ORIGINAL ARTICLE

# Prevalence and Risk Factors of Post-Tuberculosis Lung Disease in Kaeng Khro Hospital, Chaiyaphum

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**Background:** Thailand has a high tuberculosis (TB) burden. As a result of effective TB treatment and prevention programs, the number of TB survivors has steadily increased in recent decades. Post-tuberculosis lung disease (PTLD) has emerged as a prominent problem among TB survivors, leading to substantial disability-adjusted life year (DALY) losses.

**Objective:** To determine the prevalence and risk factors of PTLD at Kaeng Khro Hospital, Thailand.

**Materials and Methods:** The present study was a retrospective observational cohort study that included 450 patients with TB, older than 15 years of age, who underwent treatment between October 1, 2016, and September 30, 2024, with chest radiography obtained before and three months after treatment completion.

**Results:** The prevalence rate of PTLD was 83.5%, categorized into lung fibrosis 70.7%, persistent lung cavities 28.7%, bronchiectasis 27.7%, fibrothorax 6.9%, destroyed lung syndrome 6.1%, post-TB chronic obstructive pulmonary disease 3.7%, and post-TB tracheobronchial stenosis and aspergilloma 0.3%. By multivariate analysis, the statistically significant ($p<0.05$) risk factors were increasing age (adjusted odds ratio [AOR] 1.03, 95% confidence interval [CI] 1.00 to 1.06, p=0.021), smoking (AOR 3.81, 95% CI 1.17 to 12.36, p=0.026), lung cavities (AOR 3.00, 95% CI 1.45 to 6.19, p=0.000), and bilateral lung lesions before treatment (AOR 2.75, 95% CI 1.30 to 5.83, p=0.008). HIV infection significantly reduced the risk of PTLD (AOR 0.07, 95% CI 0.02 to 0.31, $p<0.001$), suggesting a potential protective effect.

**Conclusion:** The prevalence of PTLD was 83.5%. The statistically risk factors before treatment were increased age, smoking, lung cavities, and bilateral lung lesions. HIV infection with low CD4 may attenuate the host inflammatory response, thereby decreasing the risk of PTLD. This highlights the importance of monitoring smoking cessation throughout the course of treatment. Close monitoring for PTLD is warranted in elderly patients and in those with lung cavities among TB survivors.

**Keywords:** Post-tuberculosis lung disease (PTLD); Prevalence; Risk factors

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In 2015, the World Health Organization (WHO) implemented an end-tuberculosis (TB) strategy, with the goals to reduce TB incidence by 80%, deaths by 90%, and eliminate catastrophic costs for TB-affected households by 2030[1]. In 2017, the Thai Bureau of TB created the first Thai Operational Plan to End Tuberculosis, to expedite case-finding, reduce mortality, enhance human resource capacity, create a system to support sustainable strategic management, and promote research and innovation.

Thailand is one of 30 countries with a high TB burden. According to the WHO Global Tuberculosis Report 2024, Thailand has a higher incidence rate of TB than the rest of the world, with 157 incident cases per 100,000 people[2]. This indicates that TB remains a major health concern in Thailand. In Kaeng Khro Hospital, the incidence rate in 2023 was 109 incident cases per 100,000 people.

Strong TB policies and improvement of the global healthcare system have reduced the number of TB deaths by 75% over the last decade[3]. However, there are no policies or guidelines for follow-ups of TB survivors. Since 2005, the number of post-TB complications has increased[4]. This indicates that even after TB treatment is completed, TB survivors require continuous care.

Post-tuberculosis lung disease (PTLD) is an important complication of TB. In 2019, the first international symposium on PTLD was held in

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Stellenbosch, South Africa. PTLD was defined as evidence of chronic respiratory abnormalities with or without symptoms attributable at least in part to previous pulmonary TB[5]. However, the prevalence of PTLD remained unknown.

PTLD can be categorized according to the affected areas of the respiratory tract. In 2024, the second International PTLD Symposium summarized the pathophysiology of PTLD in six processes, enzymes, matrix metalloproteinase, abnormal neutrophil function, fibroblast and profibrotic pathways, programmed cell death dysfunction, granuloma inflammation, and host or TB status[6]. The risk factors for PTLD are being older than 40 years[7-12], smoking[13-17], delayed treatment of TB[18], relapse of TB[19-21], malnutrition[7], acute respiratory failure[22,23], HIV infection[24], sputum acid-fast bacillus (AFB) positivity before treatment[25-27], and multidrug-resistant TB[28,29]. It is estimated that 58 million disability-adjusted life years (DALYs) were lost due to PTLD in 2019[30].

Therefore, understanding the prevalence and risk factors for PTLD will help prevent this condition in the future, which is crucial to achieve the End-TB Strategy by 2030. The present study aimed to determine the prevalence and risk factors of PTLD in patients at Kaeng Khro Hospital, Thailand.

