

Effect of Smoking On Treatment Outcome Among Tuberculosis Patients In Malaysia; A Multicentre Study

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Abstract

Background : Smoking plays a key role in the development of tuberculosis (TB) infection and is also a predictor of poor TB treatment prognosis and outcomes.

Objectives: To determine the prevalence of smoking and to evaluate the TB treatment outcomes among TB patients. Methods : A multicenter retrospective study design was used in order to collect data of TB patients at four different states of Malaysia, namely Penang, Sabah, Sarawak and Selangor. Medical records of patients having TB admitted at the selected hospitals from January 2006 to March 2009 were included in the study. Medical records with incomplete data were excluded. A validated data collection form was used to note patient demographic and clinical data.

Results: Of all TB patients, the prevalence of smokers was 4313 (46.2%) while 5024 (53.8%) were non-smokers. Male gender (OR= 1.43, 95% CI 1.30-1.58), Chinese ethnicity (OR= 1.23, 95% CI 1.02-1.49), Sarawak indigenous ethnicity (OR= 0.74, 95% CI 0.58-0.95), urban residents (OR= 1.46, 95% CI 1.33-1.61), employed individuals (OR= 1.21, 95% CI 1.09-1.34), alcoholics (OR= 4.91, 95% CI 4.04-5.96), drug abusers (OR= 7.43, 95% CI 5.70-9.60) and presence of co-morbid condition (OR= 1.27, 95% CI 1.16-1.40) showed significant association with smoking habit. This study revealed that 3236 (75.0%) patients were successfully treated in smokers group while 4004 (79.7%) patients belong to non-smokers group. The proportion of death rate 283 (6.6%), defaulters 284 (6.6%) and treatment interruption 204 (4.7%) was high in smokers group.

Conclusions: Smoking had a strong influence on TB and is a major barrier towards treatment success (OR= 0.76, 95% CI 0.69-0.84, $p < 0.001$). Therefore, the findings point out that smoking cessations is an effective way to decrease treatment failure and drug resistance.

Introduction

Tuberculosis (TB) is the most prevalent communicable infectious disease on earth. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from this disease [1]. Smoking and tuberculosis remains two major health concerns worldwide. Some studies from China and India reported that smoking increases the severity and mortality rate of tuberculosis among patients who smoked [2, 3]. In 2010, WHO proposed that greater emphasis should be placed on preventing risk factors to TB [4]. Various studies had reported smoking as a risk factor in the development of TB in addition to cancer and coronary heart diseases [5, 6]. Tobacco associated death is projected to increase to 8.4 million by 2020 [7], along with TB, both represent major source of mortality and morbidity. Various components of the cigarette smoke such as free radicals of oxygen, acrolein, formaldehyde carbon and monoxide increases the oxidative stress in smokers, thus affects the bronchial mucosa and increases the threat of *Mycobacterium tuberculosis* infection [8]. Although TB prevalence in Malaysia has decreased enormously as compared with the early 1990s, but still Malaysia is ranked as intermediate burden country by the World Health

Organization (WHO) in 2013 with a prevalence rate of 101/100,000 and estimated mortality rate of 5.4/100,000 (excluding HIV) [1].

Despite of increasing evidences showing strong association between tobacco smoking and TB, there are only a few observational studies highlighting the association between smoking and TB treatment outcomes. Although previous studies had generally investigated the potential risk factors of poor TB treatment outcomes [9, 10]. In addition, the prevalence of smoking among TB patients is also not widely known. The present study was conducted to determine the incidence of smoking among TB patients in Malaysia and to investigate the impact of smoking on TB treatment outcomes.

Methodsology

Study design and location

A multicentre retrospective study was conducted among the TB patients in four states of Malaysia (Sabah, Sarawak, Selangor, and Penang), two representative states from west Malaysia and peninsular Malaysia, selected on the basis of highest burden of TB patients [12].

