Predictors of tuberculosis disease in smokers: a case-control study in north-eastern Malaysia

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Abstract

Objective. Tuberculosis (TB) is a leading infectious disease. However, many TB cases remain undetected and only present at a late stage of the infection. Therefore, targeted TB screening in high-risk populations, including smokers, is crucial. This study aimed to determine the predictors of TB disease among the smoker population in northeast Malaysia from 2019 to 2020.
Methods. A case-control study was conducted involving smokers aged 18 years and older from health clinics in Bachok Kelantan, Malaysia. Data were collected via face-to-face interviews or telephone calls from 159 participants, randomly selected from outpatient TB records. Simple and multiple logistic regression, using R software, were used to identify the determinants of TB.
Results. Most participants were male (59.1%) and had a secondary education (56.0%). Active smokers constituted 35.2% of the group, and the mean (SD) duration of exposure to smoking was 23.9 (16.47) and 18.4 (12.84) years for the case and control groups, respectively. Being an ex-smoker (adjusted odds ratio [AOR] 6.17; 95% CI: 1.55, 28.32; p = 0.013), weight loss (AOR 13.45; 95% CI: 4.58, 44.46; p < 0.005), night sweats (AOR 63.84; 95% CI: 8.99, 1392.75; p < 0.005) and duration of symptoms (AOR 1.02; 95% CI: 1.01, 1.04; p = 0.022) were shown to be significant predictors for TB disease.
Conclusion: Four predictors of TB disease in the population of smokers were recognised in this study and should be prioritised for early TB screening and diagnosis. This may help increase TB detection, initiate prompt treatment and reduce complications among the group at risk for TB.
Keywords: Tuberculosis, smoking, predictors, case-control

Introduction

Tuberculosis (TB) is the leading infectious disease globally, and it significantly impacts countries' health and financial burden. The World Health Organization (WHO) reports that in 2020, almost 10 million people were diagnosed with TB and nearly 1.5 million died from the disease (WHO, 2021). Most of these came from lower- and middle-income countries. Generally, TB cases show a declining trend, but the reduction has been slower than expected. For example, in 2018, the TB rate had declined by only two per cent relative to 2017 (WHO, 2018). One of the reasons for this is that many TB cases remain undetected. In 2015, the WHO estimated that, globally, approximately 3.6 million TB cases went undetected (WHO, 2015).

To enhance TB detection, the WHO has advocated a global approach to implementing a systematic TB screening programme that targets high-risk groups, including smokers, diabetic patients, people living with HIV and the elderly (WHO, 2013). Smoking is considered high-risk behaviour for TB disease (Toosi, 2000; Davies *et al*., 2006; Mahishale *et al*., 2015). Few known chemicals in cigarette smoke such as formaldehyde, tar and acrolein act as irritants to the respiratory system by causing inflammatory processes and injury to the epithelium and submucosal secretory glands (Aghapour et al., 2018). These pathological changes lead to mucus hypersecretions and deficiency of ciliary oscillations. Mucus accumulation and delay in mucociliary clearance make the environments favourable for *Mycobacterium tuberculosis* colonisation.

In Malaysia, TB screening of smoker populations is conducted when they present themselves at the Quit Smoking Clinic (Ministry of Health [MOH] Malaysia, 2016). All smokers who come for appointments at that clinic will be screened for TB disease annually or, based on symptomatic screening, will be subjected to chest X-ray examination. To date, there are no specific criteria outlining TB screening protocols for smokers, although a few studies have reported the determinants of TB disease among this group. Lin *et al.* (2009) report that older smokers and smokers who live in crowded homes are at greater risk for TB. Smokers who are heavy alcohol drinkers are also at higher risk for active TB disease (Jee *et al.*, 2009). According to smoking status, a higher risk of TB was reported among current smokers, ex-smokers and passive smokers compared to non-smokers (Bates *et al.*, 2007; Jee *et al.*, 2009; Leung *et al.*, 2010; Lindsay *et al.*, 2014). Furthermore, the longer the duration of smoking and the higher the number of cigarettes smoked both increase the risk of contracting TB (Leung *et al.*, 2004; Bates *et al.*, 2007; Jee *et al.*, 2009; Smith *et al.*, 2015; Zhang *et al.*, 2017).

Other factors shown to be related to higher risk of TB were male gender (Jee *et al.*, 2009; Lin *et al.*, 2009), patients with a low body-mass index (Leung *et al.*, 2004; Saunders *et al.*, 2017), immigrants (Pareek *et al.*, 2016; Chan, Kaushik & Dobler*, 2017), those with a low level of education and in a lower-income group (Pablos-Méndez, Blustein & Knirsch, 1997; Lin *et al.*, 2009), those with a TB contact (Morrison, Pai & Hopewell*, 2008; Saunders *et al.*, 2017), those with previous TB disease (Jee *et al.*, 2009; Said *et al.*, 2017), patients with chronic diseases, such as diabetes, human immunodeficiency virus and other immunosuppressed diseases (Moss *et al.*,

