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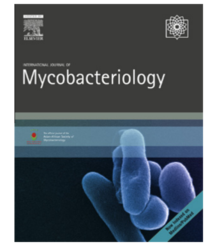

Previous treatment, sputum-smear nonconversion, and suburban living: The risk factors of multidrug-resistant tuberculosis among Malaysians

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The number of multidrug-resistant tuberculosis patients is increasing each year in many countries all around the globe. Malaysia has no exception in facing this burdensome health problem. We aimed to investigate the factors that contribute to the occurrence of multidrug-resistant tuberculosis among Malaysian tuberculosis patients. An unmatched case-control study was conducted among tuberculosis patients who received antituberculosis treatments from April 2013 until April 2014. Cases are those diagnosed as pulmonary tuberculosis patients clinically, radiologically, and/or bacteriologically, and who were confirmed to be resistant to both isoniazid and rifampicin through drug-sensitivity testing. On the other hand, pulmonary tuberculosis patients who were sensitive to all first-line antituberculosis drugs and were treated during the same time period served as controls. A total of 150 tuberculosis patients were studied, of which the susceptible cases were 120. Factors found to be significantly associated with the occurrence of multidrug-resistant tuberculosis are being Indian or Chinese (odds ratio 3.17, 95% confidence interval 1.04–9.68; and odds ratio 6.23, 95% confidence interval 2.24–17.35, respectively), unmarried (odds ratio 2.58, 95% confidence interval 1.09–6.09), living in suburban areas (odds ratio 2.58, 95% confidence interval 1.08–6.19), are noncompliant (odds ratio 4.50, 95% confidence interval 1.71–11.82), were treated previously (odds ratio 8.91, 95% confidence interval 3.66–21.67), and showed positive sputum smears at the 2nd (odds ratio 7.00, 95% confidence interval 2.46–19.89) and 6th months of treatment (odds ratio 17.96, 95% confidence interval 3.51–91.99). Living in suburban areas, positive sputum smears in the 2nd month of treatment, and was treated previously are factors that independently contribute to the occurrence of multidrug-resistant tuberculosis. Those with positive smears in the second month of treatment, have a history of previous treatment, and live in suburban areas are found to have a higher probability of becoming multidrug resistant. The results presented here may facilitate improvements in the screening and detection process of drug-resistant patients in Malaysia in the future.

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Introduction

Tuberculosis (TB) is a disease that has long brought harm to many people in the world, and until now, the formula or recipe to eliminate the disease is still vague and has yet to be found [1]. Recently, the world does not only have to face higher numbers of new TB cases each year, but another challenge arises in the form of multidrug-resistant TB (MDR-TB). This new development can shake the efforts done in tackling and managing this disease. By definition, a TB patient is classified as MDR-TB if he or she shows resistance to two most potent anti-TB drugs, namely, isoniazid and rifampicin, with or without resistance to other first-line drugs [2]. According to a recent report, an estimated 3.6% of new TB cases and 20.2% of those previously treated patients are MDR-TB globally in year 2012 [2].

Even though Malaysia is classified as an intermediate TB-burden country and a low MDR-TB burden (0.3–1.3% of all culture-positive TB patients were detected MDR-TB) by the World Health Organization [3], yet we are surrounded by countries with higher burdens of TB and high prevalence of MDR-TB, for example, Myanmar and Indonesia. In year 2013, an estimated 22% and 13% of all TB patients in Myanmar and Indonesia were detected and notified to be MDR-TB, respectively [2]. The influxes of foreign workers from these countries, TB/human immunodeficiency virus (HIV) coepidemic, and poor treatment to some extent are believed to contribute to an increase in the incidence of TB and the emergence of drug-resistant cases in Malaysia. Consequently, TB has become the top leading cause of death among other communicable diseases in Malaysia for 8 consecutive years since 2006 until 2013 [4,5]. Even more alarming, since 2013, we are seeing confirmed cases of extensively drug-resistant TB being detected and started treatment in Malaysia [2]. This rare type of multidrug-resistant patients (who are not only resistant to isoniazid and rifampicin, but also to fluoroquinolones and at least one injectable second-line anti-TB drugs) brings more challenges in tackling TB in Malaysia. However, fortunately until now, no cases of totally drug-resistant TB were reported in Malaysia.