## Materials and Methods

### Study design and participants

The present study was an observational, retrospective cohort study. Data was collected from paper and electronic medical records at Kaeng Khro Hospital and the National Tuberculosis Information Program. The present study was approved by the Chaiyaphum Provincial Health Office Research Ethics Committee (approval no. 57/2024). Patient confidentiality was strictly maintained throughout the research process. All data were de-identified and anonymized prior to analysis. Unique codes were assigned to each participant, and no personally identifiable information was collected or stored in the final dataset.

### Population

The study population comprised of 450 TB patients who underwent treatment between October 1, 2016, and September 30, 2024, at Kaeng Khro Hospital, determined through searching medical records for ICD-10 codes A15 and A16. All patients were older than 15 years and had chest radiographs performed at baseline and three months after treatment completion. No sample size calculation was performed, as all consecutive TB cases diagnosed during the study period and meeting the inclusion criteria were included in the analysis. The inclusion and exclusion criteria for the study are detailed in Figure 1.

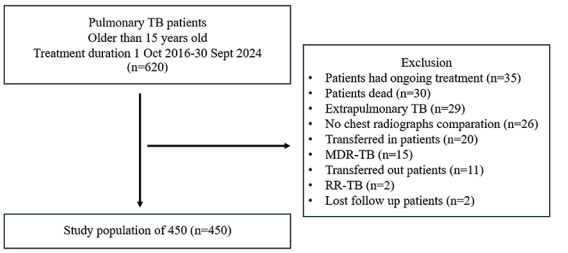


**Figure 1.** Study population.

TB, tuberculosis; MDR-TB, multidrug-resistant TB; RR-TB, rifampicin-resistant TB

### Data collection and measurements

The following data were collected from the medical records of the patients who met the inclusion criteria, which are basic patient information, TB symptom information, and laboratory results, including sputum AFB, complete blood count, liver function test, and kidney function test for creatinine (Cr). Bronchoscopy results were used to diagnose post-tuberculosis tracheobronchial stenosis (PTTS). Pulmonary function test results included those used to diagnose post-tuberculosis chronic obstructive pulmonary disease (PT-COPD). Chest radiography results before treatment were classified as either pulmonary cavity or non-cavity lesions, including reticular infiltration, reticulonodular infiltration, patchy consolidation, lobar consolidation, miliary infiltration, and pleural thickening. The location of lesions in one or both lungs were recorded.

Three months following treatment, the patients were classified as either normal or having PTLD based on the definition of the International Post-Tuberculosis Symposium in 2019. Post-treatment chest radiography was comprehensively evaluated, including both previously affected and unaffected lung regions. The types of PTLD included the following:

- PTTS: a condition in which large airways become stenotic after TB infection, with diagnosis confirmed by bronchoscopy.
- PT-COPD: chronic obstructive pulmonary disease that develops following TB. Diagnosed through pulmonary function testing with FEV1/FVC of less than 0.7.

**Table 1.** Basic data of included patients

| Data | Value | PTLD (376 cases) | Non-PTLD (74 cases) | p-value |
|---|---|---|---|---|
| Male; n (%) | 327 (72.7) | 285 (75.8) | 42 (56.8) | |
| Female; n (%) | 123 (27.3) | 91 (24.2) | 32 (43.2) | 0.001* |
| Average age (years); mean±SD | 55.2±14.9 | 56.05±14.56 | 50.88±16.18 | 0.006* |
| Average BMI (kg/m$^2$); mean±SD | 19.0±3.8 | 18.8±3.8 | 20.3±4.1 | 0.002* |
| Malnutrition (BMI <18.5 kg/m$^2$); n (%) | 227 (50.4) | 202 (53.7) | 25 (33.8) | 0.002* |
| Alcohol consumption; n (%) | 100 (22.2) | 89 (23.7) | 11 (14.9) | 0.096 |
| Smoking; n (%) | 154 (34.2) | 144 (38.3) | 10 (13.5) | <0.001* |
| Comorbidities; n (%) | | | | |
| Diabetes | 145 (32.2) | 113 (30.1) | 32 (43.2) | 0.026* |
| Chronic kidney disease | 46 (10.2) | 39 (10.4) | 7 (9.5) | 0.813 |
| COPD | 21 (4.7) | 20 (5.3) | 1 (1.4) | 0.139 |
| HIV infection | 16 (3.6) | 7 (1.9) | 9 (12.2) | <0.001* |
| Liver cirrhosis | 3 (0.7) | 3 (0.7) | 0 (0.0) | 0.441 |

PTLD=post-tuberculosis lung disease; SD=standard deviation; BMI=body mass index; COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus

* Statistical significance

- Bronchiectasis: bronchial dilation following TB. Chest radiography reveals tram-track signs and ring opacities.
- Cavitation: pulmonary cavities remaining after TB.
- Destroyed lung syndrome (DLS): extensive lung parenchymal destruction after TB, characterized by reduced lung volume, widespread fibrotic changes, thickened pleura, extensive bronchiectasis, an elevated diaphragm, and a mediastinal shift.
- Fibrotic changes: lung fibrosis occurring after TB, showing reticular infiltration in previously infected areas.
- Aspergilloma: fungal infection by *Aspergillus* within a pulmonary cavity post-TB, with chest radiography showing the "air-crescent sign" for air surrounding the fungal mass, resembling a crescent moon or Monod sign to indicate mobility of the fungal mass with changes in patient posture.
- Fibrothorax: pleural fibrosis post-TB, including conditions such as trapped or non-expandable lungs. Chest radiography reveals pleural thickening.

