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 assess the effects of smoking on treatment outcomes among TB patients. Methods: A multi-center retrospective study design was used to collect data from TB patients in four different states of Malaysia, namely Penang, Sabah, Sarawak, and Selangor. The study included medical records of TB patients admitted to the selected hospitals in the period from January 2006 to March 2009. Medical records with incomplete data were not included. Patient demographics and clinical data were collected using a validated data collection form. Results: Of all patients with TB (9337), the prevalence of smokers was 4313 (46.2%). Among smoker’s, 3584 (83.1%) were associated with pulmonary TB, while 729 (16.9%) were associated with Extra-pulmonary TB. 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 found that 3236 (75.0 %) patients were successfully treated in the smoker group, while 4004 (79.7 %) patients were non-smokers. The proportion of death rate 283 (6.6%), defaulters 284 (6.6%) and treatment interruption 204 (4.7%) was high in the smoker's 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 are an effective way to decrease treatment failure and drug resistance.

Background

Global data on tuberculosis (TB) provided by the World Health Organization revealed that 10.0 million (range, 9.0–11.1 million) people were ill with TB in 2018. In addition, in 2018, 1.2 million TB fatalities among people who are HIV negative and 251 000 more deaths among those who are HIV positive. The leading cause of death from a single infectious agent has been TB since 2007, which ranks above HIV / AIDS [1]. Smoking and tuberculosis remain two major health concerns worldwide [2]. 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, the WHO suggested a stronger focus on preventing exposures to tuberculosis [4]. In addition to cancer and coronary heart disease, numerous studies have identified smoking as a risk factor in the development of TB [5, 6]. Tobacco-associated deaths are projected to increase to 8.4 million by 2020[7], along with TB, both of which are a 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], and it might be the affecting reason for less likely TB treatment outcomes among specific population [9,10]. Although the prevalence of TB in Malaysia decreased significantly compared to the early 1990s, still Malaysia is ranked as an intermediate burden country by the World Health Organization (WHO) in 2018 with an incidence rate of 92/100,000 and estimated mortality rate of 4.9/100,000 population [1].

Despite increasing pieces of evidence showing a strong association between tobacco smoking and TB [1, 11], there are only a few observational studies highlighting the association between smoking and TB treatment outcomes with limited study population [7] and or single-center study [12,13] which are difficult to generalize. Though previous studies have typically identified potential risk factors for poor results of TB treatment [7,9,10]. In this study, the prevalence of smoking in TB patients in Malaysia was determined and the impact that smoking has on the outcomes of tuberculosis treatment was investigated.

Methods

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 same from peninsular Malaysia, selected based on the highest-burden of TB patients [14].

Inclusion & exclusion criteria
All TB patients (new, relapse, treatment failure and treatment defaulters) of both genders either with
or without co-morbidity who were presented to the chest clinic from January 2006 to March 2009 were included in the study. Patients with incomplete medical records were removed from the study.

Disease classification, treatment protocol and treatment outcomes were defined as per the Malaysian tuberculosis treatment guideline [15], which is in pipeline with world health organization criteria.

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 of successful and unsuccessful treatment. Cured and treatment-completed patients have been placed in the treatment successful category, while the remainder has been 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 extrapulmonary) presence of the co-morbid condition along with respective medications, results of sputum culture and treatment outcomes.

**Statistical Analysis**

The data were analyzed 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 ± standard deviations were calculated for continuous variables. Univariate and multivariate binary regression analyses were used to examine whether tobacco smoking had contributed to poor treatment outcomes in TB patients or not. The results were presented as P-value, odds ratio (OR) and
95% confidence interval (CI). A P-value ≤ 0.05 was considered statistically significant.

