

Extra-Pulmonary Presentation of Tuberculosis among Patients Managed for Tuberculosis at a Tertiary Hospital in South-West Nigeria: A Retrospective Study

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Article Submitted: 1st November, 2021. Published 22nd January 2022.

ABSTRACT

Tuberculosis (TB) is one of the infectious diseases responsible for high morbidity and mortality across the world and more so in developing countries. According to WHO, one-third of the world's population is infected with the tubercle bacillus. A large proportion of patients with tuberculosis present with an extra-pulmonary disease which is often misdiagnosed or under-diagnosed. This study aimed to determine the burden of Extra-Pulmonary Tuberculosis (EPTB) and its associated factors in a Tertiary Hospital, South-West Nigeria. This was a cross-sectional, retrospective study involving all the TB cases seen between January 2015 and December 2019. Relevant information was retrieved from the clinical records of patients with the use of a well-structured proforma. Data obtained was analysed using the Statistical Package for Social Sciences (SPSS) version 23.0, and the relationship between categorical variables was determined using chi-square. Five hundred and nine subjects were involved with a mean age of 39.8±16.99 years. Males accounted for 62.1% while 37.9% were females. Sixty-nine (13.6%) participants were HIV positive. Eighty-three (16.3%) had EPTB, of these 38.6% had spinal tuberculosis while 27.7% had pleural tuberculosis, other forms of EPTB accounted for 33.7%. Age, new cases of TB, and smear-negative TB were found to be significantly associated with the development of EPTB. Extra-pulmonary tuberculosis is in existence in the study area and is common in newly diagnosed TB patients. The commonest presentation is spinal tuberculosis.

Keyword: Mycobacterium tuberculosis, Tuberculosis, Extra-pulmonary tuberculosis.



Article Access

Website: www.wjmb.com

 [10.5281/zenodo.5905595](https://doi.org/10.5281/zenodo.5905595)

How to cite this article

Ojewuyi AR, Odeyemi AO, Odeyemi AO. Extra-Pulmonary Presentation of Tuberculosis among Patients Managed for Tuberculosis at a Tertiary Hospital in South-West Nigeria: A Retrospective Study. *West J Med & Biomed Sci* 2022; 3 (1): 81-88. DOI: [10.5281/zenodo.5905595](https://doi.org/10.5281/zenodo.5905595)

INTRODUCTION

Tuberculosis (TB) is a chronic granulomatous disease of mammals. It is a global emergency and a major cause of death worldwide, especially in people with secondary or coexisting illnesses such as Human Immunodeficiency Virus (HIV).⁽¹⁾ This disease is caused by the *Mycobacterium tuberculosis* complex, a closely related group of variants of a single species of acid-alcohol fast bacilli.⁽²⁾ About one-third of the world's population is infected with *M. tuberculosis* and thus at risk of developing tuberculosis⁽¹⁾ as people who are infected by the tubercle bacilli have about a 10% chance of developing the disease in their lifetime.^(1,2) In 2018, about 10 million new cases of tuberculosis were reported from all regions of the world and eight countries accounted for two-thirds of the global total record: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%).⁽¹⁾ These and 22 other countries in WHO's list of 30 high tuberculosis burden countries accounted for 87% of the World's cases.⁽¹⁾

There are many recent advances in the diagnosis and treatment of *M. tuberculosis* infection and as a result, tuberculosis prevalence is on the decline worldwide.⁽³⁾ However, the prevalence of this disease is still high in some low-income and middle-income countries.⁽³⁾ The persistent high prevalence is due to the higher incidence of drug resistance in *M. tuberculosis*, co-infection with HIV and also poverty. Poverty account for some indices such as overcrowding, malnutrition, and inability to access appropriate health care which all, in turn, are responsible for the high disease burden in the low- and middle-income countries.^(1,3)

Extra-pulmonary tuberculosis (EPTB) is tuberculosis occurring at any other part of the body apart from the pulmonary parenchyma.^(4,5) Such site includes lymph nodes, pleura, and osteoarticular systems.^(4,5) Up to 25% of all tuberculosis cases present as extra-pulmonary disease and it is usually from the hematogenous or lymphatic spread of the bacilli to other organs.^(4,5)

