Predictors of treatment outcome in multidrug-resistant tuberculosis in Portugal

To the Editor:

Despite progress in tuberculosis (TB) control, the response to the multidrug- resistant (MDR) TB and extensively drug-resistant (XDR) TB epidemic continues to be limited. The proportion of MDR-TB patients who successfully completed treatment varied from 44% (Eastern Mediterranean Region) to 58% (South-East Asia Region) [1]. Overall, treatment success was 48%, while 28% of cases were reported as lost to follow-up or had no outcome information [1]. The Global Plan's target for 2015 of achieving at least 75% treatment success in MDR-TB patients was only reached by 30 out of 107 countries [1].

In the present paper, we evaluated the treatment outcomes of M/XDR-TB patients in Portugal. Patients with pulmonary TB resistant to isoniazid and rifampin, who started treatment at some point between January 2000 and December 2008, were selected from the national database, which integrates the data from the mandatory registration of TB cases. The evaluation of treatment outcomes was conducted from February to April 2011. Patients were classified as having received no previous treatment for TB or as having received previous treatment(s) for TB. The World Health Organization (WHO) standard definitions were used to MDR-TB, XDR-TB and treatment outcome (treatment success, died, failure, default and transferred out) [1, 2]. Was analysed the relationship between treatment outcome and clinical and demographic factors. It were also identified the predictors of poor outcome in a population of M/XDR-TB patients. The association between explanatory variables and treatment outcome was evaluated by logistic regression models. The crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were determined.

We assessed MDR-TB treatment outcomes in 364 patients (257 with MDR-TB and 107 with XDR-TB), while 11 (3%) patients had no recorded final outcome (transferred out). The median age of the patients was 40 years (range: 13–86) and 259 (71.2%) patients were male. The amount of the patients that were HIV-positive was 108 (30.5%). The proportion of cases resistant to all first-line anti-TB drugs was 19.2%. Results of drug susceptibility testing (DST) to second-line drugs (amikacin, kanamycin, capreomycin, ofloxacin, ciprofloxacin, cycloserine, ethionamide, para-aminosalycilic acid, thiacetazone) were analysed. Patients with MDR-TB had a median resistance to four drugs (with a range of 2–10) and those with XDR-TB had a median resistance to eight drugs (with a range 4–10) ($p<0.001$). The assessment of treatment outcomes revealed that 42 (11.5%) patients were cured, 184 (50.5%) completed treatment, 92 (25.3%) died, 21 (5.8%) experienced treatment failure, and 25 (6.9%) defaulted treatment. Thus, 226 (62.1%) patients achieved a successful outcome. The treatment success rate was significantly different for patients who were never treated for TB and for patients who received previous TB treatment (68% *versus* 54%; $p=0.01$), and between patients with MDR-TB and XDR-TB (66% *versus* 52%; $p=0.018$).

Univariate analysis indicated that treatment outcome was significantly associated with injection drug use only (OR 3.34, 95% CI 1.53–7.31; $p=0.003$), alcohol abuse and injection drug use (OR 10.56, 95% CI 1.21–92.25; $p=0.033$), HIV-positive status (OR 3.38, 95% CI 2.11–5.42; $p<0.001$), previous TB treatment (OR 1.76, 95% CI 1.25–2.70; $p=0.010$), resistance to kanamycin alone (OR 1.89, 95% CI 1.20–2.99; $p=0.006$), and XDR-TB (OR 1.78, 95% CI 1.13–2.82; $p=0.014$) (table 1).

The considered multiple logistic regression model included HIV-positive status, previous TB treatment and resistance to kanamycin alone as independent variables. This model indicated that HIV-positive status (adjusted OR 3.56, 95% CI 2.20–5.77; $p<0.001$), previous TB treatment (adjusted OR 1.72, 95% CI 1.08–2.74; $p=0.023$), and resistance to kanamycin alone (adjusted OR 1.68, 95% CI 1.02–2.75; $p=0.013$) were significant risk factors for poor treatment outcome (table 1).

In the present study, the overall treatment success rate was 62%, which is higher than the global success rate of 48% estimated by WHO [1], and is similar to the success rates reported for other individual countries (62%) [3, 4] In the current study's population, poor outcome was related to the high case-fatality rate (25%). The average case-fatality rates in other countries have been reported as 9% [4] and 11% [3]. The high case fatality in our study may be explained by the high prevalence of HIV-positive patients (30.5%).

