# Survival Analysis of Time to Early TB Treatment Interruption: a Longitudinal Study on Psycho-social Risk Factors Among Newly Diagnosed TB Patients in a State of Malaysia

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**Research Article**

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## Abstract

**Background:** This prospective multi-centric longitudinal study aimed to determine the prognostic factors for time to intensive phase treatment interruption among new pulmonary Tuberculosis (TB) smear positive patients in urban districts of Selangor, Malaysia.

**Methods:** The sample included 439 new pulmonary TB smear positive patients who started treatment at 39 public treatment centres from November 2018 to August 2019. A pre-tested self-administered questionnaire and standardized data collection form were utilized to assess baseline characteristics and treatment status. Multivariate Cox proportional hazard (PH) regression analyses were performed to analyse the prognostic factors of treatment interruption.

**Result:** Of 439 participants, 104 (23.7%) developed treatment interruption and with 67.3% of treatment interruption occurring in the first month of treatment. Median survival time was 56.00 days (95% CI=55.00-56.00), with overall survival probability of 73.9%. Being a current smoker and having a history of hospitalization, internalized stigma, low TB symptoms score, and waiting time spent at Directly Observed Treatment, Short-course (DOTS) centre were prognostic factors of treatment interruption.

**Conclusion:** Our findings indicate that intensive phase treatment interruption was high in this study setting. The treatment adherence strategy in urban districts, Selangor is therefore to prioritize the high risk groups. Efforts to quit smoking cessation program and to promote stigma reduction intervention are crucial.


## Background

Despite the advancement of TB management, the last decade has chronicled suboptimal treatment outcome and significant preventable TB deaths across the continents (1,2). World Health Organization (WHO) defines TB treatment interruption as history of stopping treatment for two and more consecutive months (3). Early interruption is defined as 14 days or more of treatment interruption during intensive phase, as presented in Malaysian Tuberculosis Clinical Practice Guideline, warranting a re-start of treatment (4).

It appears that TB treatment interruption has resulted in delayed sputum conversion, drug resistance (5,6), prolonged infectiousness in the community, high mortality rate (7,8), prolonged treatment course, hence leading to economic and psychosocial affliction (9,10). In averting public heath impact of treatment interruption, WHO has echoed a range of policy and legislative initiatives. These include Directly Observed Treatment, Short-course (DOTS) policy, free drugs policy, fixed-dose combination (FDC) tablets, financial incentive, and defaulter tracing system (4,11–13). Despite these strategies, TB treatment interruption continues to upsurge in developing countries ranging from 10–30% (14–17).

Malaysia is an intermediate to high TB burden country which has depicted an increasing trend of TB mortality (per 100 000 population) from 5.33 in 2014 to 6.55 in 2018 (18,19). Notwithstanding the free drugs policy, treatment interruption in Malaysia remained above 4% spanning from 2014 to 2018—the national target was 2% (20,21). This represents a major economic strain for the government, where an additional annual projection of USD 5.3 million has been estimated for treatment restart, prolonged hospitalization, and drug resistance treatment (22). Selangor, the most populous and urbanized state in Malaysia, has faced challenges in implementing TB control strategies. An increasing trend of TB incidence (per 100 000 population) of 63.00 in 2012 to 78.62 in 2018 was observed in the said state (18,23) and the rising TB mortality rate (per 100 000 population) was 3.14 in 2014 to 5.76 latest in 2018 [18, 19]. From 2014 to 2018, TB treatment interruption rate in Selangor was far above the predetermined target, latest was 10.9% in 2018 (24).

Understanding the time to treatment interruption is crucial to tailor the time-relevance adherence strategy. Most prior studies have revealed that median time of treatment interruption was at the maintenance phase of treatment (25–27). However, poor compliance during intensive phase was found to contribute to unfavourable treatment outcomes and high risk of mortality, thus raising a priority need to retrieve non-adherence patients during intensive phase (7,28). Based on previous longitudinal studies, prognostic factors of treatment interruption included having a previous history of TB diagnosis (29,30), travel distance (25,29), and HIV disease (26,29–31). Of elicits, the lack assessment for cognitive and psychosocial determinants may obscure the anticipation of social risk profiling in TB management (32–34).

Indeed, positive urbanization impacts on biomedical and health services delivery can be hampered if individual's psycho-cognitive social attributes were ignored (34–36). The Information-Motivation-Behavioural Skills (IMB) model was originally designed to conceptualize psychosocial determinants of HIV preventive behaviour (36). As a theoretical framework, the model has depicted its potential strengths to develop behavioural interventions in chronic diseases (37).

