ORIGINAL ARTICLE

Adult Tuberculosis Patients in Sabah: Influencing Factors for Mortality

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ABSTRACT

Introduction: Tuberculosis (TB) still accounts for a significant proportion of the annual mortality rate, even in the era of potent treatment. With 11.5/100,000 deaths from TB in 2016 and 12.9/100,000 deaths the subsequent year, Sabah continues to grapple with a high TB mortality rate. The study's aim was to identify the influencing factors for TB mortality in adult TB patients in Sabah. **Methods:** Secondary data from the Malaysia TB Information System (MyTB) were in this retrospective cohort study. From 2016 to 2017, all TB cases reported in Sabah were extracted from the database. The parameters impacting TB mortality in adult patients receiving tuberculosis therapy were determined using a Cox proportional hazards regression analysis. **Results:** During the course of the study, 10,058 TB patients were registered in MyTB. After excluding cases under the age of 18 (n=826) and cases with a changed diagnosis (n=65), 9,167 cases were used for the analysis. There were 842 (9.2%) deaths among patients included in the study. In the multivariable analysis, age ≥ 65 years old (aHR =5.16, 95% CI: 4.31–6.18) and TB-HIV co-infection (aHR=5.31, 95% CI: 3.90–7.22) were considered as clinically important factors influencing TB mortality. **Conclusion:** It is essential to identify the factors influencing mortality among TB patients so that appropriate strategies and interventions can be developed to achieve the End TB Strategy's objective of 95% mortality reduction by 2035. To lower the TB mortality rate in adult patients, additional follow-ups are required for older patients and cases of TB-HIV co-infection.

Keywords: Factors; Tuberculosis mortality; Adult; Sabah

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INTRODUCTION

Tuberculosis (TB) cases still pose a threat to public health globally, and accounts for a significant proportion of annual mortality rate, despite the era of potent treatment. Even in areas with advanced medical resources, an early diagnosis is still challenging (1). In the modern world, TB is the main infectious agent causing illness and mortality, surpassing even human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). In 2019, 10 million new cases of TB were detected, with an additional of 208,000 people living with HIV (PLWH) dying from TB in comparison to HIV-negative people, resulting in a total of 1.2 million fatalities from TB (2). The World Health Organization (WHO) set the target that every nation reduced TB mortality from 2015 by 35% in 2020 and 95% in 2035, respectively (3). However, according to a global tuberculosis report in 2020, however, most countries still had not achieved the End TB Strategy's target (2).

The World Health Organization (WHO) anticipated that Malaysia would have 92 tuberculosis cases for every 100,000 people, which ranked the country with an intermediate TB burden (2) and four cases of death per 100,000 people in 2019 (4). More specifically, Sabah, the second largest state in Malaysia, contributed to around one fifth of the TB patients in the country with 128 incidents per 100,000 individuals (5) and a mortality rate of 11.5/100,000 people in 2016, and 12.9/100,000 people the subsequent year (4).

Numerous research globally focused on the risk factors for TB deaths. However, there are limited studies which investigated Malaysian TB mortality risk factors. This study was conducted in Sabah, which is recognised as the poorest state in Malaysia. The state is also considered to be more underdeveloped compared to Peninsular Malaysia in terms of its economic status. Sabah has also suffered from the long-term influx of illegal immigrants and refugees from neighbouring nations like Indonesia and the Philippines, which account for roughly 25% of Sabah's TB cases (6). Therefore, the TB mortality factors in Sabah might be different from other states due to the complexities of its population structure. Hence,

this study aimed to identify the influencing factors for mortality in adult TB patients in Sabah.

MATERIALS AND METHODS

Study Design and Study Population

Secondary data from the Malaysia TB Information System (MyTB) were used in this retrospective cohort study. Information was extracted from the system for every TB case reported in Sabah between January 1st, 2016, and December 31st, 2017.