Inclusion & exclusion criteria

All TB patients (new, relapse, treatment failure and treatment defaulters) of both genders either with or with co-morbidity who were presented to the chest clinic from January 2006 to March 2009 were included in the study. Patients having incomplete medical record were excluded from the study. Disease classification, treatment protocol and treatment outcomes were defined as per WHO guidelines [1]. Sputum smear examinations were done at the end of two, four and six months of treatment in new cases and at the end of two, three, five and eight months in retreatment cases. Sputum examination was repeated again after one month if positive at two months of treatment. Treatment outcomes initially recorded as cured, treatment completed, defaulted, transferred out, expired and treatment continued were then classified into two categories successful and unsuccessful treatment. Cured and treatment-completed patients were placed in treatment successful category whereas the rest were placed in the category of unsuccessful treatment. Owing to the main objective of the study, patients were grouped into either ever smokers (those who currently smoke cigarettes at the time of diagnosis of TB or who had previously quit smoking) or never smokers (those who never smoked or who have smoked less than 100 cigarettes during their lifetime).

Data collection

A purposive developed pre-validated data collection form was used to collect demographic and clinical data. Demographic data included patients' gender, age, weight, ethnicity, residential area, marital status, smoking and alcohol consumption status. Clinical data collected included clinical presentation, serum

biochemistry results, nature of TB case [new, retreatment (failure, default and relapse)], site of TB infection (pulmonary or extra pulmonary) presence of co-morbid condition along with respective medications, results of sputum culture and treatment outcomes.

Statistical Analysis

The data were analysed using the Statistical Package for Social Sciences (SPSS), version 20.0 (SPSS, Inc., Chicago, IL, USA). Percentages and frequencies were used for categorical variables, while means \pm standard deviations were calculated for continuous variables. Univariate and multivariate binary regression analysis were used to examine whether tobacco smoking had contributed to poor treatment outcomes in TB patients. The results were presented as P-value, odd ratio (OR) and 95% confidence interval (CI). A P-value \leq 0.05 was considered statistically significant.

Ethical approval

Ethical Approval were taken from all relevant local authorities, and obtained from the Medical research Ethics Committee (MREC), registration number NMRR (National Medical Research Registration) # (2) KKM/NIHSEC/08/0804/P 67-177.

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Funding

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Conflict of interest

There is no conflict of interest in this research.

Results

Out of 9337 TB patients, the prevalence of smokers was 4313 (46.2%) while 5024 (53.8%) were non-smokers. The mean age of patients among smokers and non-smokers group was about 42.18 ± 15.97 and 41.12 ± 17.05 years, while the mean weight was 42.02 ± 10.48 and 41.53 ± 9.77 kg respectively. The male gender was more predominant among both smokers and non-smokers group i.e. 3261 (75.6%) and 3181 (63.3%) patients respectively. There was a high male to female ratio in the smokers group (3:1). Most of the cases in smoker group lie in the age group 26–55 years. Malay ethnicity, 1232 (28.6%) followed by Chinese ethnicity 1153 (26.7%) were in higher proportion in smokers group. About 2958 (68.6%), 3159 (73.2%) and 3010 (69.8%) smoker patients belong to urban areas, were unmarried and unemployed respectively. The prevalence of alcohol and drug abusers were also high in smoker group as compared to non-smoker group which was about 802 (18.6%) and 602 (14%) respectively. Majority of the smoker patients 3584 (83.1%) were having PTB while co-morbidity was observed in 1907 (44.2%) patients (Table 1)

Patient variables were further analyzed based on smoking habit using univariate and multivariate analysis. Multivariate binary logistic regression in Table 2 showed that the odds of smoking showed significant association with Male gender (OR = 1.43, 95% CI 1.30–1.58), Chinese ethnicity (OR = 1.23, 95% CI 1.02–1.49), Sarawak indigenous (OR = 0.74, 95% CI 0.58–0.95). The odds were high and statistically significant with urban residents (OR = 1.46, 95% CI 1.33–1.61), employed individuals (OR = 1.21, 95% CI 1.09–1.34), alcoholics (OR = 4.91, 95% CI 4.04–5.96), drug abusers (OR = 7.43, 95% CI 5.70–9.60) and presence of co-morbid condition (OR = 1.27, 95% CI 1.16–1.40).