In response to these data, several studies had been carried out by previous researchers in some states in Malaysia to try to look into the epidemiology of the disease, reasons for patients defaulting treatment, evaluation of TB treatment outcomes, as well as the prevalence of drug-resistant-TB cases in Malaysia [6–8]. However, to the best of the authors' knowledge, far too little attention has been paid to the cause of patients' resistance to the two most potent anti-TB drugs in Malaysia. Therefore, this present study aimed to determine the factors that influence the occurrence of MDR-TB among Malaysian TB patients. This study is expected to assist treatment providers in Malaysia in designing the preventive approach and in the detection of drug-resistant cases, tailored to local circumstances. Previous international studies have demonstrated a significant association between several risk factors, such as history of previous TB treatment, HIV positive, diabetes, smoking, treatment noncompliant, and alcoholism, and MDR-TB [9–11].

Methods

Ethical considerations

This study has received ethical approval from the Malaysian Research & Ethics Committee, Ministry of Health Malaysia, and is registered under the National Medical Research Registry (NMRR-12-1218-12850). In addition, this study also received approval from the Secretariat of Medical Research & Innovation, Universiti Kebangsaan Malaysia Medical Centre. Clear explanations had been given to each participant at the beginning of the study, and simultaneously, an informed consent was obtained. Participants were recruited on a voluntary basis.

Study population and design

This recent study was carried out at the Institute of Respiratory Medicine located in Jalan Pahang, Kuala Lumpur, Malaysia. This government tertiary hospital was formerly known as the National Tuberculosis Centre. We conducted an unmatched case-control study among TB patients who received anti-TB treatments from April 2013 until April 2014 at this health institute. Cases were purposively selected among those who are clinically, radiologically, and/or bacteriologically diagnosed as pulmonary TB patients; aged 18 years old and above; have local citizenship; and were confirmed to be resistant to both isoniazid and rifampicin through drug-sensitivity testing. On the other hand, pulmonary TB patients who fulfilled the mentioned criteria and were treated during the same time period, but sensitive to all first-line anti-TB drugs were randomly selected as controls.

Data collection

Data were obtained from both the patients' medical records and a set of pretested self-administered questionnaires. The patients' medical records were reviewed to obtain information, such as age at diagnosis, gender, home address, type of TB, drug and sensitivity test results, diabetic status, HIV status, and sputum-smear status at three intervals (at diagnosis, 2nd month, and 6th month). On the other hand, the questionnaire was used to obtain information regarding their marital status, occupation, ethnicity, education level, history of imprisonment, exposure to other TB cases, adherence to treatment, smoking history, alcohol intake, history of drug abuse, and house characteristics. Household crowding was categorized according to the definition of person per bedroom. A household is classified as crowded if more than two persons stay in the same bedroom [12]. The classification of patients' area of living, either urban or suburban, was carried out by referring to the standardized definition by the Department of Statistics Malaysia based on the Population and Housing Census of 2010 [13]. The level of nicotine dependency was measured using the Malay version of the Fagerstrom test for nicotine dependence adapted from a previous study [14]. A *passive smoker* is defined as someone who is reported to be regularly aware of seeing and smelling, or inhaling other people's tobacco smoke [7]. *Noncompliance* is defined as missing more than 25% of treatments in a month (i.e., missed more than 1-week injection [daily/intermittent], or missed more than 1 week for collection of oral drugs) (known as defaulters), or defaulting for more than 1 month (known as abandoned treatment). The noncompliance group is also included in the group of return-after-default patients [7].

Statistical analysis

Data were analyzed using SPSS software version 20.0 for Windows (IBM Corporation, New York, United States). Descriptive data are presented in the terms of mean, median, frequencies, percentage, or interquartile range. In the univariable analysis, Pearson chi-square test or Fisher's exact test was used in analyzing the differences and associations between categorical variables. Meanwhile, the differences and association between continuous variables (age and duration of smoking) were tested using Mann–Whitney *U* test. The nonparametric tests were used whenever the variables were not normally distributed. Variables found to be statistically significant in the univariable analysis were further analyzed using a multiple binary logistic-regression analysis to determine the factors that independently influence the occurrence of MDR-TB. The level of significance was set to .05 at a 95% confidence interval.

Results

A total of 51 clinically confirmed laboratory MDR-TB cases were found in this center during the period of study. Out of this number, 37.3% ($n = 19$) were non-Malaysian patients. For the purpose of this study, all 32 local Malaysian patients who were eligible for this study were purposively approached to participate. Meanwhile, all of the non-Malaysian multidrug-resistant cases were excluded from this study. The response rate is 93.8% (two of the local multidrug-resistant patients refused to take part due to other commitments). At the end of this study, 30 local MDR-TB cases and 120 drug-susceptible controls were involved. The studied

Table 1 – Sociodemographic characteristics of cases and controls.

	Cases ($n = 30$)		Controls ($n = 120$)		Chi square[a]	*p*	Crude odds ratio[b] (95% CI)
	n	%	*n*	%			
Sex							
Male	20	66.7	72	60.0	.45	.503	1.33 (.57–3.09)
Female	10	33.3	48	40.0			Ref.
Marital status							
Single	21	70.0	57	47.5	4.87	.031	2.58 (1.09–6.09)
Married	9	30.0	63	52.5			Ref.
Occupation							
Laborer	5	16.7	39	32.5	3.08	.230	.46 (.14–1.48)
Unemployed	15	50.0	45	37.5			1.20 (.48–2.99)
Nonlaborer	10	33.3	36	30.0			Ref.
Ethnicity							
Indian	6	20.0	13	10.8	15.24	.001	3.17 (1.04–9.68)
Chinese	10	33.3	11	9.2			6.23 (2.24–17.35)
Malay	14	46.7	96	80.0			Ref.
Education							
Primary	4	13.3	13	10.8	2.03	.368	.87 (.24–3.19)
Secondary	14	46.7	73	60.8			.54 (.23–1.29)
Tertiary	12	40.0	34	28.4			Ref.
History of incarceration							
Yes	3	10.0	12	10.0	.00	>.950	1.00 (.26–3.79)
No	27	90.0	108	90.0			Ref.
Exposed to TB patients							
Yes	4	13.3	25	20.8	.87		.59 (.19–1.83)
No	26	86.7	95	79.2	.357		Ref.

Note: History of incarceration: history of imprisonment or drug-rehabilitation inmates prior to tuberculosis diagnosis. CI = confidence interval; TB = tuberculosis.

[a] Pearson chi-square test was performed.

[b] Simple binary logistic regression was performed.

populations were not recently immigrated and were living in Kuala Lumpur, Malaysia for more than 10 years.

The median age of the cases is 47 years old, with a range between 35 years old and 58 years old. Meanwhile, the median age for the controls is 36 years old with a range between 27 years old and 50 years old. Majority of the patients are males (61.3%) and are still single (52%). It is also found that 73.3% ($n = 110$) of the patients are Malays.

As Table 1 shows, those who are single have three times the possibility of developing MDR-TB compared to those who are married (odds ratio [OR] 2.58, 95% confidence interval [CI] 1.09–6.09). With regard to ethnicity, those who are Chinese are found to be six times more likely to develop MDR-TB compared to Malays (OR 6.23, 95% CI 2.24–17.35). On the other hand, Indians are three times more likely to develop MDR-TB as compared to Malays (OR 3.17, 95% CI 1.04–9.68). Unfortunately, no significant relationship was seen between other sociodemographic characteristics and the occurrence of MDR-TB in this study.

Next, this study revealed significant relationships between the patients' living areas and diabetes, and the occurrence of MDR-TB. As shown in Table 2, it is found that those who live in suburban areas are three times more likely to develop MDR-TB as compared to those who live in urban areas (OR = 2.58, 95% CI 1.08–6.19). Similarly, those who are diabetic are two times more likely to develop MDR-TB as compared to those without this metabolic disease (OR 2.44, 95% CI 1.02–5.83). However, this study failed to prove a significant association between household crowding and HIV with MDR-TB.

In the univariable analysis, it was also found that those who are not in compliance with their treatment schedules are five times more likely to develop MDR-TB compared to those who religiously comply to their treatments (OR 4.50, 95% CI 1.71–11.82). On the other hand, patients with a past history of TB treatment are nine times more likely to develop MDR-TB as compared to newly diagnosed patients (OR 8.91, 95% CI 3.66–21.67) (Table 3).

Moreover, sputum-smear conversions at the 2nd and 6th months of treatment are also found to be significantly associated with the occurrence of MDR-TB. Based on the results, those with positive sputum smears at the 2nd month of treatment are seven times more likely to develop MDR-TB as compared to those with negative sputum smears (OR 7.00, 95% CI 2.46–19.89). Meanwhile, those with positive sputum smears at the 6th month of treatment are 18 times more likely to develop MDR-TB as compared to those with negative sputum smears (OR 17.96, 95% CI 3.51–91.99) (Table 3).

This study failed to prove any significant relationship between smoking status and the occurrence of MDR-TB. However, significant associations are observed between the duration of smoking among smokers and the status of passive smokers to the occurrence of MDR-TB. As shown in Table 4, with an increase of 1 year of smoking, it will increase the odds of developing MDR-TB by one unit (OR 1.08, 95% CI 1.02–1.14). Interestingly, passive smoke is found to be a preventive factor from developing MDR-TB in this recent study. The results of this study suggest that those who are passive smokers have 75% less chance of developing MDR-TB compared to nonpassive smokers (OR .25, 95% CI .07–.87). Yet, this study failed to prove significant associations between nicotine dependency, alcoholic status, and substance abuse, and the occurrence of MDR-TB.

All the factors that are found to be significantly associated with the occurrence of MDR-TB during the univariable analysis are once again introduced in a multiple logistic-regression model to determine the factors that independently influence the occurrence of MDR-TB. Based on the results, the factors that are independently associated with the occurrence of

Table 2 – Living and clinical characteristics of cases and controls.

	Cases ($n = 30$)		Controls ($n = 120$)		Chi square[a]	p	Crude odds ratio[b] (95% CI)
	n	%	n	%			
Area of living							
Urban	19	63.3	98	81.7	4.701	.030	Ref.
Suburban	11	36.7	22	18.3			2.58 (1.08–6.19)
Household crowding (person/room)[c]							
Crowded	3	10.0	14	11.7		>.950	.84 (.23–3.14)
Not crowded	27	90.0	106	88.3			Ref.
Diabetes							
Yes	11	36.7	23	19.2	4.19	.041	2.44 (1.02–5.83)
No	19	63.3	97	80.8			Ref.
HIV[c]							
Positive	3	10.0	17	14.2		.766	.67 (.18–2.47)
Negative	27	90.0	103	85.8			Ref.

Note: Statistically significant at $p < .05$. CI = confidence interval; HIV = human immunodeficiency virus.

[a] Pearson chi-square test was performed.

[b] Simple binary logistic regression was performed.

[c] Fisher's exact test was performed.

Table 3 – Treatment-related factors of cases and controls.

	Cases (*n* = 30)		Controls (*n* = 120)		Chi square[a]	*p*	Crude odds ratio[b] (95% CI)
	n	%	*n*	%			
Compliance to treatment[c]							
Not compliant	10	33.3	12	10.0		.003	4.50 (1.71–11.82)
Compliant	20	66.7	108	90.0			Ref.
Type of case[b]							
Previously treated	20	66.7	22	18.3	27.81	<.001	8.91 (3.66–21.67)
New case	10	33.3	98	81.7			Ref.
Smear at diagnosis[b]							
Positive	21	70.0	66	55.0	2.22	.140	1.91 (.81–4.51)
Negative	9	30.0	54	45.0			Ref.
Smear at 2nd month[c]							
Positive	10	33.3	8	6.7		<.001	7.00 (2.46–19.89)
Negative	20	66.7	112	93.3			Ref.
Smear at 6th month[c]							
Positive	7	23.3	2	1.7		<.001	17.96 (3.51–91.99)
Negative	23	76.7	118	98.3			Ref.

Note: Statistically significant at $p < .05$. CI = confidence interval.
[a] Pearson chi-square test was performed.
[b] Simple binary logistic regression was performed.
[c] Fisher's exact test was performed.

Table 4 – Smoking status, alcoholic status, and history of substance abuse among cases and controls (*N* = 150).

	Cases (*n* = 30)		Controls (*n* = 120)		Chi square[a]	*p*	Crude odds ratio (95% CI)[b]
	n	%	*n*	%			
Smoking							
Current smoker	8	26.7	41	34.2	.68	.713	.72 (.29–1.83)
Former smoker	5	16.7	16	13.3			1.16 (.37–3.61)
Nonsmoker	17	56.6	63	52.5			Ref.
Duration of smoking (y)[c]							
Median	37.00	25.00		.012	1.08 (1.02–1.14)		
(IQR)	(26.00; 43.50)	(14.5; 35.00)					
Passive smoker							
Yes	3	10.0	37	30.8	5.33	.031	.25 (.07–.87)
No	27	90.0	83	69.2			Ref.
Pack years (*n* = 70)							
More than 15	10	77.0	31	54.4	2.22	.148	2.79 (.69–11.24)
15 or less	3	23	26	45.6			Ref.
Nicotine dependency (*n* = 49)[d]							
High	4	50.0	8	19.5		.067	.50 (.15–1.66)
Moderate	2	25.0	6	14.6			.33 (.07–1.65)
Low	2	25.0	27	65.9			Ref.
Alcoholic status[d]							
Yes	3	10.0	8	6.7		.460	1.56 (.39–6.26)
No	27	90.0	112	93.3			Ref.
Substance abuse[d]							
Yes	3	10.0	16	13.3		.766	.72 (.19–2.66)
No	27	90.0	104	86.7			Ref.

Note: Statistically significant at $p < .05$. CI = confidence interval; IQR = interquartile range.
[a] Pearson chi-square test was performed.
[b] Simple binary logistic regression was performed.
[c] Mann–Whitney *U* test was performed.
[d] Fisher's exact test was performed.

Table 5 – Multiple logistic-regression model of factors influencing the occurrence of multidrug-resistant tuberculosis.

Characteristics	p	Adjusted odds ratio[a]	95% CI
Living in suburban areas	.013	4.88	(1.39–17.04)
Is married	.052	3.18	(.99–10.22)
Positive sputum smears at the 2nd month of treatment	.011	6.82	(1.54–30.15)
Positive sputum smears at the 6th month of treatment	.058	7.41	(.93–58.98)
Was treated previously	<.001	9.48	(3.12–28.77)

CI = confidence interval.

[a] Adjusted for sex, occupation, ethnicity, level of education, history of incarceration, exposure to tuberculosis patients, household crowding, compliance, smoking status, passive smokers, duration of smoking, level of nicotine dependency, alcoholic status, and substance abuse.

MDR-TB are living in suburban areas (OR 4.88, 95% CI 1.39–17.04), positive sputum smears at the 2nd month of treatment (OR 6.82, 95% CI 1.54–30.15), and were treated previously (OR 9.48, 95% CI 3.12–28.77) (Table 5).

Discussion

In this present study, the median age for the cases was found to be 47 years old. Meanwhile, the median age for the controls was 36 years old. A similar age range was reported in two other previous studies conducted in eastern China and Iran with a mean age of MDR-TB cases at 47 years old and 44 years old, respectively [15,16]. A pooled meta-analysis study supported that MDR-TB is more common in patients under 65 years old compared to those under the age of 45 [17]. However, the findings of this study are in contrary with several other previous studies that showed that patients with MDR-TB are slightly younger as compared to the non-MDR-TB patients [9,18,19]. Young people are believed to be more accessible to MDR-TB because they are more mobile and busier with work, hence have less time for treatments. Meanwhile, MDR-TB among the older age group indicates reactivation of past infections with resistant strains.

Sputum-smear conversion is often used as a method to monitor the treatment response in patients with pulmonary TB. In this current study, it was found that positive sputum smears in the 2nd month of anti-TB treatment are one of the predictors for the occurrence of MDR-TB. The finding is consistent with findings from an earlier study by Hovhannesyan and Breeze in 2012 [20]. Their study showed that the time taken for conversion to negative sputum in patients resistant to MDR-TB in Armenia is more than 2 months [20]. However, the findings of this study differ with another independent study conducted in Iran, which tried to look at the time to sputum-smear conversion among MDR-TB patients. The research team found that most patients with MDR-TB converted to negative sputum smears within 51 days of treatment [21].

Many studies had successfully proven a significant association between the past history of TB treatment and the occurrence of MDR-TB [17,18,22]. Patients who had been treated with TB treatments were more likely to be resistant to anti-TB drugs than those who never received any treatments. Similar results were also shown in our recent study. It is said that this group of patients acquired MDR-TB through poor compliance, lack of supervision during treatment, improper drug regimen, inadequate or irregular drug supply, and poor infection control measures in treatment settings [23]. However, all the three latter factors were not examined in this study. Further research on this issue in Malaysia and its relationship with the occurrence of MDR-TB is deemed necessary in the future.

A study in Georgia demonstrated that those in cities had 43% greater MDR-TB risk compared to those in rural areas [24]. In this recent study, a significant relationship was found between the patients' area of living and MDR-TB. It may occur due to an indirect relationship with their exposure to foreign immigrants in the community and workplace. Malaysia faces an influx of immigrants from neighboring countries, such as Indonesia, Myanmar, and Bangladesh, each year. As we are aware, these countries have been classified by the World Health Organization as countries with higher percentages of previously treated TB cases with MDR-TB in the Southeast Asia region as compared to Malaysia [2]. These immigrants are mostly employed in the construction, farming, agriculture, and housekeeping industries [25], and most of them live in squatter settlements that are numerous in suburban areas.

Adherence to treatment has been considered as one of the keys in preventing the occurrence of drug-resistant TB cases. Every patient diagnosed with TB should adhere to the treatment regime for at least 6 months, starting with 2 months of intensive treatment and continuing with the continuation phase of treatment for another 4 months. In this study, we also look at the relationship between compliance and the occurrence of MDR-TB. Our univariable analysis demonstrated that there is a significant association between these two. This finding is also supported by several other studies that have been conducted previously [26–28]. However, there are also other studies that show the opposite. It was said that treatment failure occurs only at high rates of nonadherence (between 60% to 80% of nonadherence). Drug resistance are believed to occur not due to noncompliance, but due to patient pharmacokinetic variability [29]. Conflicting findings on the relationship between nonadherence and drug-resistant TB might also occur due to the lack of uniformity in how we define and measure nonadherence [30].

Another factor that was found to have a significant association with the occurrence of MDR-TB is patients' marital status. In this study, it was found that patients with TB who are single are three times more likely to become MDR-TB than those who are married. Single people are believed to be more vulnerable to anti-TB drug resistance because of the lack of moral support that comes from couples and families where the support factor has been shown to play a role in supporting, monitoring, and motivating patients to adhere to treatments [31]. Moreover, those who are single are more vulnerable to engage in high-risk behaviors, such as drug abuse, smoking, HIV infections, and alcohol consumption, which also have an impact on treatment compliance [32].

Diabetes was found to be significantly associated with MDR-TB in our study's univariable analysis. This is in line with other previous studies that showed that diabetic patients were 2.0–2.6 times more likely to be MDR-TB compared to nondiabetics [11,33]. In some other studies, the association between these two factors was only seen in new TB cases, but not in previously treated patients [34,35]. There is no direct explanation on how diabetes could affect drug-resistant TB. Previous researchers had tried to find a correlation between these two issues by looking at the corner of genetic differences and at the interference of hyperglycemic states on anti-TB drug absorption [36,37].

Our study has a few limitations. First, this recent study was only conducted in one government treatment center and does not include patients who go to private health-care facilities. Therefore, we cannot generalize the findings to the other treatment settings in other parts of Malaysia. Second, the data on *Mycobacterium tuberculosis* strain variability were not included in this study. This factor has been found to be associated with the transmission of MDR-TB in other previous microbiological studies. However, this study has successfully contributed new ideas about the background and the factors that influence the occurrence of MDR-TB among local TB patients. In return, it helps in better planning of MDR-TB case detection and management of these patients.

Conclusions

In conclusion, this study has found that those previously treated patients, have positive sputum smears at the 2nd month of treatment, and living in suburban areas are at higher odds of developing MDR-TB. Therefore, greater emphasis should be given to patients with these characteristics in order to facilitate improvements in early case detection, and thus, better treatment can be given.

Conflicts of interest

The authors have no conflict of interest to declare.

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