

Factors Associated with Medical Follow-Up Adherence for Patients on All-Oral Regimen for Multidrug-Resistant Tuberculosis in Shenzhen, China

Hui Li^{1,*}
Hailin Zhang^{1,*}
Juan Xiong^{2,*}
Yi Wang¹
Weiyu Wang¹
Jingjing Wang¹
Yi Lin¹
Peize Zhang¹ 

¹Department of Pulmonary Medicine & Tuberculosis, The Third People's Hospital of Shenzhen, Shenzhen, People's Republic of China; ²School of Public Health, Health Science Center, Shenzhen University, Guangdong, People's Republic of China

*These authors contributed equally to this work

Purpose: The aim of this study is to identify factors affecting medical follow-up adherence of pulmonary multidrug-resistant tuberculosis (MDR-TB) patients on an all-oral regimen in Shenzhen, China to enhance intervention measures for increased treatment success.

Methods: A cohort study was conducted in The Third People's Hospital of Shenzhen on MDR-TB patients switched to an all-oral regimen to evaluate effectiveness following the WHO's recommendation in late 2018. We recruited patients in the group for an opinion survey on medical follow-up adherence from May 2019 to June 2020. The survey was designed with socio-demographic questions in collecting baseline characteristics and importance and Likert closed-ended questions for measuring opinions and relevance of different factors to adherence. Linear regression model was used to analyze data collected.

Results: The findings revealed that gender difference ($P = 0.828$) had no correlation with adherence. Marital status ($P = 0.014$), financial situation ($P < 0.001$) and difficulties encountered with medical appointment booking procedures ($P = 0.001$) were significantly associated with medical follow-up adherence. Single (including widowed and divorced) patients, those with low household income and patients having difficulties making online medical appointment booking, were at higher risk of defaulting from routine MDR-TB medical follow-up.

Conclusion: Our survey revealed that financial burden, being single and a non-user friendly medical appointment booking system are the main barriers to patients' medical follow-up compliance. More financial assistance, better patient support and simplifying medical appointment booking procedures are facilitators of better treatment adherence.

Keywords: MDR-TB, patient care, treatment adherence, all-oral regimen, patient support

Introduction

China is one of the high-burden countries of multidrug-resistant tuberculosis (MDR-TB).¹ MDR-TB is a situation where the causative bacteria of TB are proved to be resistant to at least isoniazid and rifampicin, two of the most potent anti-TB drugs. Despite being one of the top ten infectious diseases, most MDR-TB is curable.² Traditional regimen of MDR-TB contains 4–5 oral medication and one of the two injectable agents which can only be administered at a clinical setting for a minimum period of six months. Complexity of treatment and adverse events with injectables have been reported to result in limited adherence.³ In August 2018, the World Health Organization (WHO) recommended a shorter all-oral regimen which

Correspondence: Yi Lin; Peize Zhang
Department of Pulmonary Medicine & Tuberculosis, The Third People's Hospital of Shenzhen, No. 29, Bulan Road, Longgang District, Shenzhen, Guangdong, 518112, People's Republic of China
Tel +86-0755-6122 2333
Fax +86 0755 6123 8928
Email 514195263@qq.com;
82880246@qq.com

prioritizes newer medications and oral regimens over injectable drugs for MDR-TB.^{4,5} The Third People's hospital of Shenzhen, being the only designated hospital for tuberculosis treatment in the city, initiated the regimen and a cohort study (Chinese registration number: ChiCTR2000032298) to evaluate the effectiveness and safety of the novel all-oral regimen. Enhanced patient management was given to the group and patients were recommended to adhere to medical follow-up on a monthly basis. Defaulting from routine MDR-TB follow-up was defined in this study as interrupted visit schedule over a two-month period. We recruited patients in the group for an opinion survey to find out factors associated with medical follow-up adherence for improving treatment adherence and success.

Materials and Methods

Study Population

Eighty-five patients switching to the new all-oral regimen for MDR-TB treatment endorsed by the WHO were enrolled in an observational cohort from May 1, 2019 to June 12, 2020. The study group was invited to participate in an opinion survey to identify factors affecting treatment adherence. Eighty-two patients agreed to participate (response rate = 96.5%). Patients in this cohort group were offered dedicated patient care including follow-up by TB nurses, text message reminders, online patient groups for emotional support and Q&A on the disease. These measures are designed to enhance adherence via reinforcing quality of health care. All participants were informed about the purpose of the study and provided written consent to participate in this study. This study is approved by The Ethics Committee of The Third People's hospital for the National Key Project for Infectious Disease and complies with the Declaration of Helsinki in regard to confidentiality and ethical standards.

