ORIGINAL ARTICLE

Factors associated with mortality to drug-resistant tuberculosis and their programmatic management in treatment centres of Punjab, Pakistan

Shamsa Kanwal, Abdul Majeed Akhtar, Anzar Ahmed

Abstract

Objective: To describe the characteristics and assess the factors of mortality in drug-resistant tuberculosis patients.

Methods: This retrospective study was conducted at 11 programmatic management of drug-resistant tuberculosis centres located in different cities of the Punjab province of Pakistan, and comprised record of patients with drug-resistant tuberculosis from January 2010 to September 2015. Data was retrieved from patient medical records using electronic nominal review system of the provincial tuberculosis control programme. Cox's proportional hazards model was performed to identify the factors for death. SPSS 17 was used for data analysis.

Results: Of the 1,136 patients, 472(41.5%) died during treatment and 664(58.5%) were declared cured or their treatment was completed. Of those who expired, 97(20.6%) expired within 3 months of the start of the treatment. Men had higher rates of death which was not significantly associated with the drug-resistant tuberculosis mortality ($p>0.05$).

Conclusion: The number of patients who died from drug-resistant tuberculosis treatment was relatively high.

Keywords: Drug-resistant tuberculosis, Mortality, PMDT sites, ENRS. (JPMA 67: 858; 2017)

Introduction

Tuberculosis (TB), according to a 2015 report of the World Health Organisation (WHO), is still a major health problem globally and is the second-biggest cause of deaths worldwide after the human immunodeficiency virus (HIV). Pakistan is the sixth-most populous country in the world and ranks fifth among 22 high burden TB countries. The country is also on the list of the 27 high burden multidrug-resistant tuberculosis (MDR-TB) countries in the world.[1,2] The latest WHO report estimated the TB death rate at 26(95% confidence interval (CI): 6.0-61) per 100,000 people while the percentage of TB with MDR-TB in new cases was 3.7(2.5-5) and in retreatment cases 18(13-23) and 858(54%) MDR-TB patients with outcome of treatment from 2014 data in Pakistan. The WHO estimated that 123,000 patients with rifampicin-resistant tuberculosis or multidrug-resistant tuberculosis were notified, of whom approximately 70% lived in the South Africa, Europe, China and India.[2] Drug-resistant tuberculosis (DR-TB) has become an emerging health issue with great challenges for public health sector in Pakistan. As Punjab is the most populous province of the Pakistan, 56% cases of TB are detected in the province, of which 75% cases fall in productive age group (15-45) years.[3] Despite availability of appropriate DR-TB treatment that cures most patients, cases with DR-TB have unacceptably high mortality. Some studies have determined that mortality was the highest among MDR-TB with HIV co-infected patients and the majority of these patients lived in low- and middle-income regions.[4-6] A large body of literature describes the characteristics associated with MDR-TB. These characteristics explain patients-related factors, such as lower socio-economic status, alcoholism, drug use, lost to follow-up history, previously TB treated, type of disease and type of resistance.[7-13] Currently, no study of mortality is available in Punjab, Pakistan, for DR-TB. The current study was planned to describe the characteristics and assess the factors of mortality in DR-TB patients in Punjab.

Patients and Methods

This retrospective study was conducted at 11 programmatic management of drug-resistant TB (PMDT) centres located in different cities of the Punjab province of Pakistan, and comprised data of DR-TB patients from January 2010 to September 2015. All records of patients enrolled in the PMDT sites and their follow-up information during their anti-TB therapy till declared cured or death (censorship) were collected. DR-TB refers to a form of TB in which strains of mycobacterium tuberculosis are resistant to any first-line TB drugs (rifampicin, isoniazid, ethambutol, pyrazinamide and rifabutin) and/or second-line injectable drugs with or without fluoroquinolones. We used national guidelines and WHO case definitions to define treatment cure, completion and death as treatment completed (minimum 18 months past culture

