Prevalence of rifampicin-resistant tuberculosis and its associated factors in a tertiary health care center, South-west Nigeria.

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Research Article

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Abstract

Background Tuberculosis is a chronic disease with associated high morbidity and mortality. In recent decades, there has been an increase in resistance to drugs used in treatment of tuberculosis. This is a major stumbling block in the global fight against tuberculosis. This study was to demonstrate the current prevalence of rifampicin-resistant tuberculosis and its associated predisposing factors in a Teaching Hospital in Nigeria.

Methods This was a cross-sectional retrospective study involving 359 consecutive patients with bacteriologically confirmed tuberculosis seen between January 2015 and December 2019. Ethical approval was obtained from relevant authority. Drug susceptibility testing was performed for rifampicin using GeneXpert MTB/RIF assay. Relevant information was obtained from the clinical records of the patients with use of a well-structured proforma. The data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) version 23.0.

Results There were a total of 359 patients out of which majority, 235 (65.5%) were males. The mean age was 39.78±16.31 (range 1 - 90 years). A larger percentage of the subjects were new cases of tuberculosis (n=312, 86.9%), 49(13.6%) were HIV positive. The overall prevalence of rifampicin resistance found was 2.5% (n=9/359). There was significant association between gender (p=0.005) and re-treatment (p=0.003). There was no significant association between rifampicin resistance and other factors including age and HIV.

Conclusion Male gender and patients on re-treatment for tuberculosis are more at risk of developing resistance to rifampicin in our environment. There is a need to ensure compliance with all guidelines in the management of tuberculosis to prevent an increase in drug resistance.

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by a group of acid fast bacteria called the *Mycobacterium tuberculosis* complex (MTC)(1). It has been decades since the tubercle bacilli was identified and described, and with a consensus agreement on the treatment guidelines(2). Despite the tremendous progress made in diagnosis and management of patients including introduction of rapid diagnostic techniques such as GeneXpert MTB/RIF system(3), tuberculosis is still among the 10 highest causes of death, in the developing world and it is the leading cause of death from an infectious disease(3). The persistent high rate in morbidity and mortality from tuberculosis is in part due to a higher incidence of drug-resistance *Mycobacterium tuberculosis* resulting in more expensive and difficult treatment options(2). In addition, some factors such as poverty, civil unrest or wars in some countries, internally displaced persons (IDP) camps and recently the SARS-CoV-2 pandemic have all resulted into poor life quality. In addition, poor housing systems, overcrowding, malnutrition and inability to access appropriate health care are also contributing to an increase in disease burden and poorer outcomes(3).

There were an estimated 10 million new cases of TB in 2019 and the Africa continent accounted for 25% of these cases(2), some eight countries accounted for two thirds of the total cases globally: India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%)(2).

Rifampicin resistance (RR-TB) is resistance to rifampicin (one of the first line drugs used in treatment of tuberculosis) detected using either phenotypic or genotypic methods, with or without resistance to the other anti-TB drugs(4). It includes any resistance to rifampicin whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance(4). Rifampicin resistance is accepted as a surrogate marker of multidrug-resistant tuberculosis and it often reveals presence of greater than 90% of isoniazid resistance(5).

Multidrug-resistant TB (MDR-TB) is defined as resistance to isoniazid and rifampicin(4). In the past few decades, there was a record of low prevalence of drug-resistant TB in Sub-Saharan Africa(6). However, recent studies have shown an increase in cases of drug-resistant TB on the continent. Some studies have reported a high prevalence of MDR-TB in patients from Nigeria ranging from 4% to 76.4% (7) (8)(9) (10), these studies were done at different times and at different regions in different categories of patients. However, the highest prevalence from these reports were in patients who were previously treated for tuberculosis.

Worldwide in 2019, close to half a million people developed rifampicin-resistant TB (RR-TB), and 78% of these cases were multidrug-resistant TB (2). It was also found worldwide that a large number of the patients with MDR-TB were previously treated tuberculosis patient. The World Health Organization (WHO) reported that globally in 2019, 3.3% of new TB cases and 17.7% of previously treated cases were MDR/RR-TB cases(2). Transmission of Drug-resistant TB is both from person to person and emergence in a previously treated tuberculosis patient(2) and this poses a great challenge in the global fight against tuberculosis.

Despite the success made so far in the control of TB, Nigeria remains one of the 30 high burden TB countries in the world(2). One of the factors negatively affecting the fight against TB is the on-going transmission of Drug-resistant TB(2). It is imperative to carry out surveys to determine the prevalence of resistance to all commonly used drugs in the management of tuberculosis on regular basis, this will aid development of policies in management of patients with tuberculosis.

