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Modeling the Survival of Tuberculosis Patients in Eastern Zone of Tigray Regional State

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Background: Tuberculosis (TB) is still a public health problem and amongst the top ten leading causes of death. The aim of this paper was to identify the factors that significantly affect the survival of tuberculosis patients.

Methods: A retrospective cohort study was carried out in Adigrat General and Wukro hospitals, Eastern Zone of Tigray region, Ethiopia. Data for this study were obtained from medical records of all TB cases registered from September 2016 to August 2017 in the two hospitals. Log-rank test and Kaplan–Meier plot were used to evaluate the survival pattern of TB patients. A multivariable Cox proportional regression model was employed to identify the predictors of mortality. Factors with a *P*-value smaller than 0.05 were taken as statistically significant facilitators of TB death.

Results: Of the 397 patients studied over the specified period, 23 (5.8%) had died. A statistically significant survival difference was observed among gender, residence, HIV status, treatment category, and age category of patients. In multivariable cox regression, lower survival rates were observed among patients aged ≥45 years (HR = 5.315, 95% CI: 1.231–22.959), relapse cases (HR = 4.069, 95% CI: 1.636–10.119), patients with extrapulmonary TB (HR = 3.054, 95% CI: 1.044–8.940), patients from rural areas (HR = 2.834, 95% CI: 1.161–6.916), patients with a bodyweight of ≤50 kg and HIV-positive patients.

Conclusion: Based on the survival experience of TB patients, advancing age, extrapulmonary TB infection, living in rural residence, lower bodyweight at beginning of treatment, HIV co-infection, and being a retreatment patient were predictors of mortality. To achieve the "End TB Strategy" goal of zero death, proper targeting of care to these vulnerable groups should be advised.

Keywords: hazard probability, mortality, tuberculosis, survival

Background

Tuberculosis (TB) is still a public health problem and amongst the top ten leading causes of death. About 1.3 million people died due to TB and an additional 0.4 million people died due to TB among HIV-positive patients in 2017. In the same year, an estimated 10 million people developed TB, among them 0.92 million people were HIV-positive.[1] A new program known as the "End TB Strategy" was adopted by WHO which targets to reduce TB mortality by 95% by the end of 2035. To attain this goal, the number of individuals who die of TB in the year 2025 should decline to 6.5%.[2] The TB incidence rate has fallen since 2000. Worldwide, the number of TB deaths among HIV-negative people has dropped by 29% since 2000, from 1.8 million in 2000 to 1.3 million in 2017, and by 5% since 2015. The number of TB deaths among HIV-positive people has dropped by 44% since 2000, from

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0.534 million in 2000 to 0.3 million in 2017, and by 20% since 2015 (the baseline year of the End TB Strategy).[1,3] Morbidity and mortality of TB have declined meaningfully in several parts of the developed world in recent years, but unsatisfactory achievement has been noted in other countries. A key obstacle in this respect is the absence of political decisions.[3]

Ethiopia started a standardized TB prevention and control program that implements the WHO-suggested DOTS strategy in 1992.[4] According to the WHO report,[1] Ethiopia is among the 30 high TB burden countries with incidence rate 164/100,000 and 5.2 per 100,000 cases were notified for MDR TB. According to this report, TB mortality (excluding causes of death from HIV+TB) rate is projected at 24 per 100,000 population.

Improving case notification of TB is required in order to provide reliable data for direct measurement of TB incidence and mortality.[1] About 39% of estimated cases of TB in Ethiopia are missed; either not detected, treated, or reported to NTB. Those unnotified cases remain infectious and could be the reason for the transmission of TB within the community.[5]

Identifying the risk factors for TB mortality is vital for predictive purposes, but also for proper targeting of highly susceptible groups.[6] To identify the causes of mortality and to make effective interventions to reduce mortality rates, studying the survival of TB patients will be essential.[7] A number of risk factors including the age of the patient, gender, HIV status, MDR, disease severity were facilitators of death due to TB.[8,9] Several studies have associated TB-HIV coinfection as a significant predictor of TB mortality. In contradiction to these findings, a study in Saudi Arabia reported an insignificant association between TB-HIV coinfection and TB mortality, which is also explained by the low TB-HIV mortality rate (0.06/100,000 people).[10]

The causes of mortality are different across studies; therefore, to improve the survival experience of TB patients, investigating the facilitators of mortality due to TB in the local setting is critical. The aim of this paper was to identify the factors that significantly affect the survival of tuberculosis patients.

