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Research Article

Survival Analysis of Loss to Follow-Up Treatment among Tuberculosis Patients at Jimma University Specialized Hospital, Jimma, Southwest Ethiopia

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Background. Tuberculosis (TB) patients who do not complete treatment pose a potential public health risk through disease reactivation, increased transmission, and development of drug-resistance. This study is aimed at analyzing the time to loss to follow-up treatment and risk factors among TB patients. *Methods*. This was a retrospective cohort study based on record review of 510 TB patients enrolled in Jimma University Specialized Hospital. The Cox's proportional hazard model and Kaplan-Meier curves were used to model the outcome of interest. Loss to follow-up was used as an outcome measure. *Results*. Out of 510 TB patients, 69 (13.5%) were lost to follow-up (LTFU) treatment. The median times of survival starting from the date of treatment initiation were 5.7 months. The majority of LTFU patients interrupted treatment during continuation phase. Treatment LTFU has an association with HIV status, weight, and residence. However, living in the rural area has a cause for LTFU patients on multivariate analysis (HR 4.4, 95% CI 1.58–12.19). *Conclusions*. High rate of LTFU was observed among TB patients in Southwest Ethiopia. Treatment LTFU was more frequently observed among patients who came from rural areas. This underlines the need for distributing TB treatment to the rural area.

1. Introduction

Despite the availability of highly efficacious treatment for decades, tuberculosis (TB) remains a major global public health problem [1]. In 2013, 9 million new cases and 1.5 million deaths were reported due to TB [1, 2]. Over 95% of new TB cases and deaths occur in low- and middle-income countries [2, 3]. Ethiopia ranked 10th among the world's 22 high burden TB countries, having an estimated prevalence of 211 (170–257)/100,000 population [4]. The Ethiopian Ministry of Health (MOH) hospital statistics data showed that tuberculosis is the leading cause of morbidity, the third cause of hospital admission (next to deliveries and malaria), and the second cause of death in Ethiopia, after malaria [4].

Early diagnosis and treatment of TB are essential to reduce morbidity and mortality and interrupt transmission. Ethiopia has adopted the WHO Stop TB strategy, which is reflected in Ethiopia's various policy documents and many implementation guidelines. The directly observed therapy short course (DOTS) was implemented since 1991 in Ethiopia. The national TB control program has currently achieved 100% geographical coverage and 92% of public hospitals and health centers offer DOTS [5].

Correct treatment of tuberculosis aimed at curing the patient, interrupting transmission of tuberculosis to other persons, and preventing bacilli from becoming drug resistant. These aims are not achieved in many regions of the world even when antituberculosis drugs are available [6]. The current anti-TB therapies are fraught with problems, predominantly because of the long-term treatment and the increasing occurrence of drug resistance *M. tuberculosis* strains [7, 8]. Tuberculosis patients who do not complete treatment pose a potential public health risk. Failure to

complete treatment poses a significant public health risk through disease reactivation, increased transmission, and development of drug resistance [9].

Despite the extensive expansion of DOTS services and the massive involvement of health extension workers (HEWs) in TB prevention and control activities, the patients still are failing to complete their treatment to declare cure or complete the treatment [10, 11]. According to WHO 2012 report, considerable TB cases failed after several treatments, many were relapsing and became retreatment after completion of treatment, and many cases are developing MDR-TB among retreatment cases [12]. The reason for this was partly due to treatment lost to follow-up among TB patients.

Loss to follow-up treatment is defined as a TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more [13]. Directly observing patients while they are taking the medication only is not sufficient to prevent TB loss to follow-up treatment. However, a better understanding of the time when TB patients are lost to follow-up treatment and assessment of associated factors influencing loss to follow-up treatment are corner stones for designing time relevant intervention strategies. This study had two main objectives: (i) to determine time to treatment lost to follow-up and (ii) to identify associated risk factors among TB patients in Southwest Ethiopia.

2. Methods

2.1. Study Setting. The study was carried out at Jimma University Specialized Hospital, Jimma zone, Oromia, Southwest, Ethiopia. Jimma town is the main city of Jimma zone and located 350 kilometres away from the capital city, Addis Ababa, in the southwest direction. Jimma town has two governmental hospitals and five health centers which provide health care services for the surrounding community. Jimma University Specialized Hospital (JUSH) is one of the oldest public hospitals in the country. It was established in 1930 E.C during the Italian occupation for the service of their soldiers. It became the only teaching and referral hospital in the southwestern part of the country. It provides services for approximately 9,000 inpatient and 80,000 outpatient attendances. It has a bed capacity of 450 and a total of more than 750 staffs of both supportive members and professionals.