Questionnaire Design

The questionnaire was designed with basic background demographic questions to collect respondents' baseline characteristics and 18 importance and Likert closed-ended questions with a 5-point rating scale to screen risk factors that are most likely to increase patients' non-adherence. Background questions are on the following aspects: (1) sociodemographic characteristics, (2) emotional support from family, (3) financial situation, (4) travel time involved in medical visits. Socio-demographic

characteristics including age, gender, marital status, occupation and education level were collected. Emotional support was expressed in the form of patient's relationship with their family and support and care they received. Financial situation was measured by household income, insurance coverage and out-of-pocket medical expenses for TB treatment. Travel time involved was measured by time spent on clinic visits from home.

Factors affecting patient's adherence to medical follow-up are measured via closed-ended importance and Likert questions, with answers being on a rating scale from 1–5 to represent the significance the different factors hold for the respondent. Problems encountered with medical service acquisition were rated based on difficulties in making doctor's appointments and waiting times at clinics. Sample questions are "How do you rate the waiting time at the Hospital for medical appointment?" 1 - very long and unacceptable ... to 5 - fast and acceptable or "Will you consider the current patient support in Shenzhen enough?" 1 - severely lacking to ... 5 - enough and satisfactory.

Statistical Analysis

Data analyses were conducted using SPSS version 25.0 (SPSS, IBM, West Grove, PA, United States). All statistical tests were 2-tailed. Statistical significance was set at a P -value < 0.05 . Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as median and interquartile range (IQR). Normality was assessed using the Shapiro–Wilk test. Between-group comparisons of continuous variables were performed using Mann–Whitney or Kruskal–Wallis test, respectively. Simple linear regression was also conducted to assess the relationship between patient's adherence and variables.

All variables having P -value less than 0.1 in the simple linear regression analysis were included as candidate independent variables in the multivariate linear regression model. Stepwise selection method was applied to find the best multivariate linear regression model to identify factors associated with patient's adherence. The regression coefficients and their associated 95% confidence intervals (CIs) were calculated.

Results

Demographic Characteristics, Emotional Support and Insurance Coverage

The study recruited and interviewed 52 male and 30 female adult patients. Among them 65% were under 45

years old, 62.2% were married. In terms of occupation, 28% (23) were office executives, 36% (30) were self-employed, unemployed or in part-time jobs. In our study, 75.6% (62) of the patients considered themselves to have a good relationship with and receive care and emotional support from their family. Regarding finances, 47.6% (39) had an average monthly household income of RMB2000–5000 (USD308–770), 24.4% (20) had an average monthly household income of RMB5000–10,000 (USD770–1540), and 51.2% (42) of the patients were covered by social medical insurance which is largely funded by the Chinese government (Table 1).

Socio-demographic Differences and Barriers to Treatment Adherence

To identify the significance that different factors have on patients' determination to follow through the regimen, we compared statistical data from the questionnaire among different variables (gender, age, marital status, occupation, household income and medical expenses). The likelihood to comply with medical follow-up were similar between both genders but varies across different education levels, marital status, and household income. Single (including widowed and divorced) patients showed a higher incidence of defaulting medical follow-up than married patients ($P=0.014$). Patients with lower household income were also associated with a significantly higher risk of failing adherence than patients with higher household income ($P=0.004$) (Table 2).

Interaction of Risk Factors and Follow-Up Interruption

There are four main aspects of risk factors to treatment adherence – personal (knowledge and beliefs), structural (poverty, gender, and law), social (family, community, stigma) and health service-related, with different settings being affected by a combination of different aspects.^{6–9}

The results of simple linear regression analysis and multivariate stepwise regression analysis for the association of demographic and other characteristics with adherence default are shown in Table 3. Marital status ($P=0.064$), household income ($P<0.001$), travel distance to hospital ($P=0.015$), difficulty in making medical appointments ($P=0.001$) and waiting time in hospital ($P=0.004$) were shown to account for failing follow-up adherence by simple linear regression. Each variable with P -value <0.1 in the simple linear regression model was put in the

