Survival Analysis and Associated Risk Factors of Tuberculosis In-Hospital Patients' Death in Hawassa City and at Yirgalem Town Health Centers

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Abstract: A prospective cohort study was conducted on 202 tuberculosis (TB) in-hospital patients who were treated in Hawassa University referral hospital and Adare and Millennium health centers in Hawassa city and in Yirgalem hospital at Yirgalem town to determine the survival rate and the risk factors associated with TB in-hospital patients' death after properly followed-up for six months; from December, 2012 to May, 2013. Of the 202 registered patients, 190 (94.1%) survived the entire follow-up period. The general mortality rate was 1.02 per 100 person-months (12.3/100 person-years observation per annum) for the cohort. Of the 12 patients who died, 58.3% died within 2 months of the start of treatment. The survival probability in the sixth month was 100% while the cumulative survival probability at the end of the treatment period was 94%. Tuberculosis patients who followed up their treatment at Adare health center, Millennium health center and Hawassa University referral hospital were respectively 73%, 62% and 38% less likely to die compared with those who followed up their anti-TB treatment at Yirgalem health center. Tuberculosis patients who had middle and low income were respectively 90% and 87% less likely to die compared with those who had high socio-economic level. The result of this study revealed that of the TB patients who died in this study, 58.3% died within 2 months of the start of treatment while the entire patients survived in the sixth month warranted early diagnosis and the start of the appropriate treatment. Moreover, improved health service coverage should be required in the health centers in which high TB in-hospital patients' death have been reported.

Key words: Survival Probability · Tuberculosis In-Hospital Patients' Death · Risk Factors · Sidama Zone · Southern Ethiopia

INTRODUCTION

Tuberculosis remains a major global health problem and ranks second in being the cause of death from an infectious disease worldwide following human immunodeficiency virus (HIV). Despite the availability of treatment that cures most TB cases, the latest report of World Health Organization (WHO) showed that there are an estimated 1.3 million TB deaths. The African region is currently not on track to achieve the mortality and prevalence targets (reduce deaths by 50% by 2015) due to resource constraints, conflict and instability and generalized HIV epidemics [1]. In Ethiopia, TB has been identified as one of the major public health problems in the last five decades and it is also a well known disease that is a cause for a large population death in our country [2].

In a study conducted by Borgdorff *et al.* [3] in Netherlands revealed that the survival probabilities for tuberculosis patients have been estimated as 95% after six months of treatment and 6% died still while on treatment. Pardeshi [4] documented that studying the survival patterns can help in identifying the risk factors for mortality in TB patients. Identifying risk factors for death

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following diagnosis of TB is important to predict prognosis in TB patients and planning effective interventions to reduce death rates [5-8].

WHO reported that infection with the HIV is the main reason for failure to meet TB control targets in regions with high HIV prevalence and this is driving the TB epidemic worldwide. However, other risk factors such as lack of resources to effectively manage and deliver healthcare have also contributed toward the persistent increase in the burden of TB in developing countries. Reduction of the high death and defaulter rates due to TB, coupled with improved reporting of treatment outcomes for patients transferred to other sites, will significantly improve the treatment success rates [9].

Moreover, studies have indicated that mortality was highest among HIV infected and multidrug-resistant TB (MDR-TB) patients [10,11]. The vast majority of these cases (MDR -TB patients) occur in patients living in low- and middle-income regions[12].High recurrence rates may also increase TB incidence, reduce treatment success and increase post-treatment mortality or reduce post-treatment survival of successfully treated TB patients [13,14]. To the best of our knowledge, no follow-up study has been conducted in the Sidama zone of southern Ethiopia to determine the survival rate and the risk factors associated with TB in-hospital patients' death.

MATERIALS AND METHODS

Description of Study Area and Population: The study was conducted in Sidama Zone of the southern Ethiopia, Hawassa city and Yirgalem town. Hawassa is the capital city of southern nations and nationalities regional state and located at 275kms from Addis Ababa, the capital of Ethiopia.The research site has geographic coordinates of 5° 45'to 6° 45'N latitude and, 38° and 39°Eastlongitudewith an elevation ranges from 1500 to 2500 meters above sea level. The climate of Sidama Zone is characterized aswarm conditions, cover 54% of the area. Mean annual temperature ranges between 15°C to 19.9°Cand mean annual rainfall between 1200 mm and 1599 mm [15]. The study populations were TB in-hospital patients that had been treated for six months in Hawassa University referral hospital, Adare health center, Millennium health center in Hawassa city and in Yirgalem hospital at Yirgalem town.

Study Design and Sample Collection: A prospective cohort study was conducted on 202 TB in-hospital patients who were under the follow up treatments in Hawassa University referral hospital, Adare health center,

Millennium health center in Hawassa city and in Yirgalem hospital at Yirgalem town to determine the survival rate and the risk factors associated with TB in-hospital patients' death after properly followed-up from December, 2012 to May, 2013 in each health center and hospital.

