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Factors Associated with Mortality in Tuberculosis Patients at Debre Birhan Referral Hospital, Ethiopia: A Retrospective Study

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Abstract

Background: Tuberculosis (TB) is the major cause of mortality worldwide and deaths from tuberculosis continue to occur despite the availability of effective antimicrobial agents. Understanding the factors associated with death is important to decrease mortality from TB. Hence, the aim of this study was to assess the magnitude and factors leading to death among TB patients registered at Debre Birhan Referral Hospital, Debre Birhan, Ethiopia.

Methods: This is a retrospective cross-sectional study. Data was obtained by assessing medical records of 262 tuberculosis patients registered at Debre Birhan Referral Hospital from January 2013 to January 2015. Socio-demographic and clinical characteristics of the patients were collected from medical records using data extraction sheet. Chi-square analysis was used to determine the risk factors for TB mortality.

Result: From a total of 262 registered TB patients included in the study, 249 were included in the analysis of which 41(16.5%) died during TB treatment. Of the patients with unsuccessful treatment outcome in this study, death was the most common advsserse TB treatment outcome. TB Mortality was significantly associated with the type of TB, HIV Co-infection, co-morbidity, sputum smear results and time to visit the hospital for diagnosis ($p<0.05$).

Conclusion: The proportion of death among hospitalized TB patients was found to be high and several factors were associated with TB mortality. Hence, monitoring those factors is important to reduce the death rate in TB patients.

Keywords: Tuberculosis; Mortality; Risk factors; Ethiopia

Introduction

Tuberculosis is a chronic infectious disease caused by the bacillus *Mycobacterium tuberculosis*. It commonly affects the lungs but can also affect other sites of the body [1]. Despite the availability of many antibiotics, TB becomes the biggest killer disease in the world [2]. If untreated, it may cause death within 2-3 years [3].

TB is the major cause of morbidity and mortality among infectious diseases worldwide [4] and is one of the top ten causes of death worldwide [1]. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people and an additional 374 000 deaths among HIV-positive people. Overall, Africa and South East Asia account for 85% of the total TB deaths in HIV-negative and HIV-positive people [1]. The incidence of TB in Africa continues to rise, because of the HIV pandemic and poverty [5].

Tuberculosis is a major cause of morbidity and mortality in Ethiopia [6]. Ethiopia is among the top 20 high TB burden countries [1] and among the 27 high MDR (Multi Drug Resistance) TB burden countries in the world [6]. According to the latest WHO report, there were an estimated 182,000 (177 per 100,000) incident cases of TB in Ethiopia in 2016. In the same year, there were an estimated 30,000 deaths (29 per 100,000) due to TB, including HIV related deaths [1]. The treatment success rate of TB among 30 high TB burden countries varied from 71% in Congo to 94% in Cambodia, with an 80% success rate in Ethiopia [1]. Overall, TB is the third cause of hospital admissions and the second cause of death in Ethiopia [3].

The population at greatest risk for TB death include patients with human immunodeficiency virus, patients taking immunosuppressive drugs and people with chronic respiratory disorders, diabetes mellitus, renal failure and malnutrition [7]. Deaths from tuberculosis have been implicated in multidrug resistance, HIV infection, and delayed therapy [8]. Moreover, an increased risk of death in TB patients has been found in co-morbid conditions [9], old age and male gender [10]. Understanding the leading factors of death among TB patients is essential to predict the prognosis of TB patients [9].

A study conducted in Gondar, Ethiopia showed that the treatment success rate of tuberculosis patients was unsatisfactorily low and it became a serious public health concern [11]. Being male, older age [12-14], smear-negative pulmonary or extrapulmonary tuberculosis and being rural resident was associated with lower treatment success rate [4,11]. Therefore, TB control programs should be strengthened to prevent unnecessary deaths [14]. Another study conducted in Nigeria reported that factors that affected the TB outcome negatively were smeared positive status at diagnosis, lack of consent for HIV test, HIV co-infection, and extrapulmonary TB [15]. High HIV prevalence in the population increases the risk of morbidity and mortality from TB. Thus, prevention of HIV should be a priority for TB control and TB

prevention should be priority concerns of HIV/AIDS programmes [16].

