ORIGINAL ARTICLE

# Risk Factors of Unfavourable TB Treatment Outcomes in Hulu Langat, Selangor

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## ABSTRACT

**Introduction:** Over the last decade, tuberculosis (TB) has remained the main cause of death from communicable diseases in Malaysia. This study was aimed to determine the risk factors of unfavourable treatment outcomes (UTO) among new TB cases in Hulu Langat. **Methods:** A cohort study was prospectively conducted among the new TB cases registered in the government health clinics of Hulu Langat district. The event was defined as any one of the UTO (default, transferred out, treatment failure and death) whichever came first. This data was analysed using SPSS version 25.0. Survival pattern was assessed by Kaplan-Meier plots and Log rank test. Hazard ratios of unfavourable TB treatment outcomes among the new TB cases at 95% confidence interval and level of significance set at 0.05 were calculated using Cox proportional hazard model. **Results**: Of the 321 patients analysed, 80.4% (n=258) had favourable treatment outcomes and 19.6% (n=63) had UTO with 10.9% (n=35) transferred out, 6.9% (n=22) defaulted and 1.9% (n=6) died. There was no treatment failure. The mean survival time was 5.2 (SD=0.09) months. The risk factors of hazard probability of UTO were male, ethnicity type Others, positive human immunodeficiency virus (HIV) status and not done sputum at 2 months of treatment. **Conclusion:** Transferred out and default formed the bulk of the UTO in Hulu Langat. New interventions to improve the existing TB prevention and control program should be planned in the first three months of treatment.

**Keywords:** Tuberculosis, Unfavourable treatment outcomes, Survival analysis, Malaysia

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## INTRODUCTION

Despite the availability of adequate medications, tuberculosis (TB) continues to be the main cause of death from a single infectious disease across the world (1). Malaysia is geographically situated in two World Health Organization (WHO) regions, the Western Pacific Region and the South-East Asia Region, where 62% of the global tuberculosis burden is concentrated (1). According to WHO, Malaysia is classified as an intermediate TB burden country in 2019 with a TB incidence rate of 92 per 100 000 population (2). In 2014, Malaysia was ranked as the 4th country to have low TB treatment success rate in comparison to other WPRO countries (3). Efficacy of the existing TB control programs can be assessed by monitoring treatment outcomes (4). Malaysia classifies the treatment outcomes as successful treatment outcomes which includes cured and completed treatment and unsuccessful treatment outcomes which includes default, transferred out, treatment failure and death in accordance with WHO guidelines (5). Malaysia has not been able to meet the WHO target as the success rate of TB treatment (84%) and mortality rate (3.69%) in 2019 was not close to 90% and 3 respectively (6).

Thirty-three deaths related to TB were recorded per week in Malaysia and one out of every 5 patients had unfavourable treatment outcome (7). There is heterogeneity of TB disease burden among the various states in Malaysia and the TB incident rate of Selangor increased by 54.1% from 51.8 per 100 000 population in 2010 to 79.8 per 100 000 population in 2019 (8-13). Among the communicable diseases in Selangor, Tuberculosis incidence rate remained in the top three with 60.2 per 100 000 population in 2011 (14) and 75 per 100 000 population in 2015 with (80%) majority of the cases of pulmonary TB (PTB) type (15). This puts the population of Selangor at greater risk of contracting TB as it is the PTB patients that are mainly involved in transmission of the disease through their infected aerosols which get expelled upon sneezing or coughing (16). In 2015, Hulu Langat district of Selangor had the

highest TB incidence rate of 94/ 100 000 population while the national TB incidence rate was only 79.45/ 100 000 population (15). In Selangor the number of TB deaths, TB-defaulter rate and multi-drug resistant tuberculosis (MDR-TB) cases increased in 2015 when compared to 2010 (14,15). However, there is a scarcity of literature on prospective study designs and on time to unfavourable treatment outcomes of tuberculosis in Selangor. To prevent drug resistance, monitor TB transmission, strengthen local TB programs, and contribute to the elimination of TB in Hulu Langat, it is important to recognize and resolve preventable risk factors for UTO. The aim of this study was to identify risk factors for UTO and the time it took for new TB cases in Hulu Langat to reach UTO

## MATERIALS AND METHODS

Hulu Langat is the fifth largest district of Selangor state with a population of 1.5 million in 2020 which was 21% of the total population of the Selangor state (17). Hulu Langat district is divided into 7 administrative units called as sub-districts/ mukims (18). The new cases of TB aged ≥ 18 years were recruited from the 10 government health facilities for a duration of nine months (26.11.2018 - 31.08.2019) and then each patient was followed up for seven months (01.06.2019 - 1.03.2020). The TB patients excluded from this study were those who were aged < 18 years, pregnant, retreatment cases, attending the government health facilities only for directly observed short therapy (DOTS), with bone/ joint TB, tuberculosis meningitis and whose TB diagnosis was changed by the attending physician. The zero time was defined as the date of the diagnosis of tuberculosis mentioned in the medical records (T0). The time of event was defined as time to any one of the UTO such as treatment failure, default, transferred out or death whichever occurs first (T1) from the zero time (T0). Each TB patient recruited was followed up for a period of seven months. The cases who did not have the event (UTO) till the end of study period were considered censored. Data collection was carried out using two pretested instruments: self-administered questionnaires and standardized data collection form. The enumerators were trained prior to data collection and collected the completed questionnaire along with the consent form from the participants. The standardized forms were filled by the researcher only whereby the information from medical records pertaining to the disease and treatment outcomes were extracted. All information from the completed forms was transferred into password protected excel sheet by the researcher.

