DRUG-INDUCED HEMATOLOGICAL, RENAL AND HEPATIC INJURIES AMONG IN-PATIENTS ON TUBERCULOSIS TREATMENT AT KENYATTA NATIONAL HOSPITAL

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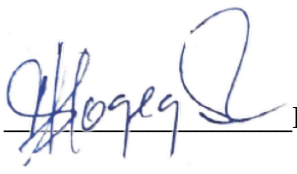
Signature  Date 27th Nov 2022

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DEDICATION

I dedicate this research work to my loving wife, Diana Nyamweya, and my children. Gabby and Emmanuel, for their love, encouragement and endless support during my study.

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TABLE OF CONTENTS

UNIVERSITY OF NAIROBI DECLARATION OF ORIGINALITY FORM ii

SUPERVISORS' APPROVAL iii

DEDICATION iv

ACKNOWLEDGEMENT v

TABLE OF CONTENTS vi

LIST OF TABLES x

LIST OF FIGURES xii

LIST OF ABBREVIATIONS AND ACRONYMS xiii

OPERATIONAL DEFINATIONS xiv

ABSTRACT xv

CHAPTER ONE: INTRODUCTION 16

1.1 Tuberculosis 16

1.2 Anti-tuberculosis treatment side effects 16

1.3 Problem statement 19

1.4 Research questions 20

1.5 Main objective 21

1.6 Specific objective 21

1.7 Study justification 21

CHAPTER TWO: LITERATURE REVIEW 23

2.1 Epidemiology of tuberculosis 23

2.2 Pharmacovigilance of anti-tuberculosis medications 23

2.3 Drug Induced Renal Injury 24

2.3.1 The RIFLE Classification of Acute Renal Injury 24

2.3.2 Acute kidney injury 27
2.4 Hematological injury induced by anti-tuberculosis drugs 28
2.4.1 Drug induced aplastic anemia 29
2.4.2 Drug induced megaloblastic anemia 30
2.4.3 Drug induced Thrombocytopenia 31
2.4.4 Immune thrombocytopenia 31
2.5 Drug induced Liver injury (DILI) 31
2.5.1 Epidemiology of drug induced liver injury 31
2.5.2 Drug induced Liver injury (DILI) in tuberculosis 32
2.6 Conceptual framework 33
CHAPTER THREE: METHODOLOGY 35
3.1 Study design 35
3.2 Study site 35
3.3 Study population 35
3.3.1 Eligibility criteria 35
3.4 Sample size 36
3.5 Sampling method 37
3.6 Data collection 38
3.7 Case definition 38
3.8 Study variables 40
3.9 Data management 40
3.10 Data Analysis 40
3.11 Ethical considerations 41
CHAPTER FOUR: RESULTS 42
4.1 Participant recruitment and reasons for exclusion 42

4.2 Socio-demographic and anti-tuberculosis medication used by the study participants 42
4.3 Medications used by the patients 43
4.3.1 Use of antimicrobial agents in patients with tuberculosis in Kenyatta National Hospital 43
4.3.2 Other medicines used by patients with Tuberculosis in Kenyatta National Hospital... 44
4.4 Baseline Prevalence of hematological, renal and liver disorders before treatment initiation among hospitalized adult patients with tuberculosis in Kenyatta National Hospital 46
4.5 Changes in hematological profile post treatment 46
4.5.1Treatment progression and incidence of anemia 46
4.5.1 Incidence of anemia 47
4.5.2 Changes in hemoglobin levels in patient who had anemia at baseline 47
4.5.3 Factors affecting hemoglobin levels post treatment amongst patients who had normal levels at baseline 48
4.6 Changes in white blood cells counts 51
4.6.1 Progression of patients who had leucopenia and leukocytosis at baseline 52
4.7 Changes in WBC in Patients who had normal white blood cell counts at baseline 53
4.7.1 Progression of patients who had leukocytosis at baseline 53
4.7.2 The overall prevalence of Leukocytosis post treatment initiation 54
4.8 Changes in Platelets levels 56
4.9 Changes in liver function 59
4.9.1 Change in liver function among those with normal ALT levels at treatment initiation 62
4.10 Renal injury 65
4.10.1 Factors associated with renal injury. 65
CHAPTER FIVE: DISCUSSION 68
CHAPTER SIX: CONCULUSION AND RECOMMENDATIONS 73

6.1 Conclusion 73
6.2 Recommendations 73
6.2.1 Recommendations for future research 73
6.2.2 Recommendations for policy and practice 73
REFERENCES 75
APPENDICES 85
APPENDIX A: KNH-UoN ERC APPROVAL 85
APPENDIX B: DATA EXTRACTION FORM 87

LIST OF TABLES

Table 1.1 Tuberculosis treatment regimen……17
Table 1.2 Side effects of antituberculosis drugs……18

Table 2.1 Comparison of RIFLE and AKIN classification systems (26). 26

Table 3. 1 Severity of anemia as per the WHO guidelines... 39
Table 3. 2 RIFLE classification of Acute Kidney injury (AKI). 39

Table 4. 1 The socio-demographic and clinical characteristics of in-patients with tuberculosis at Kenyatta National Hospital..... 42
Table 4. 2 Antimicrobial used by patients with tuberculosis in Kenyatta National Hospital..... 44
Table 4. 3 Drugs used by patients with tuberculosis in Kenyatta national hospital 45
Table 4. 4 Changes in hemoglobin levels from treatment initiation to lowest level post baseline48
Table 4. 5 Generalized linear regression modelling to identify variables associated with the reciprocal of highest hemoglobin levels after treatment initiation in patients with Tb at Kenyatta National Hospital 49
Table 4. 6 Changes in white blood cell count from baseline and post treatment..... 51
Table 4. 7 Progression of patients who had leucopenia and leukocytosis at baseline 52
Table 4. 8 Changes in WBC in Patients who had normal white blood cell counts at baseline..... 53
Table 4. 9 Progression of patients who had leucopenia and leukocytosis at baseline 54
Table 4. 10 The median, interquartile rand and prevalence of thrombocytopenia 57
Table 4. 11 Generalized linear regression modelling to identify variables associated with the reciprocal of highest platelet levels after treatment initiation in patients with Tb at Kenyatta National Hospital 59
Table 4. 12 Summary of liver function bio-markers at baseline and post-treatment initiation 60
Table 4. 13 Severity of liver injury by fold elevation of ALT levels 61
Table 4. 14 Grouping of patients based on AST to ALT ratio and the suggested type of liver injury 62

Table 4. 15 Change in liver function among those with normal ALT levels at treatment initiation 63
Table 4. 16 Generalized linear regression analysis to identify risk factors for elevated reciprocal of highest documented ALT levels in patients on tuberculosis medication. 63
Table 4. 17 Classification of renal toxicity..... 65
Table 4. 18 Association between pre-treatment renal injury and age, sex, smoking, alcohol..... 66
Table 4. 19 Association between post-treatment renal injury and age, sex, smoking, alcohol 67

LIST OF FIGURES

Figure 2.1**:** RIFLE classification of acute kidney injury(26).....**Error! Bookmark not defined.**5

Figure 2.2: Conceptual framework for the risk factors for hematological, renal and kidney injury in patients on anti-tuberculosis medications 344

Figure 4.1 Prevalence of hematological, renal, and liver disorders in patients with tuberculosis with HIV co-infection before initiation of treatment 46

Figure 4.2 Severity of anemia pre and post treatment initiation 47

Figure 4.3 Scatter diagram for the relationship between baseline and the highest hemoglobin levels in patients with tuberculosis..... 50

Figure 4. 4 Overall Prevalence of leukocytosis post treatment initiation stratified by status at treatment initiation 55

Figure 4. 5 The overall prevalence of leucopenia post treatment initiation stratified by the status at baseline 56

Figure 4.6 Changes in platelet count from baseline to lowest level post treatment initiation (n=88) 58

Figure 4.7 Box plot of highest ALT levels post treatment for patients on fluoroquinolones 64

LIST OF ABBREVIATIONS AND ACRONYMS

ADR	Adverse drug reaction
ADQI	Acute dialysis quality initiative
AKF	Acute kidney failure
AKI	Acute kidney injury
ANTI-TB	Anti-tuberculosis
BUN	Blood urea nitrogen
DILI	Drug induced liver injury
DOTS	Direct observation treatment systems
GFR	Glomerular filtration rate
KNH	Kenyatta National Hospital
MDR	Multiple drug resistance
RIFLE	Risk Injury Failure, Loss of Kidney Function End stage
TB	Tuberculosis
WHO	World Health Organization

OPERATIONAL DEFINATIONS

Adult: A patient who is 18 years old and above

Adverse drug reaction: An undesired or unwanted effect that occurs because of taking a drug within the recommended clinical use

Anemia: Hemoglobin levels of <13g/dl for males and <12g/dl for the females

Anti-tuberculosis medication: A chemical substance(s) used in the treatment, cure or prevention of **tuberculosis.**

Anti-tuberculosis regimen: A treatment plan for the management and treatment of tuberculosis patients with specified medication, dose and treatment duration.

Anti-tuberculosis treatment: Medication care given to a tuberculosis patient

Co-morbidities: An existence of two or more medical conditions or diseases in an individual patient

Drug-induced Hepatotoxicity: Liver injury caused as result of a reaction and response to a drug

Multi drug resistant tuberculosis: A disease that is caused by bacteria that are resistant to two of the most important antituberculosis drugs.

Side effects: Unwanted effects caused by medication at the normal therapeutic doses and can be mild, moderate or severe.

ABSTRACT

Introduction: Anti-tuberculosis medications are very toxic with high number of adverse drug reactions (ADRs) that include hematological, renal and hepatic injuries. These ADRs can lead to low rates of treatment compliance, poor treatment outcomes and increased morbidity and mortality rates among the patients.

Objective: To determine the prevalence and the risk factors of hematological, renal and liver toxicity among hospitalized adult patients on tuberculosis treatment at Kenyatta National Hospital.

Methodology: A retrospective review of files of tuberculosis patients admitted at Kenyatta National Hospital between December 2016 and December 2020 was done. The main outcomes of interest were hematological injuries (anemia, leucopenia, and thrombocytopenia) renal injury and liver toxicity (hepatocellular, cholestatic and mixed injury). Descriptive and inferential data analysis was conducted. Binary logistic regression models were fitted to evaluate factors individually associated with the outcomes. Model building to identify key predictors for toxicity was conducted using a forward stepwise approach then data was analyzed to use STATA version 13 software the statistical tests were carried out at a level of significance of 0.05.

Results: Most of the participants were between the age of 31 and 35 years and most were males (74.9%). Almost all the participants (99%) were treated with rifampicin, isoniazid, pyrazinamide, ethambutol and pyridoxine regimen. The most prevalent comorbidities were diabetes mellitus (14.3%), hypertension (14.3%) and pneumonia (10.7%).

The prevalence of pre-treatment anemia was 64.6% while the prevalence post treatment anemia was 74.2%, The prevalence of renal injury was 37.0% after the initiation of tuberculosis treatment and the incidence of kidney injury was 11.6% (n=8) of whom 3 were in stage 1 (risk), 3 were at stage 2(injury) and 2 were in stage 3 (failure) as per the RIFLE grading. Based on the fold elevation of the ALT levels (19.5%) of the patients had some form of liver injury; 6 (7,8%) had mild liver injury while 7(9.1%) had moderate injury and one (1.3%) had severe injury at baseline.

Conclusion and Recommendations: Anemia was the most common hematological injury in both the pre and post treatment period. This brings about the need to study the reason as to why most of the tuberculosis patients developed anemia before the initiation of tuberculosis treatment.

CHAPTER ONE: INTRODUCTION

1.1 Tuberculosis

Tuberculosis is one of the leading causes of death among all the infectious diseases in the world. According to World Health Organization (WHO) latest estimates, 10.4 million people were infected and developed tuberculosis in 2016 and 1.6 million died from the disease (1), with tuberculosis accounting for 40% of all mortality from the communicable diseases (2). Everybody is at risk of acquiring TB infection although HIV infected individual and health care workers are at high risk. Adults make up 90% of all the TB cases with a ratio of males to females of 2:1 (3) . People that have weak immune systems are at the highest risk of contracting tuberculosis. People with HIV infection, those who have undergone organ transplant, people suffering from diabetes mellitus and those who have previously been infected by the *Mycobacterium tuberculosis* bacteria are considered at high risk(4) .

1.2 Anti-tuberculosis treatment side effects

Treatment of tuberculosis consist of a short course therapy of 6 months regimen with a four-drug intensive phase and a two-drug continuous phase as indicated in the Table 1.1 (6,7). The six-month therapy has shown to be highly effective in the treatment of the *Mycobacterium tuberculosis* infection.

Table 1.1: Tuberculosis treatment regimen (5)

PHASE	**Intensive Phase**	**Continuation Phase**
DURATION	Daily treatment with appropriate patient support, including DOT, for two months	Daily treatment with appropriate treatment support, including DOT, for four or six months.
DRUG USED	Rifampicin (R) Isoniazid (H) Pyrazinamide (Z) Ethambutol (E)	Ethambutol (E) and Isoniazid (H), 6 months. Or Rifampicin (R) and Isoniazid (H), 4 months.