Monitoring the outcome of treatment is essential in order to evaluate the effectiveness of the Direct Observation and Treatment Strategy (DOTS) program. Furthermore, understanding the Specific reasons for mortality is important in order to improve treatment systems [17]. Information about the risk factors associated with death caused by tuberculosis is essential to improve the clinical care of TB patients and to enhance the survival of TB patients. Hence, the aim of this study was to determine the magnitude and leading factors of mortality among hospitalized TB patients.

Materials and Methods

Study setting and period

This study was conducted in Debre Birhan Referral Hospital, which is located in Debre Birhan, Ethiopia. The hospital is located 130 km away from Addis Ababa, the capital city of Ethiopia. The institution-based retrospective cross-sectional study was conducted among TB patients registered at Debre Birhan referral hospital from January 2013 to January 2015. This study was conducted from March 15 to April 30, 2018.

Study participants and sampling techniques

The participants of this study were all TB patients who meet the inclusion criteria. The inclusion criteria for this study were all TB patients registered for anti-tuberculosis treatment from January 2013 to January 2015 at Debre Birhan Referral Hospital and those who had complete medical records. Hospitalized TB patients with incomplete data, patients with uncertain diagnosis and patients who were admitted due to other illness were excluded from the current study.

The required sample size for this study was calculated using the statistical formula for single population proportion by taking the proportion of unsuccessful TB treatment outcomes as 19.2% [18], 95% confidence interval, 5% marginal error and adding 10% incomplete recoding as non-response. Hence, a total of 262 records of hospitalized TB patients during the study period were selected using systematic sampling methods.

Data collection procedures and operational definitions

Before the actual data collection, ethical clearance was obtained from the ethical committee of the Department of Public Health, Debre Birhan University and then, permission was obtained from Debre Birhan Referral Hospital Director office. Socio-demographic characteristics and clinical data of the patients were collected from medical records. We have reviewed all medical records of TB patients, who were registered from January 2013 to January 2015. Information for this study was extracted from medical records and TB registry by trained nurses using data extraction sheet.

TB treatment outcomes were classified using the definitions from Ethiopia National Tuberculosis and Leprosy Control Program guideline (NLCP) [3] adapted from the WHO as: cured (when smear-positive patients becomes negative at 1 month before completion of the treatment or at the end of treatment), treatment completed (patients who were completed the medication), failure (a patients who smeared positive after five months), defaulter (patients who took the treatment for at least 1 month and interrupted for at least 2 consecutive months), died (patient who dies for any reason during the course of treatment), transferred out (patients transferred to another health institution to continue the medication) and successfully treated (patients who were cured or completed the treatment).

Data quality control

To ensure the quality of data; training before the data collection was given for data collectors, the principal investigator supervised the data collection process strictly and any error was corrected immediately, data was checked for accuracy, any incomplete data which affects outcome of the study outcome was excluded, all the complete data of the patients were incorporated only during the study period, pre-test was done and necessary modification of the structured data extraction sheet were carried out.

Statistical analysis

After completion of the data collection process, the collected data was entered, cleared and analyzed using SPSS version 20 computer programs. Descriptive statistics were computed to present socio-demographic and clinical characteristics of the study participants. Chi-square analysis was used to assess the association between dependent variable and outcome variables.

Results

Socio-demographic characteristics of study participants

A total of 262 patients diagnosed as TB were included in the study. Of these, 13 (4.9%) patients had incomplete medical records and the data was collected on 249 registered TB patients. The mean age of the participants was 35.5 years, ranging from 3-81 years. Out of the total study participants during the study period, 41 (16.5%) of them died and the remaining 208 (83.5%) of the participants were alive. Majority of the patients 18 (43.9) who died during the course of treatment were found in the age group of 15-44 years, 26 (63.4%) were rural residents and 23 (56.1%) were females. Of the total study participants; 128 (51.4%) were males, 97 (38.9%) had more than high school education and 172 (69.1%) were Orthodox Christian by religion (Table 1).

