Original Article

Predictors of Mortality among Drug-Resistant Tuberculosis Patients in Kaduna State, Nigeria

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Abstract

Background: Specific death due to DR-TB has significantly contributed to tuberculosis (TB) mortality and overall global deaths. **Aim:** This study examines the predictors of mortality among DR-TB patients in Kaduna State, Nigeria. **Subject and Method:** This was a retrospective longitudinal study of DR-TB mortality carried out among 370 DR-TB patients from the 23 LGAs in Kaduna State. It involves a retrospective review of the MDR-TB records of the patients over a period of 10 years (2012–2021). Demographic and clinical data of all DR-TB patients enrolled in Kaduna State, Nigeria, between April 1, 2012, and March 31, 2021, were used. Survival analysis was performed with SPSS version 25, using Kaplan–Meier and Cox proportional hazard regression modeling, at 5% significance level. **Results:** The majority of the patients, 255 (68.9%), were below the age of 40 years, while 53 (14.3%) of the patients died within the study period. Most deaths 26 (49.1%) were associated with HIV co-infection and the disease severity. Results for the Cox proportional model show that there was a significantly lower risk of death when a patient had MDR-TB compared to pre-XDR-TB (adjusted hazard ratio, AHR = 0.34, 95% CI = 0.16–0.72, $P = 0.04$). Both models show that age, sex, residence, or year of treatment had no significant association with survival or death. **Conclusion:** HIV co-infection and DRTB with progression to more resistant and difficult-to-treat strains contributed to higher deaths. There is a need for concerted efforts from all DR-TB stakeholders to control the disease.

Keywords: *DR-TB, HIV co-infection, Kaplan–Meier, mortality, predictors, survival*

Introduction

Drug-resistant tuberculosis (DR-TB) occurs when laboratory results confirmed that mycobacterium tuberculosis are resistant to at least one of the first-line anti-tuberculosis drugs.[1]

DR-TB is a form of antimicrobial resistance to drug therapy, and this can be very difficult to diagnose and treat. A patient with drug-sensitive (DS-TB) tuberculosis can progress to DR-TB if they are poorly treated with inadequate medications or if they failed to strictly adhere to the complete regimen for the DS-TB.[2] Another critical issue is the prescription of wrong drugs and/or when substandard medications are prescribed.[3,4] The WHO reported in 2019 that of the 500,000 people who developed MDR-TB that year, only one-third of patients were appropriately enrolled on the correct anti-DR-TB regimen.[5]

Incidence of a DR-TB can be primary or transmitted drug-resistant.[6] Primary DR-TB occurs due to

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antimicrobial resistance when drug-sensitive TB cases are poorly managed. Transmitted DR-TB occurs when an individual with DR-TB spread the disease for example in close settings such as the hospital, prisons, and hostels.[7,8] As treatment is long and hard, DR-TB patients often stop treatment before they should and when untreated or inadequately treated, they continue transmitting drug-resistant bacteria to others and tend to have a higher risk of mortality.[8]

The pattern of the DR-TB can be multi-drug-resistant TB, (MDR-TB), isoniazid-resistant TB, Rifampicin-resistant TB (RR-TB), pre-extensively drug-resistant TB (pre-XDR-TB), or extensively drug-resistant tuberculosis (XDR-TB).[9] Isoniazid or Rifampicin resistance are mono-resistant forms of DR-TB to the specified first-line anti-TB drugs. Pre-XDR-TB is resistant to fluoroquinolone (FQ) in addition to resistance to Rifampicin and Isoniazid. XDR-TB is resistant to Rifampicin and Isoniazid, plus any FQ and at least any of the Group A drugs—bedaquiline or linezolid or both.[10] The DR-TB patients will need to be managed on second-line drugs or an individualized regimen as the cases may demand.[10] The outcome of management of these complicated forms of TB can be very fatal depending on several factors including age, comorbidities, drug toxicities, and drug–drug interactions especially in HIV co-infected patients, adherence to therapy, and social and psychological factors.[11] Specific deaths due to DR-TB have significantly contributed to TB mortality and overall global death[12] Out of the estimated 500,000 cases of DR-TB reported in 2019, the case fatality rate was 36.4% (182,000 death) globally. Higher mortality was recorded among patient with XDR-TB as only one-third of these categories of patients were successfully treated.[13]