77 2000; Sonnenberg *et al.*, 2005; Benito *et al.*, 2015; Lee *et al.*, 2016; Al-Rifai *et al.*, 2017) and
78 those with TB symptoms (Valença *et al.*, 2015; Hanifa *et al.*, 2017).
79   TB disease predictors in smokers need to be determined in relation to local population
80 and background. The current practice that screens all smokers without prioritising according to
81 predictors consumes more resources. Furthermore, failure to recognise specific risk criteria
82 among smokers will contribute to late TB detection and treatment, and finally, would hinder the
83 aim of ending the global TB epidemic by 2030, as stated in the UN sustainable development goal
84 number 3. Due to the lack of local studies and data on the factors or determinants of TB disease
85 in smokers, a cross-sectional study was conducted to determine the predictors of TB disease
86 among the smoker population in a north-eastern state of Malaysia.
87

Materials and Methods

Study Design and Participants

90   A case-control study was conducted in Kelantan, Malaysia, between March and
91 December 2021. The participants were selected according to inclusion and exclusion criteria.
92 The inclusion criteria were outpatient attendees who came for TB screening between 2019 and
93 2020; smokers, whether active smokers, ex-smokers or passive smokers; aged 18 years and
94 above; and of Malaysian citizenship. Potential participants who fulfilled the study criteria were
95 randomly selected for inclusion in either the case or control groups. However, participants with
96 incomplete contact numbers or addresses were excluded from the study. The 'cases' were
97 patients diagnosed with TB disease, while the 'controls' were patients investigated for TB
98 disease but whose TB results were negative. The study flowchart is shown in Figure 1.
99   The sample size was calculated for each predictor for TB disease using Power and
100 Sample Size calculation software to compare two independent proportions. The largest estimated
101 total sample was 168, using the proportion of current smokers among patients not diagnosed with
102 TB disease in South Africa: 0.59 (Pinto *et al.*, 2013). The estimated proportion was 0.82, 5%
103 type 1 error, 80% power, ratio 1 case to 2 controls, and an additional 10% for missing data. We
104 used a simple random sampling method to obtain 56 cases and 112 controls from the sampling
105 frame to compare tuberculosis with non-tuberculosis participants. The participants were
106 interviewed via telephone or face-to-face, and information was gathered on their social history,
107 medical history, smoking history, contact or TB history, and symptom history, using a proforma
108 guideline constructed by the researchers. Data were also retrieved from the patients' clinical
109 records in the health clinics, which included the patient's medical, contact, TB and symptom
110 histories to ensure the accuracy of the data taken directly from participants.
111

Operational Definitions

113   In this study, 'active smokers' referred to patients who were smoking any number of
114 cigarettes, who had smoked within the last six months or who had quit smoking less than six
115 months before. Patients who had quit smoking for more than six months were considered 'ex-
116 smokers'. A 'passive smoker' was a patient who had never smoked but was currently living with

117 an active smoker. The healthcare workers included the laboratory technicians, radiology
118 technicians, medical attendants and ambulance drivers who were directly involved with patient
119 management in any health facility. An area with high TB incidence was defined as an area or
120 village with two or more TB cases in 2018 and 2019. Meanwhile, 'immunosuppressed' referred
121 to patients with any illnesses that suppressed their immune systems, such as chronic renal failure,
122 ischaemic heart disease, liver disease, gastrectomy patients, and cancer, or who were prescribed
123 medications for these. Participants were considered to have been immunised with the Bacilli
124 Calmette-Guerin (BCG) vaccine if they had a scar on their left or right upper arm. A TB contact
125 was defined as having been exposed to an index TB case, who could be a family member, a
126 colleague, or a friend.
127
128 **Statistical Analysis**
129   All data were recorded in Microsoft Excel and analysed using R software version 3.1.6.
130 Descriptive data were presented using mean (standard deviation (SD)) for numerical data and
131 number of patients (percentage (%)) for categorical data. Simple logistic regression was applied
132 to obtain each variable's crude odds ratio (OR). The associations between TB disease and the
133 independent variables were analysed using simple and later, multiple logistic regression
134 analyses. A simple logistic regression analysis was applied to all independent variables to
135 determine their association with TB disease. Variables with a p-value of less than 0.25 were
136 included in the multiple logistic regression analysis. The forward likelihood ratio (LR), the
137 backward LR and Enter methods were applied to obtain the preliminary final model.
138 Multicollinearity, two-way interactions of variables, homogeneity of variance using the Hosmer-
139 Lemeshow goodness of fit test and area under the curve were checked to ensure the model fit
140 before presenting the final model of the study.
141
142 **Ethical approval**
143   This study was approved by the Medical Research and Ethics Committee (MREC),
144 Ministry of Health Malaysia (NMRR-19-3325-51853) and Human Research Ethics Committee
145 (JEPeM), Universiti Sains Malaysia (USM/JEPeM/19110813).
146