Tuberculosis is one of the mandatory notifiable diseases by the Malaysian law under the Prevention and Control of Infectious Diseases Act 1988 (Act 342) (7). Within seven days from the date of the diagnosis, the TB cases must be notified to the closest District Health Office (8). In Malaysia, the diagnosis of TB cases mostly relies on radiological findings and laboratory results such as chest X-ray (CXR), sputum direct smear for acid fast bacilli (SAFB), and confirmed by sputum mycobacterium tuberculosis culture. Because of the cost and advanced laboratory infrastructure requirements, molecular methods and artificial intelligence (AI) algorithms on radiographs are not a routine part of the diagnosis among suspected TB patients.

Data on TB patients who received treatment at all TB treatment facilities were available through MyTB. During each visit over the course their of therapy, medical and nursing staff at the relevant healthcare facilities recorded information about sociodemographic factors, medical history, and co-morbidities each patient in MyTB.

Data Collection

For each TB case, the data extracted included age, sex, nationality, location of living, smoking status, diabetes mellitus (DM) status, HIV status, characteristics of TB disease (such as TB case detection, type of TB, sputum smear, chest radiological results), year of TB case registered, and the outcome of TB treatment.

The outcome of TB treatment included cured, completed treatment, death, failed treatment, change diagnosis, loss to follow-up, and transfer out. These outcomes were regrouped into death (mortality) and other treatment outcomes (cured, completed treatment, failed treatment, loss to follow-up, and transfer out).

All Sabah TB cases that were officially reported between the years of 2016 and 2017 were enrolled in this study. Throughout the year of their follow-up, the cases' TB treatment outcomes were identified and reported. The study included all patients who were at least 18 years old, and with known treatment outcomes in that duration. Cases that had their diagnosis changed during the study duration were excluded.

Operational Definition of TB

The operational definitions for TB treatment outcomes utilised in this study, in accordance with the WHO definition and reporting framework for TB (9) and the Clinical Practice Guidelines Management of Tuberculosis (3rd Edition) by the Ministry of Health, Malaysia (10) is as follow:

1. Cured: A patient with bacteriologically confirmed TB who had negative smears or cultures in both the month prior to treatment ending and on at least one previous occasion (9 p. 6) (10 p. 81).
2. Completed treatment: A patient who completed TB treatment but did not achieve the requirements to be categorised as either cured or failure. (9 p. 6) (10 p. 81).
3. Treatment failed: A patient undergoing TB treatment whose sputum smear or culture showed positive at five months or later. (9 p. 6) (10 p. 81).
4. Died (Mortality): A patient who passes away for any reason before starting their TB treatment or while undergoing TB treatment (any-cause mortality) (9 p. 6) (10 p. 81).
5. Loss to follow up: A patient with TB who did not begin treatment or whose treatment had been discontinued for two months or longer. (9 p. 6) (10 p. 81).
6. Not evaluated: A patient for whom no specified treatment outcomes were provided. We included TB patients in this analysis even though they had been "transferred out" to another nation because their treatment outcomes were unknown (9 p. 6) (10 p. 81).
7. New case: A patient who had never received TB treatment or who had only taken anti-TB drugs for a month or less (9 p. 4) (10 p. 80).

Statistical Analysis

To gather data, clean data, and conduct statistical analyses for this study, Microsoft Excel and IBM Statistical Package for the Social Science (SPSS) version 23 (Armonk, NY, USA) was used.

Differences in patient characteristics between two groups, TB death cases from all forms of TB (any-cause mortality), and treatment outcomes other than death were tested using Fisher's exact test or the $\chi 2$ test. P value < 0.05 was used to indicate a significant difference. For the purpose of survival analysis, other treatment outcomes other than death were considered as a non-event, and thus labelled as censored data.

The Cox proportional hazards regression technique was utilised in survival analyses to identify independent risk variables for mortality from any cause. To identify the important variables linked to TB death from any cause, a univariable analysis was conducted. The crude hazard ratio with 95% confidence interval was

also estimated for each independent variable. The multivariable analysis took into account the variables that were considered clinically significant.