There is a paucity of data on DR-TB mortality in Nigeria. There are varied reports on the specific death rate due to DR-TB in different parts of the country, and this ranges from 15%[14] from a previous survey in southern Nigeria to 25. 9% from a recent national survey.[15] Epidemiological reports showed that previous TB episode, comorbidities with chronic organic diseases, HIV, and/or diabetes could worsen the clinical conditions of DR-TB patients with a resultant risk of high mortality among DR-TB cases.[16,17] This study determines the predictors for mortality among DR-TB patients in Kaduna State.

Materials and Methods

Study design and locations

The study was retrospective longitudinal in design among DR-TB patients enrolled for treatment in Kaduna State, Nigeria. The state consists of twenty-three (23) local government areas. The National Tuberculosis and Leprosy Training Centre ((NTBLTC), located in Saye Zaria, was the site for the facility management of the DR-TB patients. It also has an outpatient unit for the community management of the DR-TB. Other sites in the state for the community management (CM) of the DR-TB are the Barau Dikko Teaching Hospital, Kaduna, Gwamnan Awan, Rigasa and Kafanchan General Hospitals. The private hospital used for the community model is the Nasiya Hospital, Rigasa and WILBRESUN Hospital, Narayi, Kaduna.

The study population

This comprised patients who had DR-TB in the state ten years preceding the survey. These included patients that had been treated with the conventional regimen for DR-TB and those on the new shorter regimen.

The inclusion criteria comprised DR-TB patients in the 10 years preceding the survey who had their hospital records in the repository of the Kaduna State Ministry of Health. It also involved DR-TB patients who were at the community clinics and those who were on admission at the NTBLTC in Saye Zaria during the period of this study.

The exclusion criteria comprised the DR-TB patients with incomplete relevant information, the critically ill patients; those who could not respond questions, those loss to follow up, and the newly diagnosed who were less than one month on treatment. The DR-TB records of 370 patients between April 1, 2012, and March 31, 2021, were reviewed. The Gene Xpert test was performed at the baseline to diagnose the resistant to Rifampicin by the mycobacterium tuberculosis (Xpert MTB/Rif assay) and that was the point of entry into DR-TB care for the enrolled patients.

Sample size estimation

The minimum sample size (n) was calculated using the Fisher's formula for calculating sample size for cross-sectional study. $n = Z^2pq/d^2$, where n = the minimum sample size, Z = standard normal deviate at for type 1 error (α) at 5% = 1.96; p = 28.4% = 0.284 from a previous study[18]; q = complimentary probability = 1-p which is 0.716; d = maximum sampling error allowed at 95% confidence interval which is 5% (0.05). By substituting the subjects in the formula above; $n = 1.96^2 \times 0.284 \times 0.7I6/(0.05^2) = 0.7811/0.0025 = 312.5$. Adjustment for 10% non-response was estimated by dividing the calculated sample size by 1-non-response rate, that is, 312.5/(1-0.1) = 312.5/0.9 = 347.

The sample size was however increased to 370 to capture all eligible participants and increase accuracy and power of the study.

Ethical approval to conduct the study was obtained from Barau Dikko Teaching Hospital Health Research Ethic Committee (BDTH-HREC) with reference number BDTH/2021/032/vol 1 and registration number NHREC/30/11/21A and from the Kaduna State Ministry of Health.