147 # Results

148   A total of 159 participants fulfilled the study criteria and consented to participate. Table 1
149 presents the basic characteristics of the study participants. Overall, more than 70% (n = 94) were
150 male, 73% (n = 116) had studied to secondary school level at least, and 87.4% (n = 139) lived in
151 areas with low TB incidence. About 98% (n = 157) of the participants had a monthly income
152 below RM 4850. Regarding smoking status: 35.2% (n = 56) were active smokers, 21.4% were
153 ex-smokers (n = 34), and 43.4% (n = 68) were passive smokers. The mean (SD) duration of
154 exposure to smoke for the cases was 23.9 (16.47) years and 18.4 (12.84) years for the control
155 group. Only 6.3% (n = 10) of participants had been previously diagnosed with TB. The majority

156   of participants had a history of cough (86.2%, n = 137), and the median (IQR) duration of
157   symptoms was 30 (76) days for the cases and 7 (11) days for the control group.
158   Simple and multiple logistic regression analyses were used to determine the significant
159   determinants for TB disease. Based on simple logistic regression analysis, 10 variables were
160   significantly associated with TB disease. Another seven variables had p-values of less than 0.25.
161   All 17 variables were included in the multiple logistic regression analysis. Being an ex-smoker,
162   weight loss, complaints of night sweats, and duration of symptoms were significant predictors of
163   TB disease in the smoker population (Table 2).
164

165   **Discussion**

166   This study shows a higher proportion of smokers among males than females in Bachok,
167   Kelantan, between 2019 and 2020. This is consistent with other local and global reports
168   indicating higher prevalence of smoking in males than in females (Jee *et al.*, 2009; MOH,
169   Malaysia, 2015). Males tend to smoke to show that they are mature enough to be accepted in
170   society and are able to be independent. Some males think that smoking demonstrates their
171   masculinity to the opposite gender. Moreover, the peer pressure of wanting to be included in a
172   group with their friends causes men to smoke more than females (Allen *et al.*, 2016; Kodriati,
173   Pursell & Hayati, 2018).
174   This study shows that four predictors were significantly associated with TB disease:
175   being an ex-smoker (adjusted OR (AOR) 6.17; 95% CI: 1.55, 28.32; p = 0.013), having weight
176   loss (AOR 13.45; 95% CI: 4.58, 44.46; p < 0.005), having night sweats (AOR 63.84; 95% CI:
177   8.99, 1392.75; p < 0.005) and duration of symptoms (AOR 1.02; 95% CI: 1.01, 1.04; p = 0.022).
178   The odds of developing TB disease increased by 6.2% for ex-smokers compared to passive
179   smokers. This finding is congruent with other studies reporting similar observations (Jee *et al.*,
180   2009; Pinto *et al.*, 2013; Smith *et al.*, 2015; Zhang *et al.*, 2017). However, a prospective study
181   using secondary data from 2,504 newly diagnosed pulmonary TB patients from 2012 to 2013 in
182   India, observed that in both current smokers and ex-smokers, sputum smears and cultures were
183   likely to remain positive after two months of treatment (Mahishale *et al.*, 2015). They
184   hypothesised that smoking was associated with more extensive lung disease, lung cavitation and
185   positive sputum smear and culture results at baseline. A 14-year prospective cohort study (1992–
186   2006) in South Korea reported a contradictory finding, in which current smokers had a greater
187   risk of TB incidence than former smokers (HR = 1.4, 95% CI: 1.3, 1.5) (Jee *et al.*, 2009).
188   Another review paper on epidemiological evidence from the UK, China, India, and the
189   USA summarises the association between smoking and tuberculosis (Davies *et al.*, 2006). They
190   report an increase in TB case rates of between two- and four-fold in smokers who smoke more
191   than 20 cigarettes a day. The possible proposed mechanism is the effect of nicotine, which turns
192   off the production of TNF-α by the macrophages in the lungs, rendering the patient more
193   susceptible to the development of progressive disease from latent *Mycobacterium tuberculosis*
194   infection. However, this study did not control for other factors, particularly alcohol consumption.
195   Smoking is also reported to have a widespread effect on lung structure, such as lung obstruction,