Because of the necessity of utilization of multiple drug regimen in the treatment of tuberculosis there is increased incidences of the anti-tuberculosis side effects, these side effects may be mild to severe and life-threatening adverse drug reactions that could lead to the withdrawal of treatment. These may increase the rate of mortality, morbidity and increased coast of treatment as a result of using alternative regimens with increased risk of toxicity problems and noncompliance to the treatment leading to treatment (6).(7)

Anti-tuberculosis side effects are an inherent risk for patients on any anti-TB medication. The development of these side effects mainly depends on the patient characteristics and other factors during drug therapy. These medications can cause different kinds of ADRs that affect almost all the body organs. Hepatotoxicity reactions, gastrointestinal disorders, drug allergies, arthralgia, hematological disorders and renal injuries are some of the most common anti-tuberculosis

medication side effects(8). Table 1.2 highlights some of the most common side effects of anti-tuberculosis.

Table 1.1 Side effects of antituberculosis drugs(9)

DRUGS	SIDE EFFECTS
Isoniazid	Peripheral neuritis, Hepatitis, Central nervous system effects like (Convulsions, muscle twitching, dizziness) and Rashes
Ethambutol	Optic neuritis, Skin rash
Rifampicin	Orange urination and saliva, Hepatitis, Thrombocytopenia, Hemolysis and Renal failure
Pyrazinamide	Hyperuricemia, Hepatotoxicity, Anorexia and Nausea
Streptomycin	Nephrotoxicity, 5th cranial nerve damage, Dermatitis and Anaphylaxis
Ethionamide	Nausea, skin rash, Hepatotoxicity
Cycloserine	Headache, Tremor, Vertigo, Seizure, psychosis
Kanamycin	8th cranial nerve damage, Nephrotoxicity, Vestibular toxicity
Capreomycin	8th cranial nerve damage, Hypokalemia, Nephrotoxicity, Urticaria

The incidence rate of the Anti-tuberculosis ADRs varies among different studies with different population and is between 5.5% and 57%,(10). The risk of ADRs increase with age, malnutrition, history of hepatitis and are influenced by environmental factors, HIV co-infections and genetic factors like isoniazid–metabolizing enzymes gene polymorphism. Adverse drug reactions cause a lot of pain to the patients like long duration of treatment and hospital stay as well as increase financial burden(10).

Patients who develop mild adverse drug reaction due to Anti-tuberculosis medication should be encouraged to continue with the therapy while on symptomatic treatment of the side effects. Health care providers are encouraged to provide close monitoring of tuberculosis patients and report any life threatening ADRs to the authority that can help minimize them(11). Anti-TB medications are some of the main causes of hepatic injuries worldwide with an incidence rate of between 5%-28%. About 20% of the patients on isoniazid develop transient asymptomatic increase of the liver enzymes that tend to reduce with continued use of isoniazid. In India, tuberculosis drugs are the main cause of drug induce acute liver failure. They contribute to about 5.7% -22% of all the acute liver failure cases (12,13).

1.3 Problem statement

The National Tuberculosis, Leprosy and Lung disease program (NTLD-program) conducted the first post-independence TB prevalence survey in 2015-2016 and established the prevalence of tuberculosis to be 558 per 100,000 adult population. The highest disease burden was on the age group of 25-34 that had the prevalence of 716 per 100,000 population, with the male having a higher prevalence than those of the female of 809 and 359 per 100,000 population respectively. Nairobi, Nyanza and Coast regions have the highest reported cases, with 10 out of the 47 counties accounting for 76% of the notification of tuberculosis cases out of which Nairobi accounts for 15% of all the cases (14).

In Africa due to the high level of poverty and increased HIV co-infection there is an increased risk of developing the tuberculosis. In Kenya the government has put in place mechanisms of identifying patient that have been exposed to tuberculosis infection and ensuing that these patients are put on treatment once they develop the infection.

Patients with tuberculosis are normally put on a cocktail of drugs, which are very toxic with high number of side effects that include hematological, renal and hepatic injuries (15). These side effects can lead to low rate of treatment compliance by the patients, which in turn leads to poor treatment outcomes and increased morbidity and mortality rates. With increased renal, hepatic and hematological injuries that will need specialized treatment the patients may require a prolonged hospital admission that will increase the financial burden to the patients and their caregivers. This patient may also suffer from psychological and emotional pain due to the cost of treatment; the long duration of hospital stays and loss of income during the time of treatment.

There are a number of studies that highlight the side effects of anti-tuberculosis medication in the world(10,13,16,17). Most of these studies tend to focus on the hepatic injuries and report varied incidence rates depending on the study population and the country of the study. Therefore, a study is required that will focus on the Kenyan population and highlight the renal and hematological toxicity in addition to liver toxicity, which can be influenced by the population characteristics and environmental factors. This study therefore seeks to measure the prevalence of selected side effects of anti-tuberculosis medication at Kenyatta National Hospital as well as and identify the risk factors for these side effects.

1.4 Research questions

1. What is the prevalence of hematological, renal and liver toxicity among hospitalized tuberculosis adult patients at Kenyatta National Hospital?
2. What are the patterns of liver and renal toxicity in terms of severity and type of injury?
3. What are the risk factors for hematological, renal and liver toxicity?

1.5 Main objective

The main objective of the study was to determine the prevalence and risk factors of hematological, renal and liver toxicity among hospitalized adult patients on anti-tuberculosis medication at Kenyatta National Hospital.

1.6 Specific objective

The specific objectives of this study were to:

1. Determine the prevalence of hematological, renal and liver toxicity among hospitalized adult patients on anti-tuberculosis medication in Kenyatta National Hospital.
2. Characterize the severity and types of liver and renal toxicity in adult patients on anti-tuberculosis medication.
3. Identify the risk factors for hematological, renal and liver toxicity among hospitalized adult patients on anti-tuberculosis medication.

1.7 Study justification

Tuberculosis patients are normally treated with tuberculosis medication that is very toxic which are taken on daily basis for long periods. For proper understanding of anti-tuberculosis medication and treatment there is need to highlight and categorize the side effects that are associated with these regimens. This study will lead to better understanding of the side effects of anti-tuberculosis medication and add to the existing data that the clinicians, patient caregivers, will use evidenced based knowledge on the adverse drug reactions of ant tuberculosis and the policy makes to ensure that tuberculosis patients receive optimal and better care.

The findings of this study will be shared with the relevant authorities at Kenyatta National Hospital (KNH), the TB clinic at KNH and the National Tuberculosis and Leprosy Control Program of the

Ministry of Health. Recommendations to ensure that there is proper understanding for both the short term and long-term side effects that are associated with the anti-tuberculosis medication will be made. This will ensure that hospitalized tuberculosis patients receive optimal care.

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of tuberculosis

It is estimated that 23% of the global population is infected by the *Mycobacterium tuberculosis* (18). The adult population contributes to 90% of the tuberculosis cases (19). Asia and Africa contribute to about 70% of all the global TB cases. In Africa, co-infection with HIV is a significant factor. This is common with 50% of the TB cases have HIV. Globally TB incidence has declined since 2017 and the number of deaths associated with tuberculosis has declined (18) . According to WHO, Kenya is among the countries with high tuberculosis burden and ranked number 22 among these countries. It is estimated that the prevalence rate of tuberculosis in Kenya is 558 per 100,000 population with male population being the most affected. The mortality rate is 20 per 100,000 population. 81,518 cases were reported in 2015, with 83% of these cases being pulmonary tuberculosis, most of these cases were patients between the age of 25 and 44 years. Informal settlements have the highest TB burden among the urban population in Kenya (14).

Tuberculosis continues to be a leading cause of death among adults despite the availability of effective treatment regimens. It causes more than 1.3 million deaths of HIV free individuals and contribute to 374,000 HIV related deaths (15),(16). In the sub-Saharan Africa there were 254,000 deaths related to tuberculosis in 2017 although the TB burden may be underestimated in Africa since it relies on the calculations from TB reports and notifications data, which could be affected by the poor laboratory and diagnostic systems (18).

2.2 Pharmacovigilance of anti-tuberculosis medications

Tuberculosis treatment leads adverse events which include, hepatitis, hyperuricemia, peripheral neuropathy and skin rash (9). These adverse drug reactions have led to reduced patient treatment compliance by 37.8% and 26% of the patients are forced to discontinue therapy(21)

Adverse drug reactions can lead to interruption of tuberculosis treatment before completion of therapy and this can result in treatment failure, reduced quality life and even death. Patient adherence to the treatment is the key to effective anti-tuberculosis treatment(21).

The use of anti-tuberculosis medication together with antiretroviral drugs and other drugs calls for a stronger pharmacovigilance system to monitor and evaluate ADRs that could result from these treatments and promote patient safety. According to WHO active tuberculosis drug-safety monitoring and management systems (aDSM) should be in place for a systematic clinical and laboratory assessment of patients who are on TB treatment. These are mainly on patients who are on new molecules or on multi drug resistant tuberculosis treatment regimens (22).

2.3 Drug Induced Renal Injury

2.3.1 The RIFLE Classification of Acute Renal Injury

Acute kidney injury (AKI) is defined as the abrupt decline in the renal function and reduced glomerular filtration rate (GFR). It manifests clinically as a reversible acute increase in nitrogenous waste products. It is diagnosed by measuring blood urea nitrogen (BUN) and serum creatinine levels. It is a severe complication that can lead to interruption of treatment(23).

The introduction of Risk Injury Failure, Loss of Kidney Function End stage (RIFLE) classification system increased the understanding of acute kidney injury. RIFLE defines three grades of severity: class R - risk, class I - injury, Class F - failure. Risk is the least severity grade of AKI with an increase of serum creatinine levels of more than 1.5mg/dl, a decrease of glomerular filtration of more than 25% and with a urine output of less than 0.5ml/kg per hour over a period of six hours. Injury is a mild grade of AKI and is determined by a decrease of glomerular filtration of more than 50% and an increase of serum creatinine levels of more than 2mg/dl with a urine output of less than 0.5ml/kg per hour over a period of 12 hours. Failure a more severe case of AKI and is

associated with an increase of serum creatinine levels of 3mg/dl and decreased glomerular filtration of more than 75% with a urine output of less than 0.3ml/kg per hour over a period of 24 hours(24) . Figure 1 is a summary of the RIFLE classification of acute kidney injury.

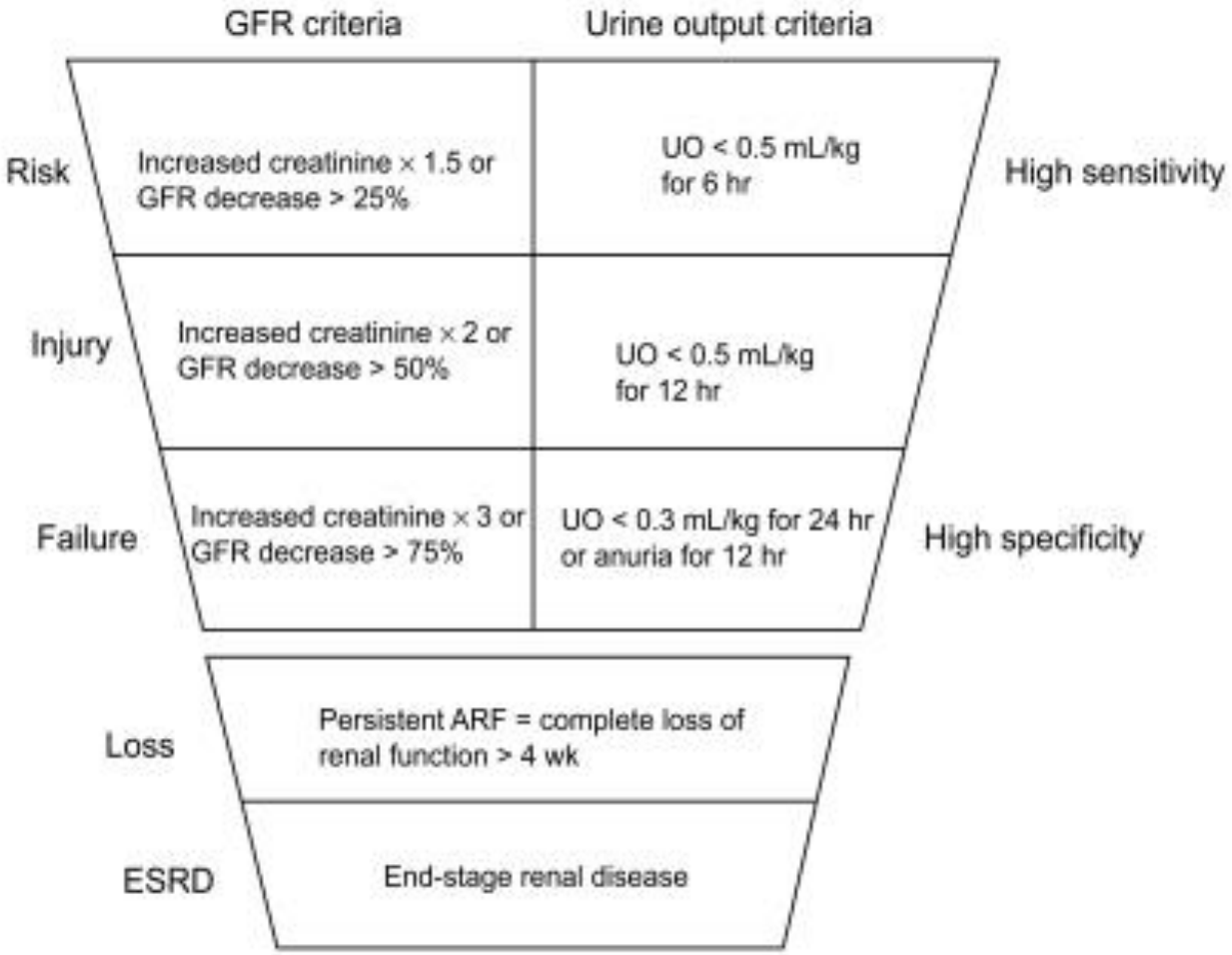


Figure 2.1: RIFLE classification of acute kidney injury (25)

RIFLE was introduced by the Acute Dialysis Quality Initiative (ADQL) in order to define and stratify the severity of acute kidney injury (AKI). This system depends on the changes of serum creatinine levels, glomerular filtration rate and the urine output (26). Table 2.1 compares the RIFLE system and AKIN stages as revised by the AKI network (26).

