Seven-Year Survival and Prognostic Factors for Pulmonary Tuberculosis Patients at Tertiary Care Centers in Kedah, Malaysia

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Abstract

Objective: Tuberculosis (TB) is a major public health concern globally. This study aimed to evaluate the survival and the prognostic factors of TB patients after the diagnosis of TB at two tertiary centers in Kedah, Malaysia.

Methods: This was a retrospective cohort study conducted at the two public tertiary centers. All adult patients above 18 years who were first clinically diagnosed with TB and hospitalized between January 2008 and December 2011 were included. The Kaplan-Meier survival analysis was applied to estimate the survival probabilities of TB patients at 7-years after diagnosis, and the comparison of survival between subgroups in relation to the variable was evaluated using the log-rank test. Cox proportional hazards regression analysis was used to determine the prognostic factors of the patients

Results: 491 patients were diagnosed with pulmonary TB during this period with mean age 46.9 years old. The most common comorbidity was DM (27.7%), HIV infection (7.5%) and hypertension (4.9%). The 7-year survival observed in the study population was 65.5% (95% CI 61.4-69.8). The median survival time following the diagnosis of TB was 11.9 years. Those having cancer have significantly five times higher risk of dying. The risk of death from TB was approximately 4.5 times among those age between 40-49 and is even higher among patient in the age group of 70 and older.

Conclusions: The findings enable the estimation of the long-term TB survival after first diagnosed and predictors of death among local population could provide opportunities for policy makers to estimate the burden of TB infection.

Introduction

Tuberculosis (TB) is a major public health concern globally and has become one of the leading causes of mortality. Affecting most parts of the world, the incidence of TB was reported to be higher in South-East Asia, followed by the Africa and the Western Pacific region [1]. While various strategies are implemented to combat TB, its mortality remains high. According to the latest Global Tuberculosis Report, approximately 10 million individuals are currently living with TB. To date, approximately 1.2 million non-HIV-infected and 251,000 HIV-infected patients had lost their lives to TB [2].

The WHO classifies Malaysia as a country with an intermediate burden of TB, based on an estimated incidence of 92 cases per 100 000. In the year 2018 alone, Malaysia recorded a TB-related mortality of 4.9 per 100 000 [12]. From the years 2000 to 2015, the TB mortality rate narrowly ranged between 4.5 to 5.5 per 100,000 [3].

The factors commonly linked to the poor prognosis of TB patients are their socio-demographic characteristics, including age, sex, and education levels; immunosuppression due to many reasons, such as HIV infection; and underlying comorbidities, such as Diabetes Mellitus (DM) and hypertension [4-7]. Besides, living in rural areas, tobacco smoking, and alcohol consumption were shown to have accelerated the progression of TB [8-10].

While Kedah emerges as one of the states with the highest mortality of TB in Malaysia [3], the region-specific information regarding the disease is still scarce. Although a few studies reported the survival of TB patients in the country, they only focused on certain geographical regions and subgroups of TB patients, such as HIV-infected patients and healthcare workers. Also, they have been limited studies which overlooked the long-term outcomes in patients registered with TB in this region. Hence, it is of our interest to conduct this study in obtaining the baseline knowledge on the long-term survival and death in TB patients who were treated within the routine health services in Malaysia.

Therefore, this study aimed to evaluate the survival and the prognostic factors of TB patients after the diagnosis of TB at two tertiary centers in Kedah, Malaysia.

Methods

This was a retrospective cohort study conducted at the two public tertiary centers (Hospital Sultan Abdul Halim and Hospital Sultanah Bahiyah) in Kedah. The study population was all adult patients above 18 years of age, who were first diagnosed with TB and hospitalized between the years January 2008 and December 2011. Only the patients who were never treated for TB or did not take anti-TB drugs for more than a month were included [11]. Those with extra-pulmonary or multidrug-resistant TB were excluded. The conduct of the study was approved by the Medical Research Ethics Committee under the Ministry of Health Malaysia (NMRR-11-1151-9233).

