Predictors of drug sensitive tuberculosis treatment outcomes among hospitalised patients in South Africa: a multinomial logit model

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To the Editor,

In the present journal, we recently reported data [1] showing that the probability of survival during hospitalization is reduced in smear-positive patients with multidrug resistant tuberculosis (MDR-TB). Among smear-positive MDR-TB patients the survival rate at the end of 12- and 24-month periods were 57 and 42%, as compared to 82 and 74% among smear-negative patients. The probability of survival was reduced in HIV positive patients and in patients older than 60 years. From our experience in this environment, we here add data on factors associated with treatment outcomes during hospitalization of patients with drug sensitive TB (DS-TB). While factors associated with outcomes of outpatients with DS-TB have been described, only few reported on hospitalised patients [2, 3]. This study aimed at describing outcomes and associated factors among patients hospitalised for DS-TB treatment from 2001 to 2010.

The retrospective study was carried out at the Specialised TB Hospital in Witbank, Mpumalanga Province, South Africa. Witbank is located between Pretoria, the capital of South Africa, and Maputo, the capital of Mozambique. The hospital is one of the few TB ospitals in the province with an estimated population of 4.2 million people. The prevalence

of HIV among women attending antenatal clinics in this province was 35.6%, and the TB incidence was 463 per 100,000.

TB patients are usually managed in this facility in line with the South African national TB treatment guidelines. The criteria for hospitalisation of patients with DS-TB in this setting include the presence of any of the following: Extrapulmonary TB; Disseminated or miliary TB; Severe haemoptysis; Severe debilitation; AIDS; Social considerations and; Co-morbid conditions requiring hospital treatment. TB patients are usually treated using the Directly Observed Treatment Short course (DOTS) strategy. While some changes occurred in TB programme management worldwide during the index period (2001-2010), the changes were not as much as to make patients in the present study incomparable.

We reviewed records of patients aged ≥ 15 years hospitalised and treated for DS-TB at the Specialised TB hospital in Witbank from January 1, 2001 to December 31, 2010. Patients who had only extrapulmonary TB, those who spent less than 24 hours on admission, and those who were transferred out were excluded so that findings can be compared to other studies.

Sample size determination was guided by the findings of the simulation studies of Peduzzi et al. Every second patient was systematically selected using the admission log of hospitalised TB patients during the ten-year (2001 to 2010) period. A sample size of 193 patients was used for this study.

For each record selected, sociodemographic characteristics and medical factors were assessed. If a patient was treated more than once, we analysed the outcome of the last treatment. Definitions of TB cases were as described by the WHO [1].

Treatment outcomes were defined according to the WHO recommended criteria. These include Cured, Completed treatment, Died, Failed, Defaulted and Transferred out. Having excluded patients who were transferred out, three categories of outcomes were defined for this study. While cured and completed treatment were categorized as treatment success, failed and defaulted were categorized as unfavourable outcome and died was analysed in a separate category in this study.

Analysis of variance or Kruskal Wallis tests were performed to compare continuous variables while chi-square or Fisher's exact test was performed for comparison of categorical variables. Univariate analysis was performed and multinomial logistic regression model was used to assess the relationships between potential predictors listed in the univariate analysis and the three-class outcome variable. The reference class was treatment success. Duration of hospitalisation was modelled as a categorical variable using 180 days and 364 days as cut-off points. Multinomial logistic regression analysis was used to assess the effect of potential risk factors on treatment success. All potential independent variables with $P < 0.25$ in the univariate multinomial logistic regression were included in the final model. A p-value less than 5% and confidence level of 95% were considered to be statistically significant. Data analysis was done using Stata version 12.

The ethical clearance for this study was obtained from the institutional review board of the Faculty of Health Sciences, University of Pretoria and the Ethics Committee of the Department of Health, Mpumalanga Province, South Africa. The study was a review of hospital records. Hence, consent and approval of the management of the Witbank Specialised TB Hospital was also obtained. Furthermore, recorded data was anonymised such that no sociodemographic variable could identify any patient.

Of the 193 hospitalised TB patients included in the present study, 61 (31.6%) were females. The mean age of the patients was 38.7 ± 10.9 years and more than four-fifths (161) were younger than 50 years. Furthermore, 139 (72.0%) were hospitalised from 2006 to 2010 and the median duration (IQR) of hospitalisation was 207 (62-277) days. In addition, the minimum and maximum duration of hospitalisation were 1 and 807 days respectively. Almost 60% of the patients were treatment-naive (new cases) and only 34.2% (66) had HIV test results.

While 66 (34.2%) were cured, 21 (10.9%) of the patients completed treatment, 27 (14.0%) defaulted, 2 (1.0%) had treatment failure, and 77 (39.9%) died. After categorization, 87 had treatment success and 77 died.

Significant factors ($p < 0.05$) associated with unfavourable outcome and death in univariate analysis include gender, year when patient was hospitalised, duration of hospitalisation, employment status, previous TB treatment history, positive finding of acid fast bacilli (AFB) on smear microscopy, and positive culture result (Table 1).

The full multinomial logit model included all variables significant at $P < 0.25$ in the univariate analysis as potential predictors (Table 1). Inclusion of potential two-way interaction terms showed that none was significant. The current study shows that male gender and duration of hospitalisation were associated with unfavourable outcome in patients hospitalised for DS-TB treatment. On the other hand, smear positivity and duration of hospitalisation were associated with death (Table 2). The final model for treatment outcomes in this study population were based on the relative contributions of each of the factors in the multinomial logistic regression model (Table 2).