Limitations of the RIFLE classification

It is a retrospective tool that uses the increase of serum creatinine levels and decrease in urine output from a hypothetical or unknown baseline value; these makers are not effective tools for monitoring kidney injury as they appear late after it has occurred and do not take into account the nature or area of the kidney that has been affected. The urine output can only be accurately assessed in patients using a urinary catheter and can also be affected by the use diuretics (26).

Table 2.1 Comparison of RIFLE and AKIN classification systems (26)**.**

SYSTEMS	**SERUM CREATININE CRITERIA**	**URINE OUTPUT CRITERIA**
RIFLE class		
Risk	Serum creatinine increase to1.5-fold OR GFR decrease >25% from baseline	Decrease to <0.5ml/kg/h for 6 hours
Injury	Serum creatinine increase to 2.0-fold OR GFR decrease >50% from baseline	Decrease to <0.5ml/kg/h for 12 hours
Failure	Serum creatinine increase to 3.0-fold OR GFR decrease >75% from baseline OR serum creatinine ≥4mg/dl with an acute increase of at least 0.5mg/dl.	Anuria for 12 hours
AKIN Stage		
Stage 1	Serum creatinine increase ≥0.3mg/dl of an increase to 1.5-2.0-fold from the baseline	Decrease to <0.5ml/kg/h for 6 hours
Stage 2	Serum creatinine increase > 2.0-3.0-fold from the baseline	Decrease to <0.5ml/kg/h for 12 hours
Stage 3	Serum creatinine increase > 3.0-fold from the baseline or serum creatinine ≥ 4.0mg/dl with an acute increase of at least 0.5mg/dl OR need for RRT	Decrease to <0.3ml/kg/h for 24 hours or anuria for 12h OR need for RRT

2.3.2 Acute kidney injury

The prevalence of AKI is 16.3% among patients with sepsis patients in sub-Sahara Africa. This is mainly due to infectious diseases like tuberculosis and HIV/AIDS. Acute kidney failure (AKF) affects about 3-7% of hospitalized patients and about 25-30%of intensive care unit patients (26).

Rifampicin is an important drug in the treatment of TB although it causes mild to moderate ADRs and is known to cause AKI which mainly occur in patient who were previously exposed to rifampicin or on intermittent anti-tuberculosis regimen; 0.1% of patients on rifampicin develop AKI(27)

Renal tuberculosis is among the most common form of extra pulmonary tuberculosis which can led total loss of kidney function. This may occur as a result of previous pulmonary tuberculosis infection and the patients can present with acute or chronic kidney failure (28).The older population is the most commonly affected by drug induced AKI and have a very poor rate of renal recovery (28).

The link between tuberculosis and CKD was fast reported in 1974(28). Chronic kidney disease is a progressive degeneration of the renal function over a period of time; globally most CKD cases progress to end stage renal disease (ESRD) with a prevalence rate of 6.9% CKD stage 3-5 and 11.9% for stage 1-5(28).

Chronic kidney disease is common among low-income population with a significantly high rate of co-morbidity of other noninfectious and infectious diseases. Drug induced interstitial nephritis is common with anti-tuberculosis treatment. For patients with advanced stage of CKD that are on tuberculosis treatment and medications will require a dose adjustment or drug replacement (28).

Risk factors for acute and chronic kidney disease are majorly the patient demographics that predispose certain patients to drug induced kidney injury. The risk factors are old age, female sex and previous history of renal diseases (29).

2.4 Hematological injury induced by anti-tuberculosis drugs

Drugs can induce a wide range of hematological disorders that affects all blood components such as the white and red blood cells, platelets and the blood clotting factor (30). Anti-tuberculosis drugs cause hematological injuries (31). The main hematological injury due to anti-tuberculosis treatment is aplastic anemia of moderate severity caused by streptomycin (31). Other disorders include hemolytic and megaloblastic anemia and polycythemia (32).

In India, the prevalence rate of anti-tuberculosis induced anemia has been reported to be 74%, with that of leukocytosis and thrombocytopenia as 26% and 24% respectively. In South Africa the prevalence rate of thrombocytopenia is 23% and 87% for lymphopenia secondary to anti-tuberculosis treatment (31).

Anemia according to the WHO guideline is described as hemoglobin of <13g/dl for males and <12g/dl for the females and can be classified according to severity. Mild anemia is defined as hemoglobin levels of 11 ≤ 13 g/dl for males and 11 ≤12g/dl for the female. Moderate anemia is defined as hemoglobin levels of 8≤11 g/dl for both the male and the female patient with severe cases being hemoglobin levels of less than 8g/dl (33). Anemia is estimated to occur in 1-8% of the world population but has shown variation depending on the regions. In the Eastern sub-Saharan Africa, it is the leading cause of years lived with disabilities (YLDs). The prevalence of anemia among tuberculosis patients ranges between 30-94% and it associated with severe forms of tuberculosis (33).

2.4.1 Drug induced aplastic anemia

Aplastic anemia is a hematological disease caused by autoimmune mediated degeneration disorder of the hematopoietic cells. In drug induced aplastic anemia, the multipotent hematopoietic stem cells are destroyed which leads to reduction in the number of circulating neutrophils, platelets and erythrocytes (34). Aplastic anemia is the main hematological injury of the anti-tuberculosis medication. Pancytopenia associated with aplastic anemia has been reported on patients who are on tuberculosis treatment which is caused by the idiosyncratic reaction to streptomycin (35).

Symptoms of drug-induced aplastic anemia include fatigue, weakness, pharyngitis, chills and fever. These symptoms may appear from a few days of taking the suspect drugs to even months from the day of initiation of treatment (34).

The pathogenic mechanism of drug-induced aplastic anemia is the generation of metabolites that bind to the DNA and protein receptors leading to failure of bone marrow and toxicity to the hematopoietic cells. The genetic variation of the bone marrow explains the idiosyncratic nature of the drug induced aplastic anemia which is characterized by the latent period before the onset of anemia and also the continuation of the bone marrow damage even after the drug has been discontinued (34).

2.4.2 Drug induced megaloblastic anemia

Megaloblastic anemia is a disease characterized by hematopoietic cell changes and unproductive hematopoiesis due to synthesis of defective nucleoproteins. It can be acquired or congenital because of deficiency in folic acid and cobalamin (vitamin B_{12}). It is reported that due to the abnormality in the replication process of the RNA synthesis or DNA assembly it can lead to megaloblastic anemia (34).

Diagnosis of megaloblastic anemia determined by measurement of folate and vitamin B_{12} levels. Some drugs can cause deficiency in the folate and vitamin B_{12} through the destruction of the vitamins and competitive reduction of the enzymes for the folate and vitamins. Drugs that cause megaloblastic anemia can be classified into drugs that alter the purine and pyrimidine metabolism process, drugs that interfere with the metabolism of folic acids and its absorption process and those that inhibit the ribonucleotide reductase (34). The treatment of megaloblastic anemia is by withdrawing the causing drug and ensuring adequate intake of folic acid and vitamin B_{12} (34). Megaloblastic anemia has been reported which is associated with anti-tuberculosis treatment due to the deficiency of vitamin B_{12}. Amino salicylic acid, isoniazid and cycloserine are some of the anti-tuberculosis drugs that can cause megaloblastic anemia (34).

Hemolytic anemia

Hemolysis is the process of premature destruction of the Red Blood Cells (RBCs) and can cause an abnormality or defective red blood cells. Drugs can induce hemolysis process, which can be either intravascular or extravascular. The most common symptoms can be malaise, pallor, fatigue and shortness of breath. Withdrawal of the offending drug is the only treatment for hemolytic anemia because most cases are mild. Rifabutin and streptomycin are some of the anti-tuberculosis

that are known to cause immune hemolytic anemia (34). Immune hemolytic anemia associated with tuberculosis treatment has an incidence rate of 1-3 per 100000 population per year (36).

2.4.3 Drug induced Thrombocytopenia

Thrombocytopenia is caused by a drastic destruction of platelets when a susceptible patient takes the offending drug. It is an uncommon side effect of anti-tuberculosis medication but can be a life-threatening ADR (37) (38). Drug induced thrombocytopenia should be suspected in patients presenting with thrombocytopenia of unknown cause which is life threatening (37).

2.4.4 Immune thrombocytopenia

Immune thrombocytopenia is an acquired thrombocytopenia that is caused by immune destruction of platelets, with platelet count of below 100 $x10^9$/L and can be present in both adult and children (39). In adults, immune thrombocytopenia is mostly chronic; these cases are considered to be primary but most of them are secondary to other coexisting conditions (38).

Drug induced immune thrombocytopenia (DITP) is idiosyncratic to a drug reaction and can occur after 5 to 10 days after the beginning of a daily exposure to the offending drug, or within hours after re-exposure to an occasionally taken drug over period of time (40).

2.5 Drug induced Liver injury (DILI)

2.5.1 Epidemiology of drug induced liver injury

Drug induced liver injury can either be non-idiosyncratic or idiosyncratic, epidemiological studies have suggested that about 20 cases per 100000 persons of DILI occur annually (41). But the true incidence of DILI is not well known because of the difficult in attributing it to a single drug(41) . DILI has become an important drug safety issue and has led to the withdrawal of some drugs from the market (42).

Drug induced liver injury can be classified as hepatocellular, cholestatic or mixed injury. Hepatocellular injury is marked by elevation of the ALT levels, while cholestatic injuries are associated with the increased levels of ALP or elevated levels of ALT/ALP ratio of <2 and can manifest with jaundice and pruritus because of bilirubin retention, and the mixed injury has increased levels of both the ALT and ALP with the ALT/ALP ratio of between 2 and 5 (43).

Liver injury is a major ADR of tuberculosis treatment and it is a significant problem in patients with chronic liver disease. Drug induced liver injury (DILI) can lead to drug induced acute liver failure (DIALF). This can occur in all age groups and the liver is the most affected organ since it plays a very important role in drug metabolism and detoxification (44).

Tuberculosis treatment causes about 58% of cases of DILI and contributes to 5.7% of all the patients who develop acute liver failure. Drug induced liver injury occurs in 2-28% of all the patients on anti-tuberculosis treatment (45). DILI may occur directly as a result of the drug toxicity which can be due to accumulation of metabolites or indirectly as a result of an immunological reaction to the anti-tuberculosis drugs (46).

2.5.2 Drug induced Liver injury (DILI) in tuberculosis

Rifampicin and isoniazid are the most common causes of anti-tubercular drug induced liver injury (ATDILI) among the tuberculosis drugs, and have a latent period of between 1 week and 12 months. Patients may present with a variety of symptoms that mimic both acute and chronic liver injury like nausea and vomiting, yellow discoloration of the skin, upper abdominal pain and anorexia (47). Hepatocellular injury is normally identified by the elevation in serum aminotransferase with a ratio of ALT/ALP that is greater than 5 and sometimes accompanied by elevated levels of total bilirubin (TBIL) (48).

Rifampicin may also interfere with the excretion of bilirubin, which can lead to hyperbilirubinemia without the elevation of transaminases. Rifampicin in a multidrug regimen increased the prevalence rate of DILI from 1.6% to 2.6% in adult patients (17). Recovery of Anti tuberculosis drug induced liver injury usually occur once the treatment with the suspected drug is stop before severe liver injury occurs (48). Malnutrition, low body weight are risk factors for DILI (48). Older patients of 35 years and above are 4 times more likely to develop DILI, although all the age groups are at risk of developing DILI. Chronic liver disease, like hepatitis B and C, and HIV infections increase the chances of developing drug induced liver injury (46) (49).