196 function, clearance mechanism, and host defences, both in the lung and systemically; therefore, it
197 could plausibly increase the incidence or worsen the prognosis for TB (Jee *et al.*, 2009).
198   The current study showed that active smokers had no significant association with TB
199 disease. A possible explanation could be that ex-smokers have poorer health-seeking behaviours
200 than active smokers. They might feel good because they are not smoking anymore, and therefore,
201 avoid seeking early TB screening if they are having mild symptoms. Smokers may also stop
202 smoking when TB symptoms arise, or when a TB diagnosis is confirmed (Jee *et al.*, 2009).
203   We also found a significant association between weight loss, night sweats and TB disease
204 in smokers. Smokers with weight loss had a 13.45 times higher odds of developing TB than
205 those without weight loss. In addition, smokers with a history of night sweats had a 63.84 higher
206 risk of contracting TB than those without the presence of night sweats. The presence of weight
207 loss and night sweats are considered constitutional symptoms, especially in patients with chronic
208 diseases (Toosi, 2000), including TB. *Mycobacterium tuberculosis* causes an inert response and
209 enhances tissue degradation, the secretion of protein that inhibits appetite, and promotes the
210 proliferation of cytokines, causing the symptoms of night sweats (Toosi, 2000; Cegielski &
211 McMurray, 2004; Chang *et al.*, 2013). Hence, patients with chronic TB infection may present
212 with these two systemic symptoms. However, the wide confidence interval for these variables
213 was mainly due to the small sample size, thus limiting the inferences or estimates that could be
214 made from these findings.
215   The current findings are in line with a study conducted in Cape Town, which reported a
216 higher value of adjusted ORs for the presence of weight loss (adjusted OR = 7.2, 95% CI = 2.5-
217 20) and night sweats (adjusted OR = 1.75, 95% CI = 0.62-7.9) (Den boon *et al.*, 2008),
218 indicating a high likelihood of chronic diseases, such as TB, when patients are complaining of
219 these symptoms. This study suggests that every patient presenting with these two symptoms
220 should be tested for the presence of TB disease. The presence of weight loss and night sweats in
221 children is also important. This is because physicians frequently face problems in diagnosing
222 children with active TB disease due to their inability to adequately explain their symptoms and
223 their difficulty in cooperating with diagnostic testing, such as producing sputum for the
224 investigation. Previous researchers have developed a list of variables, represented by specific
225 scoring, to assess the risk of TB in children. Of these, weight loss and night sweats carry the
226 highest scores among the criteria (Graham, 2011).
227   The results of this study showed that a prolonged duration of TB symptoms increases the
228 risk of having TB disease. With every one-day increase in the duration of symptoms, the odds of
229 having TB disease were increased by 1.02 times when other factors were adjusted for. The
230 longer the presence of TB symptoms, the more likely a patients is to have a positive TB culture.
231 Physiologically, prolonged TB symptoms may indicate the prolonged proliferation of
232 *Mycobacterium tuberculosis* in the body, particularly in the lung tissue. This reduces the lung's
233 ciliary function in excreting and destroying the mycobacterium, finally increasing the risk of TB
234 disease (Toosi, 2000; Centers for Disease Control and Prevention [CDC], 2016).

235   Furthermore, the longer the delay in TB diagnosis and treatment, the higher the risk of
236 more severe lung tissue damage and of the transmission of the mycobacterium to other close
237 contacts. A cross-sectional study was conducted among newly diagnosed pulmonary TB patients
238 in India to assess pulmonary TB's patients' health-seeking behaviours (Jebamalar, Senthilkumar
239 & Ramola, 2018). The researchers reported that the reasons for delays in seeking care were the
240 hope of self-resolution, financial constraints, fear of the diagnosis, incompatible timings and
241 poor health-care accessibility. The time duration of having TB symptoms has been considered a
242 crucial variable in calculating TB risk scores (Graham, 2011; Pinto *et al.*, 2013; Hanifa *et al.*,
243 2017; Jebamalar, Senthilkumar & Ramola, 2018). A significant score was given to those with a
244 longer duration of TB symptoms, particularly when they had two or more weeks history of TB
245 symptoms when they presented themselves.
246   A small sample size was one of the limitations of this study, because it limits the findings
247 regarding the association of other variables with TB disease and results in a wide 95% CI for the
248 adjusted odds ratio. In addition, this study was conducted in the years 2020 and 2021, during
249 which the COVID-19 pandemic significantly affected the data collection process. Within this
250 period, people's movements were limited, and the number of patients who attended health clinics
251 in Bachok, Kelantan was remarkably reduced, with many patients choosing not to attend the
252 health clinic if they had minor illnesses, due to the fear of being infected with COVID-19.
253

Conclusion

255   This study demonstrated that significant predictors for TB disease among smokers were
256 being categorised as an ex-smoker, losing weight, having night sweats and a longer duration of
257 TB symptoms. Delineating these TB predictors in smokers will guide health authorities to design
258 better and more comprehensive plans for a national TB control programme by formulating
259 criteria for TB screening in the smoker population. A specific protocol for TB screening of
260 smokers could be implemented in Quit Smoking Clinics and could be expanded to all Outpatient
261 Department (OPD) of primary care facilities. Consequently, early TB diagnosis and treatment in
262 groups at risk and TB transmission prevention in the wider community would be achieved.
263

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267

References

269 • Aghapour M, Raee P, Moghaddam SJ, Hiemstra PS, Heijink IH. 2018. Airway Epithelial
270   Barrier Dysfunction in Chronic Obstructive Pulmonary Disease: Role of Cigarette Smoke
271   Exposure. *American Journal of Respiratory Cell and Moleculat Biology* 58(2):157–169
272   DOI: 10.1165/rcmb.2017-0200TR.

273 • Allen AM, Scheuermann TS, Nollen N, Hatsukami D, Ahluwalia JS. 2016. Gender
274 Differences in Smoking Behavior and Dependence Motives Among Daily and Nondaily
275 Smokers. *Nicotine & Tobacco Research* 18(6):1408–1413 DOI: 10.1093/ntr/ntv138.

