Predictors of mortality among multidrug resistance tuberculosis patients admitted at Kibong'oto hospital from 2009-2016.

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PREDICTORS OF MORTALITY AMONG MULTIDRUG RESISTANCE TUBERCULOSIS PATIENTS ADMITTED AT KIBONG'OTO HOSPITAL FROM 2009-2016.

By

AiboraSamali

A Dissertation Submitted in (partial) Fulfillment of the Requirements for the Degreeof Master of Public Health of

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CERTIFICATION

The undersigned certifies that she hasread and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences of dissertation entitled **"*Predictors of Mortality Among Multidrug Resistance TuberculosisPatients Admitted at Kibong'oto Hospital from 2009-2016,*"** in fulfillment of the requirements for the degree of Master of Public Health of Muhimbili University of Health and Allied Sciences.

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Dr. G H Leyna

(Supervisor)

Date: _____

DECLARATION

AND

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

Signature…… Date……..….....….....

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ABSTRACT

Background: Treatment of Multi Drug Resistant-Tuberculosis (MDR-TB) in many patients represents the last opportunity for cure. In spite of significant investments to improve availability of chemotherapy and effective treatment options, still a significant proportion of patients die during the course of their treatment. Understanding the factors leading to early death following diagnosis and treatment of MDR-TB is important for TB programmesto improve the way they identify and manage patients and help to guide targeted interventions to improve overall survival.

Objective: To estimate mortality rate and determine predictors of mortality among MDR-TB patients admitted at Kibong'oto hospital, Tanzania.

Methodology:A retrospective cohort study was done at Kibong'oto hospital among all patients diagnosed and admitted with MDR-TB between 2009 and 2016. Individual and clinical information was abstracted from patient medical records, In-depth interviews werealso done to supplement quantitative data. Incidence of mortality was calculated using Kaplan Meier method and Cox regression was modeled to identify predictors of deathduring MDR-TB treatment adjusting for potential confounders. Hazard ratios and their 95% confidence intervals are presented. Significant level was set at $\alpha = 5\%$.

Results:A total of 583 patients were recruited with a mean age of 37.41(standard deviation = 13.62). 68.1% were men, 77.47% had a previous TB history,59.06% reported experiencing a drug adverse effect and 37.43% had other co-morbidities mainly HIV (35.49%) and anemia (9.21%).The mortality rate was 15.3%.After adjusting for other factors, mortality in MDR TB patients was significantly associated with nutrition (HR =2.90; 95%CI: 1.26-6.69) and anemia (HR = 3.03; 95% CI: 1.60-5.73).

Conclusion: In spite of improvements in provision of care and treatment for MDR-TB, a modest rate in deaths still occurs that can be explained by poor nutritional status. Monitoring co-morbid conditions like anemia and malnutritionis important to increase survival amongstMDR-TB patients. There is a need to strengthen nutrition units in health facilities offering TB services in the country.

Keywords: Mortality, Predictors, Multidrug ResistanceTuberculosis, MDR TB, Tanzania.

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ABBREVIATIONS

ART	Anti-Retroviral Therapy

BMI	Body Mass Index
CD4	Cluster of Differentiation4
CXR	Chest X-ray
DM	Diabetes Mellitus
DRS	Drug Resistance Survey
DST	Drug Sensitivity Test
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IDI	In-depth Interview
MDG	Millennium Developmental Goal
MDR	Multi Drug Resistant Tuberculosis
MOHCDGEC	Ministry of Health, Community Development ,Gender Elderly and Children.
NTLP	National Tuberculosis and Leprosy Programme
PMDT	Programmatic Management of MDR-TB
PTB	Pulmonary Tuberculosis
SDG	Sustainable Development Goals
RR	Rifampisin Resistance
TB	Tuberculosis
WHO	World Health Organization
XDR	Extreme Drug Resistance

OPERATIONAL DEFINITIONS

Case fatality ratio:The proportion of people with TB who die from the disease.

Nutrition: Is the intake of food,considered in relation to the body'sdietary need.

Mortality: Defined as a death from any cause during treatment fortuberculosis.

Previous TB history: Defined as patient who completed TB treatment afterbeing TB disease free for at least one year sincetreatment completion.

Culture conversion: Is two consecutive negative TB smears and cultures taken30 daysapart.

Successful treatment outcome: When patienthas five consistentnegative cultures for the final 12 months of treatment or completed TB treatment regardless of the availability of bacteriological confirmation .

Weight change: The difference between baseline weight and discharge weight.

CHAPTER ONE

1.0 INTRODUCTION

1.1 BACKGROUND

Multidrug Resistant Mycobacterium Tuberculosis (MDR-TB) is increasingly becoming a public health problem presenting major challengesin the clinical management of TB in many countries. MDR-TB is defined as TB caused by organisms that are resistant to at least Isoniazid and Rifampicin as the two most powerful first line anti TB drugs. Isoniazid ensures early sputum conversion and helps in decreasing disease transmission while Rifampicin has myco-bactericidal and sterilizing activities that prevent relapses. Further resistance to existing second line anti TB drugs generates extensively drug resistant tuberculosis (XDR TB) strains that are more difficult to treat.

The World Health Organization (WHO) 2015 report showed that there were 580,000 cases representing 5.3% of all TB cases that were eligible for MDR-TB treatment, in which 3.9% and 21% are new cases and previously treated cases, respectively (1).The combination of a large population of HIV infected individuals who are susceptible to TB, lack of airborne infection control measures (in health facilities and congregate settings), inappropriate drug regimens, non-adherence to treatment, substandard drug quality, erratic drug supply, limited drug-resistance surveillance and an overburdened TB treatment program are considered ideal conditions for generating drug-resistant TB strains (2).

Management of MDR-TB is accompanied by expensive second line drugs, drug toxicity with less effectiveness, prolonged duration of therapy (up to 2 years) which is associated with high rates of side effects and poor outcomes (3). In 2015 WHO reported that about 250,000 deaths resulted from MDR-TB(1). Although the number of TB deaths fell by 22% between 2000 and 2015, TB still remained one of the top 10 causes of death worldwide and cure rates continue to remain low globally (4). The MillenniumDevelopmental Goals (MDGs) required the case fatality rate to fall to 10% by 2020 and mortality by 90% in 2030 (5). To address this challenge the diagnosis and treatment of MDR-TB cases is being expanded through decentralization to scale up complex MDR-TB treatment and care services in the country(6).

In Tanzania, the first Drug Resistance Survey (DRS) was conducted in 2006 and found the proportion of MDR-TB among new and re-treatment TB cases was 1.1% and 3.1%, respectively (7). Extrapolating from this survey, it is estimated that about 320 MDR-TB cases exist in the countrywhile the 2013 and 2014 Global WHO TB report estimates an annual MDR-TB burden of 500 cases. The Tanzania Ministry of Health, Community Development, Gender, Elderly and Children (MOHCDGEC) through the National Tuberculosis Leprosy Program (NTLP) responded by introducing the Programmatic Management of MDR-TB (PMDT) in 2009 whereKibong'oto hospital in the Kilimanjaro region of Northern Tanzania was selected to be the initial referral hospital for all identified MDR-TB cases in the country (8).

1.2 PROBLEM STATEMENT

Several interventions for controlling MDR-TB have been implemented in Tanzania since 2009 with a reported treatment success rate of 79.3% - which meets the WHO target. In spite of these progress, about 10.3% of all patients diagnosed with MDR-TB still die.

High mortality among MDR-TB patients has been associated with immunesuppression due to co morbidities like HIV,Diabetes and Anemia, malnutrition, abusive alcohol and smoking in studies done elsewhere.

However, it is unclear to what extent these factors apply to the Tanzanian context. This study will generate information that will help in developingtargeted strategies to further reduce mortality among MDR-TB patients who are considered to have poor treatment prognosis and ensure quality treatment and care is provided.

Therefore, using a retrospective cohort study, weestimated the incidence and explored predictors of mortality among patients admitted with MDR-TB at Kibong'oto hospital in Tanzania.

1.3 CONCEPTUAL FRAMEWORK OF THIS STUDY

The Conceptual framework explains the hypothesized causal network that determines MDR-TB mortality. It describes a comprehensive and integrated framework for analysing individual, clinical, treatment and diagnostic factors that may be associated with patient death. The presence of any of these factors may be useful in identifying at-risk patients for death and plan a potential intervention to improve their survival and success outcome during treatment.

