PULMONARY TUBERCULOSIS MORTALITY AND ITS RISK FACTORS AMONG PATIENTS WITH TYPE 2 DIABETES AND PULMONARY TUBERCULOSIS IN FOUR COMMUNITY HOSPITALS, CENTRAL THAILAND

Sethapong Lertsakulbunlue[*], Passawith Kunsuwan[**], Ram Rangsin[***], Boonsub Sakboonyarat[***]

[*]Department of Pharmacology, Phramongkutklao College of Medicine, Bangkok, Thailand
[**]Fort Wachirawut Hospital, Nakhon Si Thammarat, Thailand
[***]Department of Military and Community Medicine, Phramongkutklao College of Medicine, Bangkok, Thailand

Abstract

Background: Tuberculosis (TB), a communicable disease, is currently a significant health problem in Thailand. Type 2 diabetes (T2D) is an indicator of poor TB outcomes; however, data according to specific antihyperglycemic use and tuberculosis outcomes in community hospital settings in Thailand remain limited. We aimed to determine TB mortality as well as explore the demographic and clinical risk factors among patients with pulmonary TB and underlying T2D.

Methods: A retrospective cohort study was conducted between January 1, 2013, and December 31, 2020, to determine tuberculosis mortality and its risk factors among patients with T2D and pulmonary TB visiting three community hospitals, in central Thailand. T2D and pulmonary TB were determined according to the International Classification of Diseases, Tenth Revision codes presented in medical records. TB mortality data were reviewed and retrieved from the tuberculosis treatment cards. Patients were classified as "dead" when they died before completing treatment regardless of the causes. Multivariable cox proportional regression analysis was performed to obtain the adjusted hazard ratios (AHR) and 95% confidence interval (CI) of factors related to TB mortality.

Results: A total of 133 patients with T2D and pulmonary TB were enrolled in the present study; 74 (55.6%) participants were males. At baseline, the average age of participants was 57.29±12.51 years. During the study period, the TB mortality rate was 15.74 (95% CI 8.13-27.50) deaths per 100 person-years. The independent risk factors for TB mortality included age ≥70 years (AHR 5.45, 95% CI; 1.36-21.84), use of insulin (AHR 4.62, 95% CI; 1.11-19.21), and positive sputum test result at 1st follow-up (AHR 16.10, 95% CI; 2.10-123.40).

Conclusion: TB mortality among patients with T2D should be emphasized. Insulin use may be a proxy indicator for poor glycemic control associated with mortality. Additionally, elderly patients should be closely observed for successful treatment as well as monitoring for any adverse events.

Keywords: Tuberculosis, Mortality, Diabetes, Community Hospital, Thailand
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Correspondence to**:**
Sakboonyarat B, Department of Community and Military Medicine, Phramongkutklao College of Medicine, Bangkok,10400 Thailand.
Email: boonsub1991@pcm.ac.th

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Introduction

Tuberculosis (TB) is a communicable disease, and currently, a significant health problem in Thailand, securing one of the top ten causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS).[1] The World Health Organization (WHO) announced TB as an emergency health problem worldwide, in which Thailand was included in one of the 22 high TB burden countries in 2016.[1] Type 2 diabetes (T2D) is one of the most common noncommunicable diseases, developed in more than 10% of the Thai population, aged 30 to 60 years old.[2, 3] Patients with poorly controlled diabetes develop complications such as diabetic retinopathy, diabetic nephropathy, coronary vascular diseases, and chronic wound ulcers.[2, 4–6] Furthermore, poorly controlled diabetes was also found to be associated with poor innate and adaptive immune response and worsened TB outcomes.[7–10] Several studies reported that diabetes was associated with TB treatment outcome failure and increased morbidity and mortality, especially in pulmonary TB.[11–13]