Variables	All TB patients (N=249) n/N (%)	Died (N=41) n/N (%)	Alive (n=208) n/N (%)
Age (years)			
0-14	15 (6)	6 (14.6)	9 (4.3)
15-44	142 (57.1)	18 (43.9)	124 (59.6)
45-64	81 (32.5)	13 (31.7)	68 (32.7)

≥ 65	11 (4.4)	4 (9.8)	7 (3.4)
Sex			
Male	128 (51.4)	18 (43.9)	110 (52.9)
Female	121 (48.6)	23 (56.1)	98 (47.1)
Religion			
Orthodox	172 (69.1)	20 (48.8)	152 (73)
Muslim	54 (21.7)	11 (26.8)	43 (20.7)
Protestant	12 (4.8)	5 (12.2)	7 (3.4)
Catholic	11(4.4)	5 (12.2)	6 (2.9)
Residence			
Urban	104 (41.8)	15 (36.6)	89(42.8)
Rural	145(58.2)	26 (63.4)	119 (57.2)
Educational level			
Illiterate	44 (17.7)	13 (31.7)	31(14.9)
Primary school	35 (14.1)	10 (24.4)	25 (12)
High school	73 (29.3)	12 (29.3)	61 (29.3)
Certificate and above	97 (38.9)	6 (14.6)	91(43.8)

Table 1: Socio-demographic characteristics of TB patients stratified by their outcome in Debre Birhan Referral Hospital, Debre Birhan, Ethiopia, 2013-2015 (n=249).

Clinical characteristics of the study participants

Out of the total TB cases, 114 (45.8%) were positive for HIV. Among HIV positive TB cases, 85 (40.9%) were in the alive group and the remaining 29 (70.7%) were in the death group. Of those TB patients who died, 26 (63.4%) cases were classified as extra pulmonary, 23 (56.1%) cases had negative sputum smear and 36 (87.8%) cases were late to visit the hospital for diagnosis. From the total study participants, 220 (88.4%) were new cases or had no history of previous TB. The remaining 20 (8%) and 9 (3.6%) were relapse cases and return after defaulting respectively. Chronic comorbidities were common among the TB deaths. The clinical characteristics of both alive and dead individuals are illustrated in Table 2.

Variables	All TB patients (N=249) n/N (%)	Died (N=41) n/N (%)	Alive (n=208) n/N (%)
HIV status			
Negative	135 (54.2)	12 (29.3)	123(59.1)
Positive	114 (45.8)	29 (70.7)	85 (40.9)
Type of TB			
Pulmonary TB	156 (62.7)	13 (31.7)	143(68.8)
Extra pulmonary TB	91(36.5)	26 (63.4)	65 (31.2)
MDR-TB	2 (0.8)	2 (4.9)	0
TB category			
New	220 (88.4)	35 (85.4)	185 (88.9)
Relapse	20 (8)	4 (9.7)	16 (7.7)
Return after default	9 (3.6)	2 (4.9)	7(3.4)

Smear results			
Negative	85 (34.1)	23(56.1)	62 (29.8)
Positive	164 (65.9)	18 (43.9)	146 (70.2)
The interval between symptoms and care seeking			
≤4weeks	72 (28.9)	5 (12.2)	67 (32.2)
>4weeks	177 (71.1)	36 (87.8)	141(67.8)
Co-morbidities			
Yes	105 (42.2)	34 (82.9)	71 (34.1)
No	144(57.8)	7 (17.1)	137(65.9)
Note: TB=Tuberculosis, HIV=Human Immunodeficiency Virus, MDR-TB=Multi Drug Resistance Tuberculosis.			

Table 2: Clinical characteristics of TB patients stratified by their outcome in Debre Birhan Referral Hospital, Debre Birhan, Ethiopia, 2013 to 2015 (n=249).