As one of the social determinants, TB stigma contributes to a detrimental effect on TB control via the sentiment of disgrace and blame, hence the internalization of the community's sceptical judgments that lead to the drop-out in the DOTS programme (38). Despite numerous qualitative studies, little attention has been paid to qualitatively examine the effect of TB stigma on treatment interruption in Malaysia and beyond (38–40). Taken together, the accelerated unfavourable treatment outcomes and TB mortality, as well as limited studies on longitudinal and psychosocial determinants evaluation heightens the need for psychosocial and theory-based assessment of time to treatment interruption among new pulmonary TB smear positive patient in a local setting. Therefore, this study aims to identify the time to intensive phase TB treatment interruption and its prognostic factors among new pulmonary TB smear positive patients in urban districts of Selangor.

## Materials And Methods

Methodological details of the present study have been published elsewhere [40]. Hence, only short descriptions pertaining study settings, design, and procedure are explained in below sections. The study protocol and methods of obtaining consents had been approved by National Medical Research and Ethics Committee (NMREC) of National Institute of Health, Ministry of Health Malaysia (Reference number:NMRR-18-1635-42371) and the Ethic Committee for

Research Involving Human Subject Universiti Putra Malaysia (JKEUPM). All the methods were performed in accordance with the relevant guidelines and regulations.

## Study Setting, Design and Procedure

The present multi-centric prospective cohort study was conducted at five public hospitals and 34 health clinics in the urban districts (Petaling, Hulu Langat, Gombak, Klang and Sepang) of Selangor. All new pulmonary TB smear positive patients who started treatment from November 2018 to August 2019 were consecutively enrolled in the present study. Inclusion criteria were being Malaysian, aged 18 years and above, able to understand Malay or Chinese (Mandarin) language, and mentally capable. Patients who had their diagnosis changed to non-TB diagnosis, multi-drug resistant TB patients and started TB treatment at private facilities were excluded from the study. We also excluded severely ill patients at the time of study recruitment. On daily basis, the sampling frame was retrieved from TB patient registration book that was available at treatment centre.

Following baseline assessment, participants were followed up at week 2, week 4, week 6, and week 8 after initiation of treatment to ascertain the outcome status. Data extraction from medical records and Tuberculosis Information System (TBIS) forms comprising 32 formats on recording and reporting of TB treatment history and outcome was performed by five trained enumerators (4).

In Malaysia, the mandatory notification of TB disease is imposed by the Infectious Diseases Prevention and Control Act, 1988, obliging all providers to report the TB case to district health office within 7 days of diagnosis (4). As outlined in the National TB Control Policy, all TB patients in Selangor are subjected to DOTS policy for close observation of pill takings at treatment facilities (4,41). Throughout the treatment course, patient's compliance with medication is shown in TBIS form, which record the daily dose intake. Meanwhile, if a patient failed to comply with DOTS monitoring, the treatment centre will promptly report to communicable disease unit of district health office to initiate the defaulter tracing and retrieval system (4,13).

At baseline, a self-administered questionnaire was filled up by participants to elicit information on socio-demographic, risky behaviour, information (knowledge), motivation (health belief, social support and internalized stigma), behavioural skills (cue to action and self-efficacy) and health service (questionnaire is available in Additional file 1). Meanwhile, PROFORMA was applied to elicit information on clinical characteristics (comorbidities, chest x-ray grading, baseline body weight, and history of hospitalization) and treatment status. Sample size was calculated as per the time-to-event data formula (42). Using a desired hazard ratio (HR) of 3.0 for travel distance factor (29), 0.20 for hypothesized proportion of treatment interruption, therefore the required sample size was at least 438 to achieve 95% confidence interval at 80% power.

## Definitions and Statistical Analysis

The outcome of interest was 14 days or more of interruption during the intensive phase, or loss to follow up (4). This outcome was binary with one (1) corresponds to when the subject had event occurred (treatment interruption) and zero (0) corresponds to when the subject was censored. Participants were assigned to 0 if; they did not experience the event (i.e., intensive phase treatment interruption) at day 60 of TB treatment; or died regardless the cause; or moved away or transferred to other treatment centres outside the study location. In general, the verification of event (failure or censor) was established through the TBIS forms or via phone calling to participants or their next of kin.

Cox Proportional Hazard (PH) regression was computed to identify the independent prognostic factors of treatment interruption using IBM SPSS Version 25.0 (43). The Kaplan-Meier technique was first applied to obtain the survival estimate and to plot the survival distribution. The association of potential prognostic factors with treatment interruption was inspected through univariate Cox PH regression analysis. Study variables would be tested in multivariate Cox PH regression analysis with backward elimination method, if their respective p value was $\leq 0.25$ (44). Only study variables with $p < 0.05$ were retained in the final model. Results were reported as hazard ratio (HR) and their 95% confidence interval (CI). The assumption of proportionality of hazards and model fit was checked.

# Results

## Study profile

The study profile is depicted in Fig. 1. During the recruitment period, 509 eligible patients were approached and assessed. Of these, 70 patients refused to participate. As such, the respond rate was 86.2%. The mean ± standard deviation (SD) follow up duration was 43.46 ± 20.90 days.

