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Possible Risk Factors Associated with Tuberculosis Treatment Failure Among Patients Attending Tuberculosis Treatment Centers in Kano State, Nigeria

Nabila A.A.[1], Binta M.A.[2], Fatihu A.R.[2,*]

Abstract

The widespread failure of tuberculosis chemotherapy has led to an increase in mortality and morbidity associated with tuberculosis infection. This study was aimed at assessing the possible risk factors associated with tuberculosis treatment failure in patients attending Aminu Kano Teaching Hospital (AKTH) and Infectious Disease Hospital (IDH), Kano State. Treatment outcomes of the 436 tuberculosis patients attending selected hospitals in 2018 were obtained using a retrospective study (review of the medical record). In 2019 consented subjects on TB treatment from the hospital (187 from AKTH and 213 from IDH) were randomly selected and followed up for 5 months to assess the cure and treatment failure rate. A structural questionnaire was employed to document clinical information, sociodemographic data, and other pertinent details. Tuberculosis-positive patients were confirmed by microscopic examination of sputum using Ziehl–Neelsen staining techniques. Subjects with Acid Fast Bacilli positive sputum after 5 months with or without clinical symptoms were considered to have treatment failure. The tuberculosis and drug resistance status of the subjects were confirmed using the GeneXpert System. Of the total number of 400 subjects enrolled (78.5%) had adequate treatment response and (21.51%) had treatment failure based on retrospective and prospective information. Up to (65.1%) of subjects with treatment failure were found to be Rifampicin sensitive and (34.9) were Rifampicin resistant p>0.05. Tuberculosis treatment failure rate was found to be significantly different between widows (53.8%), students (36.0%), primary level of education (73.5%), and between tuberculosis subjects with HIV (28.2%) when compared to subjects with tuberculosis only (p<0.05). Tuberculosis treatment failure was also found to be more common among males (23.9%) than females (19.33%), age group (0-9) years (75.0%), and among subjects with diabetes mellitus (30%), cigarette smokers (22.7%), those taking care by their families (30%) and poor adherence to treatment (47.4%) p>0.05. This study revealed that some factors such as marital status, occupation, western educational level, and HIV status, can predispose individuals to fail treatment and consequently increase the risk of developing drug resistance in a population. Therefore, special attention should be given to this high-risk group during TB treatment in the study area.

***Author for Correspondence**
Fatihu A.R.
E-mail: fatihurufai@gmail.com

[1]Student, Department of Microbiology, Bayero University, PMB 3011, Kano, Nigeria
[2]Faculty of Science, Department of Microbiology, Bayero University, PMB 3011, Kano, Nigeria

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INTRODUCTION

Tuberculosis (TB) is a contagious illness instigated by the bacterium known as Mycobacterium tuberculosis (MTB) [1]. Tuberculosis primarily impacts the lungs but can also affect various other body organs. In most cases, infections remain asymptomatic, referred to as latent tuberculosis.

Approximately 10% of latent infections advance to active disease, which, if not treated, results in mortality in about half of those afflicted [2].

The typical signs of active TB include a persistent cough accompanied by sputum-containing blood, fever, night sweats, and loss of weight [3]. Infections affecting other organs can lead to a diverse array of symptoms [4]. The primary reason for TB is *Mycobacterium tuberculosis* (MTB), a tiny, aerobic, and non-motile rod-shaped bacterium [2]. The pathogen's elevated lipid content contributes to numerous distinctive clinical traits [1]. It undergoes division every 16 to 20 hours, an exceptionally slow pace when compared to most other bacteria that typically divide in less than an hour [5].

Nigeria holds the fourth position among the 22 countries worldwide with a high burden of TB and is the top-ranking country in Africa for this concern [1]. The prevalence of TB and its associated sickness and death has led to the financial hardship of countless families and even entire nations. If the current trajectory persists, no other infectious disease will probably generate as many orphans or inflict as much devastation on families as TB [6, 7].

Even though tuberculosis (TB) is a disease that can be prevented, it continues to be one of the leading ten causes of death on a global scale [8]. Among all the disease burdens that pose a threat to the population, Tuberculosis has emerged as the primary cause of death attributed to a single infectious agent. It remains a significant global public health concern. The incidence of TB was 322 per 100,000 population, it also reported the prevalence of MDR-TB among new TB patients (4.3%) and previously treated cases (25%) [9].