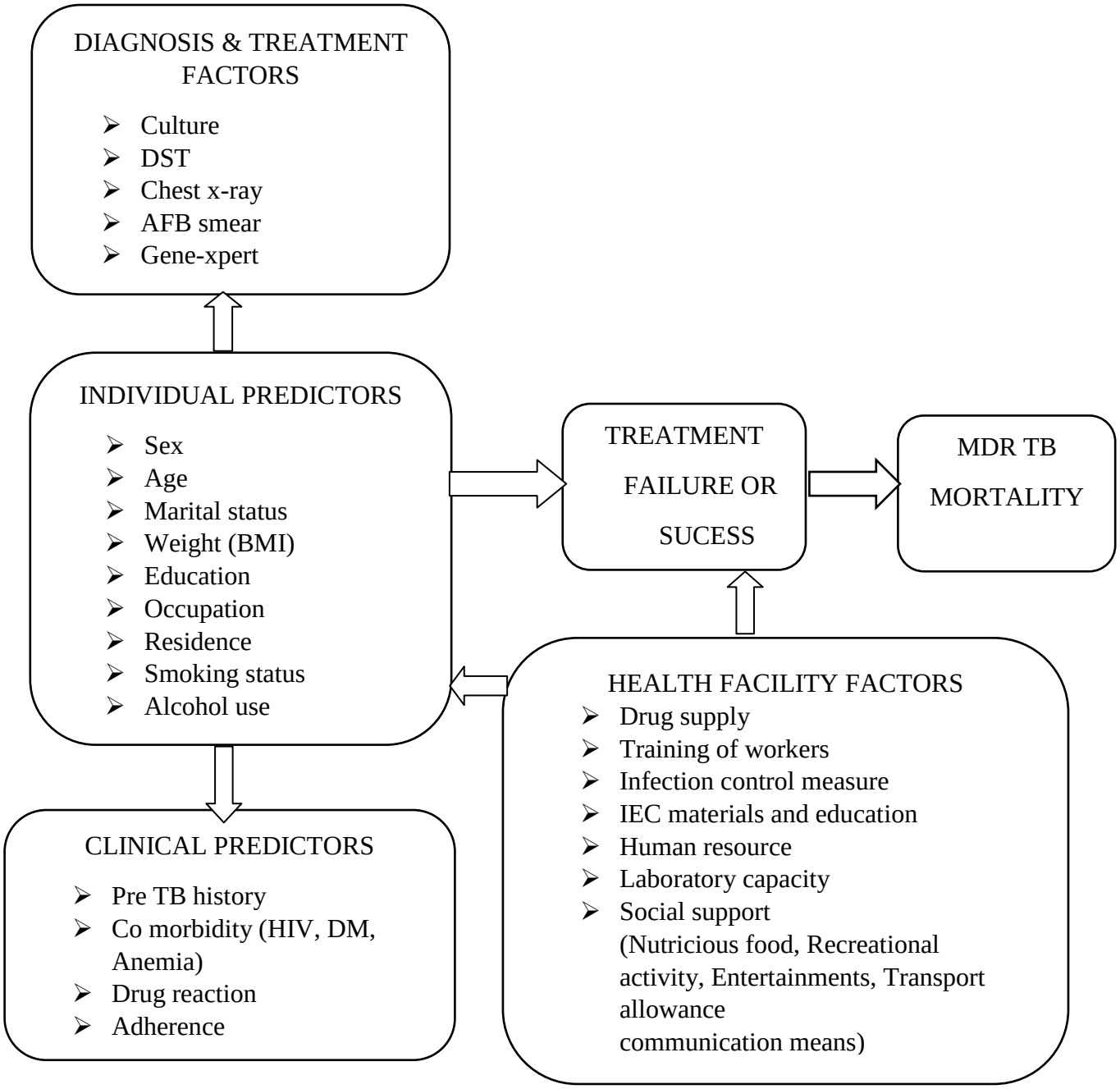

Figure 1:Conceptual framework of the study

1.5 RESEARCH QUESTION

1.4 Rationale.

Our findings will contribute to generation of local knowledge on factors leading to death following diagnosis of MDR-TB patients in Tanzania. The study findings will also contribute to improving individualized management and care of MDR-TB reducing complications that may lead to their death and enhance better outcome to facilitate the country to reach the Sustainable Development Goal (SDG) target of 90% by 2030. These findings will be useful to the hospital management, patients and the NTLP.

1.5 Research question

What are the predictors of mortality among MDR TB patients admitted at Kibong'oto hospital?

1.6 Objectives

1.6.1 Broad objective

To determine the mortality rate and its predictors among MDR TB patients admitted at Kibong'oto hospital.

1.6.2 Specific objectives

1. To calculate mortality rateamong patients admitted with MDR-TB at Kibong'oto hospital.
2. To identify individual (socio-demographic characteristics) predictors of mortality among patients admitted with MDR-TB at Kibong'oto hospital.
3. To identify clinical predictors of mortality among patients admitted with MDR TB at Kibong'oto hospital.
4. To explorehealth facility factors that may influence mortality in patients admitted with MDR-TB at Kibong'oto hospital.

CHAPTER TWO

2.0 LITERATURE REVIEW.

2.1 Magnitude of mortality

Tuberculosis remains among the top 10 causes of death worldwide with MDR-TB threatening global TB control in many countries. The magnitude of MDR-TB mortality varies in different regions of the world ranging between 67% and 91% (4). Globally there were an estimated 580,000 incident cases of Multidrug resistance /Rifampsin resistance Tuberculosis (MDR/RR-TB) and about 250,000 deaths (40%) from MDR/RR-TB in 2015(1). Although, the overall TB mortality rate fell by 47% between 1990 and 2015, treatment success was less than 50% in countries with the largest cohortslikeIndia, Russia and South Africa primarily due tohigh death rates(4). Tanzania is among the high burden TB countries with a mortality rate of 56%(excluding HIV^{+}TB) and 47% (HIV^{+}TB only) for all forms of TB (4).

Though most TB cases and deaths occur among men, the burden of disease among women is also high. In 2013, there were an estimated 510 000 TB deaths among women including 180 000 who were HIV-positive, as well as an estimated 80 000 deaths among children (9).In Africa there is a low proportion of MDR-TB reported among newly identified TB cases in contrast to that in regions such as Eastern Europe and Central Asia due to the inadequate laboratory ability to conduct drug resistance surveys (9). An indicator which allows assessment of variation in equity in terms of access to TB diagnosis and treatment among countries with high TB prevalence is case fatality rate.

Case Fatality Rate (CFR) is defined as the proportion of people with TB who die from the disease,it is used as an indicator because if everyone had access to timely diagnosis and high quality treatment the CFR is expected to be low.The global CFR (combined number of TB deaths in HIV negative and positive people) was 17% .The SDGwere adopted by the United Nationsand one of target is to end the global TB epidemic through reduction of the TB CFR to 10% by 2020, and a 90% reduction in TB deaths and 80% reduction in TB incidence by 2030.Variation in the CFR across countries ranged from below 5% in a few countries to more than 20% in most African countries during 2015.

Accurate diagnosis of TB or TB/HIV followed by provision of treatment prevents most deaths, ill-health and further transmission to others. Currently at least 23 countries in Africa and Asia have introduced shorter regimens for treatment of MDR/RR-TB which have achieved high treatment success rates of 87–90% (4)

2.2Individual predictors

Age is known to have a U shaped association with infection, with higher risk of acquisition and poor outcomes in younger and older ages. Old age has been associated with high mortality in TB infected individuals. Numerous studies have investigated the association between age and mortality in TB patients. Overall the observation is there is a 2-3 fold increase in the risk of death for age over 40 years(10), (32) although other studies did not show a significant association (12). Experts hypothesize the high mortality of MDR-TB in the elderly is related to waning immunity, physiological deterioration accompanied by weight loss or no weight gain (13) and difficulty in accessing several healthcare opportunities due to dependency.

Knowledge about health care access, importance of compliance with treatment and stable economic status are important in ensuring good health on reducing unfavorable treatment outcome. Lower education level (12, 11, 14) has been significantly associated with mortality. Lower education is believed to work through lack of exposure/awareness on TB-related issues that may lead to delay health care seeking and hence poor treatment outcomes. It also contributes to poor treatment adherence due to lack of understanding on the severity of the illness thus patients can abandon and/or misuse medications.

Low annual household income (12) is believed to work through similar mechanisms as other social determinants of health due to financial limitations. Uneasy accessibility to healthcare services due to huge economic burden on patients, families, and communities is a barrier to patient survival widely described in resource-limited communities. In addition, “one roof approach to treatment” is not implemented thus co-infected patients often attend separate clinics or facilities for TB and HIV care services, thus increasing transport and other costs. Lifestyles that may exacerbate the illness or interfere with treatment such as smoking and alcohol use have been associated with higher mortality in TB patients (30).

2.3Clinical predictors.

Untreated or poorly treated patients with infectious TB are source of drug-resistant forms of bacilli TB strains. Several studies have shown that previous poorly treated TB episodes as among the significant factors contributing to mortality in MDR-TB patients (10), (11),although this was not observed in a cohort of TB patients in Estonia(14). Individualswho develop TB again after being treated with 1st line drugs in the past are always at-risk of greater antibiotic resistance in the 2nd line of TB drug treatment compared to a patient who is newly diagnosed with MDR-TB who has not never received treatment with any TB drugs.

Treatment of MDR-TB mainly consists of regimes which included 8 months hospital-based intensive phase of Kanamycin, Levofloxacin ,Pyrazinamide, Ethionamide, Cycloserine andEthambutol followed by an additional 12 to 18 months of the same regimen omitting the injectable agent and pyrazinamide in the continuation phase. These second line drugs exposed patients to Adverse drug reactions which is also a reported factor for mortality;observed reactions aremainly gastrointestinal, neuropsychiatric disturbance, hearing impairment, gastro-intestinal manifestations, skin reactions,depression,renal toxicity and psychiatric disorders (13, 14, 15). Pyrazinamide, Ethionamide, and*p*-aminosalicylic acid (PAS) can all cause liver toxicity.Cycloserine has a higher incidence of adverse effects in both the psychiatric patient and the alcohol/drug dependent patient(19).Fluoroquinolones such asMoxifloxacin and levofloxacin have a high rate of central nervous system (CNS) adverse effects like confusion, impaired concentration, depersonalization, abnormal dreams, insomnia and dizziness during the first 2–3 weeks(6) but other toxicity typically resolve on their own and may disappear or diminish with time.Nephrotoxicity is a known complication of the injectable drugs - both of the aminoglycosides and of capreomycin. The frequency of nephrotoxicityhave been shown to be significantly higher in diabetic than non-diabetic cases in some studies (18)while other studieshave reported the most frequent side effect experienced were gastrointestinal manifestation (84%)(18)and ototoxicity (38.9%) due to extended exposure to amino glycoside and capreomycin during MDR TB treatment(20).Hypothyroidism is a late side effect provoked by PAS and Ethionamide; studies have shown the use of these agents together can produce hypothyroidism up to 10%(6).The risk of adverse drug reactions

increases with the degree of immune suppression as there is severity of toxicities to patients under both ART and second-line antituberculosis therapy(21).The longer the exposure to these drugs might increase the risk of death as combination of drugs has been proven to have higher toxicity profiles and greater incidence of adverse effects that may result to death.Although, little is known about drug-drug interactions between second line anti-tuberculosis agents and antiretroviral therapy.

