

## Predictors of treatment outcomes among hospitalized multidrug-resistant tuberculosis patients in Nigeria: A retrospective analysis

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### Abstract

Despite concerted efforts to end the tuberculosis epidemic by 2030, increasing cases of drug-resistant tuberculosis (DR-TB) have warranted up-to-date data to inform targeted policy actions needed to battle this health issue. This study evaluates treatment outcomes and associated factors among patients admitted to different multidrug-resistant tuberculosis (MDR-TB) specialized treatment centres in the six geopolitical zones of Nigeria. This was a retrospective, hospital-based, cohort study conducted in twelve (12) MDR-TB specialized treatment centres in Nigeria between January 2012 and December 2018. Data was extracted from the medical records of 832 patients using a structured proforma. Treatment outcomes were categorized as successful (cured, treatment completed) or unsuccessful (non-adherent,

treatment failure or death). Relevant bivariate and multivariate logistic regression were done to assess the factors associated with treatment outcomes as well as predictors of successful treatment outcomes. All data analyses were performed using the Statistical Package for Social Sciences (SPSS) version 23. In the treatment centres, a calculated successful treatment outcome of 85.9% was achieved. The analysis revealed strong associations between treatment outcomes and various factors, including age ( $p < 0.001$ ), HIV status ( $p = 0.038$ ), presence of comorbidities ( $p < 0.01$ ), and treatment history ( $p = 0.023$ ). Notably, age, geopolitical zone of treatment, and the presence of comorbidities emerged as significant predictors of successful treatment outcomes.

### Keywords

Tuberculosis; MDR-TB; DR-TB; End TB; Resistance; Trends

## Introduction

The World Health Organization (WHO) in 2019 estimated that globally 1.8 billion people were infected with *Mycobacterium tuberculosis* with the majority of the cases occurring in developing countries of the world. About 10 million people fell ill from this preventable and curable disease in 2019 with an estimated 1.7 million deaths globally (el Hamdouni *et al.*, 2019; MacNeil *et al.*, 2019). The high morbidity and mortality rate associated with this disease comes with a huge social and financial burden to the patients, families, and communities (Kirubi *et al.*, 2021).

Tuberculosis is caused by a bacterium known as *Mycobacterium tuberculosis* with its effect primarily occurring in the lungs (CDC, 2021) and this type is usually referred to as pulmonary TB. In addition to the pulmonary TB type, TB outside the lung is called extrapulmonary TB which occurs when the *Mycobacterium tuberculosis* attacks other parts of the body including the kidney, spine, and brain (CDC, 2021).

Anti-microbial agents such as rifampicin, isoniazid, ethambutol, streptomycin, and pyrazinamide have been used to treat this disease with varying outcomes including the development of drug resistance. Drug-resistant TB (DR-TB) which is of various types occurs when the bacteria, *Mycobacterium tuberculosis* becomes resistant to antimicrobial drugs used in treating TB in infected persons with this resistant strain becoming almost completely incurable by the standard first-line drugs (Sengul *et al.*, 2015). The emergence of DR-TB is not only a threat to the world population but raises security concerns for countries worldwide especially resource-limited ones like Nigeria (Falzon *et al.*, 2017). Multidrug-resistant TB is one of the different types of TB drug resistance that is becoming more urgent and more challenging to global TB control because of its increasing cases and is an indicator of local failure of global TB approaches (WHO, 2020). Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to isoniazid (INH) and rifampicin, with or without resistance to other first-line anti-TB drugs (Mehari *et al.*, 2019). There were estimates of about 484, 000 new cases of MDR-TB, with approximately

190,000 deaths worldwide in 2018 (WHO, 2020). More than half of these cases were in developing countries of the world including Nigeria.

According to a TB report in 2017, Nigeria ranked seventh of the countries with a high burden of MDR-TB in the world and first in Africa with an estimated prevalence rate of 19–31% for new cases and 32% for previously treated cases (Onyedum *et al.*, 2017). Studies revealed significant heterogeneity in the prevalence of MDR-TB which varied according to the methods of testing and geographic regions of Nigeria (Onyedum *et al.*, 2017; Otokunefor *et al.*, 2018).

