EPIDEMIOLOGY OF MORTALITY AMONG TUBERCULOSIS PATIENTS ON TREATMENT IN TERENGGANU STATE OF MALAYSIA

Awang H[1], Goh SN[2], Ahmad MH[3], Mohamed KA[3], Mohd Zuber MF[3], Embong K[4], Yunus NA[5].
[1]Besut District Health Office, Kampung Raja, 22200 Besut, Terengganu, Malaysia
[2]Hulu Terengganu District Health Office, 21700 Kuala Berang, Hulu Terengganu, Terengganu, Malaysia
[3]Setiu District Health Office, 22100 Bandar Permaisuri, Setiu, Terengganu, Malaysia
[4]Terengganu State Health Department, 20920 Kuala Terengganu, Terengganu, Malaysia
[5]Pahang State Health Department, 25582 Kuantan, Pahang, Malaysia

Correspondence:
Dr Hafizuddin Awang,
Public Health Medicine Specialist,
Besut District Health Office,
Kampung Raja,
22200 Besut,
Terengganu, Malaysia
Email: drhafizuddin@moh.gov.my

Abstract

Background: Mortality among tuberculosis patients while on treatment is a public health concern in Malaysia. Exploring the risk factors for tuberculosis mortality is important to evaluate the effectiveness of national tuberculosis control programs and to identify vulnerable patients. This study aimed to estimate the 5-year proportion of mortality among tuberculosis patients on treatment and determine its associated factors in Malaysian setting.

Methods: A case-control study was conducted between deceased and survived groups in Terengganu state of Malaysia. All notified cases that fulfilled the inclusion and exclusion criteria from 1st January 2016 until 31st December 2020 were included in the study. Descriptive statistics, simple and multiple logistic regressions were employed for data analysis.

Results: There were 3,603 tuberculosis cases notified and 12.4% of total notified patients had died during their course of treatment. Multiple logistic regression revealed older age, working group, prison inmate, positive HIV status, far advanced lesion on chest radiographs and disseminated form of tuberculosis were the significant factors associated with mortality among tuberculosis patients with an adjusted odds ratio (AOR) 1.06 (95%CI: 1.04, 1.07; p<0.001); 0.48 (95%CI: 0.33, 0.68; p<0.001); 0.26 (95%CI: 0.09, 0.79; p=0.017); 12.18 (95%CI: 7.15, 20.75; p<0.001); 3.56 (95%CI: 1.46, 8.64; p=0.005); and 6.95 (95%CI: 2.02, 23.97; p=0.002), respectively.

Conclusion: About 1 in 10 patients had died during the treatment of tuberculosis in Terengganu attributed to the pinpointed socio-demographic and clinical factors. The identified risk factors were useful in improving the current screening programme and clinical management to avert mortality among vulnerable patients.

Keywords**:** Tuberculosis, Mortality, Treatment, Associated Factors, Terengganu

Introduction

Tuberculosis remains a crucial public health issue and posed various challenges for control in many countries. It is the leading cause of mortality from a single infectious disease in Asia-Pacific region and globally. In 2019, approximately 10 million people fell ill with tuberculosis globally with 5.6 million men, 3.2 million women and 1.2 million children were infected (1). Malaysia is a Southeast Asian country occupying parts of the island of Borneo and the Malay Peninsula. It is an upper-middle-income nation with a total of 31.5 million of multi-ethnic populations. Currently, Malaysia is classified as a country with intermediate burden of tuberculosis with notification rate of tuberculosis less than 100 cases for every 100,000 populations. 53% of tuberculosis cases in Malaysia were from adult group, while cases among other age groups such as children, adolescents and elderly are also getting prevalent (2-4). As Malaysia is located next to countries with highest tuberculosis burden globally (Indonesia and the Philippines), tuberculosis infection among immigrants from these nations accounted for 12.3% from the total tuberculosis cases in Malaysia (1, 2). A total of 1.4 million people died from tuberculosis in

2019. Globally, tuberculosis is one of the top 10 causes of death and the leading cause from a single infectious agent (1). A total of 1.4 million people died from tuberculosis in 2019 globally. In Malaysia, tuberculosis disease had resulted in unfavourable outcomes including mortality. Tuberculosis mortality rate in Malaysia was 5.5 per 100,000 populations in 2015 (2).

