**Risk Factors Associated with Treatment Default Among Tuberculosis Patients in Adamawa State, Nigeria**

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**Abstract**

**Background.** Tuberculosis is an infectious disease caused by bacteria called *Mycobacterium tuberculosis*. The treatment of drug-resistant tuberculosis is complex, costly, and usually has poor outcomes. Treatment default is well known as a very significant factor associated with drug-resistant tuberculosis. **The aim** of this study was to investigate the hazard ratios associated with treatment default among tuberculosis patients in Adamawa State, Nigeria.

**Materials and Methods.** The Cox proportional hazards regression was used to determine the hazard ratios associated with tuberculosis patient treatment default in Adamawa State, Nigeria. The Kaplan-Meier method was used to analyze time-to-event data. The study assessed the survival status and treatment outcomes of tuberculosis patients over a six-month period (January 2019 to June 2019). Data analysis was done using R – Programming Software and the statistical significance was considered at p < 0.05.

**Results.** Out of the 197 (124 males and 73 females) tuberculosis patients, 148 (75.1%) individuals were diagnosed with pulmonary tuberculosis and 49 (24.9%) individuals were diagnosed with extrapulmonary tuberculosis. The treatment outcomes were as follows: 33 (16.8%) patients were cured; 36 (18.3%) individuals completed their treatment; 3 (1.5%) patients died during treatment; 105 (53.3%) subjects defaulted; 8 (4.1%) patients were lost to follow-up; the remaining 12 (6.1%) individuals were still on treatment at the end of the study. According to the Cox proportional hazards analysis, HIV-positive status (p < 0.05, 95% CI [0.361 - 0.879]), primary education level (p < 0.01, 95% CI [1.248 - 3.354]), poor quality of life (p < 0.01, 95% CI [1.239 - 3.511]) and age over 60 years old (p < 0.05, 95% CI [0.569 - 2.206]) were significant hazard ratios to experience the event (treatment default) in the study area.

**Conclusions.** This study revealed that HIV-positive tuberculosis patients, older patients, patients with primary education, and those with poor quality of life are significant risk factors to experience treatment default in the study area. Therefore, it is recommended that stakeholders managing the treatment and care of tuberculosis patients should be dedicated and intentional in the provision of psychosocial therapy to patients with poor quality of life.

**Keywords**

Tuberculosis; Kaplan-Meier Method; Hazard Ratio; Treatment Default; Nigeria

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**Introduction**

Tuberculosis (TB) is an infectious illness caused by bacteria called *Mycobacterium tuberculosis* [1]. According to studies, TB is the most infectious killer worldwide: in 2015, 9.6 million people, including 1.2 million individuals living with human immunodeficiency virus (HIV), fell ill with tuberculosis and 1.5 million people, including 0.4 million HIV-positive patients, died from tuberculosis. The bacterium that causes tuberculosis infection often attacks the lungs, but it can also affect the kidneys, spine, and brain [1]. In 2019, TB remained the leading cause of death due to a single infectious agent. An estimated 10.0 million individuals worldwide contracted TB in 2019, with Nigeria accounting for 4.4 percent of cases [2].
According to the World Health Organization (WHO), in 2020, 9.9 million people contracted TB, while 1.5 million died [3]. Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are two types of drug-resistant TB. The treatment of drug-resistant TB is complex, costly, and usually has poor outcomes [4].

Treatment failure and default are known as very significant factors associated with drug-resistant TB [1]. Several factors might be associated with TB patient treatment default and the median time to default treatment among different categories of patients. Several studies have been undertaken to investigate the relationship between risk factors and TB patient treatment outcomes [5–8]. Researchers employed the Kaplan-Meier survival curve to assess the survival time of TB patients based on the existing literature [9–11]. In Nigeria, however, there is a gap in information about when TB patients would likely default treatment, given that there are several prognosis factors of treatment default among patients receiving TB treatment.

The aim of this study was to investigate the hazard ratios associated with treatment default among TB patients in Adamawa State, Nigeria.

