Impact of ethnic disparities on the treatment outcomes of HIV-negative drug-resistant tuberculosis patients in Kuala Lumpur, Malaysia: A call for a culturally-sensitive community intervention approach

Noorsuzana Mohd Shariff[a,*], Shamsul Azhar Shah[b], Fadzilah Kamaludin[c]

[a] Lifestyle Science Cluster, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Kepala Batas, 13200, Pulau Pinang, Malaysia
[b] Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaakob Latif, 56000, Kuala Lumpur, Malaysia
[c] Institute for Medical Research, Ministry of Health Malaysia, Jalan Pahang, 50588, Kuala Lumpur, Malaysia

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ABSTRACT

Objective: Little is known about the treatment outcomes of HIV-negative drug-resistant tuberculosis (TB) patients in Malaysia. With respect to this issue, this study aimed to determine factors associated with unsuccessful treatment outcomes among drug-resistant TB patients at the Institute of Respiratory Medicine, Kuala Lumpur, Malaysia.
Methods: This retrospective cohort study involved laboratory-confirmed drug-resistant TB patients from January 2009 to June 2013. Multiple logistic regression was used to model the outcome, which was subsequently defined according to the recent definition by the WHO. Data were analysed using IBM SPSS Statistics for Windows version 22.0.
Results: Among the 403 patients who were analysed, 66.7% of them were found to have achieved successful outcomes (cured or completed treatment) while the remaining 33.3% had unsuccessful treatment outcomes (defaulted, treatment failure or died). Multivariable analysis showed that the type of resistance [polyresistant (aOR = 3.00, 95% CI 1.14–7.91), multidrug resistant (MDR) (aOR = 5.37, 95% CI 2.65–10.88)], ethnicity [Malay (aOR = 2.86, 95% CI 1.44–5.71), Indian (aOR = 3.04, 95% CI 1.20–7.70)], and treatment non-compliance (aOR = 26.93, 95% CI 14.47–50.10) were the independent risk factors for unsuccessful treatment outcomes among this group of patients. Notably, the odds of unsuccessful treatment outcome was also amplified among Malay MDR-TB patients in this study (aOR = 13.44, 95% CI 1.99–90.58).
Conclusion: In order to achieve better treatment outcomes for TB, effective behavioural intervention and thorough investigation on ethnic disparities in TB treatment are needed to promote good compliance.

1. Introduction

Generally, tuberculosis (TB) is an ancient disease that has yet to be eradicated and has affected millions of people all over the world. To exemplify, The Stop TB Strategy showed that the treatment outcome of TB patients is still a prevalent issue that needs to be addressed [1]. In 2017, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people [2] and the persistent threat of drug-resistant TB (DR-TB) still remains. Of note, there were an estimated 600 000 (range, 540 000–660 000)

incident cases of multidrug-resistant (MDR)/rifampicin-resistant (RR)-TB in 2016, with cases of MDR-TB accounting for 82% (490 000) of the total [3]. Nevertheless, the latest data in 2017 showed an undesirable low treatment success rate of 55% for MDR-TB globally, thus reflecting the high rates of lost to follow-up, unevaluated treatment outcomes, and treatment failures [2]. Even though Malaysia is an intermediate TB burden country with low incidence of HIV infection, recent reports by the Ministry of Health Malaysia (at the National TB & LUNG Diseases Conference 2018 on 15–18th March, Kuala Lumpur) have shown an increase in the number of drug-resistant TB patients from 41 new MDR-TB cases in 2007 to 110 new cases in 2017. Also, recent literature has shown that HIV-negative MDR-TB patients have higher rates of poor treatment outcomes and higher default rates compared with those who are HIV-positive [4]. The current study primarily aimed to further explore the factors affecting the treatment success rates of

* Corresponding author at: Lifestyle Science Cluster, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Kepala Batas, 13200, Pulau Pinang, Malaysia.
E-mail address: suzanashariff@usm.my (N.M. Shariff).

this group of patients in countries with rapidly emerging cases of drug-resistant TB like Malaysia.