All radiographic assessments were performed by the author, a general internist with direct clinical involvement in the care of all study participants.

### Statistical analysis

Data was analyzed using Stata Statistical Software, version 18 (StataCorp LLC, College Station, TX, USA). All tests were two-tailed, and the statistical significance level was set at 0.05 ($\alpha$=0.05). Comparisons between patients with and without PTLD were made using the independent t-test for normally distributed data, Mann-Whitney U test for non-normally distributed quantitative data, and chi-square test for categorical data. Factors affecting PTLD were analyzed using binary logistic regression. A univariate analysis was performed using the crude odds ratio (OR) (95% confidence interval, CI), while a multivariate analysis was performed using the adjusted OR (AOR) (95% CI). The normality of data distribution was tested using the Kolmogorov-Smirnov test. If the statistical significance of the test was greater than the significance level set at 0.05, for a p-value that is smaller than 0.05, the data used for the test followed a normal distribution.

## Results

There were 450 TB patients aged over 15 years between October 1, 2016, and September 30, 2024. Most of the patients in the present study were male, with an average age of 55 years. The average body mass index (BMI) was close to that of underweight individuals, with 50% of patients experiencing malnutrition. One hundred fifty-four patients were smokers and male (Table 1).

Most patients in the present study were new TB cases, with 92.9% having pulmonary TB, and 7.1% having both pulmonary and pleural TB. Half of the patients sought medical care late, whereas 25.8% received a delayed diagnosis. The most common chest radiographic findings were cavitary lesions at 74.0%, followed by reticulonodular infiltration at 57.8%, and patchy consolidation at 46.9%. Bilateral lung involvement was the most common at 61.6%.

**Table 2.** Clinical data of the included patients

| Data | Value | PTLD (376 cases) | Non-PTLD (74 cases) | p-value |
|---|---|---|---|---|
| Symptoms; n (%) | | | | |
| Chronic cough >2 weeks | 353 (78.4) | 295 (78.5) | 58 (78.4) | 0.988 |
| Fever | 191 (42.4) | 155 (41.2) | 36 (48.7) | 0.237 |
| Fatigue | 164 (36.4) | 141 (37.5) | 23 (31.1) | 0.294 |
| Significant weight loss | 153 (34.0) | 128 (34.0) | 25 (33.8) | 0.966 |
| Hemoptysis (coughing up blood) | 57 (12.7) | 50 (13.3) | 7 (9.5) | 0.364 |
| Loss of appetite | 36 (8.0) | 31 (8.2) | 5 (6.8) | 0.666 |
| Acute respiratory failure | 7 (1.6) | 6 (1.6) | 1 (1.4) | 0.877 |
| Duration of symptoms before hospital visit (days); median (IQR) | 21 (7, 30) | 21 (7, 30) | 30 (7, 30) | 0.803 |
| Number of patients with delayed healthcare seeking; n (%) | 238 (52.9) | 197 (52.4) | 41 (55.4) | 0.635 |
| Hospital's time to diagnose tuberculosis (days); median (IQR) | 4 (2, 15) | 4 (2, 16) | 4.5 (2, 14) | 0.986 |
| Number of patients with delayed diagnosis by the hospital; n (%) | 116 (25.8) | 98 (26.1) | 18 (24.3) | 0.755 |
| Registration status; n (%) | | | | 0.061 |
| New tuberculosis patient | 413 (91.8) | 340 (90.4) | 73 (98.7) | |
| Relapsed tuberculosis patient | 30 (6.7) | 29 (7.7) | 1 (1.4) | |
| TALF | 7 (1.6) | 7 (1.9) | 0 (0.0) | |
| Type of tuberculosis; n (%) | | | | 0.715 |
| Pulmonary tuberculosis | 418 (92.9) | 350 (93.1) | 68 (91.9) | |
| Disseminated tuberculosis | 32 (7.1) | 26 (6.9) | 6 (8.1) | |
| Sputum AFB positive result; n (%) | 303 (67.3) | 260 (69.2) | 43 (58.1) | 0.064 |
| Cells | 10 (2.2) | 9 (2.4) | 1 (1.4) | |
| 1+ | 106 (23.6) | 87 (23.1) | 19 (25.7) | |
| 2+ | 82 (18.2) | 75 (19.9) | 7 (9.5) | |
| 3+ | 105(23.3) | 89 (23.7) | 16 (21.6) | |
| Sputum AFB-negative result; n (%) | 147 (32.7) | 116 (30.9) | 31 (41.9) | 0.157 |
| Chest radiography at the time of diagnosis; n (%) | | | | |
| Cavity | 333 (74.0) | 295 (78.5) | 38 (51.4) | <0.001* |
| Reticulonodular infiltration | 260 (57.8) | 223 (59.3) | 37 (50.0) | 0.138 |
| Patchy consolidation | 211 (46.9) | 187 (49.7) | 24 (32.4) | 0.006* |
| Lobar consolidation | 65 (14.4) | 54 (14.4) | 11 (14.9) | 0.910 |
| Pleura thickening | 30 (6.7) | 30 (7.9) | 0 (0.0) | 0.012* |
| Pleural effusion | 23 (5.1) | 19 (5.1) | 4 (5.4) | 0.900 |
| Miliary pattern | 12 (2.7) | 8 (2.1) | 4 (5.4) | 0.110 |
| Location of lung lesions at diagnosis; n (%) | | | | |
| Both lungs | 277 (61.6) | 247 (65.7) | 30 (40.5) | <0.001* |
| Right lung | 111 (24.7) | 86 (22.9) | 25 (33.8) | 0.047* |
| Left lung | 63 (14.0) | 44 (11.7) | 19 (25.7) | 0.002* |
| Standard treatment regimen (6 months) (2 HRZE/4 HR); n (%) | 301 (66.9) | 249 (66.2) | 52 (70.3) | 0.499 |
| Treatment regimen >6 months; n (%) | 149 (33.1) | 127 (33.8) | 22 (29.7) | |
| PTLD types; n (%) | 266 (70.7) | | | |
| Fibrosis | 108 (28.7) | | | |
| Cavity | 104 (27.7) | | | |
| Bronchiectasis | 26 (6.9) | | | |
| Fibrothorax | 23 (6.1) | | | |
| Destroyed lung syndrome | 14 (3.7) | | | |
| PT-COPD | 1 (0.3) | | | |
| PTTS | 266 (70.7) | | | |
| Aspergilloma | 1 (0.3) | | | |
| Location of PTLD; n (%) | | | | |
| Both lungs | 180 (47.9) | | | |
| Right lung | 128 (34.0) | | | |
| Left lung | 68 (18.1) | | | |

