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Factors influencing delay in sputum conversion in smear-positive pulmonary tuberculosis patients in primary care in Kuala Lipis Pahang

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***Abstract*---**objective. This study was conducted to investigate factors associated with delay in sputum conversion at first and second months during pulmonary tuberculosis treatment. Methods. A retrospective cross-sectional study was conducted in multicentre at primary care clinics in the district of kuala lipis pahang among newly diagnosed pulmonary tuberculosis patients in 2015-2019. Sociodemographic, clinical, and treatment-related data on patients' medical charts were collected using a standardized data collection form. Results. This study enrolled 147 participants with a mean age of 47.34 years. The sputum conversion rate at the end of the second month was 78.9%. Multiple logistic regression analysis was used to predict the factors that influence the delay in sputum conversion. The results found a statistically significant association ($p < 0.05$) to those patients with diabetes mellitus (aor 2.51) during the 1st and 2nd months (aor 1.52), smokers (aor 2.66) during the 1st and 2nd months (aor 4.56), being underweight (aor 4.56) at 1st month and (aor 3.34) at 2nd month and hiv positive status during the 1st month (aor 1.18) and 2nd month (aor 2.406) were found to be predicted factors that influencing with delayed sputum smear conversion at 1st and 2nd month during pulmonary tuberculosis treatment. Conclusion. The findings of this study indicated the sputum conversion rate in the district of kuala lipis is performing well, and patients with diabetics, patients with underweight, smoker, and hiv-positive have influences

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in delay sputum conversion. We could further improve success rates by closely monitoring patients identified as having risk factors. More attention on patients with the risk factors may increase tuberculosis treatment success rates, thus reduces the tb incidence in community

***Keywords*---**sputum conversion, pulmonary tuberculosis, factor influencing.

Introduction

Tuberculosis (TB) is a contagious infectious disease that is both fatal and curable. The bacteria *Mycobacterium tuberculosis* causes it. According to the World Health Organization (WHO), one of the emerging infectious diseases has infected one-third of the world's current population, and new infections occur at a rate of one per second. Tuberculosis is a highly contagious infectious disease prevalent throughout the country and continues to be a significant global health problem. Even though tuberculosis is curable, it kills nearly 2 million people each year and infects approximately 9 million. (WHO TB 2020). According to the WHO current statistics, communicable diseases account for three out of every ten deaths worldwide and account for 51% of Years of Life Lost globally (WHO TB 2020). Tuberculosis appears to be making a comeback and re-emerging as a global public health problem.

In 2018, Malaysia recorded 25 173 tuberculosis (TB) cases nationally (WHO TB 2020). The World Health Organization's End TB Strategy establishes an ambitious goal for countries to eradicate the global tuberculosis epidemic. The Pillar, one of the integrated strategies for patient-centered care and prevention, requires countries to improve their diagnosis and management of tuberculosis in high-risk groups. Although Malaysia has not succeeded in eradicating or reversing tuberculosis (TB), it has improved the management and prevention of tuberculosis control activities. The National Strategic Plan (NSP) for Tuberculosis Control (2016–2020) is being developed following the Regional Framework for Action on Implementation of the Western Pacific End TB Strategy (2016–2020). This NSP aims to strengthen the national tuberculosis response by aligning it with the most recent international evidence, strategic policies, and programmatic guidance. (STAG-TBWHO 2015).

According to WHO, all tuberculosis patients must be monitored throughout their anti-tuberculosis treatment to determine their response to therapy. The monitoring parameters include bodyweight and sputum smear examinations, which should be performed at the end of the intensive phase of treatment, among others (WHO TB 2020). Conversion of sputum smears in patients with pulmonary tuberculosis was the most important indicator for determining the efficacy of treatment and the disease's infectiousness. Non-conversion sputum smears at the end of the intensive phase of treatment have been linked to adverse outcomes, most notably default and failure. Even among patients with drug-sensitive tuberculosis (TB) isolates, there is considerable variability in response to pulmonary tuberculosis (TB) therapy. Although the precise cause is unknown, it could be due to variation in mycobacteria and host biologic factors, as well as

host behavioral factors (WHO TB 2020). Even when highly effective regimens are used, high cure rates are not frequently achieved consistently. Recent WHO reports indicate that countries that directly observed short-course chemotherapy (DOTS) had a cure rate of 78 %, while those that did not have a cure rate of 45%. In 97-100 % of the treated population, a 6-month chemotherapy antibiotic course results in a favorable response, as defined by culture negativity at the end of treatment. By contrast, the primary therapeutic challenge has been developing feasible regimens with low (5%) relapse rates. After two or three months, conversion of sputum smears late in treatment has been considered a good predictor of an eventual cure if treatment is completed (WHO TB 2020).

The primary objective of this study is to ascertain the factors that contribute to the delay in sputum conversation. According to the study and WHO recommendations, we examine the factors contributing to delayed sputum smear conversion. Thus, to achieve TB treatment success, the factors delaying the convention sputum collection must be investigated to reduce tuberculosis infection in the community and the rate of drug-resistant tuberculosis.

2. Materials and Methods

This retrospective cross-sectional study was conducted in multicentre throughout primary care clinics in Pahang Barat, Kuala Lipis. The data were gathered from three major Primary care Clinics, namely Klinik Kesihatan Sungai Koyan, Klinik Kesihatan Padang Tengku, and Klinik Kesihatan Pos Betau.

The sampling method used in this study was convenience sampling. Data collection took place between 14th June and 14th August 2021. The data collection instrument for this study was a data collection form. The data were manually collected from the patient's medical record file. The sputum AFB is obtained from the patient's medical records. Data on demographic, comorbidity, smoking status, and alcohol use were extracted from the medical record using the Tele-Primary Care Clinic (TPC) System.