The treatment of MDR-TB is complex, long, and expensive (Calver *et al.*, 2010). It requires multiple drugs, including injectables, for prolonged periods. Many of these have significant side effects which makes treatment adherence difficult, and this affects overall treatment outcomes (el Hamdouni *et al.*, 2019).

Meanwhile, there has been a reported problem of poor documentation of MDR-TB in Nigeria for some time which likely affects WHO's actual survey (Onyedum *et al.*, 2017) with possible underestimation of Nigerian MDR-TB burden (Habib *et al.*, 2010). Although Gupta & Jorwal, intimated that the success of

any national TB program is to a great extent dependent on studies focusing on prevalence, risk factors, and treatment outcomes of the disease in the country (Gupta and Jorwal, 2018), there is poor information regarding treatment outcomes of MDR-TB and an overall MDR-TB limited data in the African regions (Mekonnen *et al.*, 2015). This underscores the need for updated data from the specialized treatment centres in Nigeria and hence, the need for this study. This study was therefore designed to determine the treatment outcomes for multidrug-resistant tuberculosis in patients admitted in the specialized treatment centres in Nigeria.

## **Methods**

### *Patients and Study Sites*

This retrospective study utilized patients records with confirmed MDR-TB cases who were admitted, registered, and treated in twelve special MDR-TB treatment centres across the six geopolitical zones of Nigeria between January 2012 and December 2018. Two MDR-TB treatment centres were conveniently selected from each of the six geopolitical zones based on the order of establishment. Convenience sampling method was utilized as it allows for a more efficient use of resources, which is crucial in a retrospective study where the focus is on

analysing existing data. Conducting a comprehensive sampling of all MDR-TB treatment centres might have been resource-intensive and time-consuming. The selected centres and their zonal distributions (Figure 1) include Southeast (Federal Medical Centre, Owerri Treatment Centre and Mile 4 Treatment Centre, Abakiliki); Southsouth, (University of Port Harcourt Teaching Hospital treatment Centre, Port Harcourt and University of Uyo Teaching Hospital treatment Centre, Uyo); Southwest (University College Hospital treatment centre, Ibadan and Sacred Heart Hospital treatment centre, Abeokuta); Northwest (National Tuberculosis and Leprosy Training centre, Zaria and Sokoto treatment centre, Sokoto);

Northeast (Abubakar Tafawa Balewa University Teaching Hospital treatment centre, Bauchi and Taraba State Specialist Hospital treatment centre, Jalingo); Northcentral (St. Vincent Alade treatment centre Benue and Jos University Teaching Hospital treatment centre, Jos). These are 32 to 100-bed specialized treatment centres operated by their parent Hospitals with support our=The partners provide training and supplies with funding from the Global Fund to fight AIDS, Tuberculosis, and Malaria. MDR-TB patients are diagnosed at selected TB clinics across the country, kept on a waiting list, and recalled for admission through phone calls based on the availability of bed space.

