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Long-term survival experience of tuberculosis patients in a rural district of Ghana

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Abstract

There are limited epidemiological studies on the survival of Tuberculosis (TB) patients in Ghana despite the high endemicity of TB in the country. The present study estimated the overall survival time of TB patients and developed a model to determine co-variates associated with death. This was a retrospective cohort study that employed a complete enumeration technique to review patient data from the TB register of the Ajumako Enyan Essiam District, Central Region, Ghana, between August and October 2023. All patients registered for TB care between 1st January 2018 and 31st December 2022, excluding patients with incomplete data and drug-resistant cases were included. We applied descriptive statistics, Kaplan-Meier survival analysis, Log-rank test, and a Cox proportional hazard model for multivariate analysis. Out of the 226 eligible patients, 149 (65.9%) were males, 205 (90.7%) were new cases and 37 (17.3%) were TB/HIV co-infected. Those who experienced death were 37 (16.4%), with an overall survival time of 5.5 months (95% CI = 5.4 – 5.7). Older age (aHR=2.6; 95% CI: 1.1-6.3), male gender (aHR=4.9; 95% CI: 1.7-14.3), relapsed TB patients (aHR=5.2; 95% CI: 2.4-10.9), and TB/HIV co-infected patients (aHR=7.1; 95% CI: 3.6-13.9) were implicated as plausible predictors for survival time to death of TB patients. We concluded there was a significantly low overall survival time for older age, male gender, relapsed TB patients, and TB/HIV co-infected patients. The provision of enhanced training for targeted health professionals and tailored community awareness creation can boost early case detection, treatment adherence, and improve overall survival.

Keywords: Survival Analysis; Kaplan-Meier; Tuberculosis; Long-term; Ghana

1. Introduction

Tuberculosis (TB) remains a global public health concern and the leading cause of mortality from a single infectious agent surpassing acquired immunodeficiency syndrome (HIV/AIDS) despite being curable with antimicrobial drugs [1]. Until the emergence of COVID-19, TB was the number one cause of death from an infectious disease [2, 3]. TB accounted for an estimated 1.6 million deaths and over 10.6 million new infections globally in 2021, with Africa accounting for approximately 25% of the cases [4]. A TB/HIV co-infection becomes lethal as almost 12% of the 1.6 million TB deaths were among people living with HIV (PLHIV) in 2021 [4–6]. Epidemiological evidence suggests that people have a 30-fold higher risk of developing active TB disease when they have HIV compared to those without HIV [3, 7, 8].

TB is an infectious disease caused by *Mycobacterium tuberculosis,* the disease can occur in any part of the body but 85% of cases manifest in the lungs (Pulmonary TB) whereas 15% occur in other parts of the body such as lymph nodes, pleura, genitourinary system, bone, joints, meninges and peritoneum also known as extrapulmonary TB [9–12]. In pulmonary disease, the clinical signs tend to be quite characteristic. They commonly involve fever, night sweats, weight

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loss, loss of appetite, overall weakness, and, in about 90% of instances, a cough. This cough typically starts as a morning cough and may progress to include a productive cough with purulent sputum and sometimes even blood [9, 13, 14].

The destructive consequences of the TB epidemic have had a widespread impact worldwide with a disproportionate burden falling on African nations. In many countries, particularly in Sub-Saharan Africa (SSA), HIV has been a driving force behind the spread of TB [7]. Furthermore, TB disease poses a significant social, economic, and political challenge to most low-middle-income countries. These include issues such as stigma, increased susceptibility to other health problems like mental illnesses, the high cost of treatment, and the absence of individuals from the workforce. In many instances, TB primarily affects the working-age population, worsening the crisis, especially in economically disadvantaged countries like Ghana [15].

The World Health Organization (WHO) listed Ghana among the high-burden TB countries in 2015 with an estimated national incidence of 152 cases and a mortality rate of 36 per 100,000 population as of 2017 [5, 16]. The unpublished 2022 Annual Report from the Ajumako Enyan Essiam District Health Directorate estimates TB incidence at 71 cases and a case fatality rate of 5.4 per 100,000 population.