### Operational definition

The treatment outcomes defined in this study are in accordance with the Clinical Practice Guidelines for Management of Tuberculosis by Ministry of Health, Malaysia (5) and also WHO (19). Former smear positive patient who was smear negative in the last month of therapy and on at least one prior occasion was defined as cured. A patient who finished treatment but did not fulfill the requirement for being classified as cured or failure was defined as completed treatment. During the course of treatment if any patient passed away for any reason it was defined as died. During the course of treatment if sputum smear was positive at five months or later it was defined as failure. A patient whose treatment was discontinued for two months or longer was defined as defaulted. A patient whose treatment outcome was unknown and who was moved to another reporting and recording facility was defined as transferred out. The treatment success or favourable treatment outcome was defined as the total number of patients who were cured and completed their treatment. The remaining treatment outcomes of died, defaulted, failure and transferred out were defined as unfavourable treatment outcomes.

### Statistical analysis

Data was analyzed using IBM SPSS version 25.0 (IBM Corporation, Armonk, NY, USA). The descriptive analysis was performed where the categorical variables were described in frequencies and percentages while the continuous variables were described in either median/ mean and interquartile range/ standard deviation. Survival analysis was used to determine the time to UTO. To estimate the probability of survival and compare survival curves between categorical variables, the Kaplan Meier method and the Log-rank test were used. The analysis performed subsequently to identify the predictors of UTO in new TB patients in Hulu Langat was univariate and multivariate Cox proportional hazards analysis. The data was interpreted as hazard ratio (HR) with a 95% confidence interval (CI) and significance level of 0.05.

### Ethical considerations

Ethical approval was obtained from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-18-1683-42000), Selangor Health Department, District Health Department of Hulu Langat and Ethics Committee for Research Involving Human Subject of Universiti Putra Malaysia (JKEUPM). The patients who took part in the study gave their informed consent. Anonymity of the respondents, privacy and confidentiality of information was maintained.

## RESULTS

A total of 459 TB patients were registered in the selected 10 government health clinics in Hulu Langat between 26th November 2018 and 1st August 2019. However, only 371 were eligible for the study (20 were <18 years, 28 were retreatment cases, eight were pregnant, and 41 were seeking DOTS only). Of the 371 eligible TB patients, 11 refused to participate, 10 were duplicate cases, five cases of retreatment, five cases of diagnosis changed and 19 were found to be drug resistant TB cases, leaving 321 for the analysis. Majority of the TB patients were male (66.4%, n=213) and of Malay ethnicity (55.1%, n=177).

Three fourth of the TB patients were Malaysian (82.9%, n=282) and resided in urban areas (80.2%, n=273). Half of the TB patients were married (58.2%, n=198) and had secondary school level of education (50.9%, n=173). (Table I).

Amongst the clinical factors, almost all of the new TB patients had PTB (97.8%, n=314). The chest x-rays of less than half of the TB patients had "Minimal" (48.3%, n=155) lesions. More than three fourth of the TB patients had positive sputum at the beginning of their treatment (92.5%, n=297) and negative sputum at the 2nd month of their treatment (86.6%, n=278). Majority of them were noted to have favourable treatment outcomes (80.4%, n=258) which included cured (66.4%, n=213) and completed treatment (14.0%, n=45). Less than one fourth (19.6%, n=63) patients had unfavourable treatment outcomes which included death (1.9%, n=6), defaulted (6.9%, n=22) and transferred out (10.9%, n=35). The distribution of the TB patients based on their clinical factors and treatment outcomes is shown in Table II. The time from the diagnosis of tuberculosis to the incidence of any UTO (death, treatment failure, defaulted or transferred out) was calculated as the survival time.

The mean survival time was 5.3 (SD=0.09) months as shown in Fig I. The median survival time was not calculated because the survival of the cumulative proportion was more than 50%.