2.2. Diagnosis and Treatment of Pulmonary and Extrapulmonary TB in Ethiopia. In Ethiopia a national TB program follows the DOTS strategy and uses recognized international criteria for the diagnosis and treatment of TB patients [14]. Pulmonary TB diagnosis is made with respect of WHO recommendations [15]. A person having a persistent cough for at least 2 weeks with or without one of the following, night sweet, unintentional weight loss, fever, chest pain, shortness of breath, loss of appetite, and contact with TB patient, is regarded as having presumptive pulmonary tuberculosis. He/she is requested to provide three sputum samples (spot-morning-spot) for acid-fast bacilli microscopy. The spot-morning-spot sample collection over 2 consecutive days is the standard routine for the diagnosis of TB in Ethiopia. Sputum samples are examined using Ziehl-Neelsen staining with light microscopy. Patients with at least one sputum smear positive for acid-fast bacilli are classified as smear-positive pulmonary TB cases.

A patient having (1) symptoms suggestive of TB [14] with at least three initial smear-negative examinations for AFB by direct microscopy and no response to a course of broad-spectrum antibiotics, (2) three smear-negative examinations by direct microscopy, and radiological abnormalities consistent with pulmonary tuberculosis, and decision by a clinician to treat with a full course of antituberculosis are considered as smear-negative pulmonary TB cases.

A patient is considered as having presumptive extrapulmonary TB (EPTB) if he/she has symptoms suggestive of TB related to an extrapulmonary site. Diagnosis of EPTB was based on fine needle aspiration cytology or biochemical analyses of cerebrospinal/pleural/ascitic fluid or histopathological examination or strong clinical evidence consistent with active extrapulmonary tuberculosis, followed by a decision of a clinician to treat with a full course of antituberculosis chemotherapy. In terms of classification, for patients who have TB in both pulmonary and extrapulmonary sites, they are classified as having "pulmonary TB."

All pulmonary and extrapulmonary TB cases are treated with the same standardized first-line antituberculosis regimen. Patients receive daily rifampicin, pyrazinamide, isoniazid, and ethambutol for 2 months (initial phase) followed by daily rifampicin and isoniazid for 4 months (continuation phase). While sputum microscopy examination is performed during follow-up of pulmonary TB patients, those with EPTB are monitored clinically and in particular body weight is measured and recorded during treatment on personal treatment cards (at two, five, and six months).

2.3. Study Design. This was a retrospective cohort study based on record review of patients enrolled in first-line TB treatment under DOTS from September 2011 to September 2013.

2.4. Study Population. All TB patients who were placed under DOTS and started TB treatment from September 2011 to September 2013 in Jimma University Specialized Hospital were our source populations. Among TB patients registered and started anti-TB treatment during study time, 510 TB patients were included and analysed in this study. The sample size of 510 was determined using simple random sampling technique by considering 5% probability value for TB patients lost to follow-up (LTFU).

2.5. Data Collection and Analysis. Demographic and clinical information of 510 TB patients admitted between September 2012 and September 2013 were extracted from the standardized program TB register books of JUSH. Training on record review was given to data collectors for two days before data collection task. The record to be reviewed was pretested for consistency of understanding the review tools and completeness of data items on 5% study subjects. All investigators were supervised every aspect of the review and one physician and one data clerk who worked in TB treatment follow-up room were shouldered the supervision task in

the absence of the investigators. The review checklist filled was gathered and checked for completeness by the principal investigator and supervisors on daily basis.

Information on risk factors for loss to follow-up was obtained from patients' card. Survival time was defined as the time in month from the beginning of treatment to LTFU from tuberculosis treatment as the main or associated cause. Censoring occurred at either the end of the study, complete treatment, or death from other causes. Kaplan-Meier method and log rank test were used to estimate survival probability and statistical significance for categorical covariates. The completed questionnaire was cleaned, coded, and edited before data entry. Descriptive statistics were used to describe frequency, percentage, median, mean, and standard deviation of the study variables. Kaplan-Meier method and log rank test are used to estimate survival probability and statistical significance for categorical covariates.

