           | 81 (6.6)            | 14 (17.3)              | 19 (23.5)                   | 10 (12.3)             | 12 (14.8)           | 6 (7.4)        | 4 (49)                       | 9 (11.1)       | 7 (8.6)           |
| Employment status             |                     |                        |                             |                       |                     |                |                               |                |                   |
| Unknown                       | 188 (15.4)          | 54 (28.7)              | 28 (149)                    | 9 (48)                | 22 (11.7)           | 15 (8)         | 16 (8.5)                     | 33 (17.6)      | 11 (5.9)          |
| Employed                      | 342 (28)            | 104 (30.4)             | 67 (19.6)                   | 30 (8.8)              | 25 (7.3)            | 42 (12.3)      | 22 (6.4)                     | 26 (7.6)       | 26 (7.6)          |
| Unemployed                    | 692 (56.6)          | 166 (24)               | 132 (19.1)                  | 83 (12)               | 66 (9.5)            | 59 (8.5)       | 67 (9.7)                     | 34 (4.9)       | 85 (12.3)         |

TB-DM Co-infection of TB and Diabetes Mellitus, TB-HIV Co-infection of TB and HIV, TB-Hep Co-infection of TB and Hepatitis, TB-DM-HIV Co-infection of TB with Diabetes Mellitus and HIV, TB-DM-Hep Co-infection of TB with Diabetes Mellitus and Hepatitis, TB-HIV-Hep Co-infection of TB with HIV and Hepatitis

^aIntravenous Drug Users

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Table 3 Distribution and frequency of different types of co-morbidities among patients with EPTB (n=1222)