Several systematic reviews demonstrated an increased mortality rate and TB relapse among patients with TB and underlying diabetes compared with patients with only TB.[10] Patients with poorly controlled diabetes were also found to develop TB more easily compared with a well-controlled diabetic group.[10] The prevalence of TB was also significantly higher among patients with T2D, and a recent meta-analysis found that the prevalence of T2D among patients with TB was about 21% in South Asian countries, where the prevalence is quite diverse.[9] We are interested in studying patients with pulmonary TB and underlying T2D due to its controversies, potential for diabetic treatment, and improved pulmonary tuberculosis outcomes. Although T2D is an indicator of poor TB outcomes, data according to specific antihyperglycemic and TB outcomes remain limited, especially in community hospital settings in Thailand. Rising socioeconomic status as well as lowering rural area socioeconomic status causes relatively inadequate health literacy, difficulty in accessing health care services, and a complicated specialist consultation system.[14] The persistence of TB in this setting presents a challenge for controlling tuberculosis.[15,16] Therefore, in the present study, we aimed to determine TB mortality and explore demographics and clinical risk factors among patients with T2D and pulmonary TB in community hospitals.

Methods

Study design and subjects

A retrospective cohort study was conducted between January 1, 2013, and December 31, 2020, to determine TB mortality and its risk factors among patients with T2D and pulmonary TB attending Thai community hospitals. In Thailand, the number of hospitals under the Ministry of Public Health (MoPH) totaled 833, including 33 regional, 83 general, and 717 community hospitals, of which 86% were community hospitals.[17] In the present study, we enrolled three community hospitals (F2 level; 60 to 90 beds) located in Lopburi Province and one community hospital (M2 level; 120 beds) in Chachoengsao Province. Eligible participants comprised patients with T2D receiving a diagnosis of pulmonary TB, aged at least 15 years, attending Sanam Chai Khet Hospital, Chachoengsao Province and Pattananikom Hospital, Ta Luang Hospital, and Ta Wung Hospital in Lopburi Province. A total of 133 individuals with T2D and pulmonary TB were enrolled in the present study.

Data collection

After obtaining permission from the directors of the enrolled hospitals, we retrieved data from medical records. Baseline characteristics of participants were collected including sex, age, comorbidities, smoking status, and alcohol consumption. We also collected TB diagnosis, treatment, and outcome information including a history of previous TB, sputum AFB examination, and chest x-ray. In addition, fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), and antihyperglycemic medication use were collected at the start of treatment. Pulmonary TB and T2D were determined according to the International Classification of Diseases, Tenth Revision (ICD-

10) codes A15.0 to A19.9, and sputum AFB positive test results with underlying diabetes diagnosed by ICD10 codes E10.0 to E15.0 presented in the medical records. In addition, mortality data were reviewed and retrieved from the tuberculosis treatment card. Patients were classified as 'dead' when they died before completing treatment regardless of causes.[18,19]

Statistical analysis

Data were analyzed using StataCorp 2021, *Stata Statistical Software: Release 17*, College Station, TX: StataCorp LLC. We analyzed baseline characteristics using descriptive statistics. Continuous data were presented as mean and standard deviation (SD), while categorical data were presented as a percentage. We calculated the person-time of observation for each participant as the duration between the participant's baseline data and the date at which death, complete treatment, or loss-to-follow up took place, whichever occurred first[20]. We calculated the TB mortality rate with 95% confidence intervals (CI) per 100 person-years of observation. The Kaplan–Meier estimator was used to describe survival patterns, and we computed the log-rank test to compare survival across age groups. Validity of the proportional-hazards assumption was assessed; then Cox proportional hazard regression analysis was used to investigate risk factors for TB death. The magnitude of associations, including unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals were presented. A two-sided *p*-value less than 0.05 was considered statistically significant.

Ethics consideration

The study was reviewed and approved by the Institutional Review Board, RTA Medical Department (M002h/64_Exp) in compliance with international guidelines including the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines, and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice (ICH-GCP). Due to using secondary data, a waiver of documentation of informed consent was used, and the waiver for informed consent was granted by the Institutional Review Board, RTA Medical Department.

Results

Baseline characteristics

Baseline characteristics are presented in **Table 1**. A total of 133 patients with T2D and diagnosed pulmonary TB were followed up for a mean of 209.2 days, ranging from 11 to 675 days. Of these, 67 (50.4%) participants came from the M2 level hospital. In all, 74 (55.6%) were male. The average age of participants was 57.3±12.5 years. In terms of comorbidities, the participants had HT, and CKD accounting for 27.1%, and 6.0%, respectively. The average fasting plasma glucose of participants at baseline was 203.2 ±112.6 mg/dL while the mean HbA1c was 9.7 ±3.0%. In all, 35 (26.3%) participants used insulin, while 89 (66.9%) individuals used metformin.