Data collection

A proforma was developed to extract information on treatment outcomes from the MDR-TB registers at the repository of the Kaduna State Ministry of Health. The information retrieved from the registers included patients' socio-demographics characteristics—age, sex, local government areas of the patients, rural–urban residence, the treatment groups of the patients, and treatment outcomes, either dead or alive.

Data analysis

The data were screened for completeness, coded, and then analyzed with the statistical Package for the Social Sciences (SPSS) version 25.

The primary outcome variable was death of a DR-TB patient. The independent variables were age, sex, place of treatment, HIV status, mortality outcome, (dead or alive), residence of patient, previous second line of therapy, and years of treatment. Univariate analysis was carried out with these independent variables, and the results were presented in tabular form. The results were summarized using mean and standard deviation for quantitative variables, frequencies, and percentages for categorical variables.

Kaplan–Meier analysis was used to estimate the time to death in weeks. Predictors of DR-TB mortality were assessed using Cox proportional hazard regression with hazard ratio (HR) set at 95% confidence interval (95% CI).

Results

The majority of the patients, 255 (68.9%), were below the age 40 years. The median age was 32 years. Two hundred and fifty-eight (69.7%) were males, while 112 (30.3%) were females. Most 195 (52.7%) were admitted at the treatment center, and only 175 (47.3%) had the community model of MDR-TB management. HIV co-infection was 54 (14.6%). A higher proportion of the patients 286 (77.3%) resided in urban locations compared to 84 (22.7%) from rural areas. Only five (1.4%) of the MDR-TB patients had previous second-line treatment. The study revealed that 53 (14.3%) of the patients died within the study period. [Table 1].

The mean age at death was 38.1 years. More deaths occurred among males 35 (66%), and these were reported mostly at the treatment center 32 (60.4%). HIV co-infection accounted for 12 (22.6%) deaths. Further analyses showed that more deaths occurred among urban 42 (79.2%) than rural residents 11 (20.8%), and among patients on shorter than longer regimens, 34 (64.2%) versus 19 (35.8%). The distribution of deaths showed that 26 (49.1%) were associated with MDR-TB, 24 (45.3%) with mono-resistance with Rifampicin, and 3 (5.6%) pre-XDR-TB. Most of the DR-TB deaths occurred between the years 2017 and 2022. The mean weeks on therapy before death were 11.44 ± 7.29 [Table 2].

Table 3 shows that HIV status among patients with DR-TB was significantly associated with higher hazard of mortality in the community (P = 0.006). Both Kaplan–Meier and Cox regression models showed that age, sex, residence, or year of treatment had no significant association with mortality. Table 4 shows that the progression of the MDR-TB to a more severe

Table 1: Socio-demographic characteristics and key predictors of mortality among MDR-TB patients in Kaduna State, Nigeria, from 2012 to 2021 (n=370)

Characteristics	Frequency	%
Age: median (range) 32 (84)		
<40	255	68.9
>=40	115	31.1
Sex		
Male	258	69.7
Female	112	30.3
Place of treatment		
Community	175	47.3
Facility	195	52.7
HIV status		
Positive	54	14.6
Negative	316	85.4
Residence of patient		
Rural	84	22.7
Urban	286	77.3
Previous second-line therapy		
Yes	5	1.4
No	365	370
Type of DR-TB		
MDR-TB	188	50.8
Mono-resistance	170	46.0
PRE-XDR/XDR	12	3.2
Year of treatment		
2012–2016	161	43.5
2017–2021	209	56.5
Died		
No	317	85.7
Yes	53	14.3

Table 2: Socio-demographic characteristics and clinical features of the MDR-TB patients who died in Kaduna State, Nigeria, from 2012 to 2021 (*n*=53)

