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Predictors of Survival among Patients under Multi-drug Resistant Tuberculosis Treatment in Ogun State Treatment Center, Nigeria

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Abstract

Background: Drug-resistant tuberculosis threatens global tuberculosis care and prevention and it remains a major public health concern in Nigeria. Ending this pandemic requires understanding the factors that influence mortality, especially during the interim phase of the treatment. This study assessed the predictors of survival among patients under multi-drug resistant tuberculosis treatment in Ogun State, Nigeria.

Methods: A retrospective study was conducted among patients who were resistant to rifampicin and referred to Sacred Heart Hospital Lantoro, Abeokuta, Ogun State for treatment. Complete information on 279 clients was extracted from existing records using a proforma and entered into the SPSS version 23 after correction for errors. Descriptive and inferential statistics were done using Chi square test and logistic regression and a p - value of ≤ 0.05 was considered statistically significant.

Results: One hundred and fifty eight respondents (56.6%) were aged between 20-40 years, 177 (63.4%) were male and 174 (62.4%) were married. Seventy five (26.9%) respondents had relapsed after treatment failure on first line anti- tuberculosis drugs, 36 (12.9%) were HIV positive, 11 (3.9%) had blood sugar level above 126mg/dl and 49 (17.6%) had PCV less than 30mg/dl. Liver function was deranged in 79 (28.0%) respondents. Four months after starting treatment, 256 (91.8%) were alive while 23 (8.2%) had died. Likelihood of survival was higher among those who were ever married (OR= 1.3, 95% CI= 1.5 – 1.7) but lower among retreatment cases (OR= 0.5, 95% CI= 4.5 – 6.5).

Conclusion: This study revealed that clients' marital status and treatment category predict interim survival after 4 months of treatment with drug resistant tuberculosis.

Keywords: Predictors, Survival, Multi-drug resistance, Tuberculosis

Introduction

Tuberculosis (TB) is one of the major public health problems in the world, despite the availability of preventive and control measures for the disease.[1] Tuberculosis is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* that typically affects the lungs (pulmonary TB) but can affect other sites as well (extra-pulmonary TB). The disease is spread in the air when people who are sick with pulmonary TB expel bacteria, for example by coughing.[2] Multi drug-resistant tuberculosis (MDR-TB) is TB disease caused by *Mycobacterium tuberculosis* (*M.tb.*) organisms that are resistant to at least rifampicin (RIF) and isoniazid (INH), with or without any other first-line anti-TB drug.[3] Multi drug-resistant tuberculosis can result from either primary infection or may develop in the course of a patient's treatment.[4] Extensively drug-resistant TB (XDR-TB) is defined as TB resistant to at least INH and RIF plus any of the fluoroquinolones and at least one of the injectable second-line drugs (amikacin, kanamycin, or capreomycin).[5]

Identified risk factors for drug-resistant tuberculosis include inappropriate previous treatment with anti-tubercular drugs, contact with patients known to have drug-resistant tuberculosis and high prevalence of drug-resistant tuberculosis in the community.[6] Other risk factors include co-infection with HIV, socioeconomically deprived groups in slums, prisons and other correctional facilities, intravenous drug abusers, day care centres and other immuno-compromised states such as in transplant recipients, patients with diabetes mellitus and anti-cancer chemotherapy recipients.[4] In 2015, there were an estimated 10.4 million new TB cases worldwide. Six countries accounted for 60% of the total burden, with India being the first, followed by Indonesia, China, Nigeria, Pakistan and South Africa.[7] Anti-TB drug-resistance surveillance data show that globally there are 4.1% of new and 19% of previously treated TB cases that are estimated to have rifampicin or multidrug-resistant tuberculosis (MDR/RR-TB).[8] In 2016, an estimated 600,000 new cases of MDR/RR-TB emerged globally and MDR/RR-TB caused 240,000 deaths in the same year, most cases and deaths occurring in Asia. In addition, about 6.2% of MDR-TB cases have additional drug-resistance, extensively drug-resistant TB (XDR-TB).[8]