Co-morbidities in addition to tuberculosis have been shown to lead to higher mortality before or during TB treatment. Despite geographic coverage of high prevalence (22) or low prevalence regions(23), HIV is still considered to be an important determinant of mortality. Late presentation with advanced HIV disease and low CD4 cell counts at the time of starting anti- TB treatment are major reason for the high mortality rates due to poor immunity(21,22). Mortality for HIV-infected TB cases receiving ART was reported to be 24% while without ART was 31% (26). Other co-morbidities like severe anemia due to Iron deficiency decrease T-cell numbers by reducing the proliferative response and potentially dropping the macrophage activity(27) while liver failure and diabetes mellitus alters adaptive and cell-mediated immune response that may contribute to mortality(28). Some studies have not observed an increased risk of death in TB patients also diagnosed with diabetes mellitus(29). Existing epidemiological evidence strongly suggest that the HIV and MDR-TB pandemics are fueling each other and that not only HIV infection renders people more susceptible to develop MDR-TB by weakening their immune system but anti-TB drugs can also interfere with ARV treatment by further reducing cellular immunity. Globally the proportion of TB patients who died during treatment was about four times higher among HIV-positive TB patients. Late detection of HIV-associated TB and delay in starting ART or TB treatment was the most common reason for this dual effect (30). To reduce excessive TB mortality in HIV positive people WHO recommends routine HIV testing among presumptive and diagnosed TB cases and TB screening among people living with HIV and early ART and provision of TB preventive treatment.

Adherence is defined as missing treatment doses during treatment period. A considerable amount of literature has shown poor adherence or non-adherence to poor treatment outcomes(26, 27).Patient delay especially long delays in diagnosis and staring of treatment maycontribute to severity and complications of an illness that may result in poor treatment outcomes. Late diagnosis of disease allows the disease to have a longer time to progress resulting in higher risk of treatment failure, subsequent mortality as well as infection to others compared(33). Delayed diagnosis cans also lead to drug resistant problem in TB populations, especially among older subjects. Misinterpretation of initial symptoms and laboratory findings is one of the frequently mentioned reason for delayed diagnosis and onset of treatment of which older patients are more prone to as they may have atypical presentation of TB such as negative AFB smear or no cavity/lesions on Chest Xray(CXR) thus leading to delayed health care seeking and diagnosis.

Poor or slow sputum culture conversion is predictive of successful treatment outcome(34). Patients having higher bacterial load are expected to need longer treatment until conversion occurs. Studies have observed higher mortalityin PTB+ patients who failed to convert to negative smear status after 2 months of treatment(31). This may be explained by advanced immune depression leading to deaths or due to opportunistic diseases. HIV infection whether treated or not is an independent predictor for non-conversion of sputum. Also a false negative Gene-xpert result is strongly associated with poor clinical outcome (35) this is due to inability to detect all mutation from mixed infection.The Gene-expert Mycobacteria Tuberculosis Rifampsin (MTB/RIF) assay is a rapid, automated and genotypic test that can simultaneously detect Mycobacterium tuberculosiscomplex andrifampsin resistance.Until recently eachTBepisodewasassumedtobecausedby a single clonal MTB strain however molecular-based studies have demonstrated that TB may be caused by multiple strains in the same patienthence theGene-xpertassayisbecomingaprincipalscreeningtool fordiagnosingrifampin-resistantMycobacteriumtuberculosiscomplexhowever it should only be confirmed by phenotypic Drug susceptibility Test (DST).

2.4 Health facility predictors

WHO framework describes health system in terms of six building blocks which are service delivery, leadership and governance, human resource for health, financing, health information system and procurement, logistic and supply system. Any patient in whom DR-TB is diagnosed should be provided with high quality patient centered care and quality service. The health workers involved with the management should be made familiar with the International Standards and the Patients' Charter to build better patient provider relations to contribute to improved adherence to treatment, reduced stigmatization and better treatment outcomes(6). One study point out that being admitted as an inpatient was associated with higher mortality. The numbers of deaths were not high in the initial months but gradually increased towards the end of TB treatment (10). Knowledge of service providers is important for them to provide high quality care. It has been reported that one third of health workers had poor knowledge and nearly half of them had unsatisfactory practice on tuberculosis infection control. In this study knowledge was determined by working experience and training (36). Treatment success was dependent on adherence to National TB Program guidelines, good quality and quantity of staffs, rational diagnosis, standard treatment and client satisfaction (37).

Other health system factors that may affect treatment outcomes is the procurement and supply management system were shortcomings in drug distribution, reporting and order placement were associated with poorer patient outcomesalthough in this study drug stock outsdid not affect patient management (38).Study done in four European countries - Austria, Bulgaria, Spain, and the United Kingdom have shown that perceived healthcare system factors which were key to achieve good treatment results for patients with multidrug-resistant tuberculosis were: timely diagnosis of disease, financial systems to ensure access to a full course of treatment and psychological and social support for patients; patient-centered collaborative approaches that address patient's emotional and social needs; motivated and dedicated healthcare workers with sufficient mandate and means to support patients; and cross-border management of multidrug- resistant tuberculosis to secure continuum of care between countries(39).

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study setting and design issues

A facility-based retrospective cohort study of patients admitted for MDR-TB treatment at Kibong'otohospital between 2009-2016 was conducted.A small qualitative approach was used to give insight into facility factors that may affect survival of admitted patients in order to support interpretation of the quantitative part.

Kibong'otohospital is the national referral center for treatment of MDR-TB located in Kilimanjaro region. The hospital has been providing treatment and care for MDR-TB patients since 2009.The hospital has a bed capacity of 340 catering for both susceptible and MDR-TB along with HIV co-infected patients. The hospital also has outpatient services. The MDR-TB program recommends using a standardized treatment regimen approach whereby all patients will receive the same treatment. Treatment is provided in phases with patients hospitalised for the intensive phase and thereafter receive the continuation phase at a health facility near to their homes.The MDR-TB hospital laboratory is responsible for monitoring MDR-TB patient treatment during the intensive phase while the Central TB reference laboratory (CTRL) performs culture and DST test.

Every patient admitted at Kibong'otois registered and given a unique registration number. Patient information is recorded in patient files which include thepatient's treatment card and other treatment sheets. The patient files are regularly updated throughout the admission period, during ward rounds and daily DOT admission. Afterdischarged the patient files are archived in the medical records department where they can be retrieved and used for patient review and research.

3.2 Study population, sample size and selection

The study population for this study weretwo as described below:

1) The study population for the quantitative part of the study was patientswith confirmed MDR-TB admitted at Kibong'oto hospital from 2009 to 2016. All MDR-TB patients ever admitted to the hospital were eligible forinclusion in the study(N = 600). Inclusion of all MDR-TB patients admitted between 2009-2016eliminatedtraditional sampling errors. The power of the cohort study was calculatedto assess whether the existing sample size (N= 600) was adequate to identify predictors of mortality.The study by K. C. Delgado et al, that assessed mortalityamongMDR-TBcases was used as a basis for our assumption(15).

Assuming having Diabetes Mellitus(DM) was the least likely exposure to influence mortality in MDR-TB patients (32%), the risk of mortality among those without diabetes was 4%, a risk ratio of 5.4 and an error margin of 5%.Using OpenEpi version 3.0open source calculator the power of the study was~100%.

Inclusion criteria:

1. MDR-TB patients admitted between 2009 and 2016.

Exclusion criteria:

2. Patients who were treated at the hospital but did not appear in the MDR-TB registers or those with incomplete data.

2) Key informants: Thedoctors, nurses and laboratory scientists who worked closely to help the MDR TB patients were interviewed for the qualitative component.

3.3 Variables

Independent variable:

Variables to be extracted were;

1. Socio demographic factors (age, gender, marital status, occupation, education level, residency, weight at admission, during each month of treatment and during discharge or death, smoking status and alcohol use).
2. Radiological findings (Lymphadenopathy, Pleural effusion ,Cavity),
3. Laboratory findings (AFB smear, culture, DST, G-xpert,).
4. Clinical findings (pre TB history, drug reaction like ototoxicity, nephrotoxicity, hepatotoxicity, joint pains, gastro-intestinal symptoms like nausea and vomiting, visual changes and conjunctivitis, psychosis, depression, peripheral neuropathyhy).
5. Co-morbidities (Anemia, HIV, Diabetes Mellitus, hypertension, heart failure, cardiomyopathies, asthma, chronic kidney disease, chronic liver disease, pancreatic disorders and cancers).
6. Opportunistic infections (candidiasis, recurrent oral or genital Herpes simplex virus (HSV) infection, Herpes zoster infection, Cryptococcal infection).

Dependent variables

The main outcome variable was mortality. Mortality in this study was defined as a death from any cause during treatment for MDR tuberculosis.

3.4 Data collection methods

Quantitative method

Data was extracted from the hospitals MDR-TB patient registers using a developed compilation data sheet (Appendix I). Missing and incomplete variables were assessed daily and attempts to fill in the blanks from alternative sources such as patients cards or files was made. Principal investigator (PI) with the help of two trained research assistant collected the information.

Qualitative method

In the hospital key informants were purposive selected to obtainbasic background information about possible reasons for mortality. In-depth interviews (IDIs) were held with five respondents including doctors, nurses and laboratory scientists. Throughout the in depth interviews respondents identified their perception on what might be the main determinants of poor prognosis including mortality, challenges they encountered during provision of MDR-TB treatment and give their recommendation.An interview guides was developed in English (Appendix II) and then translated into Swahili (Appendix III). The focus was on key issues concerning the health facility's ability to adequately manage MDR-TB patients. The information obtained from this part supplemented the quantitative part of the study by providing contextual information on the hospital.The principal investigator(PI) conductedall the in-depth interviews (IDIs). The IDIs were held separately for each key informant in a separate room to ensure privacy and confidentiality of each study participants and their information. Each interview took about 30-60 minutes.The interview was recorded and notes taken. Audio-recorded data was kept safe and accessed only by principal investigator. Later the recorded information was transcribed.Data collection took place in August 2017.

3.5 Data analysis

Quantitative study

Data was entered and cleaned using SPSS version 23to ensure its quality, correctness, completeness and consistency.Descriptive analysis (percentage and frequency) was done to summarize data.The mortality rate was calculated as the number of deaths per total MDR TB patients started on treatment during the intensive phase, further more incidence of mortality was calculated by dividing the number of MDR-TB cases experiencing a death event at a defined period by person-month of follow up.Kaplan Meier curves of mortality were compared by select characteristics. Cox regression models werefit to determine risk of dying by different predictors.A p value less than 0.1 in the univariate analysis was set as cut off value to choose predictors for entry into the multiple Cox proportional hazards regression analysis in order not to miss significant predictors which may have been confounded during

univariate analysis.Variables that are also known to biologically influence treatment outcome (age and sex) were included in the regression models. The duration of follow up wasdefined as the interval from the date when treatment began until the end of the intensive phase of treatment (8months) or the outcome (death) occurred. Mortality was defined as death due toany cause during treatment.Hazard ratios are presented and their 95% confidence interval. Significance level was set at alpha = 0.05.