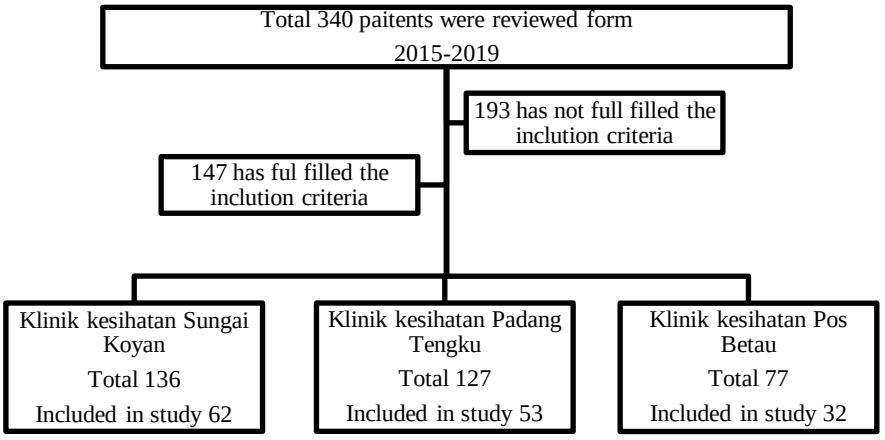
The collected data were entered into a Microsoft Xcel spreadsheet. The data has been analyzed using SPSS for Windows version 26.0 (Statistical Package for the Social Sciences) (IBM Corp, 2013). The results of categorical variables are presented as frequency and percentage, while the results of numerical variables are presented as mean and standard deviation. On the other hand, categorical data were analyzed using Pearson's chi-square, and Fisher's exact test will be used to determine the association between the variables. The level of significance was set to = 0.05. To predict the final independent variables, multiple logistic regression analysis is used. Each predictor was assigned an adjusted odd ratio (AOR), a 95% confidence interval (CI), a beta, a standard error, and a p-value. The chi-square, degrees of freedom, and p-value were used to determine the model's fit. Pseudo R square values were reported to indicate the model's percentage of variance explained. A 0.05 p-value was deemed statistically significant

The study has been registered with National Medical Research Register (NMRR) (ID NMRR-21-700-58225), and approval from the Medical Research and Ethics Committee (MREC) (KKM/NIHSEC/ P21-1199 (3)) has been obtained before

starting this study. Besides that, the Director of Public Health in Kuala Lipis District has granted access to medical records in Primary care clinics. This study has also adhered to the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline.

3. Results

A total of 340 records were reviewed on new smear-positive pulmonary tuberculosis patients who completed anti-tuberculosis treatment and attended the clinic from 2015 to 2019. From the total of 340 patients, 147 patients have been selected for this study.



Based on socio-demographic data, gender distribution was nearly equal among the 147 patient records examined. 77 patients (52.4%) are female, while 70 patients (47.6%) are male. Patients are on average 47.34 years old (SD ± 1.370). The majority, 93 (63.3%), were between the ages of 25 to 54 years, followed by 33 years (22.4 %) over the age of 65 years. The majority ethnic group was 64 (43.5%) Orang Asal, followed by 46 (31.3%) Malay. The majority of patients, 68 (46.3%), have no formal education, followed by 33 (22.4%) with secondary school education. 88 (59.9%) were of normal weight, while 44 (29.9%) were underweight. Following that, 99 (67.3 %) of respondents were non-smokers, while 48 (32.7%) were smokers. Then there is alcoholism, where only 14 (9.5%) consume alcohol. According to our population's comorbidity, 81 (55.1%) have no known medication illness, 25 (17.0%) have hypertension, 9 (6.1%) have diabetes, and 14 (9.5%) have asthma. Sputum grades at baseline were 66 (44.9%) +2, 40 (27.9%) +3, and 40 (27.9%) +1.

Sputum conversion rate is calculated by the number of smear-positive patients whose sputum was converted to smear-negative at the end of the specified time period is divided by the number of smear-positive patients who began treatment, and the ratio is multiplied by 100 to obtain the percentage. (3rd CPG Malaysia for tuberculosis) (TB RND 2004 Chennai). By week 2, a total of 55 (37.4 %) of 147 subjects had converted their sputum, while 92 (62.6 %) remained unconverted. Week 4 results indicate that 91 (61.9%) have converted, while 56 (38.1%) remain undecided. By week 8, 116 patients (78.9%) had been converted to smear-

negative status, while 31 patients (21.1%) remained unconverted. At the end of week 26, 144 (98.0%) of patients converted sputum, leaving only three 3 (2.0 %) unconverted.

Table 1 below is the summarised of the association between sputum conversion and demographic data at both months. In comparing the female population in this study, showed has higher converted sputum than males in both 1st and 2nd months of PTB treatment. The study showed a statistically significant association between gender and sputum conversion (p <0.05), whereby the female has higher sputum conversion than males in the 1st and 2nd months. The age was categorized based on Population Distribution and Basic Demographic Characteristic Report (Malaysia 2010). Most patients were at the age of 25-54 groups 59 (63.4%) were with sputum converted at 1st month and 71 (76.3%) at month 2 compare age group more than 65 only 17 (15.5%) at 1st month and 26 (78.8%) at month 2. The study showed no statistically significant association between age and sputum conversion (p >0.05) at both 1st and 2nd months. Sputum conversion was significantly higher in Bangladeshi 9 (81.8%) in the 1st month and 10 (90.9%) at the 2nd month of PTB treatment. However, there was no statistically significant association in Sputum conversion between ethnic groups in this study (p >0.05) at both months were recorded. The majority of patients have no formal education. The results indicated that patients with a university education had the highest sputum conversion rate of 17 (89.5%) at the 1st month and at month 2 was 18 (94.7%). In months 1 and 2, there was a slight difference in sputum conversion status between those with secondary education and those with no education. However, university education was higher in sputum conversion at both months, although the difference was no statistically significant association found (p >0.05) in both months.

VARIABLES	***1ST MONTH***			***2ND MONTH***		
	Converted n (%)	**Non-Converted n (%)**	**Validation** *p*-value	**Converted n (%)**	**Non-Converted n (%)**	**Validation** *p*-value
Gender						
Female	58 (75.3)	19 (24.7)	**<0.001[a] ***	68 (88.3)	9 (11.7)	**0.003[a] ***
Male	33 (47.1)	37 (52.9)		48 (68.6)	22 (31.4)	
Age						
15-24 Years	3 (75.0)	1 (25.0)	0.487[a]	3 (75.0)	1 (25.0)	0.429[a]
25-54 Years	59 (63.4)	34 (36.6)		71 (76.3)	22 (23.7)	
55-64 Years	12 (70.6)	5 (29.4)		16 (94.1)	1 (5.9)	
>65 Years	17 (15.5)	16 (48.5)		26 (78.8)	7 (22.2)	
Ethnicity						
Malay	26 (56.5)	20 (43.5)	0.365[a]	36 (78.3)	10 (21.7)	0.746[a]
Orang Asal	38	26		49	15	

