FACTORS ASSOCIATED WITH DEATH AMONG TB PATIENTS IN TANZANIA IN 2017

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FACTORS ASSOCIATED WITH DEATH AMONG TB PATIENTS IN TANZANIA IN 2017

By

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Certification

The undersigned certify that they have read and hereby recommend for acceptance of dissertation entitled ***Factors associated with death among TB patients in Tanzania in 2017***, in partial fulfilment of the requirements for the degree of Master of Science in Applied Epidemiology of Muhimbili University of Health and Allied Sciences**.**

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Declaration and Copyright

I, **Elias Musa Bukundi**, declare that this **dissertation** is my original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature……

Date……...….....

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Dedication

This work is dedicated to all my family members; Mother, Wife, Daughter, and Sons, Brothers and Sisters for their continuous love, support, and encouragement.

Abstract

Background: Tuberculosis (TB) is the main cause of death from a sole infectious agent worldwide. Tanzania is among the 30 high burden countries with a mortality of 47 per 100,000 population and a case fatality of 4%. Although there are many studies conducted on TB mortality rate and risk factors using routine data from other countries, inconsistent findings from various studies prompted further studies to be conducted to assess whether factors reported in previous studies are applicable in our local setting.

Objectives: This study intended to determine the mortality rate, survival probabilities, and factors associated with death among TB patients.

Methodology: A retrospective cohort study was conducted utilizing national TB program data of all TB cases registered from January 2017 to December 2017. Kaplan-Meier estimator was used to determine survival probabilities and an extended Cox proportional model was used to identify independent risk factors of death among TB patients. Hazard ratios and 95% confidence intervals are presented.

Results: Among 61,979 patients, 2114 (3.4%) patients died during TB treatment giving a mortality rate of 6.0 per 1000 person-months. The independent risk factors for death among TB patients included older age ≥60 years (aHR = 2.51, 95% CI = 2.11-2.99), accessing service at the hospital level (aHR = 1.15, 95% CI = 1.04-1.27), TB/HIV Co-infection (aHR = 2.89, 95% CI = 2.61- 3.20), and facility-based DOT option (aHR = 2.25, 95% CI = 1.83 - 2.79). Other factors were sputum negative results (aHR =1.37, 95% CI = 1.21-1.58), having extrapulmonary TB (aHR =1.21, 95% CI = 1.08-1.34), being referred from other sources (aHR =1.48, 95% CI = 1.22- 1.80), residing in southern highland zone (aHR =1.73, 95% CI = 1.38-2.18), Southern Zone (aHR =1.57, 95% CI = 1.22-2.01) and western zone (aHR =1.54, 95% CI = 1.21-1.97).

Conclusion: We identified several independent predictors of death among TB patients among different risk groups. To achieve the milestone of reducing TB mortality by 2035, it is critical to formulate appropriately targeted interventions on the prompt detection, diagnosis, and appropriate referral of TB patients among the risk groups.

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List of abbreviations

AFB	=	Acid-Fast Bacilli
AIDS	=	Acquired Immuno-Deficiency Syndrome
ART	=	Anti-Retroviral Therapy
CFR	=	Case fatality rate (CFR)
CPT	=	Cotrimoxazole Preventative Therapy
CTC	=	Care and Treatment Centre
DOT	=	Directly Observed Therapy
DST	=	Drug Susceptibility Test
EPTB	=	Extra-pulmonary tuberculosis
ETL	=	Electronic tuberculosis and leprosy system
ETR/ETR.net	=	Electronic TB Register
HIV	=	Human Immunodeficiency Virus
IPT	=	Isoniazid Preventative Therapy
IRIS	=	Immune Reconstitution Inflammatory Syndrome
MDG	=	Millennium Development Goal
MDR TB	=	Multi-Drug-Resistant Tuberculosis
MDT	=	Multidrug therapy
MOHCDGEC	=	Ministry of Health, Community Development, Gender, Elderly and Children
MTB	=	Mycobacterium tuberculosis
NACP	=	National AIDS Control Programme
NTLP	=	National Tuberculosis and Leprosy Programme
PLHIV	=	People living with HIV/AIDS
PM	=	Person-Month
PTB	=	Pulmonary tuberculosis
R/RIF	=	Rifampicin
RH	=	Rifampicin and Isoniazid
RHZE	=	Rifampicin, Isoniazid, Pyrazinamide, Ethambutol
RR-TB	=	Rifampicin-resistant tuberculosis
TB	=	Tuberculosis
TST	=	Tuberculin skin test
WHO	=	World Health Organization
XDR –TB	=	Extensively Drug-Resistant Tuberculosis

Definition of Terms

A cured patient: Pulmonary tuberculosis (PTB) patient who had confirmed Tuberculosis (TB) at the start of treatment and was tested negative using smear or culture in the last month of treatment and on at least one previous event.

Death: A death while on the TB treatment with confirmed TB at the time of the death irrespective of the cause.

Directly Observed Therapy (DOT): A strategy of tuberculosis treatment that involves direct monitoring and documenting of the patient taking the medication, standardized regimens, and correct diagnostic and referral systems.

Extrapulmonary TB: Any TB case involving other organs different from the lungs.

Pulmonary TB: Any TB case involving the lung parenchyma.

HIV-positive TB patient: Patient with TB (bacteriologically confirmed or clinically diagnosed) who has a documented HIV-positive result or has a positive HIV result from testing done during TB diagnosis.

HIV-negative TB patient: Patient with TB who has a documented negative HIV result from a test done during TB diagnosis.

New patients: Patients who have no TB history of before TB treatment or who have had been on anti-TB drugs in less than one month irrespective of their smear or culture results.

Retreatment TB patients: Patients who have received one month or more of anti-TB drugs in the past who present with the second episode of TB.

1 Introduction

1.1 Background

Tuberculosis (TB) is among the main ten causes of deaths and it's the main source of deaths from a sole infectious agent worldwide above HIV/AIDS (1). Globally 10.0 million people developed TB disease in 2017, of which 72% were from Africa (1). Moreover, one-third of the world population is infected with TB and is in danger of developing the disease throughout their lives (2). There were 464,633 reported cases of TB among people living with HIV, which was equal to 51% of all estimated new cases (920,000) reported in 2017 worldwide (1). In 2015, the Sustainable Development Goals (SDGs) were adopted with the purpose of Ending TB. One of the SDG targets discusses ending epidemics of AIDS, TB Malaria, and other infectious illnesses by 2030 (1). Likewise, in 2014 the WHO End TB strategy was formed with the target of reducing tuberculosis incidence by 90% and reduce TB deaths to 95% by the year 2035 (3). However, to reach the first milestone of the End TB strategy, the case fatality rate (CFR) is required to fall to 10% and 6% by 2020 and 2015 respectively (1). Both the SDGs and the End TB strategy provide the background for national and international efforts to end TB epidemic during the period 2016-2030 (1).

Tanzania is among 30 high TB burden countries and the 20 countries with a higher estimated number of TB incident cases in people living with HIV (1). In 2017, a total of 69,623 TB cases were notified, with a high incidence rate of 269/100,000 population (4). This was twice as much as the global TB incidence rate of (133/100,000) (1). The overall treatment success rate for TB cases notified in 2016 was 90%, 86%, and 81% for new, relapse, and previously treated cases respectively (4).

In Tanzania, 350 (49%) out of 700 health facilities provide TB treatment services and among them, 15% provides TB diagnostic services (4). TB management is done according to the national TB treatment guideline adopted from the WHO recommendations. TB treatment involves two months of Rifampicin, Isoniazid, Pyrazinamide, Ethambutol (RHZE) followed

by four months of Rifampicin and Isoniazid (RH). Nevertheless, other forms of TB such as TB meningitis, miliary, TB of the spine, bone, and joints are managed by two months RHZE followed by 10 months of RH. Conversely, previously treated smear-positive pulmonary TB (relapse, return after default, treatment failure) are treated by 3 months of RHZE followed by 5 months of Rifampicin, Isoniazid, and Ethambutol (RHE) (5).

There have been conflicting reports on risk factors for death among TB patients, some studies have reported a higher risk among: TB/HIV co-infected (6–9); male patients (2,9–11); Tb patients getting services at a low-level health facility (12); those with smear-negative (3,7,12–14); facility-based DOTs option (10,15); those referred from no-program liked clinics (14); pulmonary TB patients (11,16–19); and older TB patients (7–9), and re-treatment TB patients (7,14). However, other studies have reported a higher risk among female (3), smear positives TB patients (20,21), those using home-based DOT options (21), with both pulmonary and extra-pulmonary TB (8,14); extrapulmonary TB (7,17), with an absence of microbiological confirmation (14) and, with the presence of diabetic Mellitus (9). Reducing TB associated deaths is vital in high burden countries where one of the approaches is to identify risk factors for death (8). Identification of factors associated with mortality will help to plan for inventive strategies to manage TB disease and minimize TB mortality (22).

1.2 Problem statement

Tuberculosis is still a major public health problem globally. In 2017 around 1.7 million deaths from TB disease occurred with TB/HIV specific mortality of 11% Worldwide (1,22). Similarly, the reported mortality among TB and TB/HIV patients from other studies ranged from 7% to 33.4% (3,7,9,12,16,17,22–25). Tanzania met the overall treatment success rate of 90% for new and relapse cases. Yet, the TB mortality rate is estimated at 47 and 39 per 100,000 population among HIV negative and HIV positive TB patients. This mortality estimate is high above the global TB mortality rate of 17 and 4 per 100,000 population among HIV negative and HIV positive TB patients respectively (1). Similarly, In 2016 among 64,609

new and relapse TB cases reported, 3708 (6%) died and amongst 1,334 previously treated TB patients, 124 (9%) died (26).