Cox proportional hazards and log-linear model were applied to estimate the effect of risk factors. Variables selected in the bivariate analysis ($p < 0.25$) and those considered clinically relevant were included in a multivariate model. The assumption of proportional of hazards was check using Schoenfeld residuals. A 95% CI and p value of <0.05 for multivariate and <0.25 for bivariate were considered to be statistically significant.

2.6. Ethics. The study was approved by the research ethic committee of Jimma University, College of Health Sciences, Ethiopia. Letter of permission to collect data was obtained from Jimma University Specialized Hospital administration office. Any information regarding study subjects had a number on it instead of their name and was kept confidential.

3. Results

3.1. Characteristics of Patients. A total of 510 patients who initiated TB treatment from February September 2011 to September 2013 were included in this study. Out of these, 343 (67.3%) were males, 92.5% were from urban areas, and the median age was 24 years. Less than one-third (30%) of TB patients were classified as smear-positive pulmonary TB, 40.2% as smear-negative pulmonary TB, and 29.8% were EPTB cases. One hundred and ten (21.6%) were HIV-positive, 70.2% were negative, and 8.2% had no HIV test result. Regarding their TB treatment history, 481 (94.3%) of the patients were new, 13 (2.5%) were previously treated, and 4 (0.8%) were returned after default. For 12 (1.4%) TB patients their treatment history was not documented. The demographic and clinical characteristics of the TB patients included ($n = 510$) are summarized in Table 1.

3.2. Loss to Follow-Up (LTFU) during Treatment. All TB patients were supposed to start treatment and follow treatment until they were declared as cured or completed. Of 510 TB patients followed, the minimum follow-up time was 1 month and the maximum was 18 months. The mean and median follow-up period were 5.3 and 5.7 months, respectively. Sixty-nine patients (13.5%) were lost to follow-up of their treatment. With regard to timing of LTFU, 21 (30.4%) were lost to follow-up during the first two months of treatment, 32 (46.4%) during the next 3-4 months, and 16 (23.2%) after four months of TB treatment initiation. Time until LTFU treatment among tuberculosis patients ranged from 13 days to 548 days. The prevalence from tuberculosis patients LTFU on this study was 13.5%. The probability of survival after TB treatment at the end of follow-up was 85.48% (95% CI: 82.33–88.63) (Figure 1).

Table 1: Demographic and clinical characteristics of TB patients initiating TB treatment at JUSH, Ethiopia.

Variables	Frequency	Percent
Address of the patients		
Urban	472	92.5
Rural	38	7.5
Sex		
Male	343	67.3
Female	167	32.7
Smear result		
Negative	205	40.2
Positive	154	30.2
Category (patient history)		
New	481	94.3
Retreated	13	2.5
Return after default	4	0.8
Not documented	12	2.4
Types of TB		
Smear-positive PTB	153	30
Smear-negative PTB	205	40.2
EPTB	152	29.8
HIV test/result		
Negative	354	69.4
Positive	114	22.4
Unknown	42	8.2

Key: PTB: pulmonary tuberculosis, EPTB: extrapulmonary tuberculosis.

3.3. Factors Associated with LTFU. Among 69 LTFU treatments, 28 (40.6%) of them were HIV-positive and 41 (59.4%) were negative while, from those censored patients, 317 (71.9%), 82 (18.6%), and 42 (9.52%) were HIV negative, positive, and unknown HIV result, respectively (Figure 1). Out of 472 patients living in urban areas, only 59 (12.5%) of them had LTFU TB outcome while, out of 38 patients living in rural area, 10 (26.3%) had LTFU TB outcome. From 167 female and 343 male patients, 27 (16.2%) and 42 (12.2%), respectively, were LTFU TB treatment. LTFU also more frequently occurred among patients who lost their weight as compared to their counterpart. On Chi-square analysis, living in rural area, being HIV-positive and losing weight were significantly (p value < 0.05) associated with LTFU. However, at 5% probability level, type of TB, patients gender, smear result, and previous TB treatment history were statistically not significant with LTFU (p value > 0.05) (Table 2).