Table 1 Baseline characteristics of participants (N=133)

Characteristics	n (%)
Sex	
Male	74 (55.6)
Female	59 (44.4)
Age (years)	
mean±SD	57.3±12.5
median (max-min)	58 (26-85)
<70	110 (82.7)

Table 1 Baseline characteristics of participants (N=133) (Cont.)

Characteristics	n (%)
≥70	23 (17.3)
Hospital level	
Middle level (M2; 120 beds)	67 (50.4)
First level (F1; 60-90 beds)	66 (49.6)
HIV positive	2 (1.5)
Chronic obstructive pulmonary disease	4 (3.0)
Chronic kidney disease	8 (6.0)
Hypertension	36 (27.1)
Current smoker	46 (34.6)
Current alcohol use	36 (27.1)
Fasting plasma glucose (mg/dL)	
mean±SD	203.2±112.6
median (min-max)	162.5 (82-655)
80-130	32 (24.1)
>130	101 (75.94)
HbA1c (%)	
mean±SD	9.7±3.0
median (min-max)	8.9 (4.9-21.3)
<7	17 (18.7)
≥7	74 (81.3)
Metformin use	89 (66.9)
Pioglitazone use	4 (3.0)
Glipizide use	51 (38.3)
Insulin use	35 (26.3)
History of the previous TB	19 (14.3)
Clinical manifestation at diagnosis	
Typical	121 (91.0)
Atypical	12 (9.0)
Sputum grading at diagnosis	
≤2+	108 (81.2)
>2+	25 (18.8)
Chest x-ray at diagnosis	
One or no lung lesion	12 (9.0)
Multiple lung lesion	121 (91.0)

Table 1 Baseline characteristics of participants (N=133) (Cont.)

Characteristics	n (%)
1st Follow-up sputum	
Negative	104 (78.2)
Positive	29 (21.8)
Direct observational therapy	74 (61.2)
Treatment regimen	
Standard	98 (73.7)
Extended	32 (24.1)
Multidrug	3 (2.3)

SD; standard deviation

Pulmonary TB mortality rate among patients with T2D

A total of 12 (9.0%) participants died from pulmonary TB, representing an incidence rate of 15.7 (95% CI 8.1 to 27.5) per 100 person-years. The mortality rates among males and females were 14.1 (95% CI 5.0 to 30.6) per 100 person-years and 17.9 (95% CI 6.6 to 39.0) per 100 person-years, respectively. **Figures 1 to 4** show the Kaplan–Meier survival curves of pulmonary TB death overall, by age group, insulin use, and 1st follow-up sputum, respectively.