This study aimed to determine retrospectively the prevalence of rifampicin resistance (RR-TB) and its associated factors in patients who attended the tuberculosis clinic and treatment center at Bowen University Teaching Hospital (BUTH), Ogbomoso between January 2015 and December 2019.

Methods And Materials

Study Design

This was a retrospective cross-sectional study involving the review of the documented records and laboratory results of all patients with tuberculosis seen at the TB/DOTs clinic of BUTH, Ogbomoso. Drug susceptibility testing was performed for rifampicin using GeneXpert MTB/RIF assay. The study period covers from 1st January, 2015 to 31st December, 2019.

Study Site

The study was carried out at the TB/DOTs clinic of BUTH Ogbomoso. This clinic is supported by the National Tuberculosis and Leprosy control programme. On account of its location within BUTH, the clinic serves the people residing within its locality, also people from across the town and neighbouring towns. Ogbomoso is located on latitude 8" 08' 00" East and longitude of 4"16' 00" North of the Equator, and is the second-largest city in Oyo State, Nigeria after Ibadan the State capital.

The patients who had rifampicin resistance (RR-TB) were referred for treatment at the MDR-TB treatment centre University College Hospital, Ibadan but they report back at BUTH for follow up.

Inclusion and Exclusion Criteria

The data of patients of all age group and gender with microbiologically confirmed tuberculosis by GeneXpert MTB/RIF system assay were eligible and included in the study population. Patients who were managed for tuberculosis but did not have GeneXpert MTB/RIF system report were excluded from the study.

Ethical Statement

Ethical approval for this study was obtained from the Research Ethics Committee of BUTH.

Data Management and Analysis

The data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS Chicago Inc., IL, U.S.A). Continuous variables were expressed as means (standard deviation). Relationship between categorical variables was determined using Pearson chi-square. A p-value equal to or less than 0.05 was considered significant.

Results

The clinic had a total of 524 TB cases during the five-year period. Some patients were referred to other centres while some had their diagnosis made by clinical judgement. Only 359 of these patients including both new and re-treatment cases who had GeneXpert MTB/RIF system assay done were included in the study.

The majority of the patients, 235 (65.5%) were males, the mean age was 39.78±16.31 (age range 1 - 90 years) (Table 1). Majority (312, 86.9%) of the patients were newly diagnosed with tuberculosis (Table 1).

Nine (2.5%) of these patients had rifampicin-resistant tuberculosis. There was significant association between male gender and rifampicin resistance, p=0.005 (Table 2). There was also a significant association between treatment category and rifampicin resistance, p=0.003 (Table 2). Re-treatment for tuberculosis is a risk factor. No significant association was observed with age, HIV status and treatment outcome (Table 2).

Table 1: Socio-demographic characteristics

Variables	Frequency (n) n=359	Percentage (%)
Age (in years)		
1 – 20	40	11.1
21 – 40	173	48.2
41 – 60	107	29.8
61 – 80	37	10.3
81 – 100	2	0.6
Gender		
Male	235	65.5
Female	124	34.5
HIV status		
Positive	49	13.6
Negative	310	86.4
Treatment category		
New case	312	86.9
Re-treatment	47	13.1
Outcome		
Successful treatment	308	85.8
Unsuccessful treatment	51	14.2

Table 2: Relationship between rifampicin resistance and patient characteristics

Variables	Rifampicin resistance		Test statistics	P-value
	Yes, n (%) n=9	No, n (%) n=350		
Age				
1 – 20	0 (0.0)	40 (100.0)	$\chi2$=1.918	0.751
21 – 40	6 (3.5)	167 (96.5)		
41 – 60	2 (1.9)	105 (98.1)		
61 – 80	1 (2.7)	36 (97.3)		
81 – 100	0 (0.0)	2 (100.0)		
Gender				
Male	9 (3.8)	226 (96.2)	LR$\chi2$=7.749	**0.005**
Female	0 (0.0)	124 (100.0)		
HIV status				
Positive	2 (4.1)	47 (95.9)	$\chi2$=0.576	0.448
Negative	7 (2.3)	303 (97.7)		
Treatment category				
New	4 (1.3)	308 (98.7)	Fisher's Exact Test	**0.003**
Re-treatment	5 (10.6)	42 (89.4)		
Outcome			$\chi2$=0.073	
Successful treatment	8 (2.6)	300 (97.4)		0.788
Unsuccessful treatment	1 (2.0)	50 (98.0)		

Discussion

The prevalence of rifampicin-resistant tuberculosis (RR-TB) in patients who had GeneXpert MTB/RIF system assay done at our center over the period of review was 2.5% (n=9/359). Resistance to rifampicin was significantly associated with gender (p=0.005) and treatment category (p=0.003), with male patients and patients on re-treatment being more at risk of infection with rifampicin resistance tuberculosis.

