ORIGINAL ARTICLE

# Association between Smoking Habit and Pulmonary Tuberculosis at Dr. Soetomo General Academic Hospital

**Balivia Andi Permata Hapsari[1] , Prastuti Asta Wulaningrum[2]* , Rimbun[3]**

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[3]Department of Anatomy, Histology and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

**A R T I C L E   I N F O**

*\*) Corresponding author:*
prastuti_indrasaputra@yahoo.co.id

**A B S T R A C T**

**Introduction:** Smoking has been reported as one of tuberculosis (TB) risk factor. The association between smoking and TB has been proven in multiple studies, but little known about the association between smoking degree and sputum smear positive.
**Methods:** An analytic observational study using cross-sectional design. Data of patients with pulmonary TB conducted at DOTS (Directly Observed Treatment Short course)/MDR (Multi Drug Resistance) outpatient and inpatient ward in Dr Soetomo General Hospital Surabaya from January to October 2018. The degree of smoking was measured using Brinkman Index (BI). The odds ratio (OR) and 95% confidence intervals (CI) were also estimated.
**Results:** There were 94 patients with pulmonary TB, 56 non-smoker and 38 smoker. Light smoking (P = 0,120, OR = 0.200, 95% CI: 0.022-1.823), moderate smoking (P=0.377, OR = 1.667, 95% CI: 0.533-5.209), heavy smoking (P=0.076, OR= 0.333, 95% CI: 0.96-1.160). Moderate smoking compared to heavy smoking as a control (P=0.33, OR = 5.000, 95% CI=1.096-22.820).
**Conclusion:** There's no significant correlation between smoking habits and sputum smear positive, but the present study evidenced the patients with smoking habits had greater chance to get sputum smear positive than non-smokers. Patient with moderate smoking compared to heavy smoking had greater chance to get sputum smear positive.

## Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). Based on the WHO report in 2016 there were 10.4 million TB cases worldwide and 90% of the cases were adults and 62% were men. Indonesia is one of the 6 largest contributors to TB in the world.[1] WHO estimated that the number of TB patients in Indonesia is around 5.8% of the total number of TB patients in the world.[2] Based on the risk factors, pulmonary TB has exogenous and endogenous risk factors. Exogenous risk factors are risk factors that play an important role in accentuating the progression from exposure to infection while endogenous factors lead in progression from infection to active TB disease. Exogenous factors are mainly regulated of TB infection combined with intrinsic integration of the infectiousness of the source case, contact with TB patient, and another risk factor including smoking, alcohol, and indoor air pollution.[3] Transmission of pulmonary TB comes from person to person through the air. *M. tuberculosis* carried in airborne particles, called droplet nuclei, with a diameter of 1- 5 microns. The infectious droplet nuclei are produced when TB patients are talking, coughing, sneezing, screaming, or singing. Depending on the environment, these small particles can survive in the air for several hours.[4,5]

Smoking has significant association with increased risk of pulmonary TB depends on the number of cigarettes consumed every day.[6] Chronic and intermittent exposure to cigarette smoke causes morphological changes in the epithelium throughout the respiratory tract.[16] Moreover, continuous exposure to cigarette smoke can cause various changes in immunity, leading to increase in inflammation. The cigarette component will be deposited in the lung and activate many inflammatory factors causing damage to the lung structure.[7] A cross-sectional study conducted by Altet-Gomez et al 2005 found that smokers were more likely to develop *M. tuberculosis* because smokers had more cavity lesions

and were more likely to get smear positive.[8]

The association between smoking and TB has been proven in multiple studies,[3,6,8,10,17,18] but association between smoking degree and sputum smear positive has not yet received sufficient attention and it has never been done in other countries including Indonesia. Therefore, this recent study aimed to determine the association between smoking habit and sputum smear positive in one of top referral hospitals in Surabaya, Indonesia.

## Methods

This was analytic observational study performed using cross-sectional design. The study was conducted at DOTS (Directly Observed Treatment Shortcourse)/MDR (Multi Drug Resistance) outpatient clinic and inpatient room, Dr. Soetomo General Academic Hospital Surabaya from January to October, 2018. The populations of the study were all patients with pulmonary TB who were smoker and non-smoker.

