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The Median Time to Develop Recurrent Tuberculosis at a Tertiary Hospital in Kota Bharu, Kelantan, Malaysia

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ABSTRACT

This study has the intention to determine the median time to develop recurrent tuberculosis [TB] in TB patients attending the Chest Clinic at Hospital Raja Perempuan Zainab II [HRPZ II], Kelantan, Malaysia. Records of 114 recurrent TB patients from 1/1/2003-31/12/2009 were analyzed. Kaplan-Meier analysis was used to examine the median time for recurrence of TB. The overall median time to develop TB recurrence in registered TB recurrent patients was six months [95%CI: 4.58, 7.42] after the previous episode. It was found that recipients of Streptomycin (S), Isoniazid (H) and Rifampicin (R) twice weekly ($S_2H_2R_2$) drug regimen [p=0.026] or daily HR drug regimen [p=0.049] during the continuation phase took a longer duration to develop recurrent TB than non-recipients of these medicines by Kaplan-Meier analysis. Moreover, there also existed a significant time difference [P = 0.006] between the defaulters and non-defaulters of treatment to develop recurrent TB. Patients should take the complete course of therapy, to reduce recurrent TB infection. The drug regimens must contain the two most potent first line drugs Isoniazid [H] and Rifampicin [R] during the continuation phase.

INTRODUCTION

Tuberculosis (TB) remain as a potential killer for mankind killer from the prehistoric time (Daniel, 2006). Evidence suggest that TB has been present for at least 15,000 years. It has been reported that TB affecting humans bones dated back to 2400-3400 BC (Iseman, 2013). TB was epidemics in many countries which includes "Europe and North America in 18th and 19th centuries" and then subsided with the invention of streptomycin and isoniazid (Daniel, 2006). Consequently, TB declined slowly in the developed countries. TB has reappeared as a potential killer again with the emergence of HIV and AIDS (Daniel, 2006). "TB is, thus, the leading cause of mortality in people with HIV/AIDS, and HIV contributes to a substantial proportion of tuberculosis deaths" (Chaisson & Churchyard, 2010). Globally, every year more than 8-9 million people are newly infected (Uddin *et al.*, 2006). Therefore, in 1995, the World Health Organization launched the Directly Observed Treatment Short-course (DOTS) strategy for control of TB (WHO, 2006). Recurrence of TB is an important indicator to evaluate the current TB control program. Relapses are the primary cause of TB recurrences (Millet *et al.*, 2013). "True relapse can only occur when TB persists after treatment despite apparent cure" and mainly due to inadequate treatment, either due to irrational combination of medicines and duration of treatment (Lambert *et al.*, 2003).

Recurrences can also occur with a different strain (Lambert *et al.*, 2003; Fine & Small, 1999; Van Rie *et al.*, 1999). Globally, the total number of re-treated cases under DOTS programs in 2008 was 775 403 (WHO, 2010). Multple studies suggest that recurrent TB is significantly related with drug-resistance and has lower cure rates. Recurrent TB is a major clinical problem to cure and control (Cox *et al.*, 2006; El Sahly *et al.*, 2004; Mallory *et al.*, 2004; Panjabi *et al.*, 2007).

The recurrent TB are more expensive to treat and consume major portion national budgets. Only 61% of registered recurrent TB successfully treated in Malaysia (WHO, 2013).

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According to the Infectious Disease Act, 342, 1988, of Malaysia all diagnosed new case of TB should be within one of diagnosis (The Ministry of Health, 2012). The number of re-treated of TB cases in 2009 was 1181 in Malaysia.

Among these 1181 re-treated patients 36% 2%, 16%, and 46% were due to relapse, recurrences after failure, recurrences after default, and others respectively (WHO, 2013). The current study is conducted to determine the median time to develop recurrent TB in patients.

There are only a few studies has been conducted in this regard. Therefore, the findings of the current study will contribute more data about the risk of recurrent TB.

MATERIALS and METHODS

Study Design

The study was conducted by retrospective record review to address the median time to develop recurrent TB patients.

Study Participants

18 years old and above TB patients who must have taken at least one month previous TB therapy. **ii**. Those who received re-treatment therapy for TB disease. TB in these patients was diagnosed and treated by the clinical, radiological and/or bacteriological evidences according to the control and management of TB guidelines of the Ministry of Health, Malaysia (The Ministry of Health, 2012).