| Variables            | Total 1222 (%) | TB only 697 (%) | TB-DM 180 (%) | TB-HIV 188 (%) | TB-Hepatitis 60 (%) | TB-DM-HIV 7 (%) | TB-DM-Hepatitis 11 (%) | TB-HIV-Hepatitis 79 (%) | P-value |
|----------------------|----------------|----------------|----------------|----------------|----------------------|----------------|-------------------------|----------------------------|---------|
| **Gender**           |                |                |                |                |                      |                |                         |                             |         |
| Male                 | 778 (63.7)     | 381 (54.7)     | 93 (51.7)      | 178 (94.7)     | 33 (55)              | 7 (100)        | 10 (90.1)               | 76 (96.2)                   | < 0.001 |
| Female               | 444 (36.3)     | 316 (45.3)     | 87 (48.3)      | 10 (5.3)       | 27 (45)              | 0              | 1 (99)                  | 3 (3.8)                      |         |
| **Age (years)**      |                |                |                |                |                      |                |                         |                             |         |
| ≤ 15                 | 55 (4.5)       | 47 (6.7)       | 3 (1.7)        | 1 (0.5)        | 2 (3.3)              | 1 (14.3)       | 0                       | 1 (1.3)                      |         |
| 16–25                | 177 (14.5)     | 136 (19.5)     | 11 (6.1)       | 13 (6.9)       | 8 (13.3)             | 1 (143)        | 2 (182)                 | 6 (7.6)                      |         |
| 26–35                | 296 (24.2)     | 169 (24.2)     | 30 (16.7)      | 66 (35)        | 9 (15)               | 1 (143)        | 2 (182)                 | 19 (24.1)                   | < 0.001 |
| 36–45                | 224 (18.3)     | 103 (14.8)     | 22 (12.2)      | 52 (27.7)      | 15 (25)              | 1 (143)        | 0                       | 31 (39.2)                    |         |
| 46–55                | 233 (19.1)     | 114 (16.4)     | 54 (30)        | 36 (19.1)      | 14 (23.3)            | 0              | 0                       | 15 (19)                      |         |
| 56–65                | 170 (13.9)     | 81 (11.6)      | 51 (28.3)      | 16 (8.5)       | 7 (11.7)             | 3 (429)        | 6 (54.5)                | 6 (7.6)                      |         |
| ≥ 66                 | 67 (5.5)       | 47 (6.7)       | 9 (5)          | 4 (2.1)        | 5 (8.3)              | 0              | 1 (91)                  | 1 (1.3)                      |         |
| **Race**             |                |                |                |                |                      |                |                         |                             |         |
| Malay                | 389 (31.8)     | 183 (26.3)     | 54 (30)        | 89 (47.3)      | 22 (36.7)            | 2 (286)        | 4 (364)                 | 35 (44.3)                    |         |
| Chinese              | 292 (23.9)     | 155 (22.2)     | 43 (23.9)      | 52 (27.7)      | 19 (31.7)            | 2 (286)        | 2 (182)                 | 19 (24.1)                    |         |
| Indian               | 128 (10.5)     | 66 (9.5)       | 21 (11.7)      | 21 (11.2)      | 6 (10)               | 2 (286)        | 2 (182)                 | 10 (12.7)                    |         |
| Immigrants Indonesian| 63 (5.2)       | 40 (5.7)       | 12 (6.7)       | 5 (2.7)        | 2 (3.3)              | 0              | 0                       | 4 (5.1)                      | < 0.001 |
| Immigrants Philippines| 45 (3.7)      | 30 (4.3)       | 12 (6.7)       | 1 (0.5)        | 0                    | 0              | 1 (91)                  | 1 (1.3)                      |         |
| Sarawakian           | 87 (7.1)       | 58 (8.3)       | 15 (8.3)       | 7 (3.7)        | 3 (5)                | 0              | 0                       | 4 (5.1)                      |         |
| Sabahian             | 189 (15.5)     | 149 (21.4)     | 22 (12.2)      | 5 (2.7)        | 7 (11.7)             | 1 (143)        | 2 (182)                 | 3 (3.8)                      |         |
| Others               | 29 (2.4)       | 16 (2.3)       | 1 (0.6)        | 8 (4.3)        | 1 (1.7)              | 0              | 0                       | 3 (3.8)                      |         |
| **Patient category** |                |                |                |                |                      |                |                         |                             |         |
| Unknown              | 23 (1.9)       | 9 (1.3)        | 1 (0.6)        | 11 (5.9)       | 0                    | 0              | 0                       | 2 (2.5)                      | < 0.001 |
| New                  | 1131 (92.6)    | 652 (93.5)     | 169 (93.8)     | 166 (88.2)     | 57 (95)              | 7 (100)        | 6 (54.5)                | 74 (93.7)                    |         |
| Relapse              | 68 (5.6)       | 36 (5.2)       | 10 (5.6)       | 11 (5.9)       | 3 (5)                | 0              | 5 (45.5)                | 3 (3.8)                      |         |
| **Residency**        |                |                |                |                |                      |                |                         |                             |         |
| Urban                | 819 (67)       | 494 (70.9)     | 149 (82.8)     | 88 (46.8)      | 46 (76.7)            | 1 (143)        | 10 (90.1)               | 31 (39.2)                    | < 0.001 |
| Rural                | 403 (33)       | 203 (29.1)     | 31 (17.2)      | 100 (53.2)     | 14 (23.3)            | 6 (85.7)       | 1 (91)                  | 48 (60.8)                    |         |
| **Smoking habit**    |                |                |                |                |                      |                |                         |                             |         |
| Ex-smoker            | 166 (13.6)     | 105 (15.1)     | 38 (21.1)      | 8 (4.3)        | 11 (18.3)            | 0              | 1 (91)                  | 3 (3.8)                      | < 0.001 |
| No                   | 647 (52.9)     | 402 (57.7)     | 91 (50.6)      | 85 (45.2)      | 28 (46.7)            | 1 (143)        | 5 (45.5)                | 35 (44.3)                    |         |
| Yes                  | 409 (33.5)     | 190 (27.3)     | 51 (28.3)      | 95 (50.5)      | 21 (35)              | 6 (85.7)       | 5 (45.5)                | 41 (51.9)                    |         |
Table 3  Distribution and frequency of different types of co-morbidities among patients with EPTB (n = 1222)  (Continued)