MATERIALS AND METHODS

Study Area

The study is a cross-sectional study conducted in two TB treatment centers located at Aminu Kano Teaching Hospital (AKTH), and Infectious Disease Hospital (IDH) in Kano, Nigeria. Both hospitals are the largest tertiary medical facilities in the state, catering to a population of approximately 1.5 million people and receiving daily patronage of around 300 individuals [10].

Ethical Clearance

Ethical approval for the study was obtained from the ethical review committee of Aminu Kano Teaching Hospital Kano state with reference No. NHREC/31/SUB/2008/AKTH/EC/1245.

Inclusion and Exclusion Criteria

All patients attending AKTH and IDH clinics who are on anti-Tb treatment for 5 months or more with or without clinical symptoms were included in the study and all those who were newly treated were excluded.

Sample Size

Three hundred and sixty-nine (369) was the sample size for the research, but 400 samples were collected. The sample size was calculated using the standard formula based on a prior prevalence study conducted in Zamfara, located in the northwestern region of Nigeria [11].

$N = z^2 \times P(1-P)/d^2$

N = desired sample size
Z = standard normal deviation (usually set at 1.96) which corresponds to 96% confidence
P = incidence rate from past studies 40% [11].
q =1.0 – P
d = absolute error -5%
From the above formula; n = z2pq
$N = (1.96)^2 (0.4) (1.0-0.4) \div (0.05)^2$
N =369

Sample Collection and Processing

The sputum samples were gathered following the procedures outlined in the Standard Operating Procedures (SOP) of the National TB and Leprosy Control Program [12]. Two separate sputum samples were obtained from each patient, with a minimum time interval of one hour, and placed into a sterile, leak-proof falcon tube with a capacity of 50 milliliters.

Patients were advised to rinse their mouths with water and then take 3 to 4 deep breaths, holding each breath for 3–5 seconds before coughing after the final inhalation. They were instructed to expel the sputum into the falcon tube, taking care not to contaminate the outer surface of the tube.

The screw cap of the falcon tube was securely sealed and subsequently cleaned with cotton wool soaked in a tuberculocidal disinfectant, such as Lysol. The volume of the specimen was between 3 ml and 5 ml. The entire sputum specimens were produced in an open and well-ventilated space [3].

AFB Smearing and Microscopy

The AFB smear was performed using the classical Ziehl–Neelsen staining technique. A portion of sputum was picked using an applicator stick and a smear of 2–3 cm oval-shaped was made and allowed to air dry for 15–30 minutes. It was then passed through a flame for 3–4 seconds, repeating this process 3–5 times. 1% carbon fuchsine and 25% sulphuric acid were added, heated for 5 minutes, and washed with water. It was counter-stained using methylene blue (0.1%) and examined under the microscope using an x100 lens under oil immersion. AFB smear negative if they stained bluish while AFB smear positive if they stained red [13].

***Mycobacterium tuberculosis* Rifampicin Assay (Using GeneXpert System)**

The cartridges were marked with the matching specimen ID number. The reagent buffer was introduced to the sputum at a 2:1 ratio using a sterile transfer pipette, after which the lid was resealed, and the samples were stored at room temperature.

Aseptically, 2 milliliters of the processed sputum were transferred into the GeneXpert cartridge, which had been appropriately labeled, using a sterile pipette. Subsequently, the cartridge was inserted into the GeneXpert System, and the results were obtained and interpreted within 2 hours [14].

Retrospective Data Collection

Data abstraction was done from the medical records between January to December 2018. The data were taken from 436 cases in the registry from the clinic of AKTH and IDH Kano. Patients with sputum smear-positive at 5 months or later after the initiation of anti-TB treatment of all age groups of both sexes were included. Subjects with incomplete records were excluded. All data were recorded, and information collected included age, gender, adherence to treatment, marital status, and HIV status [15].

Prospective Data Collection

Sociodemographic, clinical, and other associated factors were recorded on a structural questionnaire, information collected included age, gender, marital status, occupation, highest level of education, alcohol, smoking, and presence of medical conditions including HIV and Diabetes mellitus, other factors include support from family and adherent to treatment [15].

Data Analysis

All data were analyzed by chi-square using statistical software SPSS Version 20 where a value of $p \leq 0.05$ was considered significant.