Characteristics	Frequency	%
Age: median (range) 36 (84)		
<40	30	56.6
>=40	23	43.4
Sex		
Male	35	66
Female	18	34
Place of treatment		
Community	21	39.6
Facility	32	60.4
HIV status		
Negative	41	77.4
Positive	12	22.6
Residence of patient		
Urban	42	79.2
Rural	11	20.8
Previous second-line therapy		
No	51	96.2
Yes	2	3.8
Regimen		
Shorter regimen	34	64.2
Longer regimen	19	35.8
Type of DR-TB		
MDR-TB	26	49.1
Mono-resistant	24	45.3
Pre-XDR	03	5.6
Weeks on therapy before death (mean=11.44+7.29)		
<12 weeks	25	47.2
>=12	28	52.8
Year of treatment		
2017–2021	31	58.5
2012–2016	22	41.5

form, the pre-XDR-TB, is a predictor of higher mortality. (AHR = 0.35, 95% CI = 0.17-0.72, P = 0.04).

The survival curves give a visual representation of the life table. The horizontal axis shows the time on commencement of treatment before death in weeks, while the vertical axis shows the cumulative survival. In these plots, drops in the survival curves occurred as the week progresses. The vertical axis shows the probability of survival (probability of no death). The HIV negative clients showed cumulative higher survivals than the clients with DR-TB/HIV co-infection in most of the weeks on treatment. The MDR-TB clients also showed higher survival than the pre-XDR and Rifampicin-resistant clients [Figures 1 and 2].

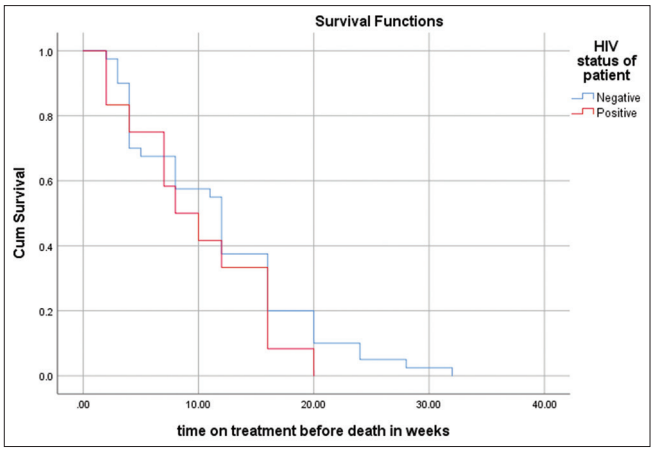

Figure 1: Kaplan–Meier survival function- HIV status

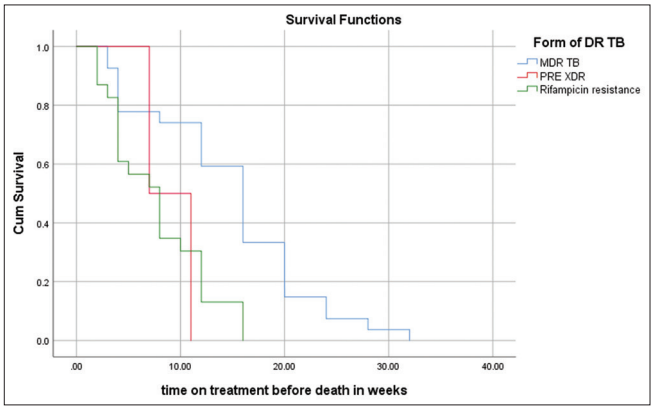

Figure 2: Kaplan–Meier survival function- Form of DR-TB

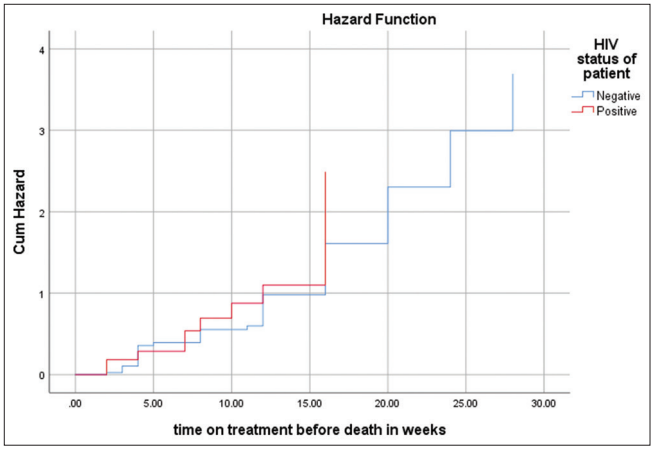

Figure 3: Hazard of death among HIV/DR-TB confected patients in Kaduna State segregated by number of weeks on treatment before death