| Variables               | Total 1222 (%) | TB only n = 697 (%) | TB-DM n = 180 (%) | TB-HIV n = 188 (%) | TB-Hepatitis n = 60 (%) | TB-DM-HIV n = 7 (%) | TB-DM-Hepatitis n = 11 (%) | TB-HIV-Hepatitis n = 79 (%) | P-value |
|-------------------------|----------------|---------------------|------------------|--------------------|------------------------|----------------------|---------------------------|-----------------------------|---------|
| **Drinking Habit**      |                |                     |                  |                    |                        |                      |                           |                             |         |
| Unknown                 | 12 (1)         | 5 (0.7)             | 2 (1.1)          | 2 (1.1)            | 0                     | 0                    | 0                         | 3 (0.8)                     | < 0.001 |
| No                      | 1094 (89.5)    | 660 (94.7)          | 176 (97.8)       | 127 (67.6)         | 56 (93.3)             | 5 (71.4)             | 10 (90.1)                  | 60 (75.9)                   |         |
| Yes                     | 116 (9.5)      | 32 (4.6)            | 2 (1.1)          | 59 (31.4)          | 4 (6.7)                | 2 (28.6)             | 1 (9.1)                   | 16 (20.3)                   |         |
| **IVDU**                |                |                     |                  |                    |                        |                      |                           |                             |         |
| Unknown                 | 23 (1.9)       | 7 (1)               | 0                | 2 (1.1)            | 1 (1.7)                | 1 (14.3)             | 0                         | 12 (15.2)                   | < 0.001 |
| No                      | 1113 (91)      | 659 (94.9)          | 177 (98.3)       | 152 (80.9)         | 53 (88.3)              | 4 (57.1)             | 10 (90.1)                 | 58 (73.4)                   |         |
| Yes                     | 86 (7.1)       | 31 (4.4)            | 3 (1.7)          | 34 (18.1)          | 6 (10)                 | 2 (28.6)             | 1 (9.1)                   | 9 (11.4)                    |         |
| **Marital status**      |                |                     |                  |                    |                        |                      |                           |                             |         |
| Unknown                 | 22 (1.8)       | 6 (0.9)             | 1 (0.6)          | 12 (6.4)           | 0                     | 0                    | 0                         | 3 (3.8)                     | < 0.001 |
| Married                 | 539 (44.1)     | 224 (32.1)          | 45 (25)          | 51 (27.1)          | 18 (30)                | 1 (14.3)             | 1 (9.1)                   | 28 (35.5)                   |         |
| Unmarried               | 832 (68.1)     | 467 (67)            | 134 (74.4)       | 125 (66.5)         | 42 (70)                | 6 (85.7)             | 10 (90.1)                 | 48 (60.8)                   |         |
| **Education**           |                |                     |                  |                    |                        |                      |                           |                             |         |
| Unknown                 | 876 (71.7)     | 512 (73.5)          | 119 (66.1)       | 121 (64.4)         | 46 (76.7)              | 4 (57.1)             | 8 (72.7)                  | 65 (82.3)                   |         |
| Primary                 | 111 (9.1)      | 69 (9.9)            | 15 (8.3)         | 17 (9)             | 3 (5)                  | 1 (14.3)             | 1 (9.1)                   | 6 (7.6)                     |         |
| Secondary               | 84 (6.9)       | 52 (7.5)            | 23 (12.8)        | 4 (2.1)            | 3 (5)                  | 1 (14.3)             | 1 (9.1)                   | 0                          |         |
| College                 | 42 (3.4)       | 20 (2.9)            | 10 (5.6)         | 8 (4.3)            | 3 (5)                  | 0                    | 0                         | 1 (1.3)                     | < 0.001 |
| University              | 8 (0.7)        | 5 (0.7)             | 0                | 3 (1.6)            | 0                     | 0                    | 0                         | 0                          |         |
| Diploma                 | 20 (1.6)       | 7 (1)               | 2 (1.1)          | 9 (4.8)            | 0                     | 0                    | 0                         | 2 (2.5)                     |         |
| No formal education     | 81 (6.6)       | 32 (4.6)            | 11 (6.1)         | 26 (13.8)          | 5 (8.3)                | 1 (14.3)             | 1 (9.1)                   | 5 (6.3)                     |         |
| **Employment status**   |                |                     |                  |                    |                        |                      |                           |                             |         |
| Unknown                 | 188 (15.4)     | 76 (10.9)           | 26 (14.4)        | 67 (35.6)          | 4 (6.7)                | 0                    | 1 (9.1)                   | 14 (17.7)                   | < 0.001 |
| Employed                | 342 (28)       | 200 (28.7)          | 63 (35)          | 44 (23.4)          | 19 (31.7)              | 4 (57.1)             | 4 (36.4)                  | 12 (15.2)                   |         |
| Unemployed              | 692 (56.6)     | 421 (60.4)          | 91 (50.6)        | 77 (41)            | 37 (61.7)              | 3 (42.9)             | 6 (54.5)                  | 53 (67.1)                   |         |

TB-DM Co-infection of TB and Diabetes Mellitus, TB-HIV Co-infection of TB and HIV, TB-Hepatitis Co-infection of TB and Hepatitis, TB-DM-HIV Co-infection of TB with Diabetes Mellitus and HIV, TB-DM-Hepatitis Co-infection of TB with Diabetes Mellitus and Hepatitis, TB-HIV-Hepatitis Co-infection of TB with HIV and Hepatitis