Patient

All TB cases in this study were clinically diagnosed based on the following conditions as recommended by the MOH: i) the acid-fast bacilli smear-positive sputum, ii) the presence of lesions in apical and posterior segments of upper or lower lobes of the lung confirmed by the chest X-ray, and iii) a reading of 10 mm or more in diameter for the Mantoux test [12].

Data collection

The clinical records of all patients were examined. The information on their age at the time of hospitalization, gender and ethnicity was gathered. Their comorbidities, including DM, hypertension, ischemic heart disease, chronic renal disease, HIV infection and cancer were also recorded. Their history of high-risk behaviors, such as cigarette smoking, alcohol consumption and drug abuse in one year before the diagnosis, were also explored and confirmed through self-reporting. The survival of a patient was referred to the period between the date of his TB diagnosis and that of his death, and deaths identified from NRD database were treated as events of interest. We also examined the clinical notes of all hospitalized patients and retrieved relevant information as described below. Patient's outcome (either alive or death) at seven years were ascertained by cross-checking the data with the National Registration Department (NRD), Ministry of Home Affairs Malaysia.

Statistical analysis

The data analysis was performed using the R statistical software version 3.5.2 [13]. The demographic characteristic of patients, the presence of comorbidities, and their history of high-risk behaviours were summarized as frequencies. The Kaplan-Meier survival analysis was applied to estimate the survival probabilities of TB patients at 7-years after diagnosis, and the comparison of survival between subgroups in relation to the variable was evaluated using the log-rank test. A p-values<0.05 was considered statistically significant [14]. Cox proportional hazards regression analysis was used to determine the prognostic factors of the patients, and the findings were summarized as hazard ratios (HRs) and their corresponding 95% Confidence Intervals (CIs). Variables showing a p-value ≤0.2 in the univariable analysis were subsequently explored in the stepwise multivariable analysis. The likelihood ratio test was used to verify the significance of the parameters of the initial and final models, and Schoenfeld residuals test was used to assess proportionality of Cox models.

Results

Between the years 2008 and 2011, 491 patients were diagnosed with pulmonary TB and hospitalized. Their mean age at the time of diagnosis was 46.9 years, and more than a quarter of them were in the age group of 40-59 years. They were mainly male (70.7%) and of Malay ethnicity (69.8%). The most common comorbidity was DM (27.7%), followed by HIV infection (7.5%) and hypertension (4.9%). Only a small number of them had cancer. In term of risky behaviours, 44.2% patients were cigarette smoker, 11.8% patients were involved in drug abuse and 4.5% patients were alcohol drinker. From January 2012 until December 2018, 37.07% deaths were registered and of this, 84 deaths were due to respiratory-related causes (Table 1).

The median survival time following the diagnosis of TB was 11.9 years (Figure 1). The 7-year survival observed in the study population was 65.5% (95% CI 61.4-69.8). A better survival was observed in those who were in the age groups of 20-29 (83.7%; 95% CI 76.0-92.2) and 40-49 (71.0%, 95% CI 62.3-80.9) years, did not have DM (74.6%; 95% CI 70.2-79.3) or hypertension (66.9%; 95% CI 62.7-71.4) or cancer (66.1%; 95%CI 62.0-70.5).

Table 2 and 3 show the findings of the univariable and multivariable Cox proportional hazards regression analysis. Seven variables yielded a p- value ≤0.20 in the univariable analysis. However, only two variables were shown to be statistically sig-

nificant in the final model. Being above 40 years of age and having cancer at the time of diagnosis were identified as the independent prognostic factors for the TB patients. Those having cancer at the time TB was diagnosed have significantly five times higher risk of dying as compared to those without cancer (Table 3). Likewise, older age groups have higher risk of dying compared to younger age group. The risk of death from TB was approximately 4.5 times among those age between 40-49 and is even higher among patient in the age group of 70 and older (HR= 14.6, 95% CI 3.44-61.71).