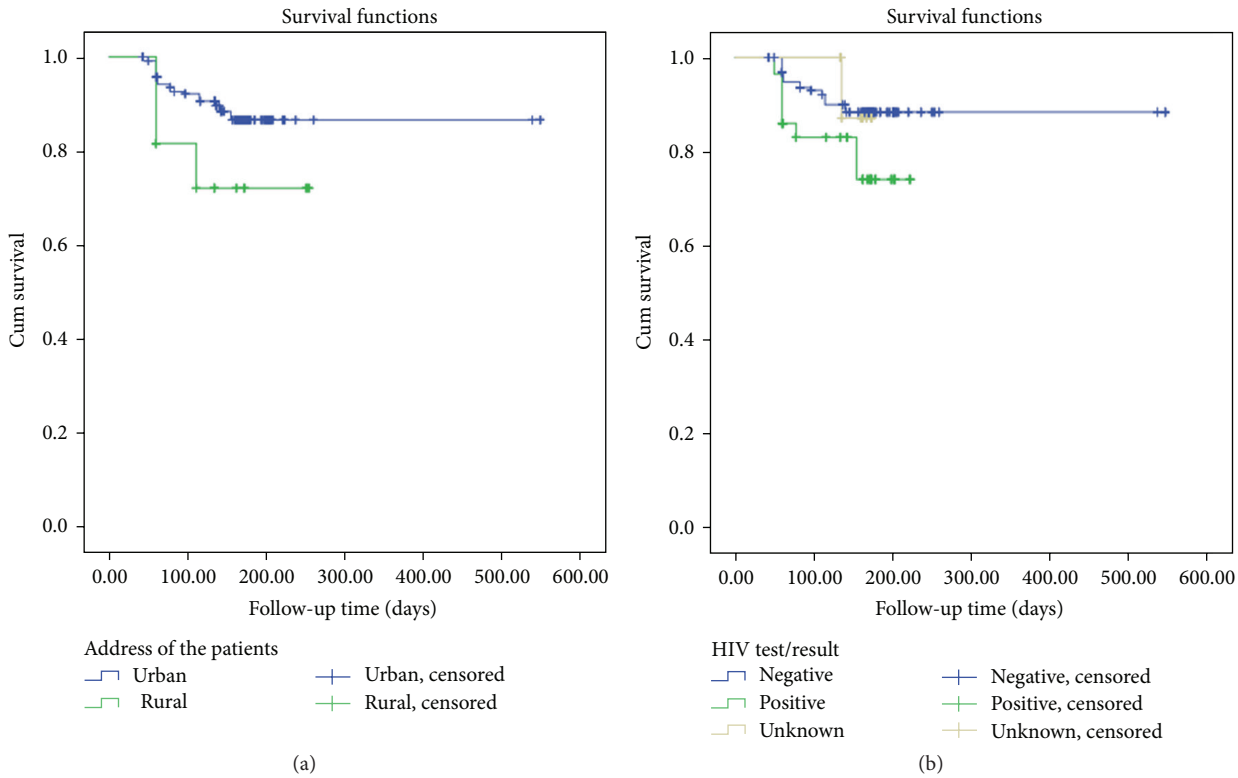

Figure 1: (a) Kaplan-Meier estimate for survival probability stratified for residence, JUSH, Sept., 2011, to Sept., 2013. (b) Kaplan-Meier estimate for survival probability stratified for HIV coinfection, JUSH, Sept., 2011, to Sept., 2013.

Table 2: Chi-square analysis of factors related to TB treatment outcome (censor or LTFU) at JUSH, Ethiopia.

Variables	TB outcome		Chi-square (p value)
	Censor	LTFU	
Address of the patients			
Urban	413 (87.5%)	59 (12.5%)	5.74 (0.017)
Rural	28 (73.7%)	10 (26.3%)	
Sex			
Male	301 (87.8%)	42 (12.2%)	1.48 (0.224)
Female	140 (83.8%)	27 (16.2%)	
Smear result			
Negative	183 (91.0%)	18 (9.0%)	3.2 (0.052)
Positive	133 (84.2%)	25 (15.8%)	
Types of TB			
S (+) PTB	137 (89.5%)	16 (10.5%)	
S (−) PTB	178 (86.8%)	27 (13.2%)	2.92 (0.232)
EPTB	126 (82.9%)	26 (17.1%)	
HIV test/result			
Negative	315 (89.0%)	39 (11.0%)	
Positive	88 (77.2%)	26 (22.8%)	10.87 (0.004)
Unknown	38 (90.5%)	4 (9.5%)	
Weight loss			
No	335 (94.4%)	20 (5.6%)	4.33 (0.037)
Yes	41 (85.4%)	7 (14.6%)	

Key: S (+) PTB: smear-positive pulmonary TB, S (−) PTB: smear-negative pulmonary TB, and ETBP: extrapulmonary TB.

