BRAZ J INFECT DIS 2018;xxx(xx):xxx–xxx

The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Original article

Predictors of mortality in multidrug-resistant tuberculosis patients from Brazilian reference centers, 2005 to 2012

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ARTICLE INFO

Article history:
Received 5 January 2018
Accepted 11 July 2018
Available online xxx

Introduction

Tuberculosis (TB), even today, remains a serious public health problem, particularly in developing countries.[1] Without treatment TB mortality is high, reaching 70% in ten years in patients without HIV infection.[2] Multidrug-resistant tuberculosis (MDRTB), defined as the simultaneous resistance to isoniazid and rifampicin, remains a major challenge for TB control.[3,4] According to World Health Organization (WHO), in 2016, 4.1% of estimated new TB cases and 19% of retreatment cases in the world were caused by MDRTB or rifampicin-resistant (RR-TB) strains. Of these, 490,000 cases were MDRTB.[5] Earlier studies indicated that survival of MDRTB cases is poor.[6] Treatment outcomes for MDRTB are significantly worse than for drug-susceptible TB. In the 2014 global WHO cohort, 16% MDRTB/RR-TB patients died.[5]

Brazil is one of the 30 countries with the highest disease burden.[5] WHO estimated that in Brazil 1.5% of new TB cases and 8.0% of retreatment cases in 2017 were MDRTB.[5] Primary resistance to isoniazid and rifampicin in regional data from Brazil in 2007 was 1.4%.[7] In 2017, 583 MDRTB cases were registered in Brazil national surveillance system.[8] Rio de Janeiro State registered 166 (28.5%) MDRTB cases in 2017.[8] However, WHO estimated that 1900 MDRTB/RRTB cases occurred in Brazil that year. Death rate from 2015 MDRTB national cohort was 8.8%.[9]

MDRTB treatment in Brazil is standardized in most cases and MDRTB regimen is composed of an injectable drug, one quinolone, ethambutol, pyrazinamide, and terizidon.[10,11] Treatment is usually completed after 18–24 months.[10]

Factors associated with poor outcomes in MDRTB identified by systematic reviews and observational studies were male sex,[12,13] low body mass index,[13,14] underweight,[15] prior treatment with second line drugs,[12] extensive resistance pattern (XDR),[13] HIV infection,[14] no-conversion of sputum culture,[16] and alcoholism.[13] Regarding the death outcome, the risks factors pointed out in literature were age over 60 years, XDR resistance,[12,17] previous use of second-line drugs,[12,14,17,18] higher number of resistant drugs on sensitivity test (ST).[19] Better survival is associated to later-generation quinolones use.[20]

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https://doi.org/10.1016/j.bjid.2018.07.002

Diabetes is associated with increased risk of death and treatment failure.[21] Immunocompromised patients had a nine-fold greater risk of death.[6] TB and HIV are the major causes of death worldwide.[5] Employment of antiretroviral therapy (ARV) in HIV-infected patients with MDRTB resulted in reduction in mortality, as well as increased survival.[22]

Objectives

Little is known about the survival of MDRTB patients in Brazil. The aim of the study is to characterize and identify the main predictors of death among MDRTB patients in Brazil.

Methods

A non-concurrent cohort study was performed to analyze the relationship between socio-demographic, clinical, radiological, laboratory aspects, and drug regimens on MDRTB patient survival. The study was conducted at Hélio Fraga Reference Center (ENSP-FIOCRUZ), Rio de Janeiro, and included MDRTB patients from whole country that started treatment between January 1, 2005 to December 31, 2012, and that have been followed until December 31, 2012. Clinical and laboratory data were extracted from the MDRTB surveillance system. Outcomes were assessed at the end of the study.

Patients included in the study were those cases who had sensitivity test showing multidrug-resistance pattern and received regimens that included in its composition the drugs recommended for MDRTB treatment by the National Tuberculosis Program (NTP-MoH).[10] Patients excluded from the study were the following: no laboratory confirmation of tuberculosis; patients with changed resistance pattern on consecutive sensitivity tests; no outcome information, or transferred out; use of regimens with less than three second-line drugs, and treatment duration less than 12 months.