The data of pulmonary TB have been completely written in medical record of each patient conducted by the expert doctor through structured interview and medical examination according to the guidelines pulmonary TB in Indonesia such as, taking medical history, physical examination, test for *M. tuberculosis* (tuberculin test), chest x-ray and bacteriologic examination of clinical specimens. The AFB was evaluated using the quickest and easiest procedure acid-fast staining technique called Ziehl-Neelsen (ZN). The smear of *M. Tuberculosis* was stained using carbol fuchsin combined with phenol. Following the carbol fuchsin, the stain was heated to enable the dye to penetrate the waxy mycobacterial cell wall. Then, acid alcohol will decolorize the stain and promalachite green as the closure stain. The smear was examined microscopically using the 100x oil immersion objective.

The data of smoker and non-smoker were obtained through structured questionnaire for smoking. Subjects who currently smoked cigarette got further questions regarding history of cigarette smoking, duration of smoking, number of cigarettes smoked per day and what age they started smoking. According to Indonesian Society of Respirology, smoking habits classified into three subgroups based on the value of Brinkman Index (BI) by multiplied the number of cigarettes smoked per day and the number of years of smoking. Light smoking (BI: 0-199), moderate smoking (BI: 200-600) and heavy smoking (BI: >600). We classified subjects who didn't have smoking history as non-smoker.[9]

Inclusion criteria in this study were subjects that agreed to participate in the study, patients with a new case of pulmonary TB were smokers (case group) and non-smokers (as a control group. The exclusion criteria in this study were patients with pulmonary TB that was not a new case (relapse, loss to follow up, and treatment failure) and subjects who refused to participate in the study. There were a total of 109 patients, 94 were included and 15 were excluded . The sample size of each group was 94 (38 were smokers, 56 non-smokers). Among 38 smokers, 6 were light smokers, 16 were moderate smoker and 16 were heavy smokers. The sampling technique in this research is conducted by using total sampling of the data. This study obtained data from questionnaire with live interview and medical records of patients with pulmonary TB.

The data obtained in this study will be analyzed using OR (Odds Ratio) to count retrospectively, then continue analyzed by SPSS v25 2018 to determine the risk estimates.

## Results

Table 1. The general characteristics of the patients

| Characteristics | Smoker n=38 | Non smoker n=56 |
|---|---|---|
| **Age (years)** | | |
| ≤20 | 2 (5,26%) | 8 (14,29%) |
| 21-30 | 2 (5,26%) | 2 (3,57%) |
| 31-40 | 6 (15,79%) | 9 (16,07%) |
| 41-50 | 11(28,95%) | 10 (17,86%) |
| 51-60 | 10 (26,32%) | 13 (23,21%) |
| 61-70 | 5 (13,16%) | 9 (16,07%) |
| 71-80 | 1 (2,63%) | 3 (5,36%) |
| 81-90 | 1 (2,63%) | 2 (3,57%) |
| **Gender** | | |
| Male | 37 (97,37%) | 25 (44,64%) |
| Female | 1 (2,63%) | 31 (55,36%) |
| **Education** | | |
| With no Education | 3 (7,89%) | 2 (3,57%) |
| Elementary School | 9 (23,68%) | 11 (19,64%) |
| Junior High School | 6 (15,79%) | 6 (10,71%) |
| Senior High School | 14 (36,86%) | 27 (48,22%) |
| Bachelor | 1 (2,63%) | 6 (10,71%) |
| Diploma 3 | 2 (5,26%) | 1 (1,79%) |
| Diploma 1 | 1 (2,63%) | 0 (0%) |
| Unknown | 2 (5,26%) | 3 (5,36%) |
| **Occupation** | | |
| Government employees | 2 (5,26%) | 3 (5,36%) |
| Private sector worker | 19 (50%) | 16 (28,57%) |
| House wife | 0 (0%) | 20 (35,70%) |
| Driver | 6 (15,79%) | 1 (1,79%) |
| Student/College Student | 1 (2,63%) | 4 (7,14%) |
| Unemployment | 2 (5,26%) | 3 (5,36%) |
| Retired | 3 (7,89%) | 5 (8,93%) |
| Teacher | 1 (2,63%) | 1 (1,79%) |
| Entrepreneur | 4 (10,54%) | 3 (5,36%) |

Table 2. Distribution of smoking degree patient with pulmonary TB based on Brinkman Index

| Smoking Degree | n | (%) |
|---|---|---|
| Light | 6 | 15,80% |
| Moderate | 16 | 42,10% |
| Heavy | 16 | 42,10% |