TABLE 1 Predictors of poor outcome among 364 patients with multidrug-resistant (MDR) tuberculosis (TB)

Predictors	Treatment success	Poor outcome	Univariate analysis		Multivariate analysis	
			OR# (95% CI)	p-value	OR# (95% CI)	p-value
Patients n	226	138				
Age years						
⩾40	111 (49.1)	76 (55.1)	1.0			
<40	115 (59.2)	62 (44.9)	0.79 (0.52–1.20)	0.270		
Sex						
Female	73 (32.3)	32 (23.2)	1.0			
Male	153 (67.7)	106 (76.8)	1.58 (0.97–2.56)	0.064		
Country of birth						
Portugal	184 (81.4)	107 (77.5)	1.0			
Foreign	42 (18.6)	31 (22.5)	1.27 (0.75–2.14)	0.370		
Risk factors¶						
None	133 (62.1)	63 (48.8)	1.0			
Alcohol abuse only	39 (18.2)	22 (17.1)	1.19 (0.65–2.17)	0.570		
Injection drug use only	12 (5.6)	19 (14.7)	3.34 (1.53–7.31)	0.003		
Alcohol abuse and injection drug use	1 (0.5)	5 (3.9)	10.56 (1.21–92.25)	0.033		
Other	29 (13.6)	20 (15.5)	1.46 (0.77–2.77)	0.253		
HIV status+						
Negative	174 (79.5)	72 (53.3)	1.0		1.0	
Positive	45 (20.5)	63 (46.7)	3.38 (2.11–5.42)	<0.001	3.56 (2.20–5.77)	<0.001
Treatment history						
Never treated for TB	141 (62.4)	67 (48.6)	1.0		1.0	
Previously treated for TB	85 (37.6)	71 (51.4)	1.76 (1.15–2.70)	0.010	1.72 (1.08–2.74)	0.023
Site of disease						
Pulmonary	211 (93.4)	123 (89.1)	1.0			
Pulmonary and extra-pulmonary	15 (6.6)	15 (10.9)	1.72 (0.81–3.63)	0.158		
Chest radiograph§						
No cavitation	115 (55.6)	55 (45.8)	1.0			
Cavitation	92 (44.4)	65 (54.2)	1.48 (0.94–2.32)	0.090		
Resistance to kanamycin						
No	170 (75.2)	85 (61.6)	1.0		1.0	
Yes	56 (24.8)	53 (38.4)	1.89 (1.20–2.99)	0.006	1.68 (1.02–2.75)	0.040
Categories of drug resistance						
MDR	170 (75.2)	87 (63.0)	1.0			
XDR	56 (24.8)	51 (37.0)	1.78 (1.13–2.82)	0.014		

Data are presented as n (%) unless otherwise stated. XDR: extensively drug-resistant. #: crude and adjusted odds ratio (OR) for poor outcome; ¶: treatment success n=214 and poor outcome n=129; +: treatment success n=219 and poor outcome n=135; §: treatment success n=207 and poor outcome n=120.

Mortality among patients with MDR-TB HIV-positive was 44%. The risk of poor outcome in our HIV-positive patients (31%) was 3.6 times higher than in HIV-negative patients.

We found significant differences in treatment outcomes of new MDR-TB patients and patients who had previous treatment for TB (68% *versus* 55%; p=0.013), and that the presence of previous TB treatment was an independent risk factor for poor outcome. In the group of previously treated patients 30% of them died during treatment and 39% of these patients were HIV- positive. It is also noteworthy that 57% of MDR-TB patients in our study had never been treated for TB. The high prevalence of new cases among MDR-TB cases could be attributed to the transmission of drug-resistant strains of *Mycobacteria tuberculosis* in our population. Molecular fingerprinting is an important tool to understand better the role of acquired or transmitted resistance among the relapsed patients with MDR and XDR-TB [5].

We also found a significant difference in the therapeutic success of MDR-TB patients and XDR-TB patients (66% *versus* 52%, p=0.018). The proportion of XDR-TB cases in our population was 29.4%, but XDR-TB was not significantly associated with a poor outcome. However, resistance to kanamycin alone was an indicator of poor prognosis. It should be noted that 109 (30%) cases in our study were resistant to

kanamycin, as well as 90 (83%) kanamycin-resistant cases had XDR-TB. MIGLIORI *et al.* [6] suggested that resistance to capreomycin, in particular, significantly increased the risk of death and treatment failure in M/XDR-TB cases, but that resistance to either kanamycin or amikacin alone did not significantly increase the risk of poor prognosis. In the largest cohort study ever published, no single drug was associated with treatment success in cases resistant to fluoroquinolones and in XDR-TB cases [4, 7].

Our study has several limitations due to its retrospective design. According to the Directorate-General of Health report in Portugal between 2000 and 2009 the coverage of DST to first-line drugs was of 69% [8]. Therefore, the number of MDR-TB cases within that period was probably underestimated. In our study 23% of cases had no results of DSTs to second-line drugs. In addition we only analysed a limited number of factors because we were only able to consider factors that were in the form of a notification. Despite these limitations, our study was the first nationwide study in Portugal to evaluate treatment outcomes of patients with MDR-TB, and to analyse the relationship between treatment outcome and various risk factors.

In conclusion, we found that the results of treatment for MDR-TB in Portugal are similar to the worldwide situation during our study period. We observed that being HIV-positive, having a previous TB treatment or resistance to kanamycin were independent risk factors for a poor outcome in our population.

The National Tuberculosis Program in Portugal was established in 1995, but it was only defined in 2007 as a specific strategy to control MDR-TB [9], based on the WHO Global Plan to Stop TB 2006–2015. To monitor the effectiveness of anti-M/XDR-TB interventions [10], similar evidence from other countries is necessary.

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