PTLD=post-tuberculosis lung disease; PT-COPD=post-tuberculosis chronic obstructive pulmonary disease; PTTS=post-tuberculosis tracheobronchial stenosis; AFB=acid-fast bacillus; IQR=interquartile range; TALF=tuberculosis patient returning after loss follow-up

* Statistical significance

**Table 3.** Baseline laboratory characteristics of tuberculosis patients at the time of diagnosis

| Laboratory test | Value | PTLD (376 cases) | Non-PTLD (74 cases) | p-value |
|---|---|---|---|---|
| WBCs; median (IQR) | 10,110 (7,920, 13,050) | 10,275 (7,935, 13,150) | 9,450 (7,530, 11,490) | 0.079 |
| Neutrophil (%); median (IQR) | 71 (63, 78) | 71.5 (64, 78) | 66 (59, 75) | 0.017* |
| Lymphocyte (%); median (IQR) | 16 (11, 22) | 16 (11, 22) | 19 (12, 23) | 0.112 |
| Hematocrit (%); mean±SD | 33.95±6.03 | 34.00±6.03 | 33.66±6.05 | 0.682 |
| Anemia; n (%) | 253 (56.2) | 217 (57.7) | 36 (48.7) | 0.151 |
| Platelets ($10^9$/L); median (IQR) | 408 (301, 518) | 413 (313, 520) | 361 (280, 472) | 0.020* |
| Thrombocytosis; n (%) | 146 (32.4) | 129 (34.3) | 17 (22.9) | 0.057 |
| Thrombocytopenia; n (%) | 9 (2.0) | 7 (1.9) | 2 (2.7) | 0.637 |
| Protein (g/dL); mean±SD | 7.77±0.97 | 7.78±0.97 | 7.79±0.98 | 0.913 |
| Albumin (g/dL); median (IQR) | 3.8 (3.4, 4.2) | 3.8 (3.4, 4.2) | 3.9 (3.5, 4.3) | 0.247 |
| Hypoalbuminemia; n (%) | 131 (29.1) | 114 (30.3) | 17 (22.9) | 0.204 |
| Globulin (g/dL); mean±SD | 3.99±0.91 | 4.00±0.89 | 3.96±1.04 | 0.742 |
| Hyperglobulinemia; n (%) | 282 (62.7) | 282 (62.7) | 38 (51.4) | 0.028* |
| Total bilirubin (mg/dL); median (IQR) | 0.5 (0.4, 0.7) | 0.5 (0.4, 0.7) | 0.5 (0.4, 0.7) | 0.773 |
| Direct Bilirubin (mg/dL); median (IQR) | 0.2 (0.1, 0.3) | 0.2 (0.1, 0.3) | 0.2 (0.1, 0.3) | 0.602 |
| Jaundice; n (%) | 8 (1.8) | 4 (1.1) | 1 (5.4) | 0.010* |
| Hepatitis; n (%) | 168 (37.3) | 141 (37.5) | 27 (36.5) | 0.869 |
| ALP (U/L); median (IQR) | 103 (79, 144) | 104 (79, 145) | 91 (70, 138) | 0.056 |
| High ALP; n (%) | 153 (34.0) | 134 (35.6) | 19 (25.7) | 0.098 |
| Cr (mg/dL); median (IQR) | 0.8 (0.6, 0.9) | 0.8 (0.6, 0.9) | 0.8 (0.6, 0.9) | 0.873 |
| GFR (mL/minute/1.73 $m^2$); median (IQR) | 96 (78, 110) | 96 (78, 110) | 98 (79, 109) | 0.832 |
| Chronic kidney disease; n (%) | 46 (10.2) | 39 (10.4) | 7 (9.5) | 0.813 |