Methods

Study Design, Area, and Period

A retrospective cohort study was carried out to identify the factors that affect the survival of TB patients on DOTS in Adigrat General and Wukro hospitals, Eastern Zone, Tigray region, Ethiopia from September 2016 to August 2017. Adigrat General Hospital is located in Adigrat, the administrative town of Eastern Zone. This town has a total population of 57,588, of whom 26,010 are men and 31,578 are women. Wukro Hospital is located in Wukro town, Eastern Zone, Tigray Regional state. This town has a total population of 30,210, of whom 14,056 are men and 15,154 are women.[11]

Study Population

Data for this study were obtained from medical records of all TB cases registered from September 2016 to August 2017 in the two hospitals.

Data Collection and Study Variables

The data were collected by physicians who are working at the two hospitals after undergoing training regarding the data collection. TB patients' demographic and clinical data (including age, gender, residence, baseline weight, history of previous treatment, treatment center, HIV status, and type of TB) were extracted from medical forms. The dependent variable was survival time, which was measured in months from the date treatment started to the date of death or the latter attendance to the health facility. If the patient terminated the treatment by heal or complete treatment, unsuccessful treatment, or loss to reexamination (follow-up) considered as censored.

Diagnosis of Tuberculosis

Diagnosis of pulmonary TB in the two hospitals was done based on the national algorithm; for any patient with signs and symptoms, specimens for bacteriologic examination were requested and examined with X-ray and the diagnostic method GenXpert MTB/RIF. In addition, new specimens were referred to culture when necessary. Diagnosis of extrapulmonary TB was mainly achieved by pathologic techniques and diagnostic methods including GenXpert and TB culture.[4]

Eligibility Criteria

All TB patients with complete medical records (irrespective of gender and age, HIV status, and type of TB) who registered in the hospitals from September 2016 to August 2017 were included.

TB patients whose medical record with missing values on the variables of interest, gender, age, HIV status, and type of TB were excluded from the study (Figure 1).

