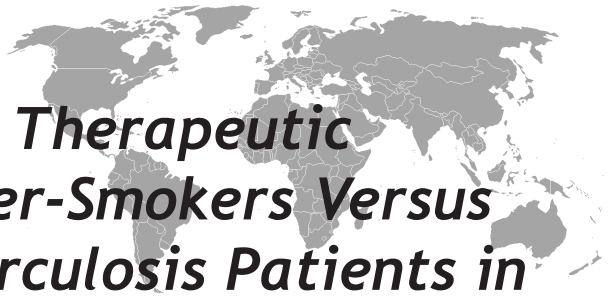

Clinical Modalities and Therapeutic Outcomes; Between Ever-Smokers Versus Never-Smokers of Tuberculosis Patients in Penang, Malaysia.

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Eur J Gen Med 2010;7(4):389-397

Received: 20.04.2010

Accepted: 17.09.2010

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ABSTRACT

***Aim:** There is consistent evidence that tobacco smoking has been implicated as a risk factor for tuberculosis infection, disease and death. Study was aimed to identify the impact of smoking on Tuberculosis (TB) clinical characteristics and treatment outcome and to emphasize this association thus may be useful in the management of TB cases.*

***Method:** The retrospective, observational and cross-sectional cohort survey was done to compare disease characteristic and clinical presentation during treatment of TB.*

***Result:** Five hundred twenty four TB patients were consecutively recruited during the period of the study. Of this, 250 [47.7%] were never smokers. Ever smoking TB patients accounted for 274 [52.3%]. There were significant relationships between smoking status of TB patient with race and initial Mantoux test. But there were no significant association between smoking habit and marital status, patients' identities, history of chronic disease, history of contact to pulmonary TB patients and BCG scar. Ever smoker TB patients' were four times more likely to have slower smear conversion at two months compared to non-smoker tuberculosis patients'.*

***Conclusion:** We found a high risk of death from smoking induce tuberculosis. Treatment outcomes were not statistically significant with/ without smoking. It was seen that smoking is consider as a risk factor for unfavorable outcomes among TB patients registered in DOTS program in term of therapeutic compliance.*

***Key words:** Tuberculosis, smoking, DOT therapy,*

Malezya Penang'ta Sigara İçicisi Tüberkülozlu Hastalarla Hiç İçmemiş Tüberkülozlu Hastaların Arasındaki Klinik Yaklaşımlar ve Tedavi Sonuçları

Amaç: *Tütün içiciliğinin tüberküloz enfeksiyon, hastalık ve ölüm için bir risk faktörü olarak suçlanmaktır ve buna dair tutarlı kanıtlar vardır. Çalışma sigaranın tüberküloz kliniği ve tedavisi üzerine etkilerini belirlemeyi amaçlamaktadır. Bu ilişki tüberkülozun yönetiminde faydalı olabilir.*

Metod: *Retrospektif, gözlemsel ve kesitsel bir kohort çalışması hastalık özelliklerini, klinik başvuruyu karşılaştırmak amaçlı tüberküloz tedavisi boyunca yapıldı.*

Bulgular: *524 ardışık TB hastası çalışma periyodunda alındı. Bunlardan 250'si(%47.7) hiç sigara içmemiş. Sigara içicisi TB hastaları sayısı 274(%52.3)'tü. TB hastalarının sigara içme durumu ile ırk ve başlangıç Mantoux testi arasında anlamlı ilişki vardı. Ancak sigara alışkanlığı ile medeni durum, hasta özellikleri, kronik hastalık hikayesi, TB'li hasta ile yakın temas ve BCG skarı arasında anlamlı ilişki yoktu. Sigara içicisi TB hastaları sigara içmeyen TB hastalarına göre 2. ayda karşılaştırıldıklarında, 4 kat daha yavaş yayma konversiyonuna sahiptiler.*

Sonuç: *Sigaranın indüklediği tüberkülozda yüksek ölüm riski bulduk.. Tedavi sonuçları sigaralı ya da sigarasız istatistiksel olarak anlamlı değildi. Sigaranın teröpatik uyum amaçlı DOT programında olan tüberküloz hastalarında istenmeyen sonuçlar için bir risk faktörü olduğu görüldü.*