276 • Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ. 2017. Association between
277 diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. *PLoS*
278 *One* 12(11):1–26 DOI: 10.1371/journal.pone.0187967.

279 • Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. 2007. Risk of Tuberculosis
280 From Exposure to Tobacco Smoke. *Archives of Internal Medicine* 167:335–342 DOI:
281 10.1001/archinte.167.4.335.

282 • Benito N, García-Vázquez E, Horcajada JP, González J, Oppenheimer F, Cofán F, Ricart
283 MJ, Rimola A, Navasa M, Rovira M, Roig E, Pérez-Villa F, Cervera, C, Moreno A. 2015.
284 Clinical features and outcomes of tuberculosis in transplant recipients as compared with
285 the general population: A retrospective matched cohort study. *Clinical Microbiology and*
286 *Infection* 21(7):651–658 DOI: 10.1016/j.cmi.2015.03.010.

287 • Cegielski JP, McMurray DN. 2004. The relationship between malnutrition and
288 tuberculosis: Evidence from studies in humans and experimental animals. The
289 International Journal of Tuberculosis and Lung Disease 8(3):286–298.

290 • Centers for Disease Control and Prevention. 2016. Chapter 2: Transmission and
291 Pathogenesis of Tuberculosis. *Available at*
292 *https://www.cdc.gov/tb/education/corecurr/pdf/chapter2.pdf* (accessed 22 December
293 2021).

294 • Chan IHY, Kaushik N, Dobler CC. 2017. Post-migration follow-up of migrants identified
295 to be at increased risk of developing tuberculosis at pre-migration screening: a systematic
296 review and meta-analysis. *The Lancet Infectious Diseases* 17(7):770–779 DOI:
297 10.1016/S1473-3099(17)30194-9.

298 • Chang SW, Pan WS, Lozano Beltran D, Oleyda Baldelomar L, Solano MA, Tuero I,
299 Friedland JS, Torrico F, Gilman RH. 2013. Gut Hormones, Appetite Suppression and
300 Cachexia in Patients with Pulmonary TB. *PLoS One* 8(1):1–7 DOI:
301 10.1371/journal.pone.0054564.

302 • Davies PDO, Yew WW, Ganguly D, Davidow AL, Reichman LB, Dheda K, Rook GA.
303 2006. Smoking and tuberculosis: The epidemiological association and
304 immunopathogenesis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*
305 100(4):291–298 DOI: 10.1016/j.trstmh.2005.06.034.

306 • Den boon S, Verver S, Lombard CJ, Bateman ED, Irusen EM, Enarson DA, Borgdorff
307 MW, Beyers N. 2008. Comparison of symptoms and treatment outcomes between actively
308 and passively detected tuberculosis cases: The additional value of active case finding.
309 *Epidemiology and Infection* 136(10):1342–1349 DOI: 10.1017/S0950268807000106.

310 • Graham SM. 2011. The Use of Diagnostic Systems for Tuberculosis in Children. *Indian*
311 *Journal of Pediatrics* 78(3):334–339 DOI: 10.1007/s12098-010-0307-7.

312 • Hanifa Y, Fielding KL, Chihota VN, Adonis L, Charalambous S, Foster N, Karstaedt A,

313   McCarthy K, Nicol MP, Ndlovu NT, Sinanovic E, Sahid F, Stevens W, Vassall A,
314   Churchyard GJ, Grant AD. 2017. A clinical scoring system to prioritise investigation for
315   tuberculosis among adults attending HIV clinics in South Africa. *PLoS One* 12(8):1–20
316   DOI: 10.1371/journal.pone.0181519.

317   • Jebamalar J, Senthilkumar P, Ramola M. 2018. Health seeking behaviour in pulmonary
318   tuberculosis: a cross sectional study. *International Journal Of Community Medicine And*
319   *Public Health* 5(4):1346–1353 DOI: 10.18203/2394-6040.ijcmph20181206.

320   • Jee SH, Golub JE, Jo J, Park IS, Ohrr H, Samet JM. 2009. Smoking and Risk of
321   Tuberculosis Incidence, Mortality, and Recurrence in South Korean Men and Women.
322   *American Journal of Epidemiology* 170(12):1478–1485 DOI: 10.1093/aje/kwp308.

323   • Kodriati N, Pursell L, Hayati EN. 2018. A scoping review of men, masculinities, and
324   smoking behavior: The importance of settings. *Global Health Action* 11:1–12 DOI:
325   10.1080/16549716.2019.1589763.

326   • Lee PH, Fu H, Lai TC, Chiang CY, Chan CC, Lin HH. 2016. Glycemic Control and the
327   Risk of Tuberculosis: A Cohort Study. *PLoS Medicine* 13(8):1–15 DOI:
328   10.1371/journal.pmed.1002072.

329   • Leung CC, Lam TH, Ho KS, Yew WW, Tam CM, Chan WM, Law WS, Chan CK, Chang
330   KC, Au KF. 2010. Passive smoking and tuberculosis. *Archives of Internal Medicine*
331   170(3):287–292 DOI: 10.1001/archinternmed.2009.506.