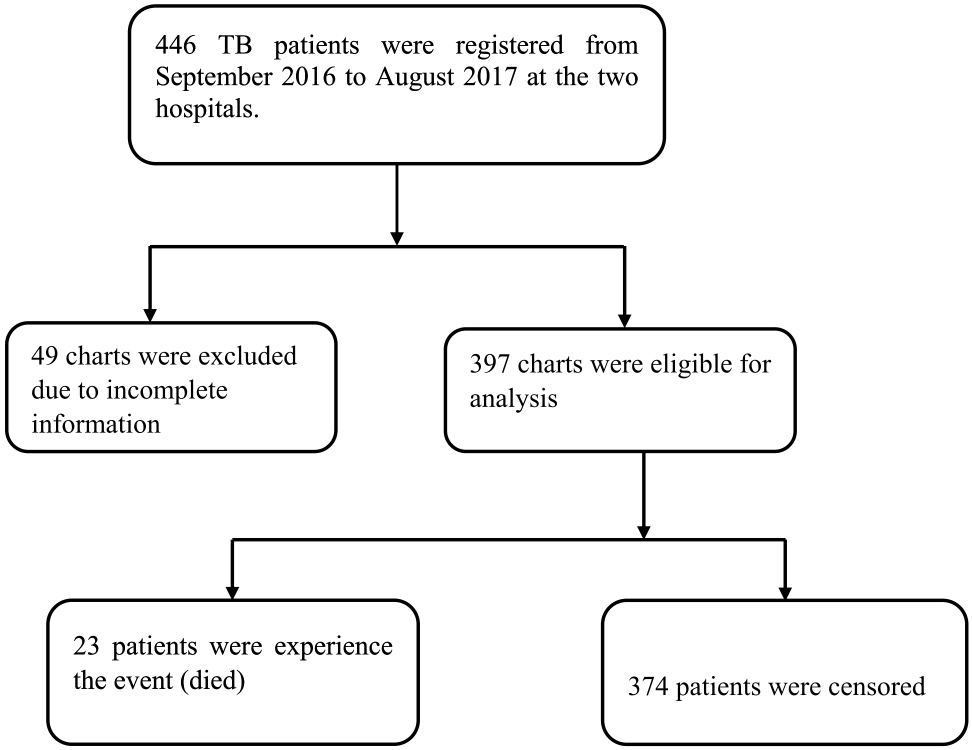

Figure 1 Flow chart showing the selection of Tuberculosis patients at Adigrat general and Wukro hospitals in Eastern Zone, Tigray region, Ethiopia, September 2016–August 2017.

Statistical Analysis

SPSS version 22 was used for data analysis. Log-rank test and Kaplan–Meier plot were used to evaluate the survival pattern of TB patients. A multivariable Cox proportional regression model was employed to identify the predictors of mortality using the default enter procedure in SPSS. Factors with a *P*-value smaller than 0.05 were considered statistically significant facilitators of TB death. AIC was used to compare the two candidate models (null and full), and the full model which had the smallest AIC was selected. The adequacy of the fitted model was assessed using the concordance statistic[12] (c-statistic=0.894), which shows the model had a good predictive ability.

Cox Regression Model

The Cox regression model was proposed by Cox[13] for the analysis of censored survival data. The model has the following form:

$$h(t) = log\, h_o(t) = \beta_1 X_{1i} + \beta_1 X_{2i} + \ldots + \beta_1 X_{ki}$$

where t is the survival time; $h_o(t)$ is the hazard function, determined by a set of k independent variables $X_{1i}, X_{2i}, \ldots X_{ki}$ for $\beta_1, \beta_2, \ldots \beta_k$ subjects; are coefficients of the independent variables; is the baseline hazard. It corresponds to the value of the hazard if all the 's are equal to zero.

Ethical Consideration

A letter of ethical clearance was received from the research ethical clearance committee of Adigrat University. Permission letters were obtained from both Adigrat General and Wukro hospitals. The study utilized existing admission information and patient histories, therefore no informed consent was required. All the patients' data obtained from records were de-identified in accordance with data protection regulations and the declaration of Helsinki.

Results

Based on the retrospective cohort study of 397 TB patients studied over the specified period, 225 (56.7%) were male and 172 (43.3%) of the patients were female, 353 (88.9%) were new TB cases, the remaining 44 (11.1%) were relapse cases. The numbers of HIV positive and negative patients were 106 (26.7%) and 291 (73.3%), respectively. About 71.3% of the patients had pulmonary TB, while 28.7% were diagnosed with extrapulmonary TB. Overall, the mortality rate was 23 (5.8%), whilst 374 (94.2%) of the patients were censored (Table 1).

Table 1 Characteristics of TB Patients and the Log-Rank Test of Predictors for Survival Time in Eastern Zone of Tigray Region, Ethiopia, September 2016–August 2017