WBC=white blood cell; IQR=interquartile range; SD=standard deviation; PTLD=post-tuberculosis lung disease; ALP=alkaline phosphatase; Cr=creatinine; GFR=glomerular filtration rate

* Statistical significance

The percentage of patients who developed PTLD was 83.5%. Most patients had fibrosis for 70.7%, whereas 28.7% had residual cavitary lesions often associated with bronchiectasis. In the patient's group with both pulmonary and pleural TB, 6.9% of developed permanent pleural thickening. Twenty-three patients, or 6.1%, had DLS, with an average age of 55±14 years. Of these, 91.3% were male and 86.9% had lesions in both lungs before treatment. Among patients with PTLD, most had lesions in both lungs (47.9%), which correlated with the chest radiography findings before treatment (Table 2).

The laboratory test results are shown in Table 3. PTLD patients have higher neutrophil counts with a median of 71.5% versus 66% (p=0.017) and thrombocytosis at 34.3% versus 22.9%. Hyperglobulinemia was significantly higher in PTLD patients at 62.7% versus 51.4% (p=0.028). Laboratory abnormalities were defined separately Anemia was defined as hemoglobin of less than 13.0 g/dL in males and less than 12.0 g/dL in non-pregnant females, in accordance with WHO criteria. Thrombocytopenia was defined as a platelet count of less than 150,000/μL, and thrombocytosis as more than 450,000/μL. Hypoalbuminemia was defined as serum albumin level of less than 3.5 g/dL. Hyperglobulinemia was defined as serum globulin level of more than 2.9 g/dL. Jaundice was defined as total bilirubin level of more than 2.0 mg/dL. Hepatitis was defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels of more than 40 U/L. High alkaline phosphatase (ALP) was defined as ALP level of more than 120 U/L. Finally, chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) of less than 60 mL/minute/1.73 $m^2$.

As shown in Table 4, the results of the multivariate analysis, factors that significantly affected the development of PTLD (p<0.05) after adjusting for other variables included age, AOR 1.03 (95% CI 1.00 to 1.06), HIV infection, AOR 0.07 (95% CI 0.02 to 0.31), smoking behavior, AOR 3.81 (95% CI 1.17 to 12.36), presence of lung cavities, AOR 3.00 (95% CI 1.45 to 6.19), and lesions in both lungs before treatment, AOR 2.75 (95% CI 1.30 to 5.8) (Figure 2). Although jaundice showed statistical significance (AOR 0.04, 95% CI 0.01 to 0.37, p=0.004), it was

**Table 4.** Univariate and multivariate analysis of factors influencing PTLD

| Data | COR (95% CI) | p-value | AOR (95% CI) | p-value |
|---|---|---|---|---|
| Male sex | 2.39 (1.42 to 4.00) | 0.001* | 1.98 (0.82 to 4.77) | 0.126 |
| Age (years) | 1.02 (1.01 to 1.04) | 0.007* | 1.03 (1.00 to 1.06) | 0.021* |
| Weight (kg) | 0.96 (0.94 to 0.98) | 0.001* | 0.96 (0.90 to 1.02) | 0.179 |
| Malnutrition | 2.28 (1.35 to 3.84) | 0.002* | 0.49 (0.16 to 1.47) | 0.205 |
| Diabetes | 0.56 (0.34 to 0.94) | 0.028* | 0.71 (0.32 to 1.56) | 0.391 |
| HIV infection | 0.14 (0.05 to 0.38) | <0.001* | 0.07 (0.02 to 0.31) | <0.001* |
| Alcohol consumption | 1.78 (0.90 to 3.52) | 0.099 | 0.64 (0.21 to 1.96) | 0.430 |
| Smoking | 3.97 (1.98 to 7.98) | <0.001* | 3.81 (1.17 to 12.36) | 0.026* |
| Recurrent TB | 6.10 (0.82 to 45.50) | 0.078 | | |
| Chest X-ray findings | | | | |
| Cavity | 3.45 (2.06 to 5.79) | <0.001* | 3.00 (1.45 to 6.19) | 0.003* |
| Patchy consolidation | 2.06 (1.22 to 3.49) | 0.007* | 1.04 (0.49 to 2.20) | 0.920 |
| Lesion location at diagnosis | | | | |
| Right lung | 0.58 (0.34 to 0.99) | 0.047* | | |
| Left lung | 0.38 (0.21 to 0.71) | 0.002* | | |
| Both lungs | 2.81 (1.69 to 4.68) | <0.001* | 2.75 (1.30 to 5.83) | 0.008* |
| AFB Positive Sputum Smear | 1.62 (0.97 to 2.69) | 0.066 | 1.02 (0.74 to 1.40) | 0.917 |
| Neutrophil Proportion | 1.03 (1.00 to 1.05) | 0.039* | 1.03 (0.99 to 1.07) | 0.175 |
| Thrombocytosis | 1.75 (0.98 to 3.13) | 0.059 | 0.86 (0.26 to 2.82) | 0.801 |
| Platelet Count | 0.97 (0.94 to 1.00) | 0.076 | 0.99 (0.99 to 1.00) | 0.873 |
| Hyperglobulinemia | 1.75 (1.06 to 2.89) | 0.029* | 1.93 (0.90 to 4.14) | 0.091 |
| Jaundice | 0.19 (0.05 to 0.77) | 0.020* | 0.04 (0.01 to 0.37) | 0.004* |
| Elevated ALP | 1.60 (0.91 to 2.81) | 0.100 | 1.67 (0.56 to 4.93) | 0.357 |
| ALP Level | 1.00 (0.99 to 1.01) | 0.181 | 1.00 (0.99 to 1.01) | 0.955 |