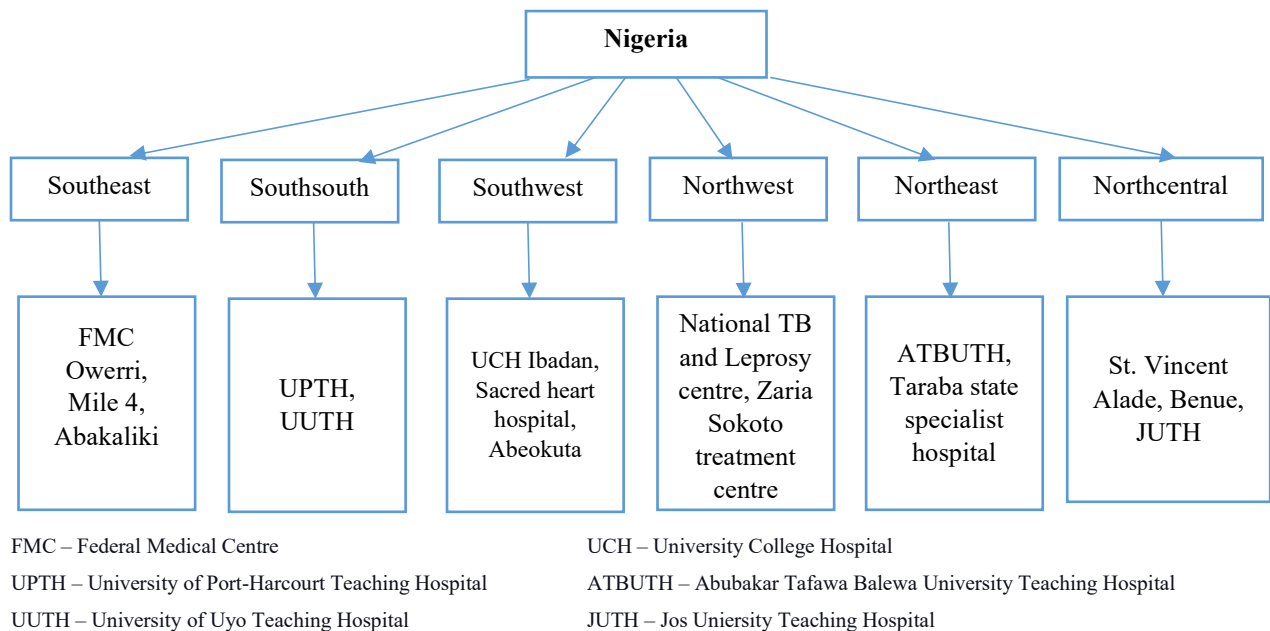


Fig. 1. Selected Study Areas

### *Study Design and Data Collection*

This was a multicentre hospital-based retrospective study designed to identify the outcome of treatment of multidrug-resistant tuberculosis in Nigeria. The medical records of bacteriologically and clinically confirmed MDR-TB patients admitted and treated in MDR-TB treatment centres from across the six geopolitical zones in Nigeria were used for the study. These patients' folders/files were reviewed, and data were collected using a purposively designed proforma. The proforma was used to collect the patient's demographics, date of admission, weight on admission, history of previous treatment of TB, HIV status, date of discharge/stopped treatment, comorbid condition, and treatment outcomes. Treatment outcomes of patients were determined and recorded in their medical records by the health team following standard WHO definitions of MDR-TB treatment performance indicators as cured, treatment completed, died, treatment failed, lost to follow-up, and not evaluated. For this study, however, this was reclassified as:

Successful: These outcomes include cured patients and those who completed treatments

Unsuccessful: Patients who fell in the remaining categories

Patients were contacted using their phone numbers as registered in the patient's medical record, for information not available in the patient's medical records. Patient relatives were contacted when the patient's phone number was not available.

Pharmacists from the MDR-TB treatment centres served as research assistants, undergoing training on data collection using the Microsoft Excel sheet proforma. This training occurred during the quarterly/annual meetings of MDR-TB logistic officers, held every three months before the initiation of data collection.

Data obtained from the study were double entered in an Excel spreadsheet to ensure accuracy and exported into Statistical Package for Social Sciences (SPSS) software, (version 23) for analysis. Frequency of TB admission, frequency of admission by geopolitical zone, and patients' demographics, were analysed using descriptive statistics. Bivariate analysis was carried out to test the association between the dependent variable (treatment outcome) and various demographic and clinical factors. A paired t-test was used to determine the effect of treatment on the weights of the patients before and after admission. An independent t-test was used to determine the sex variations in weight after treatment. One-

way ANOVA was employed to evaluate the age variations in weight after treatment. Further, multivariate logistic regression analyses were performed between treatment outcomes and the demographics, and results were expressed as odds ratios (OR) with a 95% confidence Interval (CI). For all statistical analyses, a p-value of < 0.05 was considered significant.

**Ethical Consideration**

Ethical approval with document number FMC/OW/HREC/VOL.1/10926 was obtained from the Research Ethical Committee of Federal Medical Centre, Owerri, Imo state dated March 19, 2020.

