Original Article

Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis (MDR- TB) Compared with Non-MDR-TB Infections in Peninsular Malaysia

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Abstract

Background: **Treating patients with multidrug-resistant tuberculosis (MDR-TB) strains is more complicated, complex, toxic, expensive, than treating patients with susceptible TB strains. This study aims to compare the treatment outcomes and potential factors associated between patients with MDR-TB and non MDR TB infections in peninsular Malaysia.**

Methods: **This study was a retrospective cohort study. Data were collected from the medical records of all registered MDR-TB patients and Non-MDR-TB patients at five TB hospitals in peninsular Malaysia from January 2010 to January 2014.**

Results: **A total of 314 subjects were studied, including 105 MDR-TB cases and 209 non-MDR-TB. After TB treatment, 24.8% of the MDR-TB patients and 17.7% of non MDR TB relapsed; 17.1% of the MDR-TB patients and 16.3% of non MDR TB defaulted from TB treatment. A significant difference seen in treatment success rate 17.1% for MDR-TB; 63.1% for non MDR TB (P < 0.001)). Mortality rate were 8.9% for MDR-TB; 13.2% for non MDR TB. Multivariable analysis showed the potential factors associated with poor treatment outcomes were presence of HIV infection (AOR, 1.09; 95%CI: 1.05, 1.75; P = 0.001) and previous TB treatment (AOR, 4.87; 95%CI: 2.84, 8.38; P = 0.001).**

Conclusion: **This study revealed that the treatment success rate in patients with non MDR TB infection was higher than MDR-TB. Unsuccessful treatment was seen in MDR-TB associated with potential factors such as history of TB treatment, and presence of HIV infection.**

Keywords: *Treatment outcomes, MDR-TB, tuberculosis, Peninsular Malaysia*

Introduction

Despite increased awareness, improved diagnostic facilities, and global control efforts, tuberculosis (TB) remains one of the deadliest infectious diseases in Malaysia and the rest of the world. An estimated 8–9 million new cases emerge annually with 2 million patients dying each year (1). TB control has become challenging because of HIV co-infection and the emergence of multidrug-resistant TB (MDR-TB) (2, 3).

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Extensive drug-resistant TB (XDR-TB) has also arisen as a threat to public health (3).

MDR-TB is a *Mycobacterium tuberculosis* strain that is resistant to rifampicin (RIF) and isoniazid (INH), two of the most effective anti-TB drugs. XDR-TB, a subset of MDR-TB is resistant to RIF, INH, any fluoroquinolone, and at least one of three injectable drugs (i.e., capreomycin, kanamycin, or amikacin) (4,5). According to the WHO (2013), at least one case of XDR-TB was reported in 92 countries at the end of 2012. An estimated 9.8% of all MDR-TB cases develop into XDR-TB (6, 7).

MDR-TB is a critical threat to public health, and MDR-TB care control programs in various countries are associated with high mortality and failure rates, especially in presence of HIV-infected patients (8). Moreover, treatment for patients with MDR-TB strains is more expensive, complicated, and toxic and less effective than treatment for susceptible TB strains and MDR-TB strains are transmittable over long periods of time, even under treatment (8). Primary and acquired drug resistance are common, with the latter caused by inappropriate regimen prescription or patient non-adherence (6).

Early publications on the treatment response of MDR-TB report a considerable mortality rate of 37% compared with susceptible strains (9,10). However, XDR-TB treatment is more challenging than MDR-TB treatment. XDR-TB treatment commonly fails and leaves only a few categories of drugs available to which patients can still respond. A study reported that XDR-TB carries a five-fold increase in death risk compared with MDR-TB (10).

Poor treatment outcomes are influenced by several potential factors, such as previous treatments, smear positivity during treatment, treatment interruptions during the intensive phase of the disease, alcohol or drug addiction, and defaulting from TB treatment, which likely causes the proliferation of a large number of MDR-TB strains. Primary MDR-TB transmission also plays a critical role in treatment outcomes. However, all the factors mentioned (previous TB treatment, primary resistance, treatment interruptions, etc) are well established predictors of poor outcomes (3,11–13).