Several TB studies conducted in Ghana gave little attention to the survival outcomes of TB patients. From our review of the literature, the few survival studies that focused specifically on the survival analysis of TB patients in Ghana are concentrated in the northern part of the country. A study conducted in 2016 in the Upper West Region of Ghana identified TB/HIV co-infection as the most influential factor that impacts TB survivorship [17]. This is a novel study on the survival experience of TB patients in the study area that seeks to bridge the gap in the literature on TB survival analysis.

Survival analysis focuses on assessing the duration of survival, often referred to as disease-free survival time, and understanding the various factors that impact the survival of TB patients. In survival analysis, individuals are typically monitored for a specified duration, and their survival time is recorded until a specific event of interest (death) takes place. One common situation in survival analysis is dealing with censoring, which pertains to cases where information about a subject's survival time is incomplete. The most frequently encountered type of censoring is right censoring, which occurs when the event of interest has not occurred during the follow-up period. Left censoring, on the other hand, involves situations where we know the endpoint but are uncertain about the starting time. The phenomenon of censoring needs to be considered in survival analysis to avoid bias.

In the present study, we sought to estimate the overall survival time and develop a model to determine co-variates associated with the outcome (death) of interest. We also estimated the survival time of the different groups of TB patients registered to the TB control programme in a rural district of the Central region of Ghana.

2. Materials and Methods

2.1. Study Design/Settings

This was a retrospective cohort study exploring a records review of patient data from the district TB register between August and October 2023 in the TB unit of the Ajumako Enyan Essiam District, one of the 22 districts in the Central region of Ghana. It is rural, located at 5° 27′ 48.96″ N, 0° 56′ 12.48″ W and covers an estimated land area of 541.3sqkm, about 5.5% of that of the region, with most of its inhabitants engaging in farming and other menial jobs.

Ajumako is the capital town and the seat of the local Government Administration. It is bounded on the north by Asikuma Odoben Brakwa District and on the northwest by Assin South District, on the west by Mfantsiman, on the east by Agona West and Gomoa East Districts, and on the south by Agona East and parts of Mfantsiman. There are 143 communities and 9 area councils in 5 sub-districts. Based on 2.4% projections from the 2021 population and housing census, the total population of the Ajumako Enyan Essiam District is estimated to be 126,444 [Unpublished Annual Report, 2022].

2.2. Study Population

Through a complete enumeration technique, the study population included all patients registered for TB care at the Ajumako Enyan Essiam District TB unit between 1st January 2018 and 31st December 2022. Patients with incomplete data regarding the outcome (cured, treatment completed, lost to follow-up or death) or date of diagnosis were excluded. Patients with Drug-resistant TB cases as well as those transferred out of the district were also excluded from the final analysis.