According to the Malaysian Clinical Practice Guidelines on Tuberculosis (3rd edition), tuberculosis mortality is defined as any death which occurs for any reason during the course of treatment (5). Similarly, the World Health Organization (WHO) also defined tuberculosis mortality as the number of tuberculosis patients dying during treatment, irrespective of cause of death (6). Therefore, previous studies have used all-cause mortality as a surrogate marker of mortality attributable to tuberculosis (7, 8). There are many well-recognized socio-demographic factors which contributed to tuberculosis mortality worldwide. Older age (7, 9-12), male gender (10-14), Malay ethnicity (12, 15), low education level (9), and prison inmate (16, 17), were significantly associated with tuberculosis mortality. For clinical factors, cigarette smoking (18, 19), diabetes mellitus (18, 20), human immunodeficiency virus (HIV) positive (9, 21), absent Bacillus Calmette-Guérin (BCG) vaccine scar (22-24), cavitary lesion on chest radiographic findings (8, 9, 25), and multiple sites of tuberculosis infection (10, 12, 26), were the significant clinical risk factors contributing to mortality among tuberculosis patients.

This paper focused on the epidemiology of all-cause mortality among tuberculosis patients on treatment in Terengganu state of Malaysia in line with the definition of tuberculosis mortality from the Malaysian Clinical Practice Guidelines on Tuberculosis and the WHO (5, 6). Terengganu is a sultanate and constitutive state of federal Malaysia located in the east coast of Peninsular Malaysia. About 2.6% of the total tuberculosis cases in Malaysia were contributed by Terengganu state and the mortality rate for Terengganu was 5.0 per 100,000 populations (2). To the best of our knowledge, there is no well-published study to highlight on the magnitude of mortality among tuberculosis patients, and the associated factors for mortality among tuberculosis patients on treatment in Terengganu setting. Moreover, the information regarding tuberculosis mortality and its associated factors in Terengganu state might be different from other places. Therefore, this study was conducted to estimate the prevalence of tuberculosis mortality and to determine the associated factors for mortality of tuberculosis patients on treatment in Terengganu state, Malaysia. A better understanding of the risk factors of tuberculosis mortality is one of the prerequisites to optimize the current standard of care and to pave the way in future development for better clinical management of tuberculosis.

Materials and Methods

A case-control study between deceased group and survived group using a ratio of 1:1 was conducted based on retrospective record review for all cases of tuberculosis notified to the Tuberculosis and Leprosy Control Unit, Terengganu State Health Department from the period of 1st January 2016 until 31st December 2020. Relevant study data were extracted from Tuberculosis Information System (TBIS). The reference population were all tuberculosis cases who died during the course of treatment in Terengganu state and the study samples were all tuberculosis cases notified to Terengganu State Health Department between 1st January 2016 to 31st December 2020 who fulfilled the study inclusion and exclusion criteria.

The inclusion criteria for case group were tuberculosis patients who died for any reason during the course of treatment (5). Meanwhile the inclusion criteria for control group were tuberculosis patients who survived during the course of treatment. Samples with incomplete records were excluded from the study.

The sample size was calculated for each variable of associated factors for tuberculosis relapse among tuberculosis patients using power and sample size calculation software (27), as well by comparison of two independent proportions. The largest estimated sample for each group was 390 using the proportion of survived tuberculosis patients by the factor of male gender (0.52) (14), an estimated proportion of 0.42, 5% type 1 error, 80% power and additional of 10% missing data. Therefore, the minimal sample size required is 858 samples. We included all tuberculosis mortality cases over five years and employed simple random sampling to recruit the survived (control) group from all tuberculosis cases notified in Terengganu state.

Data were collected from TBIS registry and recorded in patient's data collection sheet. TBIS is an online database for tuberculosis under the governance of Ministry of Health Malaysia. The retrieved information for independent variables included socio-demographic characteristics (age, gender, ethnicity, education level, and occupation) and clinical characteristics (diabetes mellitus status, cigarette smoking status, HIV status, presence of BCG vaccine scar, tuberculosis categories, and chest radiographic findings). The dependent variable was the tuberculosis outcome either deceased or survived during the course of treatment.