Differences in treatment outcomes can help identify the causes of treatment success or failure and guide policy-making. Data on MDR-TB treatment outcomes in Malaysia are insufficient. Therefore, this study compares treatment outcomes and potential associated factors between patients with MDR-TB and patients with susceptible to anti-TB drugs in peninsular Malaysia.

Material and Method

Study design

This study was a retrospective cohort study carried out on patients registered at or admitted to five referral TB hospitals in peninsular Malaysia from January 2010 to January 2014. All cases were confirmed by positive sputum culture for *M. tuberculosis*. Drug sensitivity testing (DST) against first- and second-line drugs was also conducted for the *Mycobacterium* isolated. The study participants were all confirmed MDR-TB and XDR-TB cases at the selected study hospitals and as for non MDR TB, a simple random sampling was applied to select participants. The study participants involved were from both inpatients and outpatients. The study also include patients on active anti-TB treatment, those who were deceased, those who had defaulted TB treatment, and those who had defaulted follow up during the study period. All patients were treated with individualised regimens based on drug sensitivity testing (DST) results and patient history of TB drug use. Directly observed short therapy (DOTS) was performed on all patients confirmed with non MDR TB and DOTS-Plus was implemented for MDR-TB infections. Treatment was administered to patients from the five referral TB hospitals. Daily doses were administered only on patients admitted to these hospitals.

All MDR-TB cases were identified through the National Public Health Laboratory in Malaysia, which maintains a list of all confirmed MDR-TB patients. The list was cross-checked against the MDR-TB registry for TB surveillance of the Malaysian Ministry of Health at each of the referred TB hospitals. TB management and control policies in Malaysia dictate that all MDR-TB cases must be reported to the MDR-TB registry of the TB and Respiratory Specialist Chest Clinic or Hospitals in Tuberculosis International Standard Registration (TBIS).

Most of cases were taken from the Institute of Respiratory Medicine Hospital, Kuala Lumpur and four TB referral hospitals in Kelantan, Perak, Penang, Johor Baharu, and the Federal Territories (Kuala Lumpur).

Definitions

The definitions of terms used in the study were as follows:

a. Cured in non MDR TB was defined as a smear-positive patient (based on the medical record), who had a negative sputum smear during the eighth month of treatment and on at least one previous occasion and for MDR-TB was defined as those who completed treatment within 18 months to over two years, followed by negative sputum culture and were finally discharged from the clinic and hospitals.

b. Completed treatment – A patient who completed the anti TB regime for 6months for non MDR TB and 18 month or over 12 months for MDR-TB.

c. Death was defined as a patient who died during treatment irrespective of the cause.

d. Failed treatment was defined as a smear-positive patient who remained smear-positive at the fifth month of treatment.

e. Defaulted treatment was defined as treated patient who did not come back to complete chemotherapy and there was no evidence of cure through the sputum result during the fifth month of therapy. Whereas the treatment interruption was defined as a patient who did not collect medications for two months or more at a particular time or at interval, but still come back for treatment and in the 8th month of treatment, the sputum result was positive.

f. Transferred was defined as a patient who was transferred to another treatment centre and for whom treatment results were not known.

g. TB relapse refers to a patient who had previous TB treatment and was cured but diagnosed again with a new TB infection.

h. Successful Treatment was defined as patients who had completed treatment course and cured of the disease.

i. Poor treatment outcome was defined as unsuccessful treatment leading to death, TB relapse, defaulted treatment, or fail to complete treatment regimen or treatment interruption.

DST testing was conducted in NPHL, Sungai Buloh, Selangor, based on the method described by Canetti et al. (14). Resistance was defined as at least 1% colony growth at critical concentrations of the drug (0.2 µg/mL INH, 1 µg/mL RIF).

Demographic characteristics, comparison treatment outcome for MDR-TB and non MDR TB, potential factors associated with poor treatment outcomes and association between history of anti-TB and MDR-TB development were recorded for analysis.