Data were extracted from the patient follow up records by health professionals working in TB clinics of those specified health centers and hospitals after attending one day orientation on the structured data sheet by the investigators. To ensure quality of the collected data the following measures were taken: (i) a one day training was given for data collectors before the start of data collection, (ii) the overall activities of data extraction were monitored by the investigators, (iii) all completed data sheets were examined for completeness during data collection, (iv) consistencies of the collected data were checked during analysis. The independent variables considered for the analysis were smoking, sex, marital status, place of residence, types of tuberculosis (Smear-negative, smear-positive and extra pulmonary tuberculosis), category of patient, HIV status, socio-economic status, level of education, history of previous treatment and treatment center. Mortality was used as an outcome.

Statistical Analysis: The quantitative data extracted from the registration follow up records were checked for completeness and consistency by the principal investigator. Data were recorded in database based on Microsoft® Excel for Windows 2007 and analyzes were performed using SPSS 17 (Statistical Package for Social Sciences, Chicago, IL, USA). Descriptive statistical methods were used to summarize the socio-demographic characteristics of the study participants. Survival trend over the follow up time was calculated using the Kaplan Meier (KM) method. Cox's proportional hazards model was used to identify risk factors for death. In all the analyses, confidence level was held at 95% and $P < 0.05$ was set for statistical significance.

RESULTS

Descriptive Statistics: Socio-demographic and medical information of 202 registered TB patients were summarized. Of the 202TB in-hospital patients who were under the followup treatments for six months, 29.7% were pulmonary positives, 31.2% were pulmonary negatives and 39.1% were extra pulmonary TB patients. Majority of the study participants (87.1%) were new cases and 24.3% were HIV positives. Moreover, the rates of death within

Table 1: The number of patients per each category of the study participants in Hawassa city and at Yirgalem town, southern Ethiopia

Factors	Number of patients under treatment (%)	Death (%)
Health Centers		
Adare	79 (39.1)	3 (3.8)
Millennium	51(25.3)	2 (3.9)
Hawassa Referral hospital	16 (7.9)	0
Yirgalem hospital	56 (27.7)	7 (12.5)
Sex		
Male	116 (57.4)	5 (4.3)
Female	86 (42.6)	7 (8.1)
Marital Status		
Single	94 (46.5)	6 (6.4)
Married	100 (49.5)	5 (5.0)
Divorce	3 (1.5)	1(33.3)
Widowed	5(2.5)	0
Place of Residence		
Urban	179 (88.6)	12 (6.7)
Rural	22 (10.9)	0
Socio-economic Status		
Low	99 (49.0)	4 (4.0)
Middle	101(50)	7 (6.9)
High	2 (1.0)	1 (50.0)
Level of Education		
No education	20 (9.9)	0
Primary	106 (52.5)	5 (4.7)
Secondary	59 (29.2)	7 (11.9)
Higher	17 (8.4)	0
Type of TB		
Pulmonary positive	60 (29.7)	5 (8.3)
Pulmonary negative	63 (31.2)	2 (3.2)
Extra-pulmonary	79 (39.1)	5 (6.3)
HIV Status		
Positive	49 (24.3)	4 (8.8)
Negative	153 (75.7)	8 (5.2)
Category of Patients		
New	176 (87.1)	7 (4.0)
Relapse	14 (6.9)	3 (21.4)
Others†	12 (5.9)	2 (16.7)

† a) treatment failure (a patient who, while on treatment remained smear-positive or become again smear-positive at the end of the five month or later after commencing treatment), (b) returned after default (a patient who had previously been recorded as defaulted from treatment and returns to the health facility and found to be smear positive sputum)

the treatment period in Adare health center, Millennium health center, Hawassa referral hospital and Yirgalem hospital were 3.8%, 3.92%, 0.00% and 12.5%, respectively (Table 1).

Survival Analysis of Tuberculosis In-Hospital Patients: Of the 202 registered patients, 190 (94.1%) survived the entire follow-up period. The 202 patients were followed for a total of 1,176 person-months. The general mortality rate was 1.02 per 100 person-months (12.3/100 person-years observation per annum)for the cohort. Of the 12 patients who died, 58.3% died within 2 months of the start of treatment and the cumulative survival probabilities were 99.5%, after the first month of treatment, 96.5% after 2 months, 95.5% after 3 months, 94.5% after 4 months and 94% after 5 months. Therefore, the survival probability in the sixth month was 100% while the cumulative survival probability at the end of the treatment period was 94% (Table 2).