## Characteristics of Study Participants

The present sample was predominantly male (65.5%), Malay (75.2%), married (52.8%), and of hospital settings (51.5%). The median family income was RM1959.50 (IQR = 1800), whereas the mean ± SD age was 41.82 ± 15.20 years. In the present sample, 34.6% were current smoker, 32.8% were diabetes mellitus patients, and 5% were HIV positive patients. About 51% of the participants had a diagnosis of grade 3 (moderately advanced) or grade 4 (far advanced) of chest x-ray findings, whereas 33.7% had practiced at least one type of alternative or traditional medicine (e.g., healers, herbal remedies, cupping, traditional massage, acupuncture, Yoga, Ayurveda, homeopathy, Islamic practice (Rukyah) and supplemental intake).

The evaluation of informational factor covered on general knowledge on treatment, regime and utilization, specific requirement for adherence, potential side effect and faulty heuristics. Accordingly, item "All TB patient who develop medication side effect, must be stopped from TB treatment" was the most wrongly answered item by 80.2% of participants. As for health belief, item "Too many pills are dangerous to human and can damage internal organs" was the most perceived barrier item as 71.8% of participants agreed with it. Meanwhile, item "We, tuberculosis patients are contagious to others" was the most perceived stigma item as agreed by 89.5% of total participants. On self-efficacy evaluation, it showed that item "How hard or easy is it for you to tolerate TB medication side effects?" was the most hardly perceived item by 55.6% of study participants.

## Survival of Pulmonary TB Smear Positive Patients during Intensive Phase

Of 439 participants, 104 of participants developed the event, hence treatment interruption rate was 23.7%. The mean and median time to intensive phase treatment interruption was 55.69 days (95% CI:53.57–57.81) and 56.00 days (95% CI:55.00–56.00) respectively. The life table and the participants' survival throughout the treatment course are demonstrated in Table 1 and Fig. 2, respectively. There was a rapid decrease in the survival curve, particularly in the first 28 days of TB treatment, but it reached a plateau after Day 42. The proportion of event was highest in the interval of Day 15 to Day 28. About 67.3% of TB interruption had occurred during the first month of treatment. The overall survival probability at the end of intensive phase treatment interruption was 73.9%.

Table 1
Life table of newly diagnosed pulmonary TB smear positive patients in urban districts, Selangor (n = 439)

| Time interval (days) | Number of entering interval | Number of events | Number of censored cases | Proportion of event | Cumulative proportion surviving at end of interval |
|---|---|---|---|---|---|
| 0–14 | 439 | 34 | 32 | 0.08 | 0.920 |
| 15–28 | 373 | 36 | 16 | 0.10 | 0.829 |
| 29–42 | 321 | 25 | 7 | 0.08 | 0.764 |
| 43–56 | 289 | 9 | 16 | 0.03 | 0.739 |
| > 56 | 264 | 0 | 264 | 0 | 0.739 |

## Prognostic Factors of Intensive Phase Treatment Interruption

The characteristics and univariate associations between risk of treatment interruption and study variables are shown in Table 2 and Table 3 respectively. At the univariate level, ethnicity, marital status, educational level, smoking status, history of hospitalization upon starting treatment, knowledge, social support, internalized stigma, and waiting time at DOTS centre were found to exert effects on risk of TB treatment interruption (Table 4). Study variables were subjected to multivariate Cox PH analysis, if their p value was $\leq 0.25$ at the univariate level. Based on the final multivariate model, being a current smoker (HR = 1.649, 95% CI:1.107–2.458, p = 0.014), having a history of hospitalization upon starting treatment (HR = 2.539, 95% CI:1.648–3.910, p < 0.001), low TB symptoms score (HR = 0.954, 95% CI:0.912–0.998, p = 0.041), internalized stigma (HR = 1.056, 95% CI:1.018–1.096, p = 0.004), and waiting time at DOTS centre (HR = 1.005, 95% CI:1.001–1.009, p = 0.042) were remained as independent prognostic factors of treatment interruption (Table 5).

Table 2
Risk of treatment interruption by socio-demographic factors and high risk behaviours (n = 439)