**Table I: Distribution of TB patients by sociodemographic factors in Hulu Langat (n=321)**

| Patient Factors | | n | (%) |
|---|---|---|---|
| **Gender** | Male | 213 | (66.4) |
| | Female | 108 | (33.6) |
| **Ethnicity** | Malay | 177 | (55.1) |
| | Chinese | 47 | (14.6) |
| | Indian | 28 | (8.7) |
| | Others | 16 | (5.0) |
| | Foreigners | 53 | (16.5) |
| **Age Group** | 18-28 years old | 72 | (22.4) |
| | 29-39 years old | 75 | (23.4) |
| | 40-50 years old | 77 | (24.0) |
| | 51-61 years old | 56 | (17.4) |
| | 62 years old and above | 41 | (12.8) |
| **BMI** | Overweight | 41 | (12.8) |
| | Normal weight | 173 | (53.9) |
| | Underweight | 107 | (33.3) |
| **Nationality** | Malaysian | 268 | (83.5) |
| | Non-Malaysian | 53 | (16.5) |
| **Residential Area** | Urban | 257 | (80.1) |
| | Rural | 39 | (12.1) |
| | Institution | 25 | (7.8) |
| **Education level** | Tertiary | 68 | (21.2) |
| | Secondary | 163 | (50.8) |
| | Primary | 68 | (21.2) |
| | No Formal Education | 22 | (6.9) |
| **Marital Status** | Married | 184 | (57.3) |
| | Single | 137 | (42.7) |
| **Employment Status** | Employed | 183 | (57.0) |
| | Unemployed | 138 | (43.0) |
| **Monthly Income (MYR)** | ≥MYR 3001 | 39 | (12.2) |
| | MYR 1501-3000 | 80 | (24.9) |
| | ≤MYR 1500 | 202 | (62.9) |
| **Incarceration Status** | No | 296 | (92.2) |
| | Yes | 25 | (7.8) |
| **Smoking Status** | Never smoker | 174 | (54.2) |
| | Current smoker | 106 | (33.0) |
| | Ex-smoker | 41 | (12.8) |
| **Smoking Type** | Not applicable | 174 | (54.2) |
| | Cigarettes | 112 | (34.9) |
| | Vape | 35 | (10.9) |
| **Drugs** | No | 294 | (91.6) |
| | Yes | 27 | (8.4) |
| **Co-morbidities** | No | 213 | (66.4) |
| | Yes | 108 | (33.6) |
| **Diabetes** | No | 236 | (73.5) |
| | Yes | 85 | (26.5) |
| **HIV Status** | No | 312 | (97.2) |
| | Yes | 9 | (2.8) |
| **ART Status** | Not applicable | 312 | (97.2) |
| | Yes | 4 | (1.2) |
| | No | 5 | (1.6) |

BMI= Body Mass Index; MYR= Malaysian Ringgit; HIV= Human Immunodeficiency Virus; ART= anti-retro viral treatment

**Table II: Distribution of TB patients by clinical factors and treatment outcomes (n=321)**

| Clinical Factors | | n | (%) |
|---|---|---|---|
| **Type of TB** | Extra-Pulmonary | 7 | (2.2) |
| | Pulmonary | 314 | (97.8) |
| **CXR Status** | No Lesion | 23 | (7.2) |
| | Minimal | 155 | (48.3) |
| | Moderately Advanced | 133 | (41.4) |
| | Far Advanced | 10 | (3.1) |
| **Sputum Smear Score** | No AFB | 23 | (7.2) |
| | Scanty | 26 | (8.1) |
| | 1+ | 69 | (21.5) |
| | 2+ | 106 | (33.0) |
| | 3+ | 97 | (30.2) |
| **Sputum Status at Beginning** | Negative | 24 | (7.5) |
| | Positive | 297 | (92.5) |
| **Sputum Status at 2months** | Not Done | 20 | (6.2) |
| | Positive | 23 | (7.2) |
| | Negative | 278 | (86.6) |
| **Distance to Clinic** | <5 km | 227 | (70.7) |
| | 5-10 km | 68 | (21.2) |
| | >10 km | 26 | (8.1) |
| **Mode of Transport** | Own, Motorcycle | 111 | (34.6) |
| | Own, Car | 104 | (32.4) |
| | Public, Bus | 64 | (19.9) |
| | Public, Prison van | 25 | (7.8) |
| | Private, Taxi | 17 | (5.3) |
| **TB treatment outcomes (all outcomes)** | Cured | 213 | (66.4) |
| | Completed Treatment | 45 | (14.0) |
| | Death | 6 | (1.9) |
| | Treatment Failure | 0 | (0) |
| | Default | 22 | (6.9) |
| | Transferred Out | 35 | (10.9) |
| **TB treatment outcomes (grouped)** | Favourable Treatment Outcomes | 258 | (80.4) |
| | Unfavourable Treatment Outcomes | 63 | (19.6) |

TB= tuberculosis; CXR= chest x-ray; AFB= acid fast bacilli

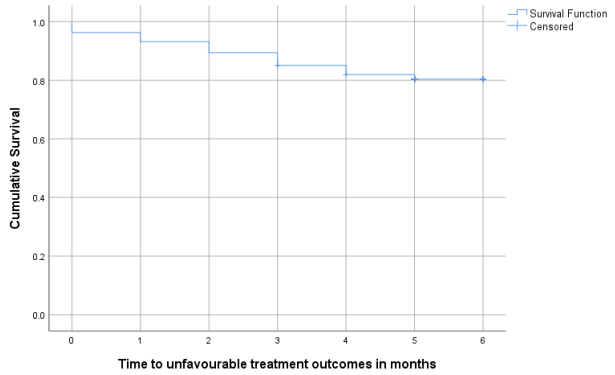


**Fig. 1 Kaplan-Meier curve of new TB patients in Hulu Langat (n=321).** The time to unfavourable TB treatment outcome was plotted against cumulative survival of the TB patients in the study. The time was measured in months at interval of 1 months.

Comparison of the survival distribution of sociodemographic and clinical factors was done using the log rank test. Statistically significant difference was noted in the survival distribution for the following factors: ethnicity, BMI, residential area, education level, marital status, employment status, monthly income, incarceration status, drugs, Human Immunodeficiency Virus (HIV) status, anti-retroviral treatment (ART) status, sputum status at 2 months and mode of transport as shown in Table III.