The hazard function curves in Figures 3 and 4 give a visual representation of the hazard (death) risk. The horizontal axis shows the time on commencement of treatment before death in weeks, while the vertical axis shows the cumulative hazard. The plot shows a progressive increase in number of death as the week progresses. All deaths in HIV co-infected clients

Table 3: Predictors of survival among MDR-TB in Kaduna State, Nigeria, from 2012 to 2021 using Kaplan–Meier (*n*=53)

		Death *n*=53			
	Variable	**Community *n*=22**	***P* (Long rank–Mantel–Cox)**	**Facility *n*=31**	***P* (Log rank–Mantel–Cox)**
Time to death in week	Mean+SD	11.37+1.89		11.7+1.13	
Age					
	<40	11	0.16	19	0.34
	>=40	11		12	
Sex					
	Male	14	0.78	20	0.38
	Female	8		11	
Residence					
	Rural	5	0.48	6	0.94
	Urban	17		21	
HIV status	Positive	4	0.006	8	0.85
	Negative	18		23	
Year of treatment					
	2012–2016[a]	03	0.02	19	0.06
	2017–2022[b]	19		12	

ST=shorter treatment regimen [a]before ST. [b]during ST

Table 4: Predictors of mortality among MDR-TB in Kaduna State, Nigeria from 2012 to 2021 using Cox regression modeling (*n*=370)

Covariate	**Adjusted hazard ratio**	**95% CI**	***P***
Median age=32 years	1.21	0.79–1.58	0.52
Sex			
Male compared to female	0.80	0.38–1.68	0.56
Residence			
Rural compared to urban location	0.88	0.43–1.85	0.76
HIV status			
HIV positive compared to HIV negative	0.79	0.34–1.70	0.56
Types of DR-TB			
MDR-TB compared to pre-XDR-TB	0.35	0.17–0.72	0.04
MDR-TB compared to mono-resistant TB	1.30	0.23–7.4	0.76
Year of treatment			
2012–2016 compared to 2017–2022	0.62	0.32–1.22	0.17

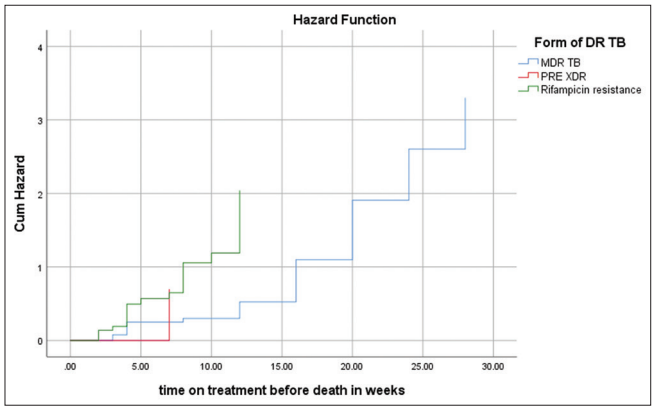

Figure 4: Hazard of death among DR-TB patients in Kaduna State segregated by number of weeks on treatment before death

had occurred before week 20, while all deaths in pre-XDR-TB occurred before week 10. Death among MDR-TB was spread over 30 weeks with increasing cumulative hazard of death as the week progresses.