This study primarily utilized existing patients’ data from different centres and consent was obtained from the various study centres to grant the researchers access to patients’ records. Informed consent from patients and/or caregivers was not obtained because of the retrospective record-based nature of the study. However, where a patient or patient relative was contacted for missing information, the study protocol was first

explained to the person and oral consent was obtained through the phone before proceeding with the information gathering. These were essentially declared and approved by the ethical board.

**Results**

*Socio-demographic Characteristics of MDR-TB patients*

The socio-demographic characteristics of the 832 confirmed MDR-TB patients included in this study are presented in Table 1. The average age of the studied patients was 35.30 ± 10.92 with more males than females and the highest number of cases (255 cases) was recorded in the Southwest region of Nigeria. A larger percentage of the patients had just primary (33.9%) and secondary (44.2%) education with more than half (52.6) having a smoking habit. About 61% of the participants denied alcohol use and almost the same number of patients denied the presence of comorbidities with more than two-thirds being HIV negative.

**Table 1:** Socio-demographic Characteristics of MDR-TB patients

Variables	Levels	Frequency (n)	Percent (%)
Age	<35	444	53.4
	35	55	6.6

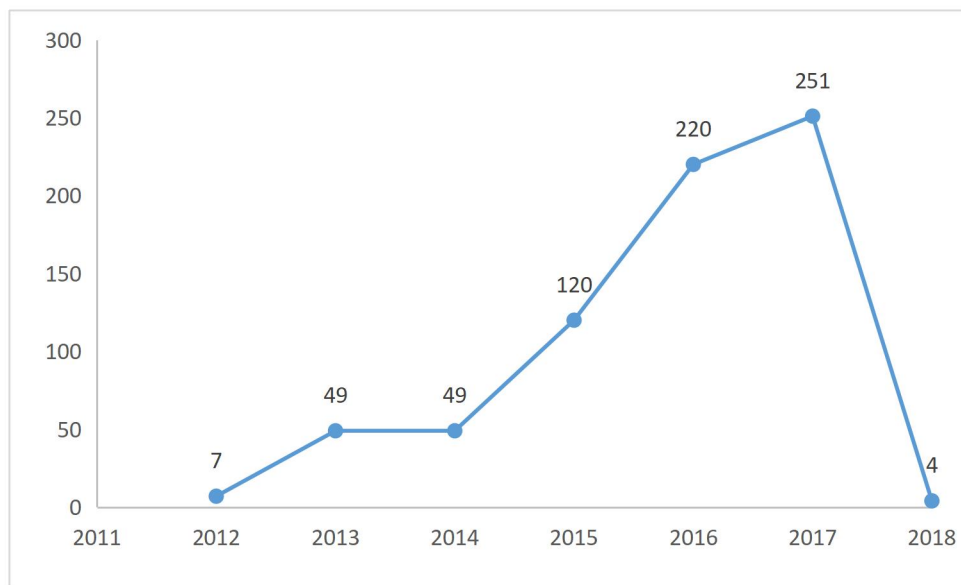
<i>Mean ± SD (35.30± 10.92)</i>	>35	333	40.0	
	<b>Total</b>	<b>832</b>	<b>100.0</b>	
<b>Sex</b>	Male	645	77.5	
	Female	187	22.5	
	<b>Total</b>	<b>832</b>	<b>100.0</b>	
<b>Location</b>	Southsouth	108	13.0	
	Southeast	87	10.5	
	Southwest	255	30.6	
	Northwest	89	10.7	
	Northeast	95	11.4	
	Northcentral	198	23.8	
	<b>Total</b>	<b>832</b>	<b>100.0</b>	
<b>Level of Education</b>	No Formal Education	58	7.5	
	Primary Education	264	33.9	
	Secondary Education	344	44.2	
	Polytechnic	67	8.7	
	HND	16	2.1	
	University Degree	30	3.9	
	NCE	15	1.9	
	<b>Total</b>	<b>778</b>	<b>100.0</b>	
	<b>HIV Status</b>	Positive	145	20.3
		Negative	569	79.7
<b>Total</b>		<b>714</b>	<b>100</b>	