A multivariable analysis was performed to determine which independent variables best predicted the TB death (any-cause mortality) from TB treatment, using a backward stepwise selection based on maximum partial likelihood estimates (with $P > 0.10$ for variable removal and $P < 0.05$ for variable entrance). The adjusted hazard ratio with 95% confidence interval was estimated for each independent variable that remained in the final model.

Ethical consideration

The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, with permission code: NMRR-20-1289-55461, and the Medical Ethics Committee of University Sabah Malaysia, with reference number JKEtika 4/20 (8), respectively, both granted their approval for this study's ethical conduct in September 2020. Access to the list of TB patients' cases in the MyTB database was authorised by the Sabah State Health Director. No patient permission was required for this study because it solely utilised patient data from MyTB database (secondary data) and all cases included were anonymised.

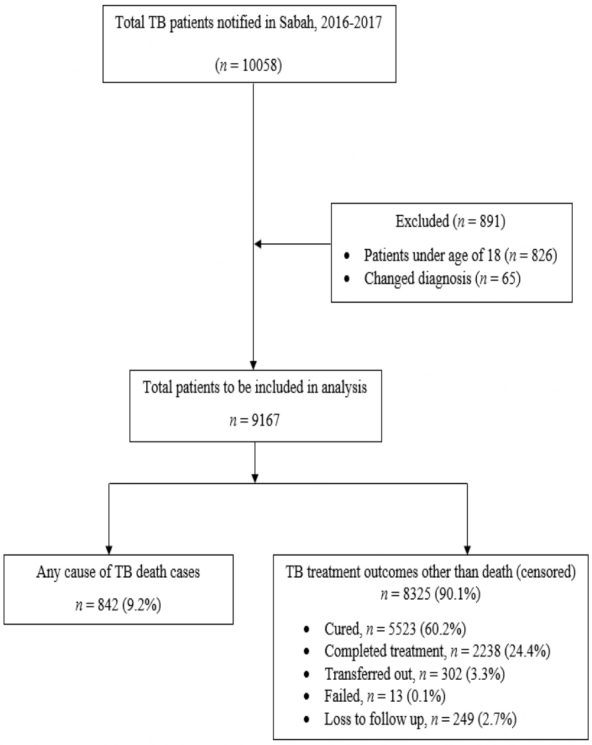

Figure 1 : Selection of study cases from TB registry 2016-2017

RESULTS

Throughout the duration of this study, a total of 10,058 TB patients were registered in MyTB. After excluding cases under the age of 18 (n=826) and cases with a changed diagnosis (n=65), the analysis includied 9,167 cases in total. There were 842 (9.2%) deaths and 8,325 TB treatment outcomes other than death, including cured (n=5,523), completed treatment (n=2,238), transferred out (n=302), failed (n=13), and loss to follow-up (n=249) (Figure 1). Treatment results for TB were determined after one year of follow up for every TB case who participated in this trial, and all of them were diagnosed during the years of 2016 and 2017.

Timing to death

166 (or 19.7%) of the TB patients passed away within a week of receiving their diagnosis. Meanwhile, majority of the patients died before receiving anti-TB medication, accounting for 580 (68.9%) of all TB deaths, and this primarily occurred within the first eight weeks of TB treatment (intensive phase) (Table I). These fatalities happened either immediately following the confirmation of a TB diagnosis, or during the TB work-up before the diagnosis was made.