| Variables | Characteristics | | | Univariate Cox PH analysis | | |
|---|---|---|---|---|---|---|
| | Event | Censor | Total | Crude HR (95% CI) | SE | pvalue |
| **Age** | | | | | | |
| < 60 | 92(24.4) | 285(75.6) | 377(85.9) | Reference | | |
| ≥ 60 | 12(19.3) | 50(80.7) | 62(14.1) | 0.836(0.458–1.526) | 0.307 | 0.559 |
| **Family income** | RM1959.50(RM1800.00) | | | 1.000(1.000–1.000) | < 0.001 | 0.227 |
| **Number of household[ Median (IQR)]** | 4(3) | | | 0.975(0.897–1.060) | 0.043 | 0.549 |
| **Gender** | | | | | | |
| Male | 76(26.0) | 216(74.0) | 292(66.5) | 1.455(0.943–2.244) | 0.221 | 0.090 |
| Female | 28(19.0) | 119(81.0) | 147(33.5) | Reference | | |
| **Ethnicity** | | | | | | |
| Malay | 66(20.0) | 264(80.0) | 330(75.2) | Reference | | |
| Non-Malay | 38(35.0) | 71(65.0) | 109(24.8) | 1.886(1.265–2.812) | 0.204 | 0.002* |
| **Marital status** | | | | | | |
| Married | 57(24.6) | 175(75.4) | 232(52.8) | Reference | | |
| Single | 34(21.0) | 127(79.0) | 161(36.7) | 0.920(0.602–1.407) | 0. 217 | 0.701 |
| Widowed | 3(12.5) | 21(87.5) | 24(5.5) | 0.470(0.147–1.502) | 0.592 | 0.203 |
| Divorced | 7(46.7) | 8(53.3) | 15(3.4) | 2.668(1.216–5.854) | 0.401 | 0.014* |
| Separated | 3(42.9) | 4(57.1) | 7(1.6) | 1.675(0.525–5.349) | 0.592 | 0.384 |
| **Educational level** | | | | | | |
| No formal education | 4(21.1) | 15(78.9) | 19(4.3) | 1.486(0.503–4.391) | 0.553 | 0.474 |
| Primary school | 24(39.3) | 37(60.7) | 61(13.9) | 3.053(1.657–5.628) | 0.312 | < 0.001* |
| Secondary school | 58(25.0) | 174(75.0) | 232(52.8) | 1.841(1.122–3.312) | 0.270 | 0.024* |
| Tertiary education | 18(14.2) | 109(85.8) | 127(28.9) | Reference | | |
| **Employment status** | | | | | | |
| Employed | 31(22.5) | 107(77.5) | 267(60.8) | 0.907(0.592–1.388) | 0.217 | 0.653 |
| Unemployed | 67(25.1) | 200(74.9) | 138(31.4) | 0.787(0.341–1.814) | 0.426 | 0.574 |
| Retiree | 6(17.6) | 28(82.4) | 34(7.7) | Reference | | |
| **Staying status** | | | | | | |
| Nuclear family | 59(24.5) | 182(75.5) | 241(54.9) | Reference | | |
| Extended family | 11(18.3) | 49(81.7) | 60(13.7) | 0.767(0.403–1.460) | 0.328 | 0.420 |
| Single parent family | 7(18.9) | 30(81.1) | 37(8.4) | 0.770(0.352–1.686) | 0.400 | 0.513 |
| Staying with other relatives | 2(50.0) | 2(50.0) | 4(0.9) | 3.878(0.94515.920) | 0.721 | 0.060 |
| Staying with friend | 9(30.0) | 21(70.0) | 30(6.8) | 1.542(0.764–3.110) | 0.358 | 0.227 |
| Staying alone | 10(23.8) | 32(76.2) | 42(9.6) | 1.051(5.370–2.054) | 0.342 | 0.885 |
| Staying with others | 6(24.0) | 19(76.0) | 25(5.7) | 1.074(0.464–2.488) | 0.429 | 0.868 |
| High risk behaviour | | | | | | |
| **Smoking status** | | | | | | |
| Non-smoker | 54(18.8) | 233(81.2) | 152(34.6) | Reference | | |
| Current smoker | 50(32.9) | 102(67.1) | 287(65.4) | 2.005(1.364–2.946) | 0.196 | < 0.001* |
| **Alcohol consumption** | | | | | | |

Note: (*)-$p < 0.05$

| Variables | Characteristics | | | Univariate Cox PH analysis | | |
|---|---|---|---|---|---|---|
| | Event | Censor | Total | Crude HR (95% CI) | SE | pvalue |
| No | 93(23.0) | 311(77.0) | 35(8.0) | Reference | | |
| Yes | 11(31.4) | 24(68.6) | 404(92.0) | 1.715(0.917–3.207) | 0.319 | 0.091 |
| **Illicit drug intake** | | | | | | |
| No | 95 (23.3) | 313(76.7) | 31(7.1) | Reference | | |
| Yes | 9(29.0) | 22(71.0) | 408(92.9) | 1.434(0.723–2.841) | 0.349 | 0.302 |
| Note: (*)-$p < 0.05$ | | | | | | |

Table 3
Risk of treatment interruption by clinical characteristics (n = 439)