Variables		Total (n=397)	Survival Status at 12 Months		Log Rank Test	
			Censored (n=374)	Died (n=23)		
		n (%)	n (%)	n (%)	Chi-Square	*P*-value
Health facility	Adigrat General Wukro	226 (56.9) 171 (43.1)	213 (94.3) 161 (94.2)	13 (5.8) 10 (5.9)	0.008	0.931
Gender	Male Female	225 (56.7) 172 (43.3)	217 (96.4) 157 (91.3)	8 (3.6) 15 (8.7)	4.774	0.029
Residence	Urban Rural	231 (58.2) 166 (41.8)	223 (96.5) 151 (91.0)	8 (3.5) 15 (9.0)	5.59	0.018
Type of TB	P/Positive P/Negative EP	159 (40.1) 124 (31.2) 114 (28.7)	150 (94.3) 120 (96.8) 104 (91.2)	9 (5.7) 4 (3.2) 10 (8.8)	3.296	0.192
HIV status	Positive Negative	106 (26.7) 291 (73.3)	90 (84.9) 284 (97.6)	16 (15.1) 7 (2.4)	23.376	<0.001
Treatment category	New Relapsed	353 (88.9) 44 (11.1)	341 (96.6) 33 (75.0)	12 (3.4) 11 (25.0)	35.833	<0.001
Age group	<24 25–44 ≥45	144 (36.3) 185 (46.6) 68 (17.1)	141 (97.9) 177 (95.7) 56 (82.4)	3 (2.1) 8 (4.3) 12 (17.7)	22.520	<0.001
Baseline weight	≤50 >50	182 (45.8) 215 (54.2)	168 (92.3) 206 (98.8)	14 (7.7) 9 (4.2)	2.093	0.148

Note: Values are presented as numbers and percentages (%).
Abbreviations: EP, extrapulmonary; HIV, human immunodeficiency virus; P/Positive, pulmonary positive; P/Negative, pulmonary negative; TB, tuberculosis.

Of the 374 patients who were censored, 104 (91.2%) had extrapulmonary tuberculosis, 151 (91%) were rural residents, 157 (91.3%) were female, 90 (84.9%) were HIV-infected, 33 (75%) were relapsed cases and 161 (94.2%) treated at Wukro Hospital. Of the 23 TB cases who died during medication, 8 (34.8%) were male, 15 (65.2%) were from rural areas, 12 (52.2%) were admitted as new patients, 16 (15.1%) were HIV-positive, and 13 (94.3%) were treated at Adigrat General Hospital.

The survival experiences of different groups were evaluated with the Log-rank test. It demonstrated that there is a statistically significant survival difference among gender (*P*-value= 0.029), residence (*P*-value = 0.018), HIV status (*P*-value <0.001), treatment category (*P*-value <0.001) and age category of patients (*P*-value <0.001) at 5% significant level (Table 1).

The Kaplan–Meier survival plots compare the survival between substratas when classified by treatment category (Figure 2A), patients who treated previously had lower survival. Based on the HIV status of TB patients, survival was lower for HIV positives (Figure 2B). When classified by age group, patients whose age was ≥45 years had the lowest survival among their groups (Figure 2C). Moreover, TB patients from rural areas and females had the lowest survival among their groups (Figure 2D and E).

Risk Factors for Mortality

Cox proportional hazard regression results showed that the six factors (residence, type of TB, HIV status, treatment category, age, and bodyweight) were significant risk factors for mortality among TB patients. Health facility and gender were not predictors of TB mortality. In multivariable Cox regression, lower survival rates were observed among patients aged ≥45 years (HR = 5.315, 95% CI: 1.23–22.959), relapse cases (HR = 4.069, 95% CI: 1.636–10.119), patients with extrapulmonary TB (HR = 3.054, 95% CI: 1.044–8.940), patients from rural areas (HR = 2.834, 95% CI: 1.161–6.916), patients with a bodyweight of ≤50 kg, and HIV-positive patients (Table 2).