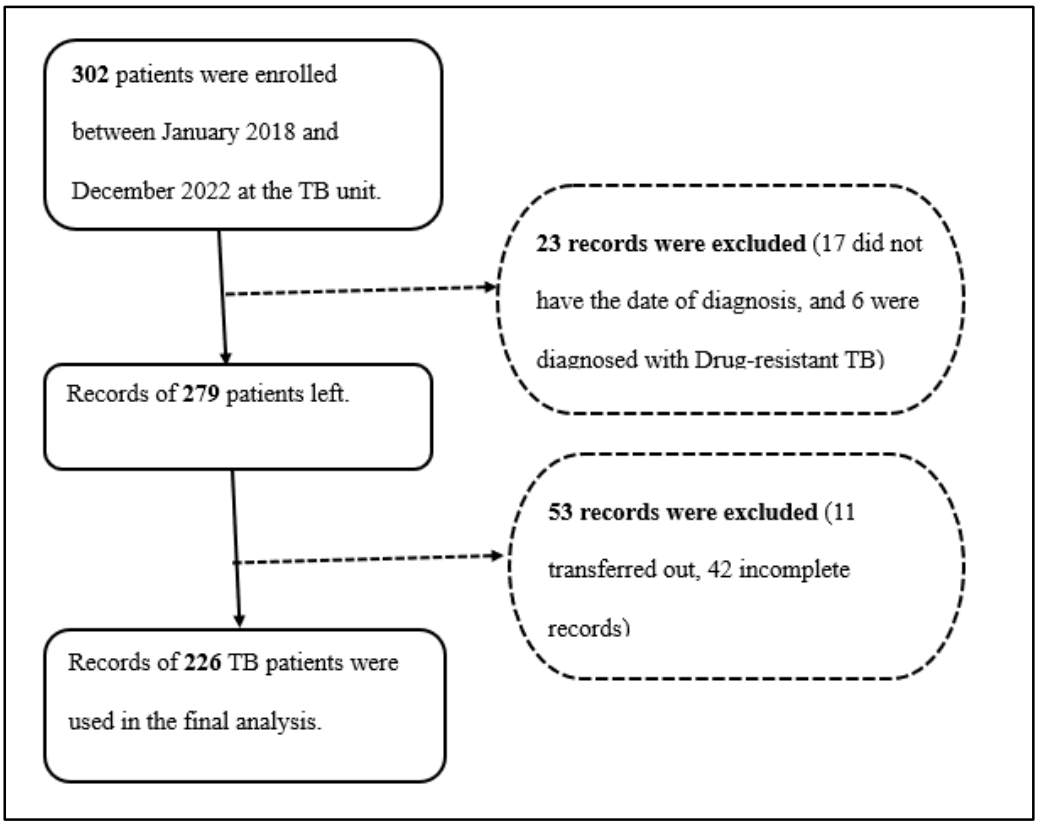

Figure 1 Enrollment, inclusion, and exclusion of study patients

2.3. Study variables

The primary event of interest in this study was death. Whereas data regarding age, sex, date of registration, pre-treatment bacteriological confirmation results, date of diagnosis, and date of starting treatment. Also, data on the classification of TB (categorized as Pulmonary positive or negative and Extrapulmonary), type of patient (categorized as new/relapse/return after loss to follow-up/ return after treatment failure/others), co-morbidities (HIV) (categorized as the presence of TB/HIV co-infection or not), treatment outcome (categorized as cured/treatment completed/treatment failure/lost to follow-up (defaulter) or death), and date of outcome were considered as predictor variables from the District TB register. Study variables were defined based on the National Tuberculosis Control Programme (NTP) of Ghana. Cured: a patient whose sputum smear or GeneXpert or culture results were positive at the beginning of treatment but who was smear or culture-negative in the last month of treatment and at least one previous occasion. Treatment complete: a patient who completed treatment but who does not have a negative sputum smear or culture results in the last month of treatment and on at least one previous occasion. Lost to follow-up: a patient whose treatment was interrupted for two consecutive months or more. Treatment failure: a patient whose sputum or culture is positive at 5 months or later during treatment. Died: a patient who dies of any reason during treatment.

2.4. Statistical Analysis

The data extracted was entered into Statistical Package for Social Sciences (SPSS), version 24, and thoroughly reviewed for consistency and completeness before being exported to STATA, version 16.0. for analysis. Descriptive statistics were presented as means, median and standard deviation for continuous variables while frequency tables were used to describe categorical variables.

In this study, we examined time-to-event data as follows: The entry point in time (t0) was defined as the date of diagnosis of TB disease, while the outcome point (t1) was determined by the occurrence of an event (death), declaration of failure, or classification as a loss to follow-up. Follow-up time was considered as the difference between the time of entry and the date of the occurrence of the event of interest. Patients were six months at risk of experiencing the event.

The primary analysis focused on overall survival, which was measured from the date of TB diagnosis to the date of the event (death). To estimate survival probabilities and the restricted mean survival time (median survival time could not be estimated from the data since survival was more than 50% at the end of follow-up), we employed the widely used

nonparametric estimator of survival function, the Kaplan-Meier survival analysis. Consequently, we compared survival and hazard functions between the different groups of TB patients through graphical representations and conducted Log-rank tests to detect significant differences between the two survival curves.