332   • Leung CC, Li T, Lam TH, Yew WW, Law WS, Tam CM, Chan WM, Chan CK, Ho KS,
333   Chang KC. 2004. Smoking and Tuberculosis among the Elderly in Hong Kong. *American*
334   *Journal of Respiratory and Critical Care Medicine* 170(9):1027–1033 DOI:
335   10.1164/rccm.200404-512OC.

336   • Lin HH, Ezzati M, Chang HY, Murray M. 2009. Association between tobacco smoking
337   and active tuberculosis in Taiwan: Prospective cohort study. *American Journal of*
338   *Respiratory and Critical Care Medicine* 180(5):475–480 DOI: 10.1164/rccm.200904-
339   0549OC.

340   • Lindsay RP, Shin SS, Garfein RS, Rusch MLA, Novotny TE. 2014. The association
341   between active and passive smoking and latent tuberculosis infection in adults and children
342   in the United States: Results from NHANES. *PLoS One* 9(3):1–8 DOI:
343   10.1371/journal.pone.0093137.

344   • Mahishale V, Patil B, Lolly M, Eti A, Khan S. 2015. Prevalence of Smoking and Its Impact
345   on Treatment Outcomes in Newly Diagnosed Pulmonary Tuberculosis Patients: A
346   Hospital-Based Prospective Study. *Chonnam Medical Journal* 51:86-90 DOI:
347   10.4068/cmj.2015.51.2.86.

348   • Ministry of Health Malaysia. 2015. *National Health & Morbidity Survey 2015: Report on*
349   *Smoking Status Among Malaysian Adults.* Putrajaya: Ministry of Health Malaysia.

350   • Ministry of Health Malaysia. 2016. *Surat Pekeliling Ketua Pengarah Kesihatan Bil*
351   *1/2016: Pengukuhan Saringan Golongan Berisiko Tinggi Tuberculosis (Tibi) di bawah*
352   *Program Kawalan Tibi Kebangsaan, Kementerian Kesihatan Malaysia.* Putrajaya:

353   Ministry of Health Malaysia.

354   •   Morrison J, Pai M, Hopewell PC. 2008. Tuberculosis and latent tuberculosis infection in
355   close contacts of people with pulmonary tuberculosis in low-income and middle-income
356   countries: a systematic review and meta-analysis. *The Lancet Infectious Diseases*
357   8(6):359–368 DOI: 10.1016/S1473-3099(08)70071-9.

358   •   Moss AR, Hahn JA, Tulsky JP, Daley CL, Small PM, Hopewell PC. 2000. Tuberculosis in
359   the homeless: A prospective study. *American Journal of Respiratory and Critical Care*
360   *Medicine* 162(2 I):460–464 DOI: 10.1164/ajrccm.162.2.9910055.

361   •   Pablos-Méndez A, Blustein J, Knirsch CA. 1997. The role of diabetes mellitus in the higher
362   prevalence of tuberculosis among Hispanics. *American Journal of Public Health*
363   87(4):574–579 DOI: 10.2105/AJPH.87.4.574.

364   •   Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. 2016. The impact of migration on
365   tuberculosis epidemiology and control in high-income countries: A review. *BMC Medicine*
366   14(1):48-57 DOI: 10.1186/s12916-016-0595-5.

367   •   Pinto LM, Dheda K, Theron G, Allwood B, Calligaro G, van Zyl-Smit R, Peter J,
368   Schwartzman K, Menzies D, Bateman E, Pai M, Dawson R. 2013. Development of a
369   Simple Reliable Radiographic Scoring System to Aid the Diagnosis of Pulmonary
370   Tuberculosis. *PLoS One* 8(1):1–7 DOI: 10.1371/journal.pone.0054235.

371   •   Said K, Verver S, Kalingonji A, Lwilla F, Mkopi A, Charalambous S, Reither K. 2017.
372   Tuberculosis among HIV -infected population: Incidence and risk factors in rural Tanzania.
373   *African Health Sciences* 17(1):208–215 DOI: 10.4314/ahs.v17i1.26.

374   •   Saunders MJ, Wingfield T, Tovar MA, Baldwin MR, Datta S, Zevallos K, Montoya R,
375   Valencia TR, Friedland JS, Moulton LH, Gilman RH, Evans CA. 2017. A score to predict
376   and stratify risk of tuberculosis in adult contacts of tuberculosis index cases: a prospective
377   derivation and external validation cohort study. *The Lancet Infectious Diseases* 17:1190–
378   1199 DOI: 10.1016/S1473-3099(17)30447-4.

379   •   Smith GS, Van Den Eeden SK, Baxter R, Shan J, Van Rie A, Herring AH, Richardson DB,
380   Emch M, Gammon MD. 2015. Cigarette smoking and pulmonary tuberculosis in northern
381   California. *Journal of Epidemiology and Community Health* 69:568–573 DOI:
382   10.1136/jech-2014-204292.

383   •   Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. 2005. How
384   Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A
385   Retrospective Cohort Study in South African Gold Miners. *The Journal of Infectious*
386   *Diseases* 191(2):150–158 DOI: 10.1086/426827.

