RESEARCH ARTICLE

Mortality during treatment for tuberculosis; a review of surveillance data in a rural county in Kenya

Osman A. Abdullahi1*, Moses M. Ngari2, Deche Sanga3, Geoffrey Katana1,4, Annie Willetts1

1 Pwani University, Department of Public Health, Kilifi, Kenya, 2 KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya, 3 Kilifi County TB Control Program, Kilifi, Kenya, 4 Kilifi County Department of Public Health, Kilifi, Kenya

* o.abdullahi@pu.ac.ke

Abstract

Background

Globally in 2016, 1.7 million people died of Tuberculosis (TB). This study aimed to estimate all-cause mortality rate, identify features associated with mortality and describe trend in mortality rate from treatment initiation.

Method

A 5-year (2012–2016) retrospective analysis of electronic TB surveillance data from Kilifi County, Kenya. The outcome was all-cause mortality within 180 days after starting TB treatment. The risk factors examined were demographic and clinical features at the time of starting anti-TB treatment. We performed survival analysis with time at risk defined from day of starting TB treatment to time of death, lost-to-follow-up or completing treatment. To account for ‘lost-to-follow-up’ we used competing risk analysis method to examine risk factors for all-cause mortality.

Results

10,717 patients receiving TB treatment, median (IQR) age 33 (24–45) years were analyzed; 3,163 (30%) were HIV infected. Overall, 585 (5.5%) patients died; mortality rate of 12.2 (95% CI 11.3–13.3) deaths per 100 person-years (PY). Mortality rate increased from 7.8 (95% CI 6.4–9.5) in 2012 to 17.7 (95% CI 14.9–21.1) in 2016 per 100PY (P_trend<0.0001). 449/585 (77%) of the deaths occurred within the first three months after starting TB treatment. The median time to death (IQR) declined from 87 (40–100) days in 2012 to 46 (18–83) days in 2016 (P_trend = 0.04). Mortality rate per 100PY was 7.3 (95% CI 6.5–7.8) and 23.1 (95% CI 20.8–25.7) among HIV-uninfected and HIV-infected patients respectively. Age, being a female, extrapulmonary TB, being undernourished, HIV infected and year of diagnosis were significantly associated with mortality.
Conclusions

We found most deaths occurred within three months and an increasing mortality rate during the time under review among patients on TB treatment. Our results therefore warrant further investigation to explore host, disease or health system factors that may explain this trend.

Introduction

Tuberculosis (TB) is the leading cause of death from a single infectious agent worldwide [1]. Global success of annual reduction in TB mortality by 3% is overshadowed by the estimated 1.7 million who died in 2016 of this curable disease, with the highest burden in sub-Saharan Africa [1, 2]. Hence an ambitious global target of reducing TB deaths by 95% from 2015 to 2035 has been set by the World Health Organization (WHO) [2].

Recent WHO estimates indicate most people with TB who die are no longer HIV-infected: 24% in 2016, a decline from 45% in 2008 [1]. The success of interventions in a policy environment focused on HIV can be attributed to access to integrated strategies for early TB diagnosis and treatment, including prioritising molecular diagnostics for these high risk populations [2]. Earlier reports on trends in risk factors for TB mortality since the recent decline in prevalence of people coinfected with HIV [3–6], a historical driver of TB [7], neglect inclusion of mortality rates, or report only on high-risk populations [8, 9]. These important reports are therefore limited to indicate the future direction of TB mortality or reflect a shift in the causal factors.

Several studies identify similar clinical and demographic characteristics among people with TB who die, primarily those with HIV co-infection without antiretroviral treatment [3, 8, 10, 11]. Other co-morbidities include older age, gender, being malnourished, concurrent diabetes mellitus, type of TB disease and antimicrobial resistance [3, 4, 8, 12, 13]. Thus, in the context of control measures against the HIV epidemic, the epidemiology of TB increasingly encompasses other high-risk populations [7].

Studies in sub-Saharan Africa potentially suggest the annual decline in TB mortality since 2000 [1] may be slowing down [14], or reversing [9], despite the sustained downward trend in new infections reported and people coinfected with HIV in the region. An urgent need exists to understand the dynamics of mortality after initiating treatment.

In this study, we aimed to estimate all-cause mortality rate, identify features associated with mortality, and describe mortality and survival trends during a five-year (2012–2016) period amongst patients during the six months of TB treatment period in Kilifi County, Kenya.

Method

Setting

Kilifi County is located on the coast of Kenya. The estimated total population is 1.4 million (national: 43 million) with an urban population at 26% [15]. The HIV prevalence is estimated as 3.7% (national 6%) and BCG immunization coverage 86% in 2016 [16]. The 2016 TB prevalence survey estimated 122/100,000 cases in Kilifi (compared to 170/100,000 nationally) and TB and HIV comorbidity at 17% [17]. Among notified TB cases a decline was observed in people coinfected with HIV at 31% in 2016 from 45% in 2008 [17, 18]. The GeneXpert Mycobacterium tuberculosis (MTB)/Rifampicin (RIF) (Cepheid USA) 4-module rapid molecular system was placed in two public hospitals in Kilifi during the study period (2012 and 2016) and reported 8–15 cases of resistance to TB treatment [17] within the study period. The main economic activity is subsistence agriculture [15].
In Kenya, all public health facilities offer TB treatment services. Health facilities send sputum for presumptive TB cases to the nearest TB diagnostic laboratory for GeneXpert MTB/RIF Cepheid or smear microscopy test with results expected to return to their respective health centers within 48 hours [19]. All TB patients are offered HIV counseling and testing after starting TB treatment. All HIV coinfected patients are linked to anti-retroviral treatment (ART) initiation and provision of HIV/AIDS care and support at the health facility, or the nearest site with services. According to national guidelines, ART is started at least two weeks after the start of TB therapy regardless of the CD4 cell count status. However, for severely immunosuppressed patients (those with CD4 <50 cells/µL), ART is initiated within the first two weeks of initiating TB treatment. People with HIV are given cotrimoxazole prophylaxis therapy (CPT) together with anti-TB treatment, provided there is no contraindication.

**Study design**

A retrospective analysis of patients receiving anti-TB treatment in Kilifi County, Kenya. The primary outcome was all-cause mortality within 180 days after starting TB treatment. The risk factors examined were demographic and clinical features collected at the time of starting TB treatment.

**Study population**

The study population consisted of persons with presumptive TB who started anti-TB treatment within the seven sub-county health facilities (Ganze, Kaloleni, Kilifi South, Kilifi North, Rabai, Malindi and Magarini) from January 2012 to December 2016, regardless of age.

**Data collection**

All patients diagnosed with TB are registered in the electronic surveillance database of Kilifi County TB program (TIBU) by the sub-county coordinators within a month of starting treatment. TB was diagnosed by either direct smear microscopy, GeneXpert MTB/RIF for sputum, chest X-ray or using clinical symptoms according to WHO guidelines [20]. In hospitals with the capacity to use GeneXpert MTB/RIF and where smear microscopy was offered to the patient first, GeneXpert MTB/RIF was usually performed for patients who tested negative for smear microscopy.

Patients attended health facilities monthly for scheduled visits to collect their drugs. The Kilifi County TB program lack resources to conduct systematic community-treated patient follow-up at home. TB patient who failed to attend two consecutive scheduled monthly visits were traced through the community-based health workers and those not traceable were considered ‘lost-to-follow-up’. Patients moving out of Kilifi County advised to continue monthly clinics near to their new home and classified as ‘transferred’. Reported deaths were confirmed by a community home visit or from hospital records for those who died in hospital. For this analysis, outcomes during six months of follow-up were considered. For the ‘lost-to-follow-up’ and those ‘not evaluated’ patients, vital status at their last visit was used.

**Data and measurements**

We categorized age into three preconceived groups; <15, 15 to 45, ≥45 years and used the ≥45 years as the reference because it had the highest mortality. The body mass Index was computed as weight (kgs) divided by the square of height in metres for adults aged ≥19 years. Children less than five years and 5 to 19 years old weight-for-height z-score (WHZ) were computed using the WHO 2006 and 2007 children growth references [21]. A nutritional status score was
computed by combining the BMI and WHZ as follows; a) undernourished if \( \text{WHZ} < -2 \) or \( \text{BMI} < 18.5 \), b) normal if \( \text{WHZ} \) -2 to +2 or \( \text{BMI} 18.5 \) to 25 and c) overweight if \( \text{WHZ} \geq +2 \) or \( \text{BMI} \geq 25 \)[22]. The TB patients were categorised as: Pulmonary vs. Extra-pulmonary and new vs. Re-treated. TB treatment outcomes were classified as ‘treatment completed’, ‘died’ or ‘lost-to-follow-up’ or ‘not evaluated’. Because this was surveillance data, smear microscopy test was not systematically performed at month five and therefore the ‘treatment completed’ included both cured and uncured patients who completed six months treatment. HIV was classified as: ‘HIV uninfected’, ‘HIV infected on ART’, ‘HIV infected not on ART’ and ‘unknown HIV status’. CD4 and viral load for HIV infected patients were not available. Anti-TB drug resistant data were not available.

**Statistical analysis**

All the statistical analysis was performed using Stata version 15.1 (StataCorp, College Station, TX, USA). For patients missing specific variable data, such as nutrition or HIV status, a separate missing category was allocated (unknown/missing) and analyzed, because data were assumed not to be missing at random.

We did a single event survival analysis since date of starting TB treatment. Follow-up time was from the date of starting anti-TB treatment to a maximum of 180 days or time of death/lost to follow-up/date last seen. Mortality rates were computed as the number of deaths per 100 person-year (PY). Yearly trend all-cause mortality rate within 180 days after TB treatment initiation was tested using an extension of Wilcoxon rank-sum test for trend across ordered groups [23].

We plotted smoothed cumulative subhazard curves using the STATA stcurve command and compared survival distributions between those alive and died using log-rank test. Since lost to follow-up or outcome ‘not evaluated’ would preclude the probability of observing death (our outcome of interest), we treated these two events as competing events. We thus used Fine and Gray competing risk analysis method instead of the conservative cox-regression models to examine putative risk factors for all-cause mortality and reported the effects using sub-distribution hazards ratios (SHR) and their respective 95% confidence intervals [24]. Briefly, the competing risk analysis calculates the cumulative hazards of death associated with the exposure of interest while adjusting for other covariates and accounts for the competing events, rather than censoring these events as is the case with cox-regression models.

In the multivariable competing risk analysis model, we used backwards stepwise approach to retain independent variables with \( P < 0.1 \) and reported adjusted SHR for variables in the final model with \( P < 0.05 \). We performed internal validation of the multivariable model by computing bootstrapped area under receiver operating curve (AUC) estimated by using probit model resampled 100 times with replacement. To account for the clustering of study patients within sub-counties, we performed both univariate and multivariable competing risk models with random effects intercept allowing for sub-counties clustering. To test heterogeneity of mortality rates across the seven sub-counties, we tested the hypothesis that the mortality rates were not different using meta-analysis method with random effects.

We also performed a sub-analysis to examine risk of death between persons with presumptive TB with a confirmed TB diagnosis using either positive sputum microscopy or GeneXpert MTB/RIF and those with clinical TB symptoms (including extra pulmonary TB).

**Ethical considerations**

Ethical approval was obtained from Pwani University Ethical Review Board (ERC/PU-STAFF/005/2018) and permission granted by the Kilifi County Ethical Research Committee to access the anonymized data.
Results

Baseline characteristics

From 2012 to 2016, 10,717 patients were started on TB treatment in 121 health facilities in Kilifi County (Fig 1). The patients’ range and median (IQR) age was 1 to 84 and 33 (24–45) years respectively and 4,529 (42%) were female. 3163 (30%) patients were HIV-infected; of which 2963 (94%) on ART while 3134 (99%) receiving cotrimoxazole prophylaxis. Approximately one third of the participants 3,694 (34%) had normal nutrition status, whilst 4,847 (45%) undernourished, mostly from Kaloleni and Rabai sub-counties. 832 (7.8%) found to be overweight or obese (Table 1 and S1 Fig).

Of the 10,717 patients, 1,009 (9.4%) were re-treatment cases. Overall, 1,304 (12%) were extrapulmonary cases and 9,413 (88%) pulmonary TB cases. A total of 4,470/10,717 (42%) had positive sputum microscopy, 163/10,717 (1.5%) were diagnosed by GeneXpert and 4,780/10,717 (45%) were diagnosed by clinical signs only (Table 1).

The number of patients starting anti-TB treatment declined from 2,610 (24% of the cohort) in 2012 to 1,689 (16%) in 2016 (P_trend = 0.02) (Fig 2). The number of study participants diagnosed for TB with GeneXpert increased across the five years (P_trend = 0.003) and those diagnosed through clinical signs declined (P_trend = 0.008) (S1 Table).

All-cause mortality rate post TB initiation

During the six months follow-up, 9,234 (86%) patients completed TB treatment and 1,483 (14%) did not complete treatment. Overall, 585 (5.5%) died, 280 (2.6%) were lost to follow-up and 618 (5.8%) outcome not evaluated (Fig 1). In total 898/10,717 (8.4%) of the patients found either lost-to-follow-up or their outcome not evaluated and included in the regression model as competing events. Table 1 shows characteristics of participants by their treatment outcome.

Patients were in follow-up for 5175.5PY; mortality rate of 12.2 (95% CI 11.3–13.3) per 100PY. The mortality rate increased from 7.8 (95% CI 6.4–9.5) in 2012 to 17.7 (95% CI 14.9–21.1) in 2016 per 100PY (P_trend < 0.0001) (Fig 2 and S1 Table). 449/585 (77%) of all the deaths occurred within the first three months after starting TB treatment; mortality rate 314.0 (95% CI 286.2–344.4) deaths per 100PY. Overall, the monthly mortality case ratio declined from
### Table 1. Characteristics of the TB patients at the time of initiating TB treatment in Kilifi County, Kenya.

| Features                        | All patients (N = 10,717) | Completed treatment (N = 9,234) | Died (N = 585) | LTFU\(^1\) (N = 280) | Outcome not evaluated (N = 618) |
|---------------------------------|---------------------------|---------------------------------|----------------|----------------------|--------------------------------|
| **Age in years**                |                           |                                 |                |                      |                                |
| <15 years                       | 1,256 (12)                | 1,166 (93)                      | 33 (2.6)       | 19 (1.5)             | 38 (3.0)                       |
| 15 to 45 years                  | 6,598 (61)                | 5,688 (86)                      | 274 (4.2)      | 196 (3.0)            | 440 (6.7)                      |
| 45 and above years              | 2,863 (27)                | 2,380 (83)                      | 278 (9.7)      | 65 (2.3)             | 140 (4.9)                      |
| **Sex**                         |                           |                                 |                |                      |                                |
| Male                            | 6,188 (58)                | 5,260 (85)                      | 338 (5.5)      | 198 (3.2)            | 392 (6.3)                      |
| Female                          | 4,529 (42)                | 3,974 (88)                      | 247 (5.5)      | 82 (1.8)             | 226 (5.0)                      |
| **Patient type**                |                           |                                 |                |                      |                                |
| New cases                       | 9,708 (91)                | 8,416 (87)                      | 512 (5.3)      | 237 (2.4)            | 543 (5.6)                      |
| Re-treatment cases              | 1,099 (9.4)               | 818 (81)                        | 73 (7.2)       | 43 (4.3)             | 75 (7.4)                       |
| **TB type**                     |                           |                                 |                |                      |                                |
| Pulmonary                       | 9,413 (88)                | 8,037 (85)                      | 521 (5.5)      | 259 (2.8)            | 596 (6.3)                      |
| Extrapulmonary                  | 1,304 (12)                | 1,105 (85)                      | 99 (7.6)       | 31 (2.4)             | 69 (5.3)                       |
| **Type of health facility**     |                           |                                 |                |                      |                                |
| Public                          | 8,361 (78)                | 7,247 (87)                      | 427 (5.1)      | 202 (2.4)            | 485 (5.8)                      |
| Private                         | 2,173 (20)                | 1,820 (84)                      | 155 (7.1)      | 73 (3.4)             | 125 (5.8)                      |
| Prisons                         | 183 (2.0)                 | 167 (91)                        | 3 (1.6)        | 5 (2.7)              | 8 (4.4)                        |
| **DOT\(^2\)**                  |                           |                                 |                |                      |                                |
| Family-based                    | 9,280 (87)                | 8,029 (87)                      | 506 (5.5)      | 223 (2.4)            | 522 (5.6)                      |
| Community volunteer             | 800 (7.5)                 | 688 (86)                        | 33 (4.1)       | 36 (4.5)             | 43 (5.4)                       |
| Health worker                   | 637 (5.9)                 | 517 (81)                        | 46 (7.2)       | 21 (3.3)             | 53 (8.3)                       |
| **Nutrition status**            |                           |                                 |                |                      |                                |
| Undernourished                  | 4,847 (45)                | 4,078 (84)                      | 322 (6.6)      | 147 (3.0)            | 300 (6.2)                      |
| Normal                          | 3,694 (34)                | 3,252 (88)                      | 155 (4.2)      | 82 (2.2)             | 205 (5.6)                      |
| Overweight                      | 832 (7.8)                 | 703 (85)                        | 45 (5.4)       | 12 (1.4)             | 72 (8.7)                       |
| Missing anthropometrics         | 1,344 (13)                | 1,109 (82)                      | 98 (7.3)       | 49 (3.7)             | 88 (663)                       |
| **HIV status**                  |                           |                                 |                |                      |                                |
| HIV uninfected                  | 7,413 (69)                | 6,556 (88)                      | 251 (3.4)      | 190 (2.6)            | 416 (5.6)                      |
| HIV infected on ARVS            | 2,963 (28)                | 2,429 (82)                      | 292 (9.9)      | 81 (2.7)             | 161 (5.4)                      |
| HIV infected not on ARVS        | 200 (1.9)                 | 139 (70)                        | 33 (17)        | 5 (2.5)              | 23 (12)                        |
| Unknown HIV status              | 141 (1.3)                 | 110 (78)                        | 9 (6.4)        | 4 (2.8)              | 18 (13)                        |
| **Treatment regimen**           |                           |                                 |                |                      |                                |
| 2RHZE/4RH                       | 9,380 (88)                | 8,126 (87)                      | 491 (5.2)      | 237 (2.5)            | 526 (5.6)                      |
| 2SRHZE/1RHZE/5RHE               | 1,078 (10)                | 872 (81)                        | 85 (7.9)       | 40 (3.7)             | 81 (7.5)                       |
| 2RHZ/4RH                        | 234 (2.2)                 | 213 (91)                        | 7 (3.0)        | 3 (1.3)              | 11 (4.7)                       |
| Others                          | 25 (0.2)                  | 23 (92)                         | 2 (8.0)        | 0                    | 0                               |
| **Sub County**                  |                           |                                 |                |                      |                                |
| Kilifi North                    | 1,757 (16)                | (16)1,717                       | 1,450 (83)     | 113 (6.4)            | 120 (6.8)                      |
| Kilifi South                    | 1,717 (16)                | 1,481 (86)                      | 59 (3.4)       | 53 (3.1)             | 124 (7.2)                      |
| Kaloleni                        | 2,049 (19)                | 1,727 (84)                      | 165 (8.1)      | 38 (1.9)             | 119 (5.8)                      |
| Malindi                         | 2,824 (26)                | 2,482 (88)                      | 107 (3.8)      | 71 (2.5)             | 164 (5.8)                      |
| Magarini                        | 1,284 (12)                | 1,160 (90)                      | 49 (3.8)       | 22 (1.7)             | 53 (4.1)                       |
| Ganzé                           | 536 (5.0)                 | 461 (86)                        | 43 (8.0)       | 13 (2.4)             | 19 (3.5)                       |
| Rabai                           | 550 (5.1)                 | 473 (86)                        | 49 (8.9)       | 9 (1.6)              | 19 (3.5)                       |
| **Year of diagnosis**           |                           |                                 |                |                      |                                |
| 2012                            | 2,610 (24)                | 2,316 (89)                      | 93 (3.6)       | 0                    | 201 (7.7)                      |

(Continued)
32% (95% CI 28 to 36) during the first month of treatment to 5% (95% CI 4 to 7) between fifth and sixth month of treatment (P\textsubscript{trend} < 0.001) \textbf{Fig 3}. Among the early deaths in the first three months of treatment, mortality rate increased from 175.8 (95% CI 138.1–223.7) in 2012 to

![Fig 3](https://doi.org/10.1371/journal.pone.0219191.g002)

\textbf{Table 1. (Continued)}

| Features | All patients (N = 10,717) | Completed treatment (N = 9,234) | Died (N = 585) | LTFU\textsuperscript{1} (N = 280) | Outcome not evaluated (N = 618) |
|----------|--------------------------|---------------------------------|---------------|-------------------------------|---------------------------------|
| 2013     | 2,274 (21)               | 1,972 (87)                      | 115 (5.1)     | 8 (0.4)                       | 179 (7.9)                       |
| 2014     | 2,271 (21)               | 1,982 (87)                      | 137 (6.0)     | 73 (3.2)                      | 79 (3.5)                       |
| 2015     | 1,873 (17)               | 1,591 (85)                      | 110 (5.9)     | 101 (5.4)                     | 71 (3.8)                       |
| 2016     | 1,689 (16)               | 1,373 (81)                      | 130 (7.7)     | 98 (5.8)                      | 88 (5.2)                       |

\textsuperscript{1}LTFU-Lost to follow-u
\textsuperscript{2}DOT-directly observed treatment; all results are N (%).

https://doi.org/10.1371/journal.pone.0219191.t001
351.0 (95% CI 290.4–424.2) deaths per 100PY in 2016 ($P_{trend} = 0.03$) S2 Fig. However, among the
136/585 (23%) deaths occurring after 3 months of treatment, there was no evidence of linear
increase in mortality; from 2.33 (95% CI 1.60–3.40) in 2012 to 3.27 (95% CI 2.17–4.93) deaths
per 100PY in 2016 ($P_{trend} = 0.43$) S2 Fig. The mortality rate was heterogeneous across the
seven sub-counties with Kilifi south having the lowest rate 7.6 (95% CI 5.9–9.8) and Rabai sub-
county with the highest rate of 20.3 (95% CI 15.3–26.8) per 100PY; $I^2 = 92.1\%$, $P < 0.0001$ (S3
Fig). Among HIV infected patients, the mortality rate increased from 15.9 (95% CI 12.1–20.8)
in 2012 to 31.8 (95% 25.0–40.4) per 100PYin 2016 ($P_{trend} = 0.001$) (Fig 2 and S1 Table).
Median time to death (IQR) declined from 87 (40–100) days in 2012 to 46 (18–83) days in
2016 ($P_{trend} = 0.04$) (S1 Table).

**Risk factors for all-cause mortality post-TB treatment initiation**

Age (age $< 45$ years was protective compared to $\geq 45$ years), female sex, extrapulmonary TB,
low nutritional status, HIV infection, 2SRHZE/1RHZE/5RHE treatment regimen and year of
diagnosis were independent risk factors for all-cause mortality within 180 days after initiation of TB treatment ([S2 Table, Fig 4A and 4B and Table 2]). There were 251/7413 (3.4%) deaths among the HIV uninfected people: mortality rate 7.3 (95% CI 6.5–7.8) per 100PY and 325/3163 (10.3%) deaths among the HIV infected people: mortality rate 23.1 (95% CI 20.8–25.7) per 100PY. Overall, HIV infection was associated with mortality, adjusted SHR: 3.26 (95% CI 2.76–3.86). Among the HIV infected patients, 33/130 (25%) died amongst those not on ARVS and 292/1,463 (20%) amongst those on ARVS. Being on ARVS was associated with 43% reduction in risk of death (crude SHR 0.57 (95% CI 0.37–0.87)) compared to not being on ARVS among the HIV infected patients. There was no significant difference in time to death between patients on ARVS and not on ARVS (P = 0.08), however those not on ARVS were in follow-up for a shorter period (mean of 142 days) compared to those on ARVS (mean of 159 days) P<0.0001) amongst HIV infected patients.

In the sub-analysis, 4,633(43%) were bacteriologically confirmed TB cases, while 6,084 (57%) were clinically diagnosed. Amongst confirmed TB cases, 169/4,633 (3.7%) died while 416/6,084 (6.8%) died among the clinically diagnosed (P<0.0001). Among confirmed TB cases, we observed a similar increase in mortality rate trend to the whole cohort; an increase from 5.7 (95% CI 3.8–8.4) deaths per 100PY in 2012 to 13.2 (95% CI 10.1–17.2) deaths per 100PY in 2016(P_trend = 0.007) ([S3 Table]). Compared to the clinically diagnosed patients, confirmed TB cases had a lower risk of dying; age, HIV and sex adjusted SHR 0.56 (95% CI 0.40–0.79). Factors associated with mortality amongst the 43% confirmed TB cases were similar to those of the overall cohort ([S3 Table]). Old age, extrapulmonary TB and HIV infection were associated with both deaths within and after three months of starting TB treatment ([S4 Table]).

Discussion

Our results provide evidence of an increase in the risk of dying and shortened time to death among patients on anti-TB treatment during a period of declining number of TB cases. This increase is driven primarily by individuals coinfected with HIV, including in the subgroup of confirmed TB cases. However, HIV infected patients on ARVs had lower risk of mortality compared to those not on treatment, as found in previous studies [25]. Earlier studies in the region, including Kenya, report a decline in both the number of TB cases and mortality, however defined by case fatality ratios [4, 5]. This study found more than three quarters of the deaths occurred within three months of starting TB treatment. These early deaths had an increasing mortality rate whilst deaths occurring after the third month of TB treatment remained fairly constant from 2012 to 2016. Undetected anti-TB resistance, poor adherence to treatment, late TB diagnosis and treatment delay observed in TB endemic countries may contribute to this increasing mortality trend [26–28].

The trend of most deaths occurring early suggests a late TB diagnosis or delay in starting treatment, including ARVS amongst HIV infected patients. More than half of TB cases were diagnosed using clinical signs suggesting using molecular tools to diagnosis TB proved challenging in the county. Clinical diagnosis conducted when symptoms are visible to the clinician potentially at a more advanced stage of TB disease. It is therefore not surprising most deaths occurred early. The policy of testing TB and having the patients receive their results after 48 hours necessarily delays starting of treatment [19]. Although we do not know the proportion of the patients who did not know their HIV status before the TB diagnosis, it is possible most of them started taking ARVS after TB treatment and therefore this provided a window for early deaths. We suspected an increasing trend in delay of HIV diagnosis and starting ARVs especially amongst the elderly as a result of an HIV testing campaign biased towards the youths in Kenya [29].
Fig 4. Kaplan-meier graphs for all-cause mortality by: A-age group and B-HIV status.

https://doi.org/10.1371/journal.pone.0219191.g004
Our study found being immunosuppressed presented a higher risk for dying during TB treatment. As documented in other studies, people of older age, malnourished (low and high BMI), and HIV coinfected are high risk groups [3, 4, 10, 12]. Patients missing BMI/z-score had elevated risk of mortality suggesting data were not missing at random and the need to be included in mortality estimates. The WHO estimates show an increase in diabetes among

### Table 2. Risk factors for all-cause mortality 180 days after initiation of TB treatment in Kilifi County, Kenya.

| Features                     | Deaths (N = 585) | Mortality rate per 100PY (95% CI) | Adjusted SHR (95% CI) | P-value |
|------------------------------|------------------|-----------------------------------|-----------------------|---------|
| **Age in years**             |                  |                                   |                       |         |
| <15 years                    | 33 (2.6)         | 5.7 (3.5–8.8)                     | 0.26 (0.22–0.32)      | <0.0001 |
| 15 to 45 years               | 274 (4.2)        | 9.3 (6.8–12.7)                    | 0.38 (0.34–0.41)      | <0.0001 |
| 45 and above years           | 278 (9.7)        | 22.3 (16.5–30.8)                  | Reference             |         |
| **Sex**                      |                  |                                   |                       |         |
| Male                         | 338 (5.5)        | 12.3 (8.6–17.6)                   | Reference             |         |
| Female                       | 247 (5.5)        | 12.1 (8.7–17.2)                   | 0.86 (0.80–0.93)      | <0.0001 |
| **TB type**                  |                  |                                   |                       |         |
| Pulmonary                    | 491 (5.2)        | 11.7 (8.2–16.6)                   | Reference             |         |
| Extrapulmonary               | 94 (7.2)         | 16.4 (11.5–24.0)                  | 1.22 (1.01–1.48)      | 0.04    |
| **Type of health facility**  |                  |                                   |                       |         |
| Public                       | 427 (5.1)        | 11.4 (8.5–15.1)                   | Reference             |         |
| Private                      | 155 (7.1)        | 16.3 (7.3–48.8)                   | 1.24 (0.83–1.85)      | 0.28    |
| Prison                       | 3 (1.6)          | 3.6 (2.7–5.3)                     | 0.33 (0.27–0.42)      | <0.0001 |
| **Nutrition status**         |                  |                                   |                       |         |
| Undernourished               | 305 (6.3)        | 14.20 (12.68,15.88)               | 1.46 (1.39–1.53)      | <0.0001 |
| Normal                       | 151 (4.1)        | 8.97 (7.65, 10.52)                | Reference             |         |
| Overweight                   | 41 (4.9)         | 11.09 (8.17,15.07)                | 1.06 (0.78–1.46)      | 0.70    |
| Missing anthropometrics      | 88 (6.6)         | 15.07 (12.23,18.58)               | 1.64 (1.07–2.52)      | 0.02    |
| **HIV status**               |                  |                                   |                       |         |
| HIV uninfected               | 251 (3.4)        | 7.5 (4.8–11.6)                    | Reference             |         |
| HIV infected on ARVS         | 292 (9.9)        | 22.7 (17.5–29.5)                  | 3.06 (2.38–3.94)      | <0.0001 |
| HIV infected not on ARVS     | 33 (17)          | 42.4 (31.9–54.4)                  | 6.12 (3.15–11.89)     | <0.0001 |
| Unknown HIV status           | 9 (6.4)          | 15.7 (6.2–54.1)                   | 1.91 (0.99–3.68)      | 0.05    |
| **Treatment regimen**        |                  |                                   |                       |         |
| 2RHZE/4RH                    | 491 (5.2)        | 11.7 (8.2–16.7)                   | Reference             |         |
| 2SRHZE/1RHZE/5RHE            | 85 (7.9)         | 18.1 (13.8–24.4)                  | 1.24 (1.05–1.46)      | 0.01    |
| 2RHZ/4RH                     | 7 (3.0)          | 6.6 (2.8–14.1)                    | 0.89 (0.49–1.61)      | 0.70    |
| Others                       | 2 (8.0)          | 16.6 (5.1–25.6)                   | 1.41 (0.50–4.03)      | 0.52    |
| **Year of diagnosis**        |                  |                                   |                       |         |
| 2012                         | 93 (3.6)         | 7.8 (4.3–14.0)                    | Reference             |         |
| 2013                         | 115 (5.1)        | 11.4 (6.8–20.1)                   | 1.32 (1.05–1.67)      | 0.02    |
| 2014                         | 137 (6.0)        | 13.5 (9.0–20.5)                   | 1.61 (1.25–2.08)      | <0.0001 |
| 2015                         | 110 (5.9)        | 13.3 (10.0–18.0)                  | 1.69 (1.14–2.50)      | 0.009   |
| 2016                         | 130 (7.7)        | 17.7 (14.4–21.8)                  | 2.43 (1.50–3.93)      | <0.0001 |
| **Model Performance**        |                  |                                   |                       |         |
| AUC (95% CI)                 |                  | 0.75 (0.73–0.76)                  |                       |         |
| Bootstrapped AUC (95% CI)    |                  | 0.74 (0.73–0.76)                  |                       |         |

SHR-Sub-distribution hazard ratios, DOT-directly observed treatment, PY-person year, AUC-Area under receiver operating curve, The SHR are obtained using Fine and Gray competing risk regression analysis.

https://doi.org/10.1371/journal.pone.0219191.t002
Kenyans, independently associated with higher TB mortality in other studies [1, 13]. The higher burden of non-communicable diseases among older Kenyan adults potentially increases mortality during TB treatment [30].

The explanation for the observed decline in survival time from starting treatment to death is unclear. All major clinical and demographic factors remained unchanged during the 5-year study period, including HIV coinfection at 27–30%. In 2012, Kilifi County started implementing the new WHO screening and testing algorithms and molecular technology for TB and drug resistance testing (GeneXpert MTB/Rif Cepheid USA) [17]. This context of heightened TB awareness may explain the decline in notified TB cases as clinical diagnosis of persons with presumptive TB reduced. The Kilifi County has recorded annual population growth of 3.1% suggesting the declining notified TB cases has no correlation with the population changes. Linking the GeneXpert drug resistance data with TIBU surveillance information potentially creates an opportunity to explain mortality trends in this type of TB.

This study identified only a brief window to intervene in the TB pathway from starting treatment to death. As reported in other studies, more than half of the deaths occur within the 2-month of intensive treatment phase [3, 12, 31]. Some authors attribute the short survival time to delays in TB diagnosis and/or initiation of anti-TB and antiretroviral treatment, severe disease, undiagnosed drug-resistant TB or co-morbidities, low adherence to anti-TB drugs and challenges in health care access [3, 32, 33]. The heterogeneity between sub-counties in mortality rates and BMI observed in this study may be explained by inequities and inadequate access to TB services across the county. Of value to the TB program is the finding that current TB, ARVS and cotrimoxazole strategies alone may not be optimal in reducing the risk of mortality, as found in other studies [11, 25]. Notably, the protective effect of ARV therapy was less (43%) in our study than in the meta-analysis conducted by Odone et al, 2014, despite 94% ARV coverage in this cohort [34, 35].

The major strength of this study was its large size, systematic data collection process and comprehensiveness of the data available for this analysis within the five-year period. Our established collaboration with the sub-county program coordinators allowed verification of inconsistencies and incompleteness in the data at facility level.

Our study is limited by several factors. TB diagnosis using the WHO clinical signs are typical in resource-limited settings however was necessarily subjective. A sub-analysis found confirmed TB cases have a lower mortality risk than clinically diagnosed patients but identified similar increasing mortality rate trend and risk factors of dying suggesting the clinical diagnosis identifies patients most at risk of death. We could not ascertain the vital status of the 898/10,717 (8.4%) patients not completing treatment due either lost-to-follow-up (LTFU) or outcome not evaluated. To account for this limitation, we treated these events (LTFU/outcome not evaluated) as competing events with the outcome (mortality) in the analysis. The higher mortality amongst adults above 45 years is potentially attributed to other old-age related illness, including non-communicable diseases (heart related or cancer), low CD4 counts or drug resistance which are not routinely collected for the TIBU database. Drug resistance surveillance systems report low incidence at County and National level [17]. Programmatic surveillance data potentially underestimates or overestimates TB mortality, for example it did not allow us to examine the causes of community all-cause mortality and undiagnosed TB. Reliance on verbal autopsy and missed TB cases underestimates the true burden of TB related mortality. These limitations are inherent in programmatic data and difficult to prevent during the analysis.

Future research is needed to better understand the dynamics of deaths among TB patients on treatment. The role of factors that delay TB diagnosis and treatment require exploring, providing vital information to inform early diagnosis and avert most of the TB attributable deaths.
HIV co-infection was the main factor associated with mortality, however little is known when the HIV diagnosis was made, ARVs started and monitoring of changing CD4 counts and viral load while on treatment. The effect of systematically screening for HIV at time of starting TB treatment and either linking those infected with HIV clinics or promptly starting ARVs should be evaluated. The role of anti-TB drug resistant, adherence to the TB treatment, health system bottlenecks and other social poverty-related constrains need further exploration.

Conclusions

We found most deaths occurred within first three months and an increasing mortality rate among patients on TB treatment. Our findings warrant further investigation to go beyond already established indicators to explore host, disease or health system factors that may explain the observed trend.

Supporting information

S1 Fig. Proportions of different levels of nutritional status from the seven sub counties. (TIFF)

S2 Fig. A- Annually mortality rate per 100PY for deaths occurring within three months of starting TB treatment and B- Annually mortality rate per 100PY for deaths occurring after three months of starting TB treatment. (TIFF)

S3 Fig. Mortality rates per 100 person-years from the seven sub counties. (TIFF)

S1 Table. Changes of selected participants’ characteristics and outcomes across the years. (DOCX)

S2 Table. Univariable associations between features at initiating TB treatment and deaths within six months of follow up. (DOCX)

S3 Table. Associations between features at initiating TB treatment and deaths within six months of follow-up among confirmed TB cases. (DOCX)

S4 Table. Associations between features at initiating TB treatment and deaths stratified by deaths within and after three months of starting TB treatment. (DOCX)

Acknowledgments

The authors wish to thank the participants and staff of Kilifi County Hospital.

Author Contributions

Conceptualization: Osman A. Abdullahi, Deche Sanga, Geoffrey Katana, Annie Willetts.

Data curation: Osman A. Abdullahi, Moses M. Ngari, Deche Sanga, Geoffrey Katana.

Formal analysis: Osman A. Abdullahi, Moses M. Ngari.

Methodology: Osman A. Abdullahi, Moses M. Ngari, Deche Sanga, Annie Willetts.

Writing – original draft: Osman A. Abdullahi, Moses M. Ngari, Annie Willetts.
References

1. World Health Organization. Global tuberculosis report 2017. Geneva: WHO; 2017 [cited 2018 May 04]. Available from: http://apps.who.int/iris/bitstream/handle/10665/250966/9789241565516-eng.pdf?sequence=1.

2. World Health Organization. The end TB strategy. Geneva: WHO; 2014 [cited 2018 March 17]. Available from: http://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1.

3. Adamu AL, Gadanya MA, Abubakar IS, Jibo AM, Bello MM, Gajida AU, et al. High mortality among tuberculosis patients on treatment in Nigeria: a retrospective cohort study. BMC infectious diseases. 2017; 17(1):170. https://doi.org/10.1186/s12879-017-2249-4 PMID: 28231851; PubMed Central PMCID: PMC5324260.

4. Heunis JC, Kigozi NG, Chikobvu P, Botha S, van Rensburg HD. Risk factors for mortality in TB patients: a 10-year electronic record review in a South African province. BMC public health. 2017; 17(1):38. https://doi.org/10.1186/s12889-016-3972-2 PMID: 28061839; PubMed Central PMCID: PMC5217308.

5. Dangiso MH, Datiko DG, Lindtjorn B. Trends of tuberculosis case notification and treatment outcomes in the Sidama Zone, southern Ethiopia: ten-year retrospective trend analysis in urban-rural settings. PloS one. 2014; 9(12):e114225. https://doi.org/10.1371/journal.pone.0114225 PMID: 25460363; PubMed Central PMCID: PMC4252125.

6. Verguet S, Norheim OF, Olson ZD, Yamey G, Jamison DT. Annual rates of decline in child, maternal, HIV, and tuberculosis mortality across 109 countries of low and middle income from 1990 to 2013: an assessment of the feasibility of post-2015 goals. The Lancet Global health. 2014; 2(12):e698–709. https://doi.org/10.1016/S2214-109X(14)70316-X PMID: 25433625.

7. UNAIDS. Ending AIDS: Progress towards the 90-90-90 Targets. 2017.: UNAIDS; 2017 [cited 2018 May 04]. Available from: http://www.unaids.org/en/resources/campaigns/globalAIDSSupdate2017.

8. Agbor AA, Bigna JJ, Billong SC, Tejiokem MC, Ekali GL, Plottel CS, et al. Factors associated with death during tuberculosis treatment of patients co-infected with HIV at the Yaounde Central Hospital, Cameroon: an 8-year hospital-based retrospective cohort study (2006–2013). PloS one. 2014; 9(12):e115211. https://doi.org/10.1371/journal.pone.0115211 PMID: 25506830; PubMed Central PMCID: PMC4266669.

9. Wobudeya E, Sekadde-Kasiyre M, Kimuli D, Mugabe F, Lukoye D. Trend and outcome of notified children with tuberculosis during 2011–2015 in Kampala, Uganda. BMC public health. 2017; 17(1):963. https://doi.org/10.1186/s12889-017-4798-y PMID: 29258581; PubMed Central PMCID: PMC5735639.

10. Zwang J, Garenne M, Kahn K, Collinson M, Tollman SM. Trends in mortality from pulmonary tuberculosis and HIV/AIDS co-infection in rural South Africa (Agincourt). Transactions of the Royal Society of Tropical Medicine and Hygiene. 2007; 101(8):893–8. https://doi.org/10.1016/j.trstmh.2007.04.023 PMID: 17597174.

11. Nagu TJ, Aboud S, Mwiru R, Matee MI, Rao M, Fawzi WW, et al. Tuberculosis associated mortality in a prospective cohort in Sub Saharan Africa: Association with HIV and antiretroviral therapy. Int J Infect Dis. 2017; 56:39–44. https://doi.org/10.1016/j.ijid.2017.01.023 PMID: 28161460.

12. Takarinda KC, Sandy C, Masuka N, Hazangwe P, Choto RC, Mutasa-Apollo T, et al. Factors Associated with Mortality among Patients on TB Treatment in the Southern Region of Zimbabwe, 2013. Tuber Lung Dis. 2017; 6232071. https://doi.org/10.1155/2017/6232071 PMID: 28352474; PubMed Central PMCID: PMC4909055 publication of this paper.

13. Menon S, Rossi R, Nshimyumukiza L, Wusiman A, Zdraveska N, Eldin MS. Convergence of a diabetes mellitus, protein energy malnutrition, and TB epidemic: the neglected elderly population. BMC infectious diseases. 2016; 16:361. https://doi.org/10.1186/s12879-016-1718-5 PMID: 27456231; PubMed Central PMCID: PMC4909055.

14. Dememew ZG, Habte D, Melese M, Hamusse SD, Nigussie G, Hiruy N, et al. Trends in tuberculosis case notification and treatment outcomes after interventions in 10 zones of Ethiopia. Int J Tuberc Lung Dis. 2016; 20(9):1192–8. https://doi.org/10.5888/ijtld.16.0005 PMID: 27510245.

15. Kenya National Bureau of Statistics. Statistical abstract 2017 Nairobi: KNBS; 2017 [cited 2018 February 16]. Available from: https://www.kenbs.or.ke/download/statistical-abstract-2017.

16. WHO and UNICEF. Kenya: WHO and UNICEF estimates of immunization coverage: 2016 revision 2017 [cited 2018 February 20]. Available from: http://www.who.int/immunization/monitoring_surveillance/data/ken.pdf.
17. National TB and Lung Disease Program. Annual Report 2016 Nairobi2016 [cited 2018 March 10]. Available from: https://www.nltp.co.ke/annual-reports/.
18. National TB and Lung Disease Program. Kenya Tuberculosis Prevalence Survey 2016. Nairobi2017 [cited 2018 April 20]. Available from: https://www.chskenya.org/wp-content/uploads/2017/04/TB-Prevalence-Survey-Key-Findings-Infographic.pdf.
19. National TB and Lung Disease Program. National Strategic Plan for Tuberculosis, Leprosy and Lung Health 2015–2018 Nairobi2014 [cited 2018 May 04]. Available from: https://healthservices.uobi.ac.ke/sites/default/files/centraladmin/healthservices/Kenya%20National%20Strategic%20Plan%20on%20Tuberculosis%20Leprosy.pdf.
20. World Health Organization. Treatment of tuberculosis: guidelines. 4Th Edition. Geneva2010.
21. WHO. WHO Anthro (version 3.2.2, January 2011) and macros. Available from: http://www.who.int/childgrowth/software/en/
22. World Health Organization. Global Database on Body Mass Index. Geneva: WHO; 2006 [cited 2018 April 06]. Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.
23. Cuzick J. A Wilcoxon-type test for trend. Statistics in medicine. 1985; 4(1):87–90. PMID: 3992076.
24. Fine JP. Regression modeling of competing crude failure probabilities. Biostatistics. 2001; 2(1):85–97. https://doi.org/10.1093/biostatistics/2.1.85 PMID: 12933558.
25. Onyango DO, Yuen CM, Cain KP, Ngari F, Masini EO, Borgdorff MW. Reduction of HIV-associated excess mortality by antiretroviral treatment among tuberculosis patients in Kenya. PloS one. 2017; 12 (11):e0188235. https://doi.org/10.1371/journal.pone.0188235 PMID: 29145454; PubMed Central PMCID: PMC5969671.
26. Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. BMC infectious diseases. 2009; 9:31. https://doi.org/10.1186/1471-2334-9-31 PMID: 19519917; PubMed Central PMCID: PMC2702369.
27. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC public health. 2008; 8:15. https://doi.org/10.1186/1471-2458-8-15 PMID: 18194573; PubMed Central PMCID: PMC2265684.
28. Collaborators GBDT. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. The Lancet Infectious diseases. 2018; 18(3):261–84. https://doi.org/10.1016/S1473-3099(17)30703-X PMID: 29223583; PubMed Central PMCID: PMC5831985.
29. Cherutich P, Kaiser R, Galbraith J, Williamson J, Shiraishi RW, Ngare C, et al. Lack of knowledge of HIV status a major barrier to HIV prevention, care and treatment efforts in Kenya: results from a nationally representative study. PloS one. 2012; 7(5):e36797. Epub 2012/05/11. https://doi.org/10.1371/journal.pone.0036797 PMID: 22574226; PubMed Central PMCID: PMC3344943.
30. Mberu B, Wamukoya M, Oti S, Kyobutungi C. Trends in Causes of Adult Deaths among the Urban Poor: Evidence from Nairobi Urban Health and Demographic Surveillance System, 2003–2012. J Urban Health. 2015; 92(3):422–45. https://doi.org/10.1007/s11524-015-9943-6 PMID: 25758599; PubMed Central PMCID: PMC4456477.
31. Harries AD, Hargreaves NJ, Kemp J, Jindani A, Enarson DA, Maher D, et al. Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1. Lancet. 2001; 357(9267):1519–23. https://doi.org/10.1016/S0140-6736(00)04639-0 PMID: 11377627.
32. Cazabon D, Alsdurf H, Satyanarayana S, Nathavitharan R, Subbaraman R, Daftary A, et al. Quality of tuberculosis care in high burden countries: the urgent need to address gaps in the care cascade. Int J Infect Dis. 2017; 56:111–6. https://doi.org/10.1016/j.ijid.2016.10.016 PMID: 27794468; PubMed Central PMCID: PMC5346036.
33. Hansen CL, Osberg M, Brown J, Durham G, Chin DP. Conducting Patient-Pathway Analysis to Inform Programming of Tuberculosis Services: Methods. J Infect Dis. 2017; 216(suppl_7):S679–S85. https://doi.org/10.1093/infdis/jix387 PMID: 29117350; PubMed Central PMCID: PMC5853893.
34. Odone A, Houben RM, White RG, Lonroth K. The effect of diabetes and undernutrition trends on reaching 2035 global tuberculosis targets. Lancet Diabetes Endocrinol. 2014; 2(9):754–64. https://doi.org/10.1016/S2213-8587(14)70164-0 PMID: 25194888.
35. Odone A, Amadasi S, White RG, Cohen T, Grant AD, Houben RM. The impact of antiretroviral therapy on mortality in HIV positive people during tuberculosis treatment: a systematic review and meta-analysis. PloS one. 2014; 9(11):e112017. https://doi.org/10.1371/journal.pone.0112017 PMID: 25391135; PubMed Central PMCID: PMC4229142.