From the total TB patients, the treatment outcomes were shared to 41 (16.5%) died, 92 (36.9%) treatment completed, 69 (27.7%) cured, 11 (4.4%) failure, 10(4.1%) defaulted and 26 (10.4%) were transferred out to another health facility. During the study period, death was the most common adverse TB treatment outcome (Figure 1).

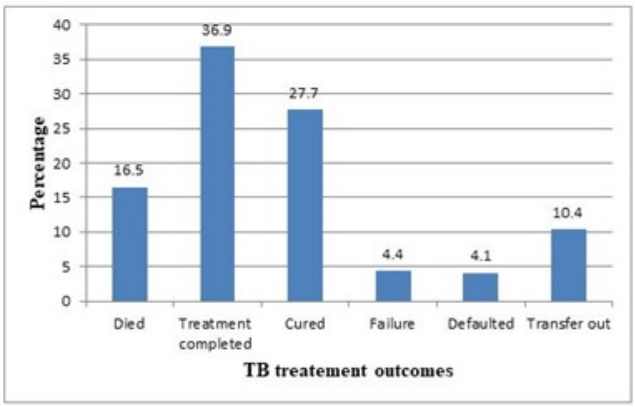

Figure 1: Overall TB treatment outcomes of TB patients who were treated at Debre Birhan Referral Hospital, Debre Birhan, Ethiopia, 2013 to 2015 (n=249).

Clinical symptoms of TB among the study participants

Regarding the clinical symptoms of TB, 176 (70.7%), 203(81.5%), 105 (42.2%) and 204 (81.9%) of the total participants had a history of a cough, night sweating, fever and loss of appetite respectively. About 56.1% of died TB patients had a fever. Night sweating and loss of appetite were reported by 87.8% and 80.5% of died TB patients (Table 3).

Variables	All TB patients (N=249) n/N (%)	Died (N=41) n/N (%)	Alive (n=208) n/N (%)
Cough duration			
≥ 2 weeks	161(64.7)	18 (43.9)	143 (68.8)
<2 weeks	15 (6)	2 (4.9)	13 (6.2)
No cough	73(29.3)	21 (51.2)	52 (25)
Night sweating			
Yes	203 (81.5)	36 (87.8)	167 (80.3)
No	46 (18.5)	5 (12.2)	41 (19.7)
Fever			
Yes	105 (42.2)	23 (56.1)	82 (39.4)
No	144 (57.8)	18 (43.9)	126 (60.6)
Loss of appetite			
Yes	204 (81.9)	33 (80.5)	171 (82.2)
No	45(18.1)	8 (19.5)	37 (17.8)

Table 3: Clinical symptoms of TB patients stratified by their outcome in Debre Birhan Referral Hospital, Debre Birhan, Ethiopia, 2013 to 2015 (n=249).

Factors associated with mortality

The results of the analysis showed that TB deaths were significantly associated with HIV co-infection (X^2=11.66, p<0.001), sputum smear results (X^2=10.52, p=0.003), type of TB (X^2=15.23, p<0.001), co-morbidity (X^2=34.73, p<0.001) and time to visit the hospital for diagnosis (X^2=6.92, p=0.008). The risk of TB death was higher among patients with extra-pulmonary TB, negative sputum smear, presences of co-morbidity, HIV co-infection, and patients who were late for the initial treatment of TB. The percentage of TB death was also higher among female participants and rural residents. However, there was no significant association between TB death and age, sex or residency (p>0.05) (Table 4).