Definitions – variables

All the outcomes were defined based on the WHO definitions criteria.[3] Therefore death was defined as death from any cause during treatment. Extensive resistance (XDR) is multidrug-resistance pattern plus resistance to fluoroquinolone and second-line injectable drugs (capreomycin, amikacin, kanamycin).[3]

Demographic variables included were sex (male, female), age group (up to 59 years, 60 years or more), schooling years (<8, +8 years), and ethnicity as self-referred (white, black/brown, others). Clinical presentation of disease, classified as exclusively pulmonary (TB involving only pulmonary parenchyma and tracheobronchial tree), extrapulmonary (pleural TB and disease involving other organs), or both presentations; x-ray was analyzed according to cavity presence and side of pulmonary involvement (unilateral, bilateral). Sensitivity test (ST) results for ethambutol, streptomycin, amikacin, capreomycin, and ofloxacin, pattern of resistance (XDR or MDR), begin treatment after failure of previous TBMDR treatment (yes/no). Drugs included in treatment regimen: injectable drug (amikacin, capreomycin, streptomycin), quinolones (ofloxacin, levofloxacin, moxifloxacin), pyrazinamide, and clofazimine.

Table 1 – Demographic and clinical characteristics (N = 3802).

Characteristic	N (%)	Characteristic	N (%)
Sex		*Resistance pattern*	
Male	2461 (64.7)	MDR	3734 (98.2)
Female	1341 (35.3)	XDR	68 (1.8)
Ethnicity		*Resistance type*	
Brown-skinned	1641 (43.2)	Acquired	3106 (81.7)
White	1403 (36.9)	Primary	696 (18.3)
Black	644 (16.9)	*Disease type*	
Indigenous	16 (0.4)	Pulmonary	3704 (97.4)
Yellow	6 (0.2)	Both	69 (1.8)
Ignored	92 (2.4)	Extrapulmonary	29 (0.8)
Age group		*Pulmonary disease*	
<60 years	3530 (92.8)	Bilateral	2673 (70.3)
60 and more	272 (7.2)	Unilateral	1099 (28.9)
Schooling (years)		Normal	30 (0.8)
None	266 (7.0)	*Pulmonary cavity*	
1–3	718 (18.9)	Yes	3087 (81.2)
4–7	1377 (36.2)	No	685 (18.8)
8–11	854 (22.5)	*Regimen*	
≥12	235 (6.2)	Individualized	464 (12.2)
Ignored	352 (9.3)	Standardized	3338 (87.8)
MDRTB treatment		*DOT*	
New case	3106 (81.7)	Yes	2761 (72.6)
After default	295 (7.8)	No	1041 (27.4)
After failure	265 (7.0)		
Relapse	106(2.8)		
Other	30 (0.7)		

MDR, multidrug-resistance; XDR, extensively drug-resistant; DOT, Directly Observed Treatment.

Comorbidities and social behaviors studied were the presence of HIV infection, silicosis, hepatitis, use of steroids, neoplasia, organ transplant, presence of renal failure, drug addiction, alcoholism, diabetes, and smoking.

The study was approved by the National School of Public Health Research Ethics Committee (CEP/ENSP), number CAAE47351815.5.0000.5240.

Data analysis was conducted using the statistical software "Rversion 3.2.3. It included (a) the estimation of the median survival time to death through Kaplan-Meier method, (b) non-parametric estimation using stratified Kaplan-Meier (KM) method comparing the curves of the strata using Mantel-Haenzel test (log-rank) and Peto test with significance level of 5%, and (c) semi-parametric Cox modelling including covariates that met the proportionality assumptions in order to define the main predictors of death.

Results

Of 3877 cases of MDRTB exported from the surveillance system, 75 cases were excluded from the study, and 3802 individuals were included in the analysis.

There were 2461 (64.7%) men, and the mean age was 39.3 years (SD = 13.1 years). Regarding ethnicity, 2285 (60.1%) were black or brown-skinned (Table 1). Completed seven years of study 55.1% patients. Concerning the type of treatment initiation, 81.7% were new cases and the patients did on average

Please cite this article in press as: Gayoso R, et al. Predictors of mortality in multidrug-resistant tuberculosis patients from Brazilian reference centers, 2005 to 2012. Braz J Infect Dis. 2018. https://doi.org/10.1016/j.bjid.2018.07.002