COR=crude odds ratio; AOR=adjusted odds ratio; CI=confidence interval; HIV=human immunodeficiency virus; TB=tuberculosis; AFB=acid-fast bacillus; ALP=alkaline phosphatase

* Statistical significance

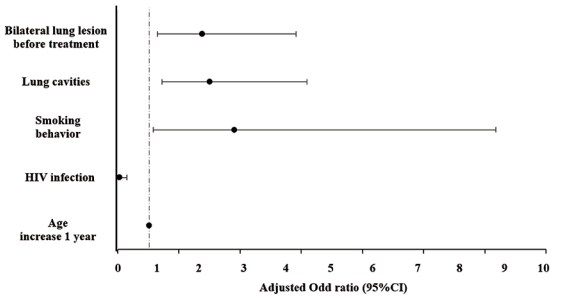


**Figure 2.** Adjusted odds ratio (AOR) of factors influencing the development of PTLD.

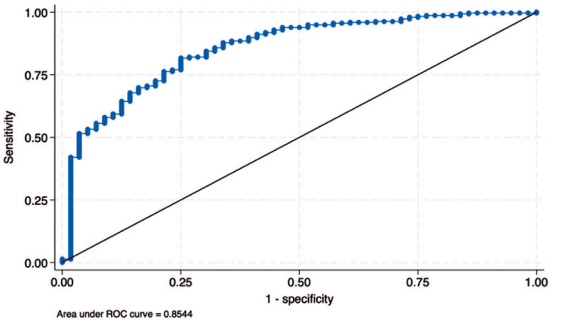


**Figure 3.** ROC curve analysis for multivariable logistic regression model predicting PTLD.

not clinically significant, as the AOR was less than 1. The prediction performance for the development of PTLD based on the five significant factors, age, HIV infection, smoking behavior, cavitation in the lungs, and lesions in both lungs, have an area under the curve (AUC) of 0.854, indicating good discriminatory ability in predicting PTLD (AUC range of 0.8 to 0.9) as shown in Figure 3.

## Discussion

The prevalence of PTLD was 83.5%, with lesions typically found in both lungs for 47.9%. Most patients had lung fibrosis, while 28.7% had residual cavities in the lungs after treatment, which are commonly associated with bronchiectasis. DLS was observed in 23 patients (6.1%), with an average age of 55±14 years. Fourteen patients (3.7%) had PT-COPD and

required continuous inhalation therapy. Only one patient had PTTS.

A female patient, 16 years old, presented with coughing and shortness of breath for 21 days. On examination, wheezing was observed in the respiratory system, which led to a diagnosis of asthma. It took 206 days to diagnose pulmonary TB on a negative AFB sputum test, which was later confirmed using a molecular diagnostic test. Six months after TB treatment, the patient developed atelectasis in the lower left lung and was referred to a tertiary hospital for further treatment, including bronchoscopy and stent placement. The treatment was successful, and her chest radiograph returned to normal, with no symptoms. This patient's condition was consistent with the previous studies, indicating that PTTS is more common in female patients[31].

In some pulmonary TB cases, wheezing may be presented on normal chest radiographs, leading to a misdiagnosis of asthma, like in this patient[32]. Case reports have shown that patients with tracheobronchial TB are often diagnosed late, as they are initially treated for asthma for several months[33,34]. One of the present study patients was male, 51 years old, with a history of smoking and alcohol consumption, presented with coughing and shortness of breath for 30 days. It took three days to diagnose pulmonary TB with a positive AFB sputum test. After six months of TB treatment, chest radiography revealed DLS in the left lung with an aspergilloma in the left upper lobe. The patient had an appointment at a tertiary hospital and occasionally developed non-massive hemoptysis.