<b>Smoking Status</b>	Yes	253	52.6
	No	228	47.4
	<b>Total</b>	<b>481</b>	<b>100</b>
<b>Alcohol Status</b>	Yes	311	39.6
	No	474	60.4
	<b>Total</b>	<b>785</b>	<b>100</b>
<b>Presence of comorbidities</b>	No	473	62.3
	Yes	286	37.7
	<b>Total</b>	<b>759</b>	<b>100.0</b>

Note that some values did not sum up to 832 because of missing values

*Frequency Distribution of MDR-TB Cases and Treatment Outcomes*

The frequency distribution of MDR-TB over the period of six (6) years and based on the different geopolitical zones in Nigeria were determined and presented in Figure 2 and Table 2 respectively.



132 files show no report on the admission date

**Fig. 2.** Frequency Distribution of MDR-TB by Year

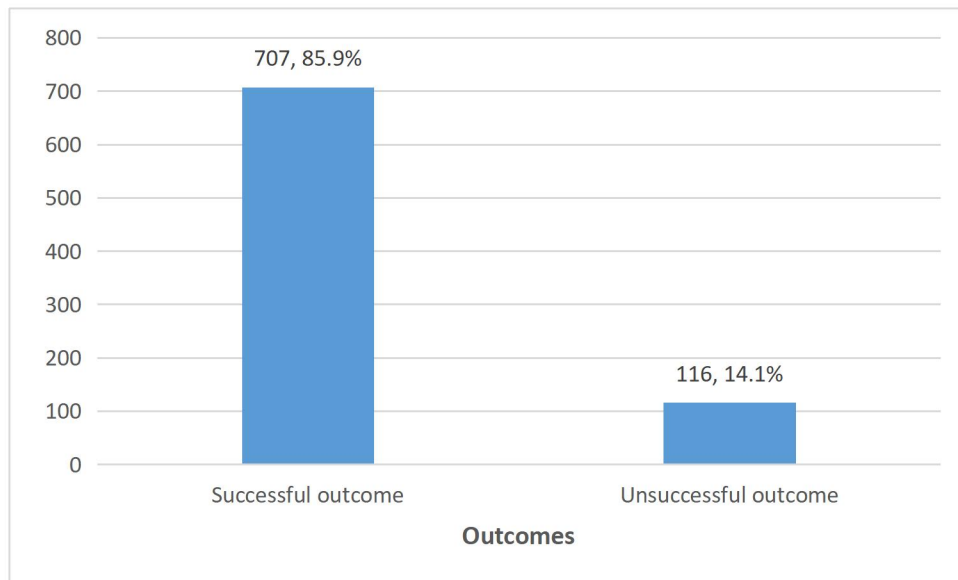


The result indicated an overall increase from 2012 to 2017 with the highest annual registered number of cases (108 cases) recorded in the Southwest in 2017. The Southwest zone also had the highest number (255) of registered MDR-TB patients within the period under study followed by the Northcentral (198) and the Southsouth (100) with the Southeast zone showing the lowest number of cases (11) within the period under study.

**Table 2:** Frequency of Admission by Geopolitical Zone

	2012	2013	2014	2015	2016	2017	2018	Total
Southsouth	7	0	27	23	22	21	0	<b>100</b>
Southeast	0	0	0	0	0	7	4	<b>11</b>
Southwest	0	21	22	27	77	108	0	<b>255</b>
Northwest	0	0	0	16	22	11	0	<b>49</b>
Northeast	0	0	0	9	36	42	0	<b>87</b>
Northcentral	0	28	0	45	63	62	0	<b>198</b>

The frequency distribution of MDR-TB treatment outcomes among the patients (Figure 3) showed a recorded successful treatment outcome of 85.9%.