RESULTS

Table 1 presents the treatment outcome among tuberculosis patients based on retrospective information. 436 patients attending AKTH and IDH were reviewed from the hospitals' records. Up to

Table 1. Treatment outcome among tuberculosis patients based on retrospective information.

Treatment outcomes	Number studies	IDH (%)	AKTH (%)	P-value
Number of subjects with ATR	342	154 (35.32)	188 (43.12)	0.08
Number of subjects with TF	94	52 (11.93)	42 (9.63%)	0.08
Total	436	206 (47.25)	230 (52.75%)	0.08

Key: ATR, adequate treatment response; TF: treatment failure; IDH: Infectious Disease Hospital; AKTH: Aminu Kano Teaching Hospital.

Table 2. Treatment outcome among tuberculosis patients based on prospective information.

Treatment outcomes	Number studies	IDH (%)	AKTH (%)	P-value
Number of subjects with ATR	314	162 (40.50)	152 (38.00)	0.21
Number of subjects with TF	86	51 (12.75)	35 (8.75)	0.21
Total	400	213 (53.25)	187 (46.75)	0.21

Key: ATR, adequate treatment response; TF: treatment failure; IDH: Infectious Disease Hospital; AKTH: Aminu Kano Teaching Hospital.

Table 3. Treatment outcome among tuberculosis patients, based on retrospective and prospective data.

Treatment outcomes	Number studies	RD (%)	PD (%)	P-value
Number of subjects with ATR	436	342 (78.4)	314 (78.5)	0.98
Number of subjects with TF	400	94 (21.6)	86 (21.5)	0.98
Total	836	436 (100)	400 (100)	0.98

Key: ATR, adequate treatment response; TF, treatment failure; RD, retrospective data; PD, prospective data.

Table 4. The Rifampicin susceptibility status of *Mycobacterium tuberculosis* isolates from the subject with treatment failure attending AKTH and IDH.

Susceptibility status	Number studies	AKTH (%)	IDH (%)	P-value
Rifampicin sensitive isolates	56	36 (41.9)	20 (23.3)	0.83
Rifampicin resistant isolates	30	20 (23.3)	10 (11.6)	0.83
Total	86	56 (65.1)	30 (41.9%)	0.83

Key: AKTH, Aminu Kano Teaching Hospital; IDH, infectious disease hospital.

342 (78.44%) patients had adequate treatment response and 94 (21.5%) had treatment failure. Patients from IDH (11.93%) had a significantly higher number of subjects with treatment failure compared to patients from AKTH (9.63%) ($p<0.05$).

Table 2 shows the treatment outcome among tuberculosis patients based on prospective information. Up to 400 samples were screened 187 (46.75%) from AKTH and 213 (53.25%) from IDH, 314 (78.50%) had adequate treatment responses and 86 (21.50%) of the subjects enrolled had treatment failure, based on the two hospitals, there was no significant difference ($p>0.05$) based on prospective data.

Table 3 compares the treatment outcome of the subjects based on retrospective and prospective data. The rate of treatment failure among the subjects was found to be statistically similar ($p>0.05$) from retrospective and prospective information (21.6% and 21.5%).

The rifampicin susceptibility status of *Mycobacterium tuberculosis* from subjects with treatment failure is shown in Table 4. Out of the 86 isolates screened 65.1% were rifampicin sensitive while 34.9% were rifampicin resistant isolates. The rate of Rifampicin resistance was found to be statistically different between the two hospitals ($p>0.05$).

Table 5 shows the occurrence of treatment failure concerning the sex and age of the subjects. Of the total number of 213 males screened 51 (23.9%) had treatment failure and out of 181 female subjects

screened 35 (19.33%) had treatment failure. Age group 0–9 years had the highest rate of TB treatment failure (75%) followed by age group 80–89 years and the least treatment failure rate was found among age group 60–69 years ($p>0.05$).

Likewise, Table 6 presents the occurrence of treatment failure concerning marital status, occupation, and educational level. TB treatment failure was higher in widows with a rate of 53.85% followed by divorcees with a TB treatment failure rate of 28.55%. The lowest treatment failure rate was found in married 20.1%. Based on occupation, the treatment failure rate was higher in students (36.0%) followed by farmers (27.9%), and the lowest treatment failure rate was found in the unemployed (6.9%), with regards to educational level, the highest TB treatment failure rate was higher in those with primary level of education with a rate of 73.5% followed by subject with non-formal educational status with TB treatment failure rate of 41.86% and the least was found in those with tertiary level of education with TB treatment failure rate of 4.9% ($p<0.05$).