Table 1: Demographic characteristics of patient diagnosed with TB at tertiary centres in Kedah and 7-year survival rate across subgroups.

Characteristic		Total, n (%)		7-years survival (%)	95% CI	p value*
Overall		491	100.0	65.5	61.4 - 69.8	
Age group at diagnosis						<0.001
	<20	23	(4.7)	91.3	80.5-100.0	
	20-29	81	(16.5)	83.7	76.0 - 92.2	
	30-39	69	(14.1)	75.4	65.9-86.2	
	40-49	95	(19.4)	71.0	62.3 - 80.9	
	50-59	95	(19.4)	62.2	52.9 - 73.1	
	60-69	73	(14.9)	45.6	35.3 - 58.9	
	70+	55	(11.2)	29.5	19.1 - 45.4	
Gender						0.083
	Female	144	(29.3)	69.9	62.5 - 78.2	
	Male	347	(70.7)	63.0	58.1 - 68.4	
Ethnicity						0.494
	Indian	39	(7.9)	65.9	51.2 - 84.8	
	Chinese	92	(18.7)	68.5	59.3 - 79.2	
	Malay	347	(70.7)	62.7	57.8 - 68.1	
	Others	13	(2.7)	72.5	49.5 - 99.8	
Diabetes Mellitus						<0.001
	No	355	(72.3)	74.6	70.2 - 79.3	
	Yes	136	(27.7)	40.4	32.9 - 49.8	
Hypertension						<0.001
	No	467	(95.1)	66.9	62.7 - 71.4	
	Yes	24	(4.9)	29.1	14.5 - 58.3	
Ischaemic Heart Disease						0.527
	No	483	(98.4)	65.7	61.6 - 70.1	
	Yes	8	(1.6)	46.9	21.5 - 99.8	
Chronic Renal Failure						0.107
	No	483	(98.4)	65.5	61.4 - 69.9	
	Yes	8	(1.6)	31.2	7.1 - 99.8	
HIV status						0.013
	Negative	454	(92.5)	64.0	59.7 - 68.6	
	Positive	37	(7.5)	83.8	72.7 - 96.5	
Presence of cancer						<0.001
	No	485	(98.8)	66.1	62.0 - 70.5	
	Yes	6	(1.2)	16.7	2.8 - 99.7	

Cigarette smoking						0.371
	No	274	(55.8)	66.8	61.4 - 72.7	
	Yes	217	(44.2)	63.0	56.9 - 69.9	
Alcohol consumption						0.801
	No	469	(95.5)	65.3	61.1 - 69.8	
	Yes	22	(4.5)	68.2	51.3-90.7	
Drug abuse						0.752
	No	433	(88.2)	65.7	61.3 - 70.4	
	Yes	58	(11.8)	59.9	47.6 - 75.2	

*Log rank test for each variable.

Table 2: Univariable Cox regression analyses of socio-demographic characteristics, comorbidities and risky behaviours of TB patients.