From surveillance data, only 54% of the MDR/RR-TB patients who started treatment in 2014 were successfully treated, while 16% of patients died and 8% of patients had treatment failure while 21% were lost to follow-up or not evaluated. The treatment success in XDR-TB patients was only 30%.[8] About 84% of TB deaths among HIV-negative people occurred in the WHO African Region and South-East Asia Region in 2015; these regions accounted for 86% of the combined total of TB deaths in HIV-negative and HIV-positive people. India and Nigeria accounted for 48% of global TB deaths among HIV-negative people and for 43% of the combined total TB deaths in HIV-negative and HIV-positive people.[7] HIV/AIDS is one of the factors that challenge effective control of TB. A study indicated that HIV-TB co-infected patients had approximately five-fold higher risk of progression to AIDS compared to those who are infected with HIV alone and patients with TB co-infection who progressed to AIDS had more than two-fold higher risk of death compared to those without TB.[9]

Tuberculosis (TB) remains the world's leading cause of death from an infectious

agent and even exceeded human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) in the year 2016.[7,10] Co-infection of TB with HIV/AIDS has become more pressing because of their effects together. While globally HIV/AIDS and TB co-infection represents only 11% of the total TB burden, in some areas of sub-Saharan Africa with a high burden of TB, as many as three-quarters of TB patients are co-infected with HIV/AIDS. In those countries, efforts to control TB are overwhelmed by the rising number of TB cases occurring in parallel with the HIV/AIDS epidemic.[10]

Both TB and MDR-TB patients are in danger of being poor. This is due to some costs associated with its management, such as travel costs, food/nutritional supplementation costs, and income loss which all contribute to the incidence of the catastrophic total costs. This risk is higher in patients from poor households, especially when they are breadwinners who lose their jobs as a result of this illness or some other reasons.[11] The African continent has high burdens of MDR /RR – TB. Also, Nigeria is one of the thirty countries with high incidence of MDR-TB.[7] MDR-TB is associated with an increased risk of mortality. Some of the factors known to be associated with this death rate are lower education, diabetes history, greater number of previous TB episodes and HIV infection.[12]

MDR-TB treatment in the understudied State started in November 2013 and since the commencement, the survival and predictors of mortality among patients under MDR-TB treatment are not well described or established. Identification of survival rate and risk factors of mortality in MDR-TB cases is essential for proper planning and effective evaluation of MDR-TB treatment. This study assessed the survival and predictors of mortality among patients under multi-drug resistant tuberculosis treatment in Ogun State Treatment Center, Nigeria.

Methodology

The study was carried out in Abeokuta, the capital of Ogun State, which comprises of two Local Government Areas (LGAs), namely Abeokuta North and South LGAs. The study was carried out at a 45-bedded Drug Resistant Tuberculosis (DRTB) facility (Sacred Heart Hospital Lantoro, Abeokuta) in Ogun State which remains the largest among other existing 66 DRTB treatment centers in 11 States across Nigeria; namely, Plateau, Benue, Kaduna, Kano, Bauchi, Cross Rivers, Taraba, Rivers, Imo, Oyo and Ogun States. The facility like all other treatment centers admits diagnosed MDR-TB patients for a minimum of four months from various states (Ogun inclusive) in the country. A retrospective study design was used for the study.

The study population consisted of patients who were resistant to rifampicin and referred to Sacred Heart Hospital Lantoro, Abeokuta, Ogun State DRTB Treatment Center from different parts of the country and had started treatment with second-line drugs. The data for the study was collected between June and September 2017 and inclusion criteria for this study were patients on treatment for DRTB with complete information in their folders.