For chest radiographic findings, 'no lesion' is defined as chest radiograph with no lesion or cavity on any lung field (5, 22). 'Minimal lesion' is defined as chest radiograph with small nodular lesion approximately 1 cm, lymphadenitis and lymphangitis with no cavity, confined to small parts of one or both lungs but the total extent not exceeding the upper zone (5, 22). 'Moderately advanced lesion' is defined as chest radiograph with dense confluent lesions not exceeding one third of one lung or disseminated slight to moderate density in one or both lungs not exceeding the volume of one lung. If cavity is present, its total diameter should not exceed 4 cm (5, 22). 'Far advanced lesion' is defined as more extensive chest radiographic lesion than moderately advanced (5, 22).

Data entry and analysis were done by using SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows,

Version 22.0. Armonk, NY: IBM Corp). Descriptive statistics with mean and standard deviation (±SD), frequency, and percentages were calculated. Simple and multiple logistic regression analysis were used to determine factors associated with mortality among tuberculosis patients on treatment in Terengganu state. All significant variables with *p*-value less than 0.25 from univariable analysis and clinically important variables were chosen for multiple logistic regression analysis. A *p*-value less than 0.05 was considered statistically significant.

Results

From 1st January 2016 until 31st December 2020, there were 3,603 tuberculosis cases notified to Tuberculosis and Leprosy Control Unit, Terengganu State Health Department. Within these five years period, 448 (12.4%) patients had died during their course of treatment for tuberculosis. The mortality rates per 100,000 population for Terengganu state from 2016 until 2020 were 6.04, 0.80, 1.70, 1.70, and 0.79, respectively. Socio-demographically, the mean (±SD) age for cases which died during the course of tuberculosis treatment was 54 (±16). Majority of mortality cases were male, Malay, attained secondary level of education and from non-working group (Table 1). For clinical characteristics, majority of mortality cases were non-smoker, non-diabetic and negative HIV status. Majority of them also had BCG scar, moderately advanced lesion on chest radiographic findings and had been diagnosed with PTB smear positive (Table 2).

Table 1: Socio-demographic characteristics tuberculosis patients in accordance to their outcomes in Terengganu (n=3603)

Characteristics	Frequency (%)	
	Died (n=448)	Survived (n=3155)
Age*	54.45 (±16.62)	42.63 (±18.08)
Gender		
Female	109 (24.3)	1086 (34.4)
Male	339 (75.7)	2069 (65.6)
Race		
Others	3 (0.7)	89 (2.8)
Malay	440 (98.2)	3023 (95.8)
Chinese	5 (1.1)	43 (1.4)
Education level		
Tertiary	37 (8.3)	683 (21.6)
Secondary	286 (33.8)	1750 (55.4)
Primary	90 (20.1)	466 (14.7)
No formal education	35 (7.8)	256 (8.3)
Occupation		
Not working	283 (63.2)	1224 (38.7)
Working	146 (32.6)	1642 (52.0)
Student	8 (1.8)	243 (7.7)
Prison inmate	11 (2.5)	46 (1.6)

*Mean (±SD)

Table 2: Clinical characteristics tuberculosis patients in accordance to their outcomes in Terengganu (n=3603)

Characteristics	Frequency (%)	
	Died (n=448)	Survived (n=3155)
Cigarette smoking		
No	247 (55.1)	2048 (64.9)
Yes	201 (44.9)	1107 (35.1)
Diabetes mellitus		
No	307 (68.5)	2291 (72.6)
Yes	141 (31.5)	864 (27.4)
HIV status		
Negative	314 (70.1)	2899 (91.8)
Positive	134 (29.9)	256 (8.2)
BCG scar		
Present	410 (91.5)	2981 (94.4)
Absent	38 (8.5)	174 (5.6)
CXR findings		
No lesion	90 (20.1)	526 (16.6)
Minimal lesion	140 (31.2)	1472 (46.6)
Moderately advanced	180 (40.2)	1050 (33.2)
Far advanced	38 (8.5)	107 (3.6)
TB categories		
Extrapulmonary	80 (17.9)	521 (16.5)
PTB smear positive	248 (55.4)	1948 (61.7)
PTB smear negative	89 (19.8)	601 (19.0)
Disseminated	31 (6.9)	85 (2.8)

CXR: Chest radiography
PTB: Pulmonary tuberculosis
TB: Tuberculosis

For the inferential case-control study, all 448 mortality cases were included, and another 448 samples were randomly selected for inclusion in the survived (control) group. In the univariable analysis, socio-demographic characteristics on age, gender, ethnicity, education level and occupation were selected for multivariable analysis as its *p*-value is less than 0.25. As for clinical factors, cigarette smoking, HIV status, presence of BCG scar, chest radiographic findings and tuberculosis categories were the significant and clinically important factors selected for multivariable analysis.