Anahtar kelimeler: *Tüberküloz, sigara, DOT tedavisi*

INTRODUCTION

There is consistent evidence that tobacco smoking has been implicated as a risk factor for tuberculosis infection, disease and death (1). Evidence suggests that smoking (both current and former) is associated with: risk of being infected with Mycobacterium tuberculosis, risk of developing tuberculosis (2), development of more severe forms of tuberculosis, and risk of dying of tuberculosis (3). Also there is a strong dose-response relationship – both in terms of quantity and duration of smoking (4). These relationships are not explained away by controlling for potentially confounding variables such as age, gender, alcohol consumption, and HIV status (1-5). It has been difficult for individuals and societies to recognize the extent of damage caused by tobacco (6). The study of the effects of tobacco use helped to create the rules of chronic disease epidemiology and many cancers and other disease categories have been causally linked to tobacco use (7). The interpretation of the tuberculin skin test is recommended for screening of tuberculosis infection. Expansion of measures to prevent and control tuberculosis and support of international control efforts are needed to ensure continued progress (8).

Several advantages of Fixed Dose Combination (FDC) over individual medicines (or single-drug formulations) have been identified: prescription errors are likely to be less frequent and fewer tablets need to be ingested, which may encourage adherence to treatment (9). For treatment of new cases of pulmonary or extrapulmonary TB, WHO recommends a standardized regimen consisting of two phases. The initial (intensive) phase uses four drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) administered for two months. This is followed by a continuation phase with two drugs (rifampicin and isoniazid) for four months or, exceptionally, with two drugs (isoniazid and ethambutol) for six months when adherence to treatment with rifampicin cannot be ensured (9).

The treatment of TB is not particularly expensive, especially if hospitalization is not required. Furthermore, patients who complete all their treatment for drug-susceptible TB have cure rates over 95%. Noncompliance (nonadherence), drug resistance, extra-pulmonary disease, and concomitant disease states reduce the overall effectiveness of chemotherapy of TB to approximately 75% (10). The morbidity and mortality of tuberculosis due to smoking are not widely appreciated by health care providers; so this study is conducted to identify the impact of smoking on TB clinical characteristics and treatment outcome, and to emphasize this association thus may be useful in the management of TB cases.

MATERIALS AND METHODS

Design, Setting and Subjects

The retrospective, observational & cross-sectional cohort survey was done to compare smoking and non-smoking TB patients with disease characteristic and clinical presentation during treatment of TB. The data were collected from patients' medical records who registered at Chest Clinic of Penang General Hospital from January 2006 to June 2008. TB cases were assessed during the treatment period. Demographic, clinical and epidemiological data were obtained manually from patients' medical records.

Table 1. *Demographics and other characteristics of ever smoking versus never smoking TB patients*

Characteristics	*Never smokers*	*Ever smokers*	*p value*
Age	*40.98±18.07*	*48.62±15.40*	*<0.001*
Weight	*51.42±14.42*	*50.55±10.30*	*ns*
Sex			*<0.001*
Male	*99 (39.6%)*	*270 (98.5%)*	
Female	*155 (60.4%)*	*4 (1.5%)*	
Race			*<0.01*
Malay	*87 (34.8%)*	*72 (26.3%)*	
Chinese	*129 (51.6%)*	*148 (54.0%)*	
Indian	*18 (7.2%)*	*42 (15.3%)*	
Others	*16 (6.4%)*	*12 (4.4%)*	
Marital Status			*ns*
Single	*95 (38.0%)*	*111 (40.5%)*	
Married	*136 (54.4%)*	*147 (53.6%)*	
Divorced/Widow	*5 (2.0%)*	*9 (3.3%)*	
Not applicable	*14 (5.6%)*	*7 (2.6%)*	
Patient identity			*ns*
Local	*233 (93.2%)*	*261 (95.3%)*	
Foreigner	*17 (6.8%)*	*13 (4.7%)*	
Alcoholic status			*<0.001*
Yes	*3 (1.2%)*	*61 (22.3%)*	
No	*247 (98.8%)*	*213 (77.7%)*	
IVDU			*<0.001*
Yes	*2 (0.8%)*	*48 (17.5%)*	
No	*248 (99.2%)*	*226 (82.5%)*	
History of chronic disease			*ns*
Yes	*33 (13.2%)*	*31 (11.3%)*	
No	*217 (86.8%)*	*243 (88.7%)*	
History of contact to PTB patients			*ns*
Yes	*57 (33.3%)*	*50 (30.3%)*	
No	*114 (66.7%)*	*115 (69.7%)*	
BCG scar			*ns*
Present	*146 (61.6%)*	*141 (54.0%)*	
Absent	*91 (38.4%)*	*120 (46.0%)*	
Initial Mantoux test			*0.002*
Not done	*161 (66.8%)*	*192 (74.1%)*	
No result	*16 (6.6%)*	*26 (10.0%)*	
<10 mm	*14 (5.8%)*	*18 (6.9%)*	
≥10 mm	*50 (20.7%)*	*23 (8.9%)*	