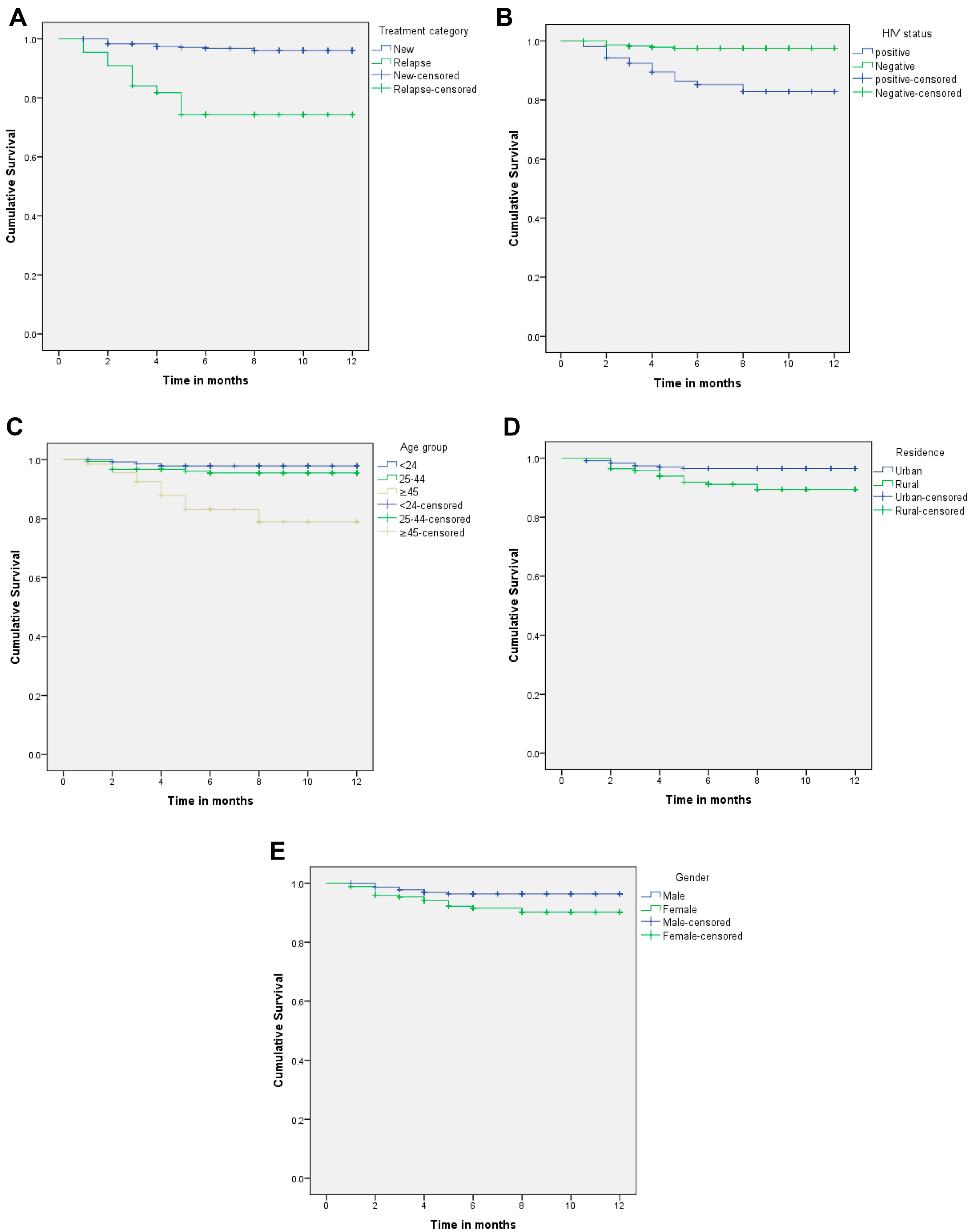

Figure 2 (**A**) 12-month survival curve of tuberculosis patients according to treatment category in Eastern Zone of Tigray region, Ethiopia, September 2016–August 2017. (**B**) 12-month survival curve of tuberculosis patients according to human immunodeficiency virus (HIV) status in Eastern Zone of Tigray region, Ethiopia, September 2016–August 2017. (**C**) 12-month survival curve of tuberculosis patients according to age group in Eastern Zone of Tigray region, Ethiopia, September 2016–August 2017. (**D**) 12-month survival curve of tuberculosis patients according to residence in Eastern Zone of Tigray region, Ethiopia, September 2016–August 2017. (**E**) 12-month survival curve of tuberculosis patients according to gender in Eastern Zone of Tigray region, Ethiopia, September 2016–August 2017.