The Kaplan-Meier survivor estimator for each health centers and socio-economic status was analyzed. Accordingly, Yirgalem hospital had slightly less survival probability as compared to others. The mean survival time of TB in-hospital patients treated in Hawassa University Referral Hospital, Adare health center, Millennium health center and Yirgalem hospital were 158.683, 155.696, 148.125 and 144.107 days, respectively. Regarding socio-economic status, TB patients with high socio-economic status had slightly less survival probability as compared to the remaining category. The mean survival times of TB in-hospital patients having low, middle and high socio-economic status were 174.848, 174.35 and 120.00 days, respectively.

Cox Proportional Hazard Regression: The cumulative hazard probability was shown in Figure 1. Among the risk factors assessed in this study, health centers and socio-economic status were significantly associated with TB in-hospital patients' death. However, the risk factors

Table 2: Kaplan Meier survival analysis of in-hospital tuberculosis patients in the Sidama zone of southern Ethiopia

Month	Number of patients under treatment	Number of deaths	Probability of death in the month	Probability of survival in the month	Cumulative survival probability
1	202	1	0.005	0.995	0.995
2	201	6	0.030	0.970	0.965
3	195	2	0.010	0.990	0.955
4	193	2	0.010	0.990	0.945
5	191	1	0.005	0.995	0.940
6	190	0	0.00	1.00	0.940

Table 3: Cox proportional hazard regression analysis of TB in-hospital patients' death

Covariates	B	SE	Hazard Ratio	95% CI	P-value
Health Center (ref: Yirgalem hospital)					0.000*
Adare	-1.30	0.44	0.27	0.12-0.64	0.03*
Millennium	-0.97	0.44	0.38	0.16-0.89	0.03*
Hawassa referral hospital	-0.47	0.51	0.62	0.23-1.71	0.36
Sex (ref: Female)					
Male	0.13	0.29	1.14	0.64-2.03	0.65
Place of Residence (ref: Rural)					
Urban	0.63	0.54	1.88	0.66-5.37	0.24
Socio-economic Status (ref: High)					0.01*
Middle	-2.01	0.96	0.10	0.02-0.87	0.03*
Low	-2.27	0.92	0.13	0.02-0.63	0.04*
Level of Education (ref: Higher)					0.18
No education	0.97	0.82	2.63	0.53-13.01	0.24
Primary	1.09	0.69	2.96	0.76-11.55	0.12
Secondary	0.92	0.69	2.50	0.65-9.62	0.18
Type of TB (ref: Extra-pulmonary)					0.28
Pulmonary positive	0.08	0.31	1.08	0.59-1.98	0.80
Pulmonary negative	-0.54	0.38	0.58	0.28-1.23	0.16
HIV Status (ref: Negative)					
Positive	-0.24	0.37	0.79	0.38-1.64	0.53
Category of Patient (ref: Others)					0.43
New	-0.78	0.61	0.46	0.14-1.50	0.20
Relapse	-0.67	0.76	0.51	0.12-2.26	0.38

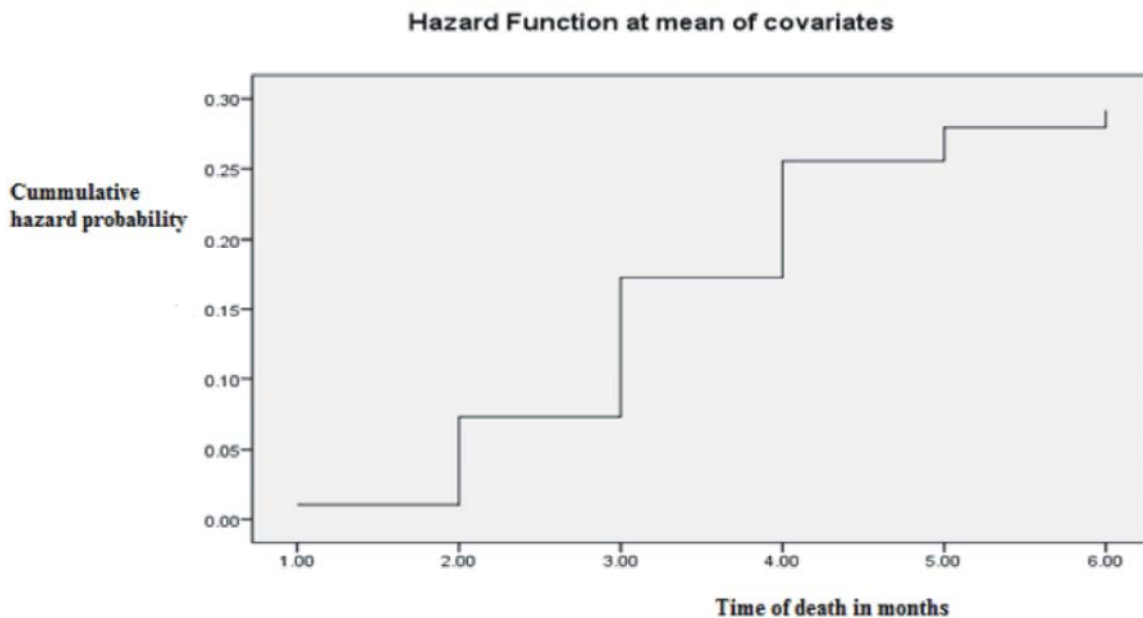*Statistically significant, CI =confidence interval, ref= reference category