Provincial TB Control Program, Punjab, DGHS, Lahore, Pakistan.
Correspondence: Shamsa Kanwal. Email: shamsa.kanwal_547@yahoo.com

conversion) without evidence of failure and 3or more consecutive cultures taken at least 30 days apart are negative after the intensive phase, treatment completed (minimum 18 months past culture conversion) without evidence of failure but no record that three consecutive cultures taken at least 30 days apart are negative after the intensive phase and a patient who dies due to TB during or after the course of treatment respectively.[1,2] The patients had been treated for at least 20 months in Gulab Devi Hospital Lahore (GDH), Jinnah Hospital Lahore (JHL), Mayo Hospital Lahore (MHL), Nishtar Hospital Multan (NHM), Rawalpindi Leprosy Hospital (RLH), District headquarter (DHQ), DHQ Hospital Faisalabad (FSD), DHQ Hospital Sargodha (SGD), DHQ Hospital Sialkot (SKT), Bahwal Victoria Hospital Bahawalpur (BVH) and Samli Sanitorium Hospital, Murree (SSM). During the study period, DR-TB data was stratified by treatment outcome. Lost to follow-up, transferred out from Punjab and treatment failure patients were excluded. Data was retrieved from patient medical records using electronic nominal review system (ENRS) of the provincial TB control programme, Punjab (PTP-Punjab).

The ENRS contains data on DR-TB patients diagnosed at PMDT sites of PTP-Punjab including the date and site of DR-TB diagnoses, socio-demographic information, drug susceptibility test (DST) results, previous history of TB treatments, as well as information on DR-TB treatments received. The quantitative data extracted from the ENRS was checked for the consistency and completeness by the expertise investigators. DR-TB patients who were declared cured or treatment completed by MDR-TB physician at PMDT sites of Punjab and expired due to tuberculosis were considered as outcome variable. Explanatory variables included demographics, socioeconomics, DR-TB history, findings of radiographic, microbiological laboratory test, DST results, and time variables (enrolment date and outcome of the disease with date). Data on lifestyle factors including smoking, other medical history, family members and weight at the start of treatment was derived from the records of patient's card (DR-TB 01). SPSS 17was used for data analysis. Descriptive statistics were applied to summarise the socio-demographic characteristics of the participants in the study. The study data was demonstrated in the form of frequency, percentages and mean ± standard deviation (SD). T-test was used to access the difference of means between cured or treatment completed and died DR-TB patients. Cox's proportional hazards model was used to estimate the magnitude of dependency on various risk factors for died cases of DR-TB and CI was held at 95%. All p-values were two-sided and $p<0.05\%$ was considered statistically significant.

Results

Of the 1,136 patients, 472(41.5%) died during treatment and 664(58.5%) were declared cured or had their treatment completed. Of those who died, 163(34.5%) patients were in GDH followed by NHM 76(16.2%), RLH

Table-1: Socio-demographic and clinical information of DR-TB cases by outcome of treatment at end of treatment.

Characteristics	Died during the treatment (N=472) n (%)	Cured or completed the treatment (N=664) n (%)
Age at diagnosis		
Mean±SD	36.3±15.2	30.9±13.0
Gender		
Male	242 (51.3)	341 (51.4)
Female	230 (48.7)	323 (48.6)
Race		
Punjabi	449 (95.1)	604 (91.0)
Other	23 (04.9)	60 (09.0)
Under Directly Observed Therapy (DOT)		
No	245 (51.9)	275 (41.4)
Yes/Partial	227 (48.1)	389 (58.6)
Outcome of Sensitive TB		
Cured & treatment completed	62 (13.1)	121 (18.2)
Treatment Failure	189 (40.0)	392 (59.0)
Lost to follow ups	21 (4.4)	23 (3.5)
Relapse	03 (0.6)	01 (0.2)
Treatment not evaluated	179 (37.9)	106 (16.0)
Any other Medical History		
Yes	76 (16.1)	97 (14.6)
No	396 (83.9)	567 (85.4)
Site of the disease		
Pulmonary	470 (99.6)	646 (97.3)
Extra- Pulmonary	02 (0.4)	18 (2.7)
Sputum and/or Culture		
Positive	427 (90.5)	529 (79.7)
Negative	45 (9.5)	135 (20.3)
Baseline weight		
<36 kg	187 (39.6)	126 (19.0)
≥ 36 kg	285 (60.4)	538 (81.0)
Type of DR-TB resistance		
PDR	08 (1.6)	26 (3.9)
RR	116 (24.4)	71 (10.7)
MDR	298 (63.0)	555 (83.6)
XDR	50 (11.0)	12 (1.8)
Adverse Reaction		
Yes	59 (12.5)	113 (17.0)
No	413 (87.5)	551 (83.0)

PDR: Poly drug resistance
RR: Rifampin resistance
MDR: Multidrug resistance
XDR: Extensive drug resistance
DR-TB: Drug-resistant tuberculosis
TB: Tuberculosis.