Table 2 Predictors of Death During TB Treatment Among Patients on DOTS Program in Eastern Zone of Tigray Region, Ethiopia, September 2016–August 2017

Variables	B	Status		HR (95% CI)	*P*-value
		Censored	Died		
Health facility					
Adigrat General	–	213 (94.3)	13 (5.8)	–	
Wukro	0.613	161 (94.2)	10 (5.9)	1.845 (0.681, 4.998)	0.228
Gender					
Male	–	217 (96.4)	8 (3.6)	–	
Female	0.564	157 (91.3)	15 (8.7)	1.758 (0.714, 4.326)	0.219
Residence					
Urban	–	223 (96.5)	8 (3.5)		
Rural	1.042	151 (91.0)	15 (9.0)	2.834 (1.161, 6.916)	0.022
Type of TB					
P/Positive	–	150 (94.3)	9 (5.7)	–	
P/Negative	−0.476	120 (96.8)	4 (3.2)	0.621 (0.174, 2.220)	0.464
EP	1.117	104 (91.2)	10 (8.8)	3.054 (1.044, 8.940)	0.042
HIV status					
Positive		90 (84.9)	16 (15.1)	–	
Negative	−1.645	284 (97.6)	7 (2.4)	0.193 (0.066, 0.565)	0.003
Treatment category					
New	–	341 (96.6)	12 (3.4)	–	
Relapse	1.403	33 (75.0)	11 (25.0)	4.069 (1.636, 10.119)	0.003
Age group					
<24	–	141 (97.9)	3 (2.1)	–	
25–44	0.082	177 (95.7)	8 (4.3)	1.085 (0.252, 4.677)	0.913
≥45	1.671	56 (82.4)	12 (17.7)	5.315 (1.231, 22.959)	0.025
Baseline weight					
≤50	–	168 (92.3)	14 (7.7)	–	
>50	−1.212	206 (98.8)	9 (4.2)	0.298 (0.111, 0.796)	0.016

Notes: (–) indicates the reference category, values are presented as number and percentage (%).
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; TB, tuberculosis; P/Positive, pulmonary positive; P/Negative, pulmonary negative.

Discussion

During the follow-up period, 5.8% of the patients died. The number of deaths in this finding was higher than the 3.9% reported from Tigray,[14] but lower than from previous findings including Dessie,[7] Mekelle,[15] and Nigeria.[16]

The current study demonstrated that lower survival probability in HIV-positive patients was observed compared to HIV-negative patients. This is due to the fact that HIV patients are likely to become malnourished from constantly being sick, from diarrhea that reduces the absorption of nutrients, from loss of appetite and sores of the mouth that make eating difficult for them, and from opportunistic infections.[17] The higher prevalence of MDR among TB-HIV coinfected patients may be another reason.[10] In contradiction to the current finding, studies in Ethiopia,[18] Saudi Arabia,[10] and southern India[19] showed that HIV status was not significantly associated with mortality of TB patients. The possible explanation for this observed variation might be differences in the socio-demographic characteristics of TB patients,[8] the quality of service in the TB/HIV clinic; health education, proper counseling, and appropriate follow-up by the clinicians. The current finding that HIV-positive patients had a higher likelihood of experiencing death during treatment than HIV-negative TB patients is congruent with a study in Nigeria,[20] which stated that TB-HIV co-infected patients were at the highest risk of death. Findings from Brazil[21] and Iran[22] revealed that the hazard of dying of TB-HIV co-infection was 1.46 and 11.9 more likely compared to HIV-negative TB patients, respectively.