Qualitative component

Qualitative data was analyzed using thematic analysis approach which involved identifying, analyzing and reporting patterns/themes within data.The themes discussed in the interview guide included experiences from their workin managing MDR-TB patients. The analysis involved several steps:audio-recorded data from the in–depth interviews was transcribed verbatim to enable the researcher to get the general idea. After transcription, a list of potential and initial codes were created through data reduction. Codes helped to identify features of the data that were interesting and had meaning. Thereafter themes were searched from the general list of codes created with focus on broad patterns in the data. Then coded data were combined with proposed themes and the relationships formed between codes and themes and between levels of themes were examined. After themes were identified the coded data were reviewed to see if coherent patterns had been formed. The existing themes were defined and refined for presentation in the final analysis and report writing.

3.6 Ethical issues

This study was reviewed and approved by Muhimbili University of Health and Allied Sciences Research and Publication Committee. Key informants for the qualitative study were briefed on the study objectives and an informed consent soughtpriorto being recruited to participate in the study.Data collection was done in a private and secure location within the hospital premises. Code names were used in the report to ensure confidentiality was maintained.

CHAPTER FOUR

4.0 RESULTS

Descriptive analysis

Medical records were reviewed for patients enrolled for treatment during the period between 2009 and 2016, 600 patients were admitted and started on MDR TB treatment atKibong'oto Hospital. 17 patients had to be excluded from the study due to repetition, wrong diagnosis, and incomplete data leaving 583(97.16%) patients with valid records. The mean age was 37.41 (standard deviation = 13.62),68.1% (397) were men, 55.42% (230) were married, 77.47% (447) had a previous TB history,52.81% (47)had primary education,71.11% (261) were self-employed, and 50.8% (296) came from coastal zone. A little over a half 59.06 % (397)experienced some form of adverse effect. Nearly 37.58% were smokers, while 44.14% reported alcohol use. About 37.43% of the patients had co-morbidities namelyanemia (9.21%) and HIV (35.49%). 90.79% (343) hadnegative sputum/bacterial culture conversion at month six,Drug susceptibility test showed that 74.39% (276) were resistant to Rifampicin and Isonizid while the remaining were resistant to more than Rifampcin and Isoniazid(Table 1).

Distribution of treatment outcomes are illustrated in Figure 2. A total of 15.3% (89)deaths occurred during the study period and 35% (204) of the cohort panel were still on treatment as of end of 2016.

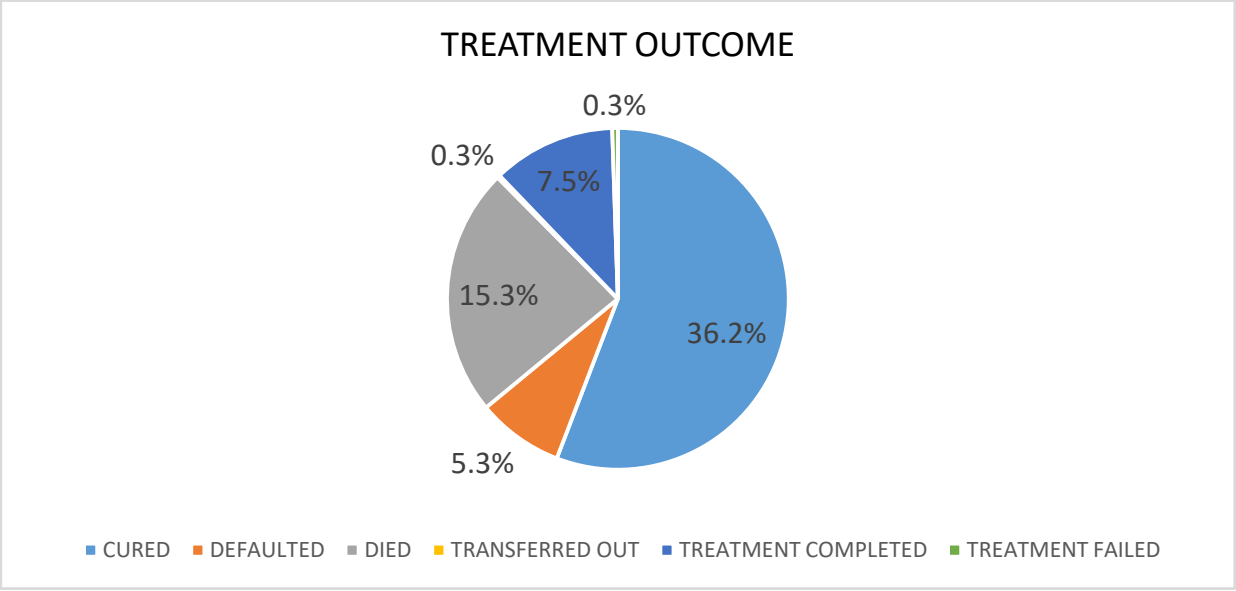

Figure 2:Treatment outcome for MDR TB patient admitted from 2009-2016.

Table 1: Descriptive statistic of social demographic characteristics of the study cohort (N = 583).

VARIABLE	TOTAL (%)	VARIABLE	TOTAL (%)
Age, years		**Education level***	
Below 24	110 (18.9)	primary	47(52.81
25-34	149 (25.5)	secondary	17 (19.10)
35-44	152 (26.1)	university	11(12.36)
45-54	108 (18.5)	No education	14 (15.73)
55+	64(11.0)	**Occupation***	
Sex			
Male	397(68.1)	Employed	54(14.71)
Female	186(31.9)	Self employed	261(71.11)
Marital status*		Unemployed	52(14.16)
Single	130(31.32)	**Smoking status***	
Married	230(55.42)	Yes	106(37.58)
Divorced/separated	31(7.46)	No	176(62.41)
Widow	24(5.78)		
Residence		**Alcohol use***	
Coastal zone	296(50.8)	Yes	132(44.14)
Northern highland	76(13.0)	No	167(55.85)
Lake zone	102(17.5)		
Central zone	36(6.2)		
Southern highland	59(10.1)		
Western zone	6(1.0)		
Zanzibar	8(1.4)		

***N will vary because of missing information.**

Table 2: Descriptive statistic of clinical characteristics of the study cohort (N = 583).

VARIABLE	TOTAL(%)	VARIABLE	TOTAL(%)
BMI*		**Anemia***	
Normal	157(40.36)	Yes	48(9.21)
Underweight	211(54.24)	No	473(90.79)
Overweight	21(5.40)	**Culture conversion at month five***	
Weight change*		Yes	473(90.79)
Gain	345(86.47)	No	48(9.21)
Loss	54(13.53)	**Drug resistance***	
Prior history of TB*		More than R &INH	95(25.61)
Yes	447(77.47)	R and/ INH	276(74.39)
No	130(22.53)	**X-ray at baseline***	
Co-morbidity*		Normal	12(2.68)
Yes	201(37.43)	Abnormal	435(97.32)
No	336(62.57)	**Adverse effect***	
HIV*		Yes	313(59.06)
Yes	203(35.49)	No	217(40.94)
No	369(64.51)		
Diabetes*			
Yes	10(1.92)		
No	511(98.08)		

***N will vary because of missing information**

Mortality rate

Themortality ratefor MDR TB patients at Kibong'otowas 15.3 % , however on further analysis our study showed that the cumulative incidence of mortality was 14.4/1000 patient months of follow up [i.e. 14.3 out of every 1000 MDR TB patients in Kibong'oto hospital die each month].

Patients were followed for a total of 4238 persons and the median observation time was 2months interquartile range(IQR) 18days-4months.

Predictors of death

Most of the deaths occurred in the first and the second months post admission. Males had relatively lower survival longevity than females(16.1/1000 vs. 10.9/1000; p = 0.174).Mortality rates for MDR-TB patients aged 55 years or above was higher compared to other age groups (Table 3).Patients who were underweight had a higher mortality rate (17.0 per 1000) compared to those who had a normal BMI category (5.8 per 1000; p = 0.006). Patients with anemia had a higher risk of mortality compared to patients with no anemia (39.2 per 1000 vs. 12.9 per 1000; p = 0.002). The difference in mortality with respect to anemia were obvious from the first month of treatment and sustained throughout the observation period (Figure 3). Patients who smoked were at higher death rate compared nonsmoker (18/1000 vs 11.5/1000;p=0.237) while alcohol user patients were 15.4 per 1000 at death risk compared to non-alcohol users (11.3 per 1000;p=0.407).HIV positive had higher mortality rate 18.6per 1000 compared to non HIV positive (11.6 per 1000;p=0.077) while Diabetic patient had higher risk of dying (28.3 per 1000)than non-Diabetes patients(14.8 per 1000;p=0.413). The patients whose culture were not converting at month five had higher risk of death compared to those who were converting (39.2/1000 VS 12.9/1000;p=0.002) while those who got adverse effect had little chance of dyingcompared to those who did not get adverse effect(20.0/1000 VS 10.9/1000;p=0.023). (Table3).

Table 3: Distribution of mortality by individual and clinical characteristics of MDR-TB patients.

