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Mortality and associated factors among adult patients on tuberculosis treatment in Tanzania: A retrospective cohort study

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ABSTRACT

Introduction: Tuberculosis (TB) is the global leading cause of death from an infectious agent. Tanzania is among the 30 high TB burden countries with a mortality rate of 47 per 100,000 population and a case fatality of 4%. This study assessed mortality rate, survival probabilities, and factors associated with death among adult TB patients on TB treatment in Tanzania.

Methods: A retrospective cohort study was conducted utilizing case-based national TB program data of adult (≥15 years) TB cases enrolled on TB treatment from January 2017 to December 2017. We determined survival probabilities using the Kaplan-Meier estimator and a Cox proportional hazard model was used to identify independent risk factors of TB mortality. Hazard ratios and their respective 95% confidence intervals were reported.

Results: Of 53,753 adult TB patients, 1927 (3.6%) died during TB treatment and the crude mortality rate was 6.31 per 1000 person-months. Male accounted for 33,297 (61.9%) of the study population and the median (interquartile range [IQR]) age was 40 (30–53) years. More than half 1027 (56.7%) of deaths occurred in first two months of treatment. Overall survival probabilities were 96%, and 92% at 6th and 12th month respectively. The independent risk factors for TB mortality among TB patients included: advanced age ≥ 45 years (adjusted hazard ratio (aHR) = 1.74, 95% confidence interval (CI) = 1.45–2.08); receiving service at the hospital level (aHR = 1.22, 95% CI = 1.09–1.36); TB/HIV co-infection (aHR = 2.51, 95% CI = 2.26–2.79); facility-based direct observed therapy (DOT) option (aHR = 2.23, 95% CI = 1.95–2.72); having bacteriological unconfirmed TB results (aHR = 1.58, 95% CI = 1.42–1.76); and other referral type (aHR = 1.44, 95% CI = 1.16–1.78).

Conclusion: Advanced age, TB/HIV co-infection, bacteriological unconfirmed TB results, other referral types, receiving service at facility-based DOT option and obtaining service at the hospital level were significant contributors to TB death in Tanzania. Appropriate targeted intervention to improve TB referral systems, improve diagnostic capacity in the primary health facilities, minimize delay and misdiagnosis of TB patients might reduce TB mortality.

1. Introduction

Tuberculosis (TB) is the global leading cause of death from infectious agents [1]. Globally 10.0 million people developed TB disease, and around 1.4 million deaths occurred from TB disease in 2019 [1]. Similarly, the reported mortality among TB patients from previous studies ranged from 7% to 33.4% [2–11]. In 2014, the World Health Organization formulated the End TB strategy with a target of a 90% reduction of the annual number of TB deaths by 2030 [1,3]. However, in order to reach the first milestone of the End TB strategy, the case fatality rate (CFR) is required to fall to 10% and 6.5% by 2020 and 2025 respectively [1]. Tanzania is among 30 high TB burden countries and 20 countries with a higher estimated number of TB incidents among people living with HIV (PLHIV) [1]. In 2018, a total of 75,845 TB cases were notified in Tanzania, with an incidence rate of 253/100,000 population [12].

While Tanzania is amongst the seven high burden countries on track

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to reach the End TB 2020 milistones [1,12], TB mortality is still twice as high as the global mortality [1]. Survival probabilities among TB patients from preceding studies ranged from 95.8% to 97% in the intensive phase and 83% to 91% in the continuation phases [13–15]. There have been conflicting reports on risk factors for death among TB patients. Several studies have reported a higher death risk among TB/HIV co-infected [6,11,16,17]; male patients [11,18–20]; smear-negative [3,6,7,21,22]; extra-pulmonary TB patients [4,10,23]; and in advanced age [6,11,17]. Other independent risk factors for death included getting services at a low-level health facility [7]; being under facility-based DOT option [19,24], and being referred from no-program liked clinics [22]. Nevertheless, other studies have reported a higher risk among female [3], smear positives [25,26], home-based DOT options (21), and pulmonary TB patients [20,27].

Various studies have been conducted describing TB mortality and risk factors using routine data from other countries. However, few utilized large individual case-based national databases especially in Sub-Saharan countries. Additionally, inconsistent findings from various studies support further studies to be conducted to assess whether factors reported in previous studies are applicable in our local setting. Likewise, numerous health TB interventions have been put in place recently in Tanzania, hence there was a need to assess if the risk factors of TB deaths have changed over time. This study used a large individual case-based national database of notified TB patients in Tanzania in 2017 to assess magnitude, survival and factors associated with deaths. The findings from this study could be used to formulate appropriately targeted interventions and re-evaluate the clinical care management among TB patients on anti-TB treatment.

2. Methods

2.1. Study design and population

We conducted a retrospective cohort study using national TB program data. We included TB patients aged 15 years and above who started TB treatment from January 2017 to December 2017 and excluded TB patients with missing information on treatment outcome or inconsistent treatment dates.

2.2. Study setting

The data involved all TB patients who started TB treatment in 2017 available in the national TB program database from all 26 Tanzania mainland regions. In 2020, Tanzania mainland population was projected to be 55,966,030 based on the 2012 national census [28]. The health care delivery system comprised of 7819 function health facilities of which 285 are hospitals, 834 health centers and 6700 dispensaries [12]. Also, in 2018, 3512 health facilities provided tuberculosis treatment services (DOT centres) of which 1200 health facilities provided TB diagnosis by microscopy services [12]. Likewise, DOT is mandatory in Tanzania and TB patients are required to choose either health facility DOT option or community-based DOT option (home-based DOT). Facility-based DOT approach requires patients to visit the health facility daily for supervised drug intake by health care workers. Patients under home-based care are required to take medications under the supervision of reliable and trustable treatment supporters. TB patients and treatment supporters under home-based DOT option have to come to the health facility for follow up visits and drug refills once a week during the intensive phase and after two weeks during continuation phase [29].

In Tanzania, TB patients are managed according to the national TB treatment guideline adopted from the WHO recommendations. TB treatment entails 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 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) [29]. Of note, all previously treated TB patients are required to provide a specimen for rapid molecular testing (GeneXpert), where available, culture and drug susceptibility test (DST). DST and culture results are used for selection of the correct TB treatment regimen [29].

TB referral mechanisms in Tanzania is categorized into four main types such as self-referral, community referral, CTC referral and other referral types. Self-referral includes patients who present themselves at the health facilities with signs and symptoms suggestive of TB. Community referral includes patients screened for signs and symptoms of TB in the community who are referred to a TB diagnostic center for sputum TB examination by a health worker or community health worker. Some HIV patients can also be referred from the CTC or PMTCT after showing signs and symptoms of TB. Presumptive TB patients linked to the health facilities from other sources such as traditional healers, private pharmacies, accredited drug dispensing outlets (ADDO) and workplaces are termed as other referral types. Diagnosis and initiation of TB treatment are done at TB diagnostic center/clinic by a health care worker who later on reports the confirmed TB cases in the TB register for surveillance [29].

2.3. Data source

The study used a national individual case information database captured in the electronic 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). In Tanzania, ETR.net is used for TB/HIV surveillance, program monitoring and evaluation. It provides standardized cohort reports of treatment and services for TB patients [17,30]. TB cases information is recorded at the primary health facilities using paper-based TB registers which are subsequently captured in ETR.net by the district TB coordinator.

2.4. Study variables

The main outcome was death while on TB treatment irrespective of the cause [31,32]. The outcome was classified as died or censored (completed treatment, cured, lost to follow up and treatment failure) [13,33,34]. Independent variables included: sex (male and female), age categorized to 14–24 years, 25–34 years, 35–44 years, and $\geq$ 45 years. Likewise, geographical zones were codified to coastal, central, lake, northern, southern highland and western zones. The level of health facilities where TB patients received treatment was categorized into dispensaries, health centres and hospitals. Dispensaries and Health centers were also termed as primary health facilities while hospitals were termed as tertiary health facilities. Referrals types were classified into self-referral, community referral, care and treatment center (CTC) referral, and other referrals. TB diagnostic category coded as new and retreatment (relapse, treatment after failure, treatment after loss to follow up) TB patients. Anatomical site of TB was classified as pulmonary (disease affecting lungs only), extra-pulmonary (disease affecting organs other than the lung) and both (disease affecting the lungs and any other organ). TB results were grouped into bacteriological confirmed (sputum-smear, culture or molecular confirmed) or bacteriological unconfirmed TB patients (smear-negative, physician-confirmed through other means). TB DOT option was used as a proxy for adherence and categorized as home and facility-based DOT options, while HIV status was grouped as HIV positive and HIV negative.

2.5. Data analysis

Categorical variables are presented using frequencies and proportions and the median (interquartile range [IQR]) is used for continuous variables. We used Pearson's chi-square test for the comparison of

categorical variables. Survival time was defined as the time between TB treatment initiation until death or censoring (time in months). TB patients on treatment were defined as patients who have been initiated TB treatment between January 2017 to December 2017, with the last follow-up date being December 2018. Patients were followed until the end of their TB treatment or death, whichever occurred first. Patients who were lost to follow-up, or who had their treatment classified as failure, success, or cured were censored based on the last visit outcome date available in the database [2,7,17]. Likewise, patients who were alive at the end of TB treatment were considered censored. We calculated overall and covariate specific TB mortality rates per 1000 person-months (pm) using the Kaplan-Meier estimator. We used Kaplan-Meier curves to estimate the survival probabilities and a log-rank test to test statistical significance differences between the survival curves. To handle the missing data on risk factors and outcome a multiple imputation method by chain equations was used after assessment of the pattern distribution of missing values that were missing at random (MAR) [17,35]. The imputed variables included age group, gender, anatomical site of TB, TB results, HIV status and DOT option. Cox proportional-hazards model was used for univariate and multivariate analyses and Schoenfeld's test for verification of the proportional-hazard assumption [27,36]. We dropped TB diagnostic category variable in our analysis after showing correlation with other variables in the regression analysis. Factors with a *p*-value of $\leq$0.2 in the univariate analysis were considered as potential risk factors and included in the multivariable model. The overall p-value for each variable is estimated using the likelihood ratio test. Hazard ratios and their respective 95% confidence intervals were reported.

3. Results

Over a 12-month period, we recorded 57,248 adult TB cases, of these, 3495 (6.1%) were excluded from the main analysis due to inconsistent treatment dates. A total of 53,753 (93.9%) remained in the final analysis, included, and excluded records did not differ in social demographic and clinical characteristics. The median (IQR) age in our cohort was 40 (30–53)) years with more than two-thirds of the TB patients 22,101 (41.1%) were aged $\leq$ 45 years. Males accounted for 33,297 (61.9%) of the study population. Majority of patients 51,205 (95.3%) were newly diagnosed TB patients and 43,554 (81%) had pulmonary TB. About one-third, 16,672 (31%) of all TB patients were HIV positive and most of the study cohort 47,921 (89.2%) were under home-based DOT options **(**Table 1**).**

Table 1
Social-demographic and clinical characteristics of the study participants (n = 53,753).

Characteristics	Number	Percentage
Sex		
Female	20,455	38.1
Male	33,297	61.9
Missing	1	0.0
Age Group (Years)		
15–24	6267	11.7
25–34	11,846	22.0
35–44	13,521	25.2
≤45	22,101	41.1
Missing	18	0.0
Health facility level		
Dispensaries	13,897	25.9
Hospitals	25,817	48.0
Health Center	14,039	26.1
Geographical Zones		
Coastal Zone	17,579	32.7
Central Zone	5886	10.9
Lake Zone	12,366	23.0
Northern Zone	9153	17.1
Southern Highland Zone	7510	13.9
Western Zone	1268	2.4
TB referral type		
Self-referrals	39,493	73.4
CTC referrals	6479	12.1
Community referrals	5955	11.1
Other referral types	1826	3.4
TB diagnostic category		
New cases	51,205	95.3
Retreatment	2548	4.7
Anatomical site of TB		
Pulmonary TB	43,554	81.0
Extrapulmonary TB	9438	17.6
Both	37	0.1
Missing	724	1.3
TB results		
Bacteriological confirmed	23,721	44.1
Bacteriological unconfirmed	27,602	51.4
Missing	2430	4.5
DOT option		
Home-based	47,921	89.2
Facility-based	1889	3.5
Missing	3943	7.3
HIV status		
HIV-negative	35,911	66.8
HIV-positive	16,672	31.0
Unknown/Missing	1170	2.2

3.1. TB Mortality rate

During the study period, a total follow-up time of 304,787 person-months in 53,753 TB patients was obtained. A total of 1927 (3.6%) participants died and the crude mortality rate was estimated at 6.31 per 1000 person-months. More than half 1027 (56.7%) of deaths occurred in the first two months of treatment. Mortality rates at the 2nd, 6th, and 12th months since treatment initiation were 208.98, 7.95, and 6.32 per 1000 person-months respectively. Mortality was highest among TB/HIV patients, TB patients referred from CTC, and retreatment TB patients. Likewise, TB patients with both pulmonary and extra-pulmonary TB and those under facility-based DOT options had the highest mortality rate. Mortality rates (per 1000 person-months) across different covariates are shown in Table 2.

3.2. Survival probabilities

The overall survival probabilities among TB patients were estimated to be 97%, 96%, and 92% at 2, 6, and 12 months respectively. Kaplan-Maier survival curves showed lower survival probabilities of 96%, 94%, and 85% among TB/HIV co-infected patients at 2, 6, and 12 months respectively compared to 99%, 98%, and 95% among HIV negative TB patients. TB patients under facility-based DOT options had a lower survival probability of 95%, 92%, and 85% at 2, 6, and 12 months of TB treatment respectively as compared to 98%, 97%, and 92% among those under home-based DOT options (Fig. 1).

3.3. Risk factors for TB mortality

In the bivariate analysis, male TB patients, advanced age, accessing TB services at the hospital level, geographical zones were demographic factors associated with TB mortality among TB patients. Similarly, clinical factors associated with TB mortality included: being retreatment TB patients, having both pulmonary and extra-pulmonary TB, being co-infected with TB/HIV, having bacteriological unconfirmed TB results and using facility-based DOT option. However, after adjusting for potential confounders and other variables, the independent risk factors for TB mortality were; being bacteriological unconfirmed TB patient (adjusted hazard ratio (aHR) = 1.58, 95% CI = 1.42–1.76); having TB/HIV co-infection (aHR = 2.51, 95% CI = 2.26–2.79); and receiving service at the hospital level (aHR = 1.22, 95% CI = 1.09–1.36). Likewise, older TB patients aged $\geq$ 45 years had the highest risk of death (aHR) = 1.74, 95% CI = 1.45–2.08) among all adult TB patients. Additionally, other independent risk factors included: receiving service

Table 2
Mortality rates per 1000 person-months among TB patients across explanatory variables (n = 53,753).

Characteristics	Person-Months (pm)	Number of Deaths	Mortality Rate Per 1000 pm
Crude mortality rate	**304,787**	**1927**	**6.32 (6.05–6.61)**
Mortality from the time since treatment initiation			
2nd month	5235	1094	208.98 (196.95 – 221.74)
6th month	218,623	1737	7.95 (7.58 – 8.33)
12th month	304,787	1927	6.32 (6.05 – 6.61)
Sex			
Female	115,661	781	6.75 (6.30–7.24)
Male	189,120	1146	6.06 (5.72–6.42)
Age Group (Years)			
15–24	35,674	136	3.81 (3.22–4.51)
25–34	67,547	340	5.03 (4.53–5.60)
35–44	76,573	519	6.78 (6.22–7.39)
≤45	124,876	932	7.46 (7.00–7.96)
Health facility level			
Dispensary	79,024	450	5.69(5.19–6.25)
Hospitals	144,280	1091	7.56 (7.13–8.02)
Health Center	81,483	386	4.74 (4.29–5.23)
Geographical Zones			
Coastal Zone	99,446	542	5.45 (5.01–5.93)
Central Zone	33,786	195	5.77 (5.02–6.64)
Lake Zone	69,697	438	6.28 (5.72–6.90)
Northern Zone	52,330	299	5.71 (5.10–6.40)
Southern Highland Zone	42,631	376	8.82 (7.97–9.76)
Western Zone	6897	77	11.16 (8.93–13.96)
TB referral type			
Self-referrals	223,880	1247	5.57 (5.27–5.89)
CTC referrals	35,806	413	11.53 (10.47–12.70)
Community referrals	35,034	178	5.08 (4.39–5.88)
Other referral types	10,067	89	8.84 (7.18–10.88)
TB diagnostic category			
New cases	289,069	1767	6.11 (5.83–6.40)
Retreatment	15,718	160	10.18 (8.72–11.89)
Anatomical site of TB			
Pulmonary TB	246,977	1464	5.93 (5.63–6.24)
Extrapulmonary TB	53,364	431	8.08 (7.35–8.88)
Both	199	4	20.10 (7.54–53.56)
TB results			
Bacteriological confirmed	135,395	568	4.20 (3.86–4.55)
Bacteriological unconfirmed	155,980	1237	7.93 (7.93–8.38)
DOT option			
Home-based	272,389	1625	5.97 (5.68–6.26)
Facility-based	10,921	147	13.46 (11.45–15.82)
HIV status			
HIV-negative	205,641	837	4.07 (3.80–4.36)
HIV-positive	92,758	1052	11.34 (10.68–12.05)

at facility-based DOT option (aHR = 2.30, 95% CI = 1.95–2.72); other referral types (aHR = 1.45, 95% CI = 1.16–1.80); and residing southern highland zone (aHR = 1.29, 95% CI = 1.13–1.48), and western zone (aHR = 2.30, 95% CI = 1.81–2.93) (Table 3).

4. Discussion

Our study aimed to determine mortality rate, survival probabilities and risk factors for TB mortality in Tanzania. We observed high mortality among TB patients in the first two months of TB treatment and lower survival probabilities among retreatment TB patients, older TB patients, and those under facility-based DOT options. The independent risk factors for death among TB patients included: advanced age, TB/HIV co-infection, receiving service at facility-based DOT option, receiving service at the hospital level, having bacteriological unconfirmed TB results, being referred from other referral types, residing in the southern highland zone, and western zone.

The overall mortality rate that we report of 6.31 per 1000 person-months during TB treatment is much lower compared to previous studies in Nigeria of 37.6 per 100 pm [22] and Northern Ethiopia (12 per 1000 pm) [14]. Similarly, the proportion of TB death found in this cohort is lower than that reported in retrospective studies conducted in South Africa (16.3%) [3], Nigeria (16.6%) [22], and Ethiopia (4.6%) [13]. Similar to our analysis, these studies included TB patients who were on TB treatment only [3,13,14,22]. Variations in death proportional in this study could be ascribed to the differences in study populations between our study as compared with other studies. Most of the previous studies did not use a large national TB program database as in our case [3,13,14,16,22,34]. However, the proportion of TB death in our cohort was similar to the Tanzania national average (4%) reported in National TB and Leprosy Program (NTLP) annual report in 2017 [12] and a prospective study conducted in Dar es salaam, Tanzania (3.4%) [16]. The high mortality in the first two months of treatment in our study was consistent with previous studies conducted in Tanzania [37], Uganda [38] and South Africa [39] and Brazil [40]. The authors suggested that the high death in the first two months of treatment could partly be related to the advanced stage of TB at diagnosis, and poor tolerance of TB drugs [14,37,40].

In our study, we observed lower survival probabilities and a higher risk of TB mortality among TB patients under facility-based DOT option as compared to home-based DOT option. Our findings were congruent with a retrospective study conducted in China [19] and a meta-analysis study conducted in 2016 [24]. Poor health status among patients under facility-based DOT option [19], inconvenience, non-flexibility and cost-associated with facility-based DOT option might be the reasons for the high mortality among this group [24]. Yet, our findings contradicted a retrospective study conducted in Nigeria [22]. However, this study was conducted in only one health facility and the findings were not significant. In the current analysis, about 60% of TB patients under the facility based DOT option were previously treated TB patients who have a known high risk of TB mortality [3,6,10,25]. This might account for the high risk of TB mortality among patients under facility-based DOT options observed in our cohort. Correspondingly, TB patients receiving service at the hospital level had an increased hazard of death compared to those accessing service at the dispensaries. This was consistent with the study conducted in Spain [41] and Uganda [42]. A retrospective study conducted in Zimbabwe acknowledged that accessing treatment from a higher-level health facility reduced the risk of mortality among TB patients [7]. Yet, a study conducted in Kenya reported similar mortality across different types of health facilities providing TB treatment [25]. Previous studies in Cameroon and South Korea reported TB patients diagnosed at the hospital level were clinically more likely to be severe cases and often referred from the primary health facilities [43,44].

TB patients referred from other referral types had an 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 TB mortality was observed in patients referred from non-program linked clinics [22]. 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. A study conducted in Buguruni hospital, Tanzania found that pharmacies and traditional healers were the main healthcare facilities for treatment-seeking after the onset of TB symptoms [45]. About 44% of TB patients did not show up in the diagnostic center after a referral from the pharmacies [45]. Similarly in the study conducted in Ethiopia, it was found that inability to correctly identify TB suspects at the private drug retail dispensing outlets led to incorrect dispensing of antibiotics and hence diagnostic delay [46].

Furthermore, residing in the Southern highland zone and Western

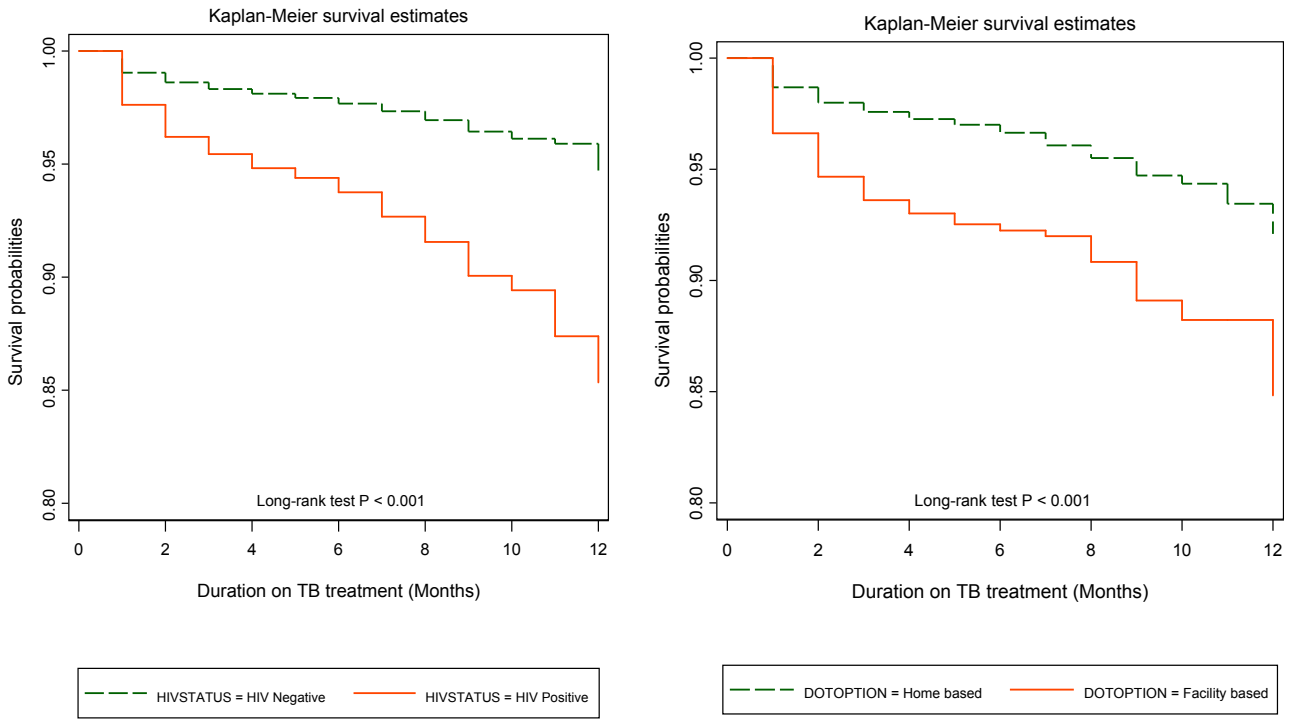

Fig. 1. Kaplan-Meier survival curves showing survival probabilities among TB/HIV and TB only, home and facility-based option patients during TB treatment.

zones were associated with an increased risk of TB mortality. A similar finding was observed in Nigeria [22] and Northern Ethiopia [4]. Previous studies reported differences in social-economic status [4,27] inadequate nutrition [27] variation in co-morbidities [22], limited access to adequate health services for early diagnosis [22,27] and shortage or interfered supply of drugs [22], might contribute to the variation in the death risk across geographical regions. Differences in the social-economic status and distribution of risk factors for TB death across the geographical zone in Tanzania could have attributed to the observed findings. According to the Tanzania HIV Impact survey, 2016–2017 the highest HIV prevalence is found in Njombe (11.4%), Iringa (11.3%), and Mbeya region (9.3%) which are regions found in the southern highland zone [47]. Likewise, in the household budget survey of Tanzania mainland 2017–2018 report, Kigoma region had the highest number of people with basic need poverty and the second greatest number of people with food poverty [48]. Correspondingly, in the basic demographic and socio-economic profile report of Tanzania mainland, the highest illiteracy rate of 44% and 32% were reported in Katavi and Kigoma respectively [49]. Therefore, poor sociol-economic status in Kigoma and Katavi region could explain the highest TB mortality in the western zone.

The current study demonstrates an elevated risk of TB death among bacteriological unconfirmed TB patients. This is coherent with previous studies conducted in Dar es Salaam in Tanzania [21], Zimbabwe [7], and South Africa [3]. However, these findings contradicted previous studies which suggested an increased risk of TB mortality among bacteriologically confirmed TB patients than pulmonary negative patients [25,26]. Earlier studies reported smear-negative TB patients tends to have advanced HIV disease with a lower cluster of differentiation 4 (CD4) counts hence are more likely to experience poor treatment outcome [7,50]. Bacteriological unconfirmed TB cases diagnosed by clinical assessment of TB patients can lead to under-diagnosis of other respiratory diseases, thus increasing the risk of death [7]. Nevertheless, delay in diagnosis after receipt of smear-negative sputum results, and misdiagnosis among bacteriological unconfirmed TB patients may have contributed to high mortality in our findings. The national TB prevalence survey in Tanzania reported standard diagnostic procedures were often not carried out during the initial presentation at health facilities with TB diagnostic capacity [51]. Likewise, most of the primary health care facilities in Tanzania (dispensaries and health centers) do not have the diagnostic capacity to rule out extra-pulmonary TB among smear-negative TB patients [52]. A survey conducted in 9 Sub-Saharan countries including Tanzania reported that only 3% of primary health facilities had chest x-ray as compared to 69% in tertiary health facilities [52].

TB/HIV co-infected patients had lower survival probabilities and increased risk of death as compared to TB HIV negative patients. This was consistent with previous studies conducted in Brazil [53], Kenya [25] and Zimbabwe [7]. As reported in the preceding studies suppressed immune system [7,11,14,25,53], delay in diagnosis [11], and presence of opportunistic disease [8] might have contributed to observed high mortality among TB/HIV patients. A study in Northern Ethiopia suggested difficulty in 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 [34]. A previous study in Brazil highlighted the necessity to strengthen HIV screening in all TB patients for prompt initiation of ARV drugs [53]. The highest mortality rate among TB-HIV co-infected patients calls for effective management strategies for TB/HIV co-infection such as improved availability of early diagnosis and improved availability of ARVs in resource-limited countries. Also, consistent with previous studies higher mortality risk was observed among older TB patients [3,7,8,17,21]. Disrupted immunity and age-related co-morbidities might have contributed to an increased risk of TB mortality among this age group [3]. Similarly, earlier studies have reported older TB patients are more likely to develop extrapulmonary and atypical forms of TB that are often hard to diagnose by conventional methods resulting in an increased risk of TB death [3,37].

Our study has several limitations. First, since the study used an existing database, only limited demographic and clinical factors were included for purposes of explaining the risk for mortality among TB patients. Other factors such as social-economic and behavior risk factors were not included in our study. Second, we did not have data on the first TB symptoms and date of diagnosis to ascertain the time to diagnosis or treatment delay. Third, our database did not have information on the severity and other co-morbidities of TB patients referred from the

Table 3
Cox regression analysis on the risk factors of TB mortality during TB treatment among TB patients (n = 54,130).

Variable	Crude Hazard Ratio (95%CI)	P-value	Adjusted Hazard Ratio (95 % CI)	P-value
Sex				
Female	Reference			
Male	0.89 (0.82–0.98)	0.022	1.02 (0.93–1.12)	0.618
Age Group (Years)				
15–24	Reference			
25–34	1.32 (1.08–1.61)		1.14 (0.94–1.39)	
35–44	1.78 (1.47–2.15)		**1.37 (1.13–1.66)**	
≤45	1.96 (1.64–2.34)	<0.001	**1.74 (1.45–2.08)**	**0.001**
Health facility level				
Dispensaries	Reference			
Hospitals	1.32 (1.18–1.47)		**1.22 (1.09–1.36)**	
Health Center	0.84 (0.73–0.96)	<0.001	**0.83 (0.73–0.96)**	**<0.001**
Geographical Zones				
Coastal Zone	Reference			
Central Zone	1.09 (0.93–1.29)		1.05 (0.89–1.24)	
Lake Zone	1.16 (1.03–1.32)		1.08 (0.95–1.22)	
Northern Zone	1.07 (0.93–1.24)		1.06 (0.92–1.23)	
Southern Highland Zone	1.60 (1.40–1.82)		**1.29 (1.13–1.48)**	
Western Zone	2.09 (1.64–2.65)	<0.001	**2.30 (1.81–2.93)**	**<0.001**
TB referral type				
Self-referrals	Reference			
CTC referrals	2.07 (1.85–2.32)		1.11 (0.98–1.26)	
Community referral	0.92 (0.79–1.08)		0.92 (0.78–1.07)	
Other referral types	1.58 (1.27–1.96)	<0.001	**1.45 (1.16–1.80)**	**0.001**
Anatomical site of TB				
Pulmonary TB	Reference			
Extrapulmonary TB	1.35 (1.21–1.50)		1.06 (0.95–1.19)	
Both	3.29 (1.23–8.78)	<0.001	2.49 (0.93 – 6.67)	0.120
TB results				
Bacteriological confirmed	Reference			
Bacteriological unconfirmed	1.89 (1.71–2.08)	<0.001	**1.58 (1.42–1.76)**	**<0.001**
DOT option				
Home-based	Reference			
Facility based	2.27 (1.92–2.67)	<0.001	**2.30 (1.95–2.72)**	**<0.001**
HIV status				
HIV-negative	Reference			
HIV-positive	2.77 (2.53–3.04)	<0.001	**2.51 (2.26–2.79)**	**<0.001**

primary health facilities. Fourth limitation in our study was missing data on some variables. However, we used multiple imputation methods to address missing data on the variables. Fifth, a number of patients who had been lost to follow-up may have died at home, this might have under-estimated the TB mortality. Correspondingly, considering the commonest methodological limitation of loss to follow up in our study patients, were censored at their last outcome date. Additionally, 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

5. Conclusions

The mortality rate found in our study was generally lower as compared to previous studies. Also, we found lower survival probabilities among TB/HIV co-infected patients, older, and retreatment TB patients. The independent risk factors of death among TB patients included; advanced age, TB/HIV co-infection, receiving service at facility-based DOT option, receiving service at the hospital level, being bacteriological unconfirmed TB patient, being referred from other referral types, and residing in the southern highland zone, and western zone. Tanzania is among the 7 TB high burden countries which are on track to achieve the End TB 2020 targets with a 19% reduction in TB mortality in 2018 [12]. However, more efforts are needed to achieve the WHO End TB strategy of reducing TB deaths to 95% by the year 2035 [3]. Strengthening TB referral system from primary health facilities, pharmacies and private drug dispensing outlets is essential for the improvement of case detection and reduction of diagnostic delay. Similarly, it is necessary to improve diagnostic capacity in primary health care facilities to minimize delay and misdiagnosis of TB patients. Reinforcement of HIV screening among TB patients and vice versa, and expanding TB-HIV screening outside of traditional facility-based testing might reduce TB death among TB/HIV co-infected patients.

CRediT authorship contribution statement

Elias M. Bukundi: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Visualization. **Francis Mhimbira:** Conceptualization, Methodology, Data curation, Writing - review & editing, Supervision. **Rogath Kishimba:** Writing - review & editing. **Zuweina Kondo:** Conceptualization, Writing - review & editing. **Candida Moshiro:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - review & editing, Supervision, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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