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 smoker's group (3:1). Most of the cases in the 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 the smoker's 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 the smoker group as compared to the 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 a 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 symptoms and showed that a significant 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 the smoker group while 4004 (79.7%) patients belonged to non-smokers group. The death rate was (283, 6.6%), defaulters (284, 6.6%) and treatment interruption (204, 4.7%) was high in the smoker's group. In multivariate analysis, treatment completion (aOR 0.87, 95% CI 0.78-0.96, p<0.01), death rate (aOR 1.57, 95% CI 1.31-1.89, p<0.001), defaulters (aOR 1.57, 95% CI 1.31-1.89, p<0.001) and treatment interruption (aOR 1.49, 95% CI 1.21-1.84, p<0.001) showed a significant association with smoking habit. The chances of treatment success rate were less for smokers (aOR 0.76, 95% CI 0.69-0.84, p<0.001), as shown in table 4.

Discussion

Based on the National Health and Morbidity Surveys in 2006, the prevalence of smoking in Malaysia was 46.5%, as revised in 2015 [12]. The current study reported the same prevalence of smoking i.e. 46.2%. The previous published studies conducted in Malaysia which had reported a higher prevalence of smokers than non-smokers among TB patients [11, 13]. The tobacco-tuberculosis association worldwide has been documented with different types of studies [1]. While the exact mechanism is not understood, nicotine may interfere with host immune reaction to M. tuberculosis [16]. The present study found that the male gender has a significant association with smoking habits. This could be due to the observed differences in TB rates between men and women. A study from China reported that intravenous drug users (IVDU’s) were found to be significantly associated with smoker’s group [17]. An additional study found that the excessive intake of alcohol has a greater chance of M. tuberculosis infection [18]. Chronic ethanol intake causes changes in the immune system and an increased risk of bacterial infections [19]. Consistent with the previous findings, the present study found that alcohol use and IVDUs were significantly associated with smoker TB patients.

If smoking is responsible for a decrease in cure rates and an increase in the risk of rapid disease progression and severity then there is a clear immunopathological association between smoking and TB [20,21]. In the current study, the treatment success rate was low among smokers groups. A person who smokes one packet of cigarettes daily inhaled 1.12 µg of iron; iron loading in the alveolar macrophages makes them more susceptible to the growth of Mycobacterium tuberculosis [22]. Cigarette smoke increases the threat of Mycobacterium tuberculosis infection in multiple ways:
declined activity of alveolar macrophage, impairment of mucociliary clearance, decrease in the immune response of pulmonary lymphocytes, modified pulmonary dendritic cells activity and reduction in the cytotoxic activity of natural killer cells [8]. Smoking also produces an alteration in both natural and acquired cell immunity, affecting macrophages and leukocytes. The effect of oxidative stress is important, as it induces apoptosis in both activated and non-activated macrophages, favoring the multiplication of the bacilli and making the process chronic [23, 24]. This is the reason tobacco smoking leads to severe clinical illness and eventually death. The current study showed that smokers were more likely to die. A previous study in China reported that the mortality rate was nine times higher among tuberculosis patients who smoked [25] while other studies from South Africa and India concluded that the higher odds of mortality were among smokers [26, 27].

Previous studies had also proved that tobacco smoking as one predictor and risk factors significantly associated with poor adherence and higher default rate in TB care settings [9, 28, 29]. 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 [30]. A recent study from Malaysia recommends that interventions are necessary to improve treatment compliance in TB patients [11]. 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 [11]. Tachfouti and co-researchers studied the 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) [31]. Few studies tested 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, 32, 35]. Fahrettin Talay et al evaluated the treatment outcomes among TB patients and identified multiple patient factors that affect TB treatment outcomes [33]. The current study showed that patient mortality is higher among smokers [OR 1.57 (91.31-1.89); p <0.01], the reason might be due to drug addiction (OR 5.7) and co-morbidities (OR 1.27), and the same picture can be drawn from the published articles [34,35].
Smoking cessation seems to be an essential means of controlling TB epidemics, improving outcomes and drug resistance particularly in high burden developing countries, as published somewhere. [33,34,35].