Indonesian	(59.4)	(40.6)		(76.6)	(23.4)	
Bangladeshi	18 (69.2)	8 (30.8)		21 (80.8)	5 (19.2)	
Education Level	9 (81.8)	2 (18.2)		10 (90.9)	1 (9.1)	
None	39 (57.9)	29 (42.6)	0.068[a]	53 (77.9)	15 (22.1)	0.196[a]
Primary	17 (63.0)	10 (37.0)		22 (81.5)	5 (18.5)	
Secondary	18 (54.5)	15 (45.5)		23 (69.7)	10 (30.3)	
University	17 (89.5)	2 (10.5)		18 (94.7)	1 (5.3)	

Table 1 Association between demographic data and sputum conversion at both months
Fisher's Exact Test [b] Pearson Chi-Square [a]

Table 2 below summarizes the association between sputum conversion and demographic data at both months. Most of the patients had normal BMI. Patients with overweight BMI have the highest sputum conversion, 12 (80%) at 1st month and 2nd month 14 (93.3%). The study showed a statistically significant association between nutrition status and sputum conversion (p <0.05) at both months, whereby the obesity has higher sputum conversion than underweight in the 1st and 2nd month.

Most of the patients in our population were non-smokers. Results showed that non-smokers have a higher sputum conversion rate compared to smokers at both months. The study showed a statistically significant association between Smoking status and sputum conversion (p <0.05), whereby the non-smokers have higher sputum conversion than smoke in the 1st and 2nd months. Most of the respondents never take alcohol, and the results showed a lower sputum conversion status among alcohol at both months compared to never taking alcohol. The study showed a statistically significant association between alcoholism status and sputum conversion (p <0.05), whereby the non-alcoholic have higher sputum conversion compared to an alcoholic in 1st and 2nd month.
From the data, patients with hypertension have the highest conversion rate, 21 (84.0%) in the 1st month and 24 (96.0%) at month 2. Meanwhile, patients with diabetes and hypertension have the lowest sputum conversion 2 (15.4%) in 1st month and 8 (61.5%) at month 2. The study showed a statistically significant association between comorbidity, especially diabetics and patients with both comorbidities (p <0.05). The patient with hypertension, asthma, and no comorbidity have no statistically significant association with delay in sputum conversion at both months. Thus, patients with hypertension have higher sputum conversion than diabetic patients in the 1st and 2nd months.

The data shows that patients with positive HIV have 0 (0%) conversion at 1st and 2nd months. The study showed a statistically significant association between HIV status and sputum conversion (p <0.05).

Form data patients with have patients with a high baseline of 3+ has the lowest conversion rate of 4 (9.8%) at 1st month and 20 (48.8%) at month 2, compared to patients with a baseline on 1+ 38 (95.0%) at month 1 and 40 (100%) at month 2. In 1st month, the study showed a statistically significant association between patients with a baseline of +2 and +3 and sputum conversion (p <0.05). Thus at 2nd month, patients with a baseline of +2 and +3 showed a statistically significant association to delay in sputum conversion. Thus, patients with +1 have no statistical association and have the highest sputum conversion compared to patients with a baseline of +3.

Variables	***1st month***			***2nd month***		
	Converted n (%)	**Non-Converted n (%)**	**Validation** *p*-value	**Converted n (%)**	**Non-Converted n (%)**	**Validation** *p*-value
Nutrition status						
Underweight	11 (25.0)	33 (75.0)	**<0.001[a*]**	22 (50.0)	22 (50.0)	**<0.001[a*]**
Normal	68 (77.3)	20 (22.7)		80 (90.9)	8 (9.1)	
Overweight	12 (80.0)	3 (20.0)		14 (93.3)	1 (6.7)	
Obesity	0 (0)	0 (0)		0 (0)	0 (0)	
Smoking History						
Smoking	17 (35.4)	31 (64.6)	**<0.001[b*]**	28 (58.3)	20 (41.7)	**<0.001[b*]**
Not Smoking	74 (74.7)	25 (25.3)		88 (88.9)	11 (11.1)	
Alcoholism			**<0.001[b*]**			**0.002[b*]**
Yes	2 (14.3)	12 (85.7)		6 (42.9)	8 (57.1)	
No	89 (66.9)	44 (33.1)		110 (82.7)	28 (17.3)	
Comorbidity						
Diabetics	3 (33.3)	6 (66.7)	**0.003[b*]**	6 (66.7)	3 (33.3)	**0.006[b*]**
Hypertension	21 (84.0)	4 (16.0)	0.144[b]	24 (96.0)	1 (4.0)	0.146[b]
Diabetic and Hypertension	2 (15.4)	11 (84.6)	**<0.001[b*]**	8 (61.5)	5 (38.5)	**0.012[b*]**
Asthma	11 (78.6)	3 (21.4)	0.410[b]	12 (85.7)	2 (14.3)	0.783[b]
No	54 (66.7)	27 (48.2)	0.188[a]	66 (81.5	15 (18.5)	0.422[b]
HIV status						
Negative	91 (64.1)	51(35.9)	**0.007[b*]**	116 (81.7)	26 (18.3)	**<0.001[b*]**
Positive	0 (0)	5 (100)		0 (0)	5 (100)	
Sputum						
Base Line	4 (9.8)	37 (90.2)	**<0.001[b*]**	20 (48.8)	21 (51.2)	**0.012[a*]**
+3	49 (74.2)	17 (25.8)	**<0.001[b*]**	56 (84.8)	10 (15.2)	**0.025[b*]**
+2	38 (95.0)	2 (5.0)	0.125[b]	40 (100)	0 (0)	0.154[b]
+1						

Table 2 Association between clinical factors data and sputum conversion at both months
Fisher's Exact Test [b] Pearson Chi-Square [a]

Tables 3 below summaries the predicted factors that contribute to the delay in sputum conversion during the first and second months of PTB treatment. Gender, nutritional status, smoking history, alcoholism, comorbidity, HIV status, and baseline sputum were all associated with sputum conversion. Multiple logistic regression was used to analyze the predicted factors. Patients with low body weight or underweight (AOR 4.563 95% CI 0.291-0.407) at the 1st month and 2nd month (AOR 3.346 95 % CI 0.094-0.365). Patients who are smokers (AOR2.664 95% CI 0.044-0.297) at the 1st month and 2nd month (AOR 2.163 95% Cl 0.012-0.274) remained significantly associated with delayed sputum conversion in treatment. The significance was also observed in diabetic patients (AOR 2.511 95% CI 0.271-0.533) during the 1st month and 2nd months (AOR 1.521 95% Cl 0.039-0.181) and also patients with both comorbidities at 1st month (AOR 3.189 95% CI 0.170-0.725) and 2nd month (AOR 1.015 95% CI 0.164-0.405). Meanwhile, patients with hypertension, asthma, and no comorbidity have no significant association with sputum conversion delay in both months. In contracts, patients with a high sputum base line+3 demonstrated significant (p = 0.002) sputum conversion during the 1st month but no significance (p = 0.064) during the 2nd month of PTB treatment.