Table-2: Cox proportional hazard regression analysis of death among drug resistance tuberculosis patients registered for treatment in PMDT Sites of Punjab from January 2010 through September 2015.

Covariates	Hazard Ratio	95% Confidence Interval	P-valve
Age at diagnosis (Years)	1.022	1.015-2.028	<0.001
Gender (ref. Female)			
Male	1.048	0.875-1.256	0.608
Under directly observed therapy (ref. Yes/Partially)			
No	1.289	1.076-1.545	0.006
Outcome of Sensitive Tuberculosis (ref. No)			**<0.001**
Cured & treatment completed	0.822	0.486-1.390	0.465
Treatment failure	0.872	0.537-1.415	0.579
Lost to follow up	1.221	0.651-2.293	0.534
Relapse	1.392	0.410-4.727	0.596
Treatment not evaluated	1.595	0.982-2.590	0.059
Any other medical history (ref. Yes)			
No	1.337	1.028-1.741	0.031
Site of disease (Extra-pulmonary)			
Pulmonary	2.193	1.382-3.479	0.216
Sputum culture (ref. Negative)			
Positive	1.745	1.282-2.376	<0.001
Baseline weight (ref. ? 36 Kg)			
<36 Kg	0.521	0.426-0.638	<0.001
Type of DR-TB (ref. PDR)			0.341
RR	2.687	1.248-5.786	0.012
MDR	1.106	0.776-1.576	0.576
XDR	1.576	1.208-2.063	0.001
Adverse reaction (ref. Yes)			
No	0.306	0.233-0.402	<0.001

PDR: Poly drug resistance,
RR: Rifampin resistance,
MDR: Multidrug resistance,
XDR: Extensive drug resistance.
PMDT: Programmatic management of drug-resistant tuberculosis.
DR-TB: Drug-resistant tuberculosis.

73(15.5%), MHL 70(14.8%), SSM 36(7.6%), whereas JHL and SGD treated 27(5.7%) patients each. There was no case of death in FSD, SKT and BVH.

The mean age of the patients who died was 36.3±15.2 years (range: 13-86 years), and 318(67.4%) of them belonged to the age group of 15-44 years. The mean age of cured and completed treated patients was 30.9±13 years (range: 10-76 years). The difference between the mean ages of the two groups was statistically significant (p<0.001). Of the patients who died, 427(90.5%) initially had positive culture, 242(51.3%) were male and 449(95.1%) were Punjabi, while 298(63%) had MDR-TB. Besides, 187(39.6%) of the patients who died had less than 36kg baseline weight, 76(16.1%) had other medical status and 413(87.5%) had adverse reaction of treatment (Table-1).

Cumulative hazard probability of time of death in terms of months of DR-TB patients was calculated (Figure).

Cox proportional hazard regression analysis showed that DR-TB patients who expired during the treatment were more likely to have been older, having the history of sensitive TB, to have any other medical history, < 36kg baseline weight, sputum culture positive and having the adverse reactions during the treatment as compared with therapy completion DR-TB patients who survived after the treatment therapy. However, the risk factors like gender, type of DR-TB and site of disease were not statistically significant (p>o.o5). Patients who did not (hazard ratio (HR) = 1.289, 95% CI: 1.076-1.545) follow up their treatment under directly observed therapy (DOTs) were more likely to die compared with those who followed up their treatment under DOTs (Table 2). Patients with <36 kg baseline weight (HR= 0.521, 95% CI: 0.426-0.638) and adverse reaction of treatment (HR= 0.306, 95% CI: 0.233-0.402) were respectively 48% and