The increasing age of patients was associated with a higher risk of developing PTLD, indicating that for every additional year of age, the likelihood of developing PTLD increased by 1.03 times. The average age of patients with PTLD was 56.05±14.56 years. A study in China found that individuals over the age of 40 and older adults seek healthcare services late because of a lack of awareness about their health conditions[7]. The prevalence of TB in older adults is 34%[35]. In the present study, the prevalence of TB in older adults was 185 patients (41%), of whom 159 (85.9%) developed PTLD. The reasons that older adults are at a higher risk for TB compared to the general population include immune system decline and underlying diseases such as diabetes, which increases the risk of TB by two to four times compared to the general population[36], CKD, chronic heart failure, chronic lung disease, and malnutrition. A study in Tanzania found that older adult patients with PTLD were linked to a low income, resulting in malnutrition due to a lack of essential nutrients and vitamins combined with dependency, financial issues, or limited access to healthcare services[9]. If older adults had high dependency needs, their health could be impacted if caregivers did not pay attention to them[37]. Furthermore, after recovering from TB, older adult patients have a high rate of PTLD due to age-related changes in pulmonary physiology, such as decreased lung elastic recoil, loss of lung compliance, and weakened respiratory muscles[11]. Along with a declining immune system, these factors allow TB to destroy the lung tissue more effectively owing to its virulence[12]. A study in South Korea found that older adult patients who developed PT-COPD had a significant decline in lung function and more COPD exacerbations compared to COPD patients who never had TB[38].

Smoking behavior indicated that patients who smoke were 3.81 times more likely to develop PTLD than non-smokers with TB. The prevalence of smokers was 154 (34.2%), with 144 patients (94.7%) developing PTLD after treatment. Smoking is a risk factor for TB in both current smokers and those who quit smoking. The risk is associated with the number of cigarettes smoked, duration of smoking[39], and type of cigarette. In TB patients who smoke, the prognosis is poorer, as supported by a study conducted in Hong Kong. Smokers with TB had more extensive lung damage, cavities in the lungs, and more positive AFB sputum than non-smokers[14]. A study conducted in Malaysia found that smokers with TB had significantly lower treatment success rates[15]. This was consistent with a meta-analysis that examined the impact of smoking on TB and showed that smokers were more likely to miss follow-up appointments and take longer to become sputum AFB-negative, resulting in lower treatment success[40]. Furthermore, a study in China analyzed the relationship between smoking and development of PTLD in a cohort of 400 male smokers who completed TB treatment. After three years of follow-up, the group with predicted FEV1/FVC indicating airflow limitation included patients who smoked for 35 years, had residual lung lesions, and were heavy smokers, with 88 pack per year, without residual lung lesions. This finding supports the fact that the number of cigarette smoked is associated with a decline in lung function[17].

Smoking increases the numbers of blood vessels and goblet cells in the respiratory system. The submucosal tissue swells, and inflammatory cells increase to produce cytokines, such as adenosine triphosphate (ATP), caspase-1, interleukin-1 (IL-1),

and IL-18, which enhance vascular permeability[41]. Consequently, TB can easily enter the respiratory system. Smoking reduces the function of mucociliary cells[42], stimulates necrosis of bronchial epithelial cells, decreases the production of cytokines that help eliminate TB, such as type 1 interferon (IFN or interferon gamma), increases mucus production, and reduces surfactant production.

Surfactant protein A (SP-A) plays a key role in the innate immune system of the lungs, and TB infection significantly lowers SP-A levels, resulting in increased lung inflammation[43]. The impact of smoking on alveolar macrophages includes increased oxidative stress, leading to macrophage death, and reducing cytokine production, which is important for eliminating TB, such as tumor necrosis factor α (TNF-α), IFNs, and IL-1β[44]. Furthermore, smoking decreases phagocytosis and transformation of macrophages into M2 types, which inhibit the inflammatory process and promote TB survival in the cells[45]. A study showed that mice exposed to cigarette smoke had fewer dendritic cells and more lung lesions than those in control groups. This is because dendritic cells produce IL-12, which stimulates T-helper cells, and the reduction in antigen uptake and presentation delays the adaptive immune response[46]. Smoking also affects neutrophils by stimulating their division[47], and signaling them to migrate to the site of infection, thereby increasing bacterial spread. This reduces phagocytosis and oxidative stress, which are crucial for eliminating TB[48]. The effects on T-cells include increasing apoptosis and interfering with cell division[49], resulting in reduced CD4+ and CD8+ T-cell counts, and significantly lowering cytokines, such as IFNs and TNFs. Another mechanism to decrease IFN production involves reducing the phosphorylation of the transcription factors responsible for the regulation thereof[50]. In summary, smoking facilitates the proliferation of TB and enhances survival by altering the environment, increasing lung tissue damage, and spreading infection to other cells or hosts.