Factors associated with any-cause mortality

Table II displays the findings of the multivariable Cox proportional hazards regression analysis on the variables correlated with mortality from any cause. Among the parameters examined, older age, underlying DM, smoking, absence of bacilli Calmette-Gu´erin (BCG) scar, extra-pulmonary TB (extra PTB) and both pulmonary TB (PTB) and extra-PTB, advanced chest radiograph (CXR), and TB-HIV co-infection were discovered as causes linked to mortality from TB. Smoking was found to be protective. On the

Table I : Time to death from diagnosis of adult tuberculosis patients in Sabah, 2016-2017

Survival time (week)	Number of risk	Deaths	Censors	Proportion of deaths (%)
0 - 1	9167	166	22	19.7
1 - 4	8979	264	66	31.4
4 - 8	8649	150	62	17.8
8 - 24	8437	211	425	25.1
24 - 52	7801	46	7225	5.5
>52	530	5	525	0.6

Table II : Risk factors associated with tuberculosis Death from any cause

Variables	Univariate			Multivariate		
	Crude HR	95% CI	*P Value*	aHR	95% CI	*P Value*
Age, in years			<0.0005			<0.0005
<45	1	Referent		1	Referent	
45–64	2.31	1.96 - 2.73	<0.0005	2.24	1.89 - 2.66	<0.0005
≥65	5.19	4.37 - 6.15	<0.0005	5.16	4.31 - 6.18	<0.0005
Sex			<0.0005			
Female	1	Referent				
Male	1.15	1.00 - 1.33	0.051			
Nationality			<0.0005			
Non Malaysian	1	Referent				
Malaysian	1.16	0.99 - 1.36	0.071			
TB case detection			<0.0005			<0.0005
Active	1	Referent		1	Referent	
Passive	1.31	1.03 - 1.66	0.026	1.25	0.98 - 1.61	0.075
Diabetes Mellitus			<0.0005			<0.0005
No	1	Referent		1	Referent	
Yes	1.80	1.47 - 2.19	<0.0005	1.37	1.12 - 1.68	0.003
Smoking			<0.0005			<0.0005
No	1	Referent		1	Referent	
Yes	0.82	0.70 - 0.95	0.008	0.84	0.72 - 0.98	0.023
Location of living			<0.0005			
Urban	1	Referent				
Rural	1.06	0.91 - 1.24	0.425			
BCG Scar			<0.0005			<0.0005
Yes		Referent		1	Referent	
No	1.58	1.38 - 1.82	<0.0005	1.31	1.13 - 1.51	
Type of tuberculosis			<0.0005			<0.0005
Pulmonary	1	Referent		1	Referent	
Extra-pulmonary	1.31	1.07 - 1.60	0.008	1.87	1.45 - 2.42	<0.0005
Pulmonary and extra-pulmonary	1.89	1.42 - 2.51	<0.0005	1.79	1.34 - 2.39	<0.0005

Sputum Smear			<0.0005			
Negative	1	Referent				
Positive	0.89	0.77 - 1.03	0.120			
CXR Results			<0.0005			<0.0005
No lesion	1	Referent		1	Referent	
Minimal	0.77	0.58 - 1.02	0.067	1.19	0.86 - 1.67	0.297
Moderately advanced	1.24	0.94 - 1.63	0.122	2.10	1.50 - 2.94	<0.0005
Far advanced	2.76	1.98 - 3.83	<0.0005	4.67	3.17 - 6.86	<0.0005
HIV Status			<0.0005			<0.0005
No	1	Referent		1	Referent	
Yes	3.23	2.42 - 4.32	<0.0005	5.31	3.90 - 7.22	<0.0005

HR = hazard ratio; CI = confidence interval; aHR = adjusted hazard ratio; TB = tuberculosis; CXR = chest radiograph.

other hand, passive detection of TB cases was not statistically significant.

DISCUSSION

This study aimed to identify the influencing factors for TB mortality in adult TB patients in Sabah. In this retrospective cohort study from 2016 until 2017, there were still a large number of TB deaths, despite TB patients being treated effectively with chemotherapy, and the availability of advanced laboratories test for mycobacterium.