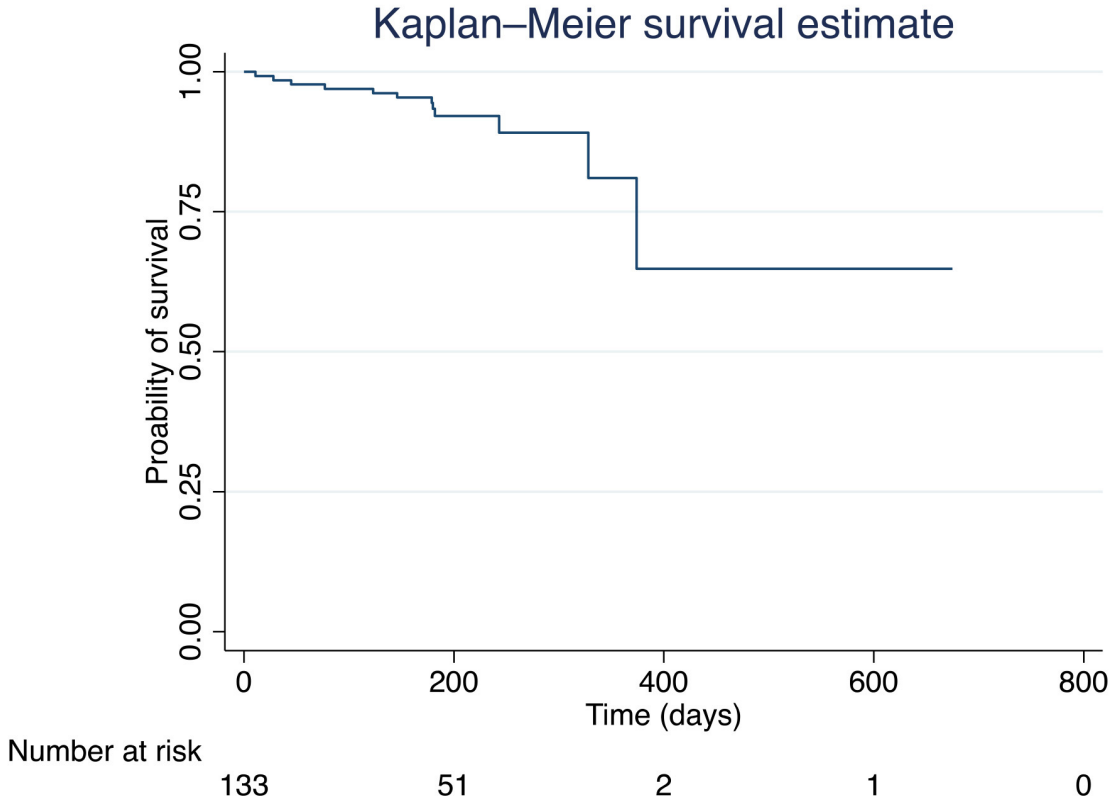

Figure 1. Kaplan–Meier survival curve of pulmonary TB mortality

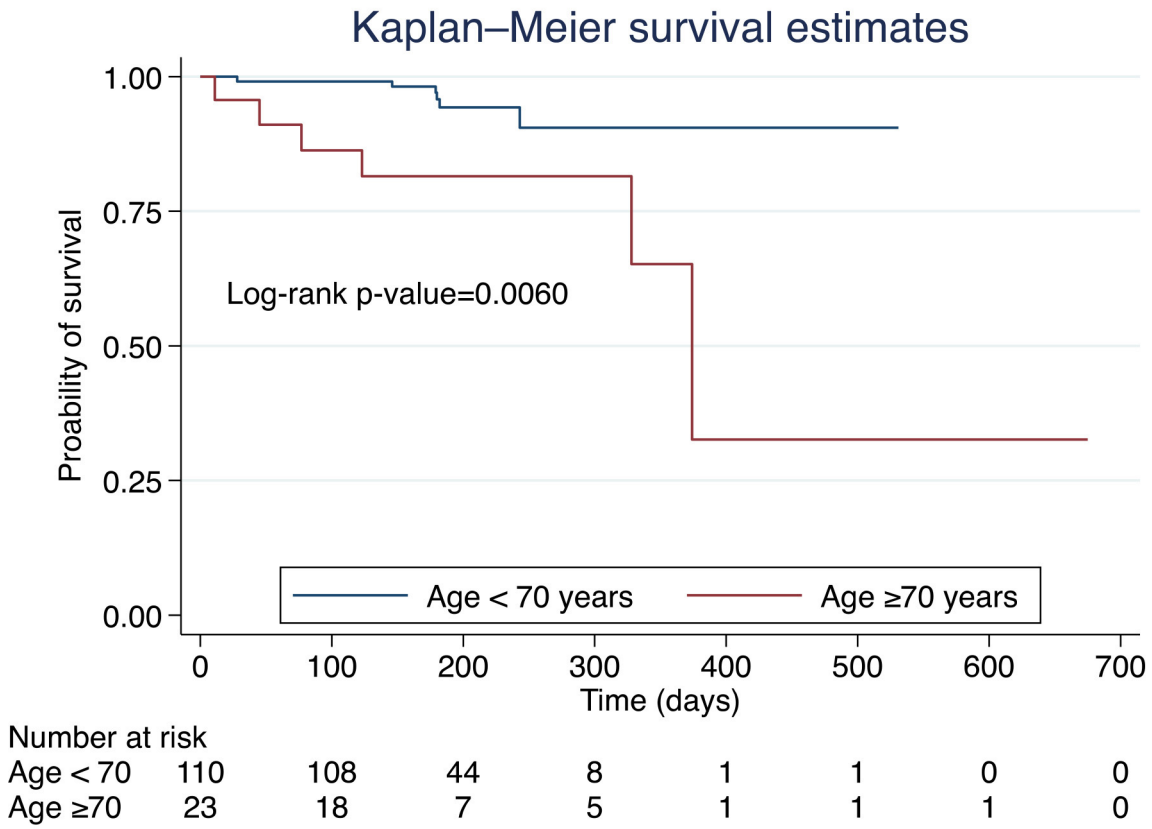

Figure 2. Kaplan–Meier survival curve of pulmonary TB mortality by age group

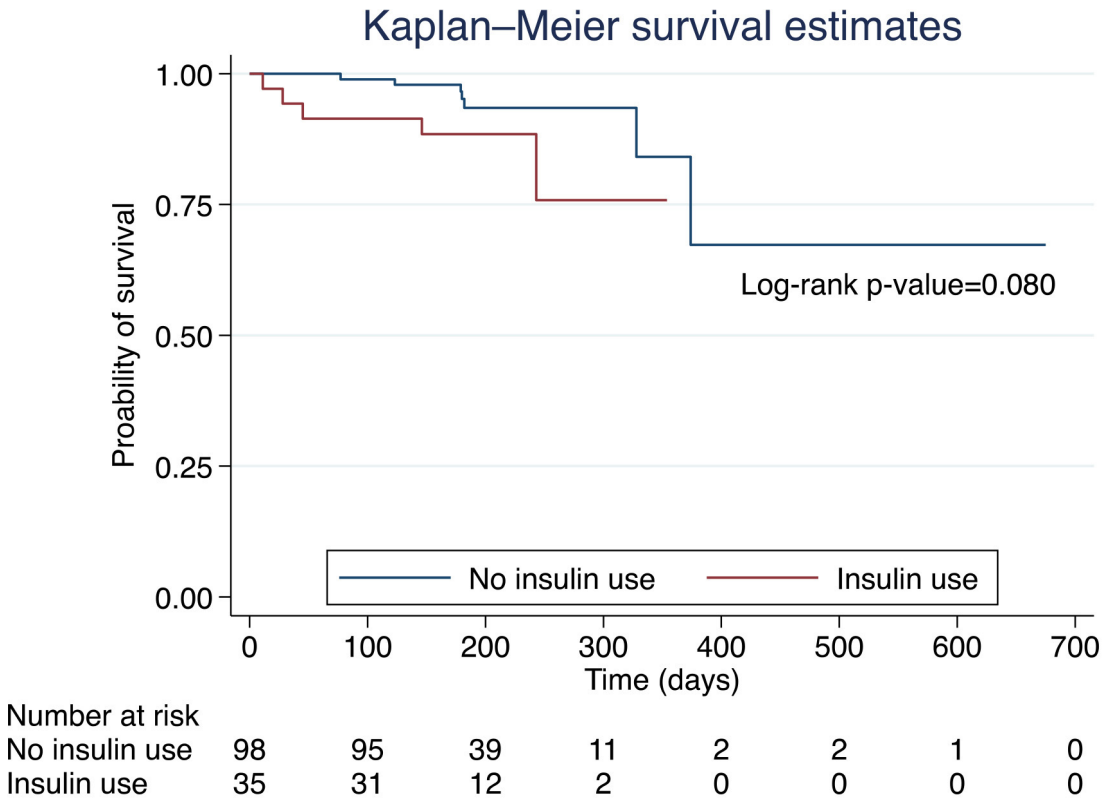

Figure 3. Kaplan–Meier survival curve of pulmonary TB mortality by insulin use

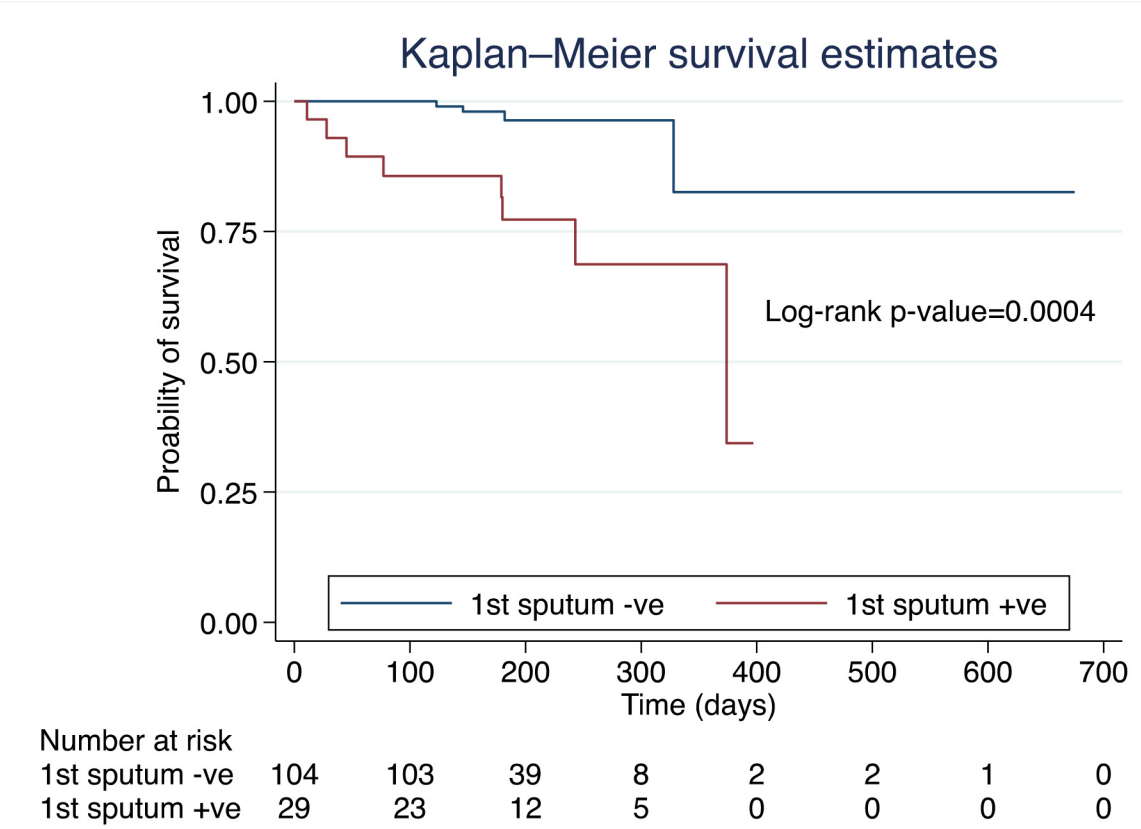

Figure 4. Kaplan–Meier survival curve of pulmonary TB mortality by 1st follow-up sputum AFB

Risk factors for pulmonary TB mortality among patients with T2D

Univariate and multivariate cox regression analysis of risk factors for pulmonary TB mortality are presented in **Tables 2 and 3**. After mutually adjusting for demographics and clinical characteristics, the mortality rate was higher for participants aged ≥70 years (HR 5.45; 95% CI 1.36-21.84), using insulin (HR 4.62; 95% CI 1.11-19.21) and having sputum AFP positive test results at first follow-up (HR 16.10; 95% CI 2.10-123.40).

Table 2. Univariable analysis of the association between demographics and clinical factors and TB mortality among patients with T2D

Factors	No. of death	Person-days of observation	Mortality rate / 100 person-years	Unadjusted Hazard Ratio	95% CI	*p*-value
Total	12	27823	15.74			
Sex						
Male	6	15584	14.06	1		
Female	6	12239	17.91	1.14	0.37-3.57	0.817
Age (years)						
<70	6	23079	9.50	1		
≥70	6	4744	46.20	4.59	1.42-14.79	0.011
Hospital level						
Middle level (M2; 120 beds)	3	13491	8.12	1		
First level (F1; 60-90 beds)	9	14332	22.94	2.38	0.63-9.07	0.203

Table 2. Univariable analysis of the association between demographics and clinical factors and TB mortality among patients with T2D (Cont.)