Variables	Survived (N=309), n (%)		Died (N=182), n (%)		Crude HR (95% CI HR)		X² stat. (df)	p value†
Age group							71.27 (6)	<0.001
<20	21	(6.8)	2	(1.1)	1			
20-29	68	(22.0)	14	(7.7)	2.15	(0.48, 9.70)		
30-39	52	(16.8)	17	(9.3)	3.67	(0.83, 16.16)		
40-49	65	(21.0)	30	(16.5)	4.37	(1.02, 18.65)		
50-59	55	(17.8)	40	(22.0)	6.34	(1.51, 26.61)		
60-69	32	(10.4)	42	(23.1)	9.93	(2.35, 41.89)		
70+	16	(5.2)	41	(22.5)	14.63	(3.46, 61.90)		
Gender							3.12 (1)	0.077
Female	100	(32.4)	44	(24.2)	1			
Male	209	(67.6)	138	(75.8)	1.35	(0.96, 1.90)		
Ethnicity							2.63 (3)	0.452
Indian	25	(8.1)	14	(7.7)	1			
Chinese	62	(20.1)	30	(16.5)	0.88	(0.47, 1.67)		
Malay	212	(68.6)	135	(74.2)	1.11	(0.64, 1.93)		
Others	10	(3.2)	3	(1.6)	0.58	(0.17, 2.03)		
Diabetes Mellitus							48.72 (1)	<0.001
No	258	(83.5)	97	(53.3)	1			
Yes	51	(16.5)	85	(46.7)	2.93	(2.20, 3.93)		
Hypertension							8.29 (1)	0.001
No	301	(97.4)	166	(91.2)	1			
Yes	8	(2.6)	16	(8.8)	2.33	(1.39, 3.89)		
Ischaemic Heart Disease							0.40 (1)	0.527
No	305	(98.7)	178	(97.8)	1			
Yes	4	1.3)	4	(2.2)	1.4	(0.52, 3.77)		
Chronic Renal Failure							2.01 (1)	0.153
No	306	(98.4)	177	(97.3)	1			
Yes	3	(1.0)	5	(2.7)	2.05	(0.84, 4.98)		
HIV status							7.95 (1)	0.005
Negative	278	(90.0)	176	(96.7)	1			

Positive	31	(10.0)	6	(3.3)	0.37	(0.16, 0.83)			
Presence of cancer								9.89 (1)	0.002
No	308	(99.7)	177	(97.3)	1				
Yes	1	(0.3)	5	(2.7)	6.34	(2.59, 15.55)			
Cigarette smoking								0.75 (1)	0.386
No	177	(57.3)	97	(53.3)	1				
Yes	132	(42.7)	85	(46.7)	1.14	(0.85, 1.52)			
Alcohol drinker								0.1 (1)	0.823
No	294	(95.1)	175	(96.2)	1				
Yes	15	(4.9)	7	(3.8)	0.92	(0.43, 1.96)			
Drug abuse								0.07 (1)	0.791
No	273	(88.3)	160	(87.9)	1				
Yes	36	(11.7)	22	(12.1)	1.06	(0.68, 1.66)			

Table 3: Independent prognostic factors of TB.

Variables	Adj HR*	(95% CI HR)	p value[†]
Age group			0.004
<20	1		
20-29	2.16	(0.48, 9.77)	0.318 [‡]
30-39	3.60	(0.82, 15.93)	0.091 [‡]
40-49	4.39	(1.03, 18.78)	0.046 [‡]
50-59	6.09	(1.45, 25.63)	0.014 [‡]
60-69	9.68	(2.29, 40.91)	0.002 [‡]
70+	14.56	(3.44, 61.71)	<0.001 [‡]
Presence of cancer			
No	1		
Yes	5.13	(2.07, 12.71)	<0.001

Adj, adjusted; HR, hazard ratio; adjusted hazard ratio; CI, confidence interval

† = Likelihood ratio test, ‡ = Z test

*adjusted for gender, DM, hypertension, chronic renal failure and HIV status.

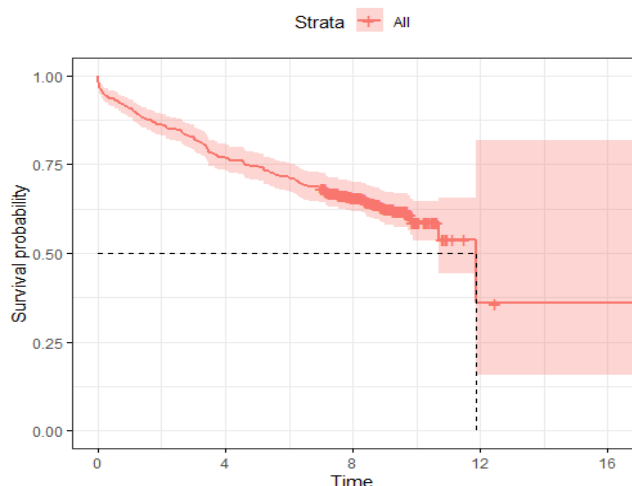**Figure 1:** Kaplan-Meier survival curve of TB patients at two tertiary centres in Kedah (n= 491).