During this study period, almost one in ten adult TB patients died with any-cause mortality (9.2%). The fatality rate was identical to a national study conducted in 2020 (11) and in 2015 (12). Our study results did not show a reduction in TB mortality when compared to the previous studies by Liew (31). Hence, national strategies such as active case detection in hotspot areas and TB screening for high-risk groups need to be strengthened to prevent delayed diagnosis and treatment.

In this study, a significant number of deaths (68.9%) during the first eight weeks (intensive phase) of anti-TB treatment was observed. This result concurred with research conducted in Mali (13), South Korea (14), and Ethiopia (15). Additionally, 19.7% of TB patients passed away in the first week following their diagnosis. A prior study found that many patients died (7.9%) either during the TB work-up, before the TB treatment began, or shortly after the TB diagnosis was established (4). Therefore, closely monitoring the patients for necessary management is extremely important during the intensive phase to prevent complications and progression of the disease. Starting anti-TB medication immediately after a confirmed diagnosis could prevent unnecessary complications and improve TB treatment outcome.

Our analysis showed that higher odds of mortality were associated with increase of age. Patients aged ≥65 years had more than five times higher odds of mortality (adjusted HR (aHR) =5.16, 95% CI: 4.31–6.18) compared to younger patients. Similar findings have been documented in many previous studies (16-20). It is possible that concomitant conditions and waning immunity could contribute to elderly TB patients' higher death rates.

Comorbidity such as DM was found to be associated with any-cause mortality (aHR=1.37, 95% CI: 1.12–1.68) in this study. This finding was similar to a study in Korea (21). Diabetes mellitus was proven to worsen the TB, increasing the chances of getting TB, and reactivating latent TB due to immunisation waning (22). An integrated approach might be needed to prevent, screen, and treat this dual disease burden. In a TB clinic, patients with TB and DM co-morbidity might require referral to an endocrinologist and a dietitian for confirmation of their diagnosis and to control their diet. Health education should be promoted by trained healthcare workers to create better awareness and understanding of the diseases including the outcome and complications during treatment. During the treatment period, patients should follow up more frequently, and close monitoring is needed for early detection of possible adverse events following the TB medication (23). Pharmacists could play important roles to counsel and explain the possible complications caused by the TB drugs, and approaches to overcome the problem. To implement education, awareness, and training to the TB and DM co-morbidity patients in the TB clinics, collaboration between multi-professional experts is needed. Normative practise recommendations for national programmes are also crucial.

In this study, smoking was not associated with mortality. This finding may be due to the data collection

which depended on self-reporting by patients, and the employment of any-causes death. In contrast, there was strong evidence showing that smoking was associated with poor TB treatment outcomes including mortality and loss to follow-up in other studies (21, 23, 24). Tobacco smoking may cause sputum or culture conversion rates to be delayed, the intensive phase of TB therapy to last longer, the length of infectiousness to be prolonged, and the requirement for a longer course of treatment (25). According to a study in Taiwan, when comparing smokers and non-smokers, the odds of death were nine times greater for smokers. Smoking cessation could effectively reduce the risk of TB infection and decrease nearly one-third of TB mortality (26). Hence, it is strongly recommended for all diagnosed TB patients to be referred to quit smoking clinics for smoking cessation, and smoking cessation should be included in the standard TB management guidelines to further reduce this public health burden (27).

Absence of BCG scar also had higher odds of mortality (aHR=1.31, 95% CI: 1.13–1.51). There is global evidence that BCG can prevent TB infection, reduce TB mortality, TB meningitis, and disseminate TB (28, 29). In this study, a total of 360 patients (42.8%) had an absence of BCG scar among the adult TB death patients. In Malaysia, the national BCG vaccination programme was launched in 1961 and was routinely administered to newborns at birth (30). A further analysis showed that, 33.3% (3056 patients) had an absence of BCG scar including 54.9% (1677 patients) were immigrants. This highlights the need to organize an outreach programme to increase awareness and knowledge about BCG vaccination.