Materials and Methods

Study Design

The design adopted for the study was a retrospective and prospective cohort study, which involved the collection of relevant data from the medical records of patients registered in selected TB treatment centers for 6 months prior to patient progress, as well as monitoring the treatment outcomes. The study was carried out in 12 TB treatment facilities in Adamawa State, Nigeria. These treatment facilities were selected from each of the senatorial zones in Adamawa State - Adamawa North, Adamawa Central, and Adamawa South. In each senatorial zone, four treatment facilities were selected. The 36-Item Short Form Health Survey (SF-36) questionnaires were administered to a cohort of new TB cases in the selected treatment facilities for one month, and these patients were followed up monthly for 6 months to monitor their quality of life (QoL). The time frame of this study was the first week of January 2019 and the last week of June 2019.

Sample Size

At the beginning of the study, in all the 12 selected TB treatment centers, 381 patients diagnosed with either Category 1 TB or Category 3 TB underwent directly observed treatment (DOT). Category 1 TB patients are patients who have been recently diagnosed with TB and have never been treated for TB or those who have taken anti-TB drugs for less than 1 month. Category 3 are smear-negative pulmonary TB patients (other than those in Category 1), and patients with less severe forms of extrapulmonary TB. Consent to participate in the study was given by 333 TB patients. The sample for this research was taken from a cohort of 333 individuals who had consented to take part in the study using the sample size formula [12]:

\[ n = \frac{N \times \chi^2 \times p \times (1-p)}{d^2 \times (N-1) + \chi^2 \times p \times (1-p)} \]

where:

- \( N \): new Category 1 or Category 3 TB patients from the selected TB treatment centers who agreed to participate in the study (333);
- \( p \): expected proportion of TB patients in the population (0.5);
- \( d \): the degree of accuracy expressed as a proportion (0.05);
- \( \chi^2 \): the critical value of chi-square for 1 degree of freedom at the desired confidence level of 0.05 (3.841).

Inclusion Criteria

1. Patients infected with Mycobacterium tuberculosis and treated at a designated TB treatment centre were included in this study.
2. Only new patients were included in the trial; they were people at the age of 18 years or older who had never received TB treatment or used anti-TB medications for more than one month and those who had never received TB treatment prior to current treatment.
3. A patient with Mycobacterium tuberculosis complex was detected in a clinical specimen by culture or a newer approach such as the molecular line probe assay. A pulmonary case was defined as tested positive for acid-fast bacilli (AFB) on another initial sputum smear examination at sites where the laboratory capacity to identify Mycobacterium tuberculosis was lacking.

Treatment Outcome Definitions [13]

1. Cure: A TB patient whose sputum smear or culture is positive at the beginning of treatment but who was smear- or culture-negative over the last month of treatment and at least once before.
2. Treatment failure: A TB patient whose sputum smear or culture is positive at month 5 or later during treatment. TB patients who die because of the disease and those who are found to harbor MDR strain of TB at any time during treatment, regardless of whether they are smear-negative or smear-positive.
3. Default: A TB patient whose treatment was interrupted for two consecutive months or more without medical approval. Those patients withdrew from the study.
4. Transfer out: A TB patient who has been transferred out to another reporting unit and whose treatment outcome is not known.
5. Not evaluated: A TB patient for whom no treatment outcome is assigned.

Censoring

In this study, patients’ data were considered as being censored if the patient did not receive default treatment before the end of the study (6 months) and there was incomplete information about the patient. Subjects whose study times were censored included the following:

1. Patients who died.
2. Patients who were transferred out before they experienced the outcome of interest.
3. Patients who relocated to another treatment centre and whose treatment records were most followed up.
4. Patients who were found to harbour MDR strain of TB at any time during treatment.

Statistical Analysis
This study used the Cox proportional hazards regression [14] to examine the relationship between the hazard ratios and treatment default and the Kaplan-Meier survival analysis [15] to examine the survival time/probabilities of TB patients as compared to different risk factors. Given that there has been no existing record of patients’ QoL, a standard structured health-related QoL (HRQoL) tool, the MOS SF-36, was used to collect data on HRQoL for each of the patients in the study. The independent variables used in this study were age, sex, place of residence, HIV status, education level, type of TB infection, and QoL of patients. The results/outcomes were recorded over several weeks. Data analysis was done using R – Programming Software [16]. A p-value < 0.05 was considered statistically significant.