Multiple logistic regression revealed older age, working group, prison inmate, positive HIV status, chest radiographic finding with far advanced lesion and disseminated form of tuberculosis were the significant factors associated with mortality among tuberculosis patients on treatment in Terengganu with an adjusted odds ratio (AOR) 1.06 (95%CI:1.04, 1.07; p<0.001); 0.48 (95%CI: 0.33, 0.68; p<0.001); 0.26 (95%CI: 0.09, 0.79; p=0.017); 12.18 (95%CI: 7.15, 20.75; p<0.001); 3.56 (95%CI: 1.46, 8.64; p=0.005); and 6.95 (95%CI: 2.02, 23.97; p=0.002), respectively (Table 3).

Table 3: Factors associated with mortality of tuberculosis patients in Terengganu by simple and multiple logistic regression (n=896)

Characteristics	TB outcome, n (%)		Crude OR (95% CI)[a]	p-value[a]	Adjusted OR (95% CI)[b]	p-value[b]
	Died (n=448)	Survived (n=448)				
Age**	54.45 (±16.62)	42.37 (±18.34)	1.04 (1.03, 1.05)	<0.001*	1.06 (1.04, 1.07)	<0.001*
Gender						
Female	109 (24.3)	150 (33.5)	1.00		1.00	
Male	339 (75.7)	298 (66.5)	1.57 (1.17, 2.09)	0.003*	1.07 (0.71, 1.63)	0.740
Ethnicity						
Others	3 (0.7)	16 (3.6)	1.00		1.00	
Malay	440 (98.2)	422 (94.2)	5.56 (1.61, 19.22)	0.007*	2.48 (0.57, 10.76)	0.225
Chinese	5 (1.1)	10 (2.2)	2.67 (0.52, 13.68)	0.240	0.86 (0.12, 5.96)	0.877
Education level						
Tertiary	37 (8.3)	92 (20.5)	1.00		1.00	
Secondary	286 (63.8)	256 (57.1)	2.78 (1.83, 4.22)	<0.001*	1.06 (0.64, 1.76)	0.833
Primary	90 (20.1)	64 (14.3)	3.50 (2.12, 5.76)	<0.001*	0.91 (0.49, 1.70)	0.773
No formal education	35 (7.8)	36 (8.1)	2.42 (1.32, 4.41)	0.004*	0.89 (0.40, 1.95)	0.764
Occupation						
Not working	283 (63.2)	166 (37.1)	1.00		1.00	
Working	146 (32.6)	232 (51.8)	0.37 (0.27, 0.49)	<0.001*	0.48 (0.33, 0.68)	<0.001*
Student	8 (1.8)	39 (8.7)	0.12 (0.05, 0.26)	<0.001*	1.43 (0.56, 3.68)	0.453
Prison inmate	11 (2.4)	11 (2.4)	0.59 (0.25, 1.38)	0.223	0.26 (0.09, 0.79)	0.017*
Cigarette smoking						
No	247 (55.1)	297 (66.3)	1.00		1.00	
Yes	201 (44.9)	151 (33.7)	1.60 (1.22, 2.09)	0.001*	1.30 (0.88, 1.92)	0.183
Diabetes mellitus						
No	307 (68.5)	323 (72.1)	1.00		-	
Yes	141 (31.5)	125 (27.9)	1.19 (0.89, 1.58)	0.262	-	-
HIV status						
Negative	314 (70.1)	422 (94.2)	1.00		1.00	
Positive	134 (29.9)	26 (5.8)	6.93 (4.44, 10.81)	<0.001*	12.18 (7.15, 20.75)	<0.001*
BCG scar						
Present	410 (91.5)	427 (95.3)	1.00		1.00	
Absent	38 (8.5)	21 (4.7)	1.89 (1.09, 3.27)	0.024*	1.37 (0.65, 2.89)	0.405
CXR findings						
No lesion	80 (17.8)	95 (21.2)	1.00		1.00	
Minimal lesion	143 (31.9)	207 (46.2)	0.97 (0.65, 1.46)	0.892	0.92 (0.48, 1.73)	0.784
Moderately advanced	187 (41.7)	127 (28.3)	1.79 (1.19, 2.68)	0.005*	1.79 (0.93, 3.46)	0.082
Far advanced	38 (8.6)	19 (4.3)	2.63 (1.37, 5.04)	0.004*	3.56 (1.46, 8.64)	0.005*
TB categories						
Extrapulmonary	80 (17.9)	88 (19.6)	1.00		1.00	
PTB smear positive	248 (55.3)	276 (61.6)	0.99 (0.69, 1.40)	0.948	0.61 (0.34, 1.08)	0.089
PTB smear negative	89 (19.9)	79 (17.6)	1.24 (0.81, 1.90)	0.326	0.82 (0.43, 1.55)	0.531
Disseminated	31 (6.9)	5 (1.2)	6.82 (2.53, 18.39)	<0.001*	6.95 (2.02, 23.97)	0.002*