2.6 Conceptual framework

The conceptual framework presents the three key outcomes of interest in this study, the renal injuries, hepatic injuries and the hematological injuries as highlighted in the **Figure 2.1**. The risk factors include gender, age, smoking and alcohol status. These risk factors have been identified in various studies (50–52). In addition, the conceptual framework gives the classification and case definition for hepatic, renal and hematological injuries (53–55). In the case of renal injury, the case definition was obtained using the RIFLE classification (56)(26).

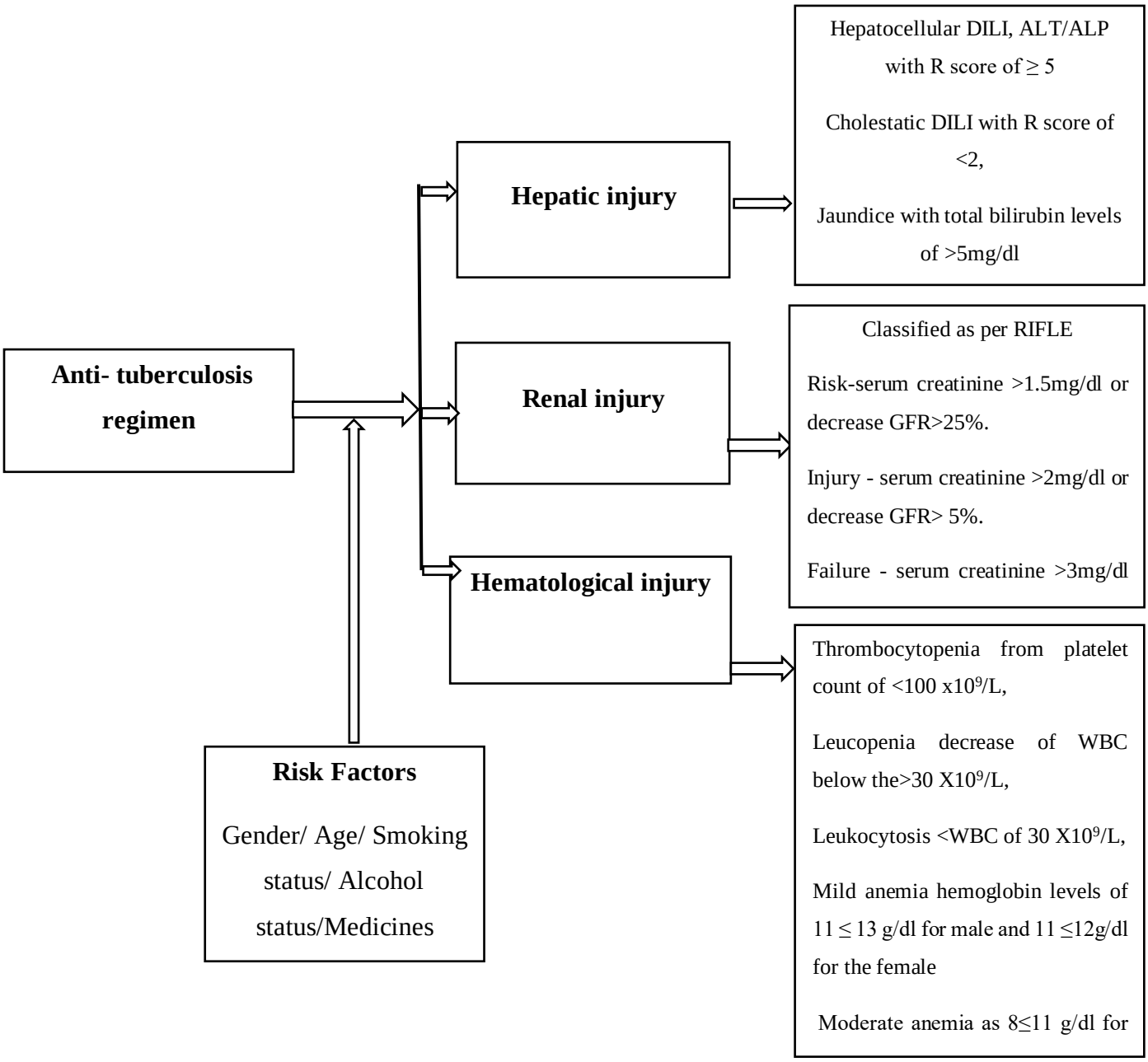


Figure 2.2: Conceptual framework for the risk factors for hematological, renal and kidney injury in patients on anti-tuberculosis medications

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a retrospective cross-sectional study, which involved data analysis collected by retrospective review of tuberculosis patient files at Kenyatta National Hospital.

3.2 Study site

The study site was Kenyatta National Hospital, which is the largest public referral hospital in Kenya, established in 1901, and it operated as a department of the Ministry of Health until 1987 when its status changed to a state corporation. The hospital has grown over the years to its present capacity of 2000 beds and attends to annual average of over 70,000 inpatients and 500,000 outpatients. KNH has a tuberculosis clinic that attends to about 3600 patients a year, with 5% of these patients admitted at the hospital and this makes the hospital with the highest number of hospitalized tuberculosis patients in Kenya.

3.3 Study population

The study population was tuberculosis patients admitted at Kenyatta National Hospital who had been on TB therapy between December 2016 to December 2020.

3.3.1 Eligibility criteria

Inclusion Criteria

Participants were included in the study if they were admitted at KNH between December 2016 and December 2020 with a documented diagnosis of tuberculosis.

Exclusion criteria

Participants were excluded if they were patients with incomplete files, and were co-infected with HIV. This is because such patients often have multiple co-morbidities and on a number of drugs that could confound the findings.

3.4 Sample size

The Cochrane formula (57), described in the **Equation 1** was used for sample size computation because this was a descriptive cross-sectional study. Studies conducted around the globe found the prevalence of various side effects of anti-tuberculosis treatment range from 8% to 85% (55)**.** Therefore, 85% prevalence level was used for sample size computation.

Equation 1: Cochrane Formula for sample size computation

$$N = \frac{Z^2 * p(1-P)}{D^2}$$

Where:

Z= z statistic for a 95% level of confidence which is 1.96.

P= estimated prevalence of side effects anti-tuberculosis medication.

D= level of precision to be used in the study; set at 5%.

Taking 85%, as the prevalence rate for the side effects of anti-tuberculosis medication, the calculated sample size was:

$$\frac{(1.96)^2 * (0.85) * (1-0.85)}{(0.05)^2} = 196$$

Given the population is finite, the Cochrane adjustment for finite population was applied using the formula prescribed in **Equation 2**.

Equation 2: Cochrane adjustment for a finite population

$$Na = \frac{nr}{1+\frac{nr-1}{N}}$$

Where:

Na is the adjusted sample size.

nr is the original required sample size.

N is the assumed population of the hospitalized Tb patients.

If the assumed number of hospitalized tuberculosis patients per year is 180 (58), the adjusted sample size was

$$Na = \frac{196}{1+\frac{196-1}{360}} = 96$$

Therefore, 96 patient records were reviewed.

3.5 Sampling method

A written application was made to KNH records department to get access to all filed tuberculosis patients records from December 2016 to December 2020. The records for hospitalized TB patients within the study period were screened for eligibility to ensure that they met the inclusion criteria.

Unique codes were then assigned to the individual files to conceal the identity of the patients. 384 files met the eligibility criteria and formed the sampling frame. These files were then randomly assigned number 1 to 384, and systematic random sampling was done by obtaining the subsequent 4^{th} file until the targeted sample size was attained.

3.6 Data collection

The data was then obtained by abstracting participant's records, to get the social, demographic and clinical characteristics, information on full hemogram test, liver function tests and renal function tests as per the data extraction tool in Appendix A.

3.7 Case definition

The guidelines for assessment of DILI (54) was used. Regarding the liver, the outcome of interest was the severity of liver injury, measured by the fold elevation of ALT levels. The AST:ALT ratio of> 2 was used to categorize the patients as having alcoholic liver disease or non-alcoholic. Simple elevation of either bilirubin or indirect bilirubin was used to confirm cholestatic liver injury, while jaundice was associated with elevated total bilirubin levels of at least twice the upper limit normal of <3mg/dl or bilirubin levels of >5mg/dl.

Regarding hematological disorders, anemia was the main outcome of interest, and was determined from the hemoglobin levels. Patients with hemoglobin (Hb) of less than 12g/dl were considered anemic. The severity of anemia was categorized as per the WHO guidelines (53) as summarized in **Table 3.1**

Table 3.1 Severity of anemia as per the WHO guidelines(53)**.**

	MALE	**FEMALE**
Anemia	Hemoglobin of <13g/dl	Hemoglobin of <12g/dl
Mild anemia	Hemoglobin levels of 11 ≤ 13 g/dl	Hemoglobin levels of 11 ≤ 12 g/dl
Moderate anemia	Hemoglobin of 8≤11 g/dl	Hemoglobin of 8≤11 g/dl
Severe anemia	Hemoglobin levels of less than 8g/dl	Hemoglobin levels of less than 8g/dl

Thrombocytopenia was inferred as a platelet count of <100 $x10^9$/L. An elevation of white blood cell count of >30 $X10^9$/L indicated the presence of leukocytosis while a decrease of WBC below the>30 $X10^9$/L was used to define leucopenia (56)(57), and a decrease in the absolute number of neutrophils below the normal cell count of 1500cells/mm^3 indicated neutropenia.

Regarding the renal injury, the outcome of interest, was the serum creatinine levels, urea level and the potassium ions, glomerular filtration rate and urine output measured through urinalysis. The severity of the renal injury was determined based on RIFLE classification of Acute Kidney injury (AKI

Table 3.2 RIFLE classification of Acute Kidney injury (AKI)(61)**.**

	GRF criteria	**Urine output**
Risk	An increase of serum creatinine levels of more than 1.5mg/dl, a decrease of glomerular filtration of more than 25%	Less than 0.5ml/kg per hour over a period of six hours.
Injury (mild AKI)	An increase of serum creatinine levels of more than 2mg/dl with a decrease of glomerular filtration of more than 50%	Less than 0.5ml/kg per hour over a period of 12 hours
Failure (severe AKI)	An increase of serum creatinine levels of 3mg/dl and decreased glomerular filtration of more than 75%	Less than 0.3ml/kg per hour over a period of 24 hours.

3.8 Study variables

The main outcome variables for logistic regression were hematological injury, renal injury and liver injury. Three logistic regression models were fitted, one for each outcome variable. Ordinal logistic regression was used. The covariates for regression analysis were the predictors like age, gender, anti-tuberculosis regimen, pyridoxine use, alcohol and smoking status. The comorbidities of interest were the HIV status and the hypertension.

3.9 Data management

The data was collated in Microsoft Excel (2013) and data cleaning was done. The data was exported to STATA version 13 software (Stata Corp USA) for analysis. The data was stored in password-protected files and a backup was created on a separate hard drive as well as on cloud computing to prevent loss the data.

3.10 Data Analysis

The Shapiro-wilk W test was used to determine if the conditions variable were normally distributed. Given that most continues variable were not normally distribute they were summarized as the median and interquartile range and clinical characteristics were summarized through frequencies and percentages for categorical variables like gender, marital status, smoking status, TB regimen, pyridoxine use, while numerical data like age was summarized using means and corresponding standard deviations or medians and their corresponding interquartile ranges. To compare the laboratory vales at baseline and after treatment initiation the non-parametric Wilcoxon signed rank test was done. Composite variables were created to measure the prevalence of hematological, renal and liver toxicity. Chi Square test /Fisher's Exact test was used to test for association between individual demographic/clinical characteristics and hematological, renal, and liver toxicity.

Binary logistic regression and generalized linear models were fitted to identify potential predictors of the outcomes. All the statistical tests were carried out at 95% confidence levels.

3.11 Ethical considerations

Approval to carry out the study was granted by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (**KNH/UON-ERC**) study approval number **P452/08/2020**. The scanned copy of the letter of approval is attached as **appendix A** on **page 85**.

The requirement for informed consent from the patients was waived since this was a retrospective cross-sectional study that involves retrieval of data from patient files at the records department of KNH. However, the study made use of codes instead of patient names to ensure confidentiality. Data collected was stored under lock and key. Electronic data was secured using password

CHAPTER FOUR: RESULTS

4.1 Participant recruitment and reasons for exclusion

During the study period, 1234 patients were admitted at Kenyatta National Hospital with tuberculosis. However, 571 were ineligible to participate in the study as they were co-infected with HIV and 192 were below the age of eighteen years; 87 participants had incomplete records. Three hundred and eighty-four participants met the eligibility criteria and formed the sampling frame. These files were then randomly assigned number 1 to 384 and systematic random sampling was done by obtaining 4th file until the targeted sample size of 96 was attained.