This study was conducted in the chest clinic of respiratory department in Penang General Hospital. Penang General Hospital is the main general hospital in Penang Island which is located in Northwest Malaysia. The dominant ethnic groups of this island include Chinese (42.6%), Malay (41.1%), Indian (9.9%) and others (6.1%).11 All TB patients over age of 15 years who registered in Chest Clinic of Penang General Hospital during the period (1st of January/2006 to 30th of June/2008) were included in the study. According to the main outcome of the study,

Table 2. *Risk estimation of smoking for sputum smear conversion among TB patients*

	Never smoker n(%)	*Ever smoker n(%)*	*OR*	*95% CI*	*p value*
Slower smear conversion					
Yes	*6 (2.4%)*	*29 (10.6%)*	*4.814*	*1.96-11.80*	*< 0.001*
No	*244 (97.6%)*	*245 (89.4%)*			
Total	*250 (100%)*	*274 (100%)*			

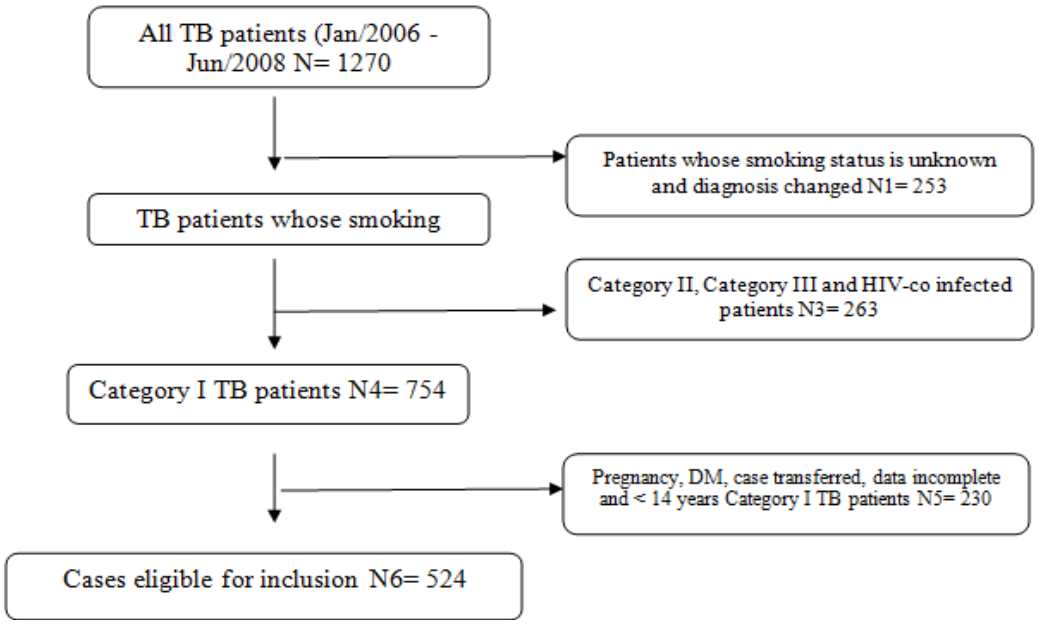

***Figure 1**. Inclusion and exclusion mode of study*

patients were categorized into two groups, those who are smoking or stop smoking at the time of diagnosis (Ever smokers group) and those who did not (Never smokers group).