Variables	Death		X2	p-value
	Yes, n (%)	No, n (%)		
Age (years)				
≥ 45	14 (15.2)	78 (84.8)	0.13	0.72
<45	27 (20.8)	130 (82.8)		
Sex				
Male	18 (14.1)	110 (85.9)	0.75	0.37
Female	23 (19)	98 (81)		
Residency				
Rural	26 (17.9)	119 (82.1)	0.49	0.46
Urban	15 (14.4)	89 (85.6)		
HIV status				
Positive	29 (25.4)	85 (74.6)	11.66	<0.001
Negative	12 (8.9)	123 (91.1)		
Type of TB				
Pulmonary TB	15 (9.5)	143 (90.5)	15.23	<0.001
Extrapulmonary	26 (28.6)	65 (71.4)		
Smear results				
Positive	18 (11)	146 (89)	10.52	0.003
Negative	23 (27.1)	62 (72.9)		
TB patient category				
New	35 (15.9)	185 (84.1)	0.28	0.55
Retreated	6 (20.7)	23 (79.3)		
Presence of another comorbidity				
Yes	34 (32.4)	71 (67.6)	34.73	<0.001
No	7 (4.9)	137 (95.1)		
The interval between symptoms and care seeking				
≤4weeks	5 (6.9)	67 (93.1)	6.92	0.008
> 4weeks	36 (20.3)	141(79.7)		
Note: Numerical data in bold indicates the level of significance (p<0.05)				

Table 4: Factors associated with death among TB patients who were treated at Debre Birhan Referral Hospital, Debre Birhan, Ethiopia, 2013 - 2015 (n=249).

Figure 1 shows the distribution of TB deaths across the years during the study period. The percentage of TB deaths has increased from 13 (31.7%) in the year 2015 to 18 (43.9%) in the year 2014 then decreased to 10 (24.4%) in the year 2015 (Figure 2).

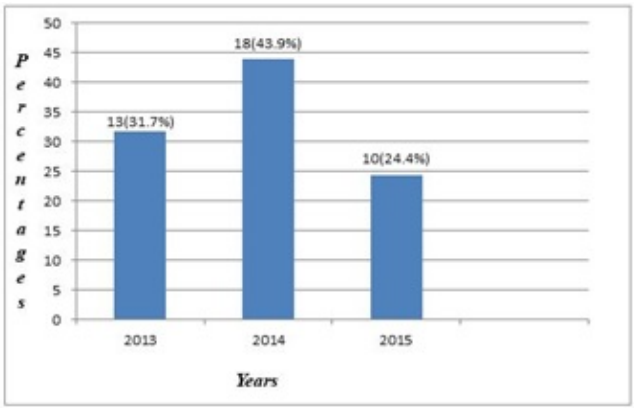

Figure 2: Distribution of death by year of hospitalization for TB patients who were treated at Debre Birhan Referral Hospital, Debre Birhan, Ethiopia, 2013 to 2015 (n=41).

Discussion

TB is the main causes of mortality in different countries. Thus, understanding the leading factors of death among TB patients is important to predict the prognosis of the patients [9]. Hence, this retrospective study investigated the magnitude and leading factors of mortality among TB patients who were treated at Debre Birhan Referral Hospital, Ethiopia.

The treatment success rate of TB in this study was 64.6%, which is less than the 2017 WHO report, where the treatment success rate among 30 high TB burden countries varied from 71% to 94% [1] and the national report of overall treatment success rate in Ethiopia (83.7%) [19]. Moreover, the treatment success rate in the current study is still below the treatment success rate reported in Bahir Dar, Ethiopia, 80.8% [18], Tigray, Ethiopia, 89.2% [20] and China, 88% [12]. The low treatment success rate observed in this study might be due to a high death rate (16.5%) and transferred out rate (10.4%).

Of the patients with unsuccessful treatment outcome in this study, death was the most common adverse TB treatment outcome. Hence, this study showed that the overall prevalence of mortality in TB patients was 41(16.5%). This finding is comparable with the previous study conducted in Bahir Dar, Ethiopia [18], Finland [21] and Zimbabwe [22], in which the proportion of died TB patients were 14.6%, 17.2%, and 16% respectively. However, it was lower than the prevalence of 29.4% in Cameroon [23] and 25% in Nigeria [15]. A study from Sidama, Ethiopia [24], Dangla, Ethiopia [25], Iran [9] and India [26] reported a prevalence of mortality among TB patients as 8.9%, 7.4%, 10.5% and 6% respectively. These variations from the current study might be due to the difference in the study population, sample size and study design. The death rate in this study was high in 2014 but decreased in the subsequent year. In line with a previous study [18], this decrement might be due to an improved prevention and control program of tuberculosis. But, further long studies are required to confirm the trends of death among TB patients.