Diagnosis of EPTB might be difficult, this is because the presentation is not usually classical as seen in pulmonary tuberculosis, and it might mimic other diseases.^(6,7) Because the patients do not present with the classical symptoms of tuberculosis, the samples obtained from the patient might not be sent for acid-fast bacilli (AFB) staining, assay or identification in the laboratory by the managing physician. Although, the routine AFB stains such as Ziehl-Nelsen and auramine stains allow a quick diagnosis but a high concentration of between 5000 and 10,000 bacilli/ml are needed in the sample before detection by these stains.^(4,6-7) Thus, when such samples are eventually obtained and sent for analysis, it could give false-negative results because of the associated difficulties in obtaining a representative sample from deep-seated infections.^(4,6-7) Histologic diagnosis involving tissue biopsy, enables representative sampling and thus is better in making the diagnosis of EPTB^(4,6-7) but it may not always be feasible. Microbiologic cultures which is the gold standard in the diagnosis of tubercle bacilli⁽⁴⁾ usually takes some weeks before results could be obtained and are not readily available in all local Hospitals. More often, Physicians rely on clinical judgement and radiologic investigations to make diagnoses of EPTB, especially in resource-poor settings.

Some factors such as female gender, black race, and comorbidities such as positive HIV status have been associated with EPTB in studies from some countries like the United States, Taiwan, Turkey, and Portugal.⁽⁸⁻¹¹⁾ However, some available data from West Africa and Nigeria have only reported male gender and positive HIV status as the recognized risks in patients who presented with EPTB.⁽¹²⁻¹⁴⁾

This study investigated retrospectively the burden of EPTB and its associated factors in the patients managed for tuberculosis at a Teaching Hospital in South-West Nigeria over a period of five years.

MATERIALS AND METHODS

Study Site

The study was carried out at TB/DOTs clinic of Bowen University Teaching Hospital, Ogbomoso, Oyo State in Nigeria. This clinic is supported by the National Tuberculosis and Leprosy control program. On account of its location, the clinic serves the people residing within its locality and those from across 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 after Ibadan the capital of Oyo State.

Study Design

This was a retrospective cross-sectional study. The clinical and relevant laboratory records of all patients, including children who were managed for tuberculosis between January 2015 and December 2019 at the centre were included in the study.

Data Collection

Data were collected from records at the Directly Observed Treatment Short-Course (DOTS) treatment centre for tuberculosis and from the clinical and laboratory records of the patients. Diagnosis of tuberculosis in these patients was by detection of *M. tuberculosis* either by Ziehl Neelsen staining, fluorescein staining technique or Gene Xpert MTB/RIF assay done on the clinical specimen from site of infection and by radiological examination. Also, some diagnoses were made based on the clinical judgment of managing physicians as recommended by WHO.⁽¹⁵⁾

Data was collated with the use of a well-structured proforma and relevant information on subjects with tuberculosis was classified under the following headings: biodata and demographic information, results of investigations, and treatment outcome. An effort was made to avoid double data entry and all database was kept strictly confidential by use of a password-protected personal computer.

Ethical Considerations

Ethical approval for the study was gotten from the Ethics and Research Committee of the Hospital (Reference number; BUTH/REC/140).

Definition of terms (according to the WHO)⁽¹⁵⁾

TB case: Either a bacteriologically confirmed biological specimen positive by either smear microscopy or GeneXpert or clinically diagnosed with TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment.

Successfully treated: Good treatment outcome

Poor treatment outcome: This refers to patients who either died or were lost to follow-up or had treatment failure.

Death: A TB patient who died for any reason before starting or during the course of treatment.

Lost-to-follow-up: A patient who did not start treatment or treatment interrupted for 2 consecutive months or more.

Treatment failure: A patient whose sputum smear or culture is positive at month 5 or later during treatment.

Statistical Analysis

The data obtained were analysed using the Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS Chicago Inc., IL, U.S.A). Continuous variables were expressed as means \pm standard deviation [SD]. Frequency distribution tables were used for categorical variables. The relationship between categorical variables was determined using chi-square. A p-value < 0.05 was considered significant.