Variables	1st month B (Beta)	SE (Standard error difference)	p value	Adjusted oR (AOR) Cl 95%	2nd month B (Beta)	SE (Standard error difference)	p value	Adjusted oR (AOR) Cl 95%
Gender Male	0.085	0.673	0.899	1.089(0.291-0.4074)	0.003	0.062	0.963	0.046(-0.119-0.125)
Nutrition status								
Underweight	0.303	0.602	**<0.001***	4.563(0.172-0.434)	0.229	0.069	**0.001***	3.346(0.094-0.365)
Overweight	-0.045	0.900	0.643	-0.500(-0.224-0.133)	0.017	0.093	0.853	0.185(-0.167-0.202)
Smoking History Yes	0.170	0.064	**0.009***	2.664(0.044-0.297)	0.143	0.066	**0.032***	2.163(0.012-0.274)
Alcoholism Yes	0.048	0.104	0.643	0.464(-0.158-0.255)	0.160	0.108	0.140	1.484(-0.053-0.373)
Comorbidity	0.115	0.141		2.511(0.271-0.533)	0.106	0.145	**0.011***	1.521(0.039-0.181)
Dm	0.053	0.128	**0.003***	0.418(-0.200-0.306)	-0.163	0.132	0.218	-0.730(-0.200-0.306)
HPT	-0.024	0.129	0.677	-0.182(-0.208-0.233)	-0.137	0.134	0.308	-1.023(-0.401-0.128)
Asthma	0.477	0.140	0.856	3.189(0.170-0.725)	0.122	0.145	**0.031***	1.015(0.164-0.409)
Both			**0.002***					
HIV status Yes	0.235	0.198	**0.002***	1.185(0.158-0.255)	0.492	0.204	**0.004***	2.406(0.088-0.896)
Sputum Base Line	0.453	0.144		3.142(0.168-0.738)	0.267	0.149	0.064	1.791(-0.028-0.561)
+3	0.032	0.127	**0.002***	0.255(-0.219-0.284)	0.151	0.131	0.251	1.153(-0.108-0.411)
+2	-0.133	0.130	0.799	-1.020(-0.391-0.284)	0.020	0.135	0.881	0.149(-0.246-0.286)
+1			0.310					

Tables 3 The predicted factors that contribute to the delay in sputum conversion during the first and second months of PTB treatment

Discussion

The best method to monitor the treatment outcomes of a pulmonary tuberculosis smear-positive case is to check for sputum conversion from smear-positive to smear-negative (Arora VK et al., 2003). The sputum conversion rate among 147

patients of newly diagnosed PTB-positive patients has been identified in this study. In this study, we found that in the 1st month, the sputum conversion rate was at 61.9%, and during the intensive phase of treatment (2nd month), the conversion rate was 78.9%. WHO considers a well-functioning national tuberculosis program to have at least a 75% conversion rate at month 2 among newly diagnosed PTB positive (STAG-TBWHO 2015). This study showed that the tuberculosis clinic in the district of Kuala Lipis appears to be performing well in this area. This result is maybe due to the effectiveness of the DOT program implemented by MOH and WHO. Comparing sputum conversion rates between studies is difficult since different researchers used different definitions of Sputum conversion rates. Some include all newly diagnosed smear-positive PTB patients (Concepcion F et al., 1997). (Fujiki A. et al.,2002). Other studies conducted by Arora VK et al., (2003), and Hadlock HP et al., (1980), included only those patients who had a smear result available following the intensive phase of treatment. Our Malaysian CPG for tuberculosis management, third edition, has also adopted this method. The sputum conversion rate among new PTB patients in our study is lower than that found in other studies conducted by Gothi GD et al. (1979) in Tanzania, 98.6 %. Another study conducted by Zhao FZ et al., (1998) in China found a sputum conversion rate of 95.0 %. Meanwhile, a few studies conducted in Thailand by Frimpong EH et al., (2005) found a sputum conversion rate of 75.0 %. Even though the sputum conversion rate at the end of two months in Malaysia remained above the target level (>85 %), in 2008, 7.65 % of infectious tuberculosis patients reported delays in sputum conversion. (MOH Report 2008).
Based on the data collected, we found that the female patients were higher than their male counterparts. In multiple regression, we found no significant association, and being male is not a predicted factor in the delay in sputum conversion at 1st and 2nd months. The rate of conversion at 1st and 2nd months showed that female patients had a higher sputum conversion rate than males, and the result showed a statistically significant association between gender and sputum conversion 1st month (p = <0.001), 2nd month (p = 0.003). The data at 2nd month after PTB treatment showed similar results that females had the highest conversion rate compared to males. This result may be explained by women having better health-seeking habits than men (Nandawula et al., 2013). In addition, the more significant proportion of women compared to men in the general population might also explain the result. The current study revealed that men were two times likely to remain sputum smear-positive compared to women. Women have better health-seeking habits, such as early seeking medical attention leading to early diagnosis and, hence, a better treatment outcome than men. Similar findings have been reported in a study done in Tanzania (Kidola, et al., 2009) in which men are about 2 times more likely to persist with a positive sputum smear than women.

The large portion 93 (63.3%) representation of patients aged 25-54 years may be explained by the large proportion of mid-aged adults in the general population in Kuala Lipis. Kuala Lipis is a district that consists of a few Felda (oil palm plantations) with many foreign workers. Kuala Lipis also has the largest orang Asal settlements in Malaysia that explaining the highest number of patients were for orang Asal 64 (43.5%), most of our patients have no formal education 68 (46.3%). The results showed that patients in the age group of 15-24 had the highest sputum conversion at 1st month then at 2nd month meanwhile patients in

age group 55-64 were the second highest. The data showed no statistically significant association between age and sputum conversion at the 1st month (p = 0.487) and the 2nd month (*p* = 0.429). However, this result is contradicted to other studies that were done. Other studies have found age to be an independent predictor of non-conversion of the positive smears at 8 weeks of treatment.