Statistical analysis

Data were analysed using SPSS windows (version 20.0) and double-checked and cleaned to screen for missing values or errors. Pearson chi-square and Fisher exact tests were performed to compare MDR-TB and non MDR TB patients. Multivariable analysis was conducted to determine significant potential factors associated with poor treatment outcomes. The multivariable analysis were included all potential associated variables regardless of univariable results. Preliminary effects were obtained using a backward and forward stepwise selection method was applied. Multicollinearity and interaction were checked and not found. The final model was checked using the Hosmer-Lemeshow test, Pearson chi-square, classification table, and receiver operation curve. The results were presented using appropriate tabulations based on determined variables, regression coefficients, and crude or adjusted odds ratio with 95% confidence interval as well as corresponding *p*-values. The significance level was set to 0.05 (15).

Results

A total of 314 patients comprising 105 cases of MDR-TB and 209 of non-MDR-TB infections were included. A total of 141 patients were confirmed with MDR-TB from 2010 to 2012 and started on treatment according to World Health Organisation and Ministry of Health Malaysia, although the exact number of MDR-TB from 2010 to 2014 in Malaysia could be higher (16). This study focused only on western Malaysia, with 105 cases collected from five referral hospitals in peninsular Malaysia. Sabah and Sarawak in eastern Malaysia were excluded from the study. Table 1 presents the demographic characteristics of MDR-TB and non-MDR-TB patients.

The median age of MDR-TB patients was 40.4 (IQR 14.75) while non-MDR-TB patients was 43.0 (IQR 16.55) years old. A significant

difference between ethnicity groups ($p < 0.001$) was observed. In both groups, the disease mostly affected those aged 45 to 64 years old. Male comprised the majority of cases which was 70 (66.7%) and 147 (70.0%) in the MDR-TB and non-MDR-TB patients respectively. The number of foreigners was 33 (31.7%) in the MDR-TB group and 22 (11.0%) non-MDR-TB group.

Table 2 compares the treatment outcomes of MDR-TB and non-MDR-TB patients. A significant difference ($P < 0.001$) between MDR-TB and non-MDR-TB patients was observed in terms of immigrant status, presence of HIV infection status, history of TB treatment, homeless status, and success rate treatment. The treatment success rate for non-MDR-TB patients and MDR-TB patients were 131 (63.9%) and 18 (17.1%) respectively. A higher mortality rate was observed in non-MDR-TB 27 (13.2%) patients compared to 9 (8.6%) MDR-TB patients. However it was not statistically significant.

Poor treatment outcomes potential associated factors for MDR-TB include defaulting of TB treatment [18 (17.1%)], TB treatment relapse [26 (24.8%)], and missing clinic appointments [18 (17.1%)]. The MDR-TB group had a higher default rate, lower treatment success, and higher mortality rate than the non-MDR-TB patients. A higher number of diabetes mellitus patients were observed in the non-MDR-TB patients compared with the MDR-TB group.

Table 3 presents the potential factors associated with poor treatment outcomes. The main significant factors associated with poor treatment outcomes include presence of HIV infection (adjusted odd ratio 1.09; 95%CI: 1.05, 1.75; P = 0.001) and history of TB treatment (adjusted odd ratio 4.87; 95%CI: 2.84, 8.38; P = 0.001).

Table 4 presents the association between history of anti-drugs and development of MDR-TB. Patients were divided into two groups based on previous TB treatment to separate patients who had history of previous anti-TB drugs from those who did not. Nine patients (17%) had previous of TB treatment and were more resistant to all first-line drugs than the six patients (11.5%) who had no history of TB treatment. Isoniazid (INH) and Rifampicin (RIF) were higher in patients who had previous history TB treatment (92.5%) than in those patients with no history of TB treatment (88.5%). Three patients developed XDR-TB; two of these patients had previous TB treatment. One of the patients died after two years of taking anti-TB drugs, on the other hand three patients (50%) died out of 6 patients MDR-TB with HIV infection.