Although there is a multitude of studies conducted on TB mortality rate and risk factors using routine data from other countries, few utilized large national databases especially in Sub-Saharan countries. Likewise, few studies have been conducted to determine risk factors associated with death among TB patients in Tanzania (6,13,27). Nevertheless, these studies had a small sample size and most were conducted in Dar es Salaam, Kilimanjaro, and Mwanza. Therefore, they were not representative of the whole country. Additionally, inconsistent findings from various studies support for further studies to be conducted to assess whether factors reported in previous studies are applicable in our local setting. Due to various health TB interventions that have been put in place recently, there was a need to assess if the risk factors of TB deaths have changed over time. This study used data from the National Tuberculosis and Leprosy Programme (NTLP) which covers the whole country. The purpose of this study was to identify the mortality rate, survival probabilities and risk factors associated with death among TB patients in the country. Furthermore, the study mapped the geographical differences in mortality among TB patients.

1.3 Conceptual framework

The indirect factors associated with TB mortality include social-economic status, demographic factors, and clinical factors. Similarly, demographic factors such as age, sex, type of health facility, geographical zones, and type of TB referral influence TB mortality. Additionally, clinical characteristics such as TB treatment category, TB smear results, anatomical site of TB, DOT options, and HIV infections affect TB mortality. Correspondingly, there is a relationship between HIV infection with TB treatment category, TB smear results, and anatomical site of TB. Other social-economic factors such as occupation and lifestyle influence acquisition of TB infections and may lead to TB mortality as shown in **Figure 1-1**.

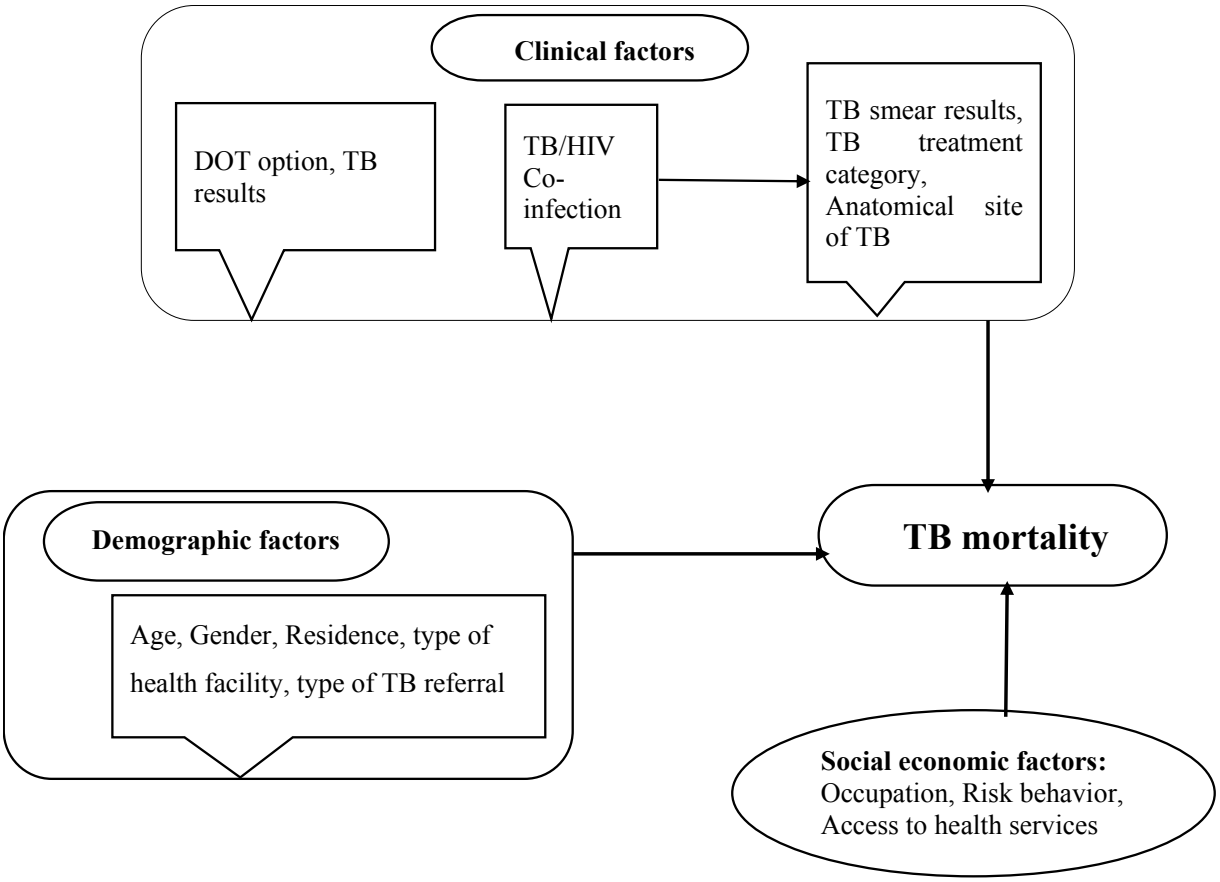

Figure 1-1:Conceptual framework on risk factors of death among TB patients

1.4 Rationale

This study was envisioned to identify the risk factors for mortality in TB patients and their survival probability. Understanding the factors leading to death among TB patients in the local context is important for program planning and formulation of appropriately targeted interventions of care of TB patients in Tanzania. Information on the risk factors of TB mortality will help the country to improve treatment outcomes, re-evaluate the clinical care management, and achieve the milestone goals to eliminate TB. Likewise, identification of regions specific TB mortality will help to map and identify most vulnerable regions with a high mortality rate for the planning of specific interventions to reduce TB mortality.

1.5 Research questions

I. What are the mortality rates of TB and TB/HIV patients in Tanzania in 2017?

II. What are the risk factors for TB death in Tanzania in 2017?

III. What are the survival probabilities during TB treatment in 2017 among?
   - TB and TB/HIV Co-infected patients?
   - Home and facility-based DOT options?

IV. Are there any geographical differences in the magnitude of TB deaths in Tanzania in 2017?

1.6 Objectives

1.6.1 Broad Objectives

To identify factors associated with death among TB patients and their survival probabilities in Tanzania, 2017.

1.6.2 Specific Objectives.

I. To determine the mortality rate among TB and TB/HIV co-infected patients, 2017.

II. To determine survival probabilities among TB and TB/HIV, home and facility-based DOT option, 2017.

III. To determine risk factors associated with death among TB patients, 2017.

IV. To map sub-national differences for TB mortality in Tanzania, 2017.

2 Literature review

2.1 Mortality rate among TB patients

Several studies have reported dissimilar findings on TB mortality ranging from 11.3% to 33.4% (3,9,12,16,17,24,25). Equally, the mortality rate also has been inconsistent ranging from 2.6 per 100 person-years to 49.1 per 100 person-years (7,12,17,19,28).In a study conducted in sub-Saharan Africa, it was noticed that mortality rate was 10.6 times higher among TB patients compared to the general population (20). The variations in the death rate among various studies in the different countries were suggested due to differences in the social-economic status among the countries (17). Studies conducted in Tanzania have reported mortality rates ranging from 3.4% to 13.9% (6,13,29). However, these studies had a small sample size and were conducted in few regions especially Dar es Salaam, therefore, were not representative of the whole country. Due to the inconsistency of TB mortality rate findings from different countries, there was a need to determine the mortality rate in our setting to know the size of the problem in our local setting.

2.2 Risk factors associated with mortality among TB patients

2.2.1 Sex

Several studies have found an increased risk of TB deaths among male patients (2,9–11). The authors pointed out that some risk behaviours such as alcohol abuse and smoking are more prominent to male TB patients compared to females (9). Correspondingly, males tend to be non-compliance to TB treatment and have poor utilization of health services compared to females (10). All these might have contributed to the observed findings. Nonetheless, conflicting findings were reported in the study conducted in Zimbabwe whereby male sex was not associated with high TB mortality (12). Additionally, a 10-year retrospective study conducted in South Africa proposed that being a male was protective against TB mortality (3). Other studies have reported that being female was protective against TB mortality (30,31).

2.2.2 Age

Advancing age was reported to be associated with an increased risk of death among TB patients (2,8,9). A study conducted in South Africa reported that older TB patients are more likely to have extrapulmonary TB which is difficult to diagnose. Additionally, frequent drug side effects, comorbidities, and drug-induced liver disease might contribute to high mortality in this group (3). Furthermore, older TB patients may have weakened immune systems and social-economic problems (9). This highlights the need for special prioritization of this group as a key population during planning, policy-making, and designing of more effective interventions (32). Nonetheless, in the study conducted in Henan Province, China, increased age was not documented as the risk factors for TB mortality. The authors described that the finding could be due to confounding the effect of age with education status, household economic status, and access to TB treatment (21).

2.2.3 Residence

Previous studies have documented that rural area was associated with a high risk of TB mortality (9,14). The study conducted in Nigeria claimed that distance from the health centre, absence of treatment centre at the place of residence might have attributed to the observed findings. Also, the authors reported that poor social-economic status and interrupted supply of TB drugs might have contributed to an increased risk of TB mortality in rural areas (14). Nonetheless, these findings were in contrast with a prospective cohort study conducted in Iran which reported that rural residence was not a predictive factor for TB deaths (2).

2.2.4 Type of health facility

In the retrospective study conducted in Zimbabwe, it was acknowledged that accessing treatment from the higher-level health facility reduced the risk of death among TB patients (12). Conversely, in the study conducted in Kenya, it was discovered that mortality among TB patients was the same regardless of the type of health facilities. The authors illustrated that patients were getting a comparable standard of care irrespective of the type of health facilities (20). Additionally, a study conducted in the USA reported that patients who were receiving

treatment in private health facilities had an increased risk of TB mortality than those receiving in public health facilities. The authors described that treatment by non-public health providers was related to inappropriate treatment regimens (33).