Conclusions
In conclusion, smoking is a risk factor for the occurrence of tuberculosis. Additionally, this study shows that the treatment effects are also poor. Tobacco also poses a strong risk factor in poor adherence and higher mortality as well as defaulter rate. Therefore, proper public awareness campaigns and smoking cessation interventions should be presented to all smoking TB patients undergoing DOTS treatment to avoid the severity and progression of the disease and to avoid drug resistance.

**Limitation of the study:**
A number of Tb patients were excluded from the analysis due to a lack of / incomplete smoking-related data.

List Of Abbreviations
TB: tuberculosis
WHO: World Health Organization
OR: odds ratio
CI: Confidence interval
MREC: Medical research Ethics Committee
DOTS: Direct Observed Treatment short course

Declarations

**Ethics approval and consent to participate**
Ethical Approval was 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.

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**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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### Table 1: Sociodemographic distribution of TB patients according to 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 based on multivariate analysis
| 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  | 0.05    | 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    | ---        |         |
| 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: Un-Successful Treatment Outcomes among smokers and Non-smokers patients Groups on Binary logistic regression
| Treatment outcome | Total N=9337 | Never smoked N=5024 | Ever smoked N=4313 | Univariate analysis | Multivariate analysis |
|-------------------|-------------|---------------------|--------------------|---------------------|-----------------------|
|                   |             |                     |                    | Crude OR | 95% CI | p-Value | aOR |  |
| Cured             |             |                     |                    |          |        |         |     |  |
| Yes               | 5319 (57)   | 2900 (57.5)         | 2419 (56.1)        | 0.93     | 0.86-1.01 | 0.111  | --- |  |
| No                | 4018 (43)   | 2124 (42.3)         | 1894 (43.9)        | 1.00     | ---     | ---     | --- |  |
| Treatment Completed |             |                     |                    |          |        |         |     |  |
| Yes               | 1924 (20.6) | 1117 (22.2)         | 807 (18.7)         | 0.80     | 0.72-0.89 | <0.001 | 0.87 |  |
| No                | 7413 (79.4) | 3907 (77.8)         | 3506 (81.3)        | 1.00     | ---     | ---     | 1.00 |  |
| Expired           |             |                     |                    |          |        |         |     |  |
| Yes               | 500 (5.4)   | 217 (4.3)           | 283 (6.6)          | 1.55     | 1.29-1.86 | <0.001 | 1.57 |  |
| No                | 8837 (94.6) | 4807 (95.7)         | 4030 (93.4)        | 1.00     | ---     | ---     | 1.00 |  |
| Defaulters        |             |                     |                    |          |        |         |     |  |
| Yes               | 502 (5.4)   | 218 (4.3)           | 284 (6.6)          | 1.55     | 1.29-1.86 | <0.001 | 1.57 |  |
| No                | 8835 (94.6) | 4806 (95.7)         | 4029 (93.4)        | 1.00     | ---     | ---     | 1.00 |  |
| Treatment interrupted |           |                     |                    |          |        |         |     |  |
| Yes               | 369 (4)     | 165 (3.3)           | 204 (4.7)          | 1.46     | 1.18-1.80 | <0.001 | 1.49 |  |
| No                | 8968 (96)   | 4859 (96.7)         | 4109 (95.3)        | 1.00     | ---     | ---     | 1.00 |  |
| Treatment Continued |            |                     |                    |          |        |         |     |  |
| Yes               | 723 (7.7)   | 407 (8.1)           | 316 (7.3)          | 0.89     | 0.77-1.04 | 0.163  | --- |  |
| No                | 8614 (92.3) | 4617 (91.9)         | 3997 (92.7)        | 1.00     | ---     | ---     | --- |  |
| Over all treatment success |         |                     |                    |          |        |         |     |  |
| Yes               | 7240 (77.5) | 4004 (79.7)         | 3236 (75)          | 0.76     | 0.69-0.84 | <0.001 | --- |  |
| No                | 2097 (22.5) | 1020 (20.3)         | 1077 (25)          | 1.00     | ---     | ---     | --- |  |