Variable	Patients-months of follow-up	Death	Incidence density per 1000 (95%CI)	P- value
Sex				
Female	1379	22	10.9 (6.6 – 18.0)	
Male	2859	67	16.1 (12.1 – 21.5)	0.174
Age, years				
Below 24	786	15	14.0 (7.7 – 25.3)	
25-34	1104	19	9.1 (4.9 – 16.8)	
35-44	1099	25	18.2 (11.7 – 28.2)	
45-54	799	17	13.8 (7.6 – 24.9)	
55+	450	13	20.0 (10.4 – 38.5)	0.348
Occupation				
Employed	393	6	15.3 (6.9-34.0)	
Self employed	1919	29	15.1 (10.5-21.7)	
unemployed	380	5	13.2 (5.5-31.6)	0.957
Smoking status				
No	1299	14	11.5 (7.0-19.2)	
Yes	779	15	18.0 (10.6-30.3)	0.237
Alcohol use				
No	1238	14	11.3 (6.7-19.1)	
Yes	975	15	15.4 (9.3-25.5)	0.407
BMI				
Normal	1199	7	5.8 (2.8 – 12.2)	
Underweight	1533	26	17.0 (11.5 – 24.9)	
Overweight	168	0	0.0	0.006

Variable	Patients-months of follow-up	Death	Incidence density per 1000 (95%CI)	P- value
Weight change				
Gain	2749	5	0.4 (0.1 – 2.6)	
Lose	430	12	2.3 (0.3 – 16.0)	0.218
Prior TB				
No	953	12	12.6 (7.2 – 22.2)	
Yes	3249	47	14.5 (10.9 – 19.3)	0.077
Any co-morbidities				
No	2453	31	12.6 (8.9 – 18.0)	
Yes	1461	28	19.2 (13.2 – 27.8)	0.113
HIV				
No	2766	32	11.6 (8.2 – 16.4)	
Yes	1401	26	18.6 (12.6 – 27.3)	0.077
Diabetes				
No	3719	55	14.8 (11.4 – 19.3)	
Yes	71	2	28.3 (7.1 – 113.3)	0.413
Anaemia				
No	3483	45	12.9 (9.6 – 17.3)	
Yes	306	12	39.2 (22.3 - 69.0)	0.002
Culture conversion				
No	306	12	39.2 (22.5 – 69.0)	
Yes	3483	45	12.9 (9.6 – 17.3)	0.002
Drug resistance				
Rifampicin and/or Isoniazid	2031	24	11.8 (7.9 – 17.6)	
>Rifampsin&Isoniazid	702	6	8.6 (3.8 – 19.0)	0.465
Adverse effects				
No	1497	30	20.0 (14.0 28.67)	
Yes	2383	26	10.9 (7.4 – 16.0)	0.023

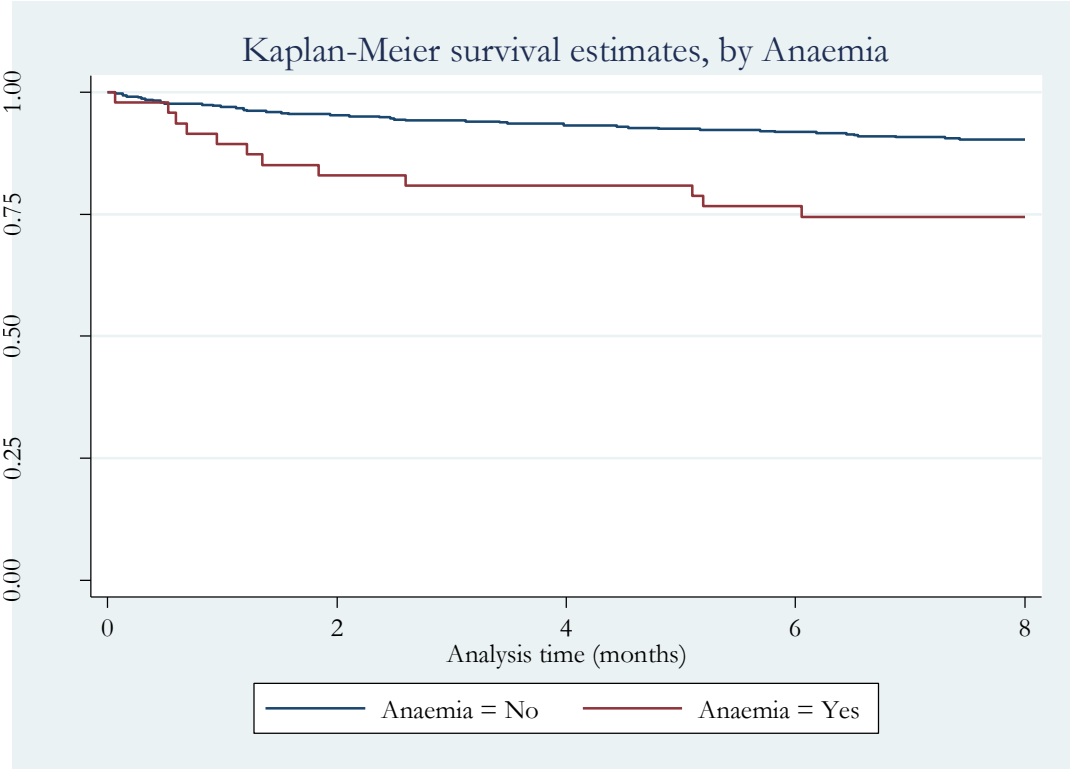

Figure 3: Kaplan Meier curves of the risk of death in a cohort of MDR TB patients by anaemia.

Predictors independently associated with mortality in MDR-TB patients after adjusting for all other potential confounders in the multivariable analysis were anemia and BMI. BMI is a strong risk factor for mortality in this study with a 2.9-fold risk of death in patients who were underweight (HR = 2.90; 95%CI: 1.26-6.69) compared to patients who were not underweight. Patients with anemia also had three fold risk of death (HR = 3.03; 95%CI: 1.60-5.73) than patients who did not have anemia. The risk of dying was increased bysex, age, occupation, alcohol use, and other co-morbidities although this did not reach statistical significance in our final model. Smoking, being HIV positive, experiencing an adverse effect and drug resistance to more than Rifampicin and Isoniazid was associated with a lower risk of mortality but in the multivariable analysis they were not significant.(Table 4) .

Table 4: Cox regression analyses of mortality by individual and clinical characteristics of MDR-TB patients.

Variable	Crude Hazard Ratio (95% CI)[§]	Adjusted Hazard Ratio (95% CI)
Sex		
Female	1.0	1.0
Male	1.48 (0.82-2.65)	1.48 (0.64-3.40)
Age, years		
Below 24	1.0	1.0
25-34	0.65 (0.27-1.52)	0.70 (0.22-2.23)
35-44	1.30 (0.62-2.71)	1.59 (0.60-4.20)
45-54	0.98 (0.43-2.27)	0.64 (0.18-2.27)
55+	1.43 (0.59-3.45)	1.38 (0.38-5.05)
Occupation		
Unemployed	1.0	NS
Employed	0.99 (0.41-2.38)	NS
Self employed	0.86 (0.26-2.82)	NS
Smoking status		
No	1.0	1.0
Yes	0.64 (0.31-1.33)	0.51 (0.19-1.37)
Alcohol use		
No	1.0	1.0
Yes	0.73 (0.35-1.52)	1.17 (0.08-16.19)
BMI		
Normal	1.0	1.0
Underweight	2.90 (1.26-6.69) **	2.63 (1.11-6.23)*
Weight change[±]		
Gain	1.0	NS

Variable	Crude Hazard Ratio (95% CI)[§]	Adjusted Hazard Ratio (95% CI)
Lose	0.83 (0.28-0.91)	NS
Prior TB		
No	1.0	1.0
Yes	1.15 (0.61-2.16)	0.64 (0.05-8.53)
Any co-morbidities		
No	1.0	1.0
Yes	1.52 (0.91-2.53)	1.85 (0.72-4.73)
HIV		
No	1.0	1.0
Yes	1.60 (0.96-2.69)	0.40 (0.11-1.53)
Diabetes		
No	1.0	NS
Yes	1.92 (0.47-7.85)	NS
Anaemia		
No	1.0	1.0
Yes	3.03 (1.60-5.73)**	5.94 (2.56-13.79)***
Culture conversion		
No	1.0	1.0
Yes	0.72 (0.30-1.77)**	0.61 (0.05-6.77)
Adverse effects		
No	1.0	1.0
Yes	0.54 (0.32-0.92)*	0.55 (0.21-1.46)
Self employed		

[§] 95% Confidence Interval; [±]Omitted due to insufficient cases in the sample;

*P value < 0.05; **P value < 0.001; ***P value < 0.0001

Qualitative responses

The five key informants were aged between 30-49 years, having more than 5years working experience and two were women.Described in this subsection are the themes identified in the respondent's interviews.

Laboratory tests and reagents

The capacity of the laboratory in terms of equipment and diagnosis hadadvanced with time and newer technologies had been adopted. BeforeTB diagnosis was done using microscope and culture andhas now advanced to molecular tests like Gene expert and Hain test /line probe assay, which also have ability to detect drug resistance. Other tests like parasitology,chemistry and haematology are also performed. However the main challenge observed is in reagent stock outswhich happen most of the time leading to failure in performing monitoring test for patientsas illustrated by the following quote:

"*…. there are ups and downs on chemistry test which are due to reagent stock out, I think that is the key issue which could be a challenge that happen frequently*" R#1

This also involves late detection of severe side effects to patients and sometimes results to patient death as illustrated by the following quote,

"*There were patients who died because of side effect and in other time you find that the side effect have been detected late, example there were patients who got renal failure because we didn't do blood test and I told you there was a time we had reagent stock out. A patient clinically started developing symptoms and the test will be done later and it appear that patient already got severe side effect because it was renal failure.* R#2

Majority of respondent advised on improving the whole reagent procuring system in order to prevent stock out to save patient lives while monitoring their treatment.

Also unavailability of other tests for diagnosing other diseases example ECHO and CT Scan tests. There are other conditions a patient needs further investigation in order to be diagnosed comprehensively, in the absence of other diagnostics, physicians are limited to diagnose other condition that would either contribute to patient death while he is on MDR TB treatment or interfere with speed of recovery, one respondent had this to say,

" *you find a patient having a condition that can't be handled here at Kibong'oto and probably he needs surgery or an ultrasound test in order to diagnose the problem, so because of delay in diagnosis the patient might lose his/her life*"R#*5*

Drugs supply

Erratic supply of drugs for both MDR-TB as well as other potential co morbidities sometimes occurs interfering with proper management and hence prognosis. Most of the time MDR-TB drugs were available although it happened once drug stocked out for about three weeks. The mostly serious concern from respondents was about stock out of drugs to treat other diseases or to counteract side effects like gastritis, depression, hypothyroidism or psychosis.One participant commented,

"*….problem we got may be is on these other drugs to manage common side effect which happened to MDR TB patients, example there were patients who got hypothyroidism and they needed drug but we failed to get them. so sometime other drugs are available and another time they are not available*" R#2

Another interviewee when asked said,

"*…challenges we met ,you find that for example our patients got numbness because of drug they use especially Ethinomide and Cycloserine so they are supposed to get Pyrodoxine which will help them to reduce side effect condition but you find them out of stock, example now they are not available so patient fail to get the alternative of those drugs*" R#*5*

These results suggest the need of government to strengthen procurement system of drugs so that they don't get out of stock.