Table 3. The association between smoking degree and sputum smear positive

| Smoking Degree | AFB (+) | P (%) | OR (-) | 95% CI (%) | P | OR | 95% CI |
|---|---|---|---|---|---|---|---|
| Light smoking | 1 | 16,67% | 5 | 83,33% | 0,120 | 0.200 | 0.022-1.823 |
| Moderate smoking | 10 | 62,5% | 6 | 37,5% | 0,377 | 1,677 | 0,533-5,209 |
| Heavy smoking | 4 | 25% | 12 | 75% | 0,076 | 0,333 | 0,96-1,160 |

Table 4. The association between moderate smoking (heavy smoking as a control) and sputum smear positive

| Smoking Degree | AFB (+) | (%) | (-) | (%) | P | OR | 95% CI |
|---|---|---|---|---|---|---|---|
| Moderate smoking | 10 | 62,5% | 6 | 37,5% | 0,33 | 5.000 | 1,096-22,820 |
| Heavy smoking | 4 | 25% | 12 | 75% | | | |

### The general characteristic of subjects

The general characteristic of patients are summarized in table 1. Among the 94 TB patients, 62 (66.0%) were males. There were 38 (40.4%) patients who had smoking habits and 37 (97.37%) were men. 10 (26.32%) out of 23 patients were 51-60 years old and had smoking habits. Based on statistic calculation from 94 samples, the mean age of the respondents was 47.34±17.22 years. Based on education, the higher number of patients were graduated from senior high school and 14 (36.86%) out of 41 patients had smoking habits. 19 (50%) out of 35 patients were private sector worker and had smoking habits. 35.70% of patients are housewives and had no smoking habits.

### The distribution of smoking degree patients

The distribution of smoking degree patients based on BI are summarized in table 2. Light smoking 6 (15.80%), moderate smoking 16 (42.10%), heavy smoking 16 (42.10%).

### The association between smoking degree and sputum smear positive

According to table 3, there's no significant correlation between light smoking (P=0.120), moderate smoking (P=1.677) and heavy smoking (P=0.333) with sputum smear positive since the P value are (P>0,05), but light smokers (OR=0.200, 95% CI=0.022-1.823) had 0.200 times more chance to get a positive smear than non-smokers. Moderate smokers (OR=1.667, 95% CI=0,533-5.209) had 1.677 times more chance to get a positive smear compared to non-smokers. Heavy smokers (OR=0.333, 95% CI=0.96-1.160) had 0.333 times more chance to get pulmonary TB with smear positive than non-smokers.

### The association between moderate smoking (heavy smoking as control) and sputum smear positive

Due to the previous results, we obtained moderate smoking had greater chance to get smear positive than heavy smoking, so as comparison we re-analyse the association between moderate smoking (heavy smoking as a control group) and sputum smear positive, as we can see in table 4, the result showed there's no correlation between moderate smoking (P =0.33) and sputum smear positive (P>0.05), but moderate smoking (OR=5.000, 95% CI=1.096-22.820) had 5 times greater chance of incident sputum smear positive than heavy smokers.

### Discussion

Elderly people are more prone to infectious diseases including TB. This condition is associated with the loss or delay in regeneration of specific CD4+ T cell mediated immunity antigens which are very important in controlling infection. Failures to control infection makes *M. tuberculosis* spreads to other organs easily. This condition is caused by changes in thymus atrophy so that T-cell production is reduced.[10] In our study, we found that the most pulmonary TB patients in this study were adults within the age range of 51-60 years.

The prevalence of TB in the world is significantly higher among men than women, in this result we found the same study conducted by Horton et al (2016). This might happened because the number of smoking habits is higher in men and it leads to changes in structural pulmonary and make men more prone to get TB than women, who are less likely to have smoking habit.[11]

Based on our research, we found a higher number of pulmonary TB patients were graduated from high school with a total of 41 people (43.6%), just a few people who graduated from university. Level of education patients and TB cases in the world are related, because the higher the education, the easier it is for patients to absorb information and knowledge about certain diseases to lead a healthy life and overcome health problems.[12]

Occupation could correlate with pulmonary TB. Occupation which required someone to socialize with other people or work in an indoor environment has greater risk of exposure to *M. tuberculosis* transmission. Whereas farmers and fishermen who work in outdoors have a lower risk of being exposed to TB bacteria.[12] That might answer why the most job who got pulmonary TB is private sector worker who might work in indoor environment. However, our findings shows some of pulmonary TB patients were housewives (21.3%). Since the housewives was the second most higher number occupation in our sample and they were all women and most of them were hadn't smoking habits. To know more better we need more information about the condition of respondence house, the smoking habits between patient householder. They might be got smear positive and became susceptible because they became a passive smokers.[13] The high amount in housewives

might be related too with unhealthy house condition such as the lack of sun exposure, lighting of the house, occupancy density, the ventilation, indoor air quality, and humidity. Those are some requirements of healthy house which has been explained in the regulation of the minister of health of the republic Indonesia number 829/Menkes/SK/VII/1999 regarding of healthy house requirements.[14]