*Intravenous Drug Users*
| Variables          | Total 1222 | Treatment outcomes | Univariate analysis | Multivariate analysis | P-value | P-value |
|--------------------|------------|--------------------|---------------------|-----------------------|---------|---------|
|                    | n (%)      | Successful (n %)   | Unsuccessful (n %)  | COR (95% CI)          | AOR (95% CI) | AOR (95% CI) |
| Gender             |            |                    |                     |                       |         |         |
| Male               | 778 (63.7) | 514 (66.1)         | 264 (33.9)          | 0.82 (0.64 to 1.06)   | 0.131   |         |
| Female             | 444 (36.3) | 312 (70.3)         | 132 (29.7)          | 1.21 (0.94 to 1.56)   |         |         |
| Age (years)        |            |                    |                     |                       |         |         |
| ≤ 15               | 55 (4.5)   | 46 (83.6)          | 9 (16.4)            | 0.39 (0.19 to 0.81)   | 0.012   | 0.47 (0.23 to 1.02) | 0.050 |
| 16–25              | 177 (14.5) | 129 (72.9)         | 48 (27.1)           | 0.67 (0.48 to 0.99)   | 0.094   |         |
| 26–35              | 296 (24.2) | 203 (68.6)         | 93 (31.4)           | 0.94 (0.71 to 1.24)   | 0.677   |         |
| 36–45              | 224 (18.3) | 146 (65.2)         | 78 (34.8)           | 1.14 (0.84 to 1.55)   | 0.393   |         |
| 46–55              | 233 (19.1) | 167 (71.7)         | 66 (28.3)           | 0.78 (0.57 to 1.08)   | 0.140   |         |
| 56–65              | 170 (13.9) | 90 (52.9)          | 80 (47.1)           | 2.07 (1.49 to 2.87)   | ≤ 0.001 | 1.65 (1.15 to 2.37) | 0.006 |
| ≥ 66               | 67 (5.5)   | 43 (64.2)          | 24 (35.8)           | 1.17 (0.70 to 1.96)   | 0.539   |         |
| Ethnicity          |            |                    |                     |                       |         |         |
| Malay              | 389 (31.8) | 264 (67.9)         | 125 (32.1)          | 0.98 (0.75 to 1.27)   | 0.889   |         |
| Chinese            | 292 (23.9) | 192 (65.8)         | 100 (34.2)          | 1.11 (0.84 to 1.47)   | 0.441   |         |
| Indian             | 128 (10.5) | 80 (62.5)          | 48 (37.5)           | 1.28 (0.88 to 1.88)   | 0.194   |         |
| Immigrants Indonesian | 63 (5.2) | 42 (66.7)          | 21 (33.3)           | 1.04 (0.61 to 1.79)   | 0.872   |         |
| Immigrants Philippines | 45 (3.7) | 31 (68.9)          | 14 (31.1)           | 0.94 (0.49 to 1.78)   | 0.850   |         |
| Sarawakian         | 87 (7.1)   | 75 (86.2)          | 12 (13.8)           | 0.31 (0.16 to 0.58)   | ≤ 0.001 | 0.36 (0.19 to 0.69) | 0.003 |
| Sabahian           | 189 (15.5) | 122 (64.6)         | 67 (35.4)           | 1.17 (0.84 to 1.62)   | 0.331   |         |
| Others             | 29 (2.4)   | 20 (69)            | 9 (31)              | 0.93 (0.42 to 2.07)   | 0.873   |         |
| Residency          |            |                    |                     |                       |         |         |
| Urban              | 819 (67)   | 551 (67.3)         | 268 (32.7)          | 1.04 (0.80 to 1.34)   | 0.736   |         |
| Rural              | 403 (33)   | 275 (68.2)         | 128 (31.8)          | 0.95 (0.74 to 1.23)   |         |         |
| Patient category   |            |                    |                     |                       |         |         |
| Unknown            | 23 (1.9)   | 20 (87)            | 3 (13)              | 0.30 (0.09 to 1.04)   | 0.058   |         |
| New                | 1131 (92.6) | 773 (68.3)     | 358 (31.7)          | 0.64 (0.41 to 0.99)   | 0.049   | 3.27 (0.79 to 13.42) | 0.009 |
| Relapse            | 68 (5.6)   | 33 (48.5)          | 35 (51.5)           | 2.33 (1.42 to 3.80)   | 0.001   | 7.07 (1.58 to 31.61) | 0.010 |
| Co-morbidity       |            |                    |                     |                       |         |         |
| Only TB            | 697 (57)   | 494 (70.9)         | 203 (29.1)          | 0.70 (0.55 to 0.90)   | 0.005   | 1.01 (0.73 to 1.38) | 0.938 |
| TB-DM              | 180 (14.7) | 98 (54.4)          | 82 (45.6)           | 1.94 (1.40 to 2.67)   | ≤ 0.001 | 1.77 (1.16 to 2.69) | 0.008 |
| TB-HIV             | 188 (15.4) | 129 (68.5)         | 59 (31.4)           | 0.94 (0.67 to 1.32)   | 0.745   |         |
| TB-Hepatitis       | 60 (4.9)   | 43 (71.7)          | 17 (28.3)           | 0.81 (0.46 to 1.45)   | 0.490   |         |
| TB-DM-HIV          | 7 (0.6)    | 2 (28.6)           | 5 (71.4)            | 5.26 (1.01 to 27.27)  | 0.048   | 4.13 (0.76 to 22.40) | 0.100 |
| Variables                      | Total 1222 | Treatment outcomes | Univariate analysis | Multivariate analysis | P-value | P-value |