It was discovered that extrapulmonary TB (aHR=1.87, 95% CI: 1.45-2.42) and both PTB and extra PTB (aHR=1.79, 95% CI: 1.34–2.39); moderately advanced CXR (aHR=2.10, 95% CI: 1.50–2.94) and advanced CXR (aHR=4.67, 95% CI: 3.17–6.86) readings were correlated with TB death. These conclusions were consistent with two earlier national studies by Keng (11) and Liew (31). These results suggest that delaying TB diagnosis and treatment might result in rapid deterioration, ending in mortality.

In comparison to HIV-negative individuals, five times as many people died when they had both TB and HIV co-infection (aHR=5.31, 95% CI: 3.90–7.22). This result was in agreement with research from Tanzania (16), Argentina (32), Netherlands (33), and a local study (4). A study in Uzbekistan (34) showed that around 80% of patients with TB-HIV co-infection could achieve successful treatment outcomes with proper follow-up and management. Hence, special follow-ups for patients with TB-HIV co-infection are needed to reduce TB mortality in the adult patients. To lessen the combined impact of TB and HIV co-infection, WHO has advised various stakeholders and provided policy suggestions on how to carry out joint nation-wide TB and HIV initiatives (35). In Sabah, the HIV adherent programme is managed by the Infectious Disease (ID) Clinic to improve treatment outcomes among PLWH. In this programme, patients are given regular and frequent follow-up dates. This ensures that they strictly adhere to their HIV treatment. If a patient is lost to treatment or appointment follow up, outreach personnel from Non-Government Organizations (NGOs) such as Sabah AIDS Support Services Association (KASIH) aid in tracing patients and personally contact and counsel the patient to follow their treatment schedule. Besides that, counselling is also conducted by a trained counsellor. These efforts help the patient adhere to their HIV treatment and indirectly help them with patients in remaining with their TB treatments too. Sabah Anti Tuberculosis Association (SABATA) periodically provides financial assistance to TB patients to ensure they can attend follow-up appointments at TB clinics. To immunise the missing vaccination population, SABATA also occasionally organises outreach programmes such as the BCG Vaccination Programme. The initiatives have been beneficial in reducing unsuccessful treatment outcomes including TB deaths.

A previous national study reported that passive case detection (PCD) was related to any-cause mortality cause by TB (11). However, our research demonstrated that PCD was not associated with TB death. Based on our results, there was no significant difference between the detection methods, either PCD or ACD, with any-cause mortality cause by TB in Sabah. The ACD programme was recommended by the WHO for case detection and early treatment initiation to effectively cure the disease and prevent disease spread (37). The key to controlling transmission and reducing incidence of TB disease is case detection and effective treatment (36). WHO states that the purpose of ACD is to find TB patients as well as to determine who qualifies for TB preventive treatment (TPT). Besides that, ACD not only reduces the cost of TB diagnosis and treatment, but also reduces the cost for patients seeking medication (37). It is also highly cost-effective when the right cohort is selected for the intervention (37). Thus, it is suggested that every district in Sabah implements the ACD interventions in identified hotspots to prevent delayed diagnosis and treatment. Consequently, unsuccessful treatment outcomes such as TB mortality can be reduced.

The use of retrospective secondary data from MyTB as a research tool was one of the study's limitations. Important variables were unavailable in the database, such as employment status, occupation, family income, alcohol consumption, drug abuse, and malnutrition

status. We suggest these variables be routinely entered into the MyTB database to conduct more effective TB control programmes in the future.

CONCLUSION

It is essential to identify the factors influencing mortality among TB patients so that suitable strategies and interventions can be developed to meet the End TB Strategy's objective of 95% mortality reduction by 2035. To lower the TB mortality rate in adult patients, special follow-ups are required for older patients and cases of TB-HIV co-infection. Early diagnosis and treatment are crucial to diminish the mortality rate of TB in adult patients.

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