4.2 Socio-demographic and anti-tuberculosis medication used by the study participants

Table 4. 1 Socio-demographic and clinical characteristics of in-patients with tuberculosis

Variables	Category	Frequency	Percentage
Age	18 – 30 years	27	28.1
	31 – 42 years	34	35.4
	43 – 54 years	22	22.9
	>55 years	13	13.6
Sex	Male	70	72.9
	Female	26	27.1
Marital Status	Single	42	43.8
	Married	52	54.2
	Divorced	2	2.1
Alcohol Intake	Yes	27	28.1
	No	69	71.9
Smoking status	Yes	19	19.8
	No	77	80.2
Anti-Tuberculosis regimen	Linezolid, Levofloxacin, Pyridoxine	1	1.1
	RHZE, Pyridoxine	95	98.9
Had a Comorbidity	No	40	41.7
	Yes	56	58.3
Comorbidities	Diabetes	8	14.3
	Hypertension	8	14.3
	Pneumonia	6	10.7
	Empyema	5	8.9
	Pleural effusion	4	7.1
	Others	25	44.6

The baseline socio-demographic and clinical characteristics are summarized in Table 4.1. Most (35.4%) of the patients were aged between 31 – 42 years with only 13.6% aged above 55 years and majority (72.9%) were males. Slightly above half of the patients were married and most did not smoke (80.2%) or take alcohol (71.9%).

Almost all (98.9%) the patients were on rifampicin, isoniazid, pyrazinamide, ethambutol and pyridoxine. Only one patient was on a different type of anti-TB regime that had linezolid and levofloxacin. About half (58.3%) had other comorbidities. The most prevalent comorbidities among these patients were diabetes (14.3%), hypertension (14.3%), pneumonia (10.7%), empyema (8.9%), and pleural effusion (7.1%) among others (44.6%) as shown in Table 4.1.

4.3 Medications used by the patients

4.3.1 Use of antimicrobial agents in patients with tuberculosis in Kenyatta National Hospital

The two most widely used antibiotics were amoxicillin-clavulanic acid (30, 31.3%) and ceftriaxone (24, 25%). Collectively 26 patients (27%) were on a macrolide antibiotic. The frequency of use of other antimicrobial was low with 5 or less patients on these other antimicrobials. The patterns of antimicrobial use are summarized in Table 4.2. Antibiotics were the most widely used class of drugs.

Table 4. 2 Antimicrobial used by patients with tuberculosis in Kenyatta National Hospital

Medication	n(%)
Macrolide antibiotics	
Azithromycin	14(14.58%)
Clarithromycin	12(12.50%)
Penicillins	
Amoxicillin and clavulanic acid	30(31.25%)
Flucloxacillin and Amoxicillin/ clavulanic acid	2(2.08%)
Meropenem	2(2.08%)
Cephalosporins	
Ceftriaxone	24(25.0%)
Cefuroxime	3(3.13%)
Ceftriaxone and ceftazidime	1(1.04%)
Ceftazidime	1(1.04%)
Fluoroquinolones	
Ciprofloxacin	3(3.13%)
Levofloxacin	2(2.08%)
Metronidazole	13(13.54%)
Cotrimoxazole	5 (5.21%)
Antifungal	
Fluconazole	3(3.13%)
Itraconazole	1(1.04%)
Other antibiotics	
Clindamycin	3(3.13%)
Amikacin	1(1.04%)
Clindamycin and meropenem	1(1.04%)
Acyclovir	4(4.17%)

4.3.2 Other medicines used by patients with Tuberculosis in Kenyatta National Hospital

After antibiotics the four most widely used classes of drugs were: opioids particularly tramadol (21, 21.9%); proton pump inhibitors; and diuretics with 28 (9.1%) on furosemide and 15 (15.6%) on spironolactone. The most widely used PPI were omeprazole (17, 17.7%) and esomeprazole (21, 21.8%). These drugs were presumably used to manage pain, hyperacidity and edema or hypertension. The other drugs that were used are summarized on Table 4.3.

Table 4. 3 Drugs used by patients with tuberculosis in Kenyatta national hospital

Medication	n(%)	Medication	n(%)
Diuretics			
Spironolactone	15(15.63%)		
Furosemide	28(29.17%		
Mannitol	1(1.04%)	**Proton pump inhibitors**	
Beta-blockers		Omeprazole	17(17.71%)
Propranolol	1(1.04%)	Esomeprazole	21(21.88%)
Carvedilol	1(1.04%)	Esomeprazole and pantoprazole	2(2.08%)
Angiotensin receptor blockers		Lomeprazole	1(1.04)
Losartan	2(2.08%)	**Antiemetics**	
ACE inhibitors		Metoclopramide	13(13.54%)
Enalapril	2(2.08%)	Ondansetron	6(6.25%)
Nifedipine and Enalapril	3(3.13%)	**Laxatives**	
Enalapril and carvedilol	2(2.08%)	Lactulose	11(11.46%)
Enalapril and hydralazine	1(1.04%)	**Spasmolytic**	
Calcium channel blockers		Hyoscine	1(1.04%)
Nifedipine	1(1.04%)	**CNS drugs**	
Amlodipine	1(1.04%)	**Anticonvulsants**	
Other combinations of antihypertensives		Carbamazepine	1(1.04%)
Nifedipine, hydralazine, carvedilol and methyldopa	1(1.04%)	Phenytoin	1(1.04%)
Miscellaneous CVS drugs		Sodium valproate	2(2.08%)
Digoxin	4(4.27%)	Pregabalin	4(4.17)
Tranexamic acid	4(4.17%)	**Opioids**	
Warfarin	4(4.17%)	Dihydrocodeine	4(4.17%)
Claxen	35(36.46%)	Tramadol	19(19.79%)
Sildenafil	5(5.21%)	Morphine	3(3.13)
Atorvastatin	2(2.08%)	Morphine and Tramadol	2(2.08%)
NSAIDs		Paracetamol and codeine	1(1.04%)
Paracetamol	45(46.88%)	**Other CNS drugs**	
Meloxicam	3(3.13%)	Haloperidol	4(4.17%)
		Amitriptyline	2(2.08%)
Diclofenac	5(5.21%)	Artane	2(2.08%)
Aceclofenac	1(1.04%)	**Corticosteroids**	
Aspirin	1(1.04%)	Prednisolone	8(8.33%)
Ibuprofen	1(1.04%)	Dexamethasone	11(11.46%)
Iron syrup	13(13.54%	**Cetirizine**	2(2.1%)
Salbutamol	3(3.13%)		

Following miscellaneous drugs were used by only one individual each: zinc sulphate, neurobion forte

4.4 Baseline Prevalence of hematological, renal and liver disorders before treatment initiation among hospitalized adult patients with tuberculosis in Kenyatta National Hospital

Before treatment was started there was a very high prevalence of disorders presented in Figure 4.1. The most prevalent disorder was leucopenia (92, 97%, n=94) with nearly all patients having reduced white blood cell count. The second most prevalent disorder was anemia. Prevalence of pre-treatment anemia was 64.6% [95% CI: 47.3 – 73.3]

Jaundice was also highly prevalent (42, 54.6%, n=77); however, jaundice could be as a result of hemolytic anemia or liver disfunction. The prevalence of reduced renal function was high at 32.6%. The other disorders were thrombocytopenia and leukocytosis

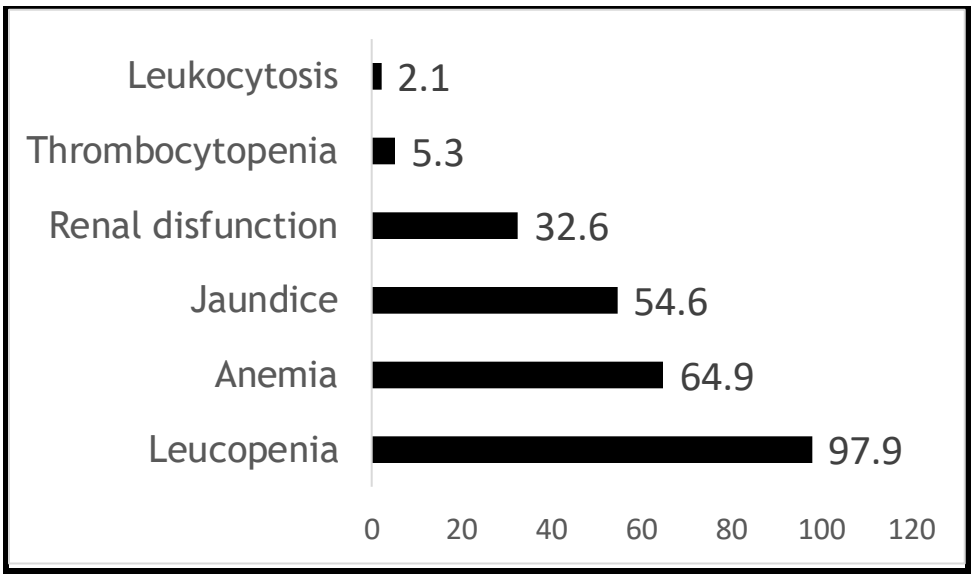


Figure 4.1 Prevalence of hematological, renal, and liver disorders in patients with tuberculosis with HIV co-infection before initiation of treatment

4.5 Changes in hematological profile post treatment

4.5.1Treatment progression and incidence of anemia

Patients were stratified according to the severity of anemia at baseline. The baseline prevalence of various types of anemia at baseline are presented in Figure 4.2. The relative prevalence of anemia by severity did not change significantly post treatment.

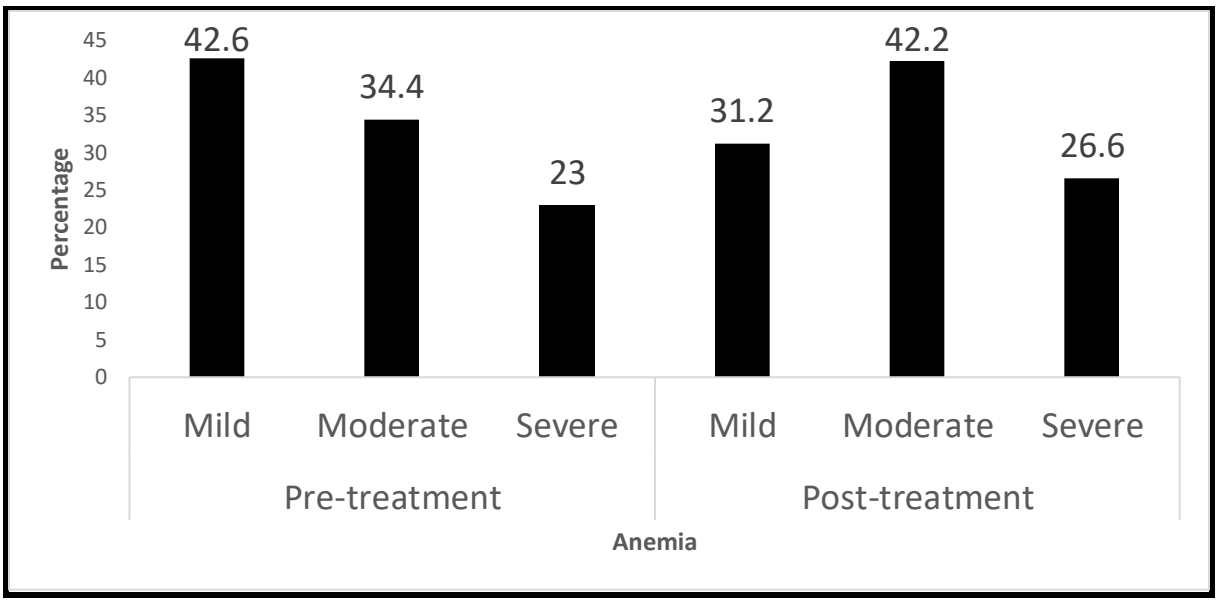


Figure 4.2 Severity of anemia pre and post treatment initiation

4.5.1 Incidence of anemia

The incidence of anemia was estimated from 34 patients who had normal hemoglobin readings at baseline. The lowest hemoglobin reading post treat for each of these patients was used to compute the incidence of anemia. The median hemoglobin levels at treatment initiation for this group was 14 mg/dl [IQR 13.4,15.3, n=34].

Out of the 34 patients one was lost to follow up. Fourteen out of the 33 patents developed anemia; the incidence of anemia post -treatment was therefore 42%. One patient developed severe anemia (3.0%), 7 developed moderate anemia (21.2%) while 6(18%) developed mild anemia.

4.5.2 Changes in hemoglobin levels in patient who had anemia at baseline

Fourteen patients had severe anemia at baseline. The highest hemoglobin levels post treatment was used to determine treatment progression. The median hemoglobin levels for the patients with severe anemia at baseline was 7.15[6.1, 7.4, n=14]. In this group of patients, none of the

hemoglobin levels normalized. However, 4 out of 14 showed some improvement in hemoglobin levels; of the 4, one improved to develop mild anemia (7.1%, n=14) and 3 improved to be classified as having moderate anemia (21.4%, n=14) and 10 remained in a state of severe anemia. For some patients the hemoglobin count declined further to a median of 5.95[IQR 4.8, 7, n=14].

Disease progression in patients with mild and moderate anemia at baseline

Four developed severe anemia while 12 patients improved. The median changes in hemoglobin levels pre- and post-treatment are summarized in Table 4.4.