A data extraction proforma that was standardized by experts in the field was used to collect general information, baseline laboratory parameters and baseline clinical information from two hundreds and seventy nine patients who had complete information in their case folders with the aid of four trained research

assistants. Data were analyzed using Statistical Product and Service Solution (SPSS) version 23. Liver function categorization was done and a score of 1was given for measurements of 40IU/L and below and was considered normal while a score of 2 was given to measurements above 40IU/L and was considered abnormal for both Alanine Transaminase (ALT) and Aspartate Aminotransferase (AST). In terms of albumin, a score of 1 was considered normal for values less than 35mg/dl while a score 2 was considered abnormal for values above 35mg/dl. Summation of all scores was done and these ranged from 4 to 7 in total. Those who scored 4 in total were regarded as having normal liver function while those who scored above 4 were categorized as having deranged liver function.

Bivariate analysis of the categorical variables were done by Chi square test, with level of significance set at $p<0.05$ while multivariate analysis was carried out using logistic regression. Data was presented in prose, frequency tables and charts.

Results

There were 177 (63.4%) males among the respondents and 158 respondents (56.6%) were aged between 20 – 40 years. One hundred and seventy four (62.4%) were married. In addition to categorization of respondents, baseline clinical data also revealed that 75 (26.9%) respondents had relapsed after treatment failure on first line anti TB drugs and 36 (12.9%) were HIV-positive (Table 1). From Table 2, 11 (3.9%) respondents had blood sugar levels above 126mg/dl and 49 (17.6%) had PCV less than 30mg/dl while 79 (28.0%) had deranged liver function tests. Figure 1 shows survival outcome of respondents after four months of starting treatment where 256 (91.8%) were alive and 23 (8.2%) had died. There was a statistically significant association between respondents' treatment categories, age and marital status and their interim survival ($P \leq 0.05$). Table 3. The likelihood of survival was higher among those ever married (OR= 1.3, 95% CI= 1.5 – 1.7) but lower among retreatment cases (OR= 0.5, 95% CI= 4.5 – 6.7). Table 4.

Table 1: Socio-demographic and clinical characteristics and clinical status of respondents (n = 279)

Variable	Frequency	Percentage
Sex		
Male	177	63.4
Female	102	36.6
Age (in years)		
less than 20years	26	9.3
20-40 years	158	56.6
Above 40 years	95	34.1
Marital Status		
Single	99	35.4
Married	174	62.4
Divorced	1	0.4
Separated	1	0.4
Widowed	4	1.4
Treatment category of patients		
New cases	49	17.6
Relapse after failure on first line anti-TB drugs	75	26.9
Treatment after failure	42	15.0
Treatment after loss to follow-up	56	20.1
Patients with unknown previous TB treatment history	57	20.4
HIV status		
HIV-positive	36	12.9
HIV-negative	243	87.1

Table 2: Categorization of respondents based on baseline laboratory parameters (n = 279)

Variable	Frequency	Percentage
Blood sugar		
High blood sugar	11	3.9
Normal	259	96.1
Packed Cell Volume		
Anaemic	49	17.6
Normal	221	82.4
Liver Function Tests		
ALT above 40	4	1.4
ALT below 40 - Normal	275	98.6
AST below 40-Normal	244	87.5
AST above 40	35	12.5
Albumin-less than 35 normal	214	76.7
Albumin-above 35	65	23.3
Normal Liver Function tests	200	72.0
Deranged Liver Function tests	79	28.0