**Table III: Survival distribution of TB patients in Hulu Langat by factors (n=321)**

| Factors | Favourable Treatment outcome n (%) | Unfavourable Treatment outcome n (%) | Mean survival time, months (95% CI) | *p* value |
|---|---|---|---|---|
| Gender | | | | |
| Male | 165(77.5) | 48(22.5) | 5.159(4.926-5.392) | 0.069 |
| Female | 93(86.1) | 15(13.9) | 5.463 (5.191-5.735) | |
| **Ethnicity** | | | | |
| Malay | 147(83.1) | 30(16.9) | 5.373 (5.514-5.592) | 0.023* |
| Chinese | 43(91.5) | 4(8.5) | 5.702 (5.414-5.991) | |
| Indian | 19(67.9) | 9(32.1) | 4.891 (4.203-5.579) | |
| Others | 11(68.8) | 5(31.2) | 4.813 (3.814-5.811) | |
| Foreigners | 38(71.7) | 15(28.3) | 4.830 (4.258-5.402) | |
| **Age Group** | | | | |
| 18-28 years old | 57(79.2) | 15(20.8) | 5.250 (4.873-5.627) | 0.980 |
| 29-39 years old | 61(81.3) | 14(18.7) | 5.253 (4.873-5.634) | |
| 40-50 years old | 62(80.5) | 15(19.5) | 5.362 (5.028-5.696) | |
| 51-61 years old | 46(82.1) | 10(17.9) | 5.339 (4.936-5.742) | |
| 62 years old and above | 32(78.0) | 9(22.0) | 5.000 (5.081-5.441) | |
| **BMI** | | | | |
| Overweight | 34(82.9) | 7(17.1) | 5.415 (5.004-5.826) | 0.021* |
| Normal weight | 147(85.0) | 26(15.0) | 5.450 (5.233-5.668) | |
| Underweight | 77(72.0) | 30(28.0) | 4.897 (4.528-5.266) | |
| **Nationality** | | | | |
| Malaysian | 220(82.1) | 48(17.9) | 5.347 (5.165-5.529) | 0.063 |
| Non-Malaysian | 38(71.7) | 15(28.3) | 4.830 (4.258-5.402) | |
| **Residential Area** | | | | |
| Urban | 216(84.0) | 41(16.0) | 5.393 (5.208-5.578) | <0.001* |
| Rural | 30(76.9) | 9(23.1) | 5.000 (4.389-5.611) | |
| Institution | 12(48.0) | 13(52.0) | 4.303 (3.514-5.091) | |
| **Education level** | | | | |
| Tertiary | 63(92.6) | 5(7.4) | 5.706 (5.448-5.964) | 0.009* |
| Secondary | 130(79.8) | 33(20.2) | 5.178 (4.911-5.444) | |
| Primary | 51(75.0) | 17(25.0) | 5.235 (4.868-5.602) | |
| No Formal Education | 14(63.6) | 8(36.4) | 4.591 (3.651-5.531) | |
| **Marital Status** | | | | |
| Married | 160(87.0) | 24(13.0) | 5.489 (5.284-5.695) | 0.001* |
| Single | 98(71.5) | 39(28.5) | 4.955 (4.643-5.267) | |