Table 4. 4 Changes in hemoglobin levels from treatment initiation to lowest level post baseline

	Normal at baseline	**Lowest Post treatment**	**Difference**
Had normal Hb at baseline (g/dL)	14.4 [13.4,15.3] n=34	13.1 [11,14.9] n=33	-1.7 [-3.1, -0.400] n=33 **(p<0.001)**
Mild to moderate anemia at baseline (g/dL)	11.05 [9.85,11.85] n=48	10.8 [9.2,12] n=42	0 [-0.5,0] n=41 **(p = 0.017)**
Severe anemia (g/dL)	7.15[6.1,7.4] n=14	5.95[4.8,7] n=14	-0.500 [-1.2, 0.900] n=14 (P =0.207)

4.5.3 Factors affecting hemoglobin levels post treatment amongst patients who had normal levels at baseline

Generalized linear modeling was done to identify the determinants of the highest hemoglobin levels post treatment regardless of the severity of anemia at baseline. The generalized linear modeling was selected because the distribution of the highest hemoglobin levels was skewed

therefore a gamma distribution was assumed. The outcome variable was the reciprocal of the highest hemoglobin levels. Only variables for which the p-value was less than 0.3 were used for model building to arrive at the most parsimonious model. The only variables that were included in the most parsimonious model were, treatment with iron syrup (Ranferon™), paracetamol, cephalosporin, initial hemoglobin levels and gender as shown in Table 4,5

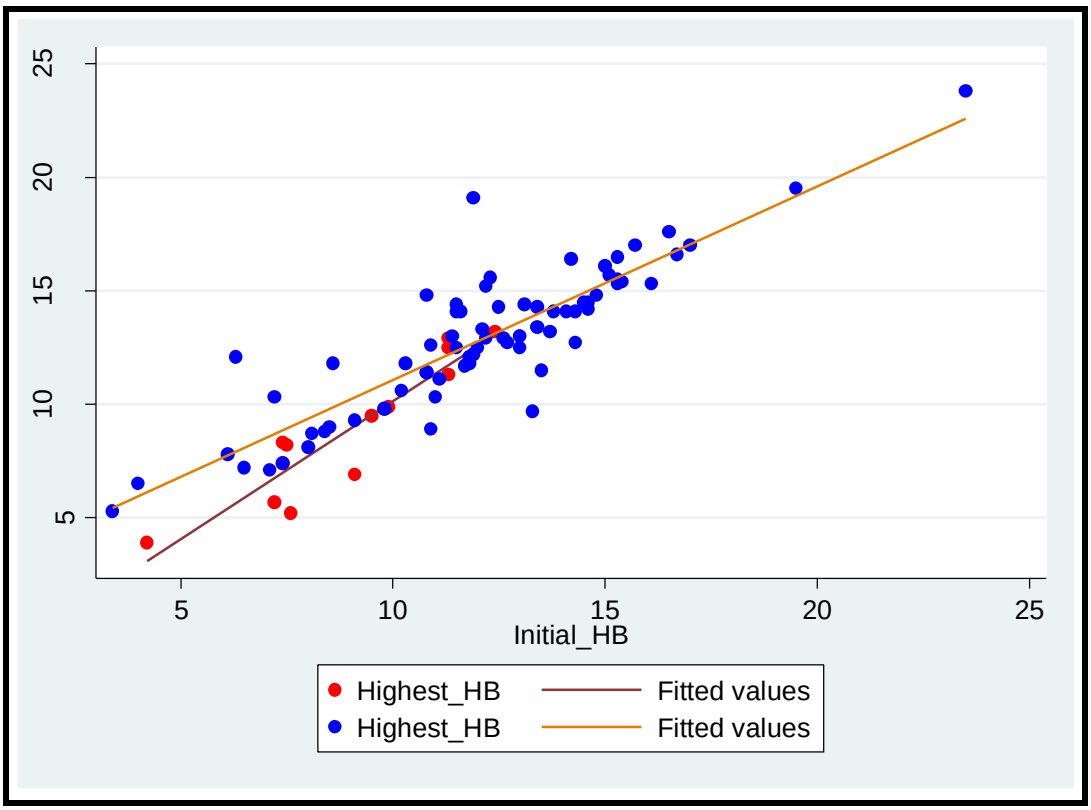
Table 4. 5 Generalized linear regression modelling to identify variables associated with the reciprocal of highest hemoglobin levels after treatment initiation in patients with Tb at Kenyatta National Hospital

Variable	**Crude β- Coefficient (95% CI)**	**P- value**	**Adjusted β-Coefficient (95% CI)**	**P- value**
Initial Hb levels at baseline			-0.005(-0.006, -0.005)	**<0.001**
Aldactone	-0.007(-0.020, 0.005)	0.263	-	-
Corticosteroids	-0.006(-0.012, 0.001)	0.077	-	-
Macrolide antibiotics	-0.007(-0.014, -0.001)	**0.038**	-	-
Paracetamol	-0.011(-0.021, -0.001)	0.025	-0.007(-0.012, 0.002)	**0.010**
Ranferon	0.035(0.018, 0.052)	<0.001	0.014(0.003, 0.025)	**0.012**
Cephalosporin antibiotics	0.004(-0.002, 0.01)	0.160	-	-
Antiemetics	0.005(-0.004, 0.013)	0.303	-	-
Sildenafil	-0.014(-0.032, 0.003)	0.114	-	-
Warfarin	0.026(-0.004, 0.057)	0.090	-	-
Cotrimoxazole	-0.013(0.031, 0.004)	0.132	0.012(0.002, 0.023)	**0.022**
Anticonvulsants	-0.004(-0.013, 0.004)	0.318	-	-
Other antibiotics	0.007(-0.003, 0.016)	0.159		
Statins	0.021(-0.019, 0.061)	0.308		
Digoxin	0.015(-0.012,0.042)	0.281		
Cetirizine	0.054(0.002, 0.107)	0.041		
Mannitol	-0.019(-0.055, 0.015)	0.272		
Lactulose	-0.006(-0.021, 0.008)	0.397		

From the records only 13 participants were treated with Ranferon™ from the most parsimonious model there was a negative association between the use of Ranferon™ and the hemoglobin levels. We attributed this finding to the indication by co-founding. In this type of bias, the indication for the drug leads to a false association between the drug the indication. It seemed that Ranferon™ was given mainly to a subset of patients with severe anemia thus creating the false indication that

Ranferon™ was associated with low hemoglobin levels. Unexpectedly use of paracetamol was positively associated with the increased hemoglobin levels.

The scatter diagram in Figure 4.3 shows a strong positive correlation between the baseline hemoglobin(g/dL) reading and the highest hemoglobin reading.



Red dots represent patient treated with iron syrup. Blue dots are those that did not get treated with iron syrup.

Figure 4.3 Scatter diagram for the relationship between baseline and the highest hemoglobin levels in patients with tuberculosis

4.6 Changes in white blood cells counts

As presented in Figure 4.4, the prevalence of leukopenia at treatment initiation was very high at 40% and only 25.5% of patients has normal levels.

Prevalence of leucopenia and leukocytosis at baseline

Generally, there was a decline in white blood cell count from baseline and the values post treatment. At baseline 55 (57.3%) participants had white blood cell counts that were within the normal baseline; 30 participants (31.3%) had leukocytosis which. Eleven (11.5%) had leucopenia. The median changes in the WBC counts are summarized in Table 4.6. The difference between the initial and highest WBC count posttreatment was statistically significant (p=0.007).

Table 4. 6 Changes in white blood cell count from baseline and post treatment.

	Initial reading at baseline	**Lowest reading Post treatment**	**Highest reading post treatment**
White blood cells (10^9/L)	8.51[5.625,12.04] n=96	6.005[4.645,8.625] n=88	9.5[6.59,13.45] n=88
Prevalence of leukopenia (n(%))	11(11.5%) n=96	26 (29.6%) n =88	5 (5.7%) n =88
Within normal range (n(%))	55(57.3%)	49(55.7%)	56(63.6%)
Prevalence leukocytosis (n(%))	30(31.3%)	13(14.8%)	27(30.7%)
Difference between highest WBC and initial value		-	0 [-0.765, 2.93] n=88 (**p= 0.036**)
Difference between lowest WBC and initial value		-1.66 [-4.18, 0] n=88 **(p=<0.001)**	-

4.6.1 Progression of patients who had leucopenia and leukocytosis at baseline

At baseline the prevalence of leucopenia was 11(11.5%). Out of the 11 patients with leukopenia at baseline, the WBC records for only 10 patients was available. Based on the highest white blood cell count post treatment 4 of these patients (40%) participants remained in a state of leucopenia and one (10%) developed leukocytosis while 5 **(**50%) participants had their state normalized. Table 4.7 summarizes the post-initiation levels of WBC of tuberculosis patients who leucopenia before treatment initiation**.**

Table 4. 7 Progression of patients who had leucopenia at baseline

	Initial reading at baseline	**Lowest Post treatment**	**Highest post treatment**
White blood cells (10^9/L)	3.6[3.44,3.88] n=11	3.675 [3.38,4.14] n=10	5.745[4.02,6.43] n=10
Prevalence of leukopenia	11(100%)	10(100%)	4(40%)
Within normal range	-	-	5(50%)
Prevalence leukocytosis	-	-	1(10%)
Difference between highest WBC and initial value	-	-	2.1[0,820,2.62] n=10
Difference between lowest WBC and initial value	-	0 [-0.4,0.110] n=10	-

4.7 Changes in WBC in Patients who had normal white blood cell counts at baseline

Those who had normal levels at baseline were 55 (57.3%) and 39 remained with normal levels while one developed leukocytosis (1.96%) and 13 (25.5%) developed leucopenia. Table 4.8 shows changes in white blood cells in patients who had normal white blood cells count before the initiation of tuberculosis treatment. Some patient experienced a decline in WBC and later recovered.

Table 4. 8 Changes in white blood cell counts in patients who had normal white blood cell counts at baseline

	Initial reading at baseline	**Lowest Post treatment**	**Highest post treatment**
White blood cells (10^9/L)	7.16[5.67,9.19] n=55	5.53[4.8,7.21] n=51	8.76[6.62,10.91] n=51
Prevalence of leukopenia	0	13(25.5%)	1(1.96%)
Within normal range	55(100%)	37 (72.6%)	39(76.5%)
Prevalence leukocytosis	0	1(1.96%)	11(21.56%)
Difference between highest WBC and initial value		-	0 [0,3.67] n=55
Difference between lowest WBC and initial value	-	-1.47[-2.75,0] n=55	-

4.7.1 Progression of patients who had leukocytosis at baseline

Thirty participants had leukocytosis at baseline but the post treatment records of most were not available. Out of these patients, the WBC of 12(44.4%) normalized and leukocytosis persisted in 12 (44.4%) as presented in Table 4.9.

Table 4. 9 Progression of patients who had leukocytosis at baseline

	Initial reading at baseline(10^9/L)	**Lowest Post treatment (10^9/L)**	**Highest post treatment (10^9/L)**
White blood cells (10^9/L)	16.78[12.19,63] n=30	10.1[7.82,12.21] n=27	11.66[9.68,19.15] n=27
Prevalence of leukopenia	-	3(11.1%) n=27	0
Within normal range	-	12(44.4%) n=27	12(44.4%) n=27
Prevalence leukocytosis	30 (100%) n=30	12 (44.4%) n=27	15 (55.6%) n=27
Difference between highest WBC and initial value	-	-	- 0.72 [-7.62,2.4] n=27 (p= 0.294)
Difference between lowest WBC and initial value	-	-6.27 [-9.5,0]] n=27 (p =<0.001)	-

4.7.2 The overall prevalence of Leukocytosis post treatment initiation

The prevalence or incidence of leukocytosis was computed from highest documented WBC post treatment. The prevalence stratified by the status of the patient at treatment initiation. The findings are presented in Figure 4.4.