Table 1 Demographic Characteristics of 82 Participants

Demographics		N (%)
Gender	Male	52 (63.4)
	Female	30 (36.6)
Age (years)	<45	62 (75.6)
	45–65	18 (22.0)
	>65	2 (2.4)
Marital Status	Single	28 (34.1)
	Divorced/Widowed	3 (3.7)
	Married	51 (62.2)
Education	Elementary School	12 (14.6)
	Middle School	34 (41.5)
	College	20 (24.4)
	Degree	13 (15.9)
	Master's or above	3 (3.7)
Occupation	Worker	14 (17.1)
	Farmer	11 (13.4)
	Student	4 (4.9)
	Office executives	23 (28.0)
	Others**	30 (36.6)
Household Income (per month) in Chinese Dollar (CNY)*	< 2000	14 (17.1)
	2000–5000	39 (47.6)
	5000–10,000	20 (24.4)
	> 10,000	9 (11.0)
Coverage of medical expenses	Social health insurance	42 (51.2)
	Out-of-pocket	40 (48.8)
Family relationship	Good	62 (75.6)
	Average	18 (22.0)
	Poor	2 (2.4)

Notes: *Household income (per month) was calculated by the sum of monthly income reported by all family members divided by the number of family members.
**Patients who were self-employed, unemployed, or on part-time jobs.

multivariate linear regression model to assess its association with non-adherence. The final model by stepwise method included the following variables: marital status, household income, and medical appointment booking procedures. The results showed that single (including widowed and divorced) patients, patients with low family income and difficulties encountered at making medical appointment were factors responsible for failing adherence.

Discussion

China is a vast country with extreme disparity of wealth and poverty across different places where infrastructure,

Table 2 Sociodemographic Difference and Intention to Treatment Adherence

Characteristics		N(%)	Follow-Up Intention*	P-value
Gender	Male	52 (63.4)	4 (1)	0.828
	Female	30 (36.6)	4 (1)	
Age (years)	≤45	62 (75.6)	4 (1)	0.206
	45–65	18 (22.0)	5 (1)	
	>65	2 (2.4)	5 (0)	
Marital Status	Married	51 (62.2)	5 (1)	0.014
	Single/Divorced/Widowed	31 (37.8)	4 (1)	
Education	Elementary School	12 (14.6)	4.5 (1)	0.700
	Middle School	34 (41.5)	4 (1)	
	College	20 (24.4)	4 (1)	
	Degree	13 (15.9)	5 (1)	
	Master's or above	3 (3.6)	4 (1.5)	
Household Income				0.004
(per month) in Chinese Dollar (CNY)	< 2000	14 (17.1)	4 (0.25)	
	2000–5000	39 (47.6)	4 (1)	
	5000–10,000	20 (24.4)	5 (1)	
	> 10,000	9 (11.0)	4 (1)	
Medical Expenses	Social health insurance	42 (51.2)	4 (1)	0.564
	Out-of-pocket	40 (48.8)	4 (1)	

Notes: *The scale ranged from 1 (lowest relevance) to 5 (highest relevance).

resources, and living standards can vary profoundly. In trying to identify risk factors of medical visit non-adherence for MDR-TB patients in a developed metropolis such as Shenzhen where most key policies are first initiated,¹⁰ we found that gender, transportation, and waiting time, which a number of studies reported to be barriers, are all not associated.

Gender showing no correlation to adherence is a new finding in this study as in conventional society men are projected a predominant role in family and society. We attributed this to gender equality in this modern city in terms of education, job opportunities, family roles and social ties, especially after the generation born in the 1970s. One-child policy and better education have given rise to more autonomy to females, and they are occupying more key positions in the workplace in the past two decades. As of the end of 2018, women accounted for more than 41.4% of the working population in Shenzhen.¹¹

Being the first established economic zone in the country, Shenzhen developed rapidly. The city is facilitated

with an extensive public transportation system. This makes travel convenient and economical which explains why transportation and travel time do not affect medical follow-up adherence. Our finding is different to studies from low resource setting countries describing poor transportation and insufficient number of medical facilities and providers being risk factors for treatment adherence.^{12,13} However, findings in the survey suggested that financial hardship, being single and the new online medical booking system are adversely associated with patient's adherence to medical follow-up.

Financial burden had been frequently reported as a barrier to treatment adherence and an important predictor for medication and follow-up non-adherence.^{8,14–16} The costs for treating MDR-TB were reported to range from US\$1218 to US\$83,365 per case.^{17,18} Previous study from our team showed that average out-of-pocket expense for an MDR-TB patient was about US\$300 per month in Shenzhen city.¹⁹ This amounts to nearly half of average monthly income based on a reported GDP per capita of

Table 3 Linear Regression Analysis Results: Factors Associated with Defaulting from Follow-Up