**Table III: Survival distribution of TB patients in Hulu Langat by factors (n=321) (Continued)**

| Factors | Favourable Treatment outcome n (%) | Unfavourable Treatment outcome n (%) | Mean survival time, months (95% CI) | *p* value |
|---|---|---|---|---|
| **Employment Status** | | | | |
| Employed | 158(86.3) | 25(13.7) | 5.470 (5.259-5.681) | 0.002* |
| Unemployed | 100(72.5) | 38(27.5) | 4.984 (4.679-5.290) | |
| **Monthly Income (MYR)** | | | | |
| ≥ MYR 3001 | 37(94.9) | 2 (5.1) | 5.821 (5.576-6.065) | 0.007* |
| MYR 1501-3000 | 69(86.3) | 11(13.7) | 5.462 (5.139-5.786) | |
| ≤ MYR 1500 | 152(75.2) | 50(24.8) | 5.074 (4.826-5.321) | |
| **Incarceration Status** | | | | |
| No | 246(83.1) | 50(16.9) | 5.341 (5.161-5.522) | <0.001* |
| Yes | 12(48.0) | 13(52.0) | 4.303 (3.514-5.091) | |
| **Smoking Status** | | | | |
| Never smoker | 143(82.2) | 31(17.8) | 5.287 (5.040-5.535) | 0.708 |
| Current smoker | 83(78.3) | 23(21.7) | 5.281 (4.984-5.578) | |
| Ex-smoker | 32(78.0) | 9(22.0) | 5.098 (4.558-5.638) | |
| **Smoking Type** | | | | |
| Not applicable | 143(82.2) | 31(17.8) | 5.287 (5.040-5.535) | 0.214 |
| Cigarettes | 91(81.3) | 21(18.7) | 5.294 (5.000-5.587) | |
| Vape | 24(68.6) | 11(31.4) | 5.029 (4.460-5.597) | |
| **Drugs** | | | | |
| No | 241(82.0) | 53(18.0) | 5.286 (5.097-5.474) | 0.025* |
| Yes | 17(63.0) | 10(37.0) | 4.988 (4.388-5.588) | |
| **Co-morbidities** | | | | |
| No | 171(80.3) | 42(19.7) | 5.272 (5.052-5.492) | 0.977 |
| Yes | 87(80.6) | 21(19.4) | 5.241 (4.927-5.554) | |
| **Diabetes** | | | | 0.256 |
| No | 186(78.8) | 50(21.2) | 5.216 (5.001-5.430) | |
| Yes | 72(84.7) | 13(15.3) | 5.388 (5.060-5.716) | |
| **HIV Status** | | | 5.295 (5.114-5.475) | 0.004* |
| No | 254(81.4) | 58(18.6) | 4.111 (2.825-5.397) | |
| Yes | 4(44.4) | 5(55.6) | | |
| **ART Status** | | | | |
| Not applicable | 254(81.4) | 58(18.6) | 5.295 (5.114-5.475) | 0.014* |
| Yes | 2(50.0) | 2(50.0) | 4.000 (1.921-6.079) | |
| No | 2(40.0) | 3(60.0) | 4.200 (2.593-5.807) | |
| **Type of TB** | | | | |
| Extra-Pulmonary | 6(85.7) | 1(14.3) | 5.571 (4.794-6.349) | 0.702 |
| Pulmonary | 252(80.3) | 62(19.7) | 5.254 (5.071-5.438) | |
| **CXR Status** | | | | |
| No Lesion | 19(82.6) | 4(17.4) | 5.348 (4.750-5.946) | 0.632 |
| Minimal | 128(82.6) | 27(17.4) | 5.342 (5.092-5.592) | |
| Moderately Advanced | 104(78.2) | 29(21.8) | 5.187 (4.895-5.479) | |
| Far Advanced | 7(70.0) | 3(30.0) | 4.800 (3.664-5.936) | |
| **Sputum Smear Score** | | | | |
| No AFB | 18(78.3) | 5(21.7) | 5.130 (4.404-5.857) | 0.780 |
| Scanty | 22(84.6) | 4(15.4) | 5.538 (5.109-5.968) | |
| 1+ | 57(82.6) | 12(17.4) | 5.319 (4.941-5.697) | |
| 2+ | 87(82.1) | 19(17.9) | 5.273 (4.955-5.591) | |
| 3+ | 74(76.3) | 23(23.7) | 5.164 (4.821-5.508) | |
| **Sputum Status at Beginning** | | | | |
| Negative | 18(75.0) | 6(25.0) | 5.000 (4.260-5.740) | 0.470 |
| Positive | 240(80.8) | 57(19.2) | 5.282 (5.097-5.468) | |
| **Sputum Status at 2months** | | | | |
| Not Done | 1(5.0) | 19(95.0) | 0.850 (0.211-1.489) | <0.001* |
| Positive | 16(69.6) | 7(30.4) | 5.043 (4.400-5.687) | |
| Negative | 241(86.7) | 37(13.3) | 5.597 (5.465-5.728) | |
| **Distance to Clinic** | | | | |
| <5 km | 185(81.5) | 42(18.5) | 5.321 (5.113-5.529) | 0.630 |
| 5-10 km | 52(76.5) | 16(23.5) | 5.059 (4.626-5.492) | |
| >10 km | 21(80.8) | 5(19.2) | 5.269 (4.690-5.849) | |
| **Mode of Transport** | | | | |
| Own, Motorcycle | 99(89.2) | 12(10.8) | 8.14 (7.68-8.60) | <0.001* |
| Own, Car | 93(89.4) | 11(10.6) | 8.30 (7.90-8.70) | |
| Public, Bus | 44(68.8) | 20(31.2) | 5.39 (4.78-5.99) | |
| Public, Prison van | 12(48.0) | 13(52.0) | 4.85 (3.91-5.79) | |
| Private, Taxi | 10(58.8) | 7(41.2) | 6.70 (7.36-7.96) | |

Note the p value obtained from Log-rank test which statistically compared the survival distribution of each group (*) = p<0.05
TB= tuberculosis; BMI= Body Mass Index; MYR= Malaysian Ringgit; HIV= Human Immunodeficiency Virus; ART= anti-retro viral treatment; CXR= chest x-ray; AFB= acid fast bacilli; The median survival time was not calculated because the cumulative surviving proportion was high (>50%)

Effect of each independent factor on time to UTO was evaluated by univariate Cox proportional hazard analysis is displayed in Table IV. There was significant association between factors such as ethnicity, BMI, residential area, education level, marital status, employment status, monthly income, incarceration status, drug status, HIV status, ART status, sputum status at 2 months and mode of transport with hazard probability of unfavourable treatment outcomes. The variables included in the multivariate analysis were the ones which had p< 0.25. The final model of Multivariate Cox Proportional Hazard analysis was computed using "Backward Likelihood Ratio" method. The predictors of hazard probability of UTO are presented in Table V.