|-------------------------------|------------|--------------------|---------------------|-----------------------|---------|---------|
|                               | n (%)      | Successful n (%)   | Unsuccessful n (%)  | COR (95% CI)          |         |         |
| TB-DM-Hepatitis               | 11 (0.9)   | 3 (27.3)           | 8 (72.7)            | 5.69 (1.50 to 21.58)  | 0.011   | 3.42 (0.83 to 14.07) | 0.087 |
| TB-HIV-Hepatitis              | 79 (6.5)   | 56 (70.9)          | 23 (29.1)           | 0.90 (0.54 to 1.47)   | 0.679   |         |         |
| Smoking habit                 |            |                    |                     |                       |         |         |
| Ex-smoker                     | 166 (13.6) | 118 (71.1)         | 48 (28.9)           | 0.82 (0.57 to 1.18)   | 0.291   |         |         |
| No                            | 647 (52.9) | 465 (70.3)         | 192 (29.7)          | 0.76 (0.59 to 0.96)   | 0.026   | 1.03 (0.69 to 1.54) | 0.856 |
| Yes                           | 409 (33.5) | 253 (61.9)         | 156 (38.1)          | 1.48 (1.15 to 1.91)   | 0.002   | 1.34 (0.86 to 2.07) | 0.185 |
| Drinking Habit                |            |                    |                     |                       |         |         |
| Unknown                       | 12 (1)     | 5 (41.7)           | 7 (58.3)            | 2.94 (0.92 to 9.33)   | 0.067   |         |         |
| No                            | 1094 (89.5)| 741 (67.7)         | 353 (32.3)          | 0.84 (0.57 to 1.23)   | 0.379   |         |         |
| Yes                           | 116 (9.5)  | 80 (69)            | 36 (31)             | 1.05 (0.70 to 1.58)   | 0.784   |         |         |
| IVDUa                         |            |                    |                     |                       |         |         |
| Unknown                       | 23 (1.9)   | 11 (47.8)          | 12 (52.2)           | 2.30 (1.00 to 5.27)   | 0.048   | 1.79 (0.68 to 4.73) | 0.237 |
| No                            | 1113 (91)  | 761 (68.4)         | 352 (31.6)          | 0.65 (0.44 to 0.98)   | 0.041   | 0.91 (0.54 to 1.54) | 0.732 |
| Yes                           | 86 (7.1)   | 54 (62.8)          | 32 (37.2)           | 1.32 (0.84 to 2.07)   | 0.228   |         |         |
| Marital status                |            |                    |                     |                       |         |         |
| Unknown                       | 22 (1.8)   | 17 (77.3)          | 5 (22.7)            | 0.77 (0.30 to 1.99)   | 0.999   |         |         |
| Married                       | 539 (44.1) | 265 (72)           | 103 (28)            | 0.75 (0.57 to 0.98)   | 0.039   | 1.27 (0.39 to 4.09) | 0.681 |
| Unmarried                     | 832 (68.1) | 544 (65.4)         | 288 (34.6)          | 1.34 (1.03 to 1.74)   | 0.029   | 1.29 (0.41 to 4.01) | 0.652 |
| Education                     |            |                    |                     |                       |         |         |
| Unknown                       | 876 (71.7) | 627 (71.7)         | 249 (28.5)          | 0.53 (0.41 to 0.68)   | ≤ 0.001 | 0.73 (0.49 to 1.07) | 0.112 |
| Primary                       | 111 (9.1)  | 67 (59.8)          | 44 (40.2)           | 1.44 (0.97 to 2.15)   | 0.069   |         |         |
| Secondary                     | 84 (6.9)   | 41 (48.8)          | 43 (51.2)           | 2.32 (1.48 to 3.62)   | ≤ 0.001 | 1.88 (1.08 to 3.28) | 0.025 |
| College                       | 42 (3.4)   | 30 (71.4)          | 12 (28.6)           | 0.82 (0.41 to 1.63)   | 0.582   |         |         |
| University                    | 8 (0.7)    | 4 (50)             | 4 (50)              | 2.08 (0.52 to 8.39)   | 0.299   |         |         |
| Diploma                       | 20 (1.6)   | 18 (90)            | 2 (10)              | 0.22 (0.05 to 0.98)   | 0.047   | 0.20 (0.04 to 0.91) | 0.038 |
| No formal education           | 81 (6.6)   | 38 (46.9)          | 43 (53.1)           | 2.51 (1.59 to 3.96)   | ≤ 0.001 | 2.26 (1.25 to 4.09) | 0.001 |
| Employment status             |            |                    |                     |                       |         |         |
| Unknown                       | 188 (15.4) | 129 (68.6)         | 59 (31.4)           | 0.94 (0.67 to 1.31)   | 0.725   |         |         |
| Employed                      | 342 (28)   | 226 (66.1)         | 116 (33.9)          | 1.09 (0.83 to 1.42)   | 0.514   |         |         |
| Unemployed                    | 692 (56.6) | 470 (67.9)         | 222 (32.1)          | 0.96 (0.75 to 1.22)   | 0.742   |         |         |