2. Materials and methods

2.1. Study population and design

This retrospective cohort study involved patients who received treatment at the Institute of Respiratory Medicine (IPR), Kuala Lumpur, Malaysia. In particular, these patients were those identified to have isolates resistant to at least one first-line anti-TB drug (ATD) from January 2009 to 30 June 2013. Accordingly, patients who exhibited a positive culture for *Mycobacterium tuberculosis* (*M. tuberculosis*) underwent drug and sensitivity testing to detect resistance to any first-line ATD. Based on the laboratory results, those found to be resistant to at least one first-line ATD were considered eligible to participate in this study. Drug-resistant TB patients were excluded from this study if they were HIV-positive. For this purpose, the identification of HIV-positive patients was performed by enzyme-linked immunosorbent assay (ELISA) testing, but some were transferred to other treatment centres due to difficulty in determining their survival status or their medical records could not be traced.

2.2. Drug susceptibility testing and data collection procedure

The lists of patients' drug and sensitivity testing (DST) results were obtained from both the National Tuberculosis Laboratory databases of the National Public Health Laboratory (NPHL) and the TB laboratory in the IPR. Details regarding the drug susceptibility testing procedure involved in this study have been explained in a previous article [5]. Patients with a positive culture for *M. tuberculosis* were tested for susceptibility against isoniazid, rifampicin, streptomycin, and ethambutol using gold-standard phenotypic fluorescence smear microscopy (BACTECTM MGITTM 960 Mycobacterial Detection System; BD Diagnostics, Sparks, MD) liquid culture. In addition, patients with a risk of MDR-TB were also

tested by a commercial genotypic resistance testing line probe assay (GenoType MTBDRplus; Hain Lifescience GmbH, Nehren, Germany) to further confirm the diagnosis. The GenoType MTBDRplus detects those resistances that have their origins in the *rpoB*, *katG* or *inhA* genes. All of the phenotypic and genotypic drug sensitivity tests were performed by the NPHL located in Sungai Buloh, Selangor, Malaysia. This public health laboratory is a government-supported laboratory equipped with a level II Tuberculosis Risk Laboratory and well-trained medical laboratory technicians [5].

2.3. Data collection procedure

The medical records and TB notification forms (Tuberculosis Information System) of DR-TB patients were traced to obtain information about their sociodemographic, clinical, and lifestyle backgrounds. Subsequently, to confirm their treatment outcomes following the recommended treatment period for DR-TB patients by the Ministry of Health Malaysia, each of the patients was followed up for at least 24 months from their date of diagnosis [6]. Importantly, patients who had been cured or completed their treatment were classified as having achieved successful treatment outcomes. Conversely, those who defaulted, failed treatment or died were classified under unsuccessful treatment outcome. This is based on World Health Organization (WHO) revised definitions of treatment outcomes for DR-TB [3].

2.4. Statistical analysis

In this study, data were stored and analysed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY). Basically, descriptive data were presented as mean and standard deviation, or frequency and percentage. Also, simple binary logistic regression was performed in the univariable analysis. After that, multiple binary logistic regression analysis was applied to determine independent predictors of unsuccessful treatment outcomes for drug-resistant TB patients. For this purpose, the

Table 1
Sociodemographic characteristics of HIV-negative drug-resistant tuberculosis in Kuala Lumpur from January 2009 to June 2013.