387   •   Toossi Z. 2000. The inflammatory response in *Mycobacterium tuberculosis* infection.
388   *Archivum Immunologiae et Therapiae Experimentalis* 48:513–519 DOI: 10.1007/978-94-
389   015-9702-9_11.

390   •   Valença MS, Scaini JLR, Abileira FS, Gonçalves CV, Von Groll A, Silva PEA. 2015.
391   Prevalence of tuberculosis in prisons: Risk factors and molecular epidemiology. *The*
392   *International Journal of Tuberculosis and Lung Disease* 19(10):1182–1187 DOI:

393   10.5588/ijtld.15.0126.

394   •   World Health Organization. 2018. *Global tuberculosis report 2018*. Geneva: World Health
395   Organization.

396   •   World Health Organization. 2021. *Global tuberculosis report 2021*. Geneva: World Health
397   Organization.

398   •   World Health Organization. 2013. *Systematic screening for active tuberculosis*. Geneva:
399   World Health Organization.

400   •   World Health Organization. 2015. *The End TB Strategy*. Geneva: World Health
401   Organization.

402   •   Zhang H, Xin H, Li X, Li H, Li M, Lu W, Bai L, Wang X, Liu J, Jin Q, Gao L. 2017. A
403   dose-response relationship of smoking with tuberculosis infection: A cross-sectional study
404   among   21008   rural   residents   in   China.   *PLoS   One*   12(4):1–13   DOI:
405   10.1371/journal.pone.0175183.

406

Figure 1

The study flowchart
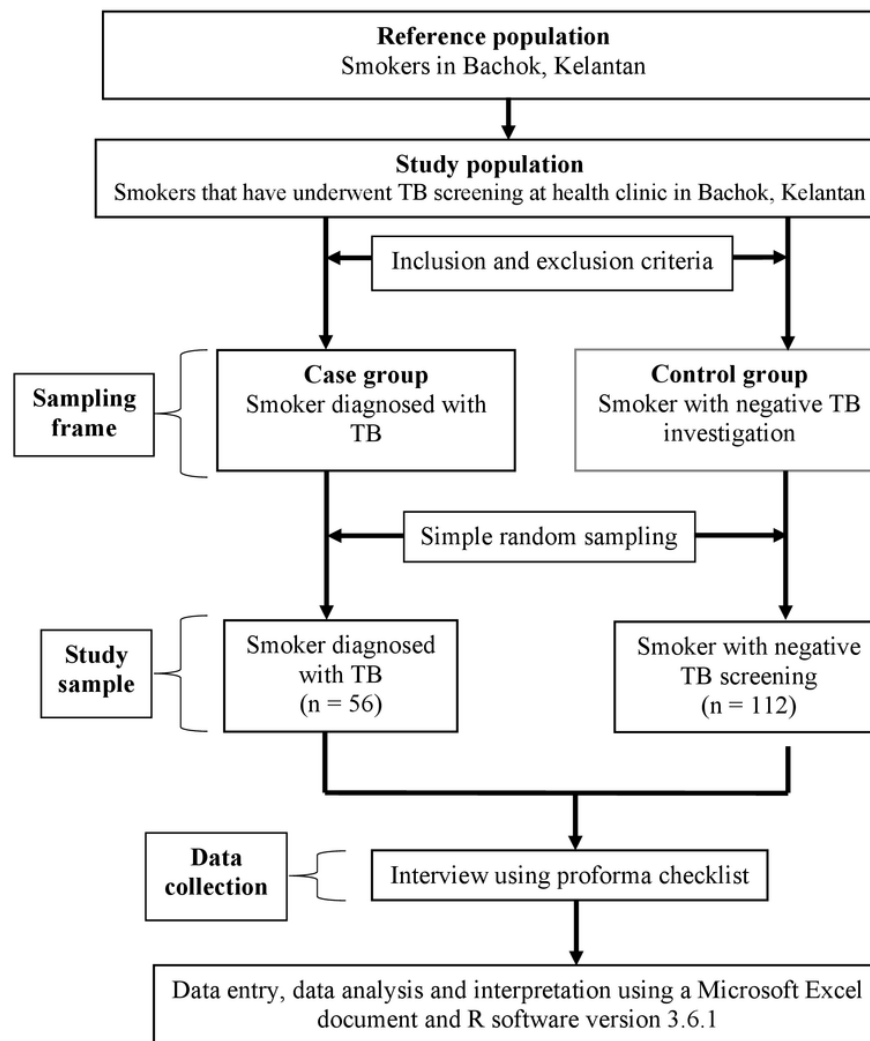
Figure 1: The study flowchart

Table 1 : Characteristics of participants in Bachok, Kelantan for phase 1 (n = 159)