In his study, Singla. et al., (2003) observed that patients over 60 years had an almost six times greater risk of remaining sputum positive after two months of treatment than patients aged 21-40 years, while patients aged 41-60 years were twice as likely to remain sputum positive. Kuaban. et al., (2009) also found age above or equal to 40 years significantly associated with sputum smear non-conversion. Banu Rekha et al., (2007) conducted a study among pulmonary tuberculosis patients that showed that being male was associated with a lack of sputum smear conversion at the end of the intensive phase. Most commonly, the explanations given by other researchers to explain the reason why men were more likely to experience a delay in sputum smear conversion after the intensive treatment compared with women were related to smoking and alcohol consumption. This result that is obtained from our study is maybe due to the smaller sample size.

Ethnicity data has shown no statistically significant association between ethnicity and sputum conversion 1st (*p* = 0.365) and 2nd month (*p*=0.746). The small population distribution among ethnicity can explain this result among patients in Kuala Lipis. There were no Chinese and Indian patients were recorded in our study populations. This result has also been similar to a study done by Shariff NM et al. (2015). There were no significant associations between ethnicity status and sputum smear conversion. Thus, Malay ethnicity has the highest conversion rate compared to another ethnicity. Next on education level showed that patients with a university as their education background had the highest sputum conversion rate at 1st month was 17 (89.5%) a month 2nd was 18 (94.7%). The results showed a slight difference in sputum conversion status among secondary and no education in months 1 and 2. However, university education was higher in sputum conversion at both months, although the difference was not statistically significant association 1st month (p = 0.068), 2nd month (*p* = 0.196). These results may explain that knowledge is not a critical factor in sputum conversion. Thus, the critical factors in tuberculosis disease will be the compliance taken care of by DOT therapy and personal hygiene. The study conducted by Shariff NM. et al. (2015) found no associations between education level and sputum conversation. He has concluded that no association between socio-demographic with sputum conversion. We can conclude that there were no significant and no association with socio-demographic data with sputum conversion. However, there is a statistically significant association between gender and sputum conversion at 1st and 2nd months. Thus, in multiple regression, it showed there was no statistically significant association between gender with delay in sputum conversion

Base on body mass index patients has been grouped on their BMI underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-24.9 kg/m^2) and obesity (>30kg/m^2). In this study, most patients are in the normal weight group 88(59.9%), and with no obesity, groups are recorded. This distribution is maybe due to our setting in non-urban. Based on data showed that overweight (at 1st

month 12 (80%), 2nd month 14 (93.9%)) patients have a higher conversion rate compared to underweight 1st month 11 (25%), 2nd month 22 (50.0%). The statistical analysis showed that the 1st month (p = <0.001) and 2nd month (p=<0.000) are statistically significantly associated with sputum conversion. In multiple logistic regression, there were significantly associated with delay in sputum conversion at 1st and 2nd month in the underweight group. Thus, underweight patients have a higher odd ratio of 4.561 (p = <0.001) in 1st month and 3.34 (p = 0.001) in 2nd month. Schaible et al. (2007) did a study that concluded that nutrition imbalance or being underweight could weaken the immune system by T cell suppression and affect TB prevalence. Our finding also that supported by a study done by Shariff NM. et al. (2015), BMI (body mass index) was shown to be significantly associated with sputum smear non-conversion after 2 months of tuberculosis treatment (p = 0.025). Being underweight and obese were proven to be a causative factor towards sputum smear non-conversion compared with those with ideal body weight. Park Ho et al. (2016) conducted another study, showed that Low BMI was an independent risk factor for failure to achieve sputum culture conversion. Another study by Putri FA et al. (2014) concluded that severe underweight was associated with a longer time to initial sputum culture conversion.

From the data, the smoking history was recorded as smoker and non-smoker. Most of the patients in this study were non-smoker, 99 (67.3%), and smokers were 48 (32.7%). Based on sputum conversion, we found that smokers had a slower conversion at the 1st month 17 (35.4%),2nd month 28 (58.3%) compared to non-smoker. However, in the 1st month (p = 0.00) and 2nd month (p = 0.000), there was a statistically significant association between smoker and non-smoker sputum conversion. A study by B. Jayakrisnan et al., (2005) contradicts our finding that no statistically significant association between smoking and sputum smear conversion at the end of the intensive treatment. His study suggests that smokers and non-smokers converted with almost the same rate to a negative sputum status. However, a study by Metanat et al., (2010) suggested a different finding, saying that there was a significant delay in sputum smear conversion time between smokers and non-smokers. These findings were contraindicating with our study. In multiple logistic regression, there were significantly associated with delay in sputum conversion at 1st and 2nd month in the smoker's group. Thus, smoker patients have an odds ratio of 2.664 (p = 0.009) at 1st month and 2.163 (p = 0.032) at 2nd month. Smoking status also is a predicted factor in the delay in sputum conversion among our population. These results also explain the risk of smokers to TB and other rays of complication. Pulmonary tuberculosis's main site of infection is the lungs and a cascade of inflammation manifests the disease. Being a smoker, the surface of the lung will be bruised or damaged by millions of chemicals that the smoker has inhaled. This is also the main triggering factor in prolonging of sputum conversion (Mokti et al., 2021).

Based on the study population, we found that most of our patients were non-alcoholic, 133 (90.5%) and 14 (9.5%) were alcoholics. This distribution may be due to the study setting in a non-urban area. We found that patients that consume alcohol have a slower sputum conversion compared to non-alcoholic patients. Based on the study's data, we found a statistically significant association between alcoholism and sputum conversion at 1st month (p = <0.001)

and 2nd month (p = <0.001). The multiple logistic regression between the predicted factors, we found alcoholism has no significant difference (p = 0.643) 2nd month (p = 0.140). This finding is maybe the small sample size of alcoholic patients in our study setting. This result is also supported by a study by Avril & Chee et al., (2017). The risk of active tuberculosis is substantially elevated in people who drink more than 40 g of alcohol per day or have an alcohol use disorder. He has concluded that alcoholism and sputum conversion did not give significantly different results at the end of the intensive phase. Another study by Soh AZ et al., (2017) found that low alcohol intake may protect against active TB, sputum conversion, and alcoholism have no association.