**Table IV: Univariate Cox PH analysis of sociodemographic and clinical factors for time to unfavourable treatment outcomes (n=321)**

| Factors | B | SE | Crude HR | 95% CI | *p* value |
|---|---|---|---|---|---|
| Gender | | | | | |
| Female | | | Ref | | |
| Male | 0.523 | 0.296 | 1.686 | 0.944-3.011 | 0.077 |
| **Ethnicity** | | | | | |
| Malay | | | Ref | | 0.038* |
| Chinese | -0.731 | 0.532 | 0.482 | 0.170-1.367 | 0.170 |
| Indian | 0.695 | 0.380 | 2.005 | 0.952-4.223 | 0.067 |
| Others | 0.677 | 0.483 | 1.968 | 0.764-5.073 | 0.161 |
| Foreigners | 0.592 | 0.316 | 1.807 | 1.107-3.515 | 0.061 |
| **Age Group** | | | | | |
| 18-28 years old | | | Ref | | 0.981 |
| 29-39 years old | -0.101 | 0.372 | 0.904 | 0.436-1.873 | 0.786 |
| 40-50 years old | -0.079 | 0.365 | 0.924 | 0.452-1.889 | 0.828 |
| 51-61 years old | -0.161 | 0.408 | 0.851 | 0.382-1.895 | 0.693 |
| 62 years old and above | 0.101 | 0.422 | 1.106 | 0.484-2.528 | 0.811 |
| **BMI** | | | | | |
| Overweight | | | Ref | | 0.027* |
| Normal weight | -0.126 | 0.426 | 0.881 | 0.383-2.031 | 0.767 |
| Underweight | 0.573 | 0.420 | 1.774 | 0.779-4.038 | 0.172 |
| **Nationality** | | | | | |
| Malaysian | | | Ref | | |
| Non-Malaysian | 0.534 | 0.296 | 1.706 | 0.956-3.047 | 0.071 |
| **Residential Area** | | | | | |
| Urban | | | Ref | | <0.001* |
| Rural | 0.427 | 0.368 | 1.533 | 0.745-3.154 | 0.246 |
| Institution | 1.324 | 0.319 | 3.760 | 2.013-7.022 | <0.001* |
| **Education level** | | | | | |
| Tertiary | | | Ref | | 0.020* |
| Secondary | 1.083 | 0.480 | 2.952 | 1.152-7.562 | 0.024* |
| Primary | 1.270 | 0.509 | 3.559 | 1.313-9.648 | 0.013* |
| No Formal Education | 1.750 | 0.570 | 5.755 | 1.882-17.595 | 0.002* |
| **Marital Status** | | | | | |
| Married | | | Ref | | |
| Single | 0.846 | 0.260 | 2.330 | 1.401-3.874 | 0.001* |
| **Employment Status** | | | | | |
| Employed | | | Ref | | |
| Unemployed | 0.765 | 0.258 | 2.149 | 1.297-3.560 | 0.003* |
| **Monthly Income (MYR)** | | | | | |
| ≥ MYR 3001 | | | Ref | | 0.015* |
| MYR 1501-3000 | 1.030 | 0.769 | 2.801 | 0.621-12.637 | 0.180 |
| ≤ MYR 1500 | 1.670 | 0.721 | 5.310 | 1.292-21.823 | 0.021* |
| **Incarceration Status** | | | | | |
| No | | | Ref | | |
| Yes | 1.260 | 0.312 | 3.524 | 1.913-6.492 | <0.001* |
| **Drugs** | | | | | |
| No | | | Ref | | |
| Yes | 0.742 | 0.345 | 2.101 | 1.069-4.129 | 0.048* |
| **Smoking Status** | | | | | |
| Never smoker | | | Ref | | 0.717 |
| Current smoker | 0.191 | 0.275 | 1.211 | 0.706-2.076 | 0.487 |
| Ex-smoker | 0.235 | 0.379 | 1.265 | 0.602-2.657 | 0.535 |
| **Smoking Type** | | | | | |
| Not applicable | | | Ref | | 0.234 |
| Cigarettes | 0.050 | 0.283 | 1.052 | 0.604-1.830 | 0.859 |
| Vape | 0.582 | 0.351 | 1.790 | 0.900-3.562 | 0.097 |
| **Co-morbidities** | | | | | |
| No | | | Ref | | |
| Yes | -0.008 | 0.267 | 0.992 | 0.588-1.676 | 0.977 |
| **Diabetes** | | | | | |
| No | | | Ref | | |
| Yes | -0.346 | 0.311 | 0.708 | 0.384-1.303 | 0.267 |
| **HIV Status** | | | | | |
| No | | | Ref | | |
| Yes | 1.250 | 0.467 | 3.491 | 1.399-8.711 | 0.007* |
| **ART Status** | | | | | |
| Not applicable | | | Ref | | 0.027* |
| Yes | 1.172 | 0.720 | 3.229 | 0.788-13.232 | 0.103 |
| No | 1.306 | 0.593 | 3.690 | 1.155-11.788 | 0.028* |
| **Type of TB** | | | | | |
| Extra-Pulmonary | | | Ref | | |
| Pulmonary | 0.376 | 1.008 | 1.457 | 0.202-10.505 | 0.709 |
| **CXR Status** | | | | | |
| No Lesion | | | Ref | | 0.651 |
| Minimal | 0.004 | 0.536 | 1.004 | 0.351-2.869 | 0.994 |
| Moderately Advanced | 0.250 | 0.533 | 1.283 | 0.451-3.651 | 0.640 |
| Far Advanced | 0.628 | 0.764 | 1.874 | 0.419-8.374 | 0.411 |
| **Sputum Smear Score** | | | | | |
| No AFB | | | Ref | | 0.795 |
| Scanty | -0.410 | 0.671 | 0.664 | 0.178-2.472 | 0.541 |
| 1+ | -0.250 | 0.532 | 0.779 | 0.274-2.211 | 0.639 |
| 2+ | -0.209 | 0.503 | 0.812 | 0.303-2.174 | 0.678 |
| 3+ | -0.081 | 0.493 | 1.084 | 0.412-2.852 | 0.870 |
| **Sputum Status at Beginning** | | | | | |
| Negative | | | Ref | | |
| Positive | -0.303 | 0.429 | 0.738 | 0.318-1.712 | 0.480 |
| **Sputum Status at 2months** | | | | | |
| Not Done | | | Ref | | <0.001* |
| Positive | 0.901 | 0.412 | 2.463 | 1.098-5.526 | 0.029* |
| Negative | 3.426 | 0.312 | 30.756 | 16.680-56.714 | <0.001* |
| **Distance to Clinic** | | | | | |
| <5 km | | | Ref | | 0.642 |
| 5-10 km | 0.276 | 0.294 | 1.318 | 0.741-2.344 | 0.347 |
| >10 km | 0.046 | 0.473 | 1.048 | 0.414-2.648 | 0.922 |
| **Mode of Transport** | | | | | |
| Own, Motorcycle | | | Ref | | <0.001* |
| Own, Car | -0.009 | 0.417 | 0.992 | 0.438-2.247 | 0.984 |
| Public, Bus | 1.190 | 0.365 | 3.288 | 1.607-6.727 | 0.001* |
| Public, Prison van | 1.748 | 0.401 | 5.745 | 2.619-12.601 | <0.001* |
| Private, Taxi | 1.496 | 0.476 | 4.466 | 1.757-11.348 | 0.002* |