Factors	No. of death	Person-days of observation	Mortality rate / 100 person-years	Unadjusted Hazard Ratio	95% CI	*p*-value
HIV positive						
No	12	417	15.99	1		
Yes	0	27406	0	N/A	N/A	N/A
Chronic obstructive pulmonary disease						
No	12	26917	16.28	1		
Yes	0	906	0	N/A	N/A	N/A
Chronic kidney disease						
No	10	1739	14.00	1		
Yes	2	26084	42.01	2.47	0.53-11.58	0.250
Hypertension						
No	7	19945	12.82	1		
Yes	5	7878	23.18	1.56	0.52-5.17	0.830
Current smoker						
No	9	17690	18.58	1		
Yes	3	10133	10.81	0.57	0.15-2.11	0.401
Current alcohol use						
No	9	19874	16.54	1		
Yes	3	7949	13.78	0.85	0.23-3.14	0.806
Fasting plasma glucose (mg/dL)						
80-130	5	6456	28.29	1		
>130	7	19090	11.48	0.43	0.13-1.41	0.163
HbA1c (%)						
<7	0	3831	0			
≥7	6	15017	14.59	N/A	N/A	N/A
Metformin use						
No	6	8702	25.18	1		
Yes	6	19121	11.46	0.41	0.13-1.28	0.125
Pioglitazone use						
No	11	27064	14.85	1		
Yes	1	759	48.12	3.33	0.41-26.75	0.258
Glipizide use						
No	8	16639	17.56	1		
Yes	4	11184	13.06	0.68	0.20-2.27	0.533
Insulin use						
No	7	21259	12.03	1		
Yes	5	6564	27.82	2.80	0.84-9.29	0.093
History of the previous TB						
No	8	23567	12.40	1		
Yes	4	4256	34.33	2.63	0.77-8.94	0.122

Table 2. Univariable analysis of the association between demographics and clinical factors and TB mortality among patients with T2D (Cont.)

Factors	No. of death	Person-days of observation	Mortality rate / 100 person-years	Unadjusted Hazard Ratio	95% CI	*p*-value
Clinical manifestation at diagnosis						
Typical	12	24938	17.58	1		
Atypical	0	2885		N/A	N/A	N/A
Sputum grading at diagnosis						
≤2+	9	22325	14.72	1		
>2+	3	5498	19.93	1.31	0.35-4.85	0.684
Chest x-ray at diagnosis						
One or no lung lesion	1	2668	13.69	1		
Multiple lung lesion	11	25155	15.97	1.06	0.13-8.35	0.959
1st Follow-up sputum						
Negative	4	22225	6.57	1		
Positive	8	5598	52.2	7	2.09-23.45	0.002
Direct observational therapy						
No	9	15557	21.13	1		
Yes	3	10156	10.79	0.32	0.09-1.10	0.071
Drug regimen						
Standard	9	17594	20.34	1		
Extended	1	8990	4.06	0.12	0.01-1.07	0.057
Multidrug	1	1239	29.48	0.47	0.04-5.01	0.530

Table 3. Multivariable analysis of the association between demographics and clinical factors and the TB mortality among patients with T2D

Factors	Adjusted Hazard Ratio	95% CI	*p*-value
Sex			
Male	1		
Female	0.91	0.24-3.52	0.897
Age (years)			
<70	1		
≥70	5.45	1.36-21.84	0.017
Hospital level			
Middle level (M2; 120 beds)	1		
First level (F1; 60-90 beds)	0.38	0.05-3.06	0.364
Chronic kidney disease			
No	1		
Yes	0.14	0.08-2.57	0.144

Table 3. Multivariable analysis of the association between demographics and clinical factors and the TB mortality among patients with T2D (Cont.)

Factors	Adjusted Hazard Ratio	95% CI	*p*-value
Insulin use			
No			
Yes	4.62	1.11-19.21	0.035
History of the previous TB			
No			
Yes	6.18	0.85-44.77	0.072
1st Follow-up sputum			
Negative			
Positive	16.1	2.10-123.4	0.007
Sputum grading at diagnosis			
≤2+			
>2+	0.38	0.11-1.76	0.245
Direct observational therapy			
No			
Yes	0.44	0.11-1.76	0.245

Discussion

This study demonstrated pulmonary TB mortality among patients with T2D attending community hospitals in central Thailand. In addition, we found that demographics and clinical characteristics were associated with pulmonary TB death. The present study reported that pulmonary TB mortality was 9.0%, comparable to a related study in Texas, USA (10.3%).[20] Compared with another study in California, USA (13.1%),[21] the pulmonary TB mortality in the present study was relatively low.