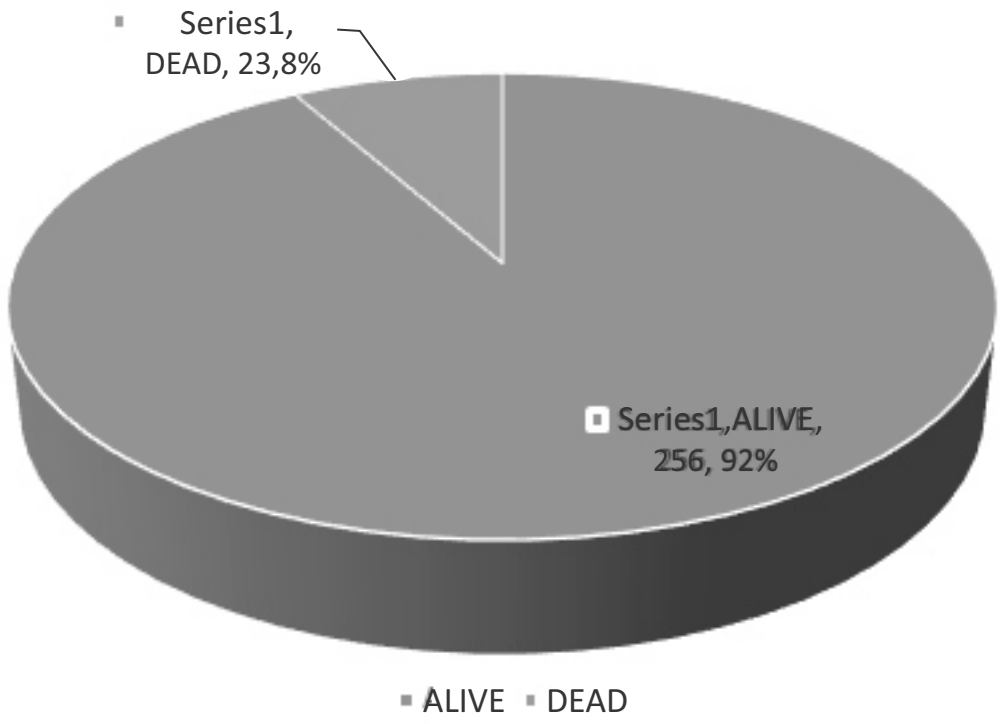

Figure 1 : Survival outcome after 4 months of treatment

Table 3: Association between socio-demographic characteristics, clinical status and survival among respondents (n = 279)

Variables	Alive (%)	Dead (%)	x^2	df	P-values
Sex					
Male	165 (93.2%)	12(6.8%)	1.3	1	0.241
Female	91(89.2%)	11(10.8%)			
Marital Status					
Single	91(91.9%)	8(8.1%)	12.8	4	0.012*
Married	161(92.5%)	13(7.5%)			
Divorcee	1 (100.0%)	0(0.0%)			
Separated	0 (0.0%)	1(100.0%)			
Widowed	3 (75.0%)	1(25.0%)			
Age (in years)					
Less than 20 years	21 (80.8%)	5(19.2%)			
20-40 years	149(94.3%)	9(5.7%)	5.60	2	0.05*
Above 40 years	86(90.5%)	9(9.5%)			
Treatment categories of patients					
New cases	48 (98.0%)	1(2.0%)	11.20	4	0.024*
Relapse after failure	69(92.0%)	6(8.0%)			
Treatment after failure	41(97.6%)	1(2.4%)			
Treatment after loss to follow-up	46(82.1%)	10(17.9%)			
Patients with unknown previous TB treatment history	52(91.2%)	5(8,8%)			
HIV Status					
HIV-positive	32 (88.9%)	4(11.1%)	0.45	1	0.503
HIV-negative	224(92.2%)	19(7.8%)			
Liver function test result					
Normal	184 (92.0%)	16(8.0%)	0.06	1	0.814
Deranged	72(91.1%)	7(8.9%)			
Packed Cell Volume					
Normal	214 (93.0%)	16 (7.0%)	2.51	1	0.085
Anaemic	42 (85.7%)	7 (14.3%)			

* Statistically significant

Table 4: Predictors of Survival after 4 months of treatment among respondents (n = 279)

Variables	Odds Ratio	95% Confidence interval	p-value
Marital status			
Never married (Reference value)	1		
Ever married	1.30	1.50 – 1.70	0.04*
Treatment categories			
New cases (Reference value)	1		
Retreatment cases	0.50	4.50 – 6.50	0.02*
Categorized Age			
Less than 20 years	0.44	0.13- 1.45	0.18
20-40 years	1.72	0.66-2 - 4.53	1.73
Greater than 40 years (reference value)	1		

* Statistically significant

Discussion

Our study revealed the predominant age group of respondents to be 20-40 years. This finding is similar to other previous studies on tuberculosis.[13,15] This age group is active, productive, autonomous and are likely to engage in high risk behaviour that can make them prone to tuberculosis infection. It is not surprising that majority of the respondents were male and married because members of this group have a lot of responsibilities to cater for and can be prone to this risk. The study showed that there were more cases of tuberculosis among the males than females with a male–to–female ratio of 1.7:1, which agrees with other findings in which seven out of every ten of tuberculosis patients were male, with 2.4:1 as the male–to–female ratio.[16] This is also consistent with reports in most low and middle income countries.[17] This suggests a potential role of gender in the epidemiology of tuberculosis.