The other clinical factor that was studied in this study is comorbidity. Patients were grouped in people with diabetes 9 (6.1%), hypertension 25 (17.0%), Both with hypertension and diabetics 13 (8.8%), asthma 14 (9.5%), and patients with no comorbidity 81(55.1%). Based on our study, a large percentage were with no comorbidity. We found that patients with both diabetics and hypertension (1st month 2 (15.4%), 2nd month 8 (61.5%) have the lowest sputum conversation compared to other comorbidities and also patients with people with diabetes also found be the next slowest sputum conversion compared to another comorbidity. Thus both of these comorbidity showed a statistically significant association in sputum conversion at both months. Other comorbidity does not show a statistically significant association to sputum conversion at both months in PTB treatment. The statical analysis showed an association between diabetic status and sputum conversion in the 1st month (p = 0.003) and 2nd month (p = 0.006). In multiple regression, we found that patients with people with diabetes (p =0.003 AOR 2.511 95% Cl 0.271-0.533) at 1st month and at 2nd month (p = 0.011 AOR 1.52195% Cl 0.039-0.181) and patients with both hypertension and diabetics also showed a statistically significant association (p = 0.002 AOR 3.189 95%Cl 0.170-0.725) at 1st month and 2nd month was (p = 0.031 AOR 1.015 95% Cl 0.164-0.409). From this data, we can predict that people with diabetes have influenced the delay of sputum conversion in PTB treatment. This result was also supported by a study done by Shariff NM. et al., (2015), which found that patients with diabetes mellitus were three times more likely to have sputum smear non-conversion at the end of intensive treatment than those without this metabolic deficiency. This positive association was increased up to four times after controlling for other risk factors in the multivariable analysis.

The other study that we conducted in Indonesia (B. Alisjahbana et al., 2007), China (F. Mi et al., 2013), Saudi Arabia (L.A. Chaudhry et al., 2012), and India (A.A. Viswanathan et al., 2014). These studies agree that diabetes significantly impacts the patients' sputum smear conversion. According to Pablos-Mendez A et al. (1997), that diabetic patients as a group are more susceptible to having a more aggressive course of tuberculosis disease. According to Bashar et al. (2001) suggesting that diabetic patients have some degree of impaired gastrointestinal drug absorption, even in the absence of clinical gastroparesis. Not only that, the hyperglycaemic state may additionally interfere with achieving adequate tissue levels of the medications. This finding can have a better care plan for patients with diabetes in managing their diabetics and tuberculosis diseases.

In our study population, we found only 5 (3.4%) of patients with positive HIV. The analysis found that all patients with positive HIV did not have their sputum converted at the end of week 14 the conversion happened at week 20, 2 (40%) patients, and another 3 (60%) patients at week 28. The statistical analysis found a statistically significant association with the delay in sputum smears after two months. In multiple logistic regression, we found that HIV positive has a statistically significant association between delay in sputum conversion with HIV Positive (p =0.002 AOR 1.185 95% Cl 0.158-0.255) at 1st month and 2nd month (p =0.004 AOR 2.406 95% Cl 0.088-0.896). This result is similar to several studies showing that HIV-positive patients co-infected with pulmonary tuberculosis show delayed sputum conversion. A study conducted by Fortún J et al., (2007) showed that HIV and sputum conversion is highly associated with sputum conversion delays. Bwire et al., (1999) found that HIV was a primary factor in delaying sputum smear conversion among tuberculosis patients at St. Francis hospital Buluba. Kayigamba FR et al., (2013) conducted the other study found that HIV infection is a significant independent predictor of failure of sputum smear conversion at 2 months among PTB+ patients. Poor adherence to TB treatment is a significant independent determinant of mortality. According to Akolo et al., 2010 the isoniazid effect will be decreased by drug interaction with anti-viral therapy drugs. Thus, special care and attention are needed for patients in co-infection of positive HIV to avoid transmission of TB to the community.

The final clinical factor was the baseline sputum. Patients were grade into +1 40 (27.2%), +2 66 (44.9%), +3 41 (27.9%). From the data, we can conclude that patients with a high baseline (+3) have a slower conversion rate than patients with a lower baseline (+1). The statistical analysis showed that for patients with a baseline of +3 in 1st month (p = <0.001), 2nd month (p = 0.012) and patients with baseline +2 in 1st month (p = <0.001), 2nd month (p = 0.025), has statistically significant association between baseline sputum and sputum conversion in both months. However, no statistically significant association was found for patients with a baseline of +1 in 1st month (p = 0.125), 2nd month (p=0.154). In multiple logistic regression, we found that patients with a high baseline (+3) showed a significant association in delay in sputum conversion at 1st month (p = 0.002 AOR 3.142 95% Cl 0.168-0.738) and but at 2nd month (p = 0.064 AOR 1.791 95% Cl -0.028-0.561) it showed no significant difference in sputum delay in 2nd month of PTB treatment. Thus, this result is also supported by few studies that were conducted. A study conducted by Yihunie Akalu Tet al., (2018) showed that patients smear +2 and +3 resulted in delayed culture conversion time at 1st month in PTB treatment. The other study conducted in Indonesia Putri FA et al., (2014) and Korea by Lee HY et al., (2014), found that patients with high smear grading had a high bacillary load. A high bacillary burden suggests stronger infectivity and requires a longer isolation period and more intensive treatment. Thus, Lee HY et al., (2014) has concluded that it needs to clear the bacilli if the bacillary load is high. The other finding of Caetano Mota et al., (2012) was that the presence of a high bacillary load is better associated with a reduction in bacterial killing and sterilizing activity of anti-TB drugs. It may be natural that patients with higher colony counts take a longer time to convert sputum cultures.

Based on these results and finding from this study population data, we can conclude that there is a significant and association between comorbidity,

especially patients with diabetics, HIV status, patients with underweight, and smoking status showed significantly and association in delay sputum conversion at 1st month and 2nd month.

Conclusion

In conclusion, numerous factors were predicted to cause a delay in the sputum conversion. We predicted that males have a more significant delay in sputum conversion than females. However, there were no a statistically significant association between male and delay in sputum conversion in multi regression analysis. Whereby other socio-demographic factors remain unrelated to sputum conversion delay.