**TB-DM** Co-infection of TB and Diabetes Mellitus, **TB-HIV** Co-infection of TB and HIV, **TB-Hepatitis** Co-infection of TB and Hepatitis, **TB-DM-HIV** Co-infection of TB with Diabetes Mellitus and HIV, **TB-DM-Hepatitis** Co-infection of TB with Diabetes Mellitus and Hepatitis, **TB-HIV-Hepatitis** Co-infection of TB with HIV and Hepatitis

*Intravenous Drug Users*
Risk factors of EPTB

With EPTB as the case group and PTB as the control group, we assessed the associations between the variables and having EPTB based on logistic regression model. Based on the result of the adjusted odd ratio (AOR), females appeared to have a higher risk for having EPTB (1.524 [CI: 1.311–1.746]; \( p < 0.001 \)) than males (Table 5). Malays (1.251 [1.056–1.482]; \( p = 0.010 \)), Indians (1.450 [1.142–1.842]; \( p = 0.002 \)), urban residents (1.272 [1.109–1.459]; \( p = 0.001 \)), patients with no formal education (1.361 [1.018–1.820]; \( p = 0.037 \)), those with married (1.199 [1.038–1.384]; \( p = 0.014 \)) and with unknown marital status (2.757 [1.611–4.717]; \( p < 0.001 \)) had significantly higher odds for having EPTB. Among

![Types of EPTB](image)

**Fig. 1** Proportion of default and deaths among different types of EPTB among patients

![EPTB and Co-morbidities](image)

**Fig. 2** Proportion of default and deaths among patients with EPTB and different co-morbidities
### Table 5 Logistic regression models to determine independent risk factors for having EPTB