*p<0.05; B= unstandardized coefficient; SE= Standard Error; HR=Hazard Ratio; CI= Confidence Interval; TB= tuberculosis; CXR= chest x-ray; AFB= acid fast bacilli; BMI= Body Mass Index;
MYR= Malaysian Ringgit; HIV= Human Immunodeficiency Virus; ART= anti-retro viral treatment

The significant predictors of hazard probability of unfavourable TB treatment outcomes were gender, ethnicity, HIV status and sputum status at 2 months. The male TB patients were 1.9 times more likely to have the hazard probability of an UTO compared to the female TB patients (HR=1.910, 95% CI=1.017-3.586, p=0.044). The TB patients who have the ethnicity of "Others" were 3.1times more likely to have the hazard probability of an UTO compared to the TB patients of Malay ethnicity (HR=3.056, 95% CI=1.102-8.474, p=0.032). The HIV positive TB patients were 3.5 time more likely to have the hazard probability of an UTO compared to the HIV negative TB patients (HR=3.537, 95% CI=1.303-9.605, p=0.013).

The TB patients whose sputum at 2 months of their treatment was not done were 34.2 times more likely to have the hazard probability of an UTO compared

**Table V: Predictors of hazard probability of unfavourable TB treatment outcomes (n=321)**

| Factors | | B | SE | Adjusted HR | 95% CI | *p* value |
|---|---|---|---|---|---|---|
| **Gender** | Female | | | Ref | | |
| | Male | 0.647 | 0.322 | 1.910 | 1.017-3.586 | 0.044* |
| **Ethnicity** | Malay | | | Ref | | |
| | Chinese | -0.519 | 0.544 | 0.595 | 0.205-1.728 | 0.340 |
| | Indian | 0.688 | 0.398 | 1.991 | 0.912-4.344 | 0.084 |
| | Others | 1.117 | 0.520 | 3.056 | 1.102-8.474 | 0.032* |
| | Foreigners | 0.450 | 0.356 | 1.568 | 0.780-3.512 | 0.207 |
| **HIV Status** | No | | | Ref | | |
| | Yes | 1.263 | 0.510 | 3.537 | 1.303-9.605 | 0.013* |
| **Sputum at 2months** | Negative | | | Ref | | |
| | Positive | 0.653 | 0.428 | 1.920 | 0.829-4.447 | 0.128 |
| | Not Done | 3.533 | 0.371 | 34.235 | 16.529-70.906 | <0.001* |

*p<0.05; B= unstandardized coefficient; SE= Standard Error; HR=Hazard Ratio; CI= Confidence Interval; BMI= Body Mass Index; [a]Adjusted for gender, age, ethnicity, BMI, nationality, residential area, educational level, marital status, employment status, incarceration status, drugs, smoking type, HIV status, ART status, sputum at 2 months, mode of transport

to those whose sputum at 2 months of treatment was negative (HR=34.235, 95% CI= 16.529-70.906, p<0.001). Checking of interactions between the variables of the final model was conducted and it did not reveal any significant interaction term. The assumption of the proportional hazards was met as all significant variables, showed parallel lines in the log minus log plot and hazard plot.

## DISCUSSION

Hulu Langat is the second most populated district of Selangor (20) where this prospective study was carried out. In this study, almost one in five TB patients (19.6%, n=63) patients experienced an UTO, with majority of the UTO being transferred out (55.6%, n=35). Among those transferred out TB patients three quarters (74.3%, n=26) were Malaysians. This finding is different from the previous Malaysian studies conducted where the majority of those being transferred out were of foreign nationality (7, 21). In accordance with the Malaysian Health Policy foreign workers with active TB are deported to their home countries within a period of one month (22). Certain developed countries have already established a cross border system whereby the continuity of TB treatment and treatment outcomes of those repatriated is being monitored and shared with each other (23). A locally customized system based on the same lines can be replicated in Malaysia for not only across international but also regional borders within the country. Further qualitative studies can be carried out to delineate whether the transferred-out rate was higher in Hulu Langat only for logistic reasons or because of their more complicated cases which required transfer out to more specialized centres.