Lower survival rate was observed among patients from rural areas, who had a higher risk of experiencing death. This demographic factor was associated with mortality in numerous studies.[7,20] This could be due to the health structure in the least-developed nations, which suffers from a deficiency of human resources and inadequate facilities for rural residents. In contradiction to this finding, other studies reported that the place of residence was not significantly associated with death.[15,23]

In the present study, patients aged ≥45 years (HR = 5.32, 95% CI: 1.23–22.96) had a lower survival rate as compared to the younger age groups. A wider confidence interval of hazard ratio for age was observed. A small sample size or the variation of events observed in each age category could attribute to this effect. The covariate age significantly affected the survival experience of TB patients, and getting older was the significant risk factor for death due to TB.[6] A higher mortality rate was reported by Adamu et al among patients aged ≥45–54 (30.8%) as compared with younger age groups (9.6%).[16] The cause of this association is that advancing age is associated with immunosenescence, which is a process that affects the entire immune system. It corresponds to multiple alterations of the immune system, which results in a higher rate of infections, an increase of comorbidities, and reduced responses to treatments.[24]

The current study revealed that patients with a bodyweight of more than 50 kg at the beginning of treatment were 70% less likely to die than patients whose bodyweight ≤50 kg. This implies an adverse outcome of malnutrition on TB patient survival. Studies in northwest Ethiopia[8] and southern India[25] showed that patients whose weight was <35 kg at the beginning of treatment were 3.9 and 3.7 more likely to die compared to patients whose weight was more than 35 kg, respectively. Bodyweight is an important indicator of malnutrition. Malnutrition adversely affects immune function,[26] and as a result, increases comorbidity.[24] Comorbidity was an important predictor of survival for patients with tuberculosis in several studies.[27–30]

Female TB patients had lower survival compared to male patients and this difference was statistically significant in the univariate model. However, this difference was not significant in multivariable Cox regression. Similar studies reported no significant variation in terms of mortality between male and female patients, but the proportion of death was higher in female patients.[16,31]

Previous studies demonstrated insignificant variation in terms of mortality between new TB patients and relapses.[7,20,32] In this study previous TB treatment was considered a significant risk factor for mortality, which is in line with a study conducted in the southern region of Zimbabwe.[9] Patients who were treated for TB in the past had a greater likelihood of developing MDR TB and were more likely to die than patients who were not diagnosed with TB previously.[33]

Concerning the relationship between the type of TB and death, only extrapulmonary TB was a significant risk factor for mortality. The likelihood of dying for patients with extrapulmonary TB was 3 times higher than for patients with pulmonary positive. Higher proportions of death among extra-pulmonary TB patients were reported in studies from Ethiopia,[15] Iraq,[34] and Cameron.[35] This noticeable rate of mortality might be due to insufficient information about the extrapulmonary TB symptoms and the lack of access to medical facilities. A recent report from China revealed that the diagnostic breach and failing to diagnose extrapulmonary TB were high; this might be due to the disease being diagnosed from clinical symptoms.[36] Extrapulmonary TB is complicated and difficult to diagnose, and it requires a high clinical diagnostic measure.[34] Time until diagnosis was significantly associated with morbidity and mortality.[37]

Limitations of the Study

This study was done retrospectively to investigate the factors associated with mortality, and some important risk factors (like ART, CPT, and other clinical variables) were not included due to incomplete information in the patients' logbook at the health centers. Furthermore, the specific reason for death may not be known exactly.

Conclusion

Based on the survival experience of TB patients, advancing age, extrapulmonary infection, living in rural residence, lower bodyweight at beginning of treatment, HIV co-infection, and being a retreatment patient were predictors of mortality and had a negative effect on the survival time. To achieve the "End TB Strategy" goal of zero death, proper targeting of care to these vulnerable groups should be advised.

Abbreviations

AIC, Akaike information criterion; ART, antiretroviral therapy; CI, confidence interval; CFR, case fatality ratio; CPT, cotrimoxazole prophylaxis therapy; HR, hazard ratio; HIV, human immunodeficiency virus; MDR, multidrug-resistant; NTB, national tuberculosis program.

Data Sharing Statement

The raw data set used for this study is offered on reasonable request.

Acknowledgments

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Disclosure

The author declares no conflict of interest concerning this paper.

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