Table 7 shows the treatment outcome concerning the HIV status of the subjects. Positive HIV had the highest TB treatment failure rate of 49 (28.2%) and the lowest treatment failure rate of 18.3% was found in subjects with negative HIV ($p<0.05$).

Table 5. Occurrence of tuberculosis treatment failure concerning age and sex of the subjects.

Age	Number of subjects enrolled		Number of subjects with treatment failure (%)			Number of subjects with adequate treatment response (%)	Total
	M	***F***		***M***	***F***		
0–9	4	0	3 (75.0)	3	0	1 (25.0)	4
10–19	19	25	7 (15.9)	5	2	37 (84.1)	44
20–29	42	41	21 (25.3)	12	9	62 (38.5)	83
30–39	58	58	27 (23.3)	14	13	89 (76.7)	116
40–49	30	28	10 (17.2)	4	4	50 (86.2)	17
50–59	30	20	8 (16.0)	2	1	42 (84.0)	58
60–69	15	7	3 (13.6)	1	2	19 (86.4)	22
70–79	12	5	3 (17.6)	7	3	7 (41.2)	50
80–89	3	3	4 (66.6)	3	1	2 (33.3)	6
	213	181	86	51	35	314	400

P value = 0.00

Table 6. The occurrence of treatment failure with respect to some sociodemographic factors.

Characteristics	Number enrolled	No with treatment failure (%)	No with P-value adequate treatment response (%)
Marital status			
Married	223	45 (20.1)	178 (79.8) 0.001
Single	157	32 (20.4)	125 (72.1)
Widow	13	7 (53.8)	6 (46.1)
Divorced	7	2 (28.5)	5 (71.4)
Occupation			
Civil Servant	28	7 (25.0)	21 (75.0) 0.025
Farmer	68	19 (27.9)	49 (72.1)
Business	161	37 (22.9)	124 (77.0)
Housewife	60	10 (10.0)	54 (90.0)
Student	25	9 (36.0)	16 (64.0)
Unemployed	58	4 (6.9)	50 (93.1)
Western educational level status			
Primary	34	25 (73.5)	99 (26.6) 0.001
Secondary	120	21 (17.9)	99 (82.5)
Tertiary	82	4 (4.9)	78 (95.1)
None/others	164	36 (21.9)	128 (78.0)

Table 7. The occurrence of tuberculosis treatment failure with respect to the HIV status of the subjects.

HIV status	Number enrolled	Subject with treatment failure (%)	Subject P-value with Adequate treatment response (%)
Unknown	23	6 (26.0)	77 (73.9) 0.00
Positive	110	31 (28.2)	79 (71.8) 0.00
Negative	267	49 (18.3)	218 (81.6) 0.00
Total	400	86	314 0.00

Table 8. Occurrence of tuberculosis treatment failure with respect to cigarette smoking, alcohol consumption, and diabetes mellitus status.

Characteristics	Number enrolled	Number of treatment failure (%)	Number with P-value adequate treatment response (%)
Cigarette smoking			
Yes	344	78 (22.7)	266 (77.3) 0.156
No	56	8 (14.0)	48 (85.7) 0.156
Alcohol consumption			
Yes	0	0 (0)	0 (0) 0.00
No	400	86 (21.5)	314 (78.5) 0.00
Diabetes mellitus			
Yes	10	3 (30)	7 (70) 0.508
No	390	83 (21.3)	307 (78.7) 0.508

Table 9. Occurrence of tuberculosis treatment failure with respect to patient caregivers and treatment follow-up status.

Characteristics	Number enrolled	Number of treatment failures (%)	Number with P-value adequate treatment response (%)
Caregivers			
Family member	390	83 (21.3)	307 (78.7) 0.106
Others	10	3 (30.0)	7 (70.0) 0.106
Adherence to treatment			
Yes	381	77 (20.2)	304 (79.8) 0.508
No	19	9 (47.4)	18 (52.6) 0.508

Moreover, Table 8 also showed that TB treatment failure was higher among those who smoke with the highest treatment rate of 22.7% than those who do not smoke (14.0%), and with regards to diabetes mellitus the highest TB treatment failure rate is in subjects with diabetes (30%) than those with tuberculosis only (21.3%) ($p>0.05$).