Discussion

This study evaluated the long-term outcome up to 7-years among pulmonary TB patients and the roles of several factors on their survival. The findings are deemed to give an insight on the the long-term survival and death's baseline knowledge among TB patients receiving standard treatment care in Malaysia. DM, HIV infection and hypertension were the most frequent comorbidities reported among the studied patients. An overall seven-year survival was observed in 65.5% of the cases. In addition, older age group at TB diagnosis and presence of cancer were the main predictors associated with lower TB survival.

In Malaysia, study evaluating the survivability of TB for a period longer than five years post-diagnosis are limited. In a study by Ismail and Bulgiba focusing on a cohort of TB-HIV coinfection, the survival rate after one year of TB diagnosis was recorded to be 78.8% [15]. In another local study using registry-based secondary data focusing of health care worker infected with TB, 23 deaths have been reported among 944 registered cases [10].

Age is shown to be an important prognostic factors for the survival of TB patients in this study. Patients above 40 years of age had a higher risk of mortality as compared with their younger counterparts, and the risk steadily increased with age. This finding would be expected, as aging increases vulnerability to a wide range of adverse health outcomes, limited access to health care, and a poorer commitment to treatment. Similar findings were reported in other studies. In a case-control study in Pakistan, more deaths were also recorded in the TB patients aged above 40 years [16]. In addition, a study from the US found that the TB patients aged above 65 years demonstrated an 8-time higher risk of mortality [17].

This is also the first study suggesting an association between cancer and the survival of TB patients in Malaysia [18]. It was previously postulated that several malignancy such as cancer of the lung, prostate, larynx and pancreas were significant risk factors for TB death [19,20]. Furthermore, malnutrition, deterioration of immunity due to local or systemic effects of cancer, and the effects of chemo therapy or radiotherapy are all likely to influence the TB reactivation [21]. The advanced stage of cancer itself may also contribute to a higher risk of death. Nevertheless, the information on cancer staging was not available at this point for further analysis.

Unexpectedly, high-risk behaviours, such as cigarette smoking, alcohol consumption and drug abuse, were not significantly associated with a poorer survival. This is different from other previous studies where these factors were among the contributing factors to TB mortality [22-24]. Similar negative findings were also obtained for DM, hypertension, and HIV infection. Nevertheless, the findings of the high proportion of patients with multiple morbidities implies the burden of the public health system in Malaysia. While both communicable and communicable diseases are equally common in Malaysia, there is a need to work toward an integrated management of these diseases as recommended by the WHO [25]. Such an approach embraces the simultaneous screening, treatment, and monitoring of multiple diseases. In addition, Marais et al. also recommended a few control measures to manage high-risk behaviours among TB patient to improve their clinical outcome through public health and advocacy campaigns, pragmatic screening including regular screening for TB on DM and HIV patient as well as patients with TB tested routinely for DM and HIV, linking smokers diagnosed with TB to smoking cessation programmes, screening for harmful drinking and alcohol misuse in TB patients, and improve health literacy among publics [26].

There are few limitations to this study. First, it is limited by its observational study design. Some of the factors potentially associated with the survival of TB patients, such as their adherence to anti-TB treatment, the duration of illness prior to treatment, and the site of TB infection were not assessed and not documented in this study.

In conclusion, the findings of this research enable the estimation of the long-term TB survival after first diagnosed, which is not well explored in Malaysia. A better understanding of the predictors of death among local population could provide opportunities for policy makers to estimate the burden of TB infection; thus, enabling informed decisions on priorities. Efficient integration in the management of TB with those of non-communicable and communicable diseases should be a priority in local health setting.

Acknowledgement

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