The most common type of drug–resistant tuberculosis was relapse after failure on first line anti–tuberculosis drugs in about a quarter of the respondents. About one out of eight of the respondents had co-infection of tuberculosis and HIV. This was not surprising because tuberculosis is an opportunistic infection in people with impaired immunity like HIV patients. The death rate among patients with co-morbidities of HIV and tuberculosis was higher compared with those that only have tuberculosis. The likely reason for this may be due to suppression of the patients' immunity. This co-infection level was much higher than that of a similar study conducted in Imo State, Nigeria which documented about one out of thirteen respondents.[16] Considering some of the baseline parameters, respondents with reduced packed cell volume comprised one–sixth of the sample size. A similar study on anaemia predicting mortality among patients with tuberculosis revealed that about two-thirds of their respondents were anaemic which was much higher than our findings in this study.[18]

Also, in the assessment of baseline liver function tests, albumin level was the most deranged parameter in about a quarter of the respondents and other parameters also show some derangement. A similar study

on effects of anti-tuberculosis drugs on liver function profile in Libyan patients with tuberculosis also revealed derangement in liver function tests at baseline but these parameters improved as treatment continued. Hence, there was no negative effects on treatment outcome.[19] In contrast to the findings of this study, another study in China showed that co-infection with hepatitis B virus among tuberculosis patients was associated with poor outcome during tuberculosis treatment.[20] This was, however, different from our study, which only considered liver function tests and not specific liver diseases.

Considering treatment outcomes (in terms of survival) after 4 months of treatment, about one out of ten patients died. This was close to what was obtained from a similar study conducted in Ogbomoso, south-west Nigeria.[21] Our study also revealed that those with poor treatment (survival) outcomes were respondents who had never been married and retreatment cases. Hence, the likelihood of survival is high among the ever married and new cases. The possible reason for this may be because of prevailing cultural norms in the study location in which being in a marital relationship is held in high esteem and some level of marital support can be given to ensure good treatment outcomes. Also, retreatment cases of tuberculosis may be too familiar with the medication and therefore, not adhere to prescribed drug regimen due to "compliance fatigue" stemming from the rather lengthy duration of therapy typical of TB treatment; thereby leading to a low likelihood of survival. This finding was different from a study conducted among drug-resistant patients in Ethiopia in which other variables such as HIV positivity, non-HIV comorbidities, clinical complications, extra pulmonary involvement, under nutrition, anaemia, treatment delay, lower body weight and older age were predictors of poor treatment outcome.[22]

The followings are the implications of this study, retreatment cases diagnosed of multidrug resistant tuberculosis as well as singles while on treatment should be closely monitored during follow up clinic visitation to ensure proper adherence to new 9 months regimen, ensure that follow up investigations are done and treatment completed so as to prevent development of extensive drug resistant tuberculosis. Also, other factors such as socio-economic, socio-cultural, mental factors that can hinder survival that were not addressed by this study should be explored by future studies.

Conclusion

This study revealed that the likelihood of survival among drug resistant tuberculosis cases is influenced by categorization of clients prior to commencement of treatment as well as their marital status. The likelihood of survival was higher among ever married and lower among retreatment cases. It is therefore recommended that the never married on tuberculosis treatment should be more socially supported and health educated on the need to adhere to treatment protocols. Also, at the commencement of treatment for retreatment clients, proper re-orientation and counselling to reiterate the importance of treatment compliance, in order to enhance good treatment and survival outcomes should be emphasised.

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