There is a significant association between comorbidity, particularly in diabetic patients, who had an AOR of 2.551 at the 1st month and 1.521 at the 2nd month. As a result of this finding, we can conclude that diabetic patients have a greater likelihood of experiencing a delay in sputum conversion during the 1st and 2nd months of PTB treatment. The following clinical factor that has a statistically significant association with delay in sputum conversion is HIV positivity. Using multiple regression, we discovered that HIV positivity is associated with delay in sputum conversion during the 1st month AOR 1.185 and 2nd month AOR 2.406.HIV positivity is the second predicted factor in sputum conversion delay during the 1st and 2nd months of PTB treatment. Patients with low body weight or underweight were found to have the highest probability of delaying sputum conversion at the 1st and 2nd month AOR 4.563 and 2nd month AOR 3.346. Thus, being underweight is the third predicted factor in the delay of sputum conversion during the first and second months. Finally, smoking status was found to be a statistically significant association with a delay in sputum conversion at the 1st and 2nd months. Multiple regression analysis revealed that smokers have AOR 2.664 in the 1st month and AOR 2.163 in the 2nd month. The smoker is the fourth and final predicted factor in the delay in sputum conversion in the first and second months, respectively.

Finally, we can increase success rates even more by closely monitoring clinical factors in patients who have been identified as having risk factors. Similarly, more attention and a strict treatment follow-up may increase tuberculosis treatment success rates. Clinicians may advise patients with diabetes to control and monitor their glycemic level even more strictly, smokers to quit, and those underweight to be closely monitored and given a fully supervised treatment and counselling regimen for the duration of chemotherapy to prevent treatment failure and improve treatment outcomes.

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References

1. World Health Organization. Tuberculosis country profiles: Malaysia Geneva: World Health Organization; 2020.
2. https://www.who.int/tb/country/data/profiles/en. Accessed 3rd April 2020.
3. Management of Tuberculosis Malaysia 3rd edition
4. Centers for Disease Control and Prevention (CDC), Division of Tuberculosis Elimination. Core Curriculum on Tuberculosis: What the Clinician Should Know. 4th edition (2000). Updated August 2003.
5. Management: Directly Observed Therapy, New York City Department of Health, 2001.
6. K. E. Dooley and R. E. Chaisson 2009, "Tuberculosis and diabetes mellitus: convergence of two epidemics," The Lancet Infectious Diseases, vol.9, no.12, pp.737–746,2009
7. Suyono, Slamet. 2004. Buku Ajar Ilmu Penyakit Dalam. Edisi ke-3. Jakarta: Fakultas Kedokteran Universitas Indonesia
8. Prayitno, A., Suyono, B., Suryanto, E., & Suparto, R. (2006). Tes Diagnostik Sputum pada Penderita Tuberkulosis Paru. BioSMART, 7(1):14-15
9. Doenges, Marilynn E. 2005. Nursing Diagnosis Manual. Philadelphia: Davis Company Francis, Caia. 2011. Pera
10. Mansjoer, A (2000) Kapita Selekta Kedokteran jilid I. Jakarta: Media Aesculapius.
11. K. E. Dooley and R. E. Chaisson, "Tuberculosis and diabetes mellitus: convergence of two epidemics," The Lancet Infectious Diseases,vol.9,no.12,pp.737–746,2009
12. Daniel TM. The origins and precolonial epidemiology of tuberculosis in the Americas: can we figure them out? Int J Tuberc Lung Dis. 2000 May;4(5):395-400. PMID: 10815731.
13. Ait-Khalid N, Alarcon E, Armengol R, Bissell K, Boillot F, Caminero JA, et al. management of tuberculosis: a guide to the essentials of good practice. Sixth ed. Paris,France: International Union Against Tuberculosis and Lung Disease; 2010.
14. Treatment of tuberculosis guideliness. Forth ed: World Health Organization; 2010. p.24-5.
15. Rieder HL. Epidemiologic Basis of Tuberculosis Control. First ed. Paris: International Union Against Tuberculosis and Lung Disease; 1999.
16. Ayele WY, Neill SD, Zinsstag J, Weiss MG, Pavlik I. Bovine tuberculosis: an old disease but a new threat to Africa. Int J Tuberc Lung Dis. 2004;8(8):924-37.
17. APIC Indiana - Extrapulmonary TB. https://apicin.org/Extrapulmonary_TB
18. R. F. Mary Jones, *Cambridge International AS and A level Biology Coursebook Third Edition* (pp. 208-211). United Kingdom: Cambridge University Press 2013
19. Payam Nahid, Susan E. Dorman, Narges Alipanah, Pennan M. Barry, Jan L. Brozek, Adithya Cattamanchi, Lelia H. Chaisson, Richard E. Chaisson, Charles L. Daley, Malgosia Grzemska, Julie M. Higashi, Christine S. Ho, Philip C. Hopewell, Salmaan A. Keshavjee, Christian Lienhardt, Richard Menzies, Cynthia Merrifield, Masahiro Narita, Rick O'Brien, Charles A. Peloquin, Ann Raftery, Jussi Saukkonen, H. Simon Schaaf, Giovanni Sotgiu, Jeffrey R. Starke, Giovanni Battista Migliori, Andrew Vernon, Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, *Clinical Infectious Diseases*, Volume 63, Issue 7, 1st October 2016, Pages e147–e195, https://doi.org/10.1093/cid/ciw376