Note: Forward LR method applied. No multicollinearity and no interaction found. Hosmer Lemeshow test, p-value=0.080. Classification table 75.7% correctly classified. Area under Receiver Operating Characteristics (ROC) curve was 83.3%.
**Mean (±SD)
*p-value<0.05
[a]Simple logistic regression
[b]Multiple logistic regression
BCG: Bacillus Calmette-Guérin
CI: Confidence Interval
CXR: Chest radiography
OD: Odd ratio
PTB: Pulmonary tuberculosis
TB: Tuberculosis

Discussion

The 5-year proportion of tuberculosis mortality in Terengganu state was 12.4% which is substantially higher than the prevalence of tuberculosis mortality reported in a previous national level study (9.69%) (9). For regional comparison, the prevalence of all-cause tuberculosis mortality in Singapore was 11.9% (12), which is slightly lower than Malaysia's prevalence of all-cause tuberculosis mortality. Developed nations such as China, United States of America and Russian Federation showed lower prevalence of all-cause tuberculosis mortality (8, 10, 11), as compared to finding in our study. The discrepancies in the prevalence between our findings with other studies could be attributed to extensive availability of free or affordable screening and treatment for tuberculosis and comorbidities associated with tuberculosis mortality in those developed nations (10, 11).

Our multivariable analysis showed that older patients were more likely to die from any cause during treatment for tuberculosis as compared to other age groups. This finding is congruent to many other local and international studies reporting significant association between older age with all-cause tuberculosis mortality (7, 9-12, 14). Elderly patients are usually immunocompromised due to declining immunity and presence of comorbidities such as diabetes. Therefore, they tend to present with non-specific symptoms which may complicate diagnosis, delay treatment of tuberculosis, and subsequently pose higher risk of mortality (11, 28). Besides that, elderly patients are more likely to encounter problems during treatment phase such as higher loss to follow-up and intolerance to anti-tuberculosis drugs due to side effects which would increase the risk of unfavourable treatment outcomes or even death (29).

Surprisingly, this study found that the working group of population was less likely to die from tuberculosis as compared to non-working group as many literatures worldwide reported otherwise (30-32). In contrast to our finding, a South African study demonstrated significant association between certain groups of occupation with tuberculosis mortality. An increased risk of tuberculosis mortality was observed among agricultural workers, cleaners and workers exposed to silica dust (31). Tuberculosis mortality is not only linked to low socio-economic working class as Liew *et al.*, reported the case fatality rate of 2.4% among healthcare workers infected with tuberculosis in Malaysia (21). We may postulate the association of working group with lower risk of tuberculosis mortality could be attributed to the working age in Malaysia which is between 15-64 years old (33). Majority of relatively young patients in the working age group diagnosed with tuberculosis were more likely to initiate treatment sooner after being diagnosed as demonstrated in an Australian study (14), hence had better treatment outcome.