Note that values did not sum up to 832 because of missing values

**Fig. 3.** Frequency Distribution of MDR-TB Treatment Outcome

*Relationship Between Patients’ Demographics and Outcome of Treatment to MDR-TB*

Bivariate logistic regression analysis conducted to show the association between treatment outcomes of MDR-TB and patient demographic characteristics (Table 3) revealed that age ( $\chi^2=17.167$ ;  $df =2$ ;  $p<0.05$ ), HIV status of patient ( $\chi^2 X=4.291$ ;  $df =1$ ;  $p<0.05$ ), presence of comorbidities ( $\chi^2=11.891$ ;  $df =1$ ;  $p<0.05$ ) and treatment history of patient ( $\chi^2=5.682$ ;  $df = 1$ ;  $p<0.05$ ) were strongly associated with treatment outcomes.

**Table 3:** Bivariate Relationship Between Patients’ Demographics and Outcome of Treatment to MDR-TB

Independent variables	Treatment outcome		Chi square value	Sig.	
	Successful	Unsuccessful			
<b>Age</b>	< 35	395	41	17.167	0.000*
	35	43	12		
	> 35	269	63		
<b>Sex</b>	Male	549	88	0.095	0.758
	Female	158	28		
<b>Location</b>	Southsouth	91	17	10.139	0.071
	Southeast	65	21		
	Southwest	225	30		
	Northwest	77	11		
	Northeast	85	10		
	Northcentral	164	27		
<b>HIV Status</b>	Positive	120	25	4.291	<b>0.038*</b>

	Negative	508	60		
<b>Smoking status</b>	Yes	223	30	0.208	0.648
	No	204	23		
<b>Alcohol status</b>	Yes	272	38	0.319	0.572
	No	408	66		
<b>Presence of comorbidities</b>	Yes	234	51	11.891	<b>0.001*</b>
	No	430	43		
<b>History of treatment.</b>	Yes	460	85	5.682	<b>0.023*</b>
	No	239	25		

\*P<0.05

However, further, multivariate logistic regression analysis (Table 4) showed age (OR: 0.277, CI: 0.078 - 0.979 p=0.046), geopolitical zone of treatment centre (OR: 0.222, CI: 0.049 – 1.000: p=0.050) and presence of comorbidities (OR: 2.240, CI: 1.067 - .4.703: p=0.033) to be significant predictors of treatment outcome. MDR-TB patients less than 35 years showed more likelihood of treatment success compared to older patients. Patients receiving treatment in centres located in South-western Nigeria, showed a greater likelihood of successful treatment (OR=2.567: CI: 0.610 – 10.803) followed by the South-south (OR=1.642, CI 0.552 - .4.884), Northeast (OR=1.546 (0.481 – 4.971) and Northwest (OR=1.054, CI 0.306 – 3.625) compared to the Northcentral. Additionally, patients with comorbidities were about 2.2 times more likely to have a successful treatment than those without comorbidities (OR=2.240, CI 1.067 - 4.703).

**Table 4:** Multivariate Logistic Regression Analysis for Determining Factors that Predict Successful Treatment Outcome of MDR-TB Patients

Predictors	Treatment outcome		Chi square value	OR (CI)	p-value
	Successful	Unsuccessful			

<b>Age</b>	< 35	395	41	17.167	0.824 (0.377 - 1.801)	0.628
	35	43	12		0.277 (0.078 - 0.979)	<b>0.046*</b>
	> 35	269	63			
<b>Sex</b>	Male	549	88	0.095	1.233 (0.524 - 4.884)	0.631
	Female	158	28			
<b>Geopolitical Zone</b>	Southsouth	91	17	10.139	1.642 (0.552 - 4.884)	0.373
	Southeast	65	21		0.222 (0.049 – 1.000)	<b>0.050*</b>
	Southwest	225	30		2.567 (0.610 – 10.803)	0.199
	Northwest	77	11		1.054 (0.306 – 3.625)	0.934
	Northeast	85	10		1.546 (0.481 – 4.971)	0.465
	Northcentral	164	27			
<b>HIV Status</b>	Positive	120	25	4.291	0.599 (0.251 – 1.430)	0.248
	Negative	508	60			
<b>Smoking status</b>	Yes	223	30	0.208	1.169 (0.472 – 2.896)	0.736
	No	204	23			
<b>Alcohol status</b>	Yes	272	38	0.319	1.457 (0.577 - 3.681)	0.426
	No	408	66			
<b>Presence of comorbidities</b>	Yes	234	51	11.891	2.240 (1.067 - 4.703)	<b>0.033*</b>
	No	430	43			
<b>History of treatment.</b>	Yes	460	85	5.682	0.526 (0.233 - 1.240)	0.142
	No	239	25			