Our finding reported that the pulmonary TB mortality rate among participants aged ≥70 years was higher than that among those aged <70 years which was compatible with recent evidence from Japan indicating that patients aged ≥75 years with pulmonary TB experienced increased mortality related to TB during treatment.[22] However, another report in Thailand presented that older patients were not associated with unsuccessful pulmonary TB outcomes including death, default, treatment failure, and transfer due to multidrug-resistant TB.[23]

We found that individuals with first follow-up sputum AFB positive had a higher mortality rate when compared with those with first follow-up sputum AFB negative. This observation was likely due to the well-documented positive relationship between unsuccessful pulmonary TB treatment and previously treated TB.[23–25] This finding may explain that previous treatment outcomes could be used to predict the development of drug-resistant TB.[24]

In terms of antihyperglycemic medication use, we observed that metformin use was also found as a protective factor for TB outcomes in several studies.[27–29] Metformin was found to inhibit intracellular growth of mycobacteria by inducing mitochondrial reactive oxygen species and facilitating phagolysosome fusion. Metformin can also modify the function of different biological pathways, such as down-regulating type I IFN pathways interfering with IFN-γ-mediated activation of macrophages, which are known to be associated with active TB improving the outcome of anti-TB therapy among patients with TB-infected DM.[29–32] However, the findings were not significant in our study possibly due to the small sample size.

Our finding reported that the pulmonary TB mortality rate among patients with T2D using

insulin was higher than that among those not using it. According to Thai Clinical Practice Guidelines of Diabetes 2017, insulin therapy would be initiated when fasting plasma glucose exceeds 300 mg/dL or HbA1c exceeds 11% with hyperglycemic symptoms or are currently treated with oral antihyperglycemic drugs.[2] In other words, insulin therapy could be an indicator of poor glycemic control leading to macrovascular and microvascular complications as well as increased mortality.[4, 5, 33] Insulin initiation tends to be delayed and irreversible complications can already be present by the time it starts especially when specialists are unavailable, in rural areas. Therefore, insulin use may also function as a marker for advanced disease and could affect hospitalization infection risk as well as outcomes.[34, 35] A global overview with a particular focus on the situation in Asian countries with high TB-DM burden also showed that patients with TB-DM with tight HbA1C control of lower than 7% had better outcomes regarding TB treatment[12] and an extensive systematic review and meta-analysis also showed that diabetes was related to increased mortality rate among patients with TB compared with those with TB without diabetes.[9] Our finding suggested that improving glycemic control should be encouraged among patients with T2D and pulmonary TB; additionally, individuals using insulin should be closely monitored for treatment and further complications.

Our study encountered several limitations. Firstly, according to a retrospective cohort study, some variables were collected very broadly. For example, we did not have detailed data on the number of alcoholic beverages consumed daily. Similarly, we did not have details of the smoking history, such as the current number of cigarettes smoked daily. Secondly, the present study comprised a small sample size; thus, the association between the well-known risk factors such as HIV co-infection and multiple lung lesions could not be presented.[9, 10] Third, the analysis did not include unmeasured confounders such as body mass index, anti-TB drug allergy, and diabetic complications, including macrovascular and microvascular complications. Another limitation was missing data, such as HbA1c, leading to the difficulty of including HbA1C in the analysis. Finally, the result of our study may not be generalized to the whole country but may reflect the situation of patients with T2D receiving a diagnosis of pulmonary TB in a community hospital setting in Thailand.

Conclusion

Mortality among patients with TB-DM should be emphasized. Insulin use may be a proxy indicator for poor glycemic control which was associated with mortality in this study population. Additionally, elderly patients should be closely observed for successful treatment as well as monitoring for any adverse events.

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Conflict of interest

The authors declare they have no conflict of interest.

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