| Variables | Characteristics | | | Univariate Cox PH analysis | | |
|---|---|---|---|---|---|---|
| | Event | Censor | Total | Crude HR (95% CI) | SE | pvalue |
| Comorbid factors | | | | | | |
| **Diabetes Mellitus** | | | | | | |
| No | 72(24.4) | 223(75.6) | 144(32.8) | Reference | | |
| Yes | 32(15.3) | 112(84.7) | 295(67.2) | 0.884(0.583–1.340) | 0.212 | 0.560 |
| **Chronic obstructive pulmonary disease** | | | | | | |
| No | 101(23.3) | 332 (76.7) | 6(1.4) | Reference | | |
| Yes | 3(50.0) | 3(50.0) | 433(98.6) | 2.188(0.694–6.901) | 0.586 | 0.181 |
| **Chronic liver disease** | | | | | | |
| No | 100(23.2) | 331(76.8) | 8(1.8) | Reference | | |
| Yes | 4(50.0) | 4 (50.0) | 431(98.2) | 2.389(0.878–6.494) | 0.510 | 0.088 |
| **Chronic renal failure** | | | | | | |
| **No** | 102(23.9) | 324(76.1) | 13(3.0) | Reference | | |
| Yes | 2(15.4) | 11(84.6) | 426(97.0) | 0.611(0.151–2.475) | 0.714 | 0.490 |
| **HIV/AIDS status** | | | | | | |
| Negative | 98(23.5) | 319(76.5) | 22(5.0) | Reference | | |
| Positive | 6(27.3) | 16(72.7) | 417(95.0) | 0.825(0.362–1.883) | 0.421 | 0.648 |
| **Underlying comorbid** | | | | | | |
| No | 56(22.9) | 188(77.1) | 195(44.4) | Reference | | |
| Yes | 48(24.6) | 147(75.4) | 244(55.6) | 1.066(0.725–1.567) | 0.197 | 0.747 |
| TB disease related factors | | | | | | |
| **TB symptoms score [Mean (SD)[** | 14.55(4.35) | | | 0.961(0.919–1.006) | 0.023 | 0.086 |
| **Body weight** [Median(IQR)] | 52.50(19.00) | | | 0.998(0.985–1.011) | 0.007 | 0.721 |
| **Chest x-ray grading** | | | | | | |
| Grade 1(no lesion ) | 6(25.0) | 18(75.0) | 24(5.5) | 1.320(0.444–3.929) | 0.556 | 0.618 |
| Grade 2 (minimal lesion) | 38(19.9) | 153(80.1) | 191(43.5) | 1.038(0.463–2.324) | 0.411 | 0.928 |
| Grade 3 (moderately advanced ) | 53(28.6) | 132(71.4) | 185(42.1) | 1.460(0.604 – 0.321) | 0.347 | 0.402 |
| Grade 4 (far advanced) | 7(17.9) | 32(82.1) | 39(8.9) | Reference | | |
| TB treatment related disease | | | | | | |
| **Alternative/ medicine practice** | | | | | | |
| No | 75(25.7) | 216(74.3) | 148(33.7) | Reference | | |
| Yes | 29(19.6) | 119(80.4) | 291(66.3) | 0.813(0.530–1.248) | 0.219 | 0.344 |
| **History of hospitalization upon starting treatment** | | | | | | |
| No | 30(14.1) | 183(85.9) | 213(48.5) | Reference | | |
| Yes | 74(32.7) | 152(67.3) | 226(51.5) | 2.874(1.880–4.396) | 0.217 | 0.001* |
| Note: (*)-$p < 0.05$ | | | | | | |

Table 4
Risk of treatment interruption by information, motivation, behavioural skills and health service factors (n = 439)

| Variables | Characteristics | | Univariate Cox PH analysis | | |
|---|---|---|---|---|---|
| | Mean (SD) | Minimum/ maximum score | Crude HR (95% CI) | SE | pvalue |
| Informational factor | | | | | |
| **Knowledge** | | | 0.948(0.903–0.996) | 0.025 | 0.035* |
| General knowledge on TB treatment | 3.59(1.22) | 0.00/5.00 | | | |
| Regime and utilization | 2.07(1.13) | 0.00/4.00 | | | |
| Specific requirement for TB adherence | 2.35(0.89) | 0.00/3.00 | | | |
| Potential side effects | 1.22(0.92) | 0.00/3.00 | | | |
| Faulty heuristics | 1.57(1.15) | 0.00/3.00 | | | |
| Total scale | 10.78(3.72) | 0.00/18.00 | | | |
| Motivational factors | | | | | |
| **Health belief** | | | | | |
| Perceived susceptibility | 15.46(2.44) | 5.00/20.00 | 0.967(0.897–1.043) | 0.038 | 0.380 |
| Perceived severity | 16.06(2.40) | 5.00/20.00 | 0.970(0.897–1.048) | 0.040 | 0.442 |
| Perceived barrier | 36.92(6.50) | 18.00/64.00 | 1.028(0.898–1.037) | 0.015 | 0.059 |
| Perceived benefit | 16.10 (2.62) | 5.00/20.00 | 0.965(0.898–1.037) | 0.032 | 0.333 |
| Social support | 33.61(5.79) | 13.00/48.00 | 0.957(0.925–0.990) | 0.017 | 0.011* |
| Internalized stigma | 24.57(4.84) | 10.00/40.00 | 1.063(1.025–1.103) | 0.019 | 0.001* |
| Behavioural skills factors | | | | | |
| Cue to action | 31.61(5.27) | 10.00/40.00 | 0.976(0.941–1.011) | 0.018 | 0.180 |
| Self-efficacy | 57.97(9.00) | 16.00/80.00 | 0.991(0.971–1.011) | 0.010 | 0.374 |
| Health services factors | | | | | |
| Travel distance to DOTS centre | 8.00(10.00)[a] | 1.00/85.00 | 1.005(0.990–1.020) | 0.008 | 0.544 |
| Travel distance to follow up centre | 8.00(10.00)[a] | 1.00/120.00 | 1.005(0.991–1.019) | 0.007 | 0.516 |
| Waiting time at DOTS centre | 30.00(40.00)[a] | 5.00/180.00 | 1.006(1.001–1.010) | 0.002 | 0.008* |
| Waiting time at follow up centre | 60.00(30.00)[a] | 5.00/240.00 | 1.001(0.998–1.004) | 0.002 | 0.518 |