Table 9 presents the occurrence of tuberculosis treatment failure with respect to patients' caregivers and treatment follow-up status. Patients not taken care of by their family had the highest number of TB treatment failure rate of 30% compared with those taken care of by their families with a TB treatment failure rate of 21.3%, and with regards to follow-up, subjects not adhering to treatment had the highest rate treatment failure (47.4%) compared to those adhering to treatment (20.2%) ($p>0.05$).

DISCUSSION

This study examined the possible risk factors associated with tuberculosis treatment failure in the TB clinic from two TB treatment centers (AKTH and IDH) in Kano, state- Nigeria. The treatment failure rate in this study is 21.5% based on prospective and retrospective data, this value is slightly lower in another study conducted in Gombe State (22.6%) [16, 17]. The study revealed that 65.1% of subjects with treatment failure were rifampicin sensitive, this confirmed that not all treatment failures are caused

by drug resistance. This necessitates the need to search for other factors associated with treatment failure ($p > 0.05$). Our study shows that tuberculosis treatment failure affects mainly the younger age of 5–10 years old compared to other age groups, and this is in line with previous reports which also revealed a high TB treatment failure rate in children [17, 18]. This might be a result of the lower immunity of the children which could contribute to their poor treatment response. In terms of gender, the males had a higher percentage compared to the females ($p<0.05$). This corresponds with similar findings in southwest Nigeria [19].

This disparity might be because males consume more alcohol and take more cigarette smoking than females which might increase their exposure and influence the rate at which the infection progresses into active disease. However, sociodemographic factors such as marital status, occupation, and knowledge had been identified as major risk factors associated with treatment failure in this study. This contributes to decreased compliance and diminished motivation to finish the treatment regimen, while individuals with a higher level of education showed improved understanding and implementation of the correct approaches for preventing and treating TB. Similarly, to the findings by Salami and Oluboyo [20], who studied sociodemographic factors including education as a medical risk factor for treatment failure, the study contradicts the findings of Hasker et al. [21], who reported none of the sociodemographic factors be associated with treatment failure ($p<0.05$). The findings of this study indicated that a majority of the participants who experienced treatment failure were those with concurrent HIV, TB, and HIV coinfection. This combination represents a highly significant global health issue because it has been documented in various research reports that the presence of both conditions has a detrimental impact on the outcomes of each disease [22]. The elevated rate of treatment failure at 28.2% among TB patients who were also HIV positive, with a significance level of $p<0.05$, was found to be greater than the rate reported in Keffi, North Central Nigeria, which stood at 16.7%. The co-occurrence of tuberculosis and HIV likely played a role in the higher treatment failure rate observed in this research [23].

However, the findings of this study show that there is no significant difference between cigarette smoking and TB treatment failure $p>0.05$ which contradicts the findings of Arora in 2006 [24], who found a strong association between cigarette smoking and TB treatment failure. The study also indicated that patients who were not receiving support from their families experienced a higher treatment failure rate compared to those who were being cared for by their families. This difference could be attributed to the fact that patients who had their medications regularly supervised by family members and received emotional encouragement from them were more likely to exhibit a high level of adherence to their treatment regimen [25, 26]. This phenomenon could be attributed to the psychological burden that TB patients often carry, which includes concerns about the possibility of treatment failure and a lack of confidence in their ability to fully recover from the disease. These factors can impede their commitment to adhering to the treatment regimen [27]. TB treatment failure was also found to be more common among subjects that were non-adherent when compared to subjects that were fully adherent $p>0.05$. Nonadherence to treatment could lead to treatment failure and drug resistance [28]. This could affect the effort towards eradicating TB [29, 30].

CONCLUSION

It has been concluded from the findings of this study that tuberculosis treatment failure in patients attending AKTH and IDH is 21.5%, based on retrospective and prospective data. The study also revealed that up to 65.1% of subjects with treatment failure were Rifampicin sensitive, this confirms that not all treatment failures are due to drug resistance. it was also concluded from the study that tuberculosis treatment failure was most likely among patients who had poor adherence to treatment, cigarette smokers, and diabetes mellitus, and common among age group 5–10 years, males, widows, students, those with primary school level of education, and those with HIV status. These factors can therefore predispose individuals to fail treatment and consequently increase the risk of developing drug resistance.

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