Model fit (R square=0.075, sig=0.042); \*significant predictors

Additional analysis showed a general appreciation in the weight of patients by an average of 2.41kg±SD (0.4) following their respective treatment regimens (Table 5). Independent t-statistics show that there is a significant difference in the mean weight between male and female MDR-TB patients with males appreciating by 2.74kg above females and an ANOVA test revealed a

significant difference in the mean weights between the age groups of the patients after treatment (f:2.702; df:2; p<0.05).

**Table 5:** The effect of treatment on the weight of MDR-TB Patients

Variable	Average weight (kg)	N	Difference in weight (kg)	t value	P value
<b>The effect of treatment on the weight of MDR-TB Patients</b>					
Weight on admission	51.48 ± 11.5	763	2.41 ± 0.4	5.863	0.000*
Weight on Discharge/Referral	53.89 ± 11.9	763			
<b>Sex variations on post-treatment of MDR-TB Patients</b>					
Male	54.54 ± 11.7	594	2.74 ± 0.4	2.702	0.007*
Female	51.80 ± 12.2	177			
<b>Sex variations on the post-treatment weight of MDR-TB Patients</b>					
	Average weight (kg)	N	df	f-value	P value
<35	53.29 <sup>a</sup> ± 11.4	420			
35	50.33 <sup>ab</sup> ± 12.4	52	2	2.702	0.005*
>35	55.42 <sup>c</sup> ± 12.3	299			

\*P<0.001      abc=weight differences      df=degree of freedom

## Discussion

The result of this study revealed a varied and progressive increase in MDR-TB cases in the 6 geographical zones of Nigeria with a recorded good treatment outcome of about 85.6%. While age, HIV status, presence of comorbid conditions, and treatment history of patients were associated with MDR-TB treatment outcomes, only age, treatment zone, and comorbid conditions were seen as significant predictors of treatment outcomes.

The study recorded successful treatment outcomes rate of 85.9%, higher than what was reported in other Nigerian studies (Bakare *et al.*, 2021; Dunga *et al.*, 2019) and some other countries including China and Netherlands that reported poor outcomes (Pradipta *et al.*, 2019; Wang *et al.*, 2018). This treatment outcome met both the national target and the standard of  $\geq 75\%$  set by WHO (WHO, 2020). The highly successful treatment outcome could be attributed to the current management

strategies being implemented in Nigeria including admitting the patients and utilization of the Directly Observed Treatment approach in addition to favourable Non-Governmental Organization and Ministry of Health (NGO-MoH) collaborations mirroring what was reported in Ethiopia (Meressa *et al.*, 2015). The availability of improved agents for MDR-TB treatment may also play a big role in the improved outcomes.

Age was found to be a predictor and to be significantly associated with MDR-TB treatment outcomes in this study. Essentially, age as a strong factor in MDR-TB development (Halilu *et al.*, 2013) was found to be strongly associated with an increased risk of MDR-TB progression especially in advancing age (Baya *et al.*, 2019; Sambas *et al.*, 2020). Our present study found patients aged more than 35 years to have less successful treatment outcomes compared to younger patients similar to the findings of other studies (Belachew *et al.*, 2022; Sharma *et al.*, 2020; Panford *et al.*, 2022). Elderly individuals are usually more vulnerable to tuberculosis (TB) and its complications due to the presence of underlying malignant conditions, immunosuppressive therapies, malnutrition, and other age-related health conditions (Belachew *et al.*, 2022).