Note: ([a])- Median (IQR), (*)-$p < 0.05$

Table 5
The independent prognostic factors of intensive phase treatment interruption (n = 439)

| Characteristics | Adjusted HR | SE | 95% CI | *p*-value |
|---|---|---|---|---|
| **Smoking status** | | | | |
| Non-smoker | Reference | | | |
| Current smoker | 1.649 | 0.203 | 1.107–2.458 | 0.014* |
| **History of hospitalization upon** starting treatment | | | | |
| No | Reference | | | |
| Yes | 2.539 | 0.220 | 1.648–3.910 | < 0.001* |
| **Baseline TB symptoms score** | 0.954 | 0.023 | 0.912–0.998 | 0.041* |
| **Baseline internalized stigma** | 1.056 | 0.019 | 1.018–1.096 | 0.004* |
| **Waiting time spent at DOTS centre** | 1.005 | 0.002 | 1.001–1.009 | 0.042* |

Note: Using Backward LR method, Cox PH regression–$\chi^2 = 53.50$, df = 5, $p < 0.001$, PH assumptions were tested using correlation tests between partial residuals and survival time rank (non-significant correlations, $p > 0.05$ were reported), no issue of multicollinearity was detected, (*) –$p < .05$.

## Discussion

This study elucidated the understanding of time to intensive phase treatment interruption and its prognostic factors. The present sample was predominantly hospitalized, male and Malays participants with t low median family income. TB interruption rate reported in this study was high (23.7%) comparable to Liew et al.'s (45) local national study. The TB interruption rate yielded in the present study surpassed the national target of 2% and recent state surveillance data of 10.9% in 2018 (4,24). This finding was also comparable to studies conducted in Gambia (i.e., 20%) and Ethiopia (i.e., 25.2%) (25,29). This study concurs the latter studies, in terms of predominant hospitalized TB patients among the recruited participants. The fact that some of the socioeconomic characteristics of the present study as reflected by poor urban population profile (i.e., high unemployment and low median family income) are relative to Selangor's median family income in 2016 (46). Poor urban groups were found to exhibit low socio-economic status, inadequate social assistance, vulnerable socio-behavioural profile, thus poor access to health care system (47,48). Above all, the variation across past prognostic studies could be attributed to the status of TB control programs in the respective country and methodological heterogeneity (in particular, operational definition of treatment interruption and duration of follow up to allow sufficient event) (32,33,43). The high interruption rate reported in this study therefore heightened the need for prompt intervention and policies which should be strategized systematically according to gathered evidence.

The median time to intensive phase treatment interruption was 56 days suggesting towards completion of intensive phase. It was comparable to the temporal evidence reported in Kenya (i.e., 56 days) and West Africa (i.e., 60 days) (31,49). Therefore, the transitioning interval from intensive to maintenance phase is crucial and should be thoroughly assessed, both in terms of cumulative social-behavioural impacts such as financial burdens, as well as health service factors especially in the flow management of referrals to other centres.

In this study, the event proportion was the highest in the first month of therapy which concurred the respective multi-centre evaluations in Kenya and Benin (30,31,50). Some salient postulations have been documented in previous studies including travelling away from the treatment site, and accumulated travel cost and financial burden (51,52). Therefore, the treatment interruption during intensive phase should be vigorously anticipated during the first point of contact between health providers and patients. This mainly to avoid rendering prolonged infectivity in the community, drug resistance, as well as financial burden and psycho-social impacts on individuals and health service system (6,9,35,53).

The significant effects of smoking status on TB treatment interruption endorsed a previous local finding in northern Malaysia reporting that current smokers had three times higher risk of treatment interruption compared to non-current smokers (54). The present study also extended previous studies by delineating a temporal association (55–58). Biologically, tobacco-induced cytochrome P450 enzyme could the plasma rifampicin levels in smokers, compromising the beliefs in effectiveness of treatment (59,60). In addition, smokers are often described as having a complex psychosocial risk profile, it is difficult if not impossible to under the relationship between smoking and unfavourable TB treatment outcomes (61). In the present study, our results have been adjusted for all of these psychosocial considerations such as alcohol consumption and illegal drug use. As the double burden of TB and smoking are prevalent in Selangor state, this finding should further inform the development of quit smoking program among TB patients.