Characteristics	Treatment outcome (N = 403)				P-value[e]	Crude OR (95% CI)
	Successful (n = 269)		Unsuccessful (n = 134)			
	n	%	n	%		
Age at diagnosis (years)[a]	38.76 ± 15.19		41.73 ± 15.04		0.065	1.01 (0.99–1.03)
Gender						
Male	199	74.0	104	77.6	0.427	1.22 (0.75–1.99)
Female	70	26.0	30	22.4		Reference
Ethnicity						
Malay	91	33.8	56	41.8	0.014*	1.88 (1.14–3.11)
Chinese	45	16.7	19	14.2	0.446	1.29 (0.67–2.48)
Indian	23	8.6	23	17.2	0.002*	3.06 (1.53–6.09)
Immigrants	110	40.9	36	26.9	Reference	Reference
Job status						
Working	155	57.6	68	50.7	0.191	Reference
Unemployed	114	42.4	66	49.3		1.32 (0.87–2.00)
Weight at diagnosis (kg)						
≤35	7	2.6	7	5.2	0.184	2.06 (0.71–6.01)
>35	262	97.4	127	94.8		Reference
Type of resistance						
Monoresistant[b]	218	81.0	72	53.7	Reference	Reference
Polyresistant[c]	21	7.8	18	13.4	0.006*	2.59 (1.31–5.14)
Multidrug resistant[d]	30	11.2	44	32.8	<0.001*	4.44 (2.60–7.58)

[a] Data were expressed as mean ± SD.
[b] Resistant to one first-line anti-tuberculosis drug.
[c] Resistant to two or more first-line anti-tuberculosis drugs other than a combination of isoniazid and rifampicin.
[d] Resistance to both isoniazid and rifampicin.
[e] Simple logistic regression was performed.
* P < 0.05.

results were presented as crude and adjusted odds ratio (OR) and 95% confidence interval (CI). In particular, the level of significance was set at 0.05.

2.5. Ethical approval

Ethical approval was given by the Malaysian Research & Ethics Committee [NMRR-12850] and was registered with the National Medical Research Registry, Ministry of Health Malaysia.

3. Results

3.1. Sociodemographic background and treatment outcome

A total of 12 799 TB patients with a positive culture for *M. tuberculosis* were screened for drug and sensitivity testing within the period of 5 years from January 2009 to June 2013. Among them, 426 patients (3.3%) were discovered to have isolates resistant to at least one first-line ATD. From these 426 patients, 403 (94.6%) were HIV-negative and the remaining 23 (5.4%) were HIV-positive. Based on the analysis conducted on these 403 HIV-negative patients, 269 (66.7%) of them achieved successful outcomes (cured or completed treatment) while the other 134 (33.3%) had unsuccessful treatment outcomes (defaulted, treatment failure or died). Comparatively, the mean age of those diagnosed with TB and having unsuccessful treatment outcomes was slightly higher compared with those who had successful treatment outcomes (41.73 ± 15.04 vs. 38.76 ± 15.19 years, respectively). Moreover, univariable analysis showed that ethnicity and type of resistance were the factors that had a significant relationship with unsuccessful treatment outcome. Specifically, Malay patients were two times more likely to have poor treatment outcomes compared with immigrants (cOR 1.88, 95% CI 1.14–3.11). Meanwhile, Indian patients were three times more likely to have unsuccessful treatment outcomes compared with immigrants (cOR 3.06, 95% CI 1.53–6.09). On the other hand, multidrug-resistant TB (MDR-TB) patients were four times more likely to have unsuccessful treatment outcomes compared with

those who were resistant to one anti-TB drug (cOR 4.44, 95% CI 2.60–7.58). Similarly, this finding was also observed among polyresistant patients who exhibited three times the odds of being unsuccessfully treated compared with mono-resistance patients (cOR 2.59, 95% CI 1.31–5.14). Evidently, this study failed to prove the significance of other sociodemographic factors on the outcome. Table 1 shows the patients' sociodemographic characteristics.