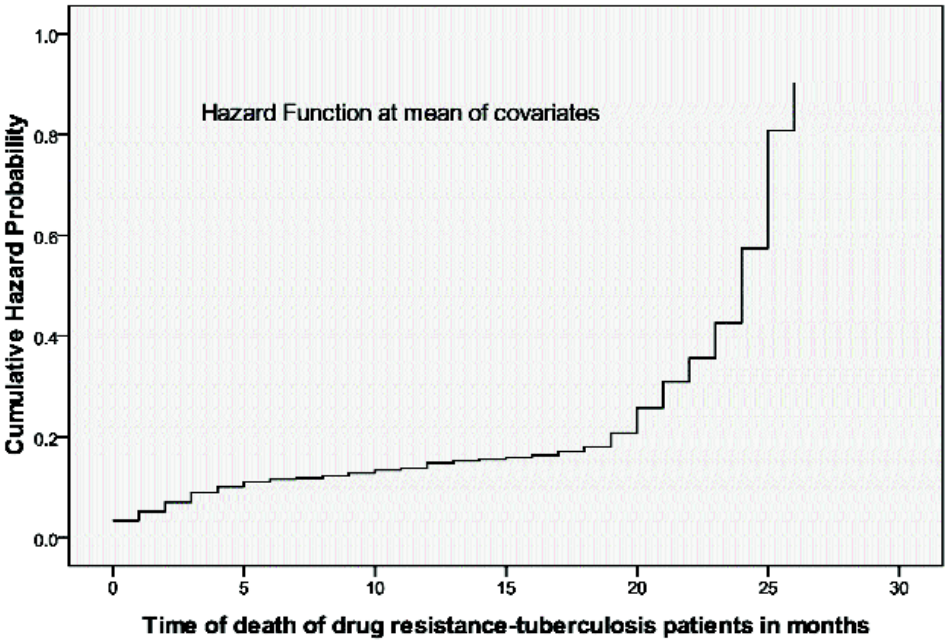

Figure: Hazard Function of Drug Resistance- Tuberculosis patient' death.

69% less likely to die compared with those who had more than 36kg baseline weight and no adverse drug reaction.

Discussion

MDR-TB is associated with an increased risk of death during treatment. Lower education, greater number of previous TB episodes and co-morbidity were independently associated with mortality among MDR-TB cases.[14] This current study, to the best of our knowledge, was the first comparison of cured or treatment completed and mortality between MDR-TB patients. Of all, 664(58.5%) patients remained alive during the entire follow-up period. Therefore, the mortality in this study was 41.5% which was lower than the mortality found than in literature (60%), approximately equal to reported by another study (40%), but lower than reported in some previous studies, including 27(4.6%) in Karachi, 29% in Henan province, China, and 21.1% in Indian-held Kashmir.[15-19] In this study, of the 472 patients who expired, 97(20.6%) expired within 3 months of the start of the treatment and 32.7% expired during the first year. The treatment success rates among drug-resistant tuberculosis patients have remained unacceptably low in Punjab as treatment of DR-TB is difficult because it entails large treatment period, toxic and higher cost than sensitive tuberculosis. The median treatment duration for the DR-TB patients who completed the treatment was 25 months (mode: 26 months) which was not in agreement with the study found by Anderson et al. who reported median treatment duration for MDR-TB cases completing treatment as 19 months.[20]

In this study, 96% of the patients who died had been treated with anti-tuberculosis drugs previously, which is a risk factor for developing DR-TB. Other authors have also reported previous anti-TB history as a risk factor of MDR-TB.[15,21] This study demonstrated the large grave frequency consequence of lower baseline body weight, sputum and/or culture positive result, adverse reaction of the treatment and no or partially under DOTs. Men had higher rates of death which was insignificantly associated with the DR-TB mortality in this study. Another study explained that the longer exposure to anti-tuberculosis drugs might also increase the risk of death as antibiotics used for MDR-TB have proven higher toxicity profiles and greater incidence of adverse effects.[22] The proportion of patients who died is among the lowest reported in other medical status (16.1%).

A limitation of this study was that information about some important risk factors, such as contact screening and co-morbid type, was not properly collected which might have affected the outcome.