Human resource

Lack of specialists in internal medicine and surgery affects patient prognosis as the management of MDR-TB patients should use a holistic approach. Some specialists do not accept these patients when referred to other hospital because they are afraid of TB particularly infectious control

issues. This has caused unnecessary delay in treatment of patient's and sometime contributing to death of patients, the comment below illustrate,

"*If a patient has a condition which need specialist care it become very hard, either we had to refer him or specialist should come to see him here. example we had a patient having upper gastro intestinal bleeding who needed surgery but we have no surgical capacity until we checked with others example KCMC.Most of times if a patient is still infectious he failed to get admission there and if the case is urgent it become very hard because of logistic issues and it take time sometime patient might die while struggling with referral arrangement process". R#2*

But respondents were very positive on the number of human resource and the number of training provided, at the beginning it was reported that the hospital had few staffs in relation to patient number because it was the only hospital in the country for initiating MDR TB treatment but as time went by new staffs were employed and allocated on the service and currently there are other ambulatory facilities initiating the treatment. One respondent said,

"M*mmh!years back number of staffs were few especially to clinicians but as time goes by the number is adequate and things are going*.."R#5

Almost majority of staffs got training since MDR TB treatment started, which are provided by different stake holders like Ministryof health under NTLP program, KNCV, PATH. And other staffs had opportunity to get trained abroad by WHO and Rwanda centre of excellence for MDR care in East Africa, the comment below illustrate,

".....there are a lot of training and they vary like health communication skills, management of drug resistance TB , HIV infected patients and so many. So staffs do get an updated information which happen frequently"R#1

Nutrition

Interestingly some of interviewees reported that poor nutrition status due to unbalanced diet has made patient health to deteriorate. They mentioned other patient who came with poor nutrition condition and having underweight at baseline of treatment which can contribute to unfavourable treatment outcome. Also there was a time the hospital failed to provide consistently balanced meals due to lack of fund which resulted in patients not getting balanced diet, although now the situation has been improved because of different aids from stakeholders. One informant reported,

"*There is nutrition issue which still is a problem especially to those patients who are malnourished. You measure a patient weight and find that he has severe malnutrition but you don't have any means of removing him on that condition. So this problem sometime might lead a person even to die if he failed to get a balanced nutrition*"R#5

This implies that there is a need of balanced diet education to patient and dietary support to the hospital.

CHAPTER FIVE

5.0 DISCUSSION

Tuberculosis diseasecause a lot of death to patients in many parts of the world particularly in developing countries. This study provides important insights especially to clinical and health facility factors ofthese patients . The main issue raised from this investigation was that still a substantial proportion of MDR-TB patients die in spite of huge investments made in their management. Anemia and under nutrition appear to be strong clinical predictors independently associated with mortality during treatment of MDR-TB cases.

5.1 Mortality rate

One of the targets of the Millennium Development Goals was to reduce TB mortality (which can be improved by measuring mortality in successfully treated cases). In our study the mortality rate for MDR-TB patients admitted between 2009-2016 was 15.3%. Our finding issimilar towhat has been reported from Ethiopia 15.43%(40)but different from South Africa 23.4% (41). This difference may be due to different follow up period in those studies. We followed up the patients for the entire intensive phase of treatment (~ 8 months) while the other studies followed up for an average of 466.5 days or 1.28 years.

The median survival of MDR-TB patients was about two months (interquartile range [IQR] 18 days – 4 months)within the intensive period of treatment. Other studies have reported that most of patients died within first three months after initiating TB treatment(42)(43) similar to our findings. This may be due to higher risk of co morbidity disease and delay in disease diagnosis and treatment which may result in a more serious illness at the time of presentation. Multiple diseases make treatment more complicated because patient might already had multiple organ failure. Delay is associated with more severe clinical presentation as the disease had longer time to progress and treatment will contribute to severity and complication of illness. This was also reported during interview with health workers that some patients come in severe diseased stage, very late and with more than one disease which made a difficult situation during medication taking and in turn contribute to a lot to unfavorable treatment outcome.

National TB and leprosy Control Programme2014 report showed that the MDR TB cumulative death rate was 10.3 %(45) compared to our findings it has increased. This implies that there is a need to reduce death rate in order to reach the SDG target of reducing the TB CFR to 10% by 2020.

5.2 Individual predictors associated with mortality among MDR-TB patients.

We did not observe a differential mortality with respect to sex of patient. Other studies have reported excess mortality in males than women that is believed to be due to socioeconomic interaction and cultural reasons which place women at a disadvantage. The excess risk among women increases with advanced age due to waning immunity(32). A possible explanation for the differences might be because of differences in the age structure of the study participants; in our study the majority of the cohort patients were within the adults group 35-44(26.1%) while majority of the study participants in these studies were elderly and delayed health care seekers.

Smoking is a risk factor of death with studies reporting one in two smokers die from smoking-related disease. Cigarette smoking has been associated with mortality by lower cytokine-producing macrophages which diminish influx of interferon gamma producing effector T-cells in the lungs for preventing bacteria(46). Our findings showed no relationship with smoking status from the similar kind of study perhaps because the sample size used in previous study was small compared to our study. Also it has been reported that the effect of tobacco take longer time to occur , probably ourpatients follow-up period was low (eight months)meaning thatlonger observation time would either give different results.

5.3 Clinical predictors associated with mortality among MDR-TB patients.

The importance of clinical features in treatment prognosis is very important to guarantee an appropriate treatment and control of both pathologies. Our finding showed that underweight patients were associated with mortality. Inline to our findings other studies explained that patients who were underweight below 35kg (48)or with unexplained weight loss (23) and moderate or severe malnutrition(49) were more likely to have unsuccessful treatment outcome and experienced higher death compared to normal/overweight patients. A study conducted to compare patient in sanatorium with a balanced diet or at home with a poorer diet found that

patients receiving better nutrition had accelerated smear conversion and resolution of radiographic abnormalities concomitant with weight gain compared to patients consuming a poorer diet (50).Indices of malnutrition may therefore indicate more advanced TB with the underlying infection rather than the nutritional defect leading to poor outcome (51). Furthermore during interview our study identified that majority of patients come with poor weight during baseline and don't gain weight during course of treatment in turn the prolonged illness predisposes them to malnutrition and underweight. It can therefore be assumed that the hospital seem to fail supporting these patients with quality nutritious food or other supplement to maintain their immune health. One study proved that half of cases receiving MDR-TB treatment at a referral hospital in Tanzania were found to have malnutrition which was related to duration of stay in the hospital (52). But It can be thus suggested that patients may have harbored TB illness for a longer duration before presenting for medical care therefore the disease may have been more advanced at the time of diagnosis. It is therefore likely that such connection to full recovery in nutritional status may take more time beyond the completion of treatment hence understanding the body composition of TB patients is important and it needs to be examined. A recent study has suggested that nutritional status measured by serum albumin concentration and hemoglobin is an important in predicting survival among patients in hospital (53). However these result were not encouraging and hospital must find a means to increase funds to provide balanced diet to enhance nutrition statusas consuming sensible balanced diet is vital for good health and wellbeing of patient.

It was hypothesized thatprevious TB infection under multiple regimens might create greater antibiotic resulting to unsuccessful treatment outcome(28)but our study did not observe any significance.Co-morbidities has shown to increase the severity ofTB disease which increased risk of unsuccessful treatment outcome(23).Some of co morbidities example HIV was estimated to cause around12% to 20% of all tuberculosis-related deaths even if highly active antiretroviral therapy(HAART) has shown to reduce the overall mortality(54) while Diabetes history was found to reduce cellular immunity and favors the progression of TB disease (28) .In contrast to earlier findings our study did not show significance to HIVsimilar to findings reported in Mwanza(55). This is probably due to the fact that patients who are HIV infected

had significantly low intensity of bacilli both in sputum smears and in culture compared to HIV negative TB patients and TBHIV infected patients tend to harbor fewer bacteria due to less formation of cavities in the macrophage where the bacteria grow and multiply(56). Surprising only Anemia was significant in our findings. Anemia in TB patient is often of iron deficiency or from chronic inflammatory process ,parasitic infection and other nutritional decencies(49). Both of these situations make iron unavailable for most biological functions including cell mediated immunity role. Iron deficiency may decrease T-cell numbers by reducing the proliferative response and potentially dropping the macrophage activity (27)hence increasing morbidity and mortality from most infections. A previous study in Tanzania had indicated that iron deficiency anemia was associated with 2-3 fold risk of death among TB patients (57) which significantly improved with TB treatment. Studies showed that a decline in the serum concentrations of C-reactive protein, the acute phase reactants coincided with the increase in hemoglobin concentration during treatment (58). Excessive production of pro-inflammatory cytokines contributes to anemia through reduced production of erythropoietin and altered iron metabolism which may in turn impair erythropoiesis (59),also poor quality diet could also account for anemia (29).Hemoglobin concentration was positively associated with sputum conversion among TB patients (60) suggesting that early hematological status examination could potentially reduce the morbidity and mortality from anemia. The study identified that frequently the laboratory has been facing the up and down challenges on reagent stock out which result to failing in performing monitoring test for patients used as an early signal and indicator on managing treatment adverse effect.Consequently many patients got severe side effect without being early noticed and quick action to be taken due to lack of other tests resulting to negative outcome. This implies that the whole reagent procuring system to be modified in order to prevent stock out to save patient lives while monitoring their treatment.