3.2. Clinical and lifestyle characteristics

Regarding patients' clinical and lifestyle characteristics, factors like types of case, treatment compliance, and history of drug abuse were found to have a significant relationship with unsuccessful treatment outcomes in the univariable analysis. Additionally, acquired TB cases (those with re-infection and previous history of TB treatment) were three times more likely to have poor treatment outcomes compared with newly diagnosed TB patients (cOR 2.90, 95% CI 1.81–4.64). On the other hand, DR patients with a history of drug abuse were six times more likely to have unsuccessful treatment outcomes compared with those who did not (cOR 5.53, 95% CI 2.09–14.59). In particular, the odds of unsuccessful outcome were found to be 23 times higher among DR-TB patients with poor compliance to the treatment (cOR 22.77, 95% CI 13.14–39.46) compared with those who religiously complied to the anti-TB treatment. However, the factors of type of TB, smoking and alcohol consumption had insignificant effect on the treatment outcome of DR patients involved in this study. Table 2 presents the clinical and lifestyle characteristics of patients.

3.3. Predictors of unsuccessful treatment outcome

In order to determine the predictors of unsuccessful treatment outcome among DR-TB patients, factors with $P < 0.25$ in the univariable analysis were simultaneously analysed using multiple logistic binary regression. By implementing the forward stepwise likelihood strategy, the final model highlighted three factors that independently predicted the unsuccessful outcomes of this

Table 2
Clinical and lifestyle characteristics of HIV-negative drug-resistant tuberculosis patients in Kuala Lumpur from January 2009 to June 2013.

Characteristics	Treatment outcome (N = 403)				P-value[a]	Crude OR (95% CI)
	Successful (n = 269)		Unsuccessful (n = 134)			
	n	%	n	%		
Diabetes mellitus						
Yes	56	20.8	31	23.1	0.595	1.15 (0.69–1.88)
No	213	79.2	103	76.9		Reference
Types of case						
Primary	222	82.5	83	61.9	<0.001*	Reference
Acquired	47	17.5	51	38.1		2.90 (1.81–4.64)
Types of TB						
Pulmonary	262	97.4	131	97.8	0.825	1.17 (0.29–4.59)
Extrapulmonary	7	2.6	3	2.2		Reference
Treatment compliance						
Compliant	243	90.3	39	29.1	<0.001*	Reference
Non-compliant	26	9.7	95	70.9		22.77 (13.14–39.46)
Smoking status						
Smoker	93	34.6	52	38.8	0.404	1.20 (0.78–1.84)
Non-smoker	176	65.4	82	61.2		Reference
Alcohol consumption						
Yes	18	6.7	15	11.2	0.124	1.76 (0.86–3.61)
No	251	93.3	119	88.8		Reference
Drug abuse						
Yes	6	2.2	15	11.2	0.001*	5.53 (2.09–14.59)
No	263	97.8	119	88.8		Reference

[a] Simple logistic regression was performed.
* $P < 0.05$.

group of patients: type of resistance, ethnicity, and treatment compliance. With relation to this finding, MDR-TB patients were identified to be five times more likely to have poor treatment outcome compared with monoresistant patients (aOR 5.37, 95% CI 2.65–10.88). In a different case, polyresistant TB patients were three times more likely to have poor treatment outcome compared with monoresistant patients (aOR 3.00, 95% CI 1.14–7.91). In terms of ethnicity, both Malay and Indian individuals are three times more likely to have unsuccessful outcomes compared with immigrants (aOR 2.86, 95% CI 1.44–5.71 and aOR 3.04, 95% CI 1.2–7.70, respectively). In this study, the likelihood of unsuccessful treatment outcome was also high among Malay MDR-TB patients (aOR 13.44, 95% CI 1.99–90.58). Those who did not comply with their anti-TB treatment had 27 times higher odds of poor treatment outcome compared with those with good treatment compliance (aOR 26.93, 95% CI 14.47–50.10). With respect to this study, this model described a 53.5% variability of unsuccessful treatment outcome among DR-TB patients and had an 83.9% predictive accuracy. Table 3 presents the predictors of unsuccessful treatment outcomes among DR-TB patients.