Inclusion Criteria

Inclusion criteria was made on the Category I of TB patients (New cases), while Category II and Category III TB patients (relapse, treatment failure, treatment after interruption and chronic cases) & new cases for which the mandatory reports are incomplete and the missing data cannot be retrieved such as smoking status is not mentioned in medical records, also new cases of pregnant women, diabetic and HIV co infected patients were conclusively excluded from study. A cluster random sampling was done to select patients who fulfilled the eligibility criteria during the period of the study. Patients were consecutively included as in the following flow chart (Figure 1).

Ethical Approval

This study was approved by National Institutes of Health NIH in The Ministry of Health Malaysia. These are the Institute for Medical Research IMR, Clinical Research Centre CRC, Institute of Public Health IPH, Institute for Health Management IHM, Institute for Health Systems Research IHSR and Institute for Health Behavioral Research IHBR.

Statistical Analysis

Descriptive analyses were performed for quantitative variables by calculating mean and Standard deviation.

***Table 3**. Differences in sputum smear conversion with regard to smoking dose in ever smoking TB patients*

	Ever smoker TB patient n (%)	*Sticks/day Mean ± SD*	*p value*
Slower smear conversion			*0.723*
Yes	*4 (6.8%)*	*16.5 ± 4.1*	
No	*55 (93.2%)*	*14.7 ± 9.7*	
Total	*59 (100%)*	*14.8 ± 9.4*	

Table 4. *Risk estimation of smoking with regard to outcomes of TB treatment after controlling the effect of confounders*

	Never smoker n(%)	*Ever smoker n(%)*	*aOR***	*95% CI*	*p value**
Cured			*0.312*	*0.17-0.57*	*< 0.001*
Yes	*83 (33.2%)*	*38 (13.9%)*			
No	*167 (66.8%)*	*236 (86.1%)*			
Treatment completed			*1.585*	*0.98-2.56*	*0.060*
Yes	*136 (54.4%)*	*155 (56.6%)*			
No	*114 (45.6%)*	*119 (43.4%)*			
Treatment failure			*13.593*	*0.59-308.69*	*0.101*
Yes	*1 (0.4%)*	*8 (2.9%)*			
No	*249 (99.6%)*	*266 (97.1%)*			
Treatment interrupted			*3.249*	*1.01-10.45*	*0.048*
Yes	*5 (2.0%)*	*35 (12.8%)*			
No	*245 (98.0%)*	*239 (87.2%)*			
Died			*0.962*	*0.48-1.92*	*0.912*
Yes	*25 (10.0%)*	*38 (13.9%)*			
No	*225 (90.0%)*	*236 (86.1%)*			

**Adjusted for age, sex, alcohol use, IVDU and history of chronic disease*

For categorical variables, percentages and frequency distributions were determined. Independent t-test was applied for continuous and normally distributed variables; otherwise Mann-Whitney U test was applied as a substitute. Chi-square test was used to show the distribution of proportion and frequencies of categorical variables for exposed group (ever smokers) and non-exposed group (never smokers). To compare the means of more than two conditions One Way ANOVA test was used for numerical and normally distributed variables; otherwise Kruskal Wallis test was applied. For all analyses, two-tailed statistical test were used with p-value ≤ 0.05 were considered statistically significant at 95% level of confidence interval. Univariate analyses were applied to test the association between individual factors and outcome variables using binary logistic regression. The adjusted odd ratio and 95% confidence interval were calculated for each predicted variables. For all dichotomous variables "yes" was coded as one and "no" was coded as two. Patients related factors used in analyses included age, alcohol use, intravenous drug use, smoking status and history of chronic disease.

Drug coding and classification: The control of TB is one of the most cost-effective health interventions any nation can pursue. The standardized regimens for anti-TB treatment recommended by WHO include five essential medicines designated as first line: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S). For treatment purposes, patients are categorized as previously untreated (categories I and III) and previously treated (categories II and IV). FDC of drugs for the treatment of all TB patients were recommended by World Health Organization. *New case of TB*: Is defined as a patient who has never had treatment for tuberculosis or has taken anti-tuberculosis drugs for less than 4 weeks' duration in the past (11). *Current smoker*: A patient who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes (12). *Ex-smoker*: A patient who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of diagnosis of disease (12). *Ever smoker*: Is defined as patient who is either current or ex-smokers (12). *Never smoker*: A patient who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime (12). *Cured*: Patient who is smear-negative at/or 1 month prior to the completion of treatment and on at least one previous occasion (11). *Treatment completed*: Patient who has completed treatment but without proof of cure (11). *Treatment failure*: A patient who, while on treatment remained or became again smear-positive 5 months or later after commencing treatment or a patient who was initially smear-negative before starting treatment and became smear-positive after the second month of treatment (11). *Treatment interrupted*: Patient whose treatment was interrupted for 2 months or more (11). *Died*: Patient who dies for any reason during the course of treatment (11).