DST results showed that resistance to more than two drugs (28)was associated with mortality among MDR TB patients and bacteriological culture results not converting to negative after month five indicating unsuccessful treatment outcome(50). DST result and culture conversion had no significance in our findings. These difference can be explained as majority of our

cohort patients were sputum culture negative following five month of treatment only few patients remained culture positive alsofew patientswere resistance to more than Rifampsin and Isoniazid.Previous findings showed that patients experienced at least one adverse drug effect during the treatment period ranging from 19-72%(42)(50)(61), in line with our study findings 59.06% patients got adverse effect with gastritis most prevalent noted effect. One interesting finding is adverse effect was not significant for mortality , this possibility is because many patients die before experiencing those adverse effect. Radiography findings showed presence of cavity to be associated with both increased and decreased poor outcome during anti-tuberculosis treatment(56).Nevertheless we did not find any association perhaps becausecavitary chest-X-ray showed a protection against mortality probably due to the well-known association between good immune system and cavitary lesions (62).

5.4 Health facility factors and mortality among MDR-TB patients.

WHO developed the End TB Strategy which has six pillars as basic components in providing health care for patient since it is important to distinguish parts of a health system, recognize the inter-dependency between building blocks and the need for a more integrated response towards disease management.

Drug supply

The findings indicated that stock out of drugs to treat other diseases like treatment side effect interfere the patient treatment and add the chances to poor outcome. The evidence showed that other patient died due to severe effect of thelong-timeMDR TB treatment which could be prevented by other drugs to suppress the effect. The results are consistent with other findings which showed that drug distribution, reporting and ordering affected patient management(38).Drug stock-out is one of the factors that hinder access to effective treatment and achievement of treatment success targets and WHO has recommended that robust procurement system to minimize such shortage and ensure timely and sufficient quantities of the anti-tuberculosis drugs. These findings suggest that government to strengthen the drug procurement system to avoid un necessary complication to patients management during treatment.

Human resource

Under staffing and lack of vital cadres of health workers has been reported to be common to many other public health facilities in developing countries as main barriers to provision of TB/HIV services in health facilities offering TB treatment. This observed problem work against the proposed strategy of using the existing human resource for provision of care as suggested by WHO. Experience from studies suggests that such staffing gaps compromise the quality of care, planning, monitoring and evaluation processes and implementation of interventions like task shifting and overtime payments which have been found to be effective in improving health services delivery in health facilities faced with understaffing(63) . Contrary to expectation the findings did not observe difference between number of staffs in relation to workload. Although our study reveal that only lack of specialists in internal medicine and surgery made patient to be referred to other hospitals when need special care but generally It was clearly that dedicated and well trained staffs play a critical role in proving support to patients during treatment by showing psychological and emotional support which increases their life and adherence to MDR-TB treatment.otherwise the observed gap may help us to understand the importance of having good referral system to help these patients accessing treatment on time.

CHAPTER SIX

6.0 CONCLUSIONS

The mortality rate of MDR-TB is still high in spite of improvements made over the past years. Nutritional status and anemia are strong positive predictors of mortality in this population. The health system needs to develop targeted intervention to support nutrition in health facilities managing MDR-TB and TB patients in general.

6.1 Study strengths, limitations and mitigation

The strength of the study was its ability to include all patients diagnosed and admitted with MDR-TB between 2009 and 2016 in the country. The cohort design offers a strong evidence of causality of excess mortality amongst this population. The main limitation of this study was that it relied on existing data that is routinely collected at health facilities. The quality of the data was not good with several missing information. Efforts to verify information in different patient records was done to limit the level of missingness. Thus, interpretation of our findings must be done with caution. Trustworthiness is a major limitation for qualitative data collection approaches. We establish credibility through IDI tactics with open and non-directive questions to ensure participant honest and uncover deliberate untruth, and explaining of study objective's to the respondents. Adetailed description of phenomenon in questions were done to ensure transferability of results to other settings and triangulation was done to show conformability.

6.2 Recommendations

To decrease mortality among MDR-TB patients requires new public health interventions and the enhancement of existing control programs to improve both prevention and treatment.

1. A special intervention for dietary support is needed in thispopulation. Priority must be on giving nutrition education and promoting balance while admitted and to continue with this approach after the intensive phase of treatment.
2. Iron supplementation is recommended for the treatment of iron deficiency anemia as a co morbidity, as well as other forms of anemia with caution not interfering ant TB drugs.

3. Frequent assessment of nutrition status during the course of treatment is needed to identify patients that may require additional therapeutic supplements by monitoring weight gain on a monthly basis as proposed in the standard of care for MDR-TB programmes.
4. Improve data recording and storage of all routinely collected data as well as to promote their use in making evidence-based improvement in the management of TB patients.

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APPENDICES

Appendix I : Compilation data sheet

S/NO	**QUESTION**	**RESPONSE**	**CODE**
SECTION A: SOCIO-DEMOGRAPHIC CHARACTERISTICS			
1.	PATIENT MDR TB NO	_____	PATIENT MDR TB NO
2.	Sex	1. Male ☐ 2. Female ☐	SEX
3.	Age	_____ Years	AGE
4.	Marital status	1. Single ☐ 2. Married ☐ 3. Cohabiting ☐ 4. Separated/divorced ☐ 5. Widow ☐	MARITAL STATUS

S/NO	QUESTION	RESPONSE	CODE
5.	Education level	1. No formal education ☐ 2. Primary ☐ 3. Secondary ☐ 4. Diploma ☐ 5. University ☐ 6. Others, _____☐ (Specify)	EDUCATION LEVEL
6.	Occupation	1. Employed ☐ 2. Unemployed ☐ 3. Others, _____☐ (Specify)	OCCUPATION
7.	Smoking status	1. Yes ☐ 2. No ☐	SMOKE STATUS

S/NO	QUESTION	RESPONSE	CODE
8.	Alcohol use	1. Yes ☐ 2. No ☐	ALCOHOL USE
SECTION B: CLINICAL CHARACTERISTICS			
9.	Weight	1.At admission_____Kilograms 2.At month 1 up to month 8	WEIGHT
10.	Height	1.At admission_____Meters	HEIGHT
11.	Prior TB history *(Has the patient ever suffered from TB before)*	1. Yes ☐ 2. No ☐	PRETB HISTORY

S/NO	QUESTION	RESPONSE	CODE
12.	Did the patient have or was diagnosed with any other disease conditions	1. Yes ☐ 2. No ☐	COMORBIDITY
	Put a tick (✓) on the disease the patient has or was diagnosed to have		
12a.	Diabetes	1. Yes | 2. No	DIABETES
12b.	Hypertension		HIGHBP
12c.	HIV		HIV
12d.	Hepatitis B		HB
12e.	Anaemia		ANAEMIA

S/NO	QUESTION	RESPONSE	CODE
12f.	Malaria	☐ ☐	MALARIA
12g	Other disease	☐	OTHER DISEASE
13.	When was the first diagnosis of MDR TB made	____/____/_____ (dd/mm/yyyy)	DATE OF DIAGNOSIS
14.	Where was this first diagnosis made?	_____ *(Write the hospital/ region)*	PLACE OF DIAGNOSIS
16.	When was the treatment started?	____/____/_____ (dd/mm/yyyy)	STARTING TREATMENT DATE

S/NO	QUESTION	RESPONSE	CODE
17 a.	Is there any history of a drug reaction or side effects?	1. Yes ☐ 2. No ☐	DRUG REACTION

S/NO	QUESTION	RESPONSE	CODE
18.	Put a tick (✓) on the drug reaction or side effects the patient has or was diagnosed to have		

		1. Yes	2. No	
18a.	GASTRITIS			GASTRITIS
18b.	NEPHROTORICITY			NEPHROTORICITY
18c.	SKIN REACTION			SKIN REACTION
18d.	ATHRITIS			ATHRITIS
18e.	PREBYOPIA (FAILURE TO SEE TO READING)			PREBYOPIA (FAILURE TO SEE TO READING
18f	DEPRESION WITH SUICIDAL IDEA			DEPRESION WITH SUICIDAL IDEA
18g	HEARING IMPAREMENT			HEARING IMPAREMENT
18h	PERIPHERAL NEUROPATHY			PERIPHERAL NEUROPATHY
18i	PSYCHOTIC			PSYCHOTIC
18j	Other reaction/side effect			OTHER REACTION/SIDE EFFECT

<table>
<tr><th>S/NO</th><th>QUESTION</th><th>RESPONSE</th><th>CODE</th></tr>
<tr><td>19</td><td>Test done during intensive phase for monitoring patient</td><td>
<table>
<tr><td>LABORATORY TEST</td><td>month 0</td><td>month 1</td><td>month 2</td><td>month 3</td><td>month 4</td><td>month 5</td><td>month 6</td><td>month 7</td><td>month 8</td></tr>
<tr><td>AFB result</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Gxpert result</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Culture</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
<table>
<tr><td>RADIOLOGICAL TEST</td><td>Month0</td><td>Month6</td><td>Month8</td></tr>
<tr><td>Lymphadenopathy</td><td></td><td></td><td></td></tr>
<tr><td>pleural effusion</td><td></td><td></td><td></td></tr>
<tr><td>cavity</td><td></td><td></td><td></td></tr>
</table>
</td><td>LABORATORY TEST
RADIOLOGICAL TEST</td></tr>
</table>

S/NO	QUESTION	RESPONSE				CODE
		DST RESULTS	Month0	Month6	Month8	LABORATORY TEST
		ISONIAZID				
		RIFAMPSIN				
		ETHAMBUTOL				
		STREPTOMYCIN				
		PYRAZINAMIDE				
20.	Treatment outcome		Date of remark			TREATMENT OUTCOME
		CURED				
		TREATMENT COMPLETED				
		DIED				
		TREATMENT FAILURE				
		TREATMENT DEFAULT				
		TRANSFER OUT				

Appendix ii : Interview guide *(English version)*

INTERVIEW QUESTIONS

Date of interview……..

1. What is your position here at the hospital?
2. For how long have you been working in this hospital?
3. Have you or any other staff members received any type of training(s) on MDR TB management?

Probe about;

- Number of training they have received, how many have received, when and who conducted the training(s).

4. What is your opinion on the number of staffs and the workload?
5. What is your hospital laboratory capacity on performing test in diagnosis and monitoring MDR TB patients?