This study evaluated the factors associated with mortality in patients with tuberculosis. The findings of the current study showed that several factors were associated with death in TB patients. One of the factors which significantly associated with death is HIV co-infection.

The result indicated that TB mortality was higher in HIV positive cases than in HIV negative cases. Several studies from different parts of the world [10,22,23,27-29] showed that being positive for HIV is the most common risk factor for mortality. This might be due to suppression of the immune system by HIV infection. As the immune system is suppressed, it leads to dissemination of TB to the other body organs which often carries a high risk of death and unfavorable prognosis [30]. Moreover, it might be due to drug mal-absorption among HIV patients 18] and delay in starting ART [31]. Additionally, previous studies conducted in different countries reported that mortality was high among patients who are not on ART [32-34] and those with low CD4 counts [23,24]. But, data on ART status and a CD4 count of the participants was incomplete and not included in this study.

The present study showed that the risk of mortality was higher among extra-pulmonary TB cases than in pulmonary TB cases. In agreement with this finding, a study conducted by Zenebe et al. [18] and Babatunde et al. [15] showed that the most unsuccessful outcome of TB treatment was observed in extra-pulmonary TB patients. Similarly, another study conducted by Djouma et al. [35] found an increased risk of death in extra-pulmonary TB cases. This might be due to delay in the diagnosis of EPTB or even missing the diagnosis completely [36]. Hence, EPTB patients will deteriorate more rapidly and have higher death rates as compared to pulmonary TB cases [31,37].

This study showed a significant association between sputum smear result and risk of death among TB patients. Consistent with other studies [11,27,38], the result of the current study found that smear-negative TB patients had a higher risk of mortality than smear-positive cases. This might be due to delay in diagnosis of smear-negative sputum TB patients [39,40].

Co-morbidity was significantly associated with mortality in our study. In line with the current study, co-morbidity was previously reported as a risk factor for mortality among TB patients [14,23,28,41]. The most common co-morbidity that were associated with mortality among TB patients were listed in previous studies and it includes diabetes mellitus, anemia [9], malignancy, cardiovascular disease, chronic renal failure, bacterial superinfection [42], drug hepatitis [9] and others. Thus, when there are AIDS-related opportunistic diseases and other co-morbid conditions among TB patients, the immune system becomes suppressed progressively and leads to death [23]. Even though this study did not identify the specific co-morbidity that leads to mortality, routine screening of TB patients for other diseases is crucial to detect the disease early, to prevent adverse outcomes and to improve treatment outcomes of TB patients.

In this study, the delay to start TB treatment was identified as a risk factor for death among TB patients. In line with this finding, a study conducted by Albuquerque et al.[43] and Albuquerque et al. [44] reported that late initial treatment was a predictive factor for death. Diagnostic delays or late initial treatment increases the severity of the disease which in turn increases the risk of death [43]. Hence, necessary actions need to be initiated to decrease the risk of death. Moreover, intensive health education with an emphasis on the importance of early TB diagnosis and treatment should be given to increase the awareness the patients.

The present study had a number of limitations. This study was a single center study and may not generalizable to the country. The other limitation of this study was data incompleteness. Since the data was collected from medical records, some of the data are incomplete to gather information about the necessary variables. Additionally, the specific cause of death may not be determined accurately because of multiple causes of death in TB patients. Despite the above limitations, this study provides valuable information about the factors associated with mortality among TB patients.

Conclusion

This study indicated that the treatment success rate in the study area was low and a high proportion of patients died. Several factors were associated with mortality among hospitalized TB patients. These are; HIV co-infection, sputum smear results, type of TB, co-morbidity, and the interval between symptoms and seeking medical advice. Hence, monitoring those factors is important to reduce the death rate in TB patients. Additionally, the patient's data recording system should be improved for completeness of the registry in our settings.

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Declaration of Conflicting of Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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