RESULTS

Five hundred twenty four TB patients were consecutively recruited during the period of the study. Of this, 250 (47.7%) were never smokers. Ever smoking TB patients accounted for 274 (52.3%). A total of n:524 (TB) patients were attending chest clinic of Penang General Hospital during January 2006–June 2008. Males were considered the vast majority and accounted for 70.4% (369/524), while females accounted for 29.6% (155/524). The majority (52.9%) was Chinese, followed by Malay (30.4%), Indian (11.5%) and other ethnicity (5.3%). The means (± SD) age and weight of the study patients was found to be 44.97±17.13 years and 50.96±12.40 kg respectively. The majority of TB patients were married. Similarly the vast majority of patients were local. The proportions of non drinker and non intravenous drug use were higher among TB patients Among 274 ever smokers TB patients in study cohort, smoking dose was indicated for 59 patients (21.5%)only; but for the majority of ever smoking TB patient (215, 78.5%), smoking dose was not indicated. The mean (± SD) for the number of cigarettes consumed per day by ever smokers TB patients was 14.86±9.43. Ever smokers TB patients were commonly associated with older age and male gender, they also had higher proportion of risk factors compared to never smokers; high alcohol consumption (61% versus 3%), Intravenous drug users (48% versus 2%). There were significant relationships between smoking status of TB patient with race and initial Mantoux test. But there were no significant association between smoking habit and marital status, patients' identities, history of chronic disease, history of contact to PTB patients and BCG scar (Table 01).

From microbiological lab reporting we identified that out of 32 TB patients whose sputum smear slowly converted, 29 were ever smokers and 6 were never smokers (82.9% versus 17.1% regarding sputum smear conversion). For those whose sputum smear converted at two months, 245 were ever smokers and 244 were never smokers (50.1% versus 49.9% regarding sputum smear conversion). Ever smokers TB patients were significantly four times more likely to have slower smear conver-

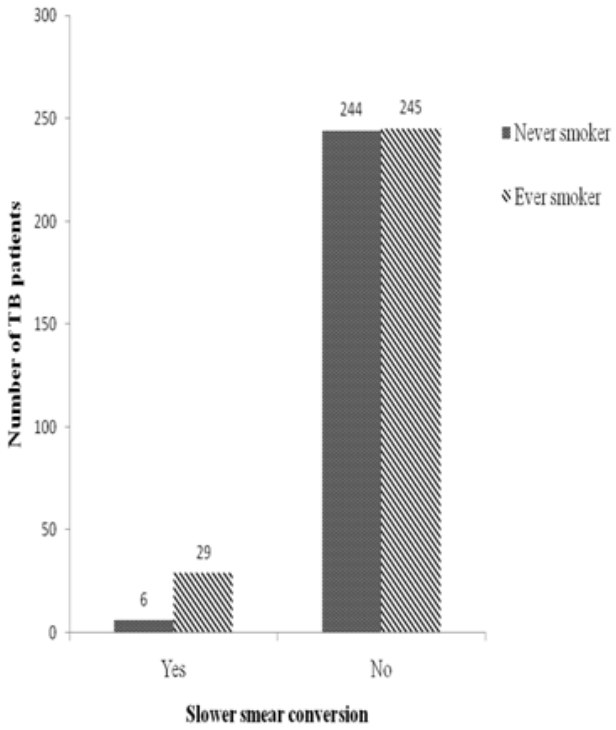

Figure 2. Smoking of TB patients according to sputum smear conversion at two months