4. Discussion

In general, Malaysia is classified as an intermediate TB burden country with low prevalence of DR-TB. According to national TB practice, DST has not yet become routine in all new cases. The procedures of culture and DST are only performed on patients who remain sputum smear positive during the second month of their intensive treatment or those who are at risk of DR-TB. Interestingly, this study found that in the period of 5 years from January 2009 to June 2013, 3.3% of the patients in this tertiary centre were confirmed to be DR-TB patients. This finding is congruent with the statistics obtained in Taiwan, another intermediate TB burden country, which showed that 1% of all new TB cases and 6% of all previously treated TB cases were infected with MDR-TB in 2015 [7].

Despite the low prevalence of detected drug resistance, the overall treatment success rate among HIV-negative DR-TB patients involved in this study was far lower than the targeted success rate by the WHO, in 2015, of at least 75–90%. Notably, the patients with

severe forms of drug resistance (the polyresistant and MDR-TB patients) in this study were categorised as the most vulnerable group and had poor treatment outcomes. It is important for this situation to be addressed, as treating patients who have polyresistant strains using the standardised first-line anti-TB drug regimens has been shown to increase the risk of treatment failure and further acquired resistance. Eventually, this setback might lead to MDR-TB if it is not properly managed [8]. As shown in the current study, the MDR-TB patients had the lowest rate of successful treatment compared with those with other forms of resistance. Specifically, 40.5% of the patients achieved desirable treatment outcomes, which was consistent with other local studies [9,10]. Nevertheless, this value is still below the latest global data of MDR-TB treatment outcomes (55.0%) for patients starting treatment in 2014 and the 7-year cohort data in Taiwan, which showed a 61.0% treatment success among their MDR-TB patients [2,11]. Primarily, both Malaysia and Taiwan share similar policies in treating DR-TB patients: free treatment to all regardless of their nationalities, active contact tracing, DST of first-line ATDs performed at quality-assured laboratories, mandatory TB notification, and directly observed treatment, short-course (DOTS). However, the higher success rate of treatment in Taiwan might be due to the extra effort taken to ensure patients' adherence to treatment through community-based DOTS, which has not yet been made compulsory in Malaysia.

The current study expounded the negative impact of non-adherence or non-compliance on the treatment outcome of DR-TB patients. Typically, compliance is difficult in DR-TB because of prolonged treatment regimens, complex treatment, and adverse effects of the drugs. In particular, the negative impact of non-compliance on the treatment outcome and survival of both drug-susceptible and DR-TB patients recorded in this current study was consistent with previous studies [12–15]. Malaysia first implemented DOTS therapy in 1999, and since then many additional initiatives, which are in line with WHO recommendations, have been applied to reduce the gap in accessing TB treatment and facilitate treatment compliance. Among these initiatives are: organising services close to the patient's home (setting up of Klinik 1 Malaysia and Health Clinics within a 5 km range); considering patient's needs (modified DOTS by family members for areas with

Table 3
Predictors of unsuccessful treatment outcome among HIV-negative drug-resistant tuberculosis patients in Kuala Lumpur from January 2009 to June 2013 (N = 403).

Characteristics	Unsuccessful treatment outcome			
	Crude OR[a] (95% CI)	P-value	Adjusted OR[b] (95% CI)	P-value
Type of resistance				
MDR-TB	4.44 (2.60–7.58)	<0.001	5.37 (2.65–10.88)	<0.001*
Polyresistant	2.59 (1.31–5.14)	0.006	3.00 (1.14–7.91)	0.026*
Monoresistant	Reference		Reference	
Ethnicity				
Malay	1.88 (1.14–3.11)	0.014	2.86 (1.44–5.71)	0.003*
Chinese	1.29 (0.67–2.48)	0.446	2.19 (0.91–5.32)	0.082
Indian	3.06 (1.53–6.09)	0.002	3.04 (1.20–7.70)	0.019*
Immigrants	Reference		Reference	
Treatment compliance				
Non-compliant	22.77 (13.14–39.46)	<0.001	26.93 (14.47–50.10)	<0.001*
Compliant	Reference		Reference	
Malay*MDR-TB[c]	–	–	13.44 (1.99–90.58)	0.008*