| Variables       | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|-----------------------|
|                 | COR (95% CI)        | P-value               | AOR (95% CI)        | P-value               |
| Gender          |                     |                       |                      |                       |
| Male            | 0.75 (0.66 to 0.86) | < 0.001               | 0.65 (0.57 to 0.75) | < 0.001               |
| Female          | 1.31 (1.16 to 1.49) |                       | 1.52 (1.31 to 1.74) |                       |
| Age (years)     |                     |                       |                      |                       |
| ≤ 15            | 1.115 (0.78 to 1.58)| 0.541                 |                       |                       |
| 16–25           | 1.11 (0.95 to 1.31)| 0.170                 |                       |                       |
| 26–35           | 0.90 (0.77 to 1.05)| 0.198                 |                       |                       |
| 36–45           | 0.96 (0.82 to 1.12)| 0.604                 |                       |                       |
| 46–55           | 1.02 (0.87 to 1.20)| 0.741                 |                       |                       |
| 56–65           | 0.94 (0.79 to 1.13)| 0.566                 |                       |                       |
| ≥ 66            | 1.06 (0.87 to 1.28)| 0.546                 |                       |                       |
| Ethnicity       |                     |                       |                      |                       |
| Malay           | 1.33 (1.16 to 1.51)| < 0.001               | 1.25 (1.05 to 1.48) | 0.010                 |
| Chinese         | 1.02 (0.89 to 1.17)| 0.740                 |                       |                       |
| Indian          | 1.58 (1.28 to 1.94)| < 0.001               | 1.45 (1.14 to 1.84) | 0.002                 |
| Immigrants Indonesian | 0.72 (0.55 to 0.94) | 0.018             | 0.76 (0.56 to 1.02) | 0.069                 |
| Immigrants Philippines | 0.65 (0.47 to 0.89) | 0.008             | 0.77 (0.55 to 1.09) | 0.144                 |
| Sarawakian      | 0.61 (0.48 to 0.77)| < 0.001               | 0.76 (0.58 to 0.99) | 0.046                 |
| Sabahian        | 0.80 (0.68 to 0.94)| 0.009                 | 0.91 (0.74 to 1.12) | 0.388                 |
| Others          | 1.63 (1.08 to 2.46)| 0.019                 | 1.51 (0.97 to 2.35) | 0.064                 |
| Residence       |                     |                       |                      |                       |
| Urban           | 1.17 (1.03 to 1.33)| 0.015                 | 1.27 (1.10 to 1.45) | 0.001                 |
| Rural           | 0.85 (0.75 to 0.97)|                       | 0.78 (0.68 to 0.90) |                       |
| Patient category|                     |                       |                      |                       |
| Unknown         | 0.30 (0.20 to 0.46)| < 0.001               | 0.21 (0.12 to 0.35) | < 0.001               |
| New             | 1.92 (1.53 to 2.40)| < 0.001               | 1.57 (1.20 to 2.05) | 0.001                 |
| Relapse         | 0.73 (0.56 to 0.94)| 0.017                 | 4.65 (2.80 to 7.73) | < 0.001               |
| Co-morbidity    |                     |                       |                      |                       |
| Only TB         | 0.73 (0.65 to 0.83)| < 0.001               | 0.89 (0.68 to 1.16) | 0.406                 |
| TB-DM           | 0.66 (0.56 to 0.78)| < 0.001               | 0.67 (0.50 to 0.91) | 0.011                 |
| TB-HIV          | 2.35 (1.97 to 2.80)| < 0.001               | 3.21 (2.34 to 4.40) | < 0.001               |
| TB-Hep          | 0.99 (0.75 to 1.31)| 0.990                 |                       |                       |
| TB-DM-HIV       | 3.33 (1.34 to 8.27)| 0.009                 | 4.36 (1.65 to 11.47) | 0.003                 |
| TB-DM-Hep       | 1.30 (0.68 to 2.50)| 0.419                 |                       |                       |
| TB-HIV-Hep      | 3.01 (2.30 to 3.95)| < 0.001               | 4.08 (2.78 to 5.98) | < 0.001               |
| Smoking habit   |                     |                       |                      |                       |
| Ex-smoker       | 1.54 (1.28 to 1.84)| < 0.001               | 1.53 (1.26 to 1.87) | < 0.001               |
| No              | 0.96 (0.85 to 1.09)| 0.599                 |                       |                       |
| Yes             | 0.85 (0.75 to 0.97)| 0.017                 | 0.78 (0.67 to 0.91) | 0.001                 |
| Drinking Habit  |                     |                       |                      |                       |
| Unknown         | 0.73 (0.40 to 1.33)| 0.314                 |                       |                       |
| No              | 0.95 (0.78 to 1.15)| 0.623                 |                       |                       |
| Yes             | 1.10 (0.89 to 1.35)| 0.356                 |                       |                       |
the co-morbid conditions, patients with EPTB-HIV (3.215 [2.347–4.405]; \( p < 0.001 \)), EPTB-DM-HIV (4.361 [1.657–11.474]; \( p = 0.003 \)) and EPTB-HIV-HEP (4.083 [2.785–5.987]; \( p < 0.001 \)) found to have increased risk of EPTB.