We further applied the Cox proportional hazard model with a stepwise variable selection procedure to identify associations between biologically plausible predictors of the outcome, assuming proportional hazard is constant over time. A significance level of $p < 0.05$ was considered statistically significant.

2.5. Ethical Consideration

This was a retrospective record review of TB data available at the Ajumako Enyan Essiam Health Directorate TB unit. Written permission and approval was obtained from the Health Directorate of the Ajumako Enyan Essiam District. All traceable identifiers linked to TB cases such as name, residential address and telephone number of patients were not collected as part of the data extraction.

3. Results

3.1. Characteristics of covariates

The present study included 226 TB patients. Male patients constituted 149 (65.9%). Age of patients revealed 145 (64.2%) were > 40 years with a mean age of 47 years (Range: 4 - 95). Out of the total registered patients, 205 (90.7%) were new TB cases whereas 5(2.0%) were returned after loss to follow-up. Most of the study participants 197 (87.2%) were pulmonary positive, 195 (86.3%) were bacteriologically confirmed, and 37(17.3%) were co-infected with HIV.

3.2. Survival Analysis of TB Patients

During the follow-up period, 37 (16.4%) patients experienced the event of interest and the remaining 189 (83.6%) who did not experience the event before the end of follow-up time were censored. Those who experienced the event contributed a total of 1246.12 person-months with an incident rate of 29.69/1000 person-months. Out of the total failures, 31 (21.4%) were in the age group > 40 years, 33 (22.1%) occurred in males, 5 (17.2%) in pulmonary negative, 10 (62.5%) in relapse TB patients, 32 (19.6%) in bacteriologically confirmed cases, 19 (43.6%) in TB/HIV co-infected patients.

Estimates from the Kaplan-Meier survival analysis showed an overall survival time of 5.5 months (95% CI=5.4-5.7) and an overall mean survival time of 3 months (95% CI= 2.7-3.4) (Table 1, Figure 2). At 6 months follow-up, the overall cumulative survival function was 0.84 (95% CI=0.78-0.88) (Figure 2). In the Log-rank test of statistical significance, older age, males, relapse TB patients, and TB/HIV co-infected patients were associated with worse cumulative survival (p-value<0.05) (Table 1, 2, Figure 3,4). The mean survival time for age group > 40 years, males, relapse TB patients and TB/HIV co-infected patients was 2.9 months (95% CI=2.5-3.3), 2.9 months (95% CI=2.6-3.3), 2.8 months (95% CI=2.0-3.6), and 2.2 months (95% CI=1.8-3.3) respectively. There was no statistical difference between the classification of TB and bacteriological confirmation status (p-value ≥ 0.05) (Table 1,2).

Table 1 Demographic and other covariates of TB patients (N=226)

Covariates	Deaths	Censored	Total (%)	Mean Survival time(months) (95% CI)
Age(years)				
≤ 40	6(7.4)	75(39.7)	81(35.8)	3.8(3.0-4.5)
> 40	31(21.4)	114(60.3)	145(64.2)	2.9(2.5-3.3)
Sex				
Female	4(5.2)	73(38.6)	77(34.1)	3.7(3.0-4.4)
Male	33(22.1)	116(61.4)	149(65.9)	2.9(2.6-3.3)
Classification of TB				
Pulmonary -	5(17.2)	24(12.7)	29(12.8)	2.4(1.4-3.4)
Pulmonary +	32(16.2)	165(87.3)	197(87.2)	3.1(2.7-3.5)

Type of patient				
New	26(12.7)	179(94.7)	205(90.7)	3.1(2.6-3.5)
Relapse	10(62.5)	6(3.2)	16(7.1)	2.8(2.0-3.6)
RALTF*	1(20.0)	4(2.1)	5(2.2)	2.6(2.4-3.5)
Bacteriological Confirmation				
Negative	5(16.1)	26(13.8)	31(13.7)	2.6(1.7-3.5)
Positive	32(19.6)	195(86.2)	163(86.3)	3.1(2.7-3.5)
TB/HIV co-infection				
No	17(9.7)	159(84.1)	176(77.9)	3.0(2.5-3.5)
Yes	19(43.6)	20(10.6)	39(17.2)	2.2(1.8-3.3)
Unknown	1(9.1)	10(5.3)	11(4.9)	2.0(1.6-3.5)
Overall	37(16.4)	189(83.6)	226(100)	3.0(2.7-3.4)

*RALTF: Return After Loss to Follow-up, CI=Confidence interval, TB=Tuberculosis, HIV=Human immunodeficiency virus.

Table 2 Log-rank test of significance for the different groups of TB patients

Covariate	**Degree of freedom**	**Log-rank test**	
		Chi-square	**P-value**
Age	1	7.52	0.006*
Sex	1	10.52	0.001*
Classification of TB	1	0.04	0.848
Type of patient	2	37.10	0.001*
Bacteriological Confirmation	1	0.00	0.999
HIV co-infection	2	40.22	0.001*

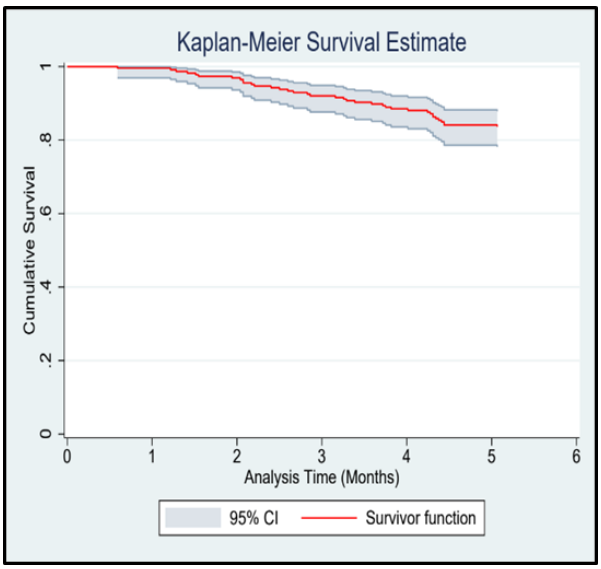

Figure 2 Kaplan-Meier overall survival curve of study participants

In the univariate Cox proportional hazard regression model, age, sex, patient type and TB/HIV co-Infection were biologically plausible and subsequently included in the multivariate analysis (Table 3). In the multivariate analysis, older age > 40 years (HR = 2.6, 95% CI = 1.1-6.3), being male gender (HR = 4.9, 95% CI = 1.7-14.3), relapse TB patients (HR = 5.2, 95% CI = 2.4-10.9), TB/HIV co-infection (HR = 7.1, 95% CI = 3.6-13.9) were identified as independent predictors associated with higher hazards of TB deaths (Table 3). There was however no statistical significance among unknown HIV co-infection status and return after loss to follow-up TB patients.

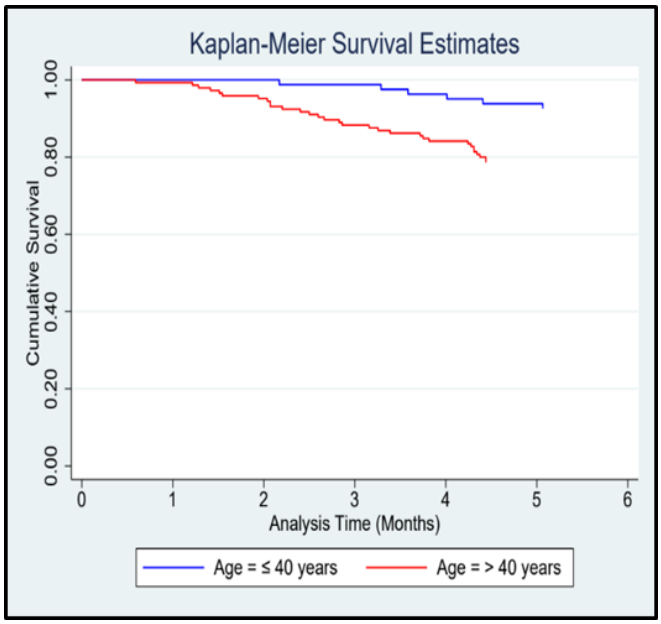

Figure 3 Kaplan-Meier survival curve of age groups ≤ 40 and > 40 years

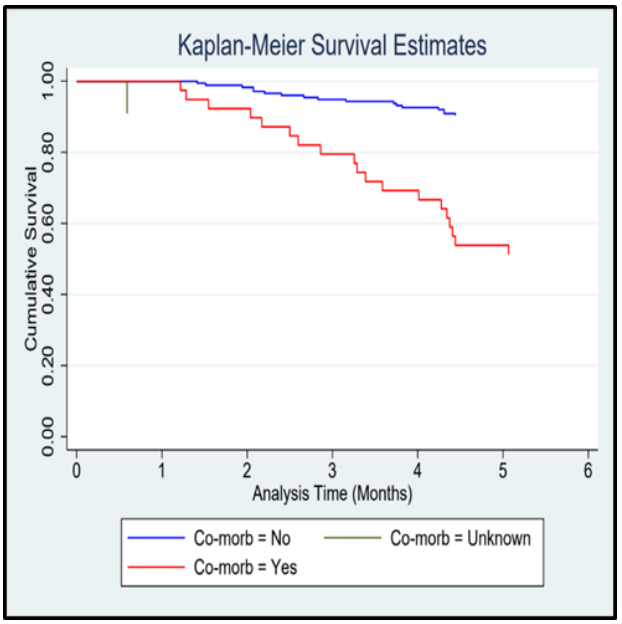

Figure 4 Kaplan-Meier survival curve of TB/HIV co-morbidity status

Table 3 Multivariate hazard estimate analysis in Cox proportional regression model (N=226)

Covariates	No of failures	Crude HR (95% CI)	Adjusted HR (95% CI)
Age(years)			
≤ 40	6(7.4)	Ref	Ref
> 40	31(21.4)	3.2 (1.3-7.6)	2.6 (1.1-6.3)
Sex			
Female	4(5.2)	Ref	Ref
Male	33(22.1)	4.7 (1.6-13.4)	4.9 (1.7-14.3)
Type of patient			
New	26(12.7)	Ref	Ref
Relapse	10(62.5)	7.1 (3.4-14.7)	5.2 (2.4-10.9)
RALTF	1(20.0)	1.6 (0.2-12.1)	1.0 (0.1-7.5)
TB/HIV co-infection			
No	17(9.7)	Ref	Ref
Yes	19(43.6)	6.2 (3.2-12.0)	7.1 (3.6-13.9)
Unknown	1(9.1)	0.97 (0.13-7.4)	1.3 (0.2-10.0)

HR=Hazard ratio, CI=Confidence interval, TB=Tuberculosis, HIV=Human immunodeficiency virus, RALTF= Return After Loss to Follow-up

4. Discussion

In this district-based TB registry retrospective cohort study, we estimated the survival time to death and evaluated covariates that independently predict TB mortalities in a rural district of the Central Region of Ghana.

In the present study, the overall survival function was 0.84 (95% CI= 0.78-0.88) at the end of the follow-up period, with an overall mean survival time of 3 months (95% CI= 2.7-3.4). Martínez-Rodríguez et al. [18] and Balaky et al. [19] reported a survival function of 0.93 higher than our findings. Perhaps, the difference in findings could be due to the use of a much larger sample size in both studies.

Out of the 226 study participants, the proportion of those who experienced the event was 16.4% occurring mostly among older age (21.4%), male gender (22.1%), relapse TB patients (62.5%) and TB/HIV co-infected patients (43.6%). Our finding is much lower than those reported by other studies [20–22]. The observed difference could be due to differences in study settings. However, the current finding is in agreement with findings documented by other studies in Ghana (13%) Brazil (17%) and Iran (15.7%) [9, 23, 24]. On the other hand, the finding of the present study is much higher than what was observed in other parts of the world ranging from 4.5% to 6.9% [3, 19, 25].