Table 1: Demographic characteristics of MDR-TB and non-MDR-TB patients (n = 314)

Variables	MDR-TB patients (n = 105)		Non-MDR-TB (n = 209)		P-value
	n	(%)	n	(%)	
Age[a]	40.4	(14.75)	43.0	(16.55)	0.139
Age					
≤ 24	23	(21.9)	28	(13.4)	0.097[b]
25–44	37	(21.9)	92	(44.0)	
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[c]
Male	70	(66.7)	147	(70.3)	
Race					
Indian	8	(7.7)	26	(12.4)	0.001[b]
Chinese	15	(14.4)	23	(11.0)	
Foreign (non-Malaysian)	33	(31.7)	22	(10.5)	
Malay	48	(46.2)	138	(66.0)	

[a] Medium and IQR

[a] Mann-Whitney test was applied for two medians comparison and data were indicated skewed to right

[b] Fisher's exact test was applied

[c] Pearson chi-square test was applied

Table 2: Comparison treatment outcome between MDR-TB and non-MDR-TB patients (n = 314)

Variables	MDR-TB (n = 105)		Non MDR-TB (n = 209)		Total	P-value
	n	(%)	n	(%)		
Immigrant status						
No	70	(84.4)	195	(93.3)	265 (84.4)	0.001[a]
Yes	14	(6.7)	35	(33.3)	49 (15.6)	
HIV infection status						
No	99	(94.3)	173	(82.8)	272(13.4)	0.001[a]
Yes	6	(5.7)	36	(17.2)	42 (13.4)	
History of had TB treatment						
No	56	(53.3)	183	(87.6)	239 (76.1)	0.001[a]
Yes	49	(46.7)	26	(12.4)	75 (23.9)	
Homeless status						
No	91	(86.7)	206	(90.6)	297 (94.6)	0.001[a]
Yes	14	(13.3)	3	(1.4)	17 (5.4)	
Alcohol abuse						
No	92	(87.6)	191	(91.8)	283 (90.4)	0.232[b]
Yes	13	(12.4)	17	(8.2)	30 (9.6)	
Intravenous drugs						
No	93	(88.6)	178	(85.2)	271 (86.3)	0.408[b]
Yes	12	(11.4)	31	(14.8)	43 (13.7)	
Diabetes Mellitus (MD)						
No	77	(73.3)	149	(71.3)	226 (72.0)	0.704[b]
Yes	28	(26.7)	60	(28.7)	88 (28.0)	
Default TB treatment						
No	87	(82.9)	175	(83.7)	262 (83.4)	0.844[b]
Yes	18	(17.1)	34	(16.3)	52 (16.6)	
Relapse TB treatment						
No	79	(75.2)	172	(82.3)	251 (79.9)	0.141[b]
Yes	26	(24.8)	37	(24.8)	63 (20.1)	
Failure to keep clinical appointment						
No	87	(82.9)	176	(84.6)	263 (84.0)	0.689[b]
Yes	18	(17.1)	32	(15.4)	50 (16.0)	
Treatment success rate						
No	87	(82.9)	74	(36.1)	149 (48.1)	0.001[a]
Yes	18	(17.1)	131	(63.9)	161 (51.9)	
Mortality rate						
No	96	(91.4)	178	(86.8)	274 (88.4)	0.232[b]
Yes	9	(8.6)	27	(13.2)	36 (11.6)	

a Pearson chi-square was applied

b Fisher's exact test was applied

Table 3: Multivariable analysis showed potential factors associated with poor treatment outcome among MDR-TB patients (n = 105)

Variables	(b)	Wald statistics	AOR[a] (95% CI)	*P*-value
HIV infectious status				
HIV seronegative	0		0	0.001
HIV seropositive	1.63	11.30	1.09 (1.05, 1.75)	
Had TB treatment				
No	0		0	0.001
Yes	1.58	32.98	4.87 (2.84, 8.38)	