Fig. 1: Hazard Function of Tuberculosis in-hospital patients' death

like sex, place of residence, educational level, category of patient, type of TB and HIV status were not statistically significant (Table 3). Tuberculosis patients who followed up their treatment in Adare health center (HR= 0.27, 95% CI: 0.12-0.64), Millennium health center (HR= 0.38, 95% CI: 0.16, 0.89) and Hawassa referral hospital (HR= 0.62, 95% CI: 0.23, 1.71) were respectively 73%, 62% and 38% less likely to die compared with those who followed up their treatment inYirgalem hospital. Tuberculosis patients who had middle (HR= 0.13, 95% CI: 0.02-0.87) and low (HR= 0.10, 95% CI: 0.02-0.63) income were respectively 90% and 87% less likely to die compared with those who had high socio-economic status.

DISCUSSION

This study was conducted to determine the survival rate and predictors of TB in-hospital patients' death during the six months of treatment period in Hawassa University referral hospital, Adare and Millennium health centers and Yirgalem hospital in the Sidama zone of southern Ethiopia. Of the 202 registered patients, 190 (94.1%) survived the entire follow-up period. Therefore, the mortality in this study was 5.9% which was higher to the mortality found than in Addis (4%) and to the National (3%) [16] but lower than in those reported in previous studies; 24% in Baltimore City, USA [17] and 14% in Vaud County, Switzerland [18]. Moreover, in the present study, general mortality rate per 100 PYO was 12.3/100(12.3%) per annum for the cohort which is higher compare to other studies. The general mortality rate per 100 PYO was 6.3/100(6.3%) per annum for the cohort conducted in Addis Ababa, Ethiopia [19], which was not different from the mortality rate of 6.1% per annum reported for rural south India cohort [20] and for the Chennai urban cohort, 6 % per annum [21]. This difference may be due to different follow up periods and number of study subjects involved in the different studies.

In this study, of the 12 patients who died, 58.3% died within 2 months of the start of treatment while the survival probability in the sixth month was 100%. Similar finding was found in other study [22] who reported that among the TB patients who died during the period of their treatment, 65% died within 2 months of the start of treatment. Likewise other studies have also found that a significant proportion of patients died in the early stages of treatment [23, 24]. Early mortality reflects advanced disease and could be attributed to delayed treatment and late diagnosis [24, 25].

In the present study, the cumulative survival probabilities were 99.5% after the first month of treatment, 96.5% after two months, 95.5% after three months, 94.5% after four months and 94% after five months. This was consistent with the report of Borgdorff *et al.* [26] who reported that the survival probabilities were 97.5% after the first month of treatment, 96% after 3 months, 95% after 6 months and 93% after 1 year. The cumulative survival probability at the end of the treatment period was 94% which was similar to the results found by Borgdorff *et al.* [3] (95%) and Vasantha *et al.* [27] (95%) whereby approximately similar percentage of patients were surviving at the end of the treatment period but in other study conducted by Kolappan *et al.* [21] showed less

survival rate (91%) compared to our study. This difference may be due to different follow up periods in those studies.

In our study, health center was significantly associated with TB in-hospital patients' death. Similar finding was observed in Addis Ababa, Ethiopia in which health center was a significant risk factor of TB in-hospital patients' death [19]. This could be due to different level of potential health service coverage in the different health centers in which the studies have been conducted. In the present study, TB patients who had middle and low income were respectively 90% and 87% less likely to die compared with those who had high socio-economic status. The current study found high income is being a risk for TB in-hospital patients' death which was discordant with the studies found by Franke *et al.* [12] and Naidoo *et al.* [28] who reported low socio-economic is a risk for mortality in TB patient. In Malawi about half of the TB cases have been reported from the urban districts of Blantyre, Zomba, Lilongwe and Mzuzu where most of the Malawi population is found. This rise may be attributed to overcrowding although HIV seroprevalence that is higher in the urban areas is a contributing factor [29].

The result of this study revealed that of the TB patients who died in this study, 58.3% died within 2 months of the start of treatment while the entire patients survived in the sixth month warranted early diagnosis and the start of the appropriate treatment. Moreover, improved health service coverage should be required in the health centers in which high TB in-hospital patients' deaths have been reported.

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