Results
Socio-Demographic Presentation of TB Patients
A total of 197 patients were included in this study (Table 1). There were 73 (37.1%) females and 124 (62.9%) males. The patients’ marital status showed that a total of 87 (44.2%) patients were married, while 110 (55.8%) patients were single. The HIV status showed that 103 (53.3%) patients were positive, while 94 (47.7%) individuals were negative. There were 92 (46.7%) patients living in rural areas and 105 (53.3%) patients living in urban areas. Based on the type of TB, there were 49 (24.9%) patients with extrapulmonary TB (EPTB), and 148 (75.1%) patients with pulmonary TB (PTB). In terms of education level, 75 (38.1%) patients had no educational background, 55 (27.9%) individuals attended primary school only, 23 (11.7%) patients had the Senior Secondary Certificate of Education (SSCE), 44 (22.3%) patients attended tertiary institutions. Finally, the age group of TB patients showed that 33 (16.8%) patients were less than 20 years old, 57 (28.9%) patients were at the age of 20 to 40 years, 79 (40.1%) patients were at the age of 41–60 years, and 28 (14.2%) subjects were over 60 years old.

Treatment Outcomes of TB Patients
During the follow-up period, 33 (16.8%) patients were cured, 36 (18.3%) patients completed their treatment, 4 (1.5%) individuals died during treatment, 105 (53.3%) subjects defaulted or were lost to follow up, 8 (4.1%) patients required medical transfer and the remaining 12 (6.1%) subjects were on treatment (Table 2).

Adequacy of the Model
Table 3 shows three statistics: the likelihood ratio test, the Wald test, and the Score (log-rank) test with 14 degrees of freedom and very small p-values (p < 0.001) below the 0.05 significance level. All three statistics are, thus, significant, indicating that at least one of the model coefficients is not zero and, thus, the Cox regression model can be used to explain the model explicitly.

According to the Cox proportional hazards analysis, the HIV status (HIV-positive), education level (CPE), and poor QoL were identified as significant risk factors to experience treatment default in the study area (Table 4). However, TB patients at the age of 20–40 years were less likely to default TB treatment. There was a significant difference between HIV-positive and HIV-negative TB patients. HIV-negative TB patients had the hazard ratio of 0.563 (p < 0.05, 95% CI [0.361 - 0.879]). Therefore, HIV pa-

| Table 1. Socio-demographic presentation of tuberculosis patients in the study area. |
|---------------------------------|----------|----------|
| Variables                        | Frequency | Percentage (%) |
| Gender                          |          |           |
| Female                          | 73       | 37.1     |
| Male                            | 124      | 62.9     |
| Type of TB                      |          |           |
| EPTB                            | 49       | 24.9     |
| PTB                             | 148      | 75.1     |
| HIV status                      |          |           |
| Positive                        | 103      | 52.3     |
| Negative                        | 94       | 47.7     |
| Age group                       |          |           |
| <20 years old                   | 33       | 16.8     |
| 20 – 40 years old               | 57       | 28.9     |
| 41 – 60 years old               | 79       | 40.1     |
| Over 60 years old               | 28       | 14.2     |
| Marital status                  |          |           |
| Married                         | 87       | 44.2     |
| Single                          | 110      | 55.8     |
| Place of residence              |          |           |
| Rural                           | 92       | 46.7     |
| Urban                           | 105      | 53.3     |
| Education level                 |          |           |
| No formal education             | 75       | 38.1     |
| Primary (CPE)                   | 55       | 27.9     |
| Secondary (SSCE)                | 23       | 11.7     |
| Tertiary                        | 44       | 22.3     |

| Table 2. Treatment outcomes of TB patients. |
|---------------------------------|----------|----------|
| Treatment Outcome              | Frequency | Percentage (%) |
| Cured                           | 33       | 16.8     |
| Completed treatment             | 36       | 18.3     |
| Died                            | 3        | 1.5      |
| Defaulted                      | 105      | 53.3     |
| Transferred out                 | 8        | 4.1      |
| On treatment                    | 12       | 6.1      |

| Table 3. Testing the global null hypothesis. |
|---------------------------------|----------|----------|
| Test                            | χ²        | DF  | p-value   |
| Likelihood ratio test           | 58.69    | 14   | <0.0001  |
| Wald test                       | 53.69    | 14   | <0.0001  |
| Score (log-rank) test           | 59.62    | 14   | <0.0001  |
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Table 4. Parameter estimate for the Cox proportional hazards regression.