Characteristics	Coefficient	P-value	Adjusted Coefficient	P-value
Gender (male)	-0.001(-0.303, 0.301)	0.993	-	-
Marital status (Married)	0.277(-0.016, 0.571)	0.064	0.310(0.060, 0.560)	0.016
Education		0.281		
Middle School	-0.750(-1.589, 0.089)		-	-
College	0.122(-0.399, 0.642)		-	-
Degree	0.033(-0.441, 0.508)		-	-
Master's or above	-0.123(-0.559, 0.314)		-	-
Household Income (per month) in Chinese Dollar (CNY)		<0.001		
> 10,000	0.730(0.224, 1.236)		0.575(0.093, 1.058)	0.020
5000-10,000	0.886(0.473, 1.298)		0.789(0.401, 1.177)	<0.001
2000-5000	0.747(0.378, 1.116)		0.675(0.330, 1.019)	<0.001
Insurance coverage	-0.049(-0.339, 0.242)	0.739	-	-
Travel Distance to TB clinic	-0.156(-0.280, -0.032)	0.015	-	-
Occupation	-0.100(-0.235, 0.034)	0.142	-	-
Family relationship	-0.078(-0.235, 0.080)	0.330	-	-
Medical service booking procedures	-0.248(-0.392, -0.104)	0.001	-0.208(-0.341, -0.075)	0.003
Waiting time	-0.218(-0.364, -0.071)	0.004	-	-

USD7808 in 2018.²⁰ Our study established a direct relationship between treatment adherence and household income.

Consistent with other studies, our survey found that single patients are at higher risk of defaulting from medical follow-up. This is interpreted as a lack of emotional support and encouragement from a supportive relationship. Numerous studies documented that a close relationship with immediate family and strong social ties assured positive effect on adherence. Home-based care in MDR-TB treatment has also been reported to show promise in improving treatment adherence and outcomes.²¹

The online medical appointment booking system was first introduced at the end of 2009 to facilitate patients in seeking timely medical care and minimize waiting times.²² Patients are required to book their medical appointment online in advance.²³ It turns out to be associated with defaulting from routine medical follow-up, which was not expected. This was the first time that the electronic booking system has accounted for treatment adherence. We believed while this new system was welcome by most tech-savvy patients, others found it difficult to use. Without making an online booking in advance, waiting times were unbearable for walk-in outpatients.

Our study is subject to several limitations. Firstly, all participants only comprised MDR-TB patients registered in our hospital for treatment, patients who were diagnosed at TB clinics or co-infected with HIV but refused further treatment were not included in our study, therefore selection bias might lead to underestimation of the difficulties overall MDR-TB patients are facing. Secondly, other factors such as psychological stress and side-effects of some second-line medicines were not measured in this survey, which might play a role that leads to non-adherence during treatment.

Conclusion

In summary, financial aid in medical expenses and a user-friendly medical service booking system can promote a higher degree of treatment adherence for MDR-TB patients in cities. Devoted efforts are needed on medical care system enhancement such as simplifying medical appointment booking procedures. Financial assistance and better patient support from both society and family are an integral part to promoting treatment adherence.

Acknowledgments

The authors are grateful for the continued academic support from The National Clinical Research Center for

Infectious Disease in China and Clinical Research Center for Infectious Diseases (tuberculosis) of Guangdong Province. This study was funded by Technology Project of Guangdong Province (2020B111170014) which is a government fund for the research of tuberculosis treatment and control. Juan Xiong was supported by the Shenzhen University Top Ranking Project (8600000210).

Disclosure

The authors report no conflicts of interest in this work.