Discussion

The report from this study reveals that the hazard of death is associated with the DR-TB among the affected study population. The disease was associated with 53 deaths (14.3%) deaths among 370 patients just in a period of 10 years, with majority of the deaths occurring among the working, productive and reproductive age groups, with a mean age at death for the DR-TB patients at 38 + 17.5 years. This implies that several of the family members of the deceased are left as widows, widowers, and orphans, and several homes have lost their breadwinner to the scourge of DR-TB, thereby increasing the catastrophic cost of TB treatment. If the

trend continues without focused interventions in a TB endemic country like Nigeria, the country will be at risk of a weaker community and state economies, thus pushing several families further into poverty.[19] The death rate observed in the study is comparable to the case fatality rates reported for some diseases undergoing high-level surveillance in Nigeria such as Lassa fever (CFR = 12%)[20] and Monkey pox (CFR = 7%).[21] Nevertheless, the DR-TB death rate is by far higher than the death rate for the COVID-19 (CFR = 0.8%) reported from a previous national survey in Nigeria.[22] This shows a need for policy direction that will ensure the deployment of more effective strategies and resources for the prevention and control of the DR-TB both at the national and sub-national levels in the country.

Another concern from this study is the death rate attributed to HIV co-infection (22.6%). This was similar to 22% death rate from MDR-TB co-infection reported in a study from Kano, North Western Nigeria[23] Similarly is also comparable to the 18.1% pooled death rate in MDR-TB co-infection recorded in Sub-Sahara Africa.[24] A South African study however reported a much higher rate of 72% death attributed to MDR-TB and HIV co-infection among individuals that were not on any antiretroviral therapy.[11] Wells CD *et al*.[25] described the MDR-TB and HIV co-infection as a perfect storm. This shows that HIV co-infection with MDR-TB is a major public health problem in DR-TB endemic zones and will require concerted efforts from the relevant stakeholders to control this "perfect storm."

This study also revealed the danger of complications of the DR-TB progression to a more severe disease form such as the pre-XDR/XDR-TB. About a quarter of the patients diagnosed with the pre-XDR-TB in this study population died. This study also showed significant relationship between mortality and the type of DR-TB, with higher death among patients with severe form of the disease. This is similar to a report of 39% death due to pre-XDR/XDR-TB in a multi-country study carried out in Côte d'Ivoire, Democratic Republic of the Congo, Kenya, Nigeria, Peru, South Africa, and Thailand.[26] This report showed the need for the DR-TB patients and their caregivers to cooperate with the healthcare providers to ensure compliance with the treatment to prevent progression of the disease to DR-TB strains that are highly resistant to the current medications.

This study unlike some previous surveys on DR-TB shows that the age, sex, residence, or year of treatment had no significant association with survival or death of the DR-TB patients and that the main culprits for death among these patients were HIV co-infection and progression of the DR-TB to a more severe form. This finding might be peculiar to this study population who had access to DR-TB care regardless of their age, sex, or place of residence dichotomy, but however, exposes the varied clinical conditions of the patient at the point of treatment as the risk factor for the mortality. This position is further corroborated by the mean time from diagnosis to death of less than 12 weeks reported in this study. This emphasizes the need for improved TB and DR-TB case finding and early recruitment into drug treatment, surveillance, patients, and community education on TB and MDR-TB on the consequences of TB complications to enhance early presentations of identified TB and MDR-TB cases.

Limitation of the study

The MDR-TB records provided no information about the socioeconomic status of the patients such as their occupation, monthly income, information on community support, and other chronic comorbid medical conditions that could have had influence on the treatment outcomes.

There is therefore a need to conduct a prospective study to see how these other variables affect DR-TB outcome.

Conclusion

The predictors of mortality were the HIV co-infection and progression of the DR-TB to a more severe form. There is a need to strengthen the national and state TB and DR-TB programs to prevent and control the morbidity and mortality outcomes due to increased severity of DR-TB and HIV comorbidity.

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Conflicts of interest

There are no conflicts of interest.

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