A similar study in Nassarawa (11), Delta(12) and Benue(13) states in Nigeria, reported a higher prevalence of 6%, 7.3% and 13.9% RR-TB respectively in patients with tuberculosis. The disparity in the prevalence found could be due to different patient groups, socioeconomic class, sampling methods, period of sampling and regional variations in tuberculosis prevalence. In addition is the higher prevalence of IDP camps in the aforementioned states compared to where this study was carried out.

MDR-TB/RR-TB is found more in patients on re-treatment(2), and in this study, there was a significant association between TB re-treatment and RR-TB (p=0.001). Five (55.6%) of the 9 patients with RR-TB were patients on re-treatment, this is similar to reports from other states reporting a higher prevalence of RR-TB in patients on re-treatment(13)(14). From previous studies, it has been established that acquired resistance to anti-tuberculous drugs is usually from previous exposure to drugs used in treatment of tuberculosis, poor compliance with drug regimen and also a breach in the laid down protocols(15)(16)(17). This could explain the higher prevalence of RR-TB found in patients on re-treatment.

We found a significant association between male gender and RR-TB (*p=0.003*). All nine patients (100%) who had rifampicin-resistant TB were males, this is different from some reports from Southwest and Southeastern part of Nigeria which found no significant association between gender and MDR-TB(10)(18). However, a study done in Delta state, Nigeria also reported the male gender as one of the independent variables in the development of RR-TB(12).

WHO also reported TB to be commoner in male gender and they are at risk of dying from the disease more than women(19). Several factors could be responsible for this including MDR-TB.

There was no significant association between age group and RR-TB in this study. However, a larger percentage 66.7% (n=6) of the patient with RR-TB were within age group 21-40 years, a similar report from Benue state in Nigeria and Ethiopia reported 30 year as the mean age for presentation with RR-TB(13)(5). There was also no significant association between HIV status and infection with RR-TB and this is similar to the report from Delta state in Nigeria, which also found no association between HIV status and RR-TB(12). However, the study done in Nassarawa state with a high prevalence of HIV infection found an association between HIV and RR-TB(11). This disparity could be due to the higher prevalence of HIV infection and subsequent higher prevalence of tuberculosis infection in Nassarawa state(11).

Majority (88.9%, n=8) of the subjects involved in this study were cured, having completed treatment as recommended by the national policy without evidence of failure and with three or more consecutive cultures taken at least 30 days apart remaining negative after the intensive phase as recognized by WHO(4).

Conclusion

Our study found a low prevalence of RR-TB in our community with male gender and re-treatment for tuberculosis as risk factors for development of rifampicin resistance. There is a need to increase

awareness on the threat posed by drug-resistant tuberculosis and encourage more compliance with laid down guidelines in management of tuberculosis. More efforts should also be put in place to ensure accurate diagnosis and prompt treatment of all patients with tuberculosis.

Limitations

1. There was sparse data on occupation/income, housing structure, and history of interaction with confirmed cases of TB/RR-TB. These factors could also have been considered in the assessment of risk factors.
2. There was no culture report for rifampicin resistance nor other drugs used in treatment of tuberculosis which could have contributed to the outcome of the study.

Declarations

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Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

AR, AO and AO were involved in data collection, processing, analysis, Interpretation of data and major contributors in writing the manuscript. TS analysed the samples and interpreted data. AA also contributed in writing the manuscript.

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Data Availability Statement

The datasets used and/or analysed during the study are available from the corresponding author on reasonable request.

Disclaimer

The views expressed in this article are those of the authors and not an official position of the institution.

List Of Abbreviations

TB – Tuberculosis

MTC – Mycobacterium tuberculosis complex

SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2

RR-TB – Rifampicin resistant tuberculosis

MDR-TB – Multidrug resistant tuberculosis

DOTs- Directly Observed Treatment, short-course

BUTH – Bowen University Teaching Hospital

SPSS – Statistical Package for Social Sciences

HIV – Human Immunodeficiency Virus

WHO – World Health Organization

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