The prevalence of UTO in Hulu Langat district was similar to the national prevalence rate of UTO of 19.3% (21) and 21.5% (7) of Malaysia where the definition of UTO was same as our study. Another Malaysian study conducted at district level of Kota Bharu reported a lower prevalence of UTO of 7.0% (24). The Kota Bharu study included only PTB patients and defined UTOs with death and treatment failure unlike the present study. The prevalence of higher UTO was reported among TB/HIV coinfected patients (25) in another Malaysian study which was conducted among four tertiary health centres. The tertiary health centres usually receive the complicated cases of TB from the primary and secondary health centres as this could be explained for the higher UTO at these centres as opposed to our study which was carried out among the public clinics only. The heterogeneity in the prevalence of UTO within the different regions of the country despite similar prevention and control methods in place highlights the importance of understanding the local epidemiology of the disease.

The mean time to UTO was 5.3 (SD=0.09) months with highest proportion in the 3rd month (44.0%) and 2nd month (37.0%). A Malaysian study conducted among PTB patients, revealed that half (50.6%) of the patients had duration of intensive phase of more than 2 months and 62.4% did not completed their continuation phase within four months (26). This could be attributed to the fact that the study was carried out in a chest clinic in a hospital setting which makes it a likely place for referral of complicated cases from other health clinics of the district. Another study from Nigeria reported a shorter time to death among TB patients with 50.6% of proportionate mortality in the first week of commencement of treatment (27). Najera-Ortiz (28), reported that treatment duration of less than six months was associated with poorer survival among PTB patients in Mexico. Comparison of new and retreatment TB cases in a Kenyan study reported that default in the initial 2-3months of treatment was higher among the retreatment cases when compared to new TB cases (29). These results are similar to the findings of our study. Since previous studies including ours reaffirms the fact that majority of the UTO occurs within the first three months of TB treatment, new strategies or interventions should be planned in these crucial months of TB treatment to get higher TB treatment success rate.

The male TB patients in our study were more likely to have the hazard of an UTO compared to the female patients. These findings are in agreement with the previous studies done in Malaysia (7,23,30), Yemen (31) and Brazil (32). However, an American study showed that there was no significant difference in the hazards of death among the male and female TB patients (33). Men are often associated with more dangerous professions, such as mining, and a high-risk lifestyle such as alcohol abuse and smoking (30-34). It is well recognised that smoking damages the lungs and weakens the immune system which in turn prolongs the treatment duration and so increasing the chances of developing an UTO (35).

The TB patients of the ethnicity "Others" were more likely to have the hazard of an UTO compared to the patients of Malay ethnicity in Hulu Langat. This finding is refuted by other Malaysian studies which reported higher risk of poor treatment outcomes among the Malays (7,25,36). More research is required to understand ethnic disparities in TB patients' access to healthcare, poverty, education, and other factors. The HIV positive TB patients were found to be more likely to have the hazard of an UTO compared to the HIV negative TB patients in Hulu Langat. This finding is similar with the previous studies conducted in Malaysia (7, 21,37) and also other countries (38-42). The HIV epidemic in Malaysia too contributed to the increase TB burden (25). Under the revised National TB Control Program, it is mandatory to test HIV status among new TB patients and conduct TB screening among newly diagnosed HIV patients. This practice allows early diagnosis of HIV and timely start of anti-retroviral treatment which in turn improves the treatment outcome of the HIV-infected TB patient. The patients whose sputum was not done at 2months of their treatment were more likely to have the hazard of UTO compared to those whose sputum at 2nd month of treatment was negative. This was related to the fact that the sputum not done at 2nd month reflects at either death or defaulted or transferred out prior to the second month. So even if the sputum at 2nd month recorded as positive implicating a delay in sputum conversion it is still better compared to having death, default or loss to follow-up which were considered part of UTO in this study. This was evident from the fact that all but one (19 out of 20 patients) of the TB patients who had not done as the sputum at 2nd month status had an UTO. Prado (43), reported similar findings in Brazil where those in the category of not done in the group of sputum smear at 2nd month had highest proportions of death (56.32%) and default (48.39%). However, a Moroccan study contradicted our finding where failure, default and early relapse was more likely among TB patients whose sputum smear was positive after 3 months of treatment (44). If the sputum smear remains positive at 3rd month of treatment, this is a reliable indicator of consequent poor outcomes and should prompt drug susceptibility testing (DST) in all patients (44).

## CONCLUSION

The results showed that one fifth of the new TB patients in Hulu Langat government clinics had an UTO with majority being either transferred out or default. The highest hazard rate of UTO was in the third month of treatment making the first three months of TB treatment very important time frame for future interventions. The risk factors of UTOs identified in this study were male, ethnicity type "Others", positive HIV status and not done sputum status at 2nd month of treatment. These results provide valuable insights to improve the local TB control programs. Future qualitative studies are recommended to explore the reasons for high transfer outs and defaults among TB patients in Hulu Langat. It is suggested that studies be conducted to identify a method for improving collaboration between treatment centres in order to keep track of the treatment outcomes of TB patients regardless of their transfer from one center to another.

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