The present study showed that treatment outcomes were generally poor. The death rate was high, being slightly lower than treatment success rate. Furthermore, male gender was

Table 1: Univariate analysis of factors associated with treatment outcomes in hospitalised TB patients

Covariate		**Odds Ratio (95% CI)**	**P value**	**Odds Ratio (95% CI)**	**P value**
		Unfavourable outcome		**Death**	
Gender	Female Male	1.00 5.44 (1.20-24.63)	 0.028	1.00 0.51 (0.27-0.97)	 0.041
Age category	15-49 50-72	1.00 0.61 (0.19-1.99)	 0.415	 0.57 (0.25-1.33)	 0.194
Year of hospitalisation	2001-2005 2006-2010	1.00 0.34 (0.21-0.57)	 0.000	1.00 0.93 (0.65-1.34)	 0.713
Duration of hospitalisation (days)	0-180 181-364 365-807	1.00 0.29 (0.18-0.48) 0.08 (0.01-0.64)	 0.000 0.017	1.00 0.10 (0.05-0.07) 0.25 (0.22-0.89)	 0.000 0.032
Employment status	Unemployed Employed	1.00 0.32 (0.16-0.64)	 0.001	1.00 0.50 (0.28-0.89)	 0.020
Previous TB treatment	No Yes	1.00 0.31 (0.16-0.62)	 0.001	1.00 0.99 (0.63-1.60)	 0.99
Smear microscopy	Negative Positive	1.00 0.42 (0.23-0.76)	 0.004	1.00 1.47 (0.96-2.25)	 0.073
Sputum culture	Negative Positive	1.00 0.30 (0.18-0.52)	 0.000	1.00 0.71 (0.48-1.07)	0.104

Table 2: Multivariate analysis of factors associated with treatment outcomes in hospitalised TB patients

Covariate		Odds Ratio (95% Cl)	P value	Odds Ratio (95% Cl)	P value
		Unfavourable Outcome		Death	
Gender	Female	1.00		1.00	
	Male	7.07 (1.46-34.2)	0.015*	0.67 (0.21-2.14)	0.500
Age	15-49	1.00		1.00	
	50-72	0.63 (0.17-2.38)	0.499	0.56 (0.12-2.59)	0.454
Year of hospitalisation	2001-2005	1.00		1.00	
	2006-2010	1.33 (0.29-6.11)	0.712	0.67 (0.13-3.59)	0.642
Duration of	0-180	1.00		1.00	
hospitalisation	181-365	0.25 (0.07-0.82)	0.023*	0.01 (0.00-0.03)	0.000*
(days)	365-807	0.07 (0.01-0.68)	0.022*	0.02 (0.00-0.12)	0.000*
Employment status	Unemployed	1.00		1.00	
	Employed	0.69 (0.26-1.84)	0.460	0.58 (0.19-1.82)	0.351
Previous TB treatment	No	1.00		1.00	
	Yes	0.90 (0.32-2.57)	0.847	1.69 (0.54-5.27)	0.366
Smear microscopy	Negative	1.00		1.00	
	Positive	1.85 (0.73-4.71)	0.197	4.00 (1.38-11.56)	0.011*
Sputum culture	Negative	1.00		1.00	
	Positive	0.81 (0.29-2.28)	0.687	0.61 (0.21-1.80)	0.371

* significant at $p < 0.05$

associated with unfavourable outcome while positive smear microscopy at diagnosis was associated with death. In addition, patients who spent more than 180 days on hospital admission had reduced odds of unfavourable outcome and death. Although previous studies have shown factors associated with TB treatment outcomes, analyses were in relation to dichotomous outcomes [4]. Hence, factors exclusively associated with death were not addressed independently. In this study, we used the multinomial logistic regression model which has the ability to determine differential characteristics of groups by estimating the coefficients for each level of the comparison of the independent/dependent variable relationships. In addition, this study was conducted exclusively among hospitalised DS-TB patients unlike other studies.

Treatment success rate reported in the present study was lower than those of previous studies [4-6]. This may be related to the peculiar characteristics of the population of patients in this study. While most studies were carried out among ambulatory patients, the present study was carried out exclusively among patients hospitalised for DS-TB treatment.

Although there was no association between death and gender in the present study, male patients were seven times more likely to have unfavourable outcome. This contrasts with the findings of a similar study in Brazil where gender was not significantly associated with successful treatment outcome among TB patients [4].

While smear positivity at diagnosis was not associated with unfavourable outcome in this study, patients who were smear positive at diagnosis were four times more likely to die. This finding is slightly different from those of a similar study in Cameroon where delay in sputum conversion was associated with unfavourable treatment outcomes [7]. The study in Cameroon [7] categorized death, treatment failure, treatment default, and transferred out as unfavourable outcome while death was analysed as a separate category in the present study.

Studies regarding association between the duration of hospitalisation and TB treatment outcomes are uncommon. The present study showed that DS-TB patients hospitalised for more than 180 days were about four to fourteen times less likely to have unfavourable outcome and fifty to one hundred times less likely to die. No previous study has reported on duration of hospitalisation and association with treatment outcomes.

Missing data is a major limitation of this study. The extent of completeness in the dataset varied among different variables. While data regarding age and year of hospitalisation were complete, HIV status was not recorded in the records of a large number of participants. Furthermore, a conservative size of ten per variable in logistic regression was used due to financial implications [8, 9]. We excluded variables with more than 50% of missing data (such as smoking) from our analysis to minimize bias in the study.

TB treatment programmes at national, provincial and district levels should be strengthened to ensure hospitalised patients are treated for the optimal duration of time.

Acknowledgements

The authors wish to thank the Research Committee of the School of Health Systems and Public Health, University of Pretoria for the financial support for data collection for the study. In addition, we wish to thank Loveness Dzikiti for her immense contributions in the statistical analysis of this study. Dr Rose of the University of Free State is thanked for his suggestions.

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