The present study depicted that TB symptoms was negatively associated with treatment interruption. This is consistent with previous qualitative and empirical studies (50,58,62). On the one hand, less symptoms give rise to the feeling in patients that their illness is not severe enough and to the intention of seeking opinion from unreliable third parties, thereby leading to early withdrawal (63). On the other hand, experiencing more symptoms leads to fear that nurtures susceptibility and severity, hence motivations to persevere with treatment (64). It appears that sputum conversion and treatment response are frequently expedited in patients with mild symptoms which in turn induce the sensation of being cured, resulting in early drop out (65). This however, warrants further evaluations to explore the patterns of discontinuation of treatment among those with mild symptoms upon diagnosis.

In the present study, 226 participants (51.5%) depicted history of hospitalization upon starting treatment, thus in agreement with surveillance data reporting most of the TB cases in Selangor were started treatment at hospitals settings (66). In a large scale assessment in Cameroon, Pefura-Yone et al. identified that history of hospitalization was a protective factor in that prolonged hospitalization was meant to isolate the marginalized population (27). This inconsistent finding could be ascribed by diverse health service system and policy across the study locations. In Malaysia, some hospitalized TB patients would have subsequent DOTS monitoring at health clinics or other treatment centres. Thus, individual and health system changes occur during the transition phase of treatment need to be addressed via instituting appropriate measures that could minimize the probability of loss to follow-up during this period. In this regard, the special needs for ill hospitalized TB patients should be thoroughly evaluated, particularly on anticipating functional support gained by patients. In-ward management should also have the capacity of dedicated managing team to ensure that all recording and reporting for discharge or inter-facility referral are properly documented and communicated across the level of care.

The present study found that internalized stigma was the prognostic factor of treatment interruption (15,67), thus providing new empirical evidence from the local perspective. Some TB patients fear that other people see them as HIV/AIDS patients (68,69). Other TB patients experience the suppression of the self-esteem secondary to stigmatization, contributing to treatment avoidance (70,71). Likewise, in a qualitative study involving informants from seven states (Kuala Lumpur, Johor, Kelantan, Penang, Sabah, Sarawak, and Selangor) across Malaysia, public stigma was found to be derived from community and employers (72). The foregoing postulation warrants further evaluation of public stigma among local community by clarifying the different drives and dimensions of TB stigma, hence to endeavour the framework of stigma reduction strategy.

Our findings suggest that the longer waiting time spent by participants at the DOTS centre, the higher the risk of treatment interruption (14,73). This does not lend support to a meta-analytic study (74). In this light, several mechanisms were postulated. The experience of long wait is burdensome for patients, in the sense of frequent medical leave from their jobs, and impairs their income for living expenses, thus compromising the consistency of DOTS monitoring (72). In addition, longer waiting time undermines the patients' satisfaction towards health system delivery, resulting in high drop out from DOTS (75). Meanwhile the waiting time at DOTS monitoring centre could be attributed by the disparity in staffing capacity, flow process of DOTS delivery, and facility resources in health

centres. Therefore, the flow management of DOTS monitoring should be refined to optimize the capacity of providers and efficient process flow by taking the waiting time and infection control policy into due consideration.

No significant effects of health belief subscales on TB treatment interruption were reported in the present study. Our recent findings do not support Hill et al. (25). Perceived benefit was found to be a prognostic motivational factor of treatment interruption,but resembles previous conceptualization of motivational factors by Ajzen and Fishbein (76) which suggested the inconsistent effect of health belief domain on preventive behaviour. Instead, an elicitation study or focus group discussion is pre-requisite for a prospective study, primarily to identify the salient attitudinal or normative factor that is specific to the evaluated population (36).

No significant effects of travel distance on TB treatment interruption were reported. Our findings contradict previous claims that patients with a travel time of more than half an hour had a higher risk of default even after three months of treatment (25). The correlation between built-up cost over time and risk of defaulting was postulated. Our findings somehow could relate the evolvement of health service system in Malaysia. According to National TB Control Programme, patients were allowed to have DOTS monitoring at the nearest community clinic in their neighbourhood. This decentralization policy has contributed towards improvement of the travel distance among TB patients in Malaysia (4).

In essence, the present study provides local updates, beyond the biomedical attributes extracted from medical records or disease registry. The present study also offer a better understanding and simpler explanation of treatment interruption in the lights of psychosocial influence via IMB model framework. Therefore, the present findings may benefit involving organizations and policy makers in designing time relevant, theory based adherence strategies in TB case holding and management. Above all the present study was conducted at public health centre settings, thus limiting its generalizability to other study populations. Thus, future studies should be replicated to cater TB patients started their treatment at private facilities in an attempt to better understand TB treatment interruption in urban population.