Prisons are among the well-established reservoirs for tuberculosis, and non-infected individuals are likely to become infected when they become prison inmates (34). Moreover, studies had shown that mortality among tuberculosis patients were higher among prisoners (16, 17). However, our study found that inmates diagnosed with tuberculosis in Terengganu's prison were less likely to die irrespective of causes throughout the course of tuberculosis treatment. The correctional and administrative officers in Malaysian prisons demonstrated good level of knowledge concerning tuberculosis symptoms, mode of transmission, preventive measures and treatment as reported in a previous local study (35). All active tuberculosis patients in Malaysian prisons are managed appropriately in accordance with special guideline for tuberculosis management and control in prisons. All new prison inmates are screened for tuberculosis within 24 hours of prison admission. Healthcare workers in prisons employ directly observed therapy when treating prisoners with active tuberculosis disease. Besides, prisoners exposed to tuberculosis cases are carefully screened to contain the transmission of tuberculosis in the institutions (36). Besides that, healthcare workers in prisons also maintain good rapport with district health offices and hospitals, and sick inmates would be brought to health facilities to be examined by specialists whenever indicated (36). All these measures ensure optimal management of tuberculosis cases in prisons and directly reduce the risk for tuberculosis mortality in prisons.

In our study, tuberculosis patients with HIV co-infection had 12-times higher odds of dying during the course of treatment as compared to HIV negative tuberculosis patients. Our finding resonates well with findings from other local and international studies (15, 21). HIV positive patients with tuberculosis have higher risk of dying due to complications of HIV infection which is associated with profound immunosuppression (37, 38). Besides that, HIV infection may give unusual clinical features of tuberculosis and subsequently can cause diagnostic difficulties and delay in treatment (38). Side effects of antituberculosis drugs are more frequent in HIV positive patients and may result in severe or fatal reactions in certain cases (38).

Chest radiographs are used to stratify pulmonary tuberculosis severity based on the radiographic changes (22). In our study, tuberculosis patients with far advanced lesions on chest radiographic findings were more likely to die during the course of treatment as compared to tuberculosis patients with less severe chest radiographic changes. Consistent with our finding, other local and Russian studies showed tuberculosis patients with cavitary lesions or extensive lung involvement on chest radiographs was associated with higher mortality rate among tuberculosis patients (7-9). Cavitary lesions on chest radiograph at diagnosis was significantly associated with higher baseline acid-fast bacilli density in sputum (39). The number of bacilli depends on the extent of the lesion or the presence of cavitation of lungs in case of pulmonary form of tuberculosis. Larger cavitary lesion indicates larger amounts of bacilli present in patient, indicating more severe form of tuberculosis which poses higher risk for mortality (22, 39).

The nature of tuberculosis occurrence is protean and unique as it can take place in pulmonary and/or extrapulmonary sites (22). In this study, patients with disseminated form (tuberculosis affecting pulmonary and extrapulmonary sites) of tuberculosis were significantly associated with mortality during the course of treatment as compared to other forms of tuberculosis. A Singaporean study also reported the significant association between multiple sites involvement (disseminated form) of tuberculosis with mortality rate (12). On the contrary, few studies had reported extrapulmonary form of tuberculosis as significant determinants for tuberculosis mortality (9, 26). It was postulated that high mortality among patients with disseminated form of tuberculosis is attributed to lethal combination of reactivation and newly acquired infection of tuberculosis which worsens the severity of tuberculosis disease and complicates its treatment (40).

Due to the limitation of secondary data, our study did not include some known confounders such as anti-tuberculosis regimen and housing conditions. Nevertheless, this study had enough sample size. Future researchers may employ other study designs such as cohort study for better understanding of other associated factors with tuberculosis mortality.

In conclusion, about 1 in 10 tuberculosis patients died during the treatment course in Terengganu state. Older age, working group, prison inmate, positive HIV status, chest radiographic finding with far advanced lesion and disseminated form of tuberculosis were the significant factors associated with mortality among tuberculosis patients on treatment in Terengganu state.

Future recommendations

Early case detection via intensified case findings and screening of symptomatic outpatients are recommended as these measures are crucial to diagnose case at earlier stage as far advanced lesions posed higher risk for tuberculosis mortality. Meticulous follow-up and care among elderly and HIV positive tuberculosis patients are prerequisite to ensure their adherence to treatment and tolerance towards anti-tuberculosis medications. Effective communication between healthcare workers and among different agencies is needed to prevent patients from loss to follow-up especially those prison inmates who had been released. Complicated tuberculosis cases such as disseminated form and extensive involvement of lungs should be managed appropriately and preferably referred to family medicine specialists and respiratory physicians to ensure optimal treatment. Health promotion to increase knowledge and awareness regarding tuberculosis among community members is important to ensure cases presented at early stage of disease.

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Competing interests

The authors declare that there is no conflict of interest.

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