RESULTS

The clinic had a total of 524 TB cases during the five years. Fifteen of these were excluded from the analysis because they were transferred to other centres to complete their treatment on account of proximity to their places of abode; hence, 509 TB cases were analyzed. The patient age range was between 1 and 90 years, with a mean age of 39.8 ± 16.99 years. There were 316 (62.1%) males, and 193 (37.9%) were females. Sixty-nine (13.6%) patients had HIV co-infection (Table 1). Eighty-three (16.3%) of the subjects had EPTB. Of these, 32 (38.6%) had TB spine, 23(27.7%)

had pleural tuberculosis, 9 (10.8%) had abdominal TB and 10 (12%) patients presented with disseminated TB. There were three (3.6%) cases each of TB meningitis and TB adenitis, two patients had TB pericarditis and there was only one case of miliary TB. (Table 2). Age, treatment category (new cases/retreatment), non-detection of *M. tuberculosis* from a clinical specimen, and treatment outcomes were significantly associated with the occurrence of extrapulmonary TB (Table 3). There was no significant association between gender, HIV status, rifampicin resistance, and EPTB

Table 1: Characteristics of the TB patients

Variables	Frequency (n) n=509	Percentage (%)
Age (in years)		
1 – 20	68	13.4
21 – 40	223	43.8
41 – 60	153	30.1
61 – 80	61	12.0
81 – 100	4	0.8
Gender		
Male	316	62.1
Female	193	37.9
HIV status		
Positive	69	13.6
Negative	440	86.4
Treatment category		
New case	455	89.4
Re-Treatment	54	10.6
MTB detected		
Yes	359	70.5
No	120	29.5
Rifampicin Resistance		
Yes	9	1.8
No	500	98.2
Outcome		
Successfully Treated	426	83.7
Died	62	12.2
Lost to follow-up	7	1.4
Treatment failure	14	2.8

Table 2. Pulmonary and Extra-pulmonary TB Types among the subjects (N=509).

Variables	Frequency	Percentage (%)
Pulmonary TB	426	83.7
Extra-Pulmonary TB	83	16.3
Types of Extra-Pulmonary TB (n=83)		
TB spine	32	38.6
TB meningitis	3	3.6
Pleural TB	23	27.7
Miliary TB	1	1.2
TB pericarditis	2	2.4
TB abdomen	9	10.8
Disseminated TB	10	12.0
TB Lymphadenitis	3	3.6

Table 3: Relationship between Subjects' Characteristics and the Occurrence of EPTB

Variables	Extrapulmonary TB		Test statistics	p-value
	Yes, n (%) n=71	No, n (%) n=329		
Age				
1 – 20	16 (23.5)	52 (76.5)	$\chi^2=14.646$	0.005
21 – 40	23 (10.3)	200 (89.7)		
41 – 60	28 (18.3)	125 (81.7)		
61 – 80	16 (26.2)	45 (73.8)		
81 – 100	0 (0.0)	4 (100.0)		
Gender				
Male	51 (16.1)	265 (83.9)	$\chi^2=0.017$	0.896
Female	32 (16.6)	161 (83.4)		
HIV status				
Positive	13 (18.8)	56 (81.2)	$\chi^2=0.376$	0.540
Negative	70 (15.9)	370 (84.1)		
Treatment category				
New	82 (18.0)	373 (82.0)	$\chi^2=9.248$	0.002
Re-treatment	1 (1.9)	53 (98.1)		
MTB detected				
Positive	16 (4.5)	343 (95.5)	$\chi^2=125.337$	0.000
Negative	67 (44.7)	83 (55.3)		
Rifampicin Resistance				
Yes	2 (22.2)	7 (77.8)	$\chi^2=0.235$	0.628
No	81 (16.2)	419 (83.8)		
Outcome				
Successfully treated	65 (15.3)	361 (84.7)	LR $\chi^2=10.203$	0.017
Died	17 (27.4)	45 (72.6)		
Lost to follow-up	1 (14.3)	6 (85.7)		
Treatment failure	0 (0.0)	14 (100.0)		

χ^2 implies Pearson chi square, LR χ^2 implies like hood ratio chi square

DISCUSSION

In this study, we described some factors such as age, treatment category (new cases/retreatment), non-detection of *M. tuberculosis* from a clinical specimen, gender and HIV status observed in patients with extra-pulmonary tuberculosis (EPTB). In a total of 509 patients with tuberculosis managed at our centre, 83 (16.3%) were found to have EPTB. This finding is similar to reports from previous studies on tuberculosis done in the Northern part of Nigeria and in some West African countries such as Benin and Ghana which reported a prevalence between 9% and 32% for EPTB.^(9,12-13,16) Studies from Korea and the United States have also reported a high prevalence of 20% for both countries while a higher prevalence of 33.4% was reported from China.^(6,17-18)