Furthermore, comorbidity is prevalent among middle-aged and elderly patients, often recognized as a significant contributor to unfavourable treatment outcomes in various medical conditions due to complex factors such as drug-drug interactions and drug-disease interactions as well as lowered immunity (Samuels *et al.*, 2018). Previous research consistently demonstrated that the presence of comorbid conditions heightened the risk of adverse outcomes, including in multidrug-resistant TB treatment (Kim *et al.*, 2008; Yusupova *et al.*, 2016). However, contrary to these findings, our study suggests that the awareness of these predisposing factors might have positively influenced patients, akin to the health belief model. This concept can be explained within the health belief model framework, where older individuals, particularly those with comorbidities, may perceive a higher risk of experiencing adverse outcomes, prompting conscious efforts to mitigate risks and enhance overall health (Kibler *et al.*, 2018). Consequently, it is noteworthy that patients with comorbidities in our study were approximately 2.2 times more likely to achieve treatment success compared to those without comorbidities.

Geopolitical zone/treatment centre was also discovered to be a predicting factor in

successful treatment outcome with patients in the south-western region showing better likelihood of treatment success. This may be attributed to the identified factors influencing access to diagnosis and treatment of TB and MDR-TB in Nigeria including individual factors, family influences, and community-level involvements as well as health systems factors including the availability of equipment and human resources (Oga-Omenka *et al.*, 2020; Oga-Omenka *et al.*, 2021).

Most MDR-TB patients are malnourished and chronically ill (Van Deun *et al.*, 2010), and as such, an increase in weight by 5% is a useful biomarker for treatment success. Overall, patients had a significant change in weight over the course of treatment with an average weight gain of 2.4kg (4.7%) which is close to the expected post-treatment weight gain and could account for increased successful treatment outcomes in the study as prior studies showed that lack of weight gain is associated with worse outcomes (Chung-Delgado *et al.*, 2013; Gler *et al.*, 2013; Putri *et al.*, 2014).

The study showed a persistent increase and high overall percentage distribution in MDR-TB from 2012 to 2017. Other studies have also reported a similar high presence of MDR-TB (Onyedum *et al.*, 2017; Habib *et al.*, 2010; Dunga *et al.*, 2018). The lack of

recorded incidence in some years may be related to the security challenges in the region and the patient's acceptability to be admitted. Similar high percentage distributions in the southwest in 2016 and 2017 have also been previously reported (Adetunji, 2020).

There are some limitations to this study. As a facility-based retrospective study, there were limitations to the quantity and quality of information/data available in the patient's records. However, the availability of contact information for the majority of the patients ameliorated the problem's magnitude. The use of different personnel for data collection may have impaired information uniformity, although, the data collectors were extensively trained before the start of the work.

The identification of predictors and associations allows for a more nuanced understanding of MDR-TB treatment outcomes, enabling a targeted and effective approach to address this public health challenge in Nigeria.

### **Conclusion**

This retrospective study observed increasing and varied cases of MDR-TB disease in the different geographic regions of Nigeria although, with wonderful treatment outcomes. The MDR-TB treatment outcomes were seen to be associated significantly with age, geopolitical zone of the treatment centre, and

presence of comorbid conditions. The high occurrence of MDR-TB in a country already facing a huge epidemic of TB and HIV shows an urgent need for early TB detection and prompt treatment. All detected cases should be admitted and treated in specialized treatment centres.

### **Author Statements**

#### *Ethics Approval and Consent to Participate*

Ethical approval with document number FMC/OW/HREC/VOL.1/10926 was obtained from the Research Ethical Committee of Federal Medical Centre, Owerri, Imo state dated March 19, 2020.

### **Availability of data and materials**

All data files/datasets analyzed are available in the Mendeley database and could be accessed using the URL; <https://data.mendeley.com/datasets/wxfdf7nyg2/1>

### **Competing Interests**

The authors declare that they have no competing interests.

### **Funding**

No funding was received for this research.

### **Authors' Contribution**

SON and KEN designed the study. KEN, IJN and OO was responsible for data collection. MAN, KEN and OO analysed and interpreted the data. SON, OO, MAN and IJN drafted the manuscript. All authors reviewed and approved the manuscript. All Authors have complete access to the study data that support this publication.

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