We found that there was no significant correlation between smoking habits and sputum smear positive but patient with smoking habits had greater chance to get sputum smear positive than non-smokers. Aside from that, we discovered unusual condition that moderate smoking had greater chance to get smear positive than heavy smoking.

Smoking habits highly contribute to functional changes, immunities, important structural changes in the respiratory epithelium. Chronic and intermittent exposure to cigarette smoker tend to be more vulnerable than non-smokers because of a structural change along the respiratory epithelium and decreasing viability of cell. In higher level of cell damage, regeneration of respiratory cell are hampered, inducing apoptosis of respiratory hair cells. Apoptosis effects itself depend on cigarettes exposure, low exposure of cigarettes concentration can cause hyperplasia to occur, higher concentrations lead to metaplasia and loss of cilia with keratinization and submucosal thickening.[15]

There's a difference between alveolar macrophages in patients with smoking habit and patients who have stopped smoking. When patient with current smoking habit and patients who have stopped smoking are infected with M. tuberculosis, their macrophages don't significantly secrete TNF-α, IFN-γ and IL-1β compared to macrophages of non-smokers. Although smokers produce many macrophages, the component of the macrophages itself are not enough to kill the pathogen compared to macrophages in non-smokers that are much more healthier and could eradicate the pathogen from the body.[16] The study by Qiu et al in 2017 said that smokers stimulate macrophages to produce more IL-8 which causes excessive inflammation rather than macrophage function itself against the pathogen.[17] This might explain that current smokers and patients who have stopped smoking are more at chance in getting smear positive than non-smokers because the alveolar macrophages function does not work properly.

Kalra et al. (2002) conducted an experimental study of chronic exposure to cigarette smoke. The experimental animals were given exposure to nicotine with dose of cigarettes similar to humans around two packs a day for 3-4 weeks. They found the exposure to cigarette smoke can affect the responsiveness of T cells, decrease proliferation of T cells and antibody responses. However, the mechanism of cigarette smoke towards T cell function is still unclear. The exposure to cigarette smoke could damage the antigen mediated signalling in T cells. Inositol-1,4,5-Triposhpat was sensitive to Ca2+ and it could reduce the ability of Ca2+ production in the body. Meanwhile the Ca2+ functions as ligation between T cell receptors and antigens. So, the T cell becomes anergy and it showed functional inaction to recognize the antigens. This suggesting people with heavy smoking habits have a higher chance of smear positive than non-smokers, because exposure of smoking cigarettes chronically could inhibit antibody cell formation and the body becomes more susceptible to the bacteria and other pathogen because of chaotic condition in immunity system.[18]

According to studies performed by Arcavi and Benowitz (2004), the number of CD4+ and CD8+ cells in light to moderate smokers were significantly increased, meanwhile in heavy smokers, CD4+ was decreased and CD8+ was increased. When the CD4+ is decreased, it indicated of low immune system and make it more susceptible to the infection. Other variant condition that could be found in heavy smokers were the low CD4+, high CD8+, or both were low that indicates of low immune system and make it more susceptible to infection too. The higher number of CD8+ could be related to neoplasia occurrence.[16] In addition, Matsumoto et al. (2012) found that most patient who had smoking habits had cavitary lesions and a high degree of sputum smear positive, which may lead to poorer treatment outcomes, and may also expose more surrounding people to infection.[19]

This study has several limitations. First, we did not have data regarding smoking habits between patient householder, because several studies have reported the underlying mechanisms of the impact of passive smoking on pulmonary TB. Second, we found that moderate smoking had greater chance of incident sputum smear positive compared to heavy smoking. This condition might be caused by the sample size of our study may not have been sufficient due limited time we had.

## Conclusion

There was no significant correlation between smoking degree and sputum smear positive, however, patient with pulmonary TB and having smoking habits had greater chance to get sputum smear positive than non-smokers which may lead to poorer treatment outcomes, and may also expose more surrounding people to infection.