The differences in the prevalence of EPTB could be a result of the local prevalence of tuberculosis and also in diagnostic capacity available at different centres. Centres with more advanced clinical, radiological, and laboratory support are more likely to make more rapid diagnoses of EPTB.⁽⁷⁾

In this study, we found a significant association ($p=0.005$) between age and the occurrence of EPTB. The highest presentation of EPTB was found in patients between 21-60 years. In contrast, studies from the United States and China have reported higher cases of EPTB in younger female patients.⁽¹⁷⁻¹⁸⁾ This observed difference in the age group with the commonest presentation of EPTB could as well be due to regional variations from one country to another in the prevalence of tuberculosis. There were no cases of EPTB in the geriatric age group above 80 years at our centre, this is not surprising as pulmonary tuberculosis is said to be commoner than EPTB in this age group from previous reports.⁽¹⁸⁾

A majority of the patients managed for tuberculosis, both pulmonary tuberculosis and EPTB at our hospital were males, accounting for 62.1%. However, there was no significant association between gender and EPTB in this study. A report from Northern Nigeria actually

found a higher prevalence of EPTB in men than women.⁽¹⁶⁾ Meanwhile, some other studies from Benin and Ghana in Africa, and some from the United States and China have reported female gender to be a risk factor in the development of EPTB,^(12-13, 17) contrary to findings from this study. However, it is important to note that some of the studies with reports of a higher rate of EPTB in women were done among people of different races, these included women of black race origin who could have emigrated from a tuberculosis endemic region. Also, the local prevalence of tuberculosis in men and women could be responsible for the regional variations in the cases of EPTB found in both genders.

There was no significant association between HIV status and EPTB in this study. A study from the North-Eastern part of the country reported a lower prevalence of EPTB in patients living with HIV.⁽¹⁶⁾ However, several studies have discussed a very close association between HIV infection, tuberculosis, and EPTB in literature over the years,^(8-9, 12-13) with more patients presenting with EPTB in regions with a higher prevalence of HIV.

A significant association was observed between treatment categories and the occurrence of EPTB in this study ($p=0.002$). The majority of the patients who had EPTB at our centre were newly diagnosed with tuberculosis. This is possibly responsible for an overall successful treatment outcome observed in these patients, as well as the low level of rifampicin-resistance tuberculosis found in these patients since they were not previously exposed to TB treatment. The reasons for this association remain to be determined by further studies.

There was a close association between detection/non-detection of *M. tuberculosis* from clinical specimen and EPTB. About 82.7% of the patients with EPTB were smear-negative, diagnoses in these patients were majorly by clinical assessment, and by radiological methods especially for those with spinal TB. This is an important factor and could be responsible for lower

cases of reported EPTB, not only at our centre but also from other regions⁽⁷⁾ as some cases of EPTB might go undetected clinically.

In this study, tuberculosis of the spine was the commonest presentation of the EPTB cases. Pleural tuberculosis was also fairly common among the patients. Tuberculosis of the bone especially the spine has been reported in several articles from Nigeria, China, the United States and other regions as a very common form of EPTB.^(4, 16-18) TB spine is said to be common as a result of previous haematogenous foci, or a contiguous disease and it could also be by lymphatic spread from pleural disease.⁽²⁾ We, however, observed a lower presentation of tuberculous adenitis than what was reported from Northern Nigeria (16). This is probably because the mean age of the patients in this study is 39.8±16.99 years and lymph node tuberculosis has been documented to be more frequently found in children.^(4, 10, 12, 18)

CONCLUSION

Overall, from this study, we found that EPTB is a common form of tuberculosis in our environment especially among new cases of TB. The patients could present as smear-negative cases.

Recommendations

There should be regular awareness campaigns to inform both the public and healthcare providers on the different forms of presentation of EPTB and more efforts should be put in place to ensure accurate diagnosis and prompt treatment of these patients.

Limitations of the study

Our study involved secondary analyses of data from the TB clinic, the laboratories and patients' clinical records. Consequently, it was not possible to verify the diagnosis of EPTB or assess whether some of the study participants were misdiagnosed as EPTB.

Acknowledgements

The authors acknowledge with gratitude the staff and patients of the Bowen University Teaching Hospital where the study was conducted.

Conflict of interests

The authors declare no conflict of interests.

Authors' contributions

AR, AO, and AO were all involved in data collection, processing, analysis, interpretation of data, and in writing the manuscript. AR wrote the first draft of the article.

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