Table 3 is based on the clinical sign and symptom and showed that significance difference existed among both smokers and non-smokers groups. Despite this, data analysis indicated that the prevalence of night sweat (1462, 33.9%), cough (3579, 83%), shortness of breath (1911, 44.3%), fever (2794, 64.8%), loss of weight (2969, 68.8%) and loss of appetite (3181, 73.8%) was significantly higher than the smokers group.

This study revealed that the overall success rate was 7240 (77.5%) patients out of which 3236 (75%) patients were successfully treated in smokers group while 4004 (79.7%) patients belongs to non-smokers group. The proportion of death rate (283, 6.6%), defaulters (, 6.6%) and treatment interruption (204, 4.7%) was high in smokers group. In multivariate analysis, the treatment completion 0.87 (95% CI 0.78–0.96, $p < 0.01$), death rate 1.57 (95% CI 1.31–1.89, $p < 0.001$), defaulters 1.57 (95% CI 1.31–1.89, $p < 0.001$) and treatment interruption 1.49 (95% CI 1.21–1.84, $p < 0.001$) showed significant association with smoking habit. The odd ratio for treatment success rate was less likely 0.76 (95% CI 0.69–0.84, $p < 0.001$) among smokers patients. The details are shown in Tables 4 and 5.

Discussion

Based on the National Health and Morbidity Surveys in 2006, prevalence of smoking in Malaysia was 46.5% [11]. The current study reported the same prevalence of smoking i.e. 46.2%. The proportion of smokers was less than that of non-smokers among TB patients (46.2 vs 53.8). These results were found

in contrast to previous studies conducted in Malaysia which had reported a higher prevalence of smokers than non-smokers among TB patients [12, 13]. Association between tobacco smoking and tuberculosis had been reported around the world using different type of study designs. Although the exact mechanism is not known, however, it is proposed that nicotine in tobacco smoke might interfere with the immune response of host to *M. tuberculosis* [14].

The present study revealed that male gender had a significant association with smoking habit. This could be due to differences observed in rates of TB among men and women. A study from China reported that IVDUs had found to be significantly associated with smokers group [15]. Another study revealed that the excessive alcohol intake is associated with a higher chance of *M. tuberculosis* infection [16]. The chronic consumption of ethanol causes alteration in immune system, resulting in an enhanced susceptibility to bacterial infections [17]. Consistent with the previous findings, the present study found that alcohol use and IVDUs was significantly associated with smoker TB patients.

If smoking is responsible for a decrease in cure rates and increase in the risk of rapid disease progression and severity then there exists a clear immunopathological association between smoking and TB [18, 19]. In the current study, the treatment success rate was low among smokers groups. A person who smokes one packet of cigarettes daily inhales 1.12 µg of iron; iron loading in the alveolar macrophages makes them more susceptible for the growth of *Mycobacterium tuberculosis* [20]. Cigarette smoke increases the threat of *Mycobacterium tuberculosis* infection by multiple ways: declined activity of alveolar macrophage, impairment of muco-ciliary clearance, decrease in immune response of pulmonary lymphocytes, modified pulmonary dendritic cells activity and reduction in cytotoxic activity of natural killer cells [8]. Smoking also produces alteration in both natural and acquired cell immunity, affecting macrophages and leukocytes. The effect of oxidative stress is particularly important, as it induces apoptosis in both activated and non-activated macrophages, favouring the multiplication of the bacilli and making the process chronic [21, 22]. This is the reason why tobacco smoking leads to severe clinical illness and eventually death. The current study showed that the smokers were more likely to die. A previous study at China reported that mortality rate was nine times higher among tuberculosis patients who smoked [23] while other studies from South Africa and India concluded that the higher odds of mortality were among smokers [24, 25]. Previous studies had also proved that tobacco smoking as one of the predictors and risk factors significantly associated with poor adherence and higher default rate in TB care settings [9, 26, 27]. A study from Hong Kong also showed that smoking habit is a good indicator to evaluate the risk of defaulters from TB treatment under DOTS (OR = 3.00, 95% CI 1.41–6.39, p = 0.004) [9]. Patients who default treatment are at greatest risk of developing drug resistance and spreading TB in the community [28]. A recent study from Malaysia recommends that interventions are necessary to improve treatment compliance in TB patients [12]. Improving compliance among smoking TB patients is a great challenge and should be addressed by securing support from families and social organizations as well as providing smoking cessation interventions [12]. Tachfounti and his co-workers studied association of smoking among TB patients and reported that the TB treatment failure rate was higher among smokers compared to non-smokers (9.1% vs 4.5%, p <0.01) [29]. Few studies evaluated the effect of smoking on treatment outcomes and concluded that treatment failure was higher among current and