-Backward Step wise LR Multiple Logistic Regression was applied

-multicollinearity and interaction term were checked and did not found

-Hosmer-Lemeshow test (p = 0.441), Pearson chi-square test (0.453), Classification table (overall correctly classified percentage (75.4%) and area under Receiver Operating Characteristics (ROC) curve (81.8%) were checked the fit of the model and reported to be fit)

[a] Adjusted Odd Ratio

(b) Regression coefficient

Discussion

Previous studies in Malaysia have reported treatment outcomes for non-MDR-TB patients. However none of these studies included treatment outcomes of MDR-TB, MDR-TB with HIV, nor XDR-TB. Poor treatment outcome can be overcome by strengthening health systems, including better case holding and effective mechanism to trace defaulters. Published data on treatment outcomes are highly limited. Thus, the present study was designed to compare the treatment outcomes and associated factors between MDR-TB patients and non-MDR-TB patients in peninsular Malaysia.

The results reveal a significant difference (P < 0.001) between MDR-TB and non-MDR-TB patients in terms of history of TB treatment, HIV infection status, immigrant status and homeless status were potential associated with poor outcomes in this study. However in this study, defaulted clinical appointments, alcohol or drug addiction and defaulted treatment were not significantly associated with poor outcomes.

This study included a total of 314 patients, including 105 MDR-TB cases and 209 non-MDR-TB patients. The treatment success was 63.9% for non-MDR-TB patients and 17.1% for MDR-TB patients. Table 2 presents the poor treatment outcomes of MDR-TB patients. The overall treatment success rate in this study for MDR-TB patients was 17.1%, which is lower than the reported success rates in European and South Korean studies (39%–54%) (17,18).

MDR-TB occurrence in different parts of the world is an alarming phenomenon because of the poor therapeutic outcomes obtained when isolated strains were resistant to INH and RIF (9, 19). The occurrence of MDR-TB among patients with AIDS was associated with rapid progression from infection or re-infection to disease, nosocomial transmission, and high mortality (20,21), which were related to poor program conditions or patient non-adherence (22). This study suggests that poor treatment outcomes were associated with TB history.

Besides the well-known causes of drug resistance and poor treatment outcomes, this study revealed high rates of defaulting of TB treatment (17.1%), homeless status (13.3%), and intravenous drug addiction (11.4%), all of which resulted in the high rate of unsuccessful outcomes at the end of treatment, with relapse accounting for 24% and missing clinical appointments for 17.1%. Defaulting of TB treatment seems to be a global phenomenon with rates of over 15% in several countries, including Korea (32%) (23), Taiwan (29%) (24), Russia (20%) (25), South Africa (29%) (26), Argentina (20%) (27), and Peru (19%) (28). The treatment default rate in this study (17%) was higher than that revealed by a study in Spain (16%) (29) and similar to that reported by a study in Italy (30).

DOTS and DOTS-Plus strategies have improved MDR-TB rates in some high-prevalence countries, such as Latvia, where new MDR cases decreased by over twofold between 2000 and

2007 (Leimane, unpublished data). Under these improved circumstances, published default rates were above 10% (31). This study did not include a DOTS variable evaluation even though all patients had DOTS and DOTS-Plus as a TB control strategy. Despite the preventive measures which have been taken, patients who defaulted or relapsed in their TB treatment were still higher than the expected target.

The strongest risk factor for MDR-TB and XDR-TB resulting in poor treatment outcomes was a history of TB treatment (32). Special attention must be given to improving treatment adherence of re-treatment cases. The present study confirms that previous anti-TB treatment significantly increases poor treatment outcomes in MDR-TB, which is in line with the results of previous studies (29). A history of previous of TB treatment of MDR-TB was two times more common (46.7%) in the MDR-TB patient population than the non-MDR TB population (12.4%), which is likely to be due to the acquisition of resistance over time.

