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Adverse Treatment Outcomes among Tuberculosis Patients Enrolled Under Directly Observed Treatment Strategy in Murang'a County: A crossectional study.

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Abstract

Purpose: Despite advances in TB control, over 20% of TB patients in low and middle income countries end up with adverse treatment outcomes. We aimed to describe adverse treatment outcomes and explore the associated factors among TB patients enrolled in Murang'a county between 2017 and 2019.

Methodology*:* We conducted a *crossectional* study in which data was abstracted from patients records and analysed using Computer package (SPSS 24). Univariate and Multivariate analyses were done to describe relationships between individual or confounding independent variables and treatment outcomes. ($p<0.05$) and 95% CI. Incidence rate ratio and Odds ratio (OR) were calculated to asses effects of variables and strength of relationships.

Findings: Of 4414 participants, 87.4 % were aged ≤54 years, 57.8% were underweight and 21.5% were HIV positive. 7.5 % had adverse treatment outcomes with 85.3% dying, 9.6% failing and 5.1% converting to multi-drug resistance. Older age, underweight, being treated in Health centers and Hospitals, and negative mycobaterial test result were attributed to death, while older age, Male gender and negative or unknown mycobacterial test results predicted an adverse treatment outcome. Our study demonstrated importance of separate analyses for single and aggregated outcome, MDRTB as a treatment outcome and revealed un-known and negative myco-bacteriological test results as factors for death.

Unique contributor to theory, policy and practice: Special attention such as direct government funds transfer, treatment support, and close clinical care is reccommended for elderly patients to cater for inequities in their access to health care, and general welfare so as to prevent death and other adverse treatment outcomes among them. Behavior change programs should be prioritized for male patients to address substance abuse, poor health seeking behaviour and treatment adherence. Strict management, close monitoring and nutrition support is reccommended for patients treated in hosptals and health centers, and those at risk or already immune compromised such as the elderly, undernourished and those with co-morbidities . Strict case management and adherence counseling for patients with un-known sputum status as well as a further enquiry into the association between un-known sputum status and deaths is reccommended

Keywords: *Adverse treatment outcomes, tuberculosis patients, Murang'a County*

1.0 Introduction

Tuberculosis, (TB) is a communicable disease caused by the bacillus *Mycobacterium tuberculosis* that affects mainly the lungs, but can affect other parts of the body. [1] It affects all age groups, but is more prevalent among the ages between 35 and 54 years and among the elderly, It spreads when people who are sick with TB expel bacteria into the air; for example by coughing. [1] Most of the infections with the bacteria do not cause TB disease and 90-95% of the infections remain asymptomatic hence known as latent TB. 10 % of the latent infections can develop into active disease, half of which can cause death. [2] Symptoms of TB include coughing, with sputum or blood, chest pains, fever, weight loss and night sweats. [3] Medical evaluation of TB includes history of exposure, infection and other risk factors like HIV infection, physical examination to asses patient's general health to inform treatment plan; chest x-ray to detect chest abnormalities; and microbiological tests using samples of sputum. [4] TB is preventable and curable. [1] About 85% of people infected can be treated successfully. [1] The treatment regimen in adult patients with no previous TB treatment history should have a two months initial treatment phase which consists of isoniazid, rifampicin, Ethambutol and and Pyrazinamide, then be continued in the second phase for four months with a combination of isoniazid and rifampicin in all forms of TB except TB Meningitis and osteoatticular TB. Continuation phase consists of isoniazid and rifampicin for ten months in case of TB Meningitis and osteoatticular TB. [5] The primary goal for initiating therapy is to achieve a successful treatment outcome, and significant effects on control of tuberculosis has been shown to result from effective treatment of the disease, [6] as treatment of TB cases reduces the incidence rate by minimizing the pool of infectious people in the community, thereby lowering the chances of case-contact interaction and subsequently inturrupting transmission. [7] Treatment completion and cure is therefore the key priority of TB control programmes. [8]

Tuberculosis remains one of the world's bigest public health problem, accounting for 10 million cases and 1.4 million deaths around the world in 2019 alone. [1] Over 95% of TB cases and deaths occur in low and middle - income countries, eight of which account for 87 % of the burden, with India leading the account followed by Indonesia, China, Pillipines, pakistan, Nigeria, Bangladesh and South Africa. [9] Despite availability of highly effective medication and world wide DOTS strategy, over 20% of TB patients put on treatment in the low and middle income countries end up with adverse treatment outcomes. [9] Kenya is ranked among the 30 high TB burdened countries in the world, [10] and according to the Division of National Tuberculosis, Leprosy and Lung Diseases control Programe (DNTLDP), treatment success rate among the 2018 cohort was 84% against the target of 90% and the cure rate was 71% while the national death rate was 6.5% against the target of 5%. [11]

Acording to the Murang'a county Health Strategic Plan (CHSIP 2020 -2024), TB is ranked 8th among causes of death and the major factor responsible for the large TB disease burden in

Muranga county is HIV epidemic. [12] Between 2013 and 2015, 5,959 cases of TB were notified in the county, 1817 being reported in 2015 alone. Out of the cases reported in 2015, 1046 (56%) were new bacteriologically confirmed cases. Adult new smear negative cases were 324 (17%), while childhood cases were 58 (3.1%). 13% of cases registered under DOTS in the County are not treated successfully. [12] Studies conducted around the world have shown varying proportions of treatment outcomes among TB patients. In Ethiopia for example, from 2003 to 2016, successful treatment outcomes (cure and treatment completed ranged between 81.1% and 86.3%) [13] While adverse treatment outcomes Failure,death and LTFU) varied between 7.5% to 26% between 2017 and 2020. [14]

In another study carried out among drug-susceptible TB patients in Latvia, [15] out of the 2476 patients studied, 2167 (88%) had successful treatment outcomes with 79.9% cured and 7.6% treatment completed, while 12% had unfavorable outcomes with 6.4% dying, 5.4% lost to follow up, 0.45% failure and 0.2 others. In yet another study conducted by Akinola A,.et al (2009) in Nigeria, Ibadan, 76.6% of Plumonary tuberculosis patients put on treatment were cured, 8.1 % failed, 6.6% defaulted, 4.8% transfered out and 1.2% died. [16] Many studies have shown several factors associated with adverse treatment outcomes including older age, male sex, previous treatment, positive sputum smear, HIV co-infection, diabetes melitus, body mass index, treatment interruption and other chronic conditions.

Currently, there exists no reliable way to predict patients' treatment completion with cure and no study has been conducted in Murang'a County on treatment outcomes and associated factors. This study aimed to determine the adverse treatment outcomes and the associated factors among TB patients in Murang'a county, so as to guide interventions towards improved treatment outcomes.

2.0 Literature review

The purpose of therapy in tuberculosis infection includes eradication of *Mycobacterium tuberculosis* from the patient, preventing relapse and prevention of drug resistance so as to achieve a successful treatment outcome. [17] Treatment has been shown to have have significant effects on control of the disease, [6] as treatment of TB cases reduces the incidence rate by minimizing the pool of infectious people in the community, thereby lowering the chances of case -contact interaction and subsequently inturrupting transmission.[18] Monitoring TB treatment outcomes is therefore important for evaluating the efficacy and improvement of TB treatment as well as identifying barriers to TB control. [19], [20] biruk, ayakaka The categories of treatment outcomes "Cured, treatment completed, treatment failed, died, and defaulted" have been used as a benchmark for global TB data collection and treament success assessment. [21] muluye The number of TB patients who are cured or completed treatment are considered to have a good treatment outcome while those who missed treatment, defaulted, or died are considered to have poor treatment outcome.[22], [23]). Teferi , izudi Global targets and milestones for reductions of

the burden of TB disease as set out in the SDGS and the WHO's End TB strategy include a target to end the global TB epidemic by 2030, with milestones of reducing TB deaths and incidence.[9] TB control efforts have not been on track to fast achievement of set targets. [24] Its however hoped that all global stake holders will increase provision of essential TB services such as levels of TB case detection and treatment to achieve desired outcomes. [9]

2.1 Impacts of adverse treatment outcomes

Adverse treatment outcomes have negative consequences. Treatment failure lengthens the treatment period, since people continue to receive the medication and inappropriate management can have life threatening results, [25], [26] on-going infectivity, and development of drug resistance, fatality as well as higher treatment costs. [6] Other consequences associated with adverse treatment outcomes include sustained disease prevalence and social problems following illness or death of family members, such as child labor, child headed homes, increased HIV/AIDS vunerability, school drop outs and declined competitiveness in the fast changing innovative global environment. [27] Conversion from drug susceptible to drug resistant increases vulnerability to negative consequences of adverse treatment outcomes. The acquired drug resistance complicates case management and the challenge is compounded by the catastrophic economic and social costs that patients on treatment incur while seeking help. [24] Likelihood of unsuccessful and poor treatment outcome is usually higher among patients with multi-drug resistant tuberculosis. [28], [29] In 2018 there were about 214,000 deaths from MDR TB.[24]

Other consequences are grief, depression and in some cases difficult cultural practices faced by close family members left behind, and the draining of family resources during funerals. [30]

2.2 Prevalence of poor treatment outcomes

Several reviews on treatment outcomes have been done in Afarica by pooling the proportion of successful TB treatment and evaluating predictors of poor treatment outcomes. Torres et al. reviewed 151 studies published from January 2014 to November 2019 from 59 countries representing five continents. The pooled treatment success rate for adults was 80.1% but was lower among the 47 studies from Africa (success rate 78.9%) the review included one study from Kenya limited to smear positive PTB patients aged 15 to 49 years only. [31] In a separate review of 31 studies from a Sub Sahara Africa, published from July 2008 and June 2018 a pooled treatment success rate of of 76.2% was reported. In Ethiopia, from 2003 to 2016, successful treatment outcomes (cure and treatment completed ranged between 81.1% and 86.3%) [13] While adverse treatment outcomes Failure,death and LTFU) varied between 7.5% to 26% between 2017 and 2020. [14] For Kenya, death and lost to follow up are the bigest challenges. Treatment success rate among the 2019 cohort was 85.2% against the target of 90% and the cure rate was 71.2% while the national death rate was 6.3% against the target of 5% and 5.7% were

lost to follow up,1% got treatment failure, while 2,500 developed drug resistance in the same year. [5]

2.3 Factors associated with adverse treatment outcomes ;

Studies in different parts of the world have associated older age, being HIV positive, Underweight, co- morbidities, alcohol use, smoking, patient condition, delayed initiation of therapy, Undernutrtrition, Anaemia, clinical complications, multidrug-resistance, diabetes melitus, positive smear status and previous treatment to poor treatment outcomes. [22],[32], [33], [34], [35], [36], [37]

3.0 Materials and methods

3.1 Study site:

This study was conducted in Murang'a county locatedd in central region of Kenya with a population of 1,154,948 (projected from 2019 census). There are 7 hospitals, 26 health centers and 123 dispensaries belonging to government and 138 non - government facilities. TB treatment is done in 101 sites.

3.2 Study design :

It was a cross sectional study in which epidemiological data was extracted from the health records for patients enrolled at TB treatment sites in Murang'a county during the period 2017-2019. The data was categorized into the treatment outcomes, and analysed to determine the relationships between the treatment outcomes and other variables.

The investigator determined the treatment outcomes for the patients whether favourable (successful) or adverse (unsuccessful) at the end time of treatment period for each of the patients, then ANOVA was used to determine the relationship between independent variables and the treatment outcomes.

3.3 Study population :

Study population was all the New confirmed adult TB patients registered at the facilities under DOTS programme in Muranga county during the period 2017 -2019

The study included all New confirmed adult TB patients registered for treatment at the facilities during the period under study.

3.4 Inclusion and exclusion friteria:

Patients transfered out of the study treatment sites with unknown treatment outcome were excluded from the study due to unavailable record or data.

Cases with unclear or incomplete records were also excluded because the data on variables to be measured was absent from the records and hence it was not possible to assess the associations.

Patients who were on treatment for resistant forms of TB were also excluded due to the fact that they were not new patients and they were on a different regimen.

3.5 Sample Size and Sampling Technique:

Consecutive sampling technique was used in which every case meeting the inclusion criteria was selected until all cases were checked. The total number of patients registered for treatment within the county during the study period was 5075, out of these 661 patients who failed to meet the inclusion criteria were excluded due to either incomplete or inconsistent data, had been transfrerred to different centers without adequate information or were registered for multi-drug resistant TB treatmement. 4414 participants fulfilled the inclusion criteria and were all included in the study.

3.6 Data collection tools and method:

structured data abstraction tool was used to capture socio-demographic and clinical data from each patient record including age, sex, marital status, place of residence (urban or rural), TB type, previous TB treatment, HIV status, co-morbidity, dates they were registered and the treatment outcomes at the end of treatment period. The information was entered into computer on an exel spread sheet for analysis.

3.7 Data processing and analysis,

Data abstracted from the records was checked and cleaned to ensure completeness, consistency, credibility and eligibility for purposes of excluding cases with missing or incomplete information.

In this study, treatment outcomes "cured" and "treatment completed" was combined as successful outcome, while "treatment failure, died, development of multidrug-resistant TB" were grouped as un-successful or adverse outcome. Individual records were also stratified into socio-demographic and clinical characteristics. Descriptive frequencies were calculated to give proportions. Computer package (SPSS 24) was used for univariate analysis to describe relationships between individual variables and treatment outcome.Variables found to be statistically significant ($p<0.05$) in the univariate analysis were included in the multivariate model to capture the interrelationships between the independent confounding variables and the treatment outcomes. Incidence rate ratio (IRR) with 95% connfidence interval (CI) and 5% statistical significance was calculated to asses the independent effects of each variable on the treatment outcome where few variables were significant during the univariate analysis. Odds ratio (OR) was used to determine the strength of relatinships.

3.8 Operational definitions

Treatment outcome The final known status of a TB patient who started anti TB treatment, which for purposes of this study they include treatment failure, conversion to multi drug resistant TB and death.

Treatment failure A patient whose sputum smear or culture is positive at 5 months or later during the treatment period or patient found to habour a multi drug resistant (MDR) strain at any time during the treatment period, whether they are smear-negative or positive

Previously treated patient A patient who has received 1. One month or more of anti- TB drugs in the past, may be positive or negative bacteriologically, and may have the disease at any anatomical site.

Died A TB patient who dies for any reason during the course of treatment

3.9 Ehical approval:

Approval was obtained from the Knyatta National Hospital and University of Nairobi Ethics and Research Committee (KNH -UoN ERC). Permision to extract data granted by Department of health and Sanitation Murang'a county. The information collected was anonymous and records were coded to ensure confidenciality of information for patients to whom the records refered. The results of the study will guide improvement of future treatment outcomes and the health of the community at large.

4.0 Study results

4.1 Distribution of study participants characteristics and treatment outcomes

Among the 4414 participants involved in the study, 76.4% were males while 23.6 were females. Participants demographic and clinical characteristics, and treatment outcomes are shown in table 1. Two sub-counties had the highest number of participants and almost equal distribution among them with Maragua (n=936, 21.2%) and Kiharu (n=933, 21.1%), followed by three subcounties also having almost equal distribution with Kandara (n=637, 14.3%), Gatanga n=637 (14.43%) and Kigumo (n=608, 13.4%), while Kangema and Mathioya sub counties also showed equal proportions with the lowest numbers (n=334, 7.6%) and (n= 329 7.5%) respectively

Majority (n=3859, 87.4 %) of the participants were aged ≤54 years, among whom there was a near equal distribution between the age groups 15 to 34 years (n=2013, 45.6%) and 35 to 54 years (n= 1846, 41.82 %). while only (12.6 %, n= 555) of the participants were aged ≥55 years with only (2.42% n=107) of them being aged 75 years and above. Slightly over three quarters (n=3,374, 76.4%) of the participants were females.

When analysed by BMI, majority of the participants (n=2,547, 57.8%) were underweight (BMI<18.5 kg/m^2) while 37.4% (n= 1,649) were within normal BMI range of 18.5-25kg/m^2 and only 4.9% (n=218) were overweight and obese (BMI>25kg/m^2).

Slightly over one fifth of the participants (n=948, 21.5%) were HIV positive with only a few (n= 26, 0.6%) whose status was unknown

Over three quarters (77.5%) of the participants had positive mycobacterium test results while less than a fith of them (n=871, 19.7%) had negative test results and (n= 121, 2.74%) were not tested for the presence of mycobacteria.

Whereas majority (n=4109, 93.1%) of the participants were first time TB patients, (n=305, 6.9%) had previously been treated successfully for TB prior to the 2017-2019 study period

Almost all (n= 4,359, 98.8%) of the participants were on nutrition supplement during treatment.

Over two thirds (n= 3,066, 67.21%) of the participants had been treated in level two and three faclities with (n=1,237, 28.03%) and (n=1,729, 39.2%) of them attending health centers and dispensaries respectively, while slightly less than a third (n=1,447, 32.8%) attended level 4 and 5 refferal facilities which are sub-county and county referal hospitals respectively. Majority (n= 3,913, 88.7%) of the patients were treated in public health facilities, while the rest attended non-public facilities

Almost all (n=4,400, 99.7%) of the participants had treatment supporters, majority of whom (n= 4,124, 93.3%) had been supported by members of their household while the rest were supported by by health care workers and community Health volunteers (n=257, 5.8%) and (n= 19, 0.4%) respectively.

Overall, majority, (92.46%) of the participants had combined non-adverse treatment outcomes that included those Cured (n=2,781,63%), and those with treatment completed (n=1,074, 24.3%), while 333 participants (7.54%) had adverse treatment out comes which included death (n=284, 6.4%), treatment failure (n=32, 0.72%) and conversion to MT4 (n=17, 0.39%). The rest had no specific treatment outcome and included those lost to follow up (n=222, 5%) and those whose tr

Table 1. Demographic and clinical characteristics, and treatment outcomes of Adult tuberculosis patients enrolled for treatment in Murang'a county between 2017 and 2019.

Table 4.1: Characteristics of study participants

Variable	Category	Frequency (n)	Percentage (%)
Patarticipant's Sub-County	Gatanga	637	14.43
	Kandara	637	14.43
	Kangema	334	7.57
	Kigumo	608	13.77
	Maragua	936	21.21
	Mathioya	329	7.45
	Muranga Kiharu	933	21.14
Age	15-34	2013	45.6
	35-54	1846	41.82
	55-74	448	10.15
	75 and above	107	2.42
Sex	Female	3,374	76.44
	Male	1,040	23.56
Previous TB	Yes	4,109	93.1
	No	305	6.9
BMI	Underweight	2547	57.8
	Normal	1649	37.36
	Overweight	218	4.94
HIV Status	Positive	948	21.48
	Negative	3440	77.93
	Un-known	26	0.59
Mycobacterium Test Results	Positive	3,422	77.53
	Negative	871	19.73
	Un-known	121	2.74
Patient on Nutrition Supplement	Yes	4,359	98.75
	No	55	1.25
Facility Levels	Hospital	1,447	32.79
	Health Centre	1,237	28.03
	Dispensary	1729	39.18
Service Provider Sector	Public	3,913	88.65
	Non-public	501	11.35
Source of Treatment Support	Community Health Volunteer	19	0.43
	Health Care Worker	257	5.82
	House hold member	4,124	93.43
	Not Done	14	0.32
Out come 1(Died)	Yes	284	85.3
	No	49	14.7
Out come 2 (Treatment Failure)	Yes	32	9.6
	No	301	90.4
Outcome 3 (Converted to MT4)	Yes	17	5.1
	No	316	94.9
Aggregated Outcome	Adverse	333	7.54
	Non Adverse	4,081	92.46

4.2 Factors associated with treatment outcomes

4.2 .1 Univariate Analysis for Outcomes

This study aimed to investigate factors associated with adverse treatment outcomes. Separate variables turned significant (P<0.05) on separate adverse treatment outcomes and on the combined adverse treatment outcome. (Table 2)

Mycobacterium test results was significantly associated with each of the adverse treatment outcomes both separately and when agregated.

Several variables were seen to be significantly associated with death and the combined treatment outcome. These included level of facility where the participant attended treatment, particicipant's sex, age on enrollment, HIV status and BMI. BMI was also found to be significantly associated with treatment failure separeately, while previous TB was olny significantly associated with conversion to MT4 separately.

Whereas service provider sector was not significantly associated with any adverse treatment outcome separately, there was a significant association between itself and the aggregated adverse treatment outcome.

Three variables were not significantly associated with any of the adverse treatment outcomes either separately or when combined. These included the subcounty where the patient resided, whether the patient received nutrient supplements and source of treatment support.

Table 2: Univariate p-values examining association between independent variables and treatment outcomes

Treatment Outcome	Died	Failure	MT4	Aggregated Outcome
Variables	**p-values**			
Age at enrollment	0.000*	0.594	0.795	0.000*
Sex	0.000*	0.847	0.957	0.000*
Sub-County	0.207	0.399	0.792	0.410
Facility Level	0.005*	0.926	0.582	0.006*
Service Provider Sector	0.091	0.191	0.567	0.045*
Patient on Nutrition Supplement	0.180	0.179	0.111	0.345
HIV Status	0.000*	0.891	0.325	0.000*
Previous TB	0.135	0.419	0.044*	0.115
Source of Treatment Support	0.185	0.156	0.935	0.105
Mycobacterium Test Results	0.000*	0.007*	0.035*	0.000*
BMI on enrollment	0.001*	0.010*	0.442	0.000*

4.2.2 Multivariable Analysis for Outcomes

4.2.2 (i) Multivariable Analysis for Outcome 1 (Death)

As shown in table 3 bellow, likelihood of death was shown to increase with age, with adults aged ≥75 years and above being 3.6 times more likely to die than the youth and teenagers aged 15 to

35 years (p>0.000, 95% CI 1.88 - 6.72) while male patients enrolled for treatment were 1.4 times more likely to die compared to female patients (p> 0.035, 95% CI 1.02 -1.79)

The study found that patients enrolled and treated in health centers and Hospitals (level 4 and 5) were 1.4 and 1.6 times more likely to die compared to those enrolled and treated in dispensaries (level 2). (p>0.05, 95% CI1.00 -1.91) and (p>0.002,95% CI 1.21-2.23) respectively.

HIV positive status was strongly associated with increased likelihood of death, compared to HIV negative status with the risk of death being 3.6 times higher among HIV positive patients than those with negative and un-known status. However there was no statistical significance in the difference between both groups.

In this study, positive bacteriological test result was showed to diminish the likelyhood of the patients to die. Patients who had negative mycobaterial test result and those with unknown test result were 2.5 and 1.8 times more likely to die (p>0.000, 95% CI 1.90 - 3.30) and (p>0.043, 95% CI 1.02 - 3.44) respectively, compared to those who had positive MTB test result.

Low BMI at enrollment was shown to be associated with increased likelihood of death among the participants, with BMI <18.5 categorised as underweight being 2.8 times more likely to die compared to those who were either overweight or obese (BMI range 25 and above) (p> 0.003, 95% CI CI 1.41 - 5.55). The study also found that being overweight reduduced the risk of death among TB patients, compared to patients with normal BMI, although the effect was insignificant.

Table 4.3: Multivariable Analysis for Outcome 1 (Death)

Treatment_Outcome1	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
Age category (years)						
35-54	1.365518	0.2082518	2.04	0.041	1.012704	1.841247
55-74	3.223999	0.6312467	5.98	0	2.196509	4.732133
75 and above	3.559281	1.155031	3.91	0	1.884242	6.723382
Sex						
Male	1.35147	0.193098	2.11	0.035	1.021379	1.788241
Facility type						
Hospital	1.638311	0.2564149	3.15	0.002	1.205517	2.226483
Health Centre	1.383523	0.2288136	1.96	0.05	1.000485	1.913208
HIV status						
Positive	3.603627	3.727314	1.24	0.215	0.4745946	27.36258
Negative	1.000295	1.033431	0	1	0.1320472	7.577519
Mycobacterium test result						
Negative	2.503642	0.3431006	6.7	0	1.913917	3.275076
Unknown	1.872745	0.5800867	2.03	0.043	1.02051	3.436688
BMI category						
Underweight	2.800785	0.9762434	2.95	0.003	1.414439	5.545939
Normal	1.908671	0.6765429	1.82	0.068	0.9528321	3.823366
_cons	0.0070007	0.0076893	-4.52	0	0.0008132	0.060265

Key for BMI; Under weight - BMI < 18.5kg/m², Normal weight - BMI 18.5 to 24.5kg/m², Over weight - BMI 25kg/m² to 29,9, Obese - 30 and over

4.2.2 (ii) Multivariable Analysis for Outcome 2 (Treatment failure)

This study revealed that patients with negative mycobacterial test result were less likely to have a treatment failure compared to those who had un-known test result (IRR 3.63e-07(p>0.000, 95% CI 2.31e-07 - 5.69e-07) (Results of Multivariable Analysis for treatment failure are shown in table 4)

Patients who were underweight (BMI < 18.5) at enrollment were 9.2 times more likely to have a treatment failure compared to those who with normal BMI 18.5kg/m^2 to 24.5kg/m^2 . while being overweight did not significantly affect treatment failure. (p>0.002, 95% CI 2.249 - 37.716)

Table 4 Multivariable Analysis for Outcome 2 (Treatment failure)

Variables	IRR	Robust Std. Err.	z	P>z	[95% Conf.	Interval
Age category						
35-54	1.087468	0.4187369	0.22	0.828	0.511276	2.313009
55-74	1.748318	1.008822	0.97	0.333	0.56423	5.417322
Above 75	2.872561	3.066214	0.99	0.323	0.354556	23.2731
Mycobacterium test result						
Negative	3.63E-07	8.33E-08	-64.51	0	2.31E-07	5.69E-07
Unknown	0.8614848	0.9102515	-0.14	0.888	0.108608	6.833351
BMI category						
Underweight	9.211622	6.625059	3.09	0.002	2.249812	37.71602
Overweight	4.215723	5.280461	1.15	0.251	0.361983	49.09712
_cons	0.0020444	0.0023667	-5.35	0	0.0002114	0.019767

4.2.2 (iii) Multivariable Analysis of Aggregated Outcome

This study investigated the relationship between independent variables and the aggregated treatment outcome. The results are shown in table 5 below.

The study revealed that patients enrolled and treated in Health centers and Hospitals (levels 3 and 4 or 5) were 1.5 and 1.6 times more likely to have an adverse treatment outcome (p>0.007, 95% CI 1.11 - 2.0) and (p>0.001, 95% CI 1.20 - 2.13) respectively compared to those treated in dispensaries (level 2)

The sector to which a facility where Patients enrolled and treated belongs did not significantly affect the agregated treatment outcome. However when analysed as a univariable, it is shown to be significanly associated with combined adverse treament outcome.

Male patients were 1.7 times more likely to have an adverse treament outcome compared to their female counterparts. (p>0.000, 95% CI 1.34 - 2.22)

Patients who had negative mycobaterial test result and those whose MTB test was unknown were 2.12 and 1.95 times more likely to have an adverse treatment outcome (p>0.000, 95% CI 1.64 - 2.73) and (p>0.02 , 95% CI 1.11 - 3.41) respectively, compared to those who had positive MTB test result.

Adverse treatment outcome was generally higher among patients aged ≥35 compared to the teenagers and youth aged 15 to 35 years, with adults aged 55 - 74 who were 2.7 times more likely to have an adverse treatment outcome carying the highest risk.(p>0.000, 95% CI 1.93 - 3.92)

Patients who were underweight at enrollment were 3.3 times more likely to have an adverse treatment outcome compared to those who were overweight. (p> 0.000, 95% CI 1.71 - 6.21)

Table 5 Multivariable Analysis of Aggregated Outcome

General Outcome	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
Facility type						
Hospital	1.598133	0.234534	3.19	0.001	1.198657	2.130743
Health Centre	1.491998	0.222672	2.68	0.007	1.113606	1.998965
Service provider Sector						
Private	1.200161	0.216996	1.01	0.313	0.84205	1.710572
Sex						
Male	1.724315	0.224012	4.19	0	1.3367	2.224332
Mycobacterium test result						
Negative	2.118265	0.274592	5.79	0	1.643004	2.731003
unknown	1.946493	0.556943	2.33	0.02	1.110968	3.41039
Age category						
35-55	1.725934	0.232264	4.06	0	1.325793	2.246843
55-74	2.745997	0.497306	5.58	0	1.925509	3.916107
Above 74	2.490604	0.766823	2.96	0.003	1.36217	4.553841
BMI category						
Underweight	3.262668	1.072082	3.6	0	1.713468	6.212549
Normal	1.853765	0.620332	1.84	0.065	0.962086	3.571868
_cons	0.0106962	0.003841	-12.64	0	0.005291	0.021623

5.0 Discussion

In this retrospective crossectional study, epidemiological data were extracted from the health records for 4,414 patients registered under DOTS during the period between 2017 and 2019 in the entire Murang'a County in Kenya. Out of these, 333 (7.54 %) had varied adverse treatment outcomes. Out of the 333 patients, 85.3% (n=284) died while 9.6% (n=32) experienced treatment failure and 5.1% (n=17) converted to multi-drug resistant strain (MT4). Using the entire 4414 study participants, factors associated with death among the TB patients included age, sex, health facility level attending the patient, HIV status, BMI and bacteriological test results ($P<0.05$). Under the same analyses, factors associated with treatment failure among the TB patients included BMI and bacteriological test results. On aggregating all diverse adverse treatment outcomes as one dependent variable, HIV status dropped from the model. These findings continue to highlight the burdens associated with TB including mortality and development of resistant strains in developing country settings. Our findings also signified the importance of analyzing adverse treatment outcomes separately.

Our study reports that older study participants were more likely to die when infected with TB relative to younger ones. Similar findings were reported by Achieng' R. L in a study conducted in Nyando Sub County in Kenya [38]. This relationship may be broadly attributable to aging

[39], [40] As patients age, they are more likely to experience chronic co-morbidities such as diabetes melitus, hypertension and cancers among others [41]. However, our study was limited in that data on chronic co-morbidities were not available to support this hypothesis. Other studies have attributed higher TB deaths among the elderly due to lowered immunity and poor treatment adherence perhaps arising from the aforementioned chronic co-mobidities, poor nutrition [40]

and poor heath seeking behavior. [42] Elderly people with chronic co-morbidities are more likely to be faced with specific age related problems such as financial dificulties. [43], [44] physical inability (e.g., poor eyesight or low manual dexterity) or psychosocial factors (eg, cognitive incapacity). [45] Physiological changes such as slow gastric emptying, dry mouth, loss of taste and smell are associated with ageing and have negative effect on food intake and absorption. [46]

Such factors may disproportionately disadvantage the elderly patients in accessing and uptaking health care services, leading to non adherence and subsequently high likelihood of death. Special attention need to be given to elderly patients to cater for inequities in their health care, and general welfare so as to prevent death and other adverse treatment outcomes among them. Some studies have also reported association between older age and development of extrapulmonary and atypical firms of the disease, that are more difficult to diagnose using convetional methods leadong to elevated death risk among TB patients.[40] Our study also found that patients when enrolled and treated in health centers and Hospitals (level 4 and 5) were 1.4 and 1.6 times more likely to die compared to those enrolled and treated in dispensaries, similar to findings in a study conducted in Brazil. [47] The observation can be attributed to the fact that hospitals act as referral centers for more severe and complicated cases refered from dispensaries and health centers. Owing to severity of illnes for such patients, a proportion of them end up being hospitalised, whereas conventionally, health centers and dispensaries rarely admit patients. [48] It follows that patients who are severely ill and therefore hospitalised are more likely to die than those attending outpatient facilities. The findings of this study can also be attributed to the fact that unlike dispensaries, heath centers and hospitals provide comprehensive care for HIV patients and therefore majority of the TB-HIV co-infected patients were registered at Health centers and hospitals. Contrary to this findings, some previous studies have shown higher mortality among TB patients

This study found HIV co-infection to be strongly associated with higher mortality. Similar findings were also made in studies in Kenya, Ethiopia, Brazil, and South Korea respectively [38], [49], [50], [51] This is explained by the fact that when TB and HIV infections co-occur, the two propagate each other, overburdening the immune system thereby paving way for opportunistic infections that contribute to premature death if unadequately managed. [52,[53]. Several studies have advocated for additional interventions such as prophylaxis, intensified surveillance and case finding to reduce and ultimately prevent TB-HIV coinnfection.[54] This

finding also underscores the importance of TB- HIV integrated interventions already under implementation such as screening for co-nfection, nutritional support and appropriate treatment to achieve better outcomes. [55]

Higher mortality among TB-HIV co-infected patients could also be attributed to the fact that TB-HIV co-infection makes HIV associated TB diagnosis difficult. Studies have shown that negative blood smear test results are higher among TB-HIV patients compared to the TB only group. [56] Smear negativity is reportedly caused by immunodefficiency due to HIV [57] which compromises accurate diagnosis of tuberculosis by immunodiagnostic methods. This scenario is likely to hamper early diagnosis and hence result to poor prognosis or treatment outcomes. Another study linked higher mortality among HIV infected tuberculosis patients to delayed diagnosis due to stigma of being sent to HIV clinic for screening. [58] Currently, screening for HIV of all clients is normally carried out prior to utilization of health care services. this should be sustained.

This study found Male gender to be associated with higher death risk among TB patients. This findings were consistent with those of several other researchers who found male gender to be associated with death among TB patients. [6, 36, 38] This findings are attributed to poor health seeking behavior among male patients leading to delayed diagnosis and treatment initiation. Poor treatment adherence owing to higher alcohol consumption among males can also be attributed to elevated risk of death. This relationship has been documented in Mumbai where alcohol consumption combined with deprivation of adequate nutrition was likely to cause severe reactions like vomiting and nausea, promoting non-adherence to TB treatment among patients owing to ill health. [59]

In our study, BMI was categorised according to WHO classification of Adult Body Weight as underweigt (<18.5kg/m²), normal (18.5-25kg/m²) and overweight. (>25kg/m²) [60] Being underweight was found to be associated with increased risk of death among the TB patients. Similar findings were reported by Yung-Feng Yen et al 2016 [61] who found underweight to be significantly associated with higher risks of TB- specific deaths (AOR, 2.14; 95% CI,1.18- 3.89) while overweight was not. This increase in mortality among underweight TB patients may be attributed to decreased immunity due to greater severerity of illness among the TB cases.

Underweight can suppress lumhpocyte stimulation and reduce the Th 1 cytokines interleukin-2 interferon-γ, and tumor necrosis factor -α) [60] which could cause higher burden of TB infection and increase the severity of TB disease in underweight patients. The finding can also be attributed to loss of appetite associated with TB leading to reduced energy intake and subsequent impairment of physical action that increases mortality among the patients. [62] Furthermore, BMI of <18.5 increases the risk for TB-HIV co-infection. [63] which confers poor nutritional status owing to low appetite and nutrient malabsorption as a result of diarrhoea and vomitting associated with oportunistic infections in HIV patients. Nutritional support to optimize

nutritional intake as part of routine TB management is therefore reccommended [64], [65] to improve immune recovery, reduce disease severity and achieve better treatment outcomes. Prevention and effective management of other oportunistic infetions among TB-HIV co-infected patients is also advocated for, to promote nutrient intake.

Negative mycobacterium test result was strongly associated with death. this association has been shown by other studies elsewhere. [66], [67], [68] This relationship can be explained by the fact that in settings with high HIV prevalence, sputum smear-negative result is the expression of advanced immune depression [69] and thus the deaths in these cases is due to opportunistic diseases related to AIDS. Screening of TB cases for HIV co-infection and close monitoring of CD4 cell count among them, coupled with appropriate measures to boost immuninity is reccommended to prevent deaths among TB cases. On the other hand, in a diferent study in Taiwan, It was observed that positive sputum smear result was a risk factor for TB deaths, [70] which is consistent with the common experience wherein patients typically have positive sputum smear tests with severe TB cases and these patients would easily be classified as TB deaths. In this study, unknown mycobacterium test result was also found to be associated with death among TB cases. Similar results were shown in Kano state, Nigeria and Free State Province of South Africa. [71, [72] This study could not establish the factors attributable to this relationship. Hypothetically, owing to un-confirmed status about the presence of tuberculosis, both the patient and care givers or providers may be relactant to ensure strict adherence to treatment and proper case management during treatment course, leading to worsening of illness and death. We recommend futher investigation to explain the relationship between un-known sputum results and death among TB cases.

This study found patients with negative mycobacterial test result to have a significantly lower risk of having a treatment failure compared to those who had positive test result (IRR 3.63e-07($p>0.000$, 95% CI 2.31e-07 - 5.69e-07). This result is consistent with the results of studies cunducted in china and Uganda, [73], [74] which revealed a significant association between positive mycobacterium test result and treatment failure. Another study conducted in Nigeria [75] showed no significant difference in treatment failure between the smear positive and smear negative test results. The findings of this study can be attributed to presence of atypical mycobacterium bacilli that are not sensitive to the first line treatment of TB treatment 2(RHZE) 4(RH) [76] Second line treatment starts in already advanced bacillary load. Futhermore it has been established that patients who initiated treatment with high bacillary load at the initial phase of treatment are more likely to have treatment failure than those with lower bacillary load. [76] This findings underscores the need to screen patients for atypical TB bacilli prior to initiation of treatment and minimization of delay between development of symptomatic TB and diagnosis.

Being underweight (BMI < 18.5) was found to be associated with treatment failure. Similar results was shown in a study conducted in Adis Ababa, Ethiopia and in Chenango India [77] This

relationship can be atributted to poor adherence due to adverse drug reactions. Low body mass index has also been linked with increased incidence of adverse drug reactions to the first line TB therapy [77] An adverse drug reaction is any undesirable effect of a drug beyond its intended therapeutic effects occuring during clinical use. [78]

Low BMI synonymous with underweight as the case may be is associated with undernutrition which weakens the immunity, increases the likelihood of latent TB developing into active and severe forms of TB. [78] Severe TB paves way for other infectious diseases, which interfere with adherence and the effect of drugs on the current disease, [79], [80] resulting in unfavourable treatment outcomes. We highly reccommend couselling for underweight patients to increase energy intake combined with provision of nutritional supplements starting early in the initial treatment phase so as to improve body weight, adhrence and ultimately treatment failure among other adverse outcomes.

Our study demonstrated the importance of doing analysis of single and aggregated outcome separately. These method enabled us to explore the factors associated with each outcome on its own and those associated with the general adverase treatment outcome. It came out clearly that eventhough some factors could not influence separate treatment outcomes, they contributed to an effect on combined outcomes.

6.0 Conclusion

This study concluded that 7.54 % of the patients enrolled for tuberculosis teatment in Muranga County end up with adverse treatment outcome which includes death, treatment failure and conversion to multi drug resistance. This study confirmed that several factors including older age, male gender, HIV -co infection, underweight, previous TB, and being treated in health center or hospital facilities are responsible for the adverse treatment outcomes.

7.0 Recommendations

Special attention such as direct government funds transfer, family treatment support, and close clinical care is reccommended for elderly patients to cater for inequities in their access to health care, and general welfare so as to prevent death and other adverse treatment outcomes. Behavior change programs should be prioritized for male patients to address substance abuse, poor health seeking behaviour and treatment adherence. Strict management, close monitoring and nutrition support is reccommended for patients treated in hosptals and health centers, and those at risk or already immune compromised such as the elderly, undernourished and those with co-morbidities. Strict case management and adherence counseling for patients with un-known sputum status to avoid worsening patient condition due to laxity on acount of both patients and health workers. The study also reccommends further investigation to confirm the relationship between negative myco-bacteriological test results and treatment failure as well as the relationship between un-known test results and death among TB patients.

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