3.4. Risk Factors for LTFU. Cox regression model implies that there was a significant relation between TB outcome and address of the patients. The urban patients had lower hazard ratio (HR, 0.37; 95% CI 0.19–0.73), which implies the risk for LTFU decrease by around 63% as compared with rural patients. Weight loss also has an effect on the risk of LTFU (HR, 2.71; 95% CI 1.15–6.5) which implies that the patients who lost their weight are 2.7 times more likely to have LTFU at 5% level of significance (Table 3). Considering the HIV test, the probability to LTFU difference among HIV result implies no significance difference between unknown and positive test result but there is a difference between negative and positive result (Figure 1).

On univariate analysis, factors associated with LTFU were rural area (HR 4.4, 95% CI 1.58–12.19), being positive for HIV (HR 1.16, 95% CI 0.44–3.04), unknown HIV result (HR 1.68, 95% CI 0.47–5.98), and weight loss (HR 1.94, 95% CI 0.73–5.17). However on multivariate analysis address is the only significant variable at 5% probability level which impels being rural can increase risk of LTFU (Table 3).

Among the variables list on Table 4, HIV status and weight loss have no significant effect on treatment LTFU but address has a significant effect on it which implies that people living in rural areas are 4.4 time more likely to have LTFU as compared to patients who live in urban area.

Factors associated with LTFU were rural area (HR 4.4, 95% CI 1.58–12.19), being positive HIV (HR 1.16, 95% CI 0.44–3.04), unknown HIV result (HR 1.68, 95% CI 0.47–5.98), and weight loss (HR 1.94, 95% CI 0.73–5.17). However

Table 3: The Cox regression analysis of factors associated with LTFU at, JUSH, Southwest Ethiopia.

Variable	Outcome		COR [95% CI]
Censor			
LTFU			
Address of the patients			
Urban	413 (87.5%)	59 (12.5%)	0.375 [0.19, 0.73]**
Rural	28 (73.7%)	10 (26.3%)	1
Sex			
Male	301 (87.8%)	42 (12.2%)	0.74 [0.46, 1.20]
Female	140 (83.8%)	27 (16.2%)	1
Smear result			
Negative	183 (91.0%)	18 (9.0%)	1
Positive	133 (84.2%)	25 (15.8%)	1.72 [0.942, 3.15]
Types of TB			
S (+) PTB	137 (89.5%)	16 (10.5%)	0.56 [0.30, 1.05]
S (−) PTB	178 (86.8%)	27 (13.2%)	0.76 [0.44, 1.31]
EPTB	126 (82.9%)	26 (17.1%)	1
HIV result			
Negative	315 (89.0%)	39 (11.0%)	1
Positive	88 (77.2%)	26 (22.8%)	2.34 [1.4, 3.84]**
Unknown	38 (90.5%)	4 (9.5%)	0.83 [0.29, 2.31]
Total	**441 (86.5%)**	**69 (13.5%)**	
Weight loss			
No	335 (94.4%)	19 (5.6%)	1
Yes	41 (85.4%)	7 (14.6%)	2.710 [1.146, 6.509]*
Total	**376 (93.3%)**	**27 (6.7%)**	

Key: ∗ and ∗∗ shows significant at 5% and 1% probability level respectevelly. COR: crude odds ratio.

Table 4: Lost to follow-up outcome according to a multivariate analysis, JUSH, Sept. 2011 to Sept. 2013.

	B	SE	Wald	df	Sig.	Exp(*B*)	95.0% CI for Exp(*B*)	
							Lower	Upper
HIV			.653	2	.721			
HIV-Positive	.146	.493	.087	1	.768	1.157	.440	3.042
HIV unknown	.517	.649	.636	1	.425	1.678	.470	5.983
Weight loss	.663	.500	1.758	1	.185	1.941	.728	5.172
Rural address	1.480	.521	8.082	1	.004	4.393	1.583	12.186

address is the only significant variable at 5% probability level which impels being rural can increase risk of LTFU (Table 4).