Although, the calculated sample size was 120, there was a scantiness of patients. Therefore, no sampling method was applied. 114 patients who fulfilled the inclusion and exclusion criteria were incorporated in this study. The patients who are below 18 years and do not receive anti-tubercular treatment and re-treatment were excluded.

Study Area

The study was conducted at the Chest Clinic in 920-bedded HRPZ II Hospital in Kota Bharu having estimated the population of 577 301 in 2009.

Data Collection

Researchers with the help of the staff retrieved the data of recurrent cases registered at the Chest Clinic of HRPZ II, by using the proforma documents from June to July 2010.

Case Definitions

The case definitions were used according to the Malaysia practice guideline for the control and management of TB except those for defaulter case and recurrent TB case (The Ministry of Health, 2012). A patient who took the previously anti-tubercular therapy for at least one month and then missed more than six doses of daily treatment or more than two doses of biweekly treatment was considered as a defaulter case. A patient who had the previous history of TB disease regardless of pulmonary involvement and sputum smear results and has developed another episode after complete treatment or treatment failure or after default was defined as a relapse or recurrent or re-treatment case. The survival time was referred to re-take another round of treatment with a TB patient.

Statistical Analysis

Data entry and analysis were performed by using SPSS software version 18. The median survival time with 95% confidence intervals for recurrence the TB incidents was determined by the use of the Kaplan-Meier analysis. Categorical independent variables with two levels. The *P* value was set at < 0.05.

Regarding variables with more than two levels, pair-wise comparison result. A *P* value was compared with Bonferroni-corrected alpha level.

Ethical Approval

This study had obtained ethical approvals from Universiti Sains Malaysia [USMKK/PPP/JEPeM {224.4.} (2.7), Date: 29 July 2010] and National Medical Research Registry [NMRR: 6300S1, Date: July 20, 2010] from the Ministry of Health, Malaysia.

RESULTS

There were altogether 363 recurrent TB cases at HRPZ II from 01/01/2003-31/12/2009. However, only 114 records were retrieved (Table 1). The remaining cases had inadequate information and official papers were damaged. Among 114 records, 93.86% had only one previous episode, and the other 6.14% had between 2-3 episodes of TB. Those with more than 1 previous TB infection, data of the most recent infection was collected. The survival time was "duration between the last date of previous therapy and the first date of taking treatment for the next infection."

All patients received the intensive phase of TB treatment during which some patients took more than one drug regimen. 21 patients took SHRZ regimen, 84 patients received EHRZ regimen, and 12 patients took HRZ regimen. The median (IQR) duration to receive the treatment for SHRZ, EHRZ, and HRZ regimens were 2.0 (0.0), 2.0 (1.0), 2 (1.8) months respectively. Thirty-six patients (31.6%) did not take the treatment for the continuing phase, and during that period, some patients had to take more than one treatment regimen as in the previous stage.

The H_2R_2 regimen was given to 26 patients, 14 people got $S_2H_2R_2$ regimen, 40 people got HR regimen, and 7 people took the other drug regimens. The (IQR) months to take the treatment for H_2R_2, $S_2H_2R_2$, HR and other drug regimens were 4.5 (2.3), 4.0 (2.3), 5.5 (5.0) and 4.0 (7.0) correspondingly. With regard to treatment compliance, 60 patients (52.6%) defaulted and did not take the complete course of therapy.

Table 1: Median Time to get recurrent TB according to sociodemographic features (n=114).

Sociodemographic Characteristics		Frequency (%)		Median Time Months (95% CI)		*p*-value
Gender	Male	95	(83.3)	6	(4.21, 7.79)	0.268
	Female	19	(16.7)	6	(3.16, 8.84)	
Age	< 40	64	(56.1)	6	(4.19, 7.81)	0.954
	≥ 40	50	(43.9)	5	(2.69, 7.31)	
Marital Status	Single	41	(36.0)	5	(2.49, 7.51)	0.340
	Married	53	(46.5)	7	(3.96, 10.04)	0.112
	Divorced	20	(17.5)	4	(1.81, 6.19)	
Race	Malay	110	(96.5)	5	(3.60, 6.40)	0.339
	Chinese	3	(2.6)	12	(0.00, 24.80)	0.449
	Siamese	1	(0.9)	18	(- , -)*	
DM	Absent	101	(88.6)	5	(3.36, 6.64)	0.895
	Present	13	(11.4)	6	(3.65, 8.35)	
Liver Disease	Absent	113	(99.1)	6	(4.58, 7.42)	0.665
	Present	1	(0.9)	13	(- , -)*	
Smoking	Absent	42	(36.8)	6	(3.89, 8.12)	0.525
	Present	72	(63.2)	5	(3.08, 6.92)	
Alcohol dependent	Absent	102	(89.5)	6	(4.26, 7.74)	0.866
	Present	12	(10.5)	5	(3.30, 6.70)	
Drug Addict	Absent	59	(51.8)	7	(4.95, 9.05)	0.145
	Present	55	(48.2)	5	(3.70, 6.30)	
HIV	Absent	45	(39.5)	7	(4.82, 9.18)	0.300
	Present	69	(60.5)	5	(2.97, 7.03)	
Other diseases	Absent	98	(86.0)	5	(3.24, 6.76)	0.967
	Present	16	(14.0)	7	(4.06, 9.94)	

*95% Confidence Interval could not be determined.
Log-Rank test was applied.

Table 2: Median Time to get recurrent TB according to Laboratory and Radiographic characteristics (n = 114).

Laboratory and radiographic Characteristics		Frequency (%)		Median Time Months (95% CI)		*P*-value
Value of ESR	< 104	42	(36.8)	7	(4.63, 9.37)	0.405
	≥ 104	41	(36.0)	5	(2.31, 7.69)	
Not done or missing data		31	(27.2)			
BCG scar	Absent	21	(18.4)	6	(3.01, 8.99)	0.533
	Present	92	(80.7)	5	(3.43, 6.57)	
	Missing data		(0.9)			
Tuberculin test results	Negative	23	(20.2)	3	(2.33, 3.67)	0.101
	Positive	16	(14.0)	12	(9.47, 14.53)	
Not done or missing data		75	(65.8)			
Sputum culture results	Negative	8	(7.0)	5	(3.66, 6.34)	0.334
	Positive	12	(10.5)	5	(3.33, 6.67)	
Not done or missing data		94	(82.5)			
First time sputum smear results	Negative	33	(28.9)	9	(5.25, 12.57)	0.491
	Positive	66	(57.9)	5	(3.88, 6.12)	
Not done or missing data		15	(13.2)			
Amount of sputum smear positivity for 66 patients	1-49/3L(+)	26	(39.4)	5	(3.03, 6.98)	
	50/>1L(++)	8	(12.1)	4	(0.00, 10.93)	0.906
	11-49/L(+++)	2	(3.0)	5	(- , -)*	0.626
	>50/L(++++)	26	(39.4)	4	(2.34, 5.66)	0.197
	Missing data	4	(6.1)			
X-ray results	No lesion	18	(15.8)	3	(0.62, 5.38)	
	Minimal lesion	62	(54.4)	7	(4.63, 9.37)	0.696
Moderately advanced lesion		27	(23.7)	4	(2.30, 5.70)	0.500
Far advanced lesion		4	(3.5)	9	(1.16, 16.84)	0.180
	Missing data	3	(2.6)			

*95% Confidence Interval could not be determined.
Log-Rank test was applied.

The overall median developing time was 6 months [95% CI: 4.58, 7.42] for TB recurrence in patients of the current study (Figure 1). There were statistically significant differences [p= 0.026] found between the recipients and non-recipients of $S_2H_2R_2$ drug regimen, and also between the recipients and non-recipients of daily HR drug regimen [p=0.049] during the continuation phase of Kaplan-Meier analysis. Moreover, there was a considerable time difference (p=0.006) between defaulters and non-defaulters of treatment to get recurrent TB. The time to develop recurrent TB was statistically significant between defaulters and non-defaulters [Table 1, 2, 3 and Figure 2a, b, c].

Table 3: Median Time to recurrent TB according to the treatment regiments and compliance factors (n = 114).

Treatment and compliance factors		Frequency (%)		Median Time Months (95% CI)		*P*-value
In The Intensive Phase						
SHRZ Drug	Taken	21	(18.4)	7	(4.31, 9.69)	0.202
	Not taken	93	(81.6)	5	(3.43, 6.57)	
Duration of taking SHRZ regimen	≤ 2months	17	(14.9)	8	(5.35, 10.65)	0.659
	≥ 3 months	4	(3.5)	4	(0.00, 8.90)	
EHRZ Drug	Taken	84	(73.7)	5	(3.37, 6.63)	0.370
	Not taken	30	(26.3)	7	(3.78, 10.22)	
Duration of taking EHRZ regimen	≤ 2 months	52	(45.6)	5	(2.88, 7.12)	0.988
	≥ 3 months	32	(28.1)	5	(3.16, 6.84)	
HRZ Drug	Taken	12	(10.5)	5	(0.00, 12.92)	0.187
	Not taken	102	(89.5)	6	(4.52, 7.48)	
Duration of taking HRZ regimen	≤ 2 months	8	(7.0)	5	(0.00, 15.16)	0.391
	≥ 3 months	4	(3.5)	2	(- , -)*	
Other drug regimens	Taken	8	(7.0)	7	(0.00, 16.24)	0.189
	Not taken	106	(93.0)	5	(3.56, 6.44)	
Duration of taking other drug regimens	≤ 2 months	4	(3.5)	3	(- , -)*	0.784
	≥ 3 months	4	(3.5)	13	(7.91, 18.09)	
In The Continuation Phase						
H_2R_2 regimen	Taken	26	(22.8)	5	(3.03, 6.98)	0.414
	Not taken	88	(77.2)	6	(4.28, 7.72)	
Duration of taking H_2R_2 regimen	≤ 4 months	13	(11.4)	4	(2.24, 5.76)	0.605
	≥ 5 months	13	(11.4)	5	(2.65, 7.35)	
$S_2H_2R_2$regimen[a]	Taken	14	(12.3)	8	(2.50,13.50)	0.026
	Not taken	100	(87.7)	5	(3.37, 6.63)	
Duration of taking $S_2H_2R_2$ regimen	≤ 4 months	11	(9.6)	9	(2.53, 15.47)	0.572
	≥ 5 months	3	(2.6)	6	(0.00, 14.00)	
HR Daily Regimen [b]	Taken	40	(35.1)	8	(4.90,11.10)	0.049
	Not taken	74	(64.9)	4	(2.31, 5.69)	
Duration of taking HR regimen	≤ 4 months	16	(14.0)	5	(2.65, 7.35)	0.436
	≥ 5 months	24	(21.1)	9	(6.13, 11.87)	
Other drug regimens	Taken	7	(6.1)	7	(0.00, 17.27)	0.389
	Not taken	107	(93.9)	6	(4.56, 7.44)	
Duration of taking other drug regimen 2	≤ 4 months	4	(3.5)	8	(2.12, 13.88)	0.062
	≥ 5 months	3	(2.6)	3	(0.00, 6.20)	
Defaulter Status [c]	Non- defaulters	54	(47.4)	7	(3.80, 10.20)	0.006
	Defaulters	60	(52.6)	4	(2.48, 5.52)	

[s] Figure 2a, [t] Figure 2b, [u] Figure 2c , Streptomycin (S), Isoniazid (H), Rifampicin (R) and Pyrazinamide (Z) [SHRZ], Ethambutol (E), Isoniazid (H), Rifampicin (R) and Pyrazinamide (Z) [EHRZ], Isoniazid (H), Rifampicin (R) and Pyrazinamide (Z) [HRZ], Isoniazid (H) and Rifampicin (R) twice weekly [H2R2], Streptomycin (S), Isoniazid (H) and Rifampicin (R) twice weekly [S2H2R2], *95% Confidence Interval could not be determined. Kaplan-Meier Survival analysis and Log Rank Test was applied.

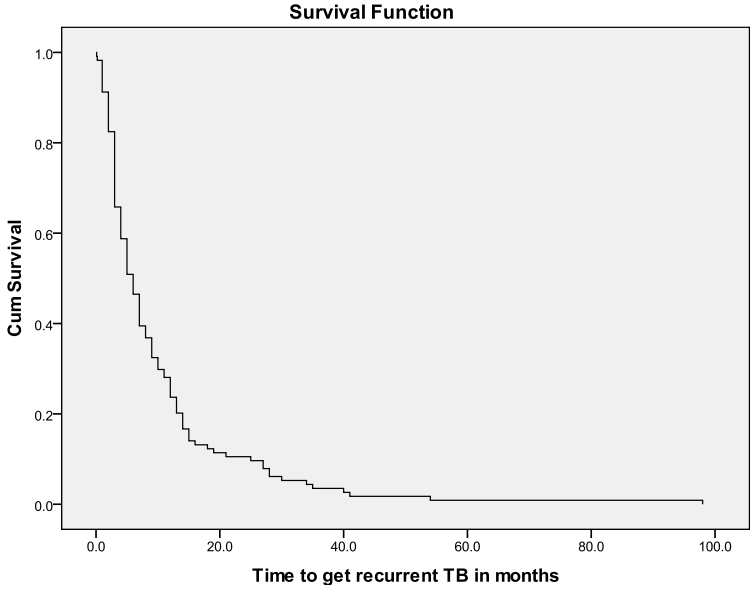

Fig. 1: Kaplan-Meier Survival Curve of Expressing the Probabilities of Getting Recurrent TB.

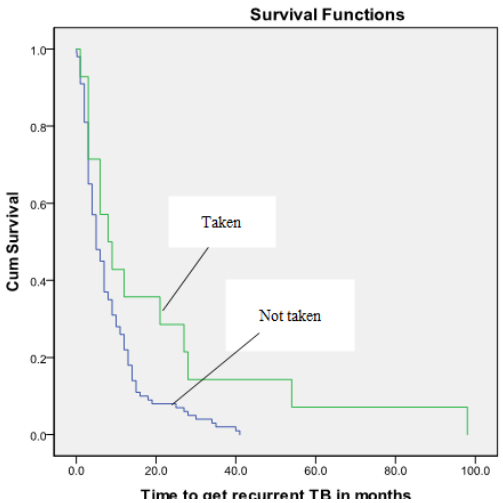

Fig. 2a: Kapalan-Meier Survival curve displaying the median time to get recurrent TB of recipients and non-recipients of $S_2H_2R_2$ drug regimen during the continuation phase.

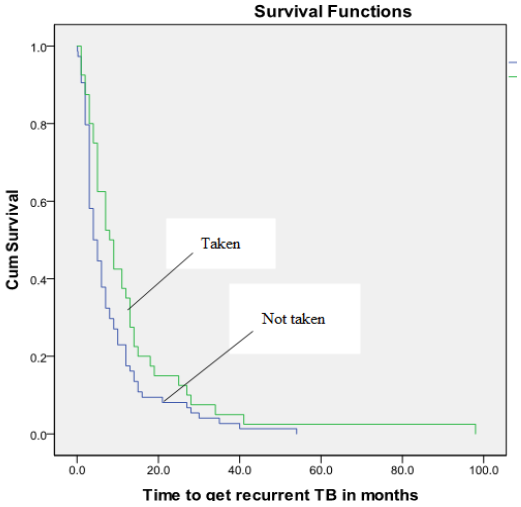

Fig. 2b: Kapalan-Meier Survival curve showing the median time to get recurrent TB of recipients and non-recipients of daily HR drug regimen during the continuation phase.

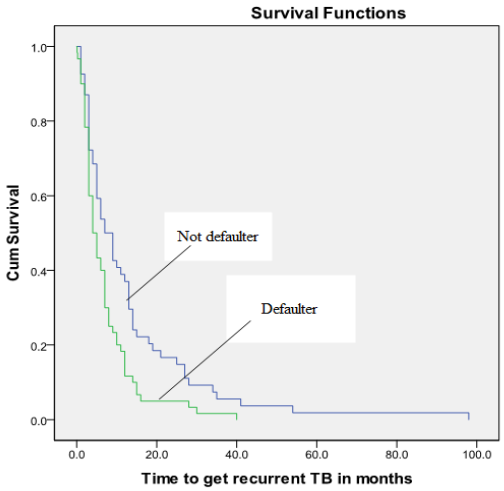

Fig. 2c: Kapalan-Meier Survival curve is presenting the median time to get recurrent TB of defaulters and non-defaulters of treatment.

DISCUSSION

This study found that the overall median time to develop recurrent TB was 6 months [95% CI: 4.58, 7.42] after the end of the previous disease episode. Various case definitions of recurrence of TB and diverse inclusion and exclusion criteria, as well as different studied variables, exist among various reports. Most of the previous studies were analyzed only on completely cured patients; whereas this study was done on a heterogeneous group constituting cured not only patients but also defaulters and treatment failure cases. One study in Uganda whose inclusion criteria is the same as this study reported that most instances [about 80%] had recurrent TB within 8 months of the previous disease episode (Anyama *et al.*, 2007). The analyses done only on cured patients, recurrent TB was found to occur within 6-9 months from the start of treatment (Driver *et al.*, 2001). Again, multiple studies reported that the majority of the cured cases had recurrences within 6 months after completely healed (Thomas *et al.*, 2005; Dholakia *et al*, 2000; TRC, 1997 and 1983; EABMRC, 1976). Therefore, TB clinicians and health care personnel should be more cautious about the risk of recurrent TB in less than one year after completion of anti-tubercular regimen. Recurrences could be consequences of the inappropriate treatment regimens, inadequate therapy attributable to poor or non-compliance with treatment (Yamagishi & Toyota, 2009; Kopanoff *et al.*, 1998). This study found that defaulters were found to have recurrent TB earlier than non-defaulters. Studies conducted in South Africa and Brazil also elucidated that the defaulters were found to experience higher recurrent TB (Golub *et al.*, 2008; Verver *et al.*, 2005). The patients having a history of default in the preceding episode are more likely to be defaulters in succeeding episodes also (Chandrasekaran *et al.*, 2006). Poor compliance with treatment resulting in unnecessary prolongation treatment duration, elevated risk of treatment failure, emergence of acquired drug resistance TB, and continue as open case, remains an obstacle to the accomplishment of a TB control program (Vijay *et al.*, 2010). Nowadays, TB clinicians recognized the importance of rifampicin in treating TB. Several studies proved that the better treatment outcomes came out with rifampicin containing regimen than

bacteriostatic Thiacetazone (T) (EABMRC, 1972 and 1977). The current study found that patients who received $S_2H_2R_2$ drug regimen or daily HR drug therapy during the continuation phase took a longer duration to get recurrent TB. The findings of the present work advocate the use of 2 first line anti-tubercular drugs: Isoniazid, and Rifampicin; in both initial and continuation phase. Recurrent TB is attributable to reactivation of the previous disease or re-infection with different strains of *M. Tuberculosis*. The relapse or endogenous reactivation results from low potent regimen or poor compliance even though treatment is completed (Korenromp *et al.*, 2003). On the contrary, exogenous re-infection is related to background TB incidence and HIV prevalence of a country (Cox *et al.*, 2006). One study report suggested that relapse mostly occurred within 6 months following the end of the previous treatment (Jasmer *et al.*, 2004) whereas incidence of exogenous re-infection escalated with the time interval between the end of therapy for the last episode and the start of taking treatment for subsequent one (Shen *et al.*, 2006). There is evidence that there is a relationship between strains of *M. Tuberculosis* and recurrent TB. Beijing strains are prevalent in Asia and North America, and they are mostly related to relapse of the previous infection (Burman *et al.*, 2009; Sun *et al.*, 2006). One study reported that strains of Beijing family were also widespread in West Malaysia but not in East Malaysia (Dale *et al.*, 1999). Consequently, the recurrent cases in this study could be consequences of relapse of the previous infection. Malaysia holds an intermediate burden of TB with a prevalence of 109 [47-173] cases per 100 000 population (WHO, 2013) and has 10.88 HIV incidence rate in 2009 (Ministry of Health, 2009). Current research has found that the accessibility and availability to use of DNA fingerprinting method is limited. Thus, our study cannot differentiate the underlying causes of recurrent TB in this studied area, and further research is necessary to investigate the epidemiology of recurrent TB.

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