| Variable               | Coefficient | Standard Error of the Coefficient | Z-Value | P-Value | Hazard Ratio Exp (Coefficient) | 95% CI Lower | 95% CI Upper |
|------------------------|-------------|-----------------------------------|---------|---------|--------------------------------|--------------|-------------|
| Gender                 |             |                                   |         |         |                                |              |             |
| Female (ref)           |             |                                   |         |         |                                |              |             |
| Male                   | 0.273       | 0.238                             | 1.146   | 0.252   | 1.314                          | 0.824        | 2.096       |
| Type of TB             |             |                                   |         |         |                                |              |             |
| EPTB (ref)             |             |                                   |         |         |                                |              |             |
| PTB                    | -0.226      | 0.264                             | -0.857  | 0.391   | 0.798                          | 0.476        | 1.338       |
| Marital status         |             |                                   |         |         |                                |              |             |
| Single (ref)           |             |                                   |         |         |                                |              |             |
| Married                | -0.058      | 0.209                             | -0.275  | 0.783   | 0.944                          | 0.626        | 1.423       |
| HIV status             |             |                                   |         |         |                                |              |             |
| HIV-positive (ref)     |             |                                   |         |         |                                |              |             |
| HIV-negative           | -0.574      | 0.563                             | -2.531  | 0.011*  | 0.563                          | -0.361       | 0.879       |
| Age group              |             |                                   |         |         |                                |              |             |
| <20 years old (ref)    |             |                                   |         |         |                                |              |             |
| 20 – 40 years old      | -0.659      | 0.322                             | -2.049  | 0.041*  | 0.517                          | -0.275       | 0.972       |
| 41 – 60 years old      | -0.039      | 0.299                             | -0.13   | 0.897   | 0.962                          | 0.535        | 1.731       |
| Over 60 years old      | 0.114       | 0.346                             | 0.329   | 0.742   | 1.121                          | 0.569        | 2.206       |
| Place of residence     |             |                                   |         |         |                                |              |             |
| Rural (ref)            |             |                                   |         |         |                                |              |             |
| Urban                  | -0.158      | 0.213                             | -0.739  | 0.459   | 0.854                          | 0.563        | 1.297       |
| Education level        |             |                                   |         |         |                                |              |             |
| None (ref)             |             |                                   |         |         |                                |              |             |
| Primary                | 0.713       | 0.252                             | 2.838   | 0.004*  | 2.046                          | -1.248       | 3.534       |
| Secondary              | 0.293       | 0.325                             | 0.899   | 0.368   | 1.339                          | 0.708        | 2.534       |
| Tertiary               | -0.169      | 0.327                             | -0.515  | 0.606   | 0.845                          | 0.445        | 1.604       |
| Quality of life        |             |                                   |         |         |                                |              |             |
| Excellent (ref)        |             |                                   |         |         |                                |              |             |
| Very good              | -0.296      | 0.319                             | -0.927  | 0.354   | 0.743                          | 0.398        | 1.391       |
| Fair                   | 0.213       | 0.313                             | 0.681   | 0.496   | 1.237                          | 0.671        | 2.283       |
| Poor                   | 0.735       | 0.266                             | 2.768   | 0.005*  | 2.086                          | -1.239       | 3.511       |

Note: * significant at p<0.05.

Fig. 1 shows the HIV status of TB patients. Despite the wide differences in the HIV status of TB patients, the p-value of the likelihood ratio (p < 0.01, 95% CI [1.248 - 3.54]) times more likely to default TB treatment than those with no education. According to patients’ QoL, patients with poor QoL were about 2 (p < 0.01, 95% CI [1.239 - 3.51]) times more likely to default TB treatment than those with excellent QoL.