2 Table 1: Characteristics of participants in Bachok, Kelantan for phase 1 (n = 159)

Variable	Case (n = 45)				Controls (n = 114)			
	n	(%)	Mean	(SD)	n	(%)	Mean	(SD)
SOCIODEMOGRAPHY								
Age, year			48.5	(17.77)			44.2	(15.33)
Male	32	(71.1)			62	(54.4)		
Marital status								
Never married	10	(22.2)			23	(20.2)		
Married	33	(73.3)			82	(71.9)		
Divorced/widowed	2	(4.5)			9	(7.9)		
Crowded home, Yes	11	(24.4)			43	(37.7)		
Resided in high TB incidence area	10	(22.2)			10	(8.8)		
Work in a non-medical field	45	(100.00)			109	(95.6)		
Education status								
Primary school level	11	(24.4)			16	(14.1)		
Secondary school level	29	(64.4)			60	(52.6)		
Tertiary level/College/ University	5	(11.2)			38	(33.3)		
Monthly income								
Less than RM 4,850	44	(97.8)			113	(99.1)		
RM 4,850 – RM 10,959	1	(2.2)			1	(0.9)		
More than RM 10,959	0	(0.0)			0	(0.0)		
MEDICAL HISTORY								
Diabetic patient	14	(31.1)			30	(26.3)		
HIV patient	1	(2.2)			1	(0.9)		
Immunosuppressed, yes	9	(20.0)			13	(11.4)		
SMOKING HISTORY								
Smoking Status								
Active smoker	15	(33.3)			41	(36.0)		
Ex-smoker	17	(37.8)			17	(14.9)		
Passive smoker	13	(28.9)			56	(49.1)		
Duration of exposure to smoke, year			23.9	(16.47)			18.4	(12.84)
TB HISTORY								
BCG vaccination, yes	45	(100.0)			103	(90.3)		
Exposed to TB index case, yes	18	(40.0)			35	(30.7)		
Past history of TB disease, yes	6	(13.3)			4	(3.5)		
TB SYMPTOM								
Cough, yes	36	(80.0)			101	(88.6)		
Any sputum, yes	24	(53.3)			78	(68.4)		
Weight loss, yes	34	(75.6)			17	(14.9)		
Night sweat, yes	22	(48.9)			1	(0.9)		
Chest pain, yes	10	(22.2)			3	(2.6)		
Loss of appetite, yes	29	(64.4)			29	(25.4)		
Fever, yes	27	(60.0)			57	(50.0)		
Hemoptysis, yes	9	(20.0)			12	(10.5)		

Duration of symptoms, day[1]	30	(76)	7	(11)

3   [1]Reported in median (IQR)

Simple and multiple logistic regression models on the factors associated with TB disease among smokers in Bachok, Kelantan (n = 159)

1 Table 1: Simple and multiple logistic regression models on the factors associated with TB
2 disease among smokers in Bachok, Kelantan (n = 159)

Variable	Simple logistic regression		Multiple logistic regression	
	Crude OR (95% CI)	*p*-value[1]	Adjusted OR (95% CI)	*p*-value[2]
Social History				
Age (year)	1.02 (1.00, 1.04)	0.128		
Gender: Male (ref: Female)	2.06 (1.00, 4.54)	0.056		
Type of residential				
Crowded home: Yes (ref: No)	0.53 (0.24, 1.14)	0.114		
High incidence area: Yes (ref: Low)	2.97 (1.13, 7.83)	0.026		
Education status				
Primary school level	5.23 (1.63, 18.94)	0.007		
Secondary school level	3.67 (1.41, 11.53)	0.014		
Tertiary level/College/ University	Reference			
Medical History				
Immunosuppressed disease: No (ref: Yes)	0.51 (0.20, 1.34)	0.162		
Past TB disease: Yes (ref: No)	4.23 (1.15, 17.30)	0.032		
Smoking History Smoking status				
Active smoker	1.58 (0.68, 3.71)	0.291	2.94 (0.77, 12.90)	0.126
Ex-smoker	4.31 (1.77, 10.87)	0.002	6.17 (1.55, 28.32)	0.013
Passive smoker	Reference		1.00	
Duration of exposure to smoke (year)	1.03 (1.01, 1.05)	0.030		
Presence of TB Symptom				
Cough: Yes (ref: No)	1.94 (0.74, 4.90)	0.162		
Sputum: No (ref: Yes)	1.90 (0.93, 3.85)	0.076		
Weight loss: Yes (ref: No)	17.64 (7.76, 43.12)	<0.001	13.45 (4.58, 44.46)	<0.001
Night sweat: Yes (ref: No)	108.09 (21.08, 1984.47)	<0.001	63.84 (8.99, 1392.75)	<0.001
Chest pain: Yes (ref: No)	10.57 (3.04, 49.14)	0.001		
Loss of appetite: Yes (ref: No)	5.31 (2.57, 11.38)	<0.001		
Hemoptysis: Yes (ref: No)	2.13 (0.81, 5.45)	0.118		

Duration of symptoms (days)	1.03 (1.01, 1.04)	<0.001	1.02 (1.01, 1.04)	0.022

4   [1]Simple logistic regression

5   [2]Multiple logistic regression: No significant two-way interactions and no multicollinearity between the independent variables

6   Hosmer-Lemeshow test showed $p=0.888$. The Area Under the Curve is 0.94.