**Discussion**

To the best of our knowledge, this is the first study in Malaysia to describe the epidemiological, clinical characteristics and treatment outcomes among patients with EPTB and its co-morbidities. Patients with EPTB constituted 13.1% of all notifications, with some parts of the country showing higher prevalence than others. There were important variations in the proportion of EPTB patients in the different states of the country; and this could be related to the implication of medical doctors in the diagnosis of EPTB. The proportion of patients diagnosed with EPTB in the present study was lower than that reported from other parts of the world [14–16]. Predominant sites of EPTB were lymph node followed by pleural effusion. The higher prevalence of lymph node and pleural effusion was observed at higher proportion, followed by miliary and meningitis TB. Association between HIV and sites of EPTB has been determined more than a decade ago [19] however; the data is limited or almost absent for DM and HEP. Consistent with previous studies [20, 21] we found advanced HIV strongly correlated with the occurrence of EPTB. These findings are in contrast to [22] but are in agreement with [23]. Furthermore, severe immunosuppression like low CD4+ lymphocyte cell counts and advanced HIV infection, increases the risk of having EPTB as opposed to PTB alone [24, 25]. Moreover, on comparing CD4+ lymphocyte cell counts with smoking, CD4+ lymphocyte cell counts < 100 was significantly recorded for smokers (\( p < 0.05 \)). This is the first study in identifying smoking association with CD4+ lymphocyte cell counts < 100 among EPTB-HIV. The previous study by Feldman and companions suggested lower CD4+ lymphocyte cell counts in HIV patients with smoking habit [26].
A significant association was observed between co-morbidities and age, gender, ethnicity, patient category, education and marital and employment status. Proportions of co-morbidities were greater in males, unmarried and unemployed patients comparative to their counterparts. The results show that the risk of developing co-morbidities remained higher at the age of 26 years and older. Of total 1222 patients in the present study, 525 were recorded for different co-morbidities with EPTB-HIV and EPTB-DM being the most common. Moreover, 11.4% of patients had EPTB-HEP and 15% cases were seen with EPTB-HIV-HEP co-infection. During last decade, one case-control study in US demonstrated association of hepatitis C infection with TB disease [27]. Later on, it was confirmed by further studies showing that hepatitis C infection and TB share the same high risks population [28–30]. Very recently study conducted in Taiwan has reported that hepatitis C infection intensifies the risk of developing TB [31]. The mechanism behind this finding remains unclear. Future studies in this perspective are needed.

Treatment success rate in our study was 67.6% (826/1222). On multivariate analysis, age group 56–65 years, relapse cases, EPTB-DM, patients with no formal and secondary level of education were recorded as statistically positive significant risk factors for unsuccessful treatment outcomes. Treatment success rate among patients on HAART was 79.9% which is far better than that mentioned in a study conducted in Kelantan, north-east Malaysia [32]. On the other side, EPTB-DM patients had higher odds for unsuccessful treatment outcomes. Poor outcomes in patients with DM-TB could be due to immune deficiency triggered by diabetes [33]. Increased deaths were observed in meningoencephalitis, miliary TB, EPTB-DM-HEP and EPTB-DM-HIV. Meningeal TB is particularly challenging to diagnose, since cerebrospinal fluid is commonly smear and culture negative. Meningitis and a CD4+ lymphocyte cell counts < 200 have been reported as risk factor for deaths among EPTB patients by [25]. Meningitis, disseminated disease, patients with EPTB-HIV and EPTB-DM also have been reported as risk factors of poor TB outcomes, including increased mortality in other studies [22, 33].

The finding of females, Malays, Indians, urban residents, patients with EPTB-HIV, EPTB-DM-HIV and EPTB-HIV-HEP as independent predictors for having EPTB at the study sites is consistent with studies from other countries [3, 34–37]. The differences in the proportion of EPTB by ethnicity are notable. Malay and Indian patients were generally far more likely to present with EPTB than others. Differences in the likelihood of EPTB for racial differences have been observed in various studies [16, 38]. The mechanism of a racial difference in infectiousness by MTB is the result of a complex interaction between the environmental, immunologic and genetic factors [38]. However, more studies among larger number of patients are needed to further ratify these results. Weak immune system among DM patients could led them to get infections, including TB [39]. Patients with DM are identified as risk factors for PTB in numerous studies [39, 40] but data is scarce among EPTB patients. One of the remarkable finding of our study therefore includes patients with DM at greater risk of EPTB that is in line with the study conducted at Georgia [33].

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. In addition, effect of TB treatment on CD4+ lymphocyte cell counts was not studied.

Conclusions

With continuous growing trend, EPTB is a grave concern to public health in Malaysia for mainly affecting nationals. High prevalence of EPTB-DM, EPTB-HIV and EPTB-HEP as well as their further compound co-morbidities among EPTB in the present study signifies the fact that these patients are at high risk of developing EPTB. Active screening measures for patients with co-morbidities are therefore recommended in patients with EPTB which could improve the diagnosis and early management of co-morbidities complications. This strategy together with educating patients can further increase the treatment success rate.

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

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Authors' contributions

Study design: AHK, SAS and MAH. Data collection: AHK and ARM. Data analysis: ML and BAT. Data interpretation: ML, LCM and ZB. Drafting of the manuscript: ML and AHK. Revision of the manuscript: AHK, BAT and ARM. All the authors have read and approved the final version of the manuscript. AHK and SAS take responsibility for the integrity of the data analysis.

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Availability of data and materials

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

The authors declare that they have no competing interests.

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