Abbreviations: TB, tuberculosis; MDR-TB, multidrug-resistant tuberculosis.
[a] Simple binary logistic regression was performed.
[b] Forward stepwise likelihood ratio method multiple logistic regression was performed (adjusted for job status, age at diagnosis, alcohol consumption, drug abuse, weight at diagnosis, and type of TB cases).
[c] Significant interaction between ethnicity and type of resistance.
* $P < 0.05$.

high-density populations such as Klang Valley); and providing incentives in the form of free medication and monetary reimbursement. Another privilege offered in Malaysia is that medications are fully funded by the government. In light of this mindful planning, charity organisations also provide travel allowances and pocket money to underprivileged patients [15]. However, despite these preventive measures, this study highlights the consequence of ethnic disparities on the treatment outcomes of DR-TB patients.

In this study, among the three main ethnicities in Malaysia, Malays and Indians had the highest risk of poor treatment outcome when compared to immigrants. Arguably, this finding was dissimilar to Atif et al., who studied new smear-positive pulmonary TB patients in north Malaysia. Based on their study, foreign nationalities — which are also known as immigrants from other neighbouring countries such as Indonesia, Myanmar, The Philippines, Nepal, and Bangladesh — were associated with unsuccessful treatment outcomes [16]. Undoubtedly, this variation might be due to the different level of support provided to the foreign TB patients in the studied area. Furthermore, each of the immigrants, especially those from Myanmar, were closely supervised by the Union Refugee Agency (UNHCR) staff during their treatment period. Specifically, these staff are required to be translators to convey the information regarding treatment; as a result, this may contribute to higher compliance to treatment among the immigrant patients. On the other hand, this current study also highlighted a significant relationship between Malay ethnicity and a severe form of DR-TB: MDR-TB, which normally leads to poor treatment outcomes. However, the mechanism behind this medical predicament still remains unclear. Most importantly, this finding stresses the immediate need to incorporate non-pharmacological treatment that is culturally-sensitive and tailored to specific ethnicity. Future research is needed to investigate the local ethnic differences in relation to care access, environmental setting, social aspect of the patients' needs, preferred options of care, and other socio-behavioural factors among DR-TB patients.

Inevitably, this study also had several limitations. First, the collected data were only from a single national TB referral tertiary hospital; thus, the findings might not accurately reflect the whole population of Malaysia. With regard to this mater, the findings gathered in this study should be interpreted with care. Second, the effects of variation in treatment regimens on patients' treatment outcome were not studied. Therefore, further information on the treatment regimens may offer insight into the quality of treatment delivered to the patients.

5. Conclusion

In conclusion, this study was conducted to determine predictors of unsuccessful treatment outcome among HIV-negative DR-TB patients. This study showed that the factors of being resistant to more than two anti-TB drugs, having poor treatment compliance, and Malay and Indian ethnicities were independently associated with unsuccessful treatment outcomes among this group of patients. In connection with this finding, more emphasis should be given to the management of DR-TB patients with these characteristics. Along this line, effective behavioural intervention, support at community-based settings, ambulatory care, and thorough future investigation on ethnic disparities in TB treatment (through sound methodology research that incorporates both qualitative and quantitative approaches) are needed to promote good compliance in order to achieve better treatment outcomes.

Competing interests

None declared.

Ethical approval

Ethical approval was given by the Malaysian Research & Ethics Committee [NMRR-12850] and was registered with the National Medical Research Registry, Ministry of Health Malaysia.

Authors contributions

Author 1: involved in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and critically revising it for important intellectual content, final approval of the version to be submitted.

Author 2: involved in the conception and design of the study, acquisition of data, analysis and interpretation of data, critically revising the article for important intellectual content, final approval of the version to be submitted.

Author 3: involved in the conception and design of the study, critically revising the article for important intellectual content, final approval of the version to be submitted.

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