Although HIV infection was relatively uncommon among those with MDR-TB, multivariable analysis revealed an association of poor MDR-TB treatment outcomes with HIV infection. HIV prevalence was lower in MDR-TB patients (4.9%), compared to non MDR-TB patients (17.6%). Therefore, poor treatment outcomes in the non-MDR-TB could also be associated with high HIV infection in this subpopulation. Efforts should be made to reduce HIV prevalence and early diagnosis and aggressive treatment of MDR-TB should focus on HIV/MDR-TB co-infected patients.

This study observed that, among six patients, three (50%) of MDR-TB patients with HIV died during the first year of treatment. This observation agrees with a study conducted in the United States wherein 50% of MDR-TB patients with HIV died (33); most patients these were severely immunosuppressed. The early mortality rate of MDR-TB patients with HIV has also been studied in South Africa and Malaysia (6,34). The high early mortality rate in this study argues for early initiation of second-line TB drugs in MDR-TB patients. A common theme in prior studies of MDR-TB patients with HIV is rapid death in the absence of effective treatments.

Our data demonstrate that three MDR-TB patients developed XDR-TB during the course of MDR-TB treatment; this finding was similar to a review of treatment outcomes in Russia (35). The number of patients who developed XDR-TB after treatment completion was distressing. During the study, one patient died, which indicates a poor survival rate for XDR-TB patients. Treatment of XDR-TB patients was more complicated and challenging than treatment of MDR-TB patients. XDR-TB patients have been reported to present 50% risk of death compared with MDR-TB [8], although subsequent studies report improved outcomes (24). Therapeutic options for XDR-TB are exceedingly limited because second-line drugs are less effective and more toxic and expensive than first-line drugs; by definition, XDR-TB strains are resistant to more potent second-line options. Several new drugs are being evaluated for XDR-TB treatment but none are currently available (23).

Each retrospective study has limitations. The precision of findings and conclusions were limited by the relatively small size of the study; thus, we could not cover all MDR-TB cases in Malaysia. This study only focused on peninsular Malaysia because of logistics and financial limitations. A nationwide MDR-TB study that covers the whole country is highly recommended. Data collection was through, and documentation on a wide variety of variables was available. Despite the limitations encountered, this analysis expands previous reports on MDR-TB treatment in the region and highlights areas where further research is needed to guide policy-making. Published data on the treatment outcomes for MDR-TB patients are extremely limited in Malaysia. Therefore, this study promotes and improves MDR-TB treatment outcomes in Malaysia.

Conclusion

This study revealed that the treatment success rate in patients with non-MDR-TB infection was higher than MDR-TB. Unsuccessful treatment was seen in MDR-TB associated with potential factors such as history of TB treatment and HIV infection status. Non-MDR-TB patients were associated with lower treatment responses, longer outcome courses, and higher survival rates than MDR-TB patients. Three MDR-TB patients developed XDR-TB after a year of treatment. No breakthrough for XDR-TB treatment has yet been reported. In trying to promote new drug developments or combinations of existing anti-TB drugs to control XDR-TB, standardizing TB treatment strategies, improving case detection rates, decreasing treatment default rates, and sufficient political will and financial support must be stressed. Education programs must be developed, evaluated, and implemented to reduce TB treatment default. Furthermore, nationwide

research on survival rates and treatment outcomes must be conducted on MDR-TB patients.

Ethical Approval

Relevant ethical issues were considered for all patient medical records from the five selected TB referral hospitals. Ethical approval was obtained from the Human Research and Ethics Committee of the Hospital Universiti Sains Malaysia [Ref. No.: USMKK/PPP/JEJeM/243.3, (4.1)] and the Medical Research Ethics Committee (MREC) in the Ministry of Health Malaysia [MREC No.: 12-90-10809)].

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Conflict of Interests

All authors have declared there is no conflict of interest in this study.

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Author's Contributions

Conception and design: HH, SA, ZB, NNN, MZMJ
Analysis and interpretation of the data: SA, ZB, NNN
Drafting of the article: SA
Critical revision of the article for important intellectual content: HH, ZB, MZMJ
Final approval of the article: HH
Provision of study materials or patients: NNN, MZMJ
Statistical expertise: SA, NNN
Obtaining of funding: NNN
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