## Conclusions

The present findings suggest that the intensive phase TB treatment interruption among new pulmonary TB smear positive patient in urban district was high and was dictated by smoking status, history of hospitalization upon starting treatment, lower TB symptoms score, internalized stigma, and longer waiting time at DOTS centre. As informed by our recent findings, the strategies towards improving TB treatment adherence and TB treatment outcome in urban district Selangor should be targeting on high risk groups endeavouring stigma reduction strategy and quit smoking intervention as well as improving waiting time at DOTS centre. It is also hoped that future studies could not only assess more study domains by catering objective assessment of health service but also incorporate various drives and dimensions of TB stigma such as public or organizational stigma.

## Declarations

### Ethics approval and consent to participate

The study protocol and methods of obtaining consents had been approved by National Medical Research and Ethics Committee (NMREC) of National Institute of Health, Ministry of Health Malaysia (Reference number:NMRR-18-1635-42371) and the Ethic Committee for Research Involving Human Subject Universiti Putra Malaysia (JKEUPM). All the methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from participants. Additional information sheets to further explain on study objectives and methods were distributed. Confidentiality of personal information and survey responses were maintained in the strictest confidence by keeping the identifiable information anonymous during data analysis. Throughout the follow-ups, the defaulter tracing system was ensured by all level of care.

### Availability of data and materials

The datasets analyzed during the current study are available in the Mendeley data, http://dx.doi.org/10.17632/pc773fty8m.1

The Questionnaire is available in Additional file 1.

### Competing interests

The authors declare no conflict of interest.

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### Authors' contributions

Conceptualization, QS, PY, SM, KA, NA; Methodology, QS, PY, SM, KA, NA; formal analysis, QS, PY; writing—original draft preparation, QS; writing—review and editing, PY, SM, KA, NA; All authors have read and agreed to the published version of the manuscript.”.

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## Figures

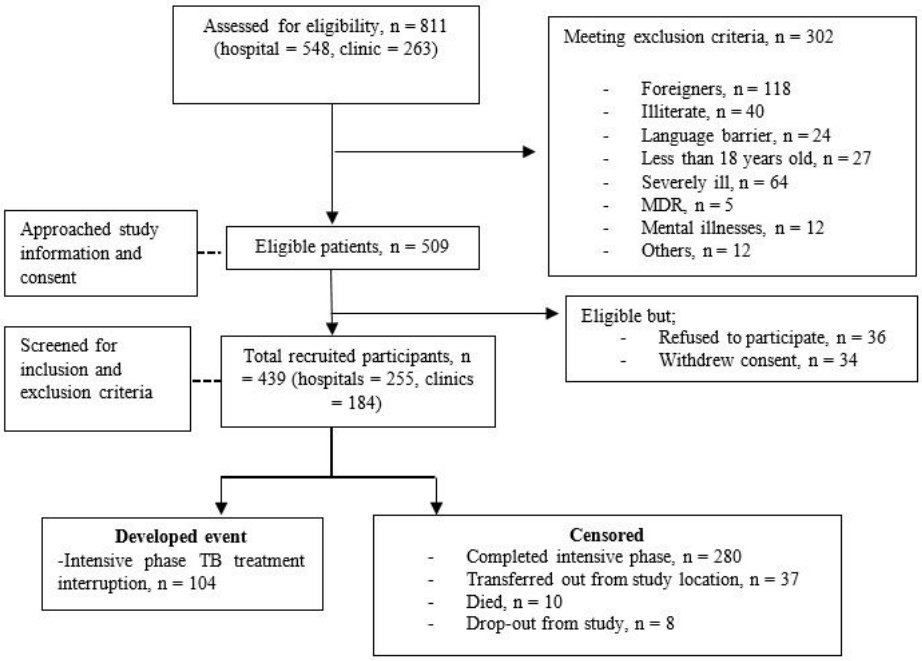


**Figure 1**

Study profile for assessment of risk of intensive phase treatment interruption among pulmonary TB smear positive patients in urban districts, Selangor.

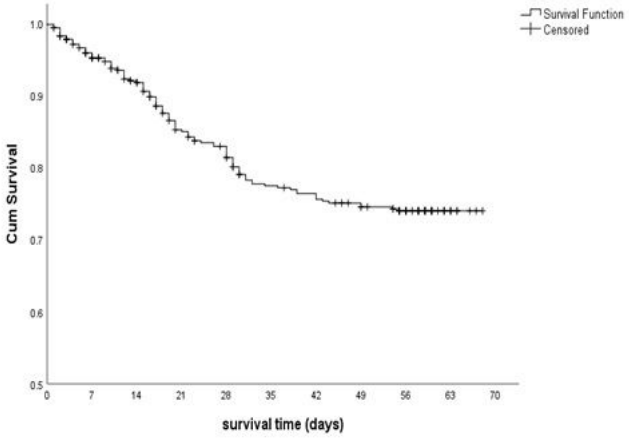


**Figure 2**

Kaplan-Meier curve for overall survival estimate among new pulmonary TB smear positive patients in urban districts, Selangor (n = 439).

## Supplementary Files

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- Additionalfile1.pdf