In Table 5, the median survival time before defaulting TB treatment for HIV-positive patients in the study was 9 weeks (95% CI [7 - 11]) as compared to 12 weeks (95% CI [9 - 16]) for patients without HIV/AIDS. This implies that patients without HIV/AIDS appear to have a survival advantage over their counterparts.

Fig. 2 shows education status of TB patients. The p-value of the likelihood ratio (p < 0.001) test indicated that there was a significant difference between the survival curves. TB patients with no educational background had a better chance of surviving at the initial stage only, while TB patients who attended tertiary institutions had a significantly better chance of surviving treatment default as compared to HIV-negative TB patients. The Kaplan-Meier survival plot revealed that there was a significant difference between the patients’ HIV status (Fig. 1). The curve did not overlap from the beginning to the end of the study and HIV-positive patients continued to record more treatment default and had less chance of surviving treatment default than their classical counterparts (i.e., HIV-negative patients). Therefore, we can remarkably say that the HIV status is a significant factor for determining patient survival trends in the study area.

Figure 1. Kaplan Meier survival plot according to the HIV status.
Table 5. Estimate for the median survival time (in weeks).

| Factors          | n   | Events | Median | 95% CI Lower | 95% CI Upper |
|------------------|-----|--------|--------|--------------|--------------|
| HIV status       |     |        |        |              |              |
| Positive         | 103 | 69     | 9      | 7            | 11           |
| Negative         | 94  | 36     | 12     | 9            | 16           |
| Age groups       |     |        |        |              |              |
| <20 years old    | 33  | 20     | 9      | 7            | 14           |
| 20 – 40 years old| 57  | 41     | 16     | 6            | 21           |
| 41 – 60 years old| 79  | 25     | 14     | 8            | 19           |
| Over 60 years old| 28  | 19     | 8      | 7            | 16           |
| Education level  |     |        |        |              |              |
| None             | 75  | 40     | 7      | 6            | 13           |
| Primary          | 55  | 35     | 9      | 7            | 16           |
| Secondary        | 23  | 16     | 12     | 10           | 18           |
| Tertiary         | 44  | 17     | 14     | 9            | 21           |
| Quality of life  |     |        |        |              |              |
| Excellent        | 43  | 26     | 18     | 11           | 21           |
| Good             | 46  | 28     | 13     | 8            | 17           |
| Fair             | 36  | 21     | 9      | 7            | 16           |
| Poor             | 72  | 20     | 6      | 4            | 12           |

Figure 2. Kaplan Meier survival plot according to education level.

Figure 3. Kaplan Meier survival plot according to quality of life.

Figure 4. Kaplan Meier survival plot according to age.

compared to those with primary and secondary education and those who had no educational background. In Table 5, the median survival time for patients with no formal education in the study was 7 weeks (95% CI [6 - 13]), the median survival time for patients with primary education in the study was 9 weeks (95% CI [7 - 16]), the median survival time for patients with secondary education in the study was 12 weeks (95% CI [10 - 18]), while the median survival time for patients with tertiary education in the study was 14 weeks (95% CI [9 - 21]).

According to the Kaplan Meier survival plot in Fig. 3, there was a significant difference according to patients’ QoL. The p-value of the likelihood ratio (p < 0.05) test indicated that there was a significant difference between the survival curves. The graph further revealed that from the beginning of the study, patients with excellent and poor QoL had higher chances of surviving the disease and low probability of experiencing treatment default than those of the median group, i.e., patients with good and fair QoL. Furthermore, patients with excellent QoL were at the peak with the highest probability of surviving as compared to the remaining cohort of patients; this could occur due to the availability of life-support systems, good nutrition, etc. Hence, patients’ QoL is a good indicator for determining patient survival trends in the study area. The median survival time for patients with excellent QoL was 18 weeks (95% CI [11 - 21]), the median survival time for patients with good QoL was 13 weeks (95% CI [8 - 17]), the median survival time for patients with fair QoL was 9 weeks (95% CI [7 - 16]), and the median survival time for patients with poor QoL was 6 weeks (95% CI [4 - 12]). This implies that patients with excellent and good QoL have survival advantage over those with fair and poor QoL as shown in Table 5.

Fig. 4 shows the age groups of TB patients. Despite the wide differences in the age groups of TB patients, the p-value of the likelihood ratio (p < 0.001) test indicated that the difference between the age group survival curves was statistically significant. The survival curve showed that with the increase in TB patients’ age, the survival rate for surviving treatment default decreased. TB patients over 60 years old experienced treatment default more than other age groups. In Table 5, the median survival time for patients less than 20 years of age was 9 weeks (95% CI [7 - 14]), the median survival time for those at the age of 20-40 years was 16 weeks (95% CI [6 - 21]), the median survival time for patients at the age of 41-60 years was 14 weeks (95% CI [8 - 19]), while the median survival time for those over 60 years old was 8 weeks (95% CI [7 - 16]). This implies that patients below 60 years of age have a survival advantage over those over 60 years of age.

**Discussion**

The study assessed the treatment outcomes of TB patients for six months. Overall, 41.2% of patients were either
cured, completed their treatment, or alive throughout the entire period of follow-up, with 33 (16.8%) patients cured, 36 (18.3%) subjects completed their treatment, and 12 (6.1%) patients alive. Surprisingly, 105 (53.3%) TB patients defaulted treatment in the study area. In this study, age (over 60 years of age) has been identified as an important and significant risk factor for treatment default in TB patients. In line with other studies, a higher incidence of treatment default was noted in elderly patients [17–20]. This could be due to the fact that elderly people have more comorbidities, suffer from overall physiological decline with age, are less able to access health care, and are generally poorer than younger populations. The Kaplan-Meier survival curves in these data showed a steep decline in the early days of treatment, this indicated a poor prognosis for the disease. In line with other studies [21–24], this study discovered that poor education could significantly increase the chances of treatment default as well. Furthermore, in this study, HIV-negative TB patients were significantly more likely to not default treatment as compared to HIV-positive TB patients. Accordingly, some studies have shown that the risk of treatment default in TB patients is associated with HIV infection [24–30]. TB and HIV co-infection has been widely reported and linked to a high rate of ineffective TB treatment, including treatment default [31–34]. As TB patients with HIV must take numerous drugs, they may have poor adherence to treatment resulting in treatment default. In this study, the number of men with TB was higher than the number of women with TB, which implies that TB is more common in men. Although the risk factor for defaulting treatment was not significantly attributed to this discovery, however, male sex and being single had already been identified as independent risk factors for TB treatment default in TB patients [35, 36]. Furthermore, patients with excellent QoL were at the peak with the lowest probability of experiencing treatment default as compared to the remaining cohort of patients. Based on the findings of this study, the following recommendations were made:

- Since poor QoL has been identified as the most influential factor for defaulting treatment amongst TB patients receiving treatment, stakeholders involved in managing the treatment and care of TB patients should be dedicated and intentional in the provision of psychosocial therapy to patients with poor QoL; this therapy should be carried out throughout the entire period of treatment of such patients.
- During the period of TB treatment, health professionals should pay more attention to patients with primary education; they are at a higher risk of defaulting treatment.
- Organizations involved in TB management should employ community health volunteers, who will be responsible for ensuring that HIV-positive TB patients, within their communities, adhere to their treatment as prescribed by the doctor and visit the TB treatment centre at the appropriate time to restock their drug.

### Limitations

The study considered only TB cases that were reported in the selected TB treatment centers and medical records of TB patients for a 6-month period, from January 2019 to June 2019. In addition, these data do not represent the total number of TB cases within the state; they represent only the reported cases in the selected health facilities where patients willingly consented to take part in the study.

### Conclusions

This study investigated the hazard ratios associated with treatment default among TB patients in Adamawa State, Nigeria.

This study revealed that HIV-positive TB patients, older patients, patients with primary education, and those with poor QoL are significant risk factors to experience treatment default in the study area.

### Ethical Statement & Informed Consent

After face and content validity, there was obtained ethical approval for the administration of the Medical Outcome Study (MOS) SF-36 questionnaire. In addition, all participants gave their verbal consent to take part in the study. The study considered only TB cases that were reported in the selected TB treatment centers and medical records of TB patients for a 6-month period from January 2019 to June 2019 were collected.

### Conflict of Interest

The authors declare that no conflicts exist.

### Financial Disclosure

The authors declared no financial support.

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