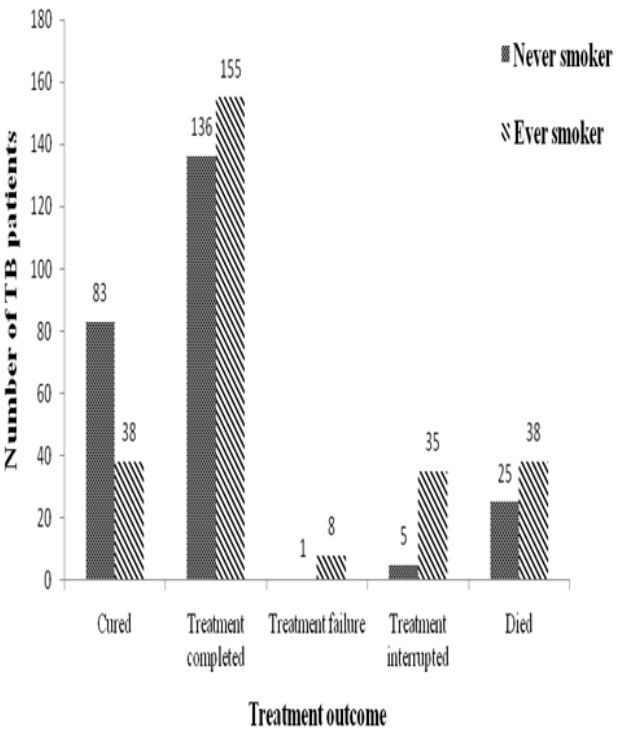

Figure 3. Smoking status of TB patients according to treatment outcomes

sion at two months compared to non-smokers (Table 2). While the differences in sputum smear conversion at two months with regard to number of cigarettes consumed per day by ever smokers TB patients whose smoking dose was indicated. There was no significant difference between those who had slower smear conversion and those who did not in term of smoking dose (Table 3).

Tuberculosis patients (ever smoked) were significantly have shorter duration of therapy compared to never smokers (never smoker; 7.45±2.43, ever smoker; 6.75±2.68, p<0.009). The majority of TB patients completed treatment without evidence of cure (291, 55.5%), followed by cured (121, 23.1%), died (63, 12.0%), defaulted treatment (40, 7.6%) and failed treatment (9, 1.7%) repectively. Treatment outcomes according to smoking status of TB patients. The majority of cured patients were never smokers (68.6%), while the majority of those who failed treatment, defaulted review and died were ever smokers (88.9%, 87.5% and 60.3%) respectively. 46.7% of those who completed treatment without proof of cure were never smokers and 53.3% were either current or ex-smokers (Figure 3).

Further analysis describes the risk estimation of smoking with regard to outcomes of TB treatment after controlling for the effect of confounders (Table 4). Binary logistic regression was used to control for the effect of confounders (age, sex, alcohol consumption, intravenous drug use and history of chronic disease). After controlling for the effects of confounders, ever smokers were significantly still less likely to be cured and more likely to fail treatment compared to never smokers. Risk of smoking to die from TB or fail treatment was statistically not significant. There were no significant differences between treatment outcomes in term of smoking dose. Although ever smokers TB patients who default treatment or died smoked more cigarettes compared to those who stated as cured or completed treatment.

DISCUSSION

Ever smokers four times more likely to have slower smear conversion at two months compared to non-smokers (OR 4.81, 95% CI 1.96-11.80). Leung found that there was no statistically significant difference in the smear conversion rate at two months between smokers and non-smokers (OR 0.89, p<0.655) (13).

Abal found smokers with far advanced radiographic abnormalities (p<0.05) or with 3+ smear status (p<0.05), were found to have a less chance of an early smear conversion (14). Out of 59 smoker patients whose smoking dose was determinant, just 4 had slower smear conversion for this reason no statistically significant difference was detected, despite that the mean of number of cigarettes consumed per day among those who had slower smear conversion was higher than those whose sputum smear converted at two months (16.5±4.1 and 14.8±9.4) respectively.

Treatment outcomes of ever smokers versus never smokers TB patients Of 524 TB patients; 121 (23.1%) were cured, 291 (55.5%) completed treatment, 9 (1.7%) failed treatment, 40 (7.6%) defaulted and 63 (12.0%) died during the period of therapy. Santha et al found that 72% successfully complete their treatment, 3% failed, 19% defaulted and 6% died which is almost corroborated the result of our study (15). The cure rate in our study is significantly lower than the average national cure rate of 85% (16). Low cure rates could actually increase the rate of transmission of the disease, and hence increase the number of cases (16).