Probe about;

- Diagnosis tests which were done to patients and equipments used in diagnosis(eg;Gxpert) since 2009 to 2016.
- System of timely following up laboratory results done at CTRL
- Reagents supply and if stock out when and for how long patients missed laboratory monitoring tests.

6. What can you say about the flow of stock and supply of MDR TB drugs in this health care facility?

Probe about;

- If drug stock out , when did it happen, how long it last, what action taken

7. What are your perceptions on what might be the main determinants of poor prognosis including mortality.
8. What challenges do you have for the management of MDR TB patients(specifically to reduce mortality).
9. What recommendations do you have for effort to scale up the management of MDR TB patients(specifically to reduce mortality).

CLOSING

Is there anything more you would like to add?

I'll be analyzing the information you and others gave me and submitting a draft report to your hospital in about one month. I would appreciate it if you could read and review the report to see if it accurately represents your views. Would you be interested in doing this?

THE END

Appendix iii : Interview guide*(Swahili version)*

MASWALI YA MAJADILIANO

Tareheyausahili……..

1. Unanyazifaganihapahospitalini?
2. Ni kwakipindi cha mudaganiumefanyakazihapahospitalini?
3. Je wafanyakaziwakowamepatamafunzoyoyotejuuyakuwahudumiawagonjwawakifuakikuusugu?

Dadisikuhusu

- Idadiyamafunzowaliyopata, lininananialihudumu.
- Idadiyawatumishiwaliopatamafunzo

4. Je ninimaoniyakokuhusuidadiyawatumishinauzitowakazizilizopokatikakuwahudumiawagonjwa
5. Je maabarayakoinauwezoganikatikakufanyavipimovyaugunduzinaufuatiliajiwamatibabukwamgonjwawakifuakikuusugu?

Dadisikuhusu;

- Vipimovilivyokuavinafanyikanavifaavyauchunguzi(Gexpert) kuanzia 2009 mpaka 2016
- Utaratibuwakufatiliamajibukutoka CTRL
- UpatikanajiwaVitendeakazikatikaufuatiliajimaendeleoyamgonjwanakamakunakipindihavikupatikanaviliishalini,ilichukuamudaganikupatikanatena

6. Je unawezakuongeaninkuhusuunununuzinaugaviwamadawakwawagonjwa upojekatikahospitaliyako?

Dadisikuhusu

- Madawa kuisha ilitokealini, kwakipindi cha mdagani, hatuazipizilichukuliwa

7. Ninimtazamowakokuhusuvituvinavyosababishamaendeleomabayakwamgonjwahasaha savifo.
8. Changamotoganimnazipatakatikakuwahudumiawagonjwawakifuakikuusuguhasahasak atikakupunguzavifo.
9. NiniUshauriwakojuuya.
   Ninikifanyikekatikajitihadazakuongezautoajihudumakwawagonjwawakifuakikuusugu(ukizingatiavifovyawagonjwa)?

HITIMISHO

Kuna kitu cha ziadaunatakakuongeza?nitachambuamaelezoambayoumenipanakurudishamrejeshokwahospital indaniyamwezimmoja.nitafurahikamautapitianakuipataripoti. Kama utapenda.

Appendixiv: Consent form (English version)

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

DIRECTORATE OF RESEARCH AND PUBLICATIONS

CONSENT FORM

ID NO……..

Introduction

Greetings! My name is AIBORA SAMALI, a Master of Public health (MPH) student from Muhimbili University of Health and Allied Sciences. I am working on a research project with the objective of determining PREDICTORS OF MORTALITY AMONG MDR TB PATIENTS ADMITTED AT KIBONG'OTO HOSPITAL.

Purpose of Study

Management of MDR TB is accompanied by many challenges associated with high rates of side effects and poor outcomes, which increase morbidity and mortality. I would like to know your opinions on health facility and service delivery challenges that may affect management and care of MDR-TB patients admitted here. I will be very thankful if you will agree to participate in this study.

What participation involves

If you agree to participate in this study you will be required to answer a series of questions that have been prepared for the study through interview.

Privacy and confidentiality

The information you give is kept private and the interview will be performed in a private environment. However your interview responses will only be shared with research team members and MUHAS for academic purposes when necessary. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Duration

Participation in the study will take about 30-60 minutes. During interview I will be taping the session because I don't want to miss any of your comments and I can't be quick enough to write everything you say.

Withdraw from the study

You can decide to withdraw from the study at any time. You may tell if you are thinking about stopping or decide to stop. However I encourage you to participate because your views are very important.

Risk and Benefits

No anticipated risks that are expected to occur as a result of your participation in the study. If you agree to participate in this study, the information collected from this study will be beneficial to you, health care workers in Tanzania. It will also improve the quality of health services resulting in improved quality of life for people with MDR TB.

Payments for your participation:

You will not be paid or charged for taking part in this study.

Who to contact

If you ever have any questions about this study you may ask those now or later, In case you wish to find out more or ask any questions later, you may contact any of the following

- principal investigator.MsAiboraSamali mobile +255 719503999 email Aiboras@yahoo.com P. O. BOX 12705, DSM
- Supervisor Dr. GermanaLeyna mobile +255782847320, MUHAS, P. O. BOX 65001 DSM. If you ever have questions about your rights as a participant, you may call
- Prof. Mohamed Aboud, Chairman (research and Publications Committee, MUHAS. P.O. Box 65001, Dar es Salaam-Tanzania, Tel +2552150302-6)

Consent

If you wish to participate in this study, you should sign below

_____

Date Participant's name Participant signature

Date Researcher's name researcher's Signature

Appendix v : Consent form (Swahili version)
CHUO KIKUU CHA AFYA NA SAYANSI SHIRIKISHI MUHIMBILI

KURUGENZI YA TAFITI NA MACHAPISHO

FOMU YA MAKUBALIANO NA RIDHAA YA KUSHIRIKI KWENYE UTAFITI

Nambayamshiriki……..

utangulizi

Salaam! Mimi ninaitwa AIBORA SAMALI mwanafunziwa shahada ya udhamilikwenyeafyayajamiikutokachuokikuu cha sayansinatiba Muhimbili.Ninafanyautafitiwenyelengo la kuangaliavibashirvinavyowezakupelekeakifokwamgonjwawakifuakikuusuguambayeanapatiwa matibabukibong'otohospitali.

Taarifakuhusuutafitihuutunaoufanya

Mfumowautoajihudumakwawagonjwawakifua kikuu suguumegubikwanachangamotombalimbaliambazozimepelekeamatokeomabayakwawagonjwa yanayopelekeakuongezekakwausuguwaugonjwanavifo.

Utafitihuuutahitajikupatamawazoyakokuhusuchangamotozilizopokatikangaziyahospitaliambaz ozinaathirihudumakwawagonjwawakifuakikuusuguwanaopatiwamatibabuhapa.

Nitashukurukamautakubalikushirikikatikautafitihuu.

<u>ushiriki</u>

ukikubalikushirikiutahitajikakujibumaswaliyaliyoandaliwakwaajiliyamahojiano

Usiriwataarifazako

Kama utakubalikushirikikwenyeutafitihuu, tutahakikisha kuwataarifazakozoteutakazotoazinatunzwasehemu salamanayasirikiasikwambahazitawezakuonwanamtuambaehausikinautafitihuu. Lakinimatokeoyautafitihuuyanawezakujadiliwakwenyetaasisiyakishule au kuchapishwakwenyemajarida yakisayansi, lakinipiahatakwenyemchakatohuu, tutahakikishakuwajinalakohalitaonekanakokotekwenyetaarifahizo.

Mudawakokwenyeutafitihuu

Tunawezakutumiamudakatiyanususaahadisaamojakwaajiliyamahojiano.wakatiwamahojianonit arekodimazungumzokwasababusitatakakupotezataarifazozotenasitaweza kwenda namwendokasiwakilakituutakachoongea

Jinsiyakushirikikwenyehuuutafiti

Ushirikiwakokwenyehuu utafiti niwahiarikabisa, hivyounahiariyakuamuakushiriki au kutokushirikikwenyeutafitihuu. Ingawajenakushauriushirikikwasababumaoniyakoni muhimusana.

Hasaranamadharautakayoyapatakwawewekushirikikwenyeutafitihuu

Hatutegemeiutapatahasarayoyotekwakushirikikwenyeutafiti huunawalahatutegemeikamakutakuwepona madharayoyoteyatakayotokananawewe kushirikikwenyeutafitihuu.

malipo

hautatakiwakulipachochotewalahautalipwachochotekwaushirikiwakokatikatafitihii.

Naniwakumwona au kuwasilianae

Kama unaswalilolotekuhusinanautafiti huu unawezakuwasilianana

- Mtafitimkuu.MsAiboraSamalisimu +255 719503999 baruapepe Aiboras@yahoo.com SANDUKU 12705, DSM

- Msimamizi Dr. GermanaLeynasimu +255782847320, baruapepe gerryleyna@yahoo.com, SANDUKU 65001 DSM.
- Prof. Mohamed Aboud, mwenyekiti (research and Publications Committee, MUHAS.sanduku 65001, Dar es Salaam-Tanzania, simu +2552150302-6)

Kuombaridhaa

Kama utakubalikushirikikatika tafitihiinitakuombauandikejinalakohapachinipamojanakutiasahihiyako.

Tarehe jina la mshiriki sahihiyamshiriki

Tarehe jina la mtafitisahihiyamtafiti

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Ref. No. MU/ PGS/SAEC/Vol.X/ 14th August, 2017

Ms. Aibora Samali
Master of Public Health
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: PREDICTORS OF MORTALITY AMONG MULTDRUG RESISTANCE TUBERCULOSIS PATINETS ADMITTED AT KIBONG'OTO HOSPITAL FROM 2009-2016

Reference is made to the above heading.

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

The ethical clearance is valid for one year only, from 11th August, 2017 to 10th August, 2018. In case you do not complete data analysis and dissertation report writing by 10th August, 2018, you will have to apply for renewal of ethical clearance prior to the expiry date.

Prof. Andrea B. Pembe
DIRECTOR OF POSTGRADUATE STUDIES

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

Appendix vi : Ethical clearance