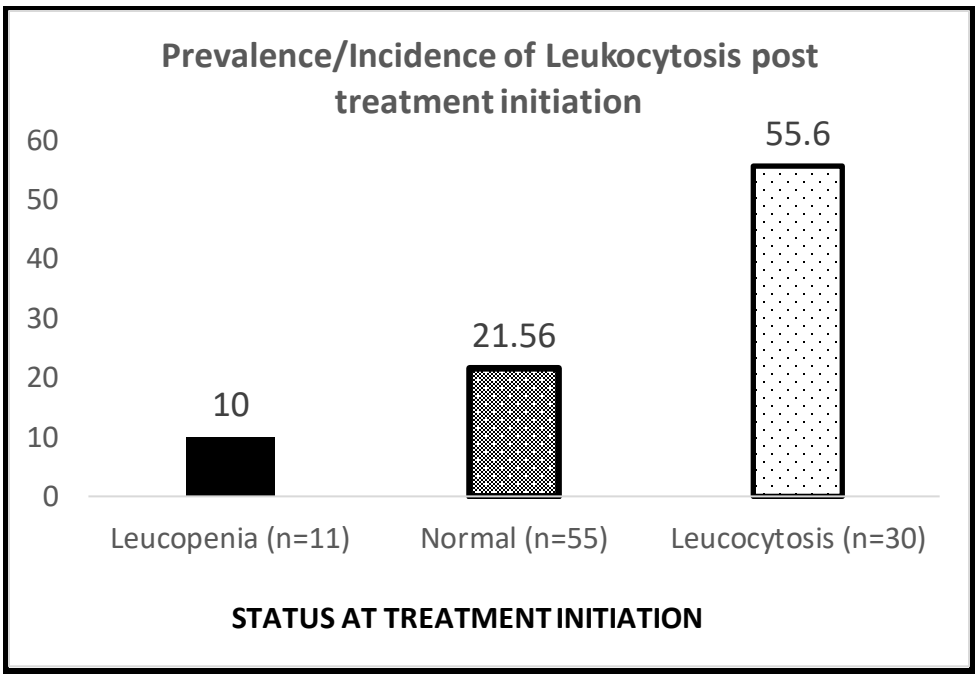


Figure 4. 4 Overall Prevalence of leukocytosis post treatment initiation stratified by status at treatment initiation

The prevalence of leukocytosis was dependent on the status at treatment initiation with the highest post treatment occurring amongst those who had leukocytosis at treatment initiation.

4.7.3 The overall prevalence of leukopenia post – treatment initiation

Figure 4.4 summarizes the prevalence of leukopenia post-treatment stratified by the status at baseline. The lowest WBC count post treatment was used to categorize patients as having leucopenia post treatment initiation. However, in the case of those who had leucopenia at the baseline, the highest WBC count was used to categorize patients as leucopenic post treatment.

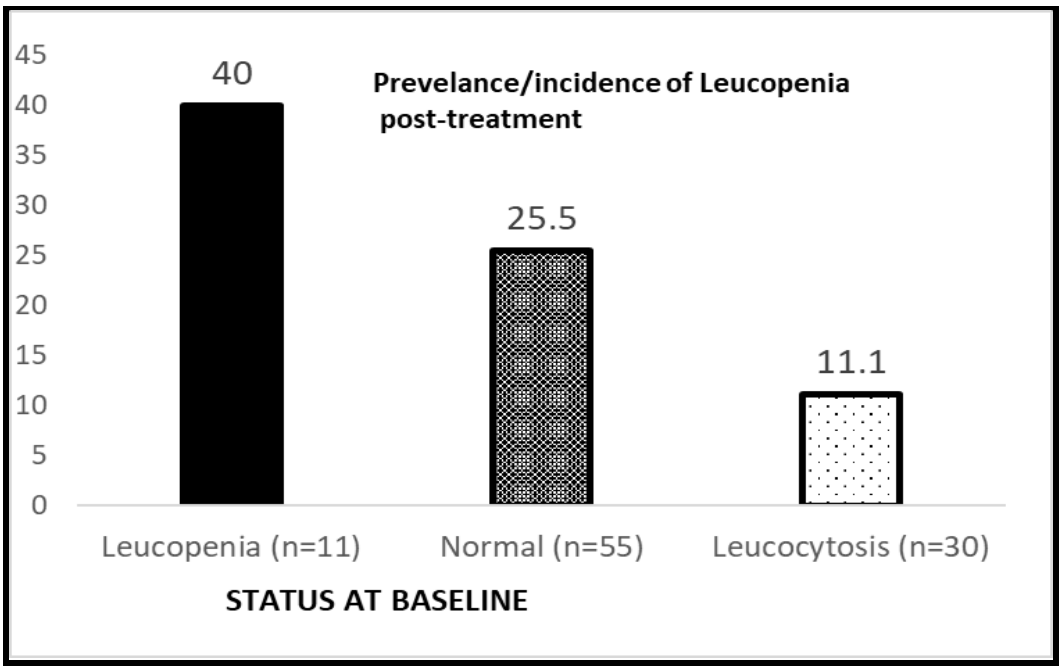


Figure 4. 5 The overall prevalence of leucopenia post treatment initiation stratified by the status at baseline

Those who had leukocytosis at treatment initiation had the lowest risk of developing leukopenia post treatment. There were 30 patients with leukocytosis at baseline and 3 of these were lost to follow up. As shown in the Figure 4.5, 11.1 % developed leukocytosis. The incidence of leucopenia amongst those with normal blood cell counts at baseline was 25.5%

4.8 Changes in Platelets levels

There were 5 cases of thrombocytopenia (5.2%) at baseline; post treatment the cases increased to 6 cases (6.8%). Among the 5 patients who had thrombocytopenia at baseline, for one patient, the levels decline by 21 units for three other patients the thrombocytes levels increased by 7, 19, 118 units post treatment; and one patient was lost to follow up. Only one patent completely recovered from thrombocytopenia while for the rest it persisted as the highest reading still show the platelet count of less than 100. Only one patient developed thrombocytopenia in the course of therapy

Table 4. 10 The median, interquartile rand and prevalence of thrombocytopenia

Sampling time	n	Median and interquartile range	Prevalence of thrombocytopenia	p-value
Baseline value	96	326[232.5, 471]	5 [5.25%]	
Lowest value post treatment	88	284.5[207,401]	6 [6.8%]	<**0.001**
Highest value post treatment	88	353[289,512.5]	3[3.4%]	**0.01**
Difference between baseline and highest reading	88	-29.5[-111,0]		-
Difference between baseline and the highest reading	88	0 [-3,81.5}		-

For all subjects the decline in post treatment platelet levels was computed by obtaining the difference between the baseline reading and the lowest reading post treatment the findings are presented in the histogram in figure 4.3. The median decline was -29.5[-111, 0, n=88]. Fifty three out of the 88 patients (60.2%) experienced decrease platelet levels but for most patients this was not sufficient to result in thrombocytopenia.

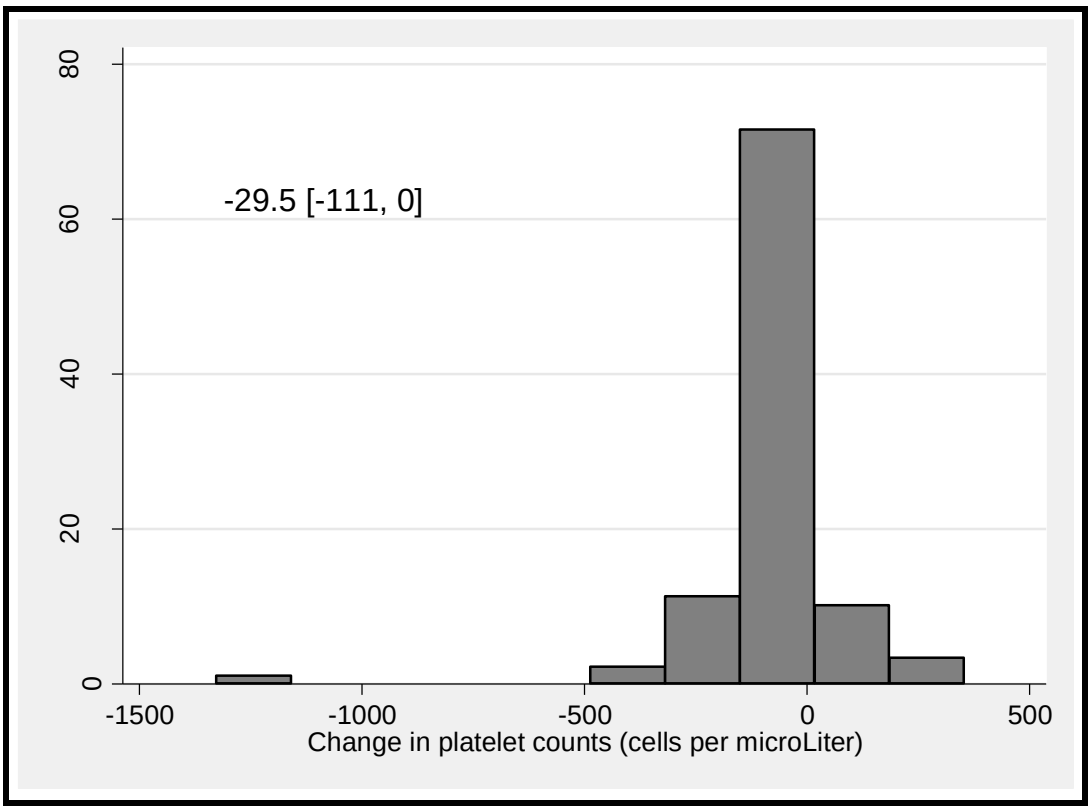


Figure 4.6 Changes in platelet count from baseline to lowest level post treatment initiation (n=88)

Regression analysis for determinants of thrombocyte levels post treatment.

Generalized Linear Regression analysis was done to identify key determinants of platelet levels post-treatment. The results are presented in Table 4.11. There was a weak positive correlation between age and platelet count. This however lost significance after adjusting for cofounding.

The most parsimonious model had the drugs cetirizine, pregabalin and tranexamic acid. Cetirizine and tranexamic acid were found to be positively associated with the platelet levels. Tranexamic acid is used as an antidote for fibrinolytic agents and is indicated to patients with excessive bleeding while cetirizine inhibits stimulation of the immunoglobin E dependent mechanism of platelets.

Pregabalin was negatively associated with low platelet levels and can be attributed to the low platelet count on patients who were on pregabalin treatment.

Table 4. 11 Generalized linear regression modelling to identify variables associated with the reciprocal of highest platelet levels after treatment initiation in patients with Tb at Kenyatta National Hospital

Variable	β- Coefficient	p- value	Adjusted β-Coefficient (95% CI)	p-value
Aldactone	0.001(-0.0001, 0.0001)	0.095		
Lasix	0.0027(-0.0002, 0.0001)	0.336		
NSAIDs	0.0003(-0.0002, 0.0007)	0.207		
Paracetamol	-0.0002(-0.0007, 0.0002)	0.326		
Opioids	-0.0001(-0.0003,0.0001)	0.161		
Cephalosporins	0.0001(-0.0002, 0.0005)	0.348		
Claxen	0.0004(-0.0001, 0,001)	0.098		
Antiemetics	-0.0002(-0.0015, 0.0002)	0.368		
Pregabalin	0.0017(-0.0001, 0.004)	0.069	0.0016(-0.0001, 0.0034)	**0.070**
Sildenafil	0.0006(-0.0006, 0.002)	0.316		
Warfarin	0.0011(-0.0006, 0.003)	0.197		
Tranexamic acid	-0.001(-0.002, 0.0004)	0.002	-0.0011(-0.002, -0.0004)	**0.001**
Antihypertensives	0.0001(-0.0000, 0.0002)	0.291		
Artane	0.0005(-0.0002, 0.001)	0.364		
Cetirizine	-0.001(-0.002, -0.0004)	0.006	-0.0012(-0.002, -0.0004)	**0.002**
Zinc sulphate	0.0024(-0.002, 0.007)	0.288		

4.9 Changes in liver function

Markers of the liver function are summarized in Table 4.12. There was a general increase in ALT levels from a median of 21.5[IQR 13,32, n=62] at baseline to a median of 29[IQR15,45, n=43]. Assessment of the effects of treatment on the liver function was adversely affected by missing data since there was only 77 participants with records at treatment initiation and only about 55 to 58 records post-treatment.

Table 4. 12 Summary of liver function bio-markers at baseline and post-treatment initiation

	Baseline	**Lowest value post treatment**	**Highest value post treatment**
ALT(U/L)(median and IQR)	26[14,41] n=77	19[10,35] n=57	38[21,71] n=57
Fold elevation of ALT ULN=40	0.65[0.35,1.025] n=77	0.475[0.25,0.875] n=57	0.95[0.525,1.775] n=57
Difference from baseline value		0.757[0.503,1] n=56	1[1,1.813] n=56
AST levels(U/L)	34.5[24,54.5] n=76	27[16.3,44.5] n=56	44[29,97] n=57
AST to ALT ratio	1.433[0.945,2.175] n=76	1.170[0.756,2.333] n=55	1.336[0.884,2.065] n=56
Proportion with AST to ALT ratio >1	53(69.7%) n=77	33(60%) n=55	37(66.1%) n=56
Bilirubin levels (µmol/L)	5.4[3.5,8.1] n=77	4.7[2.7,8.9] n=58	7.65[5.1,15.7] n=58
Proportion with elevated bilirubin levels	6 (7.8%) n=77	4 (6.9%) n=58	10 (17.2%) n=58

Based on the fold elevation of the ALT levels (19.5%) of the patients had some form of liver injury; 6 (7,8%) had mild liver injury while 7(9.1%) had moderate injury and one (1.3%) had severe injury at baseline.

After treatment initiation the number of cases of mild, moderate and severe injury increased. Two patients developed severe liver injury in addition to the one that at baseline and one more participant developed moderate liver injury as presented in Table 4.13.

