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Original Article

Multidrug-resistant tuberculosis and risk factors associated with its development: a retrospective study

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Abstract

Introduction: Multidrug-resistant tuberculosis (MDR-TB) has emerged as a major clinical public health threat and challenges the national TB control program in Malaysia. Data that elaborates on the risk factors associated with the development of MDR-TB is highly limited in this country. This study was aimed to determine the risk factors associated with the development of MDR-TB patients in peninsular Malaysia.

Methodology: This was a case control study; the data were collected from medical records of all the registered MDR-TB patients at five referral TB hospitals in peninsular Malaysia from January 2010 to April 2014. The 105 cases were all confirmed by a positive sputum culture of *Mycobacterium tuberculosis* for MDR-TB and extensively drug-resistant (XDR)-TB. As a comparison, a total of 209 non-MDR-TB cases were randomly selected as controls.

Results: A total of 105 MDR-TB and 209 non MDR-TB patients were studied. The risk factors associated with MDR-TB within the multivariate analysis were previous tuberculosis treatment, HIV infection, being an immigrant, and high load of positive for acid-fast bacillus (AFB) smear.

Conclusions: The findings of this study revealed that patients who had received previous treatment for tuberculosis, were infected with HIV, were immigrants, and had a high burden of positive testing for AFB smear were more likely to have MDR-TB. An enhanced understanding of the risk factors associated with MDR-TB strains is imperative in the development of a national policy for public health interventions.

Key words: risk factors; tuberculosis; multidrug-resistant and extensively drug-resistant tuberculosis; Malaysia.

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Introduction

Tuberculosis (TB) remains one of the world's most deadly but reassuringly curable infectious diseases if properly treated [1]. The World Health Organization (WHO) recently published data revealing that one-third of the globe's population has been infected with TB and that an estimated 9.4 million TB cases are reported annually. Around 3 million TB cases per year occur in South East Asia. There were 1.3 million deaths attributed to this infection amongst HIV-negative inhabitants and 0.38 million among HIV-positive inhabitants [2].

The problem is further exacerbated by the growing number of cases of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), drug-resistant forms of the diseases which continue to surge around the world. There were 0.44 million cases of MDR-TB reported globally in 2008, and 0.15 million deaths occurred from MDR-TB. In 2009, it was estimated that MDR-TB accounted for 3.3% of cases of TB. According to the WHO report published in 2009, at least one case of XDR-TB is currently reported as existing in 92 countries [3].

The major cause of anti-TB drug resistance development is due to infrequent and irregular consumption of anti-TB medication. Infection may occur due to direct transmission from an infected individual or it could be due to inadequate or inconsistent treatment [4].

Treatment of MDR-TB infections is much more complicated and complex, less effective, leads to high toxicity, and is very costly compared with the treatment of patients infected with susceptible TB strains [5]. The rapid spread of MDR-TB is a major concern of TB control programs worldwide. The epidemic of these infectious diseases is due to the inadequate infrastructure in health services, increasing numbers of HIV infection, and other multiple risk behaviors associated with this disease [6]. The WHO recently published a country report from Malaysia on MDR-TB in 2011 and 2012. Of 10,537 cases suspected and tested for MDR-TB in 2011, 141 cases were confirmed to be MDR-TB. Of 9,132 suspected cases of MDR-TB in 2012, 74 were laboratory-confirmed MDR-TB cases. All of the cases had commenced MDR-TB treatment. This number was expected to increase in 2013, due to a lack of adequate knowledge about disease in the community and lack of knowledge of the risk factors associated with the disease [7].

Better comprehension of the risk factors associated with MDR-TB strains is highly significant in developing a national policy for public health interventions. An appropriate treatment regimen can target certain high-risk populations by using this information to guide decisions. In addition, efficient allocation of resources on specific education programs and intervention can be implemented in patients as well as within the community [8].

Studies have consistently found a strong association between the development of anti-TB drug resistance and patients who underwent previous anti-TB treatment [9,10]. A study conducted in the United States discovered that HIV infection was also a risk factor for resistance [9-13]. Other risk factors reported included foreign birth, ethnicity, living in urban centers, and having cavitary pulmonary tuberculosis [9,11,14-17]. However, most of these studies were conducted in developed countries, particularly in the United States and European countries. Therefore, it is very interesting and rather crucial to elucidate on these risk factors that have not yet been studied in Malaysia. This study was designed to identify the risk factors responsible for the development of MDR-TB in Malaysia.

Methodology

Study design and patients

A case control study was conducted between January 2010 and January 2014. All registered cases from 2009 to 2013 were included in the study.

Regarding the sampling methods for the MDR-TB cases in this study, a list of all the patients with confirmed pulmonary MDR-TB cases tested for drug sensitivity testing (DST) against first-line and second-line drugs was obtained from National Public Health Laboratory (NPHL). NPHL is a reference laboratory that performs drug susceptibility testing of all *Mycobacterium tuberculosis* isolates in Malaysia This list was cross-checked with the MDR-TB registry in the Tuberculosis Information System (TBIS) under the Ministry of Health (MOH) for TB surveillance in the country. Under the TB surveillance program organized by the MOH Malaysia, it is mandatory for all healthcare workers to notify the MOH immediately via the TBIS online system. According to a report derived from the MDR-TB registry, there were only 141 cases reported in the country. Therefore, non-probability sampling methods were applied to the study, especially in the MDR-TB cases. This was due to a lack of sample size for the MDR-TB cases and low prevalence of MDR-TB within peninsular Malaysia. Thus, based on logistic problems, financial considerations, and available sample size, only five referral TB hospitals in peninsular Malaysia, which have been mentioned above, were selected based on the highest prevalence of MDR-TB in each hospital and on the availability of data as shown in the list obtained from NPHL.

The simple random sampling was applied to the non-MDR-TB group to ensure that each non-MDR-TB patient in the target population had an equal chance of being selected as a sample for the study. A list of names of non-MDR-TB patients from January 2010 through April 2014 was obtained from the hospital record units of two centers, namely the Respiratory Specialist Clinic at Hospital Raja Perempuan Zainab II (HPRZII) and the Institute of Respiratory Medicine (IRM) in Hospital Kuala Lumpur. The list of eligible sample names was marked from 1 through 209. Patients who were selected according to a list of random numbers were recruited as study participants. The random numbers were generated using Excel software.

In this study, a total of 314 patients were included, which comprised 105 MDR-TB cases and 209 controls for the purpose of comparison. These were all the cases of confirmed MDR-TB, while the control group comprised TB patients who were fully sensitive to all the anti-TB drugs.

All cases were recruited from the national referral TB center in Malaysia (Institute of Respiratory Medicine, Hospital Kuala Lumpur) and five other TB

referral hospitals located within five states of peninsular Malaysia (Kelantan, Perak, Penang, Johor, and the Federal Territories [Kuala Lumpur]). The inclusion criteria included all the confirmed MDR-TB and XDR-TB cases that attended or were admitted to the selected study hospitals. These included all patients who were actively on anti-TB treatment, patients who were deceased, and patients who defaulted treatment and/or were lost to follow-up during the study period. A random selection of non-MDR-TB cases sample was also included for the purpose of comparison. The exclusion criteria included all patients actively on anti-TB treatment in the private sector during the study period.

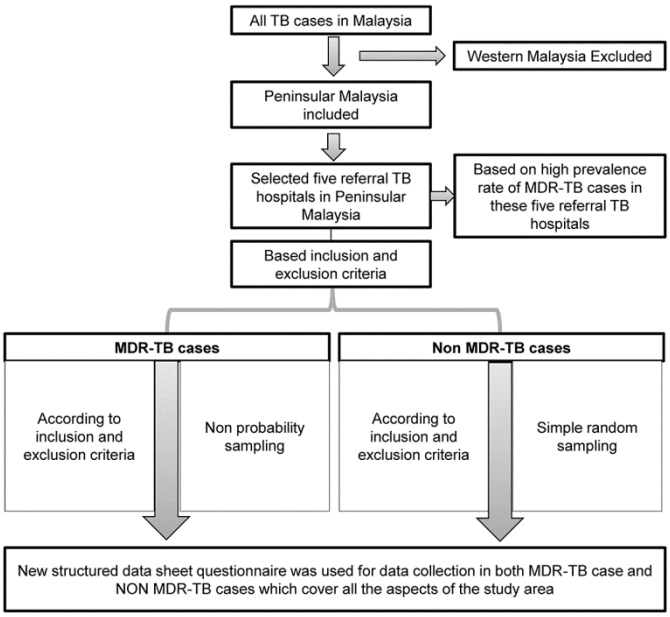
The term MDR-TB was used to define TB patients with culture-proven *M. tuberculosis* that had been proven to be resistant to both isoniazid (INH) and rifampicin (RIF) with or without resistance to other drugs. The term non-MDR-TB was applied to patients with culture-proven *M. tuberculosis* that was fully sensitive to the first-line anti-TB drug. XDR-TB was defined as TB caused by the strain of *M. tuberculosis* that was resilient to at least two first-line drugs, to second-line fluoroquinolone, and amongst second-line injectable drugs, to either amikacin, kanamycin, or capreomycin.

DST was performed according to the method described by the WHO [18]. Resistance was defined as at least 1% colony growth at critical concentrations of the drug, which is 0.2 µg/mL for isoniazid and 1 µg/mL for rifampicin. Socio-demographic characteristics, past medical history, clinical characteristics, and risk behavior information was obtained from the patients' clinical records.

The Statistical Package for Social Sciences (SPSS) version 20.0 was used for data entry and data analysis. Descriptive analysis was presented as mean and standard deviations (SD) for normally distributed numerical variables, while for non-normal distributed variables, the results were expressed as median and interquartile ranges (IQRs). Pearson's Chi-square test and Fisher's exact test were applied to determine the differences of proportion for both groups in socio-demographic characteristics of MDR-TB and non-MDR-TB cases. The level of significance was set at 0.05.

Univariate analysis (simple logistic regression) was conducted on all the independent variables. It was applied to find the association between dependent variables and potential risk factors associated with MDR-TB. Variable selection was carried from univariate analysis.

Figure 1. Flow chart of the study sampling method



Multivariate analysis by multiple logistic regression was performed to obtain a preliminary main effect of the model. The univariable analysis was selected based on a p value ≤ 0.25, best fit, a parsimonious model and biologically plausible. The backward stepwise likelihood ratio (LR) method was applied. Multicollinearity and interaction were checked to obtain the preliminary final model. The final model was obtained after checking the fit of the model using the Hosmer-Lemeshow test, Pearson's Chi-square, classification table (overall correctly classified percentage), and area under the curve receiver operating characteristic (ROC) curve.

The results were presented by appropriate tabulations based on the determined variables, regression coefficient, crude (OR) or adjusted (AOR) odds ratio with 95% confidence interval (CI) and its corresponding p values. The level of significance was set at 0.05.

Ethical approval

Ethics clearance was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (USMKK/PPP/JEJeM/243.3[4.1]) and also from the National Institutes of Health and Medical Research Ethics Committee, Ministry of Health Malaysia (NMRR N0:12-90-10809).

Results

There were 215 cases of MDR-TB reported in the national TB surveillance in Malaysia as a whole in 2011 and 2012. Only a total of 105 cases were

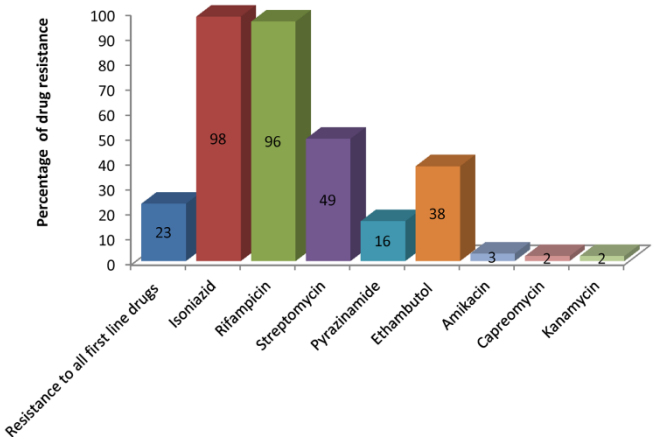
included in this study. The remaining cases were not included because the East Malaysia (Sabah and Sarawak) were excluded due to financial issues and logistic problems for the purpose of comparing 209 non-MDR-TB cases that were included in the analysis.

Table 1 indicates the comparison of socio-demographic characteristics of MDR-TB and non-MDR-TB cases. In this study, age was categorized into groups. The 45–65 year age group was the most affected age group in both MDR-TB (40; 38.1%) and non-MDR-TB (70; 33.5%) cases. However, there was no statistical significance. Males were more likely to be infected with MDR-TB (70; 66.7%) and non-MDR-TB (147; 70.3%) when compared with females. Females had a lower proportion of MDR-TB (35; 33.3%) and non-MDR-TB (62; 29.7%). There was no significant difference between both groups.

Malay ethnicity was the most common race in both MDR-TB (48; 46.2%) and non-MDR-TB (138; 60%); however, the percentage of foreigners was higher in MDR-TB (31.7%) compared to non-MDR-TB (10.5%). The race variable was found to be statistically different between MDR-TB and non-MDR-TB. Foreigners had higher rates of MDR-TB infection than non-MDR-TB infection. There was a significant difference ($p < 0.001$) in ethnic distribution between the two groups.

The antimicrobial susceptibility profile of MDR-TB and XDR-TB are shown in Figure 2. There were three patients with XDR-TB who had strains displaying resistance to second-line drugs such as amikacin, kanamycin, and capreomycin. Of three XDR-TB patients, one died during the study period. A total of 15 patients were resistant to all first-line drugs. Resistance to rifampicin was the highest, followed by isoniazid (Figure 2).

Figure 2. Drug resistance pattern of MDR-TB patients and XDR-TB Patients



The significant demographic and social factors associated with MDR-TB in the univariate analysis were young age (25–44 years) (OR = 0.49, 95% CI = 0.25–0.95, p = 0.093) and old age (≥ 65 years) (OR = 0, 95% CI = 0.10–0.99, p = 0.048), foreign race (non-Malaysian) (OR = 4.87, 95% CI = 1.86–12.71, p = 0.001), immigrants status (OR = 6.96, 95% CI = 3.53–13.70, p = 0.001), and homelessness (OR = 10.56, 95% CI = 2.96–37.65, p = 0.001) (Table 2).

Table 1. Comparison of socio-demographic characteristics of MDR-TB and non-MDR-TB cases (n = 314)

Variables	MDR-TB patients (n = 105)	Non-MDR-TB patients (n = 209)	P value
	n (%)	n (%)	
Age [a*]	40.4 (14.95)	43.0 (16.56)	0.139
Age			
≤ 24	23 (21.9)	28 (13.4)	
25–44	37 (35.2)	92 (44.0)	0.097[b]
45–64	40 (38.1)	70 (33.5)	
≥ 65	5 (4.8)	19 (9.1)	
Gender			
Female	35 (33.3)	62 (29.7)	0.507[a]
Male	70 (66.7)	147 (70.3)	
Race			
Indian	8 (7.7)	26 (12.4)	
Chinese	15 (14.4)	23 (11.0)	**0.001[b]**
Foreign (non-Malaysian)	33 (31.7)	22 (10.5)	
Malay	48 (46.2)	138 (66.0)	

*Mean and SD; [a] Pearson's Chi-square test was applied; [b] Fisher's exact test was applied; MDR-TB: multidrug-resistant tuberculosis

Table 2. Univariate analysis for demographic characteristics and factors associated with MDR-TB (n = 314)

Variable	MDR-TB (n = 105)	Non-MDR-TB (n = 209)	(b)	Crude OR (95% CI)	P value
	n (%)	n (%)			
Gender					
Female	35 (33.3)	62 (29.7)	0	1	0.507
Male	70 (66.7)	147 (70.2)	-0.17	0.84 (0.51–1.39)	
Age group (years)					
≤ 24	23 (21.9)	28 (13.4)	0	1	
25–44	37 (35.2)	92 (44.0)	-0.71	0.49 (0.25–0.95)	**0.037**
45–64	40 (38.1)	70 (33.5)	-0.36	0.69 (0.35–1.36)	0.292
≥ 65	5 (4.8)	19 (9.1)	-1.13	0.32 (0.10–0.99)	0.048
Race					
Indian	8 (7.7)	26 (12.4)	0	1	
Chinese	15 (14.4)	23 (11.0)	0.75	2.12 (0.76–5.90)	**0.037**
Foreign	33 (31.7)	22 (10.5)	1.58	4.87 (1.86–12.71)	0.292
Malay	48 (46.2)	138 (66.0)	0.12	1.13 (0.47–2.66)	0.048
Living conditions					
Live alone	72 (84.7)	116 (89.2)	0	1	0.330
Live with family	13 (15.3)	14 (10.8)	0.40	1.49 (0.66–3.36)	
Known TB contact					
Absent	61(58.1)	133 (63.6)	0	1	0.330
Present	44(41.9)	76 (36.4)	0.23	1.49 (0.66–3.36)	
Immigrants status					
Local	70 (66.7)	195 (93.3)	0	1	**0.001**
Non-local	35 (33.3)	14 (6.7)	1.94	6.96 (3.53–13.70)	
History of homelessness					
Absent	91 (86.7)	206 (98.6)	0	1	**0.001**
Present	14 (13.3)	3 (1.4)	2.35	10.56 (2.96–37.65	
History of imprisonment					
Absent	103 (98.1)	208 (99.5)	0	1	0.257
Present	2 (1.9)	1 (0.5)	1.39	4.03 (0.36–45.06)	
Default TB treatment					
Did not default	87 (82.9)	175 (83.7)	0	1	0.844
Defaulted	18 (17.1)	34 (16.3)	0.06	1.06 (0.56–1.99)	
Relapse of TB					
Did not relapse	79 (75.2)	172 (82.3)	0	1	0.142
Relapsed	26 (24.8)	37 (17.7)	4.25	1.53 (0.86–2.70)	
Loss to follow-up					
No loss	88 (83.8)	174 (84.5)	0	1	0.881
Lost	17 (16.2)	32 (15.6)	0.04	1.05 (0.55–1.99)	
Defaulted clinic appointment					
Did not default	87 (82.9)	176 (84.6)	0	1	0.689
Defaulted	18 (17.1)	32 (15.4)	0.12	1.13 (0.60–2.14)	

Simple logistic regression; MDR-TB: multidrug-resistant tuberculosis

Table 3. Univariate analysis for comorbidities risk behaviour and clinical presentation in association with MDR-TB (n = 314)

Variables	MDR-TB (n = 105) n (%)	Non-MDR-TB (n = 209) n (%)	(b)	Crude OR (95% CI)	P value
Previous history of TB treatment					
Absent	52 (49.5)	167 (79.9)	0	1	**0.001**
Present	53 (50.5)	42 (20.1)	1.39	4.05 (2.43–6.75)	
COPD disease					
Absent	95 (90.5)	203 (97.1)	0	1	**0.017**
Present	10 (9.6)	6 (2.9)	1.27	3.56 (1.25–10.08)	
HIV infection status					
HIV seronegative	99 (94.3)	173 (82.8)	0	1	**0.007**
HIV seropositive	6 (5.7)	36 (17.2)	-1.23	0.29 (0.11–0.71)	
Diabetes mellitus					
Absent	77 (73.3)	149 (71.3)	0	1	0.704
Present	28 (26.7)	60 (28.7)	-10	0.90 (0.53–1.52)	
a) Risk behavior					
Smoking status					
Non-smoker	64 (61.0)	107 (51.2)	0	1	0.102
Smoker	41 (39.0)	102 (48.8)	-0.39	0.67 (0.41–1.08)	
Intravenous drugs					
Non-user	93 (88.6)	178 (85.2)	0	1	0.409
User	12 (11.4)	31 (14.8)	-3.00	0.74 (0.36–1.51)	
Alcohol abuse					
No alcohol	92 (87.6)	191 (91.8)	0	1	0.236
Alcoholic	13 (12.4)	17 (8.2)	0.46	1.58 (0.74–3.40	
b) Clinical presentation					
Lung cavitation					
No cavity	11 (10.5)	60 (28.7)	0	1	**0.001**
Cavity	94 (89.5)	149 (71.3)	1.23	3.44 (1.72–6.87)	
Bacterial load by AFB smear					
Low	9 (8.6)	89 (42.6)	0	1	**0.001**
High	96 (91.4)	120 (57.4)	2.06	7.91 (3.78–16.51)	
Mantoux test					
Negative	23 (22.1)	44 (47.3)	0	1	
Positive	23 (22.1)	13 (14.0)	1.21	3.38 (1.45–7.89)	**0.005**
Not done	58 (55.8)	36 (38.7)	1.12	3.08 (1.60–5.92)	**0.001**
Radiographic changes					
Negative	9 (8.7)	30 (24.0)	0	1	**0.003**
Positive	95 (91.3)	94 (75.2)	1.21	3.36 (1.57–7.70)	

Simple logistic regression was applied; MDR-TB: multidrug-resistant tuberculosis; COPD: chronic obstructive pulmonary disease; AFB: acid-fast bacillus

The significant co-morbidities risk behavior and clinical presentation associated with MDR-TB by univariate analysis were previous history of TB treatment (OR = 4.05, 95% CI = 2.43–6.75, p = 0.001), chronic obstructive pulmonary disease (COPD) (OR = 3.56, 95% CI = 1.25–10.08, p = 0.017), HIV infection (OR = 0.29, 95% CI = 0.11–0.71, p = 0.007), high bacterial load by acid-fast bacillus (AFB) smear (OR = 7.91, 95% CI = 3.78–16.51, p = 0.001), Mantoux test positivity (OR = 3.38, 95% CI = 1.45–7.89, p = 0.005), (OR = 3.08, 95% CI = 1.60–5.92, p = 0.001), and pulmonary radiographic changes (OR = 3.48, 95% CI = 1.57–7.70, p = 0.002) (Table 3).

Table 4 presents the multivariate analysis, revealing that the variables that remained significant were previous tuberculosis treatment (AOR = 5.97, 95% CI = 2.73–13.04, p = 0.001), HIV infection (AOR = 0.22, 95% CI = 0.08–0.61, p = 0.001), immigrant status (AOR = 5.97, 95% CI = 2.72–13.04, p = 0.001), and a high bacterial load by AFB smear (AOR = 7.04, 95% CI = 3.16–15.70, p = 0.001).

Discussion

This study was designed to determine risk factors associated with the development of MDR-TB. Determining risk factors associated with the disease would enhance the treatment of the patients. Therefore, the information would be valuable for early suspicion of MDR-TB cases in order to start appropriate TB regimens and control spread of the disease.

The possible reason for this unexpected risk factor with the development of MDR-TB could be due to the rapid emergence of MDR-TB and XDR-TB. Moreover, Malaysia is located in South East Asia, where the high prevalence of TB and MDR-TB is found. In the era of HIV, MDR-TB is becoming a major global health issue [19-22]. The WHO enforced a worldwide stewardship program in regions where increasing trends of drug resistance are being observed [21].

Age was reportedly an independent factor associated with drug resistance among TB and MDR-TB cases; cases in the 45–64 age range had the highest MDR-TB rates [8]. Patients in the 45–64 year age group were the most affected age group in both MDR-TB (40; 38.1%) and non-MDR-TB (70; 33.5%) cases. Thus, the diseases probably affected the middle aged patients in both MDR-TB and non-MDR-TB cases.

Univariate analysis showed significant differences between age groups in MDR-TB. The frequency of MDR-TB was higher in patients in the younger age group (25–44 years). Cases in this age group were more likely to develop MDR-TB. These results are consistent with other reported findings from Hong Kong and 13 European countries [4,8]. Similarly, Law *et al.* revealed that patients under 45 years of age were more likely to develop MDR-TB [23].

A systematic review in European countries revealed that the risk of MDR-TB development among patients who were under 45 years of age was higher

Table 4. Summary of univariable and multivariable analysis for risk factors associated with MDR-TB

Variable	MDR-TB (n = 105)	Non-MDR-TB (n = 209)	Simple logistic regression			Multiple logistic regression		
			b	Crude OR (95% CI)	P value	b	Adjusted OR (95% CI)	P value
Immigrant								
No local	70 (66.7)	195 (93.3)	0	1	**0.001**	0	1	**0.001**
Local	35 (33.3)	14 (6.7)	1.94	6.96 (3.53–13.70)		1.87	5.97 (2.72–13. 04)	
HIV Infection								
HIV seronegative	99 (94.3)	173 (82.8)	0	1	**0.007**	0	1	**0.001**
HIV seropositive	6 (5.7)	36 (17.2)	-1.23	0.29 (0.11–0.71)		-1.51	0.22 (0.08–0.61)	
Previous history TB treatment								
Absent	52 (49.5)	167 (79.9)	0	1	**0.001**	0	1	**0.001**
Present	53 (50.5)	42 (20.1)	1.39	4.05 (2.43–6.75)		1.79	5.97 (2.73–13.04)	
Bacterial load by AFB smear								
Low	9 (8.6)	89 (42.6)	0	1	**0.001**	0	1	**0.001**
High	96 (91.4)	120 (57.4)	2.06	7.91 (3.78–16.51)		1.95	7.04 (3.16–15.70)	

Backward stepwise LR multiple logistic regression was applied; Multicollinearity and interaction term were checked and not found; Hosmer-Lemeshow test (p = 0.442), Pearson's Chi-square test (0.454), classification table (overall correctly classified percentage [77.4%]), and area under receiver operating characteristics [ROC] curve (82.8%) were checked for the fit of the model and reported to be fit; (b) Regression coefficient

than in patients who were over 65 years of age [4]. Another study conducted by Espinal *et al.* 2006 showed that MDR-TB was more rampant among patients in the 35–64 year age group. Other studies found that MDR-TB was more common among those under 65 years of age [4,5].

In this study, it was observed that there were significant differences in the invariable analysis between age groups and MDR-TB. The current study also found that the frequency of MDR-TB was higher in patients between 25 and 44 years of age and those 65 years of age and older, as well as in males. This finding was similar to other reported findings from Hong Kong and 13 European countries [4,23]. Similarly, Law *et al.* revealed that people younger than 45 years of age were more likely to develop MDR-TB. However, age results were not significant in the univariate analysis [23].

In the current global drug resistance survey report, the association between gender and MDR-TB was not clearly demonstrated [1]. It was thought that the possible reason behind men having a higher rates MDR-TB than women might have been due to alcohol abuse, intravenous drug abuse dependency, and imprisonment status, in which more men than women are involved.

In this study, risk factors associated with MDR-TB found to be statistically significant included immigrant status, HIV infection, previous history of TB treatment, and a high bacterial load by AFB smear.

A notable finding in this study was that being an immigrant was associated with MDR-TB. The majority of the foreigners who enrolled in this study were from South East Asian countries, specifically from Malaysia's neighboring countries. In Eastern Malaysia, it has been reported that more than 24% of the newly detected TB cases emerged from immigrants [24].

Immigrants have been documented as a major factor leading to an increased incidence of MDR-TB in some European countries, Hong Kong, and Iran [4,25,26]. Lack of adequate healthcare facilities, inappropriate/poor working conditions, and poor housing conditions are believed to be major factors contributing to an increase in the prevalence of drug resistance within the immigrant population. The risk of resistance to anti-TB drugs was reported to be threefold to tenfold higher in immigrants than in the local population, and 17% of TB cases among the immigrants were MDR-TB [27-31]. In the present study, a fivefold higher risk of resistance to anti-TB drugs in immigrants was reported, which is similar to that found in previous studies. In contrast, a study carried out in Spain revealed that immigrant status was not associated with the risk of developing MDR-TB [8].

Previous history of anti-tuberculosis treatment was most commonly reported as a significant risk factor in the development of MDR-TB [4,28,29]. This may indicate that acquired drug resistance could be a result of previous non-compliance. Interestingly, in this study, most of the immigrants had previous treatment of TB in their homeland, which could be linked to the possible risk for developing MDR-TB. An alternative reason could be the transmission of TB strains from individuals infected with MDR-TB. Thus, MDR-TB may be brought from immigrants' homelands into Malaysia. Poor living conditions could be other factors that increase the transmission of MDR-TB amongst immigrants.

A previous study conducted by Conaty *et al.* [32] reported that for HIV-positive patients, infection was an important risk factor for MDR-TB (OR = 2.5, 95% CI = 1.2–5.2). HIV infection has been shown to increase MDR-TB incidence by augmenting the risk of transmission of MDR-TB [23,30]. A systematic review conducted by Faustini *et al*. found a higher risk of MDR-TB among HIV-infected patients, and found that HIV patients were more likely to be at risk of developing MDR-TB infection compared with non-HIV-infected patients [4].

The findings of the present study were different than those mentioned above. Our findings showed that patients with HIV co-infection were 78% less likely to have MDR-TB infection, whereas in the other studies, patients with HIV co-infection were 2.5 more likely to be at risk of developing MDR-TB infection. In the present study, we observed that HIV infection was a significant associated predictor for MDR-TB infection. Patients infected with HIV were 78% less likely to have MDR-TB compared with the HIV-seronegative patients (AOR = 0.22; 95% CI = 0.08–0.61; p = 0.001).

The outcomes of this study could be due to a small proportion of MDR-TB with HIV co-infection cases enrolled and due to the fact that the majority of foreigner included in this study were screened for HIV infection before entering into the country. Only 6 of 99 cases infected with MDR-TB had HIV co-infection in this study. Despite these small numbers of cases, there were other studies conducted, with similar findings. A study from Spain reported that HIV infection was not an independent risk factor for the development of MDR-TB infection [8,29].

Other risk factors associated with HIV infection as a predictor and risk factors associated with the development of MDR-TB could be related to lifestyle and contact between HIV-infected patients. A resistant strain in one patient could easily spread to other patients. Moreover, most HIV-infected patients are more likely to be included in directly observed treatment, short course (DOTS) and more closely supervised or controlled while on treatment. Furthermore, these patients may be more likely to stop all anti-TB drugs at once rather than take drugs that fail to work or drugs that would lead to treatment failure and subsequently lead to MDR-TB development. The problem is further exacerbated by double treatment with the combination of two drugs, one for MDR-TB and another for HIV. Patients are more likely to stop medication because of high drug burden and the toxicity or side effects of medications.

Treatments for MDR-TB patients are complex, have low effectiveness, are toxic, and can be compounded with HIV treatment. The stigma of HIV often leads to HIV patients defaulting from or stopping treatment because of fear of community workers, healthcare providers, and social stigma in the society.

The clinical presentations found significant associations with MDR-TB in this study, including a high bacterial load by AFB smear. A high bacterial load by AFB smear was considered if more than three AFB smears are positive. These findings were supported by other studies [12,32,33]. The positive smear carried the risk of transmission of the infection. A high bacterial load by AFB smear counts in the smear might indicate a high organism burden and thus be more difficult to treat. Smear positivity could be the consequence of drug resistance rather than the cause. However, if notification data were being received correctly, then smear-positive status should reflect the status at the beginning of treatment rather than during the course of the treatment. Also, this relationship is much stronger in those with previous tuberculosis than those without it, which we would not expect if the relationship was simply due to mistaken direction of causation [33].

The major limitation of the present study was its small sample size; the sample therefore may not be representative of the whole of Malaysia. This study was an unmatched case control study carrying its own limitations, which included the selection of bias and founding; however, the sophisticated statistical analysis may have controlled the confounding variables. Despite these limitations, to the best of our knowledge, there are limited numbers of published data on the risk factors of MDR-TB in Malaysia. Therefore, this study could contribute information about risk factors and clinical presentation associated with MDR-TB in Malaysia.

Conclusions

Based on the findings of this study, immigrant status, HIV infection, previous anti-TB treatments, pulmonary TB, and a high bacterial load by AFB smears were factors associated with MDR-TB patients in Malaysia. Early detection of MDR-TB cases is a crucial component in TB control programs. This information would help to narrow down the target groups for the application of rapid molecular methods for MDR-TB detection and the initiation of appropriate treatment, resulting in a more cost-effective approach in the management of the disease.

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