The presence of lung cavities indicated that patients with lung cavities were three times more likely to develop PTLD than those without cavities. The present study found that 333 patients with TB (74%) had cavities in their lungs before treatment, and 295 of these patients (88.5%) developed PTLD. Among them, 100 patients (30.3%) had permanent cavities. This was consistent with previous studies that found permanent lung cavities after TB infection in 20% to 50% of patients[51]. Cavities in the lungs are unable to function as effectively as normal lung tissue in gas exchange because of incomplete healing, leading to scarring and the formation of either open or closed cavities. An open cavity is a cavity with air space, increasing the risk of secondary infections, such as *Aspergillus fumigatus*, whereas a closed cavity is a scarred or calcified mass within the lung tissue. Surgical removal of the cavitary lung tissue remains the main treatment[52], as it is effective for both drug-sensitive and multidrug-resistant TB patients, with fewer complications following surgery[53]. The pathophysiology of lung cavities caused by TB is due to TB residing in the alveoli. After the adaptive immune system is activated, granulomas form, and necrotic tissue within the granuloma erodes and enters the airways. Some necrotic tissue remains inside the granuloma. However, the elastic fibers in the walls of the cells and blood vessels remain intact, encapsulating the granuloma and forming the lung cavity[54]. White blood cells cannot enter the cavity where necrotic tissue remains, allowing TB to multiply rapidly. Additionally, because there are no blood vessels in the cavity, access to TB medication is limited. The impact of lung cavities includes rapid multiplication of TB, increasing the risk of lung damage, drug-resistant TB, and facilitating the spread of the disease[55].

Patients with lesions in both lungs had a 2.75 times higher chance of developing PTLD than those with lesions in only one lung. The present study found that 277 of 450 patients with TB (61.6%) had lesions in both lungs before treatment, with 247 patients (89.1%) developing PTLD. The present study assessed lung lesions using chest radiography in a posterior-anterior projection, a two-dimensional image that could not identify lesions in specific lung lobes. The higher incidence of PTLD in patients with lesions in both lungs is due to the greater extent of lung tissue inflammation and destruction associated with such involvement, which predisposes to worse outcomes.

Although previous studies, such as a multicenter study from West Africa, reported that HIV infection was independently associated with an increased risk of PTLD[24], the present study finding contrasts with this observation. In the present study, HIV infection was found to be a protective factor against PTLD (AOR 0.07). This discrepancy may be due to differences in study design, population, and disease stage. Additionally, a recent meta-analysis found no statistically significant difference in CLD prevalence between TB-only and TB-HIV coinfected individuals

in most included studies, which partially aligns with the present study findings[56].

Notably, the present study cohort consisted of patients who were newly diagnosed with HIV during their first TB episode, with a markedly low mean CD4 count of 66.91 cells/μL, indicating profound immunosuppression. Such a state may attenuate the host inflammatory response, potentially reducing radiographic evidence of lung damage. The present study finding is consistent with a study conducted in South Africa, which reported that HIV-infected patients with CD4 counts below 100 cells/μL exhibited minimal or no abnormalities on chest radiography, despite significantly impaired pulmonary function[57]. Moreover, a study in Malawi found that HIV-infected patients with a mean CD4 count of 229 cells/μL had significantly fewer residual airway and parenchymal pathologies than HIV-negative patients, based on high-resolution computed tomography (HRCT) findings[58].

The present study has limitations. First, smoking status was recorded as a binary variable, as smoker versus non-smoker, without quantification of exposure such as pack per year, which may have limited the ability to accurately assess the relationship between smoking intensity and PTLD risk. Second, no formal sample size calculation was performed, as all eligible TB cases during the study period were retrospectively included. Third, spirometry could not be conducted during active TB due to infection control concerns, which may have led to misclassification of patients with underlying but undiagnosed COPD.

Fourth, radiographic assessments were performed using two-dimensional chest radiographs, limiting the ability to localize lesions to specific lobes. Additionally, all radiographs were reviewed by a single physician, which may introduce observer bias, although consistency was maintained throughout. Finally, the study included only patients who completed treatment and had both pre- and post-treatment chest radiographs. Patients who died, were lost to follow-up, or did not undergo radiographic assessment were excluded, potentially introducing selection bias and limiting the generalizability of the findings.

## Conclusion

The prevalence of PTLD was 83.5%. Statistically significant factors before treatment were increasing age, smoking behavior, lung cavities, and bilateral lung lesions. As patients age, the likelihood of PTLD may be related to a decline in immune function and the ability of the body to repair lung tissue. Smoking exacerbates the risk of PTLD by damaging lung tissues, impairing immune responses, and allowing TB bacteria to proliferate and spread more easily. Lung cavities create environments where TB can survive and multiply, complicating treatment and recovery, and often leading to drug resistance and further lung damage. Bilateral lung involvement reflects more extensive inflammation and destruction of lung tissue. HIV-infected patients with low CD4 counts may have an attenuated host inflammatory response, which could reduce the risk of developing PTLD.

## What is already known about this topic?

PTLD has become an increasing health problem over the last decade. These conditions are typically a result of lung damage caused by the infection itself and might manifest long after the patient has completed TB treatment. However, its prevalence and risk factors are not well established. This has resulted in huge DALY losses. Careful monitoring and management are required to alleviate the symptoms, improve lung function, and prevent further complications.

## What does this study add?

This is the first study in Thailand to investigate PTLD risk factors in TB survivors. It offers key insights into disease progression and identifies critical predictors such as smoking and lung cavitation. These findings support the development of targeted follow-up protocols and underscore the importance of smoking cessation strategies in long-term TB care.

## Conflicts of interest

The author declares no conflict of interest.

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