4. Discussion

This is one of the first studies in its kind to determine the survival analysis of LTFU treatment among TB patients in Southwest Ethiopia. In this study, we found that 13.5% of all patients initiating first-line TB treatment during 2011–2013 were LTFU TB treatment. A similar rate of LTFU among TB patients was documented in study done in Kenya [16], in which 146 (13%) of 1094 TB registered patients were lost to follow-up treatment. A systematic review and meta-analysis by MacPherson and colleagues found that pretreatment loss to follow-up was high, from 4 to 38%, and was higher in sub-Saharan Africa (18%) than in Asia (13%), which is consistent with the result of the current study [17]. Studies in other regions of the globe indicate slightly higher rates: in Georgia 29% of all patients initiating treatment for multi-drug-resistant TB were lost to follow-up during treatment [18]. Our 13.5% LTFU rate was substantially higher than the WHO recommended target of less than 5% [12], despite the extensive expansion of DOTS services and the massive involvement of health extension workers in Ethiopia. This calls for more comprehensive approaches to reduce LTFU among TB patients by targeting those risk factors for treatment interruptions.

In our study, 70% of LTFU was documented during the continuation phase. This is due to the fact that patients may feel that they are cured after the intensive phase of treatment

or it may be because of the reason that sputum follow-up was not performed or documented during follow-up. This finding is comparable with findings from Ethiopia that reported that 81% of the defaulters interrupted treatment during the continuation phase [19]. Education should be provided for TB patients about the disease and treatment in order to promote adherence to treatment and counter the spread of multidrug resistance to anti-TB drugs.

Previous studies have identified wide ranges of factors associated with LTFU treatment among TB patients [16–19]. These include age, gender, HIV status, type of TB, smear status, place of residence, tobacco use, economic status, family support, previous history of anti-TB treatment, and body mass index (BMI), just to mention some of them. In the current study we identified three factors such as living in rural area, weight loss, and being HIV-positive that were found to be associated with LTFU treatment among TB patients on univariate analysis. Adjusting for other variables in multivariate analysis, living in the rural area was the only predictor documented for LTFU treatment in the current study. TB patients residing in the rural area were 4.4 times at greater risk of being lost to follow-up TB treatment as compared to patients in urban area. This may be explained by the fact that patients living in the rural area have little access to treatment centers in Ethiopia. Otherwise they have to pay for public transport to reach treatment center, which could not be always possible as people in rural area have lower economic income. This finding is in contrast to studies done in Arsi zone, Ethiopia [19], and Ghana [20], where distance to treatment site was not associated with the risk of treatment LTFU among TB patients.

Though we considered few risk factors due to incomplete data, our results showed no significant differences in terms of gender, age, smear result, type of TB, and previous history of anti-TB treatment between those who completed treatment and those who were classified as LTFU. In the current study, being HIV-positive appeared to be associated with LTFU in univariate but not in the multivariate analysis. However, two earlier studies in Ethiopia [19, 21] reported that HIV-positive patients are more likely to have LTFU treatment compared to HIV-negative patients. The study done in Kenya indicated that LTFU patients are associated with male gender, no salaried employment, lack of family support, and positive TB smear at diagnosis [16]. In contrast to our study, other previous studies documented male sex, older age [22], living in an urban area [23], and being diagnosed with smear-negative but culture-positive tuberculosis [24] as a predictor of LTFU TB treatment. The variation for risk factors between our study and previous studies may be due to difference in sample size, study population, treatment guideline, and regimens.

Our study was not without limitations. We were unable to consider wider risk factors in depth due to incomplete data. In addition, data were obtained from a public health database and some of the information might not be consistently captured. Using data with incomplete information might have also introduced bias. Further comprehensive study that considers wide range of risk factors amongst TB cases classified as LTFU should be warranted.

5. Conclusion

High rate of LTFU treatment was documented among TB patients in Southwest Ethiopia. Living in rural area, being HIV-positive, and losing weight were statistically associated with LTFU treatment on univariate analysis. However, living in the rural area was an independent predictor of LTFU patients on multivariate analysis. TB patients especially those from rural area should be informed about the duration of DOTS and the consequences of interrupting treatment. Moreover, in order to reduce the high rates of LTFU during treatment, health facilities should be distributed to the rural areas and if possible reduce the frequency of patients follow-up to collect the drugs.

Conflict of Interests

The authors declare that no competing interests exist.

Authors' Contribution

Geremew Muleta Akessa conceived and designed the study, analysed and interpreted data, and wrote the initial draft of the paper. Mulualem Tadesse provided overall technical and academic guidance and reviewed the final paper for important intellectual content. Gemeda Abebe helped drafting the paper and reviewed the paper. All authors read and approved the final paper.

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