20. K. Gholami, E. Kamali, M. Hajiabdolbaghi, and G. Shalviri. Evaluation of anti-tuberculosis induced adverse reactions in hospitalized patients. pharmacy practice, 2006; 4(3): 134– 138.
21. Lienhardt C, Fielding K, Sillah JS, Bah B, Gustafson P, Warndorff D, Palayew M, Lisse I, Donkor S, Diallo S, Manneh K, Adegbola R, Aaby P, Bah-Sow O, Bennett S, McAdam K. Investigation of the risk factors for tuberculosis: a casecontrol study in three countries in West Africa. Internet J Epidemiol., 2005; 34: 914-23. 8.
22. M. Sharma, KVyas, J. et. al. (2016 14th November, Updated). Sputum stain for mycobacteria. MedlinePlus Medical Encyclopedia.
23. Feng-Zeng Z, Levy M H, Sumin W. Sputum microscopy results at two and three months predict outcome of tuberculosis treatment. *Int J Tuberc LungDis.* 1997; 1:570–572.
24. STAG-TBWHO. https://www.who.int/tb/advisory_bodies/stag_tb_report_2015.pdf
25. Agarwal R, Malhotra P, Awasthi A, Kakkar N, Gupta D (2005). "Tuberculous dilated cardiomyopathy: an under-recognized entity?". *BMC Infect Dis* 5 (1): 29. doi:10.1186/1471-2334-5-29. PMID 15857515
26. Greta Musteikienė, Skaidrius Miliauskas, Jurgita Zaveckienė, Marius Žemaitis, Astra Vitkauskienė, Factors associated with sputum culture conversion in patients with Pulmonary Tuberculosis, Medicine, Volume 53, Issue 6,2017
27. Cole E, Cook C (1998). "Characterization of infectious aerosols in health care facilities: an aid to effective engineering controls and preventive strategies." *Am J Infect Control* 26 (4): 453–64. doi:10.1016/S0196-6553(98)70046-X. PMID 9721404
28. Gutierrez MC, Brisse S, Brosch R, *et al.* (September 2005). "Ancient origin and gene mosaicism of the progenitor of Mycobacterium tuberculosis." *PLoS Pathog.* 1 (1): e5. doi:10.1371/journal.pp.0010005. PMID 16201017. PMC:1238740.
29. Djouma FN, Noubom M, Ateudjieu J, Donfack H. Delay in sputum smear conversion and outcomes of smear-positive tuberculosis patients: a retrospective cohort study in Bafoussam, Cameroon. BMC Infect Dis. 2015 21st March; 15:139. doi: 10.1186/s12879-015-0876-1. PMID: 25884844; PMCID: PMC4381415.
30. Fisher D, Wilder-Smith A. The global community needs to ramp up the response to contain COVID-19 swiftly. Lancet. 2020;395(10230):1109-10.
31. Lin HH, Ezzati M, Chang HY, Murray M. Association between tobacco smoking and active Tuberculosis in Taiwan prospective cohort study. Am J Respir Crit Care Med. 2009;180(5):475–480. DOI: 10.1164/ccm.200904-0549OC
32. A.T. Abal, B. Jayakrishnan, S. Parker, A. El Shamy, E. Abahussain, P.N. Sharma, Effect of cigarette smoking on sputum smear conversion in adults with active pulmonary Tuberculosis, Respiratory Medicine, Volume 99, Issue 4,2005,
33. Kaufmann S (2002). "Protection against tuberculosis: cytokines, T cells, and macrophages." *Ann Rheum Dis* 61 Suppl 2: ii54–8. PMID 12379623.
34. OECD/WHO. (2016). Tuberculosis. Health at a Glance: Asia/Pacific 2016: Measuring Progress towards Universal HealthCoverage, OECD Publishing, Paris. Retrieved from http://dx.doi.org/10.1787/health glance ap2016
35. Diktanas, Saulius et al. "Factors Associated with Persistent Sputum Positivity at the End of the Second Month of Tuberculosis Treatment in Lithuania." *Tuberculosis and respiratory diseases* vol. 81,3 (2018): 233-240. doi:10.4046/trd.2017.0096
36. Palhares Campolina J, Gesteira Coelho S, Belli AL, et al. Effects of a blend of essential oils in milk replacer on performance, rumen fermentation, blood

parameters, and health scores of dairy heifers. *PLoS One*. 2021;16(3): e0231068. Published 2021 11th March.doi: 10.1371/journal.pone.0231068

37. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 1994; 309:901-911.
38. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med 2004; 164:2206-2216.
39. Gajalakshmi V, Peto R, Kanaka TS, Jha P. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43000 adult male deaths and 35000 controls. Lancet 2003; 362:507-515.
40. Santha T. How can the progress of treatment be monitored? In: TOMAN'S tuberculosis cases detection, treatment, and monitoring WHO Geneva, 2nd ed. 2004;250-5.
41. Singla, R., Osman, M. M., Khan, N., Al-Sharif, N., Al-Seyigh, M. O. &Sheik, M. A. (2003). Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients, 2 months after treatment. International *Journal of Tuberculosis and Lung Disease, 7*(1), 58-64
42. Kuaban, C., Bame, R., Mouangue, L. &Djella, S. (2009). Non conversion of positive smears in new smear positive pulmonary tuberculosis patients in Yaounde, Cameroon. *East African medical Journal, 86*(5), 219-225.
43. Calderwood CJ, Wilson JP, Fielding KL, Harris RC, Karat AS, Mansukhani R, Falconer J, Bergstrom M, Johnson SM, McCreesh N, Monk EJM, Odayar J, Scott PJ, Stokes SA, Theodorou H, Moore DAJ. Dynamics of sputum conversion during effective tuberculosis treatment: A systematic review and meta-analysis. PLoS Med. 2021 Apr 26;18(4): e1003566. doi: 10.1371/journal.pmed.1003566. PMID: 33901173; PMCID: PMC8109831.
44. Shariff NM, Safian N. Diabetes mellitus and its influence on sputum smear positivity at the 2nd month of treatment among pulmonary tuberculosis patients in Kuala Lumpur, Malaysia: A case control study. Int J Mycobacteriol. 2015 Dec;4(4):323-9. doi: 10.1016/j.ijmyco.2015.09.003. Epub 2015 Oct 1. PMID: 26964816.
45. Rekha B, Swaminathan S. Childhood tuberculosis - global epidemiology and the impact of HIV. Paediatr Respir Rev. 2007 Jun;8(2):99-106. doi: 10.1016/j.prrv.2007.04.010. Epub 2007 Jun 4. PMID: 17574153.
46. Soh, Avril & Chee, Cynthia & Wang, Yee-Tang & Yuan, Jian-Min & Koh, Woon-Puay. (2017). Alcohol drinking and cigarette smoking in relation to risk of active tuberculosis: Prospective cohort study. BMJ Open Respiratory Research. 4. e000247. 10.1136/bmjresp-2017-000247.
47. Soh AZ, Chee CBE, Wang Y*, et al* Alcohol drinking and cigarette smoking in relation to risk of active tuberculosis: prospective cohort study *BMJ Open Respiratory Research* 2017;4: e000247. doi: 10.1136/bmjresp-2017-000247