In the Kaplan-Meier analysis of the present study, we found a statistically significant difference in survival probability between different groups of TB patients. Older age 0.79 (95% CI=0.71 – 0.84, p-value =0.006), male gender 0.78 (95% CI=0.70 – 0.84, p-value = 0.001), relapse TB patients 0.37 (95% CI=0.15 – 0.60, p-values=0.001) and TB/HIV co-infection 0.51 (95% CI=0.35 – 0.66, p-value =0.001) showed a poorer survival probability. This is consistent with findings reported by other studies; older age [3, 4, 19], male gender [3, 4], relapse TB patients [3], and TB/HIV co-infection [4, 26]. The low survival rate of men could probably be explained by the fact that more men in the study area are exposed to risk factors of TB such as smoking, alcohol use and other occupational hazards than their female counterparts. Also, males have poor health-seeking behaviour than females in our part of the country which may adversely impact their treatment adherence and outcomes. Several studies have also reported the lethal synergy between TB and HIV [7, 27–31]. In congruence, Amante and Ahemed [32] and Teketelew et al. [20] demonstrated that younger age and Pulmonary negative TB cases were at significant risk of survival. The difference could be explained by the fact that Ethiopia where both studies were conducted is listed by WHO as a high-burden country for both TB and TB/HIV [4].

In this study, we found that TB patients > 40 years were 2.6 times (aHR = 2.6, 95% CI = 1.1 – 6.3) at risk of mortality compared to those ≤ 40 years. Similarly, the male gender was almost 5-fold (aHR = 4.9, 95% CI = 1.7 – 14.3) at risk of failure compared to females. Our study also demonstrated that relapsed TB patients were 5.2 times (aHR = 5.2, 95% CI = 2.4 – 10.9), TB/HIV co-infected patients a little over 7 times (aHR =7.1, 95% CI = 3.6 – 13.9) implicated in a higher rate of mortality than new TB cases and patients negative for HIV respectively. Comparable findings were reported by other studies; male gender [33], older age [34], TB/HIV co-infection [18, 35]. Other studies documented results higher than our findings; older age [19], and TB/HIV co-infection [33]. This could be elucidated by the difference in study settings.

The results of this study can provide vital information to health departments about the survival experiences of TB patients in the region. The provision of training to health professionals and community awareness creation can enhance early detection, treatment adherence, and improve overall survival.

This study was not without limitations. We employed a retrospective records review, hence, other important risk factors for TB mortalities such as smoking, alcoholism, economic, and nutritional status could not be accessed for analysis. The study did not consider the competing risk of the event (death). Findings from this present study should therefore be interpreted with caution. Notwithstanding, the findings provide contextual evidence on the predictors of survival based on the variables that the current TB register captures.

5. Conclusion

This is a novel epidemiological study on survival analysis of TB patients in the central region of Ghana. Findings from this study demonstrated that the overall survival function for the follow-up period was relatively low. Older age, male gender, relapse TB patients and TB/HIV co-infected patients were implicated as plausible predictors for survival time to death of TB patients.

This highlights an urgent need for policymakers, health authorities and stakeholders to initiate targeted TB management interventions that enhance the quality of care in TB management.

Further studies with a larger sample size and accommodating the competing nature of multiple causes of the event and other variables are essential to validate these findings.

Compliance with ethical standards

Acknowledgments

The authors are grateful to the Ajumako Enyan Essiam District Health Directorate for allowing us to carry out this study in the study area and granting access to the data.

Disclosure of conflict of interest

The authors declare no competing interest.

Statement of Ethical approval

This study was based on data extracted from the medical records of TB patients and this did not have any physical contact with the patients. However, written permission was obtained from the Ajumako Enyan Essiam District Health Directorate.

Statement of informed consent

This research work did not involve physical contacts with human subjects, hence informed consent was not required.

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