The International Standards for Tuberculosis Care (ISTC) intends endorsed level of care that all practitioners should seek to achieve in managing individuals who have, or are suspected of having, tuberculosis, this is essential for good patient care and tuberculosis control (17-19). Treatment failure was more common among current and ex-smokers compared to non-smokers (88.9% versus 11.1%), ever smokers was seven times more likely to fail treatment (OR 7.4, p<0.05) but after controlling for age, sex, history of chronic disease, alcohol use and IVDU fail to reach statistical significance (aOR 13.5, 95% CI 0.59-308.69, p>0.05). Santha et al found that smoking was significantly associated with treatment failure (15).

The high default rate documented here is consistent with the high default rates observed in elsewhere in the world (18, 20-23). In Russia, during the initial year of DOTS implementation, 28% of patient defaulted from treatment (23). In this study the rate of default is higher among ever smokers TB patients compared to never smokers (87.5% versus 12.5%). Ever smokers were three times more likely to default from treatment compared to non-smokers (aOR 3.6, 95% CI 1.14-11.87, p<0.05). Chang et al also found that the risk of default could be accurately predicted by smoking (OR 3.00, 95% CI 1.41-6.39, p< 0.01) (24). Patients who default treatment are

at greatest risk for developing drug resistance and for spreading untreated disease in the community (25).

Treatment interruptions were frequent in TB patients in Penang. Interventions to improve treatment compliance in patients are necessary. Social support and incentive programs should be universally available for all patients from the start of the continuation phase of treatment, during the intensive phase for patients considered to be at risk for default. Directly observed therapy DOT at home could be a recommendation for some patients. Improving compliance among smoker patients is a challenge and should be addressed by seeking support from families and social organizations.

In India the risk of dying of TB was 4.5 times greater among smokers than non-smokers. In this study 61% of TB mortality has been attributed to smoking (p=0.004) (26). Doll et al in their study on mortality in relation to smoking, they found that TB patients three times more likely to die of TB compared to non-smokers (27). In this study we do not find a greater risk of mortality in ever smoker TB patients; this is might due to ease to access to health care in Penang hospital which is available to all patients registered for TB treatment and lower cost of health services provided by the government.

Our result corroborated the result of other studies which found that smoking was not associated with risk of dying from TB (15, 28). However this issue warrants a more thorough investigation. If smoking causes a faster deterioration of TB disease, then in community in which access to health care is restricted, the lives of ever smoker TB patients would conceivably be at high risk. Our findings support the hypothesis of an increased vulnerability of smokers to the risk of infection and development of TB. If smoking increases the risk of rapid disease progression and severity, there is clearly an immune-pathological association between smoking and TB (29-31).

In conclusion, we found a high risk of death from smoking induce tuberculosis. Treatment outcomes were not statistically significant with/without smoking. It was seen that smoking is consider as a risk factor for unfavorable outcomes among TB patients registered in DOTS program in term of therapeutic compliance.

Limitations of the study: The findings of this study are subject to a number of limitations. First sociological data such as literacy, employment and patients' income were not available in medical records. Any bias introduced by lack of availability of data, however, might underestimates or overestimates the association between smoking and other outcomes. Third, small number of treatment failure cases limited the statistical power required to detect significant differences in outcomes among ever and never smokers. Fourth, it is unknown whether the smoking status recorded truthfully specially among female. If smoking is under recorded, this would mean that occasional or light smoker may have been included among never smokers, while the ever smokers group would include only regular or heavy smokers. In this case, the differences observed between TB patients who smoke and those who do not would be even greater than observed. Finally, it is difficult to completely exclude the effects of all confounders in retrospective study such as this. Although the differences between ever smokers and never smokers in term of treatment outcomes persisted after control of age, sex, history of chronic disease, alcohol use and IV drug use.

The findings of this study have prompted the implementation of smoking cessation strategy to improve treatment outcomes. Smoking cessation strategy should be performed by all health care providers. Counseling regarding stop smoking, enhanced supervision, monitoring and other efforts is recommended to improve treatment outcomes among TB patients who smoked. Smoking as a risk factor of treatment failure in TB patients needs to be corroborated by other studies. Also tuberculosis related mortality should be investigated to understand the social and medical cause of death as well as the social implications of death for families and communities.

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