References

- World Health Organization. *Global Tuberculosis Report 2020*. World Health Organization; 2020.
- Pontali E, Raviglione MC, Migliori GB. Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives. *Eur Respir Rev*. 2019;28:152. doi:10.1183/16000617.0035-2019
- Walker IF, Shi O, Hicks JP, et al. Analysis of loss to follow-up in 4099 multidrug-resistant pulmonary tuberculosis patients. *Eur Respir J*. 2019;54(1):1800353. doi:10.1183/13993003.00353-2018
- World Health Organization. *Rapid Communication: Key Changes to Treatment of Multidrug- and Rifampicin-Resistant Tuberculosis (MDR/RR-TB)*. Geneva: World Health Organization; 2018.
- World Health Organization. *WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment*. Geneva: World Health Organization; 2019.
- Javaid A, Shaheen Z, Shafiqat M, Khan AH, Ahmad N. Risk factors for high death and loss-to-follow-up rates among patients with multidrug-resistant tuberculosis at a programmatic management unit. *Am J Infect Control*. 2017;45(2):190–193. doi:10.1016/j.ajic.2016.07.026
- Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK, Mistry N. Loss-to-follow-up on multidrug resistant tuberculosis treatment in Gujarat, India: the WHEN and WHO of it. *PLoS One*. 2015;10(7):e0132543. doi:10.1371/journal.pone.0132543
- Tupasi TE, Garfin AM, Kurbatova EV, et al. Factors associated with loss to follow-up during treatment for multidrug-resistant tuberculosis, the Philippines, 2012–2014. *Emerg Infect Dis*. 2016;22(3):491–502. doi:10.3201/eid2203.151788
- Chang SH, Cataldo JK. A systematic review of global cultural variations in knowledge, attitudes and health responses to tuberculosis stigma. *Int J Tuberc Lung Dis*. 2014;18(2):168–iv. doi:10.5588/ijtld.13.0181
- Shenzhen Government Online. About Shenzhen. Available from: http://www.sz.gov.cn/en_szgov/aboutsz/index.html. Accessed June 22, 2021.
- Southern Metropolis Daily. Annual report of female employment in Shenzhen city. Available from: https://www.sohu.com/a/363916522_161795. Accessed June 22, 2021.
- Viana PVS, Redner P, Ramos JP. Factors associated with loss to follow-up and death in cases of drug-resistant tuberculosis (DR-TB) treated at a reference center in Rio de Janeiro, Brazil. *Cad Saude Publica*. 2018;34(5):e00048217. doi:10.1590/0102-311X00048217
- Kassa GM, Teferra AS, Wolde HF, Muluneh AG, Merid MW. Incidence and predictors of lost to follow-up among drug-resistant tuberculosis patients at University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia: a retrospective follow-up study. *BMC Infect Dis*. 2019;19(1):817. doi:10.1186/s12879-019-4447-8
- Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK, Das M, Daftary A. “When treatment is more challenging than the disease”: a qualitative study of MDR-TB patient retention. *PLoS One*. 2016;11(3):e0150849. doi:10.1371/journal.pone.0150849
- Laurence YV, Griffiths UK, Vassall A. Costs to health services and the patient of treating tuberculosis: a systematic literature review. *Pharmacoeconomics*. 2015;33(9):939–955. doi:10.1007/s40273-015-0279-6
- Hutchison C, Khan MS, Yoong J, Lin X, Coker RJ. Financial barriers and coping strategies: a qualitative study of accessing multidrug-resistant tuberculosis and tuberculosis care in Yunnan, China. *BMC Public Health*. 2017;17(1):221. doi:10.1186/s12889-017-4089-y
- Diel R, Vandeputte J, de Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. *Eur Respir J*. 2014;43(2):554–565. doi:10.1183/09031936.00079413
- Tanimura T, Jaramillo E, Weil D, Raviglione M, Lonroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. *Eur Respir J*. 2014;43(6):1763–1775. doi:10.1183/09031936.00193413
- Zhang P, Xu G, Song Y, Tan J, Chen T, Deng G. Challenges faced by multidrug-resistant tuberculosis patients in three financially affluent Chinese cities. *Risk Manag Healthc Policy*. 2020;13:2387–2394. doi:10.2147/RMHP.S275400
- Trading Economics. China GDP per capital. Available from: <https://tradingeconomics.com/china/gdp-per-capita>. Accessed June 22, 2021.
- Taneja N, Chellaiyan VG, Daral S, Adhikary M, Das TK. Home based care as an approach to improve the efficiency of treatment for MDR tuberculosis: a quasi-experimental pilot study. *J Clin Diagn Res*. 2017;11(8):Lc05–Lc08. doi:10.7860/JCDR/2017/27594.10401
- China Ministry of Health. The Implementation of Appointment Services in Public Hospital in China. Available from: <http://www.nhc.gov.cn/bgt/s9514/200909/fe1e60fab1a0456cae8a70cadd42ef57.shtml>.
- Shenzhen China. Brief Report of appointment registration in public hospital of Shenzhen. Available from: http://www.sz.gov.cn/szzt2010/sjfb/sjkd/content/post_8811479.html. Accessed June 22, 2021.

Patient Preference and Adherence

Publish your work in this journal

Patient Preference and Adherence is an international, peer-reviewed, open access journal that focusing on the growing importance of patient preference and adherence throughout the therapeutic continuum. Patient satisfaction, acceptability, quality of life, compliance, persistence and their role in developing new therapeutic modalities and compounds to optimize clinical outcomes for existing disease

states are major areas of interest for the journal. This journal has been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/patient-preference-and-adherence-journal>

Dovepress