2.2.5 TB smear Results

Numerous authors have found that smear-negative patient has an increased risk of TB deaths (3,12,13) A study conducted in Zimbabwe reported that most smear-negative TB patients tend to be HIV positive hence experience poor treatment outcomes (12). Likewise, a study conducted in Nigeria argued that misdiagnosis among smear-negative patients may have contributed to high mortality. The authors called for attention to the use of Gene expert to minimize misdiagnosis and delayed diagnosis among TB/HIV patients (14). Nevertheless, these findings contradicted other studies that suggested an increased risk of death in pulmonary smear positives than pulmonary negative patients (20,21). Similarly, in the retrospective study conducted in South Africa, it was revealed that not having sputum smear results was the strongest risk factor for death in TB patients (3). Additionally, a study conducted in China suggested that the mortality rate was similar between smear-negative and smear-positive TB patients (22).

2.2.6 TB diagnostic category

Several studies have described that retreatment patients have a high risk of TB mortality than new cases (3,7,16,20). A study conducted in Kenya suggested that this could be due to the uncertain efficacy of retreatment regimen due to drug-resistant TB (20). Similarly, in the retrospective study conducted in Zimbabwe, it was pointed out that retreatment TB patients were most probable to be non-compliant to TB treatment and might have undiagnosed drug-resistant (12). In contrast to these findings, a retrospective study conducted in Ethiopia observed that the treatment category was not significantly associated with mortality. The authors suggested that late access to health care services and progressive disease status might be the reasons for this finding (28). Similarly, the retrospective study conducted in the USA, it

was revealed that patients with Pulmonary and extrapulmonary TB had a high risk of TB mortality, this was due to the presence of advanced disease (34).

2.2.7 HIV status

Numerous studies have revealed that having TB/HIV comorbidities has been associated with higher TB mortality (6,9,12,24,28,30). The authors stated that a suppressed immune system (9,12), and delay in diagnosis (9) might have contributed to the high mortality in this group. Other reasons included presences of adverse events, presence of opportunistic disease (24), and difficult diagnosis of sputum smear due to atypical TB clinical presentation in TB/HIV patients (28). Yet in a study conducted in the USA, found that patients with unknown HIV status had an increased risk of TB mortality (35). It is necessary to conduct HIV screening in all TB patients for prompt initiation of ARV drugs (30).

2.2.8 Anatomical site of TB

Previous studies have found that patients with extrapulmonary TB were more likely to die than those with pulmonary TB patients (16–18). A study conducted in Ethiopia demonstrated that delays in diagnosis of extrapulmonary TB were due to a lack of awareness of the symptoms. Also, the authors suggested that lack of access to health care services, shortage of trained clinicians and laboratory personnel might have contributed to increased mortality (17). In the study conducted in Brazil, it was suggested that more refined tests are required in this group of TB patients to minimize delay in diagnosis (16). In disputing these findings, other studies revealed that patients with pulmonary TB had an increased risk of TB mortality compared to extrapulmonary TB (11,19).

2.2.9 DOT option

In the Meta-analysis study conducted in 2016, it was claimed that community-based DOT options improved treatment outcomes in TB patients because it was convenient and cost-effective (15). Congruently, a study conducted in China, discovered that TB patients under facility-based DOTs option had an increased risk of TB mortality than self-administered and

family observed management. The authors reported that most of the patients under facility-based DOTs options were poorer compared to those under community-based DOTs options (10). However protective effect against TB mortality was reported in patients using both facilities-based and community-based DOT options in the retrospective study conducted in the USA (34).

2.2.10 Type of referral

In the study conducted in Nigeria, reported a high TB mortality among TB patients referred from no-program liked clinics. The authors suggested that delay in diagnosis might have resulted from inadequate access to care among vulnerable populations unrecognized co-existing morbidities (14). A study conducted in Tanzania reported that most TB patients seek services from Pharmacies and traditional healers after the onset of TB symptoms. Also, most of the referred TB patients do not show up at the diagnostic centre (36). This might have resulted in a diagnostic delay in TB diagnostic and an increased risk of death (37).

Few studies have been conducted in Tanzania to identify the risk factors among TB patients (6,13,27). A multicenter prospective observational study conducted in Dar es Salaam revealed that the independent risk factors for mortality included HIV infection, drug resistance, and low monthly income (6). Other risk factors were being on home-based DOT options, older age, being a retreatment TB patient, having smear-positive, lower CD4 count, and HIV/TB comorbidities (13,38,39). However, most of the studies conducted in Tanzania had a small sample size and mostly conducted in Dar es Salaam and few in Mwanza and Moshi. Therefore, these studies were not representative of the whole country. Similarly, contradictory and inconsistent findings observed from various studies suggest further studies need to be conducted to determine factors associated with TB mortality especially in our setting where information is scarce. This study was intended to fill the gap on the risk factors for TB mortality in Tanzania using a large national TB program database.

2.3 Survival probabilities among TB patients.

There are diverse findings in the survival probabilities among TB patients from different studies. In the retrospective study conducted in Myanmar, the survival probabilities of TB patients was 82% at 5 years and 58.1% at 10 years (25). Similarly, a study conducted in Rio de Janeiro, Brazil reported the survival probabilities after one year from TB treatment onset was 87% (19). Numerous studies have reported high survival probabilities among HIV-negative patients compared to HIV positive patients, low immune system in HIV positive patients contributed to these finding (20,30,40).In contrast, a study conducted in south India found no significant difference in survival probabilities between HIV negative and HIV positive patients (41).

These contradicting findings suggest further studies need to be conducted in different settings to determine the survival probabilities of TB patients to plan for locally targeted interventions. This study is expected to explore the survival probabilities of TB patients among TB and TB/HIV co-infected new TB, and retreatment TB patients, adults and children.

2.4 Geographical difference of TB mortality

Several studies have shown the significance of geographical differences in TB mortality within the country (21,42–44). These differences highlighted the effect of social inequalities among the regions, authors suggested the need for regional and local strategies to reduce TB mortality (21,42–44). It was found that income and household density had substantial spatial association with TB mortality (42).TB mortality was higher in the regions which are economically developed and more affected by HIV (44). However, a retrospective study conducted in Saudi Arabia analyzing TB mortality by province did not show any significant differences (45). Little is known about the geographical differences in TB mortality in Tanzania. Identification of geographical differences in Tanzania will facilitate the identification of most vulnerable regions with a high mortality rate and plan for geographical specific targeted intervention to reduce TB mortality.

3 Methods

3.1 Study design

We conducted a retrospective cohort study of Tanzania national TB program data. The study involved TB patients who were enrolled on TB treatment from January 2017 through December 2017. The follow-up period was between January 2017 to June 2018.

3.2 Study area

The data involved all TB cases in the NTLP national TB program reported from all 26 Tanzania mainland regions. In 2020 the Tanzania mainland population was projected to be 55,966,030 based on 2012 national census. According to the projected population, female make up 51% (28,550,590) of the total while for male it is 49% (27,415,440). The projected annual growth rate is estimated at 3.1% from 2013 – 2035 (46).

3.3 Study population

The study population comprised of all TB cases who were enrolled on TB treatment from January 2017 through December 2017 from the NTLP national TB program data in all Tanzania mainland regions.

3.4 Power of the study

We calculated the power of the study using the formula for estimation of power for cohort studies (47) as shown below

$$Power = \Phi\left(\frac{\sqrt{(n_1 * \Delta^2)} - z_{1-\alpha/2}\sqrt{(1+1/\kappa) * p * q}}{\sqrt{(p_1 * q_1) + (p_2 * q_2 / \kappa)}} \right)$$

Whereby

Δ = difference of risk of disease between exposed group and non-exposed group

κ = ratio of sample size: non-exposed group / exposed group

p_1= risk of disease among the exposed group;

p_2= risk of disease among the non-exposed group;

p = (p1*n1+p2*n2) / (n1+n2)

q= 1-p

n_1= available sample size among the exposed group;

Calculation of the power of the study was done using the following assumptions:
The two-sided confidence interval of 95% was used. TB only cases were considered as a non-exposed group and TB/HIV cases as an exposed group. The number of TB/HIV cases were 18,392 while TB only cases were 42,243. The ratio of sample size among non exposed group and exposed group (K) was 2.3. Risk of mortality among exposed (TB/HIV co-infected) was 6.2% while risk among non-exposed was 2.1%. Power calculation using OpenEpi software Version 3.01 available at https://www.openepi.com/Menu/OE_Menu.htm yielded a power of 100%.

3.5 Inclusion and Exclusion Criteria

3.5.1 Inclusion criteria

The inclusion criteria were all TB patients who were enrolled on TB treatment available in the NTLP national TB program data from January 2017 to December 2017.

3.5.2 Exclusion criteria

Exclusion criteria were any patient with missing treatment outcome and inconsistent treatment dates.

3.6 Data abstraction procedure and Dataset description

This study used individual case information database captured in the TB register (ETR.net). ETR.net is an electronic database that was designed with the support of the US president's Emergency Plan for AIDS Relief (PEPFAR). ETR.net is used for TB/HIV surveillance, program monitoring and evaluation. It provides standardized cohort reports of treatment and

services for TB patients (8,48). In Tanzania, TB case information is recorded at the primary health facilities through the use of paper-based TB register which is sent to the district TB coordinator. At the district level, the paper-based reports are captured on the ETR.net which later are submitted to the regional and national level.

Data were exported from the NTLP National case-based electronic surveillance systems (ETR.net) in the DHIS2 to Microsoft Excel 2010 and then imported into Stata Version 15.0 for analysis. Before analysis, range and consistency checks were performed to ensure that the data lie within the maximum and minimum preset values and are logical. The main outcome was death while on the TB treatment with confirmed TB at the time of the death irrespective of cause (4). Independent variables were socio-demographic and clinical characteristics available in the NTLP national TB program data. Demographic characteristics included sex, age, geographical zones, types of health facilities, and type of referral. Clinical characteristics included TB diagnostic category, anatomical site of TB, TB results, DOT option, and HIV status.

In the database, these variables were recorded as follows: age as a continuous variable which we categorized as (0-14, 15-59 years, 60 and above); sex (male and female); HIV status (Negative, positive or unknown); referrals (self, community CTC, others); TB registration group (New, other, relapse, treatment after failure, treatment after loss to follow up) which was named as TB diagnostic category (new and retreatment); facility name which we categorized them as a dispensary, health centre and hospitals; disease classification (both,extra-pulmonary, pulmonary) which were renamed it as anatomical site of TB; TB result 1 (negative, positive, scanty, suggestive, Ti, not suggestive) which we merged it with TB test result (DST, X-pert, X-ray) to form TB results (sputum positive, sputum negative and other non-sputum tests); DOT option (home and facility); regions (name of reporting region) which we grouped them in zones. The dependent variable was recorded as treatment outcome (completed treatment, cured, died, lost to follow up, treatment failed) which we recorded as died/censored.

3.7 Data analysis

Categorical variables are presented using frequencies and proportions and the mean (standard deviation (SD)) is used for continuous variables. Pearson's chi-square test was used for comparison of categorical variables. The time between TB treatment initiation until death or censoring (time in months) was used as survival time. Patients who were lost to follow-up, or who had their treatment classified as failure, success, or cure were censored at the outcome date. Likewise, patients who were alive at the end of TB treatment were also considered as censored.

Overall and covariate specific mortality rate per 1000 person-months (Person-months) among TB patients was calculated. Likewise, stratum specific mortality rates among TB and TB/HIV co-infected patients were estimated.

The overall survival probabilities among TB patients at 2,6 and 12 months were calculated using the Kaplan-Meier estimator. The Kaplan-Meier curves were plotted to estimate the survival probability among TB and TB/HIV co-infected patients, home and facility-based DOT options, new and retreatment TB patients. The log-rank test was used to test statistical significance differences between the survival curves. Concerning median survival time, this could not be estimated since the median survival time was not achieved in our cohort. However, we calculated the median survival time among TB patients who died during the follow-up time using the Kaplan-Meier estimator.

To handle missing data, multiple imputation method by chain equations was used after assessment of the pattern of missing values which were missing at random (MAR) (8,49). The imputed variables included age group, gender, anatomical site of TB, TB results, HIV status and DOT option. Also, we used a multiple imputation method to account for missing values on the treatment outcome. An extended Cox model (time-dependent Cox proportional model)

was used for univariate and multivariate analyses after verification of the proportional-hazard assumption using the Schoenfeld's test (19,50). Covariates such as type of health facilities and geographical zone did not satisfy the proportional hazard assumption hence were used as time-dependent variables. Factors that were statistically significant at a p-value of ≤0.2 in the univariate analysis were considered as potential risk factors and included in the multivariable model. We assessed both a main effects multivariable model and a model including significant two-way interaction terms between covariates. The overall P-value for each variable is estimated using the likelihood ratio test. Hazard ratios and their respective 95% confidence intervals were reported.

We mapped the mortality rate per 1000 person-month for each region to identify sub-national geographic differences of TB mortality rate among TB patients. Mortality rates per 1000 person-month were exported from Stata into Microsoft Excel then imported into QGIS for Mapping.

3.8 Ethical considerations

Ethical approval was obtained from the Ethical Review Board at Muhimbili University of Health and Allied Sciences. Approval to use the national TB program data were obtained from the Program Manager of the National TB and Leprosy Programme (NTLP) in the Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC). Study data were extracted using TB unique ID number before analysis and access was limited to approved persons.

4 Results

4.1 Characteristics of TB patients

A total of 65,535 records were found in the NTLP national TB program data from January 2017 to December 2017. Of these, 3,556 (5.4%) were excluded from the analysis because of the inconsistent treatment date. A total of 61,979 (94.6%) remained in the final analysis **(Figure 4-1).** Included and excluded patients had similar demographic and clinical characteristics.

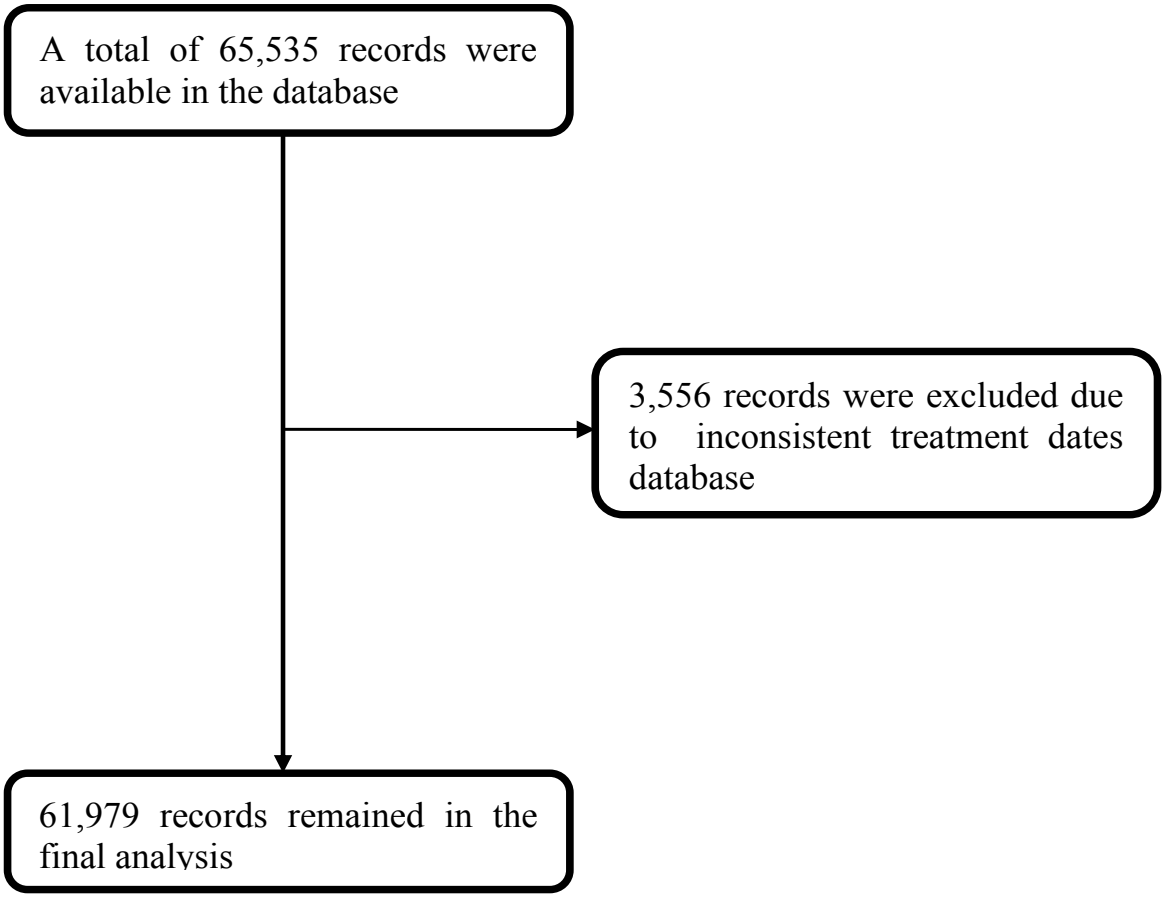

Figure 4-1: Flowchart for the selection procedure of study subjects

The baseline demographic and clinical characteristics for the study cohort are shown in **Table 4-1** and **Table 4-2** respectively. More than two-thirds, 44,198 (71.3%) of the study cohort were aged between 15-59 years and the mean (SD) age was 38 ± 19 years. Males accounted for 37,818 (61.0%) of the study population. Over 59,314 (95.7%) of patients had accessed the service care as new TB cases and above three-quarter, 49,322 (80.7%) had pulmonary TB. About one-third, 18,392 (29.6%) of all TB patients were HIV positive and a majority of the study cohort 55,518 (89.6%) were on home-based DOT options.

Table 4-1: Baseline demographic characteristics of TB patients enrolled on TB treatment from January to December 2017, Tanzania

Characteristic	Number	Percentage
Sex		
Female	24160	39.0
Male	37818	61.0
Age Group (Years)		
0-14	7849	12.7
15-59	44198	71.3
> 59	9914	16.0
Types of health facility		
Dispensaries	16053	25.9
Hospitals	29870	48.2
Health Center	16055	25.9
Geographical Zones		
Eastern Zone	17346	28.0
Central Zone	4670	7.5
Lake Zone	10416	16.8
Northern Zone	10477	16.9
Southern Zone	4568	7.4
Southern Highland Zone	7549	12.2

Western Zone	6953	11.2
Type of Referral		
Self	45038	72.7
CTC	7227	11.7
Community	7062	11.3
Other referral types	2652	4.3

Table 4-2: Clinical characteristics of TB patients enrolled on TB treatment from January to December 2017, Tanzania

Characteristic	Number	Percentage
TB diagnostic category		
New cases	59314	95.7
Retreatment	2665	4.3
Anatomical site of TB		
Pulmonary TB	49322	80.7
Extrapulmonary TB	11745	19.2
Both	42	0.1
TB results		
Sputum Positive	18154	29.3
Sputum Negative	12300	19.9
Other non-sputum tests	26591	42.9
Missing	4934	7.9
DOT option		
Home-based	55518	89.6
Facility-based	1990	3.2
Missing	4471	7.2
HIV status		
HIV-negative	42243	68.2
HIV-positive	18392	29.6
Unknown/Missing	1344t	2.2

4.2 Mortality rate

During the study period, a total follow-up time of 352130 person-months in 61,979 TB patients was obtained and 2114 (3.4%) participants died. The number of TB patients who died during the follow-up time among TB only and TB/HIV co-infected patients were 923 (2.1%) and 1146 (6.2%) respectively. The crude mortality rate was estimated to be 6.0 per 1000 Person-months (95% CI, 5.75–6.26). The mortality rates at 2, 6, and 12 months were 10.26, 3.44, and 6.96 per 1000 Person-months respectively.

Mortality rates (per 1000 Person-months) across different covariates are shown in **Table 4-3.** TB/HIV patients had almost three times higher mortality rate (11.20: 95% CI, 10.57-11.86) as compared to HIV negative TB patients. Elderly (≥60 years) TB patients had the highest mortality rate across all age groups (8.36: 95% CI, 7.63 - 9.15). Also, retreatment TB patients had approximately two-fold higher mortality rate (10.35: 95% CI,8.90-12.03) as compared to new TB patients. Correspondingly, a higher mortality rate was observed among patients referred from CTC (11.33: 95% CI, 10.34 - 12.43); TB patients using facility-based DOT option (13.65, 95% CI,11.67 -15.96); TB patients with both pulmonary and extra-pulmonary TB (17.86: 95% CI, 6.70-47.58).

Table 4-3: Mortality rates per 1000 person-months across explanatory variables among TB patients in 2017, Tanzania

Characteristic	Person-months	Number of deaths	Mortality rate per 1000 person-months (95% CI)
Crude mortality rate	**352130**	**2114**	**6.00 (5.75-6.26)**
Sex			

Female	137033	873	6.37 (5.96- 6.81)
Male	215091	1241	5.77 (5.46-6.10)
Age Group (Years)			
0-14	45061	175	3.88 (3.35- 4.50)
15-59	251182	1473	5.86 (5.57-6.17)
≥60	55770	466	8.36 (7.63 -9.15)
Types of health facility			
Dispensary	91649	487	5.31 (4.86-5.81)
Hospitals	167168	1194	7.14 (6.75-7.56)
Health Center	93313	433	4.64 (4.22-5.10)
Geographical Zones			
Central Zone	27264	102	3.74 (3.08- 4.54)
Eastern Zone	98241	480	4.89 (4.47-5.34)
Lake Zone	58680	337	5.74 (5.16- 6.39)
Northern Zone	59987	324	5.40 (4.84- 6.02)
Southern Zone	26925	159	5.91 (5.06- 6.90)
Southern Highland Zone	42325	382	9.03 (8.16-9.98)
Western Zone	38708	330	8.53 (7.65-9.50)
Type of Referral			
Self	255864	1356	5.30 (5.02-5.59)
CTC	39965	453	11.33 (10.34-12.43)
Community	41590	192	4.62 (4.01-5.32)
Other referral types	14711	113	7.68 (6.39-9.24)
TB diagnostic category			
New cases	335701	1944	5.79 (5.54-6.05)
Retreatment	16429	170	10.35 (8.90-12.03)
Anatomical site of TB			
Pulmonary TB	2800341	1584	5.65 (5.38-5.94)
Extrapulmonary TB	66500	495	7.44 (6.82-8.13)
Both	224	4	17.86 (6.70-47.58)
TB results			
Sputum Positive	104354	427	4.09 (3.72-4.50)
Sputum Negative	69291	476	6.87 (6.28-7.52)
Other non-sputum tests	150997	1033	6.84 (6.44- 7.27)
DOT option			
Home-based	316291	1784	5.64 (5.38- 5.91)
Facility-based	11501	157	13.65 (11.67 -15.96)

HIV status			
HIV-negative	242433	923	3.81 (3.57-4.06)
HIV-positive	102347	1146	11.20 (10.57-11.86)

4.3 Survival probabilities

The overall survival probabilities among TB patients was estimated to be 98%, 97%, and 92% at 2,6 and 12 months respectively. TB/HIV co-infected patients had lower survival probabilities of 96%, 94% and 86% at 2, 6 and 12 months respectively compared to 99%,98% and 95% among HIV negative TB patients **(Figure 4-2).**

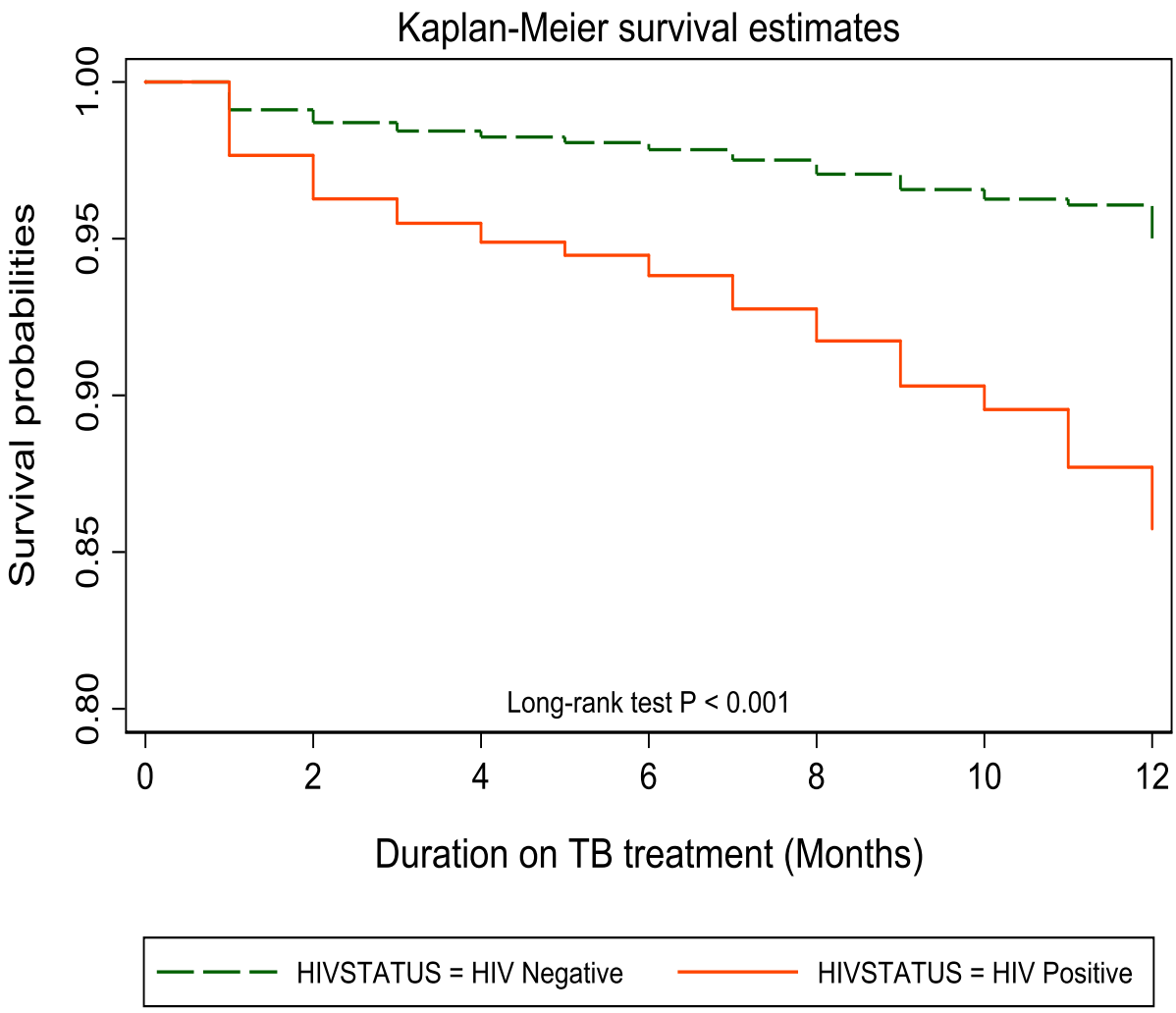

Figure 4-2: Kaplan-Meier survival curves showing survival probabilities among TB/HIV and TB only patients during TB treatment.

TB patients under facility-based DOT options had a lower survival probability of 94%, 92% and 85% at 2,6, and 12 months of TB treatment respectively as compared to those under home-based DOT options. The survival probabilities among TB patients under home-based option were 98%, 96% and 92% at 2,6 and 12 months respectively **(Figure 4-3).**

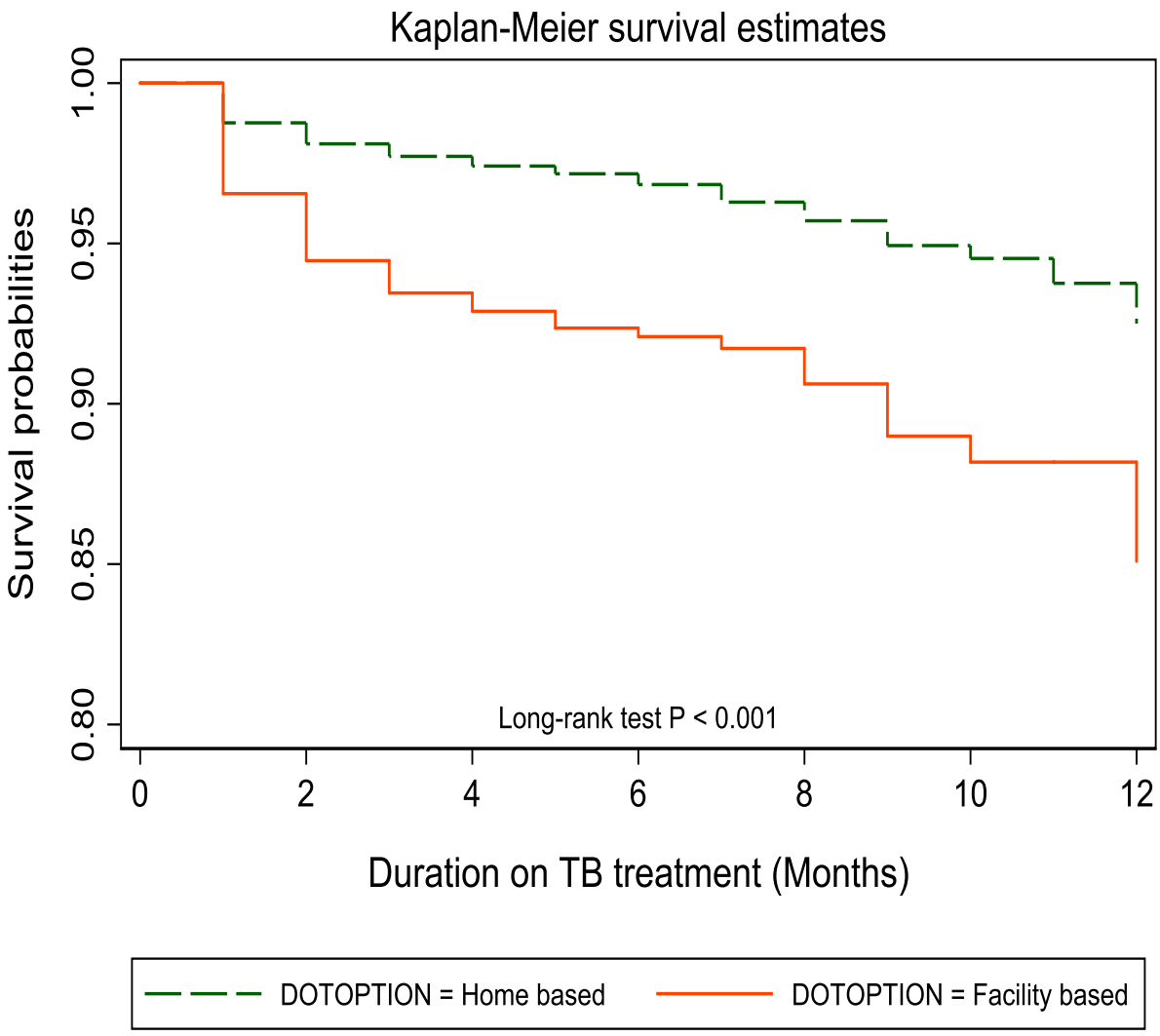

Figure 4-3:Kaplan-Meier survival curves showing survival probabilities among TB patients under home and facility-based DOT option during TB treatment

4.4 Risk factors for TB Mortality

In the Bivariate analysis, male TB patients, increased age, accessing TB services at the hospital level, geographical zones were associated with death among TB patients. Similarly, being retreatment TB patients, having both pulmonary and extra-pulmonary TB, being co-

infected with TB/HIV, and using facility-based DOT option were clinical factors associated with death among TB patients.

However, in the main effects multivariable model **(Table 4-4)** it was revealed that the independent risk factors for TB death were increasing age, being co-infected with TB/HIV, and using facility-based DOT option. Additionally, others included receiving service at the hospital level, being sputum negative TB, being referred from other TB referral types, having extra-pulmonary TB, and geographical zones.

Increasing age was associated with an increased risk of death after adjusting for potential confounders or other variables. Elderly TB patients aged ≥60 years were twice more likely to die (adjusted hazard ratio (aHR) = 2.51, 95% CI = 2.11-2.99) compared to those aged between 0-14 years. Moreover, those who were aged 15-59 years had an increased risk of death (aHR = 1.33, 95% CI = 1.13- 1.56) as compared to those aged between 0-14 years. Increased risk of death was observed in TB patients accessing service at the hospital level (aHR = 1.15, 95% CI = 1.04-1.27) as compared to those attending at the dispensary level. Likewise, being co-infected with TB/HIV were about three times more likely to die (aHR = 2.89, 95% CI = 2.61-3.20) compared to TB only patients. Furthermore, being under a facility-based DOT option had a significantly higher risk of death (aHR = 2.25, 95% CI = 1.83 - 2.79) as compared to home-based DOT option.

Additionally, being referred from other sources (aHR =1.48, 95% CI = 1.22- 1.80), having sputum negative TB results (aHR =1.37, 95% CI = 1.21-1.58), having extrapulmonary TB (aHR =1.21, 95% CI = 1.08-1.34) were also independent risk factors of death among TB patients. Lastly, comparing to the central zone, a highest risk of death was observed in TB patients from southern highland zone (aHR =1.73, 95% CI = 1.38-2.18), Southern Zone (aHR =1.57, 95% CI = 1.22-2.01) and western zone (aHR =1.54, 95% CI = 1.21-1.97).

Table 4-4: Multivariate extended cox regression on the risk factors of death during TB treatment among TB patients, January 2017 -December 2017, Tanzania.

Variable	Crude hazard Ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Sex				
Female	**Reference**		**Reference**	
Male	1.10 (1.01 -1.20)	0.029	1.02 (0.93 - 1.11)	0.684
Age Group (Years)				
0-14	**Reference**		**Reference**	
15-59	1.51 (1.29-1.76)		1.33(1.13-1.56)	
≥60	2.15 (1.81-2.56)	< 0.001	2.51 (2.11- 2.99)	<0.001
Types of health facility				
Dispensaries	**Reference**		**Reference**	
Hospitals	1.34 (1.20-1.49)		1.15 (1.04-1.27)	
Health Center	0.88 (0.77-0.99)	< 0.001	1.01 (0.89-1.13)	0.003
Geographical Zones				
Central Zone	**Reference**		**Reference**	
Eastern Zone	1.25 (1.01-1.55)		1.28 (1.02-1.62)	
Lake Zone	1.47 (1.18-1.84)		1.49 (1.19-1.89)	
Northern Zone	1.42 (1.14-1.77)		1.37 (1.08 -1.74)	
Southern Zone	1.50 (1.17-1.92)		1.57 (1.22 -2.01)	
Southern Highland Zone	2.33 (1.87-2.90)		1.73 (1.38 -2.18)	
Western Zone	2.25 (1.80-2.81)	< 0.001	1.54 (1.21-1.97)	<0.001
Type of Referral				
Self	**Reference**		**Reference**	
CTC	2.13 (1.92-2.37)		1.09 (0.97-1.24)	
Community	0.88 (0.76-1.02)		0.89 (0.77-1.04)	
Other referral types	1.45 (1.19-1.75)	< 0.001	1.48 (1.22- 1.80)	<0.001
TB diagnostic category				
New cases	**Reference**		**Reference**	
Retreatment	1.79 (1.53-2.10)	< 0.001	1.10 (0.89 - 1.36)	0.351
Anatomical site of TB				
Pulmonary TB	**Reference**		**Reference**	
Extrapulmonary TB	1.31 (1.19-1.45)		1.21 (1.08 - 1.34)	
Both	3.06 (1.15-8.18)	< 0.001	2.64 (0.99 – 7.07)	0.001
TB results				
Sputum Positive	**Reference**		**Reference**	
Sputum Negative	1.66(1.46-1.88)		1.37 (1.21 - 1.58)	
Other non-sputum tests	1.65 (1.48-1.85)	< 0.001	1.35 (1.20-1.52)	**<0.001**
DOT option				
Home-based	**Reference**		**Reference**	
Facility based	2.42 (2.06-2.84)	< 0.001	2.25(1.82 - 2.79)	**<0.001**
HIV status				
HIV-negative	Reference		**Reference**	

HIV-positive	2.92 (2.68 - 3.18)	< 0.001	2.89(2.61- 3.20)	**<0.001**

Significant interactions were observed between HIV status and age, anatomical site of TB, and TB results **(Table 4-5).** A model including these pairwise interaction terms showed that the increased risk of death associated with HIV was more pronounced among older patients than young patients among HIV negative patients. Older HIV negative TB patients had three times more likely to die (aHR =3.46, 95% CI =2.71-4.41), as compared to young HIV negative TB patients. The risk of death among HIV negative TB patients increased with age. However, the association of age and death was not statistically significant among TB/HIV co-infected patients.

Also, TB patients with both pulmonary and extra-pulmonary TB had increased risk of death (aHR = 4.12, 95% CI = 1.34-12.69) among HIV positive TB patients. On the other hand, those with extra-pulmonary TB had an increased risk of death among HIV negative TB patients (aHR =1.47, 95% CI = 1.26-1.71). Also, those with sputum negative TB results had an elevated risk of death only in HIV negative TB patients (aHR =1.60, 95% CI =1.31-1.96). However, the association between sputum negative TB results with death among HIV positive patients was statistically not significant. Inclusion of interaction terms in the multivariable model had no significant effect on the association between death and other covariates.

Table 4-5:Risk factors on death among TB patients stratified by HIV status January-December 2017, Tanzania

Variable	HIV Positive		HIV Negative	
	Hazard Ratio (95 % CI)	**P-value**	**Hazard Ratio (95 % CI)**	**P-value**

Sex				
Female	**Reference**		**Reference**	
Male	1.01 (0.89 -1.13)	0.904	1.06 (0.93 - 1.22)	0.401
Age Group (Years)				
0-14	**Reference**		**Reference**	
15-59	1.15 (0.92 -1.43)		1.44 (1.13 -1.83)	
≤60	1.32 (0.99- 1.77)	0.160	3.46 (2.71- 4.41)	<0.001
Types of health facility				
Dispensaries	**Reference**		**Reference**	
Hospitals	1.16 (1.01-1.33)		1.15 (0.99-1.32)	
Health Center	1.12 (0.96 -1.31)	0.104	0.89 (0.74-1.06)	0.003
Geographical Zones				
Central Zone	**Reference**		**Reference**	
Eastern Zone	1.68 (1.15- 2.44)		0.99 (0.74-1.35)	
Lake Zone	1.71 (1.18 -2.50)		1.35 (1.01-1.82)	
Northern Zone	1.46 (0.98-2.18)		1.29 (0.97 -1.75)	
Southern Zone	1.76 (1.17- 2.63)		1.44 (1.05 - 1.97)	
Southern Highland Zone	2.07 (1.43- 3.01)		1.47 (1.08 -1.99)	
Western Zone	1.73 (1.17-2.55)	<0.001	1.44 (1.05- 1.97)	0.001
Type of Referral				
Self	**Reference**		**Reference**	
CTC	1.08 (0.95- 1.23)		1.72 (0.93- 3.17)	
Community	0.94 (0.75-1.17)		0.84 (0.68-1.04)	
Other referral types	1.59 (1.20- 2.11)	0.007	1.38 (1.06 - 1.81)	0.008
TB diagnostic category				
New cases	**Reference**		**Reference**	
Retreatment	1.01 (0.77- 1.33)	0.935	1.23 (0.89 - 1.69)	0.202
Anatomical site of TB				
Pulmonary TB	**Reference**		**Reference**	
Extrapulmonary TB	0.99 (0.85-1.16)		1.47 (1.26 - 1.71)	
Both	4.12 (1.34-12.69)	0.048	0.29 (0.21 - 1.01)	<0.001
TB results				
Sputum Positive	**Reference**		**Reference**	
Sputum Negative	1.19 (0.99- 1.42)		1.60 (1.31 - 1.96)	
Other non-sputum tests	1.23 (1.05-1.44)	0.035	1.46 (1.22-1.75)	<0.001
DOT option				
Home-based	**Reference**		**Reference**	

Facility based	2.09 (1.58-2.78)	< 0.001	2.51 (1.83 - 3.44)	<0.001

4.5 Sub-national differences in mortality rate

A sub-national difference in mortality rate was observed across different geographical zones. Kigoma, Njombe, and Songwe regions had the highest mortality rate ranging from 10 to 20 per 1000 Person-months. However, the lowest mortality rate was found in Kagera, Geita, Arusha, Dodoma, Mtwara, Katavi, and Morogoro Regions ranging from 0 to 5 per 1000 Person-months. Kigoma was the leading region reporting the highest mortality rate among all-region with a mortality rate of 15.2 per 1000 Person-months **(Figure 4-4).**

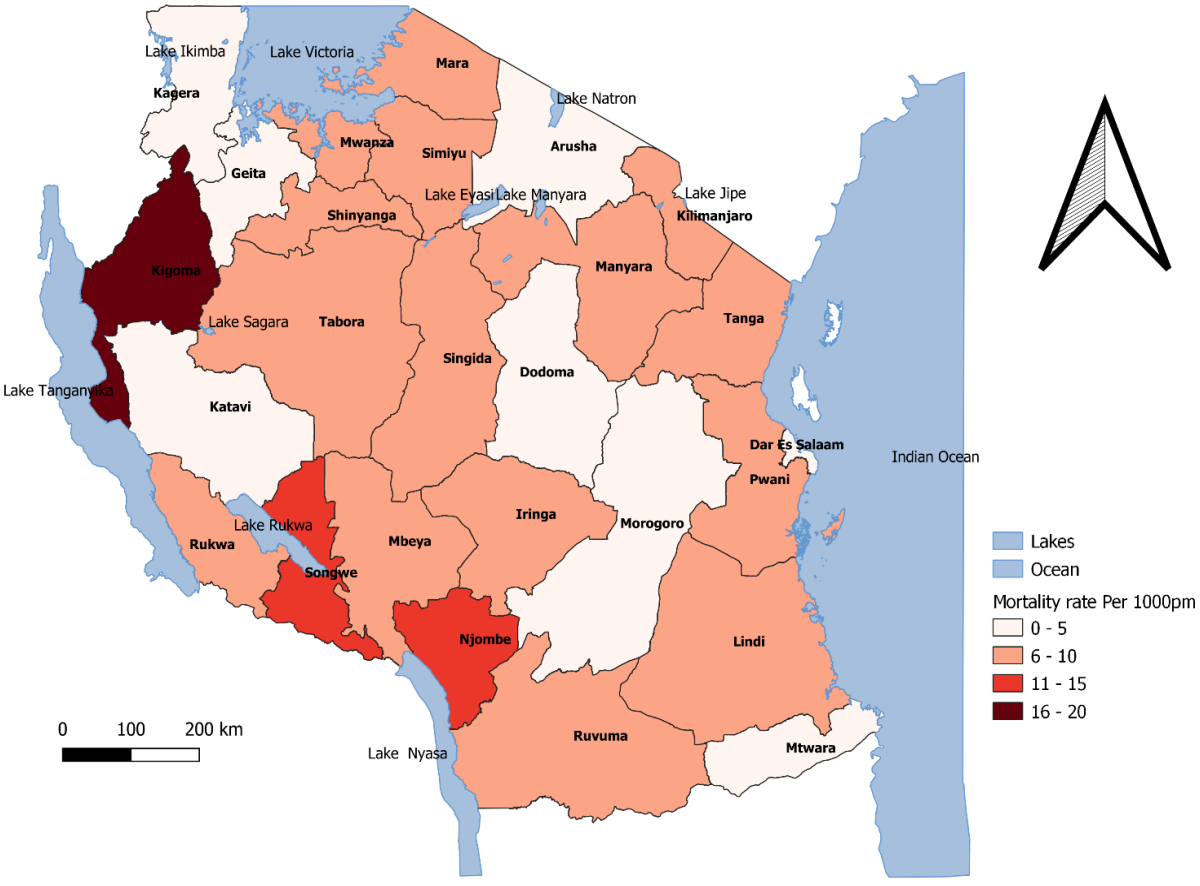

Figure 4-4: Distribution of mortality rate per 1000-person month across the region among TB patients in Tanzania

5 Discussion

Our study identified a high mortality rate among TB/HIV co-infected patients on TB treatment in Tanzania. The survival probabilities were lower among retreatment TB patients, older TB patients, and those under facility-based DOT options. The independent risk factors associated with death among TB patients included advanced age, TB/HIV co-infection, facility-based DOT option, receiving service at the hospital level, Sputum negative TB results, other referral types, both pulmonary and extra-pulmonary TB and geographical zones.

5.1 Crude Mortality rate

The overall mortality rate that we report is much lower compared with those reported in previous studies conducted in Nigeria (3.68 per 100 Person-months) (14), Northern Ethiopia (12 per 1000 Person-months) (40) and Iran 0.99 per 100 Person-months (51). Similarly, our finding is much lower than the mortality described in previous retrospective studies conducted using Nation TB program data in South Africa (16.3%) (3), Kenya (6.1%) (20) and Tanzania NTLP annual report of 2016(6%)(4). Variations in death proportional between countries could be ascribed to the differences in study populations, patterns of TB spread among the population, drug resistance, and co-comorbidities. Higher mortality among TB/HIV co-infected patients in our study is consistent with a study conducted in Northern Ethiopia which reported mortality of 18% and 0.6% among TB/HIV and TB only patients respectively (28).

Although there is a slight improvement in mitigating TB death in Tanzania, more efforts are needed to achieve the WHO End TB strategy of reducing TB deaths to 95% by the year 2035

5.2 Survival probabilities

The overall survival probabilities obtained in our study (98% and 97% at 2 and 6 months of TB treatment respectively) was almost similar as compared to survival probabilities obtained in the study conducted in Iran (97% and 94% at 2 and 6 months) (51). TB patients under the facility-based DOT option had the lower survival probabilities as compared to the home-based DOT option. This is consistent with similar research findings found in the meta-analysis conducted to assess the impact of community-based DOT on Tuberculosis treatment outcomes (15). Likewise, a lower survival probability among TB/HIV patients was consistent with the findings from studies conducted in Brazil (30) and Kenya(20). Suppressed immune system (9,12,20,30,40) and delay in diagnosis (9), difficult diagnosis of sputum smear due to atypical TB clinical presentation among TB/HIV patients (28), might have contributed to observed finding among in this group. Therefore, our study substantiates the idea of HIV screening among TB patients for early diagnosis and prompt initiation of ART.

5.3 Risk factors of death among TB patients

Our study found that advanced age, TB/HIV co-infection, facility-based DOT option, receiving service at the hospital level, Sputum negative, TB referral types, both pulmonary and extra-extra-pulmonary TB, and geographical zones. were the independent risk factors of death among TB patients.

We observed that TB/HIV co-infected patients had increased hazard of death, our finding replicates the findings from previous studies (3,6,13,19). As reported in the previous studies suppressed immune system (9,12), and delay in diagnosis (9), might have contributed to the high mortality in this group. Authors from a study conducted in Northern Ethiopia suggested that difficult diagnosis of sputum smear due to atypical TB clinical presentation in TB/HIV patients might contribute to an increased death among TB/HIV co-infection (28).

Additionally, we also suggest that TB/HIV co-infected patients are more susceptible to other opportunistic infections which might have increased their risk of death. Therefore, our study substantiates the idea of HIV screening among TB patients for early diagnosis and prompt initiation of ART.

In our study, we observed that TB patients under facility-based DOT option had a higher mortality risk compared to home-based DOT option. Our finding contradicted with the finding from a retrospective study conducted in Dar es Salaam, Tanzania whereby TB patients on home-based DOT options were more likely to die compared to facility-based options (21). However, this study was conducted in only one health facility and the findings were not significant. Yet, our finding was congruent with other previous meta-analysis study and a retrospective study conducted in Kenya (10,15). Authors from a meta-analysis study suggested that the lower risk of death among home-based DOT option TB patients might be due to its convenience and cost-effectiveness (15). We speculate that patients placed in home-based care might have less severe disease and hence, better prognosis than those under facility-based DOT options. Specifically, targeted intervention attention should be given to patients under facility-based DOT options. Also, it is necessary to tailor the home-based DOT option to its local conditions to meet the needs and preferences of TB patients.

TB patients receiving TB service at the hospital level had increased hazard of death compared to those accessing service at the dispensaries, this was consistent with the study conducted in Spain (52). However, opposed with the retrospective study conducted in Zimbabwe which acknowledged that accessing treatment from the higher-level health facility reduced the risk of death among TB patients (12). Nevertheless, a study conducted in Kenya reported similar mortality across different type of health facility providing TB treatment (20). We hypothesize that TB patients diagnosed at the hospital level might be clinically more severe cases and often involving referred cases from the primary health facilities which might have resulted in the observed findings.

TB patients referred from other referral types had increased risk of death compared to self-referred TB patients. A comparable finding was observed in the study conducted in Nigeria whereby an increased risk of death was observed in patients referred to non-program linked clinics (14). A study conducted in Buguruni hospital, Dar es salaam found that Pharmacies and traditional healers were main healthcare facilities for treatment-seeking after the onset of TB symptoms. And about 44% of TB patients did not show up in the diagnostic centre after a referral from the pharmacies (36). Similarly in the study conducted in Ethiopia, it was found that inability to correctly identify TB suspects at the private drug retail dispensing outlets lead to incorrect dispensing of antibiotics and hence diagnostic delay (37). We hypothesize that the high-risk death observed among TB patients referred from other referral types might be due to diagnostic delay caused by visiting drug retail outlets and pharmacies. Thus, strengthening intervention to improve referral practices in pharmacies and private drug dispensing outlets is essential for improved case detection and reduction of diagnostic delay.

Furthermore, residing in the Southern highland zone, Southern zone, and Western Zones were associated with increased risk of death among TB patients compared to the Central zone. A study conducted in Nigeria observed differences in the geographical distribution of death among TB patients across regions. The authors suggested that variation in co-morbidities, inaccessibility of the health facility at a place of residence, and shortage or interfered supply of drugs might have contributed to the observed finding (14). Also, a study conducted in Northern Ethiopia reported that differences in socioeconomic conditions across the regions might contribute to the variation in the death risk (13). In our study, the highest risk of death in the Southern highland zone might be attributed to the highest HIV prevalence found in this zone. According to the Tanzania HIV Impact survey, 2016-2017 the highest HIV prevalence was found in Njombe (11.4%), Iringa (11.3%), and Mbeya region (9.3%) which are regions found in the southern highland zone (53). We suggest more studies to be conducted to identify why these zones had an increased risk of deaths.

Consistent with the study conducted in South Africa, the risk of death increased with advancing age among both HIV positive and HIV negative TB patients (8). Nevertheless, our study revealed that the association between advancing age and death was very strong among HIV negative as compared to HIV positive TB patients. A study conducted in South Africa reported that ART use might have reduced the risk of death among HIV positive patients (8). Additionally, authors from a study conducted in South Africa pointed out that disrupted immunity and age-related co-morbidities might have contributed to an increased risk of death among this age group (3). Similarly, previous studies have reported that older TB patients are more likely to develop extrapulmonary and atypical forms of TB that are often hard to diagnose by conventional methods (3,54). We also speculate age-related co-morbidities might have contributed to the observed finding. Intervention to address barriers to prompt TB diagnosis is essential to minimize the high death in this group.

An increased risk of death among patients with both pulmonary and extrapulmonary TB patients was more pronounced in HIV positive TB patients than HIV negative TB patients. In congruence with a study conducted in South Africa, we found that the presence of only extra-pulmonary TB among HIV positive TB patients had no significant effect on mortality (8). However, the contrasting finding was reported in the study conducted in the USA whereby a higher risk of death was observed among HIV positive TB patients with extra-pulmonary TB (55). The increased risk of death in patients with both pulmonary and extra-pulmonary TB patients might be attributed to a limited capacity for the diagnosis of extra-pulmonary TB patients, especially at the primary care level. This might have resulted in a diagnostic delay. To reduce death among TB patients' aggressive strategies, need to be employed to actively find and promptly treat HIV positive TB patients especially with pulmonary and extra-pulmonary TB

Similar to the study conducted in China we also observed an increased risk of death among HIV positive and HIV negative TB patients with sputum negative results (22). Though, the association in our study was not statistically significant among HIV-positive TB patients.

Also, a study conducted in South Africa found an increased risk of death among HIV-negative TB patients with sputum negative results (8). Conversely, a study conducted in Zimbabwe reported that most of the TB-smear negative patients tend to be HIV-positive and hence are likely to experience poor treatment outcome (12). This was not the case in our finding, we postulate that the recent introduction of test and treat strategies among HIV positive patients might have contributed to the observed finding. However, misdiagnosis among smear-negative patients may have contributed to high mortality in HIV negative TB patients. More attention should be made on the use of Gene expert to minimize misdiagnosis and delayed diagnosis among smear-negative TB patients.

In our study, we did not find any significant association between TB treatment category (new or retreatment) and TB mortality, this was harmonious with the study conducted in Northern Ethiopia (28). The reason behind this might be due to the late diagnosis of TB disease and advanced disease progress. Similarly, sex was not associated with death among TB patients.

5.4 Sub-national differences in mortality rate

The highest mortality rate was found in Kigoma, Njombe, and Songwe regions. Similarly, a study conducted Brazil, Paraguay and Argentina reported differences in mortality rate across the regions (19,42,44). The authors suggested that the might be due to differences in poverty, inadequate nutrition, poor living conditions, and limited access to adequate health services for early diagnosis (19). Similarly, a study conducted in the tri-border region of Brazil, Paraguay and Argentina found that income and household density had substantial spatial association with TB mortality (42). TB mortality has reported being higher in the regions which are economically developed and more affected by HIV (44). However, a retrospective study conducted in Saudi Arabia analyzing TB mortality by province did not show any significant differences (45). Differences in the distribution of risk factors for TB death among the regions could have attributed to the observed findings. In Njombe region majority of our study cohorts were HIV positive (62.7%), extra-pulmonary (27%) and sputum negative TB patients (55%). In Kigoma region majority were eldely (22%) and reffered other referral type (10%). While in

Songwe region majority (39%) were HIV positive TB patients.This could have contributed to the observed finding. Although many advances have been observed in Tuberculosis control in recent years in Tanzania. The differences in geographical distribution still confirm that Tuberculosis is still a major public health problem in Tanzania. There is a need to formulate regional and local strategies, focusing particularly on the social determinants of health in Tanzania. More studies are needed to identify why Kigoma, Njombe, and Songwe regions had the highest mortality rate.

Our study has several limitations. Since the study used an existing database, a limited range of variables were included for purposes of explaining the risk for mortality among TB patients. Also, the data reflects only all-cause mortality; it does not specify whether the death was TB-related. Likewise, other limitations were missing information for some variables. However, the use of a large sample of all TB patients enrolled on TB treatment makes the study representative of the TB patients receiving treatment in Tanzania. To take into account of the commonest methodological limitation of loss to follow up in our study patients were censored at the outcome date (the day they were lost to follow up). Correspondingly multiple imputation methods were used to address for missing data on the variables.

6 Conclusions

Our study showed a slight improvement in mitigating deaths due to TB. TB/HIV co-infected patients, older, and retreatment TB patients had a lower survival probability. The independent risk factors of death among TB patients included advanced age, TB/HIV co-infection, facility-based DOT option, receiving service at the hospital level, Sputum negative, TB referral types, extra-pulmonary TB and geographical zones. were the independent risk factors of death among TB patients. Additionally, having both pulmonary and extra-pulmonary TB was also an independent risk factor among HIV positive TB patients. The association between advanced age, sputum negative smear results and extra-pulmonary TB were pronounced among HIV negative TB patients. A sub-national difference in mortality rate was appreciated in our study whereby Kigoma, Songwe, and Njombe regions had the highest mortality rate while Dodoma,

Arusha, and Geita recorded the lowest rate of mortality. The results of our study may have significant implications for health care programs. They may aid in formulating innovative strategies and new guidelines to guide targeted measures for the management of disease among subgroups of patients at risk of death from TB treatment. Appropriate targeting of care to these high-risk groups should be considered.

7 Recommendations

To achieve the WHO TB end milestones of reducing TB mortality by 95% in its appropriately to formulate targeted interventions in high-risk groups. This includes older TB patients, TB/HIV Co-infections, sputum negative, extra-pulmonary TB, facility-based DOT option and TB patients receiving TB service at a hospital facility. Also, specific targeted strategies should be formulated in highly vulnerable regions with a high mortality rate. It is necessary to tailor a home-based DOT option in its local conditions and patient preferences. Likewise, it is vital to strengthen HIV screening among TB patients for early diagnosis and prompt initiation of ART. Moreover, strengthening intervention to improve referral practices from other referral types such as pharmacies and private drug dispensing outlets is crucial for improved case detection and reduction of diagnostic delay. Further studies are required to identify why Kigoma, Njombe and Songwe region had a high mortality rate.

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9 Appendices

9.1 Ethical clearance certificate

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RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: "FACTORS ASSOCIATED WITH DEATH AMONG TB PATIENT IN TANZANIA IN 2017"

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has, on behalf of the Senate, approved ethical clearance for the above-mentioned study. Hence you may proceed with the planned study.

The ethical clearance is valid for one year only, from **28th October, 2019 to 27th October, 2020.** In case you do not complete data analysis and dissertation report writing by **27th October, 2020,** you will have to apply for renewal of ethical clearance prior to the expiry date.

Dr. Emmanuel Balandya
ACTING: DIRECTOR OF POSTGRADUATE STUDIES

cc: Director of Research and Publications
cc: Dean, School of Public Health and Social Sciences, **MUHAS**