## Acknowledgement

## Conflict of Interest

The authors declare that the manuscript with the title of Association between Smoking and Occurrence of Pulmonary Tuberculosis in Department of Anatomy, Histology and Pharmacology do not have any conflicts of interest.

## References

1. World Health Organization. The Global Tuberculosis Report. Geneva, Switzerland: WHO Press, 2016.
2. Depatermen Kesehatan Rakyat Indonesia. Pedoman Nasional Pengendalian Tuberculosis. Jakarta: Direktorat Jenderal Pengendalian Penyakit dan Penyehatan Lingkungan, 2011.
3. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. Pulm Med. 2013;2013:828939. doi:10.1155/2013/828939
4. Centers for Disease Control and Prevention, National Center for HIV, STD, and TB Prevention. Core Curriculum on Tuberculosis: What the Clinician Should Know. Sixth edition. Atlanta, Georgia: U.S. Department Of Health & Human Services Center For Disease Control and Prevention, 2013.
5. Brooks GF, Carroll KC, Butel JS, Morse SA, dan Mietzner, T.A. Mikrobiologi Kedokteran Jawetz, Melnick, & Adelberg. Ed.25. Jakarta: Buku Kedokteran EGC, 2013.
6. Alcaide J, Altet MN, Plans P, et al. Cigarette smoking as a risk factor for tuberculosis in young adults: a case-control study. Tuber Lung Dis. 1996;77(2):112-6. doi: 10.1016/s0962-8479(96)90024-6. PMID: 8762844.
7. Lee J, Taneja V, Vassallo R. Cigarette smoking and inflammation: cellular and molecular mechanisms. J Dent Res. 2012;91(2):142-149. doi:10.1177/0022034511421200
8. Altet-Gômez MN, Alcaide J, Godoy P, Romero MA, Hernández del Rey I. Clinical and epidemiological aspects of smoking and tuberculosis: a study of 13,038 cases. Int J Tuberc Lung Dis. 2005;9(4):430-436.
9. Perhimpunan Dokter Paru Indonesia. PPOK (Penyakit Paru Obstruktif Kronik) Diagnosis dan Penatalaksanaan. Jakarta: Perhimpunan Dokter Paru Indonesia (PDPI), 2011. hlm. 8-10.
10. Friedman A, Turner J, Szomolay B. A model on the influence of age on immunity to infection with Mycobacterium tuberculosis. Experimental Gerontology. 2008;43(4):275-285. https://doi.org/10.1016/j.exger.2007.12.004
11. Horton KC, MacPherson P, Houben RM, White RG, Corbett EL. Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. PLoS Med. 2016;13(9):e1002119. doi:10.1371/journal.pmed.1002119
12. Odone A, Crampin AC, Mwinuka V, et al. Association between Socioeconomic Position and Tuberculosis in a Large Population-Based Study in Rural Malawi. PLoS ONE. 2013;8(10): e77740. https://doi.org/10.1371/journal.pone.0077740
13. Leung CC, Lam TH, Ho KS, et al. Passive smoking and tuberculosis. Arch Intern Med. 2010;170(3):287-292. doi:10.1001/archinternmed.2009.506
14. Kemenkes RI. Keputusan Menteri Kesehatan Republik Indonesia Nomor: 829/Menkes/SK/VII/1999 tentang Persyaratan Kesehatan Rumah. Jakarta: Sekretariat Negara, 1999.
15. Tamashiro E, Cohen NA, Palmer JN, Lima WT. Effects of cigarette smoking on the respiratory epithelium and its role in the pathogenesis of chronic rhinosinusitis. Braz J Otorhinolaryngol. 2009;75(6):903-907. doi:10.1016/s1808-8694(15)30557-7
16. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med. 2004;164(20):2206-2216. doi:10.1001/archinte.164.20.2206
17. Qiu F, Liang CL, Liu H, et al. Impacts of cigarette smoking on immune responsiveness: Up and down or upside down?. Oncotarget. 2017;8(1):268-284. doi:10.18632/oncotarget.13613
18. Kalra R, Singh SP, Savage SM, Finch GL, Sopori ML. Effects of cigarette smoke on immune response: chronic exposure to cigarette smoke impairs antigen-mediated signaling in T cells and depletes IP3-sensitive Ca(2+) stores. J Pharmacol Exp Ther. 2000;293(1):166-171.
19. Matsumoto K, Arima K, Komukai J, et al. The association between smoking and sputum smear-positive pulmonary tuberculosis in Osaka City. Kekkaku. 2012;87(8):541-7.