Conclusion

It is important to monitor treatment outcome of DR-TB patients at PMDT sites to improve the treatment management policy. High-quality diagnosis at the time of registration and proper treatment must be ensured. The current study found that the proportion of patients who died from DR-TB treatment was relatively high. Furthermore, improved health service, evaluation of compliance, and psychological support should be required in the PMDT sites in which high DR-TB patients' death have been reported.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. National TB Control Program, Pakistan: NTP guidelines for management of drug resistance tuberculosis. [online] [cited 2014 Dec 11]. Available from: URL: http:// ntp.gov.pk/resourses.php.
2. World Health Organization (WHO). Global Tuberculosis report, Geneva, Switzerland: 2014.
3. TB-Control Program, Punjab: Health Reports, 2013.
4. Cox H, Kebede Y, Allamuratova S, Ismailov G, Davletmuratova Z, Graham B, et al. Tuberculosis recurrence and mortality after successful treatment: Impact of drug resistance. PLoS Medicine 2006; 3: e384.
5. Kang'ombe CT, Harries AD, Ito K, Clark T, Nyirenda TE, Aldis W, et al. Long-term outcome in patients registered with tuberculosis in Zomba, Malawi: mortality at 7 years according to initial HIV status and type of TB. Int J Tuberculosis Lung Dis 2004; 8: 829-36.
6. Franke MF, Appleton SC, Bayona J, Arteaga F, Palacios E, Llaro K, et al. Risk Factors and Mortality Associated with Default from Multidrug-Resistant Tuberculosis Treatment. Clin Infect Dis 2008; 46: 1844-51.
7. Kim HJ, Kang CH, Kim YT, Sung SW, Kim JH, Lee SM, et al. Prognostic factors for surgical resectionin patients with multidrug-resistant tuberculosis. Eur Respir J 2006; 28: 576-80.
8. Cox HS, Orozco JD, Male R, Ruesch-Gerdes S, Falzon D, Small I, et al. Multidrug-resistant Tuberculosis in Central Asia. Emerg Infect Dis 2004; 10: 865-72.
9. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and metaanalysis. PLoS One 2009; 4: e6914.
10. Gomes M, Correia A, Mendonça D, Duarte R. Risk Factors for Drug-Resistant Tuberculosis. J Tuberculosis Res 2014; 2: 111-8.
11. Caminero JA. Multidrug-Resistant Tuberculosis: Epidemiology, Risk Factors and Case Finding. Int J Tuberculosis Lung Dis 2010; 14: 382-90.
12. Farazi A, Sofian M, Zarrinfan N, Katebi F, Hoseini S, Keshavarz R. Drug Resistance Patterns and Associated Risk Factors of Tuberculosis in the Central Province of Iran. Caspian J Intern Med 2013; 4:785-9.
13. Flora MS, Amin MN, Karim MR, Afros S, Islam S, Alam A, et al. Risk Factors of Multi-Drug-Resistant Tuberculosis in Bangladeshi Population: A Case Control Study. Bangladesh Med Res Counc Bull 2013; 39: 34-41.
14. Kocfa CD,Sonia GB, Alejandro RM, Antonio BO. Mortality among MDR-TB Cases: Comparison with Drug-Susceptible Tuberculosis and Associated Factors. PLoS One 2015; 10: e0119332.
15. Irfan S, Hassan Q, Hasan R. Assessment of resistance in multi-drug resistant tuberculosis patients. J Pak Med Assoc 2006; 56: 397-400.
16. Khurram M1, Khaar HT, Fahim M. Multidrug-resistant tuberculosis in Rawalpindi, Pakistan. J Infect Dev Ctries 2012; 6: 29-32.
17. Rao NA, Irfan M, Mahfooz Z. Treatment outcome of multi-drug resistant tuberculosis in a tertiary care hospital in Karachi. J Pak Med Assoc 2009; 59: 694-8.
18. Sun Y, Harley D, Vally H, Sleigh A. Comparison of characteristics and mortality in multidrug resistant (MDR) and non-MDR tuberculosis patients in China. BMC Public Health 2015; 15: 1027.
19. Datta BS, Hassan G, Kadri SM, Qureshi W, Kamili MA, Singh H, et al. Multidrug-resistant and extensively drug resistant tuberculosis in Kashmir, India. J Infect Dev Ctries 2009; 4: 19-23.
20. Anderson LF, Tamne S, Watson JP, Cohen T, Mitnick C, Brown T, et al. Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: retrospective-prospective cohort study from 2004 to 2007. Euro Surveill 2013; 18: pii: 20601
21. Waheed Z, Irfan M, Haque AS, Khan MO, Zubairi A, AinN, et al.Treatment Outcome of Multi-Drug Resistant Tuberculosis Treated As Outpatient in a Tertiary Care Center. Pak J Chest Med 2011; 17: 121-9.
22. Santha T, Garg R, Frieden TR, Chandrasekaran V, Subramani R, Gopi PG, et al. Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District, South India, 2000. Int J Tuberc Lung Dis 2002; 6: 780-8.