ex-smokers, and smoking was significantly associated with low treatment success [2, 30, 33]. Fahrettin et al evaluated the treatment outcomes among TB patients and identified multiple patient factors that affect TB treatment outcomes [31]. Smoking cessation seems to be an essential means of controlling tb epidemics, improving outcomes and drug resistance particularly in high burden developing countries [32, 33].

Conclusions

In conclusion, tobacco smoke is a strong risk factor for not only TB but also a contributing factor towards treatment failure in terms of poor adherence and higher mortality and defaulter rate. Therefore, proper public awareness campaigns and smoking cessation interventions should be presented to all smoking TB patients undergoing DOTS treatment in order to avoid the severity and progression of disease and to avoid drug resistance.

Abbreviations

TB: tuberculosis

WHO: World Health Organization

OR: odd ratio

CI: Confidence interval

MREC: Medical research Ethics Committee

DOTS: Direct Observed Treatment short course

Declarations

- Ethics approval and consent to participate

Ethical Approval were taken from all relevant local authorities, and obtained from the Medical research Ethics Committee (MREC), registration number NMRR (National Medical Research Registration) # (2) KKM/NIHSEC/08/0804/P 67–177.

- Consent for publication

We would like to thank the director general of Health Malaysia for his permission to

publish this study.

- Availability of data and material

Data is saved in hard and soft copy both.

- Competing interests

There is no conflict of interest in this research.

- Funding

This study received no funding from any organization

- Authors' contributions

AHK: Principle investigator

SASS: Supervisor

MAH: Co-supervisor

KUK: Article Drafting

LCM: Reviewed and analysis

OM: Analysis & Drafting

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- Availability of data and materials

All kind of data is available in hard copy as well as in SPSS file.

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Tables

Table 1 Sociodemographic distribution of TB patients according smoking habit

Patient Variables	Total N=9337	Never smoked N=5024	Ever smoked N=4313
Weight (mean ± SD)	41.75±10.11	41.53±9.77	42.02±10.48
Gender			
Male	6442(69)	3181(63.3)	3261(75.6)
Female	2895(31)	1843(36.7)	1052(24.4)
Age (mean ± SD)	41.61±16.57	41.12±17.05	42.18±15.97
< 15	265(2.8)	172(3.4)	93(2.2)
16-25	1472(15.8)	876(17.4)	596(13.8)
26-35	1878(20.1)	1001(19.9)	877(20.3)
36-45	1754(18.8)	872(17.4)	882(20.4)
46-55	1674(17.9)	880(17.5)	794(18.4)
56-65	1279(13.7)	673(13.4)	606(14.1)
>65	1015(10.9)	550(10.9)	465(10.8)
Race			
Malay	2504(26.8)	1272(25.3)	1232(28.6)
Chinese	2211(23.7)	1058(21.1)	1153(26.7)
Indian	671(7.2)	350(7)	321(7.4)
Indigenous Sarawak	976(10.5)	614(12.2)	362(8.4)
Indigenous Sabah	1702(18.2)	1003(20)	699(16.2)
Indonesian immigrants	631(6.8)	372(7.4)	259(6)
Philippine immigrants	493(5.3)	287(5.7)	206(4.8)
Others	149(1.6)	68(1.4)	81(1.9)
Area			
Urban	5959(63.8)	3001(59.7)	2958(68.6)
Rural	3378(36.2)	2023(40.3)	1355(31.4)
Marital status			
Single	6706(71.8)	3547(70.6)	3159(73.2)
Married	2631(28.2)	1477(29.4)	1154(26.8)
Employment Status			
Employed	2531(27.1)	1228(24.4)	1303(30.2)
Unemployed	6806(72.9)	3796(75.6)	3010(69.8)
Alcohol drinkers			
Yes	941(10.1)	139(2.8)	802(18.6)
No	8396(89.9)	4885(97.2)	3511(81.4)
Intravenous drug user (IVDU)			
Yes	670(7.2)	68(1.4)	602(14)
No	8667(92.8)	4956(98.6)	3711(86)
TB-type			
PTB	7781(83.3)	4197(83.5)	3584(83.1)
EPTB	1556(16.7)	827(16.5)	729(16.9)
Co-morbidity			
Yes	3414(36.6)	1507(30)	1907(44.2)
No	5923(63.4)	3517(70)	2406(55.8)

Table 2 Distribution of TB patients according to smoking habit

Patient Variables	Univariate analysis			Multivariate analysis		
	Crude OR	95% CI	p-Value	aOR	95% CI	p-Value
Gender						
Male	1.79	1.64-1.96	<0.001	1.43	1.30-1.58	<0.001
Female	1.00	---		1.00	---	
Age						
< 15	0.62	0.48-0.80	<0.001	0.86	0.66-1.14	0.31
16-25	0.75	0.67-0.85	<0.001	0.92	0.81-1.04	0.22
26-35	1.02	0.92-1.13	0.62	---	---	---
36-45	1.22	1.10-1.35	<0.001	1.02	0.91-1.15	0.65
46-55	1.06	0.95-1.18	0.26	---	---	---
56-65	1.05	0.93-1.18	0.35	---	---	---
>65	0.98	0.86-1.12	0.79	---	---	---
Race						
Malay	1.17	1.07-1.29	<0.001	1.10	0.91-1.32	0.31
Chinese	1.36	1.24-1.50	<0.001	1.23	1.02-1.49	0.02
Indian	1.07	0.91-1.25	0.37	---	---	---
Indigenous Sarawak	0.65	0.57-0.75	<0.001	0.74	0.58-0.95	0.02
Indigenous Sabah	0.77	0.69-0.86	<0.001	1.01	0.83-1.23	0.91
Indonesian immigrants	0.79	0.67-0.94	0.007	0.91	0.72-1.16	0.47
Philippine immigrants	0.82	0.68-0.99	0.04	0.97	0.75-1.25	0.83
Others	1.39	1.00-1.93	0.04	1.30	0.89-1.90	0.16
Area						
Urban	1.47	1.35-1.60	<0.001	1.46	1.33-1.61	<0.001
Rural	1.00	---		1.00	---	
Marital status						
Single	1.14	1.04-1.24	0.005	0.97	0.88-1.07	0.63
Married	1.00	---		1.00	---	
Employment Status						
Employed	1.33	1.22-1.46	<0.001	1.21	1.09-1.34	<0.001
Unemployed	1.00	---		1.00	---	
Alcohol drinkers						
Yes	8.02	6.67-9.66	<0.001	4.91	4.04-5.96	<0.001
No	1.00	---		1.00	---	
Intravenous drug user (IVDU)						
Yes	11.82	9.16-15.24	<0.001	7.43	5.70-9.60	<0.001
No	1.00	---		1.00	---	
TB-type						
PTB	0.96	0.86-1.08	0.56	---	---	
EPTB	1.00	---		---	---	
Co-morbidity						
Yes	1.85	1.69-2.01	<0.001	1.27	1.16-1.40	<0.001
No	1.00	---		1.00	---	

Table 3 Clinical signs & Symptoms among smokers and Non-smokers patient groups

Symptoms	Total N=9337	Never smoked N=5024	Ever smoked N=4313	p-Value*
Night Sweat				
Yes	2962(31.7)	1500(29.9)	1462(33.9)	<0.001
No	6164(66)	3382(67.3)	2782(64.5)	
Unknown	211(2.3)	142(2.8)	69(1.6)	
Cough				
Yes	7365(78.9)	3786(75.4)	3579(83)	<0.001
No	1944(20.8)	1225(24.4)	719(16.7)	
Unknown	28(0.3)	13(0.3)	15(0.3)	
Sputum				
Yes	5139(55)	2947(58.7)	2192(50.8)	<0.001
No	4035(43.2)	2000(39.8)	2035(47.2)	
Unknown	163(1.7)	77(1.5)	86(2)	
Shortening of Breathings				
Yes	3944(42.2)	2033(40.5)	1911(44.3)	0.001
No	5298(56.7)	2942(58.6)	2356(54.6)	
Unknown	95(1)	49(1)	46(1.1)	
Fever				
Yes	5940(63.6)	3146(62.6)	2794(64.8)	0.002
No	3377(36.2)	1873(37.3)	1504(34.9)	
Unknown	20(0.2)	5(0.1)	15(0.3)	
Loss of Weight				
Yes	6203(66.4)	3234(64.4)	2969(68.8)	<0.001
No	3037(32.5)	1705(33.9)	1332(30.9)	
Unknown	97(1)	85(1.7)	12(0.3)	
Loss of Appetite				
Yes	6528(69.9)	3347(66.6)	3181(73.8)	<0.001
No	2694(28.9)	1575(31.3)	1119(25.9)	
Unknown	115(1.2)	102(2)	13(0.3)	
Hemoptysis				
Yes	2381(25.5)	1295(25.8)	1086(25.2)	<0.001
No	6842(73.3)	3637(72.4)	3205(74.3)	
Unknown	114(1.2)	92(1.8)	22(0.5)	

Table 4 Treatment outcomes among smokers and Non-smokers patient groups

Treatment outcome	Total N=9337	Never smoked N=5024	Ever smoked N=4313
Cured			
Yes	5319(57)	2900(57.5)	2419(56.1)
No	4018(43)	2124(42.3)	1894(43.9)
Treatment completed			
Yes	1924(20.6)	1117(22.2)	807(18.7)
No	7413(79.4)	3907(77.8)	3506(81.3)
Expired			
Yes	500(5.4)	217(4.3)	283(6.6)
No	8837(94.6)	4807(95.7)	4030(93.4)
Defaulters			
Yes	502(5.4)	218(4.3)	284(6.6)
No	8835(94.6)	4806(95.7)	4029(93.4)
Treatment interrupted			
Yes	369(4)	165(3.3)	204(4.7)
No	8968(96)	4859(96.7)	4109(95.3)
Treatment Continued			
Yes	723(7.7)	407(8.1)	316(7.3)
No	8614(92.3)	4617(91.9)	3997(92.7)
Over all treatment success			
Yes	7240(77.5)	4004(79.7)	3236(75)
No	2097(22.5)	1020(20.3)	1077(25)

Table 5 Treatment outcomes among smokers and Non-smokers patients groups on Binary logistic regression

Treatment outcome	Univariate analysis			Multivariate analysis		
	Crude OR	95% CI	p-Value	aOR	95% CI	p-Value
Cured						
Yes	0.93	0.86-1.01	0.111	---	---	---
No	1.00	---		---	---	
Treatment Completed						
Yes	0.80	0.72-0.89	<0.001	0.87	0.78-0.96	0.01
No	1.00	---		1.00	---	
Expired						
Yes	1.55	1.29-1.86	<0.001	1.57	1.31-1.89	<0.001
No	1.00	---		1.00	---	
Defaulters						
Yes	1.55	1.29-1.86	<0.001	1.57	1.31-1.89	<0.001
No	1.00	---		1.00	---	
Treatment interrupted						
Yes	1.46	1.18-1.80	<0.001	1.49	1.21-1.84	<0.001
No	1.00	---		1.00	---	
Treatment Continued						
Yes	0.89	0.77-1.04	0.163	---	---	---
No	1.00	---		---	---	
Over all treatment success						
Yes	0.76	0.69-0.84	<0.001	---	---	---
No	1.00	---		---	---	