Table 4. 13 Severity of liver injury by fold elevation of ALT levels

Severity	At baseline (n=77)	At lowest value(n=57)	At highest value(n=57)
Grade 0 (normal)	62 (80.5%)	48(84.2%)	36(63.2%)
Grade 1 (mild)	6 (7.8%)	7(12.3%)	10(17.5%)
Grade 2 (moderate)	7 (9.1%)	1(1.8%)	6(10.5%)
Grade 3 (Moderate to severe)	1 (1,3%)	-	2(3.5%)
Grade 4 (severe)	1 (1.3%)	1(1.18%)	3(5.3%)

Types of liver injury inferred from the AST: ALT Ratio

At the baseline there was a very high prevalence of patients with high AST to ALT ratio (69.7%). The AST to ALT ratio was used to arrive at a tentative diagnosis of the type of liver injury using the criteria presented in the severity grading in drug induced liver injury from the clinical and research information on drug induced liver injury(62). The findings are presented in the Table 4.15 that is the grouping of patients with liver injury based on the AST to ALT ratio.

The AST:ALT ratio gave a higher prevalence of liver injury at baseline compared to the use of ALT alone. At baseline the most prevalent for of liver injury may have been alcoholic fatty liver injury, with a prevalence of 31.6% (24 participants out of 76). After treatment initiation the prevalence of cirrhosis remained relatively constant between 7,9 and 18,2%. However, using the lowest ALT value, the prevalence of hepatocellular injury almost doubled from 13.2% at baseline to 23.6%. Based on the AST:ALT ratio of greater than 5, five participants experienced acute liver failure as shown in Table 4.14.

Table 4. 14 Grouping of patients based on AST to ALT ratio and the suggested type of liver injury

Suggested type of liver injury (AST: ALT)	At baseline (n=76)	At lowest value(n=55)	At highest value(n=56)
Normal (<1.12)	26(34.2%)	24(43.64%)	21(37.5%)
Cirrhosis (1.12-1.5)	14(18.4%)	10(18.2%)	10(17.9%)
Hepatocellular injury (1.15-2.0)	10(13.16%)	3(23.64)	10(17.9%)
Alcoholic fatty liver disease or (2.0-5.0))	24(31.6%)	13(23.6%)	14(25.0%)
Acute liver failure (>5)	2(2.6%)	5(9.1%)	1(1.8%)

4.9.1 Change in liver function among those with normal ALT levels at treatment initiation

Using the highest ALT levels post treatment a total of 41 out of 57 developed some form of drug induced liver injury; 6 (14.3%) had Grade 1(mild) drug induced liver injury, 8 (19.1%) developed Grade 2 (moderate) injury, 11 (26.2%) developed Grade 3(moderate to severe) and 1 (2.4%) developed Grade 4 (severe) and was classified as having levels suggestive of acute liver failure. This is highlighted in Table 4.15.

Although these individuals had normal ALT level at treatment initiation the AST to ALT levels was suggestive of some form of liver disease at baseline. Table4.14 summarizes the suggested form of impaired liver disfunction from treatment initiation. Alcoholic fatty liver disease seemed to be the most prevalent type of disorder with a prevalence of (31.6%) followed by the cirrhosis that had a prevalence of (18.4%) while hepatocellular was (13.16%).

Table 4. 15 Change in liver function among those with normal ALT levels at treatment initiation

severity	At baseline (n=61)	At lowest value(n=57)	At highest value(n=57)
Grade 0 (normal)	19(31.2%)	14(34.2%)	16(38.1%)
Grade 1 (mild)	13(21.3%)	8(19.5%)	6(14.3%)
Grade 2 (moderate)	9(14.8%)	2(4.9%)	8(19.1%)
Grade 3 (Moderate to severe)	18(29.5%)	13(31.7%)	11(26.2%)
Grade 4 (severe)	4(3.3%)	4(9.8%)	1(2.4%)

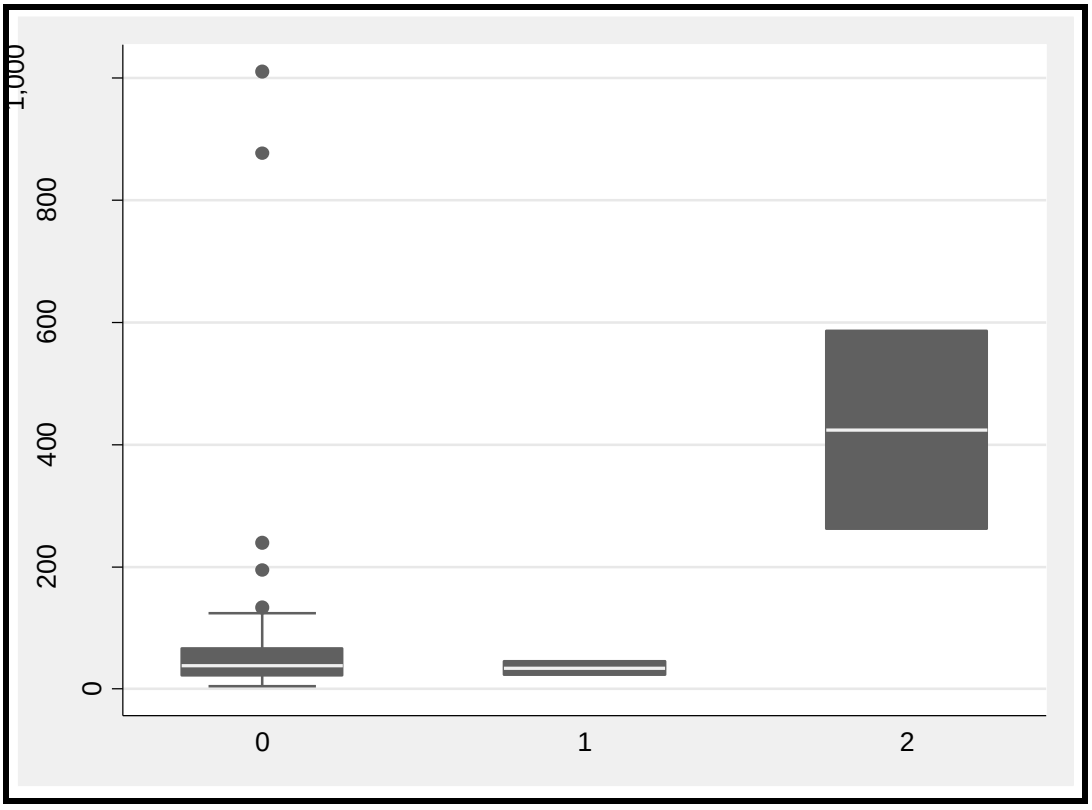
Determinants of the highest ALT levels post treatment initiation

Generalized linear regression modelling was done to identify variables that influenced the highest ALT levels after treatment initiation and the results are presented in Table 4.16

Table 4. 16 Generalized linear regression analysis to identify risk factors for elevated reciprocal of highest documented ALT levels in patients on tuberculosis medication.

Variable	β- Coefficient	P- value	Adjusted β-Coefficient (95% CI)	p-value
Fluoroquinolones	-0.005(-0.009, 0.000)	0.076	-0.005(-0.01, -0.0002)	**0.039**
Aldactone	0.112(-0.009, 0.032)	0.287		
Corticosteroids	0.006(-0.006, 0.019)	0.334		
Macrolide antibiotics	-0.003(-0.009, 0.002)	0.273		
Claxen	0.01(-0.003, 0.023)	0.140		
Antiemetics	0.009(-0.007, 0.025)	0.264		
Gender	0.011(-0.011, 0.056)	0.064		
Marital status	-0.011(-0.024, 0.002)	0.090		

Given that the most parsimonious model has fluroquinolones, a box plot was drawn to illustrate the effects of this class of drugs on the highest ALT levels post – treatment initiation. The findings are presented in Figure 4.7. As shown, patients on levofloxacin had very high ALT levels compared to those on other drugs.



Box plot of highest ALT levels post treatment for patients on fluoroquinolones (1=Ciprofloxacin, 2=Levofloxacin)
GLM was done with gamma distribution and inverse transformation of the ALT levels

Figure 4.7 Box plot of highest ALT levels post treatment for patients on fluoroquinolones

4.10 Renal injury

The prevalence of patients with compromised kidney function at baseline was 32.6% [95% CI: 23.4 – 43.3].

Table 4. 17 Classification of renal toxicity

RIFLE (n=8)	Risk (Stage 1)	3	37.5
	Injury (Stage 2)	3	37.5
	Failure (Stage 3)	2	25.0

The box plot on Figure 4.7 shows the no of patients who were on fluoroquinolones during the treatment period and recorded some change in the ALT levels post-treatment initiation. based on the highest ALT levels. Participants who were treated using levofloxacin had their ALT levels elevated compared to those that had ciprofloxacin.

4.10.1 Factors associated with renal injury.

The initial lab test at admission was used as the baseline to determine the renal profile of patient pre-treatment period. Table 4.18 shows the association between pre-treatment renal injury and age, sex, smoking status and alcohol intake.

Age, gender alcohol intake and smoking status were not significantly associated with pre-treatment renal injury. Males had high proportion (37.5%) of those with pre-treatment renal injury compared to females (18.2%). Compared to liver injury and anemia, in renal injury those who took alcohol and smokers had lower proportions with renal injury (29.2% and 31.2% respectively).

Table 4. 18 Association between pre-treatment renal injury and age, sex, smoking, alcohol

Pre-treatment renal injury				
Factor	**Category**	**Absent**	**Present**	**p-value**
Age	Mean (SD)	38.1 (13.7)	39.9 (13.9)	0.578[t]
Sex	Male Female	40 (62.5%) 18 (81.8%)	24 (37.5%) 4 (18.2%)	**0.095[c]**
Alcohol	No Yes	41 (66.1%) 17 (70.8%)	21 (33.9%) 7 (29.2%)	0.676[c]
Smoking	No Yes	47 (67.1%) 11 (67.8%)	23 (32.9%) 5 (31.2%)	0.901[c]
Comorbidity	Absent Present	22 (64.7%) 36 (69.2%)	12 (35.3%) 16 (30.8%)	0.662[c]

[t] *t-test*
[c] *Chi square*

Those with post-treatment renal injury were significantly (p=0.044) older (43 ±13.4 years) compared to those who didn't have post-treatment renal injury (36.4 ±13.4 years). Gender, alcohol, intake and smoking status were not statistically associated with post-treatment renal injury. Males had high proportion (41.5%) of those with post-treatment renal injury compared to females (25%). Compared to liver injury and anemia, those who took alcohol and smokers had lower proportions with post-treatment renal injury (33.3% and 35.7% respectively) as shown in Table 4.19.

Table 4. 19 Association between post-treatment renal injury and age, sex, smoking, alcohol

Post-treatment renal injury				
Factor	**Category**	**Absent**	**Present**	**p-value**
Age	Mean (SD)	36.4 (13.4)	43.0 (13.4)	**0.044t**
Sex	Male Female	31 (58.5%) 15 (75%)	22 (41.5%) 5 (25%)	0.193c
Alcohol	No Yes	32 (61.5%) 14 (66.7%)	20 (38.5%) 7 (33.3%)	0.676c
Smoking	No Yes	37 (62.7%) 9 (64.3%)	22 (37.3%) 5 (35.7%)	0.913c
Comorbidity	Absent Present	15 (57.7%) 31 (66.0%)	11 (42.3%) 16 (34.0%)	**0.662c**

[t] *t-test*
[c] *Chi square*

CHAPTER FIVE: DISCUSSION

This was a retrospective cross-sectional cohort study, which involved data analysis collected by retrospective review of tuberculosis patient files at Kenyatta National Hospital and sort to determine the prevalence of hematological, renal and liver toxicity among hospitalized adult patients on anti-tuberculosis medication at Kenyatta National Hospital. We also characterized the severity and the type of liver and renal toxicity among the hospitalized adult patients on anti-tuberculosis medication at KNH. The study also identified the risk factors associated with hematological, renal and liver toxicity.

The study was able to identify that fluoroquinolone and mostly levofloxacin which is the preferred as the safer drug for the treatment of multi drug resistant tuberculosis was significantly associated with elevated ALT levels.

From the social demographic characteristics of the study participant most of the patients were between the age of 31 and 42 years and majority of the participants were male at (72.9%). This clearly indicated that male patients were most predisposed to tuberculosis infection (63) **.**

Almost all the patients (98.9%) were treated with rifampicin, isoniazid, pyrazinamide, ethambutol and pyridoxine regimen which is the first line treatment regimen for the treatment of tuberculosis infection that is recommend by WHO (6).

The most prevalent comorbidities among these patients were diabetes mellitus (14.3%), hypertension (14.3%) and pneumonia at 10.7%. Type 2 diabetes mellitus (DM) has been on the rise in low- and middle-income countries that, also have high tuberculosis incidences. The prevalence of diabetes mellitus in tuberculosis have previously been found to be 12.3 % in Peru, 12.3% in Romania and 10.9 % in South Africa (64). Retrospective cohort studies explored the association between tuberculosis and hypertension found a significantly higher prevalence of

hypertension among tuberculosis patients. With some studies reporting the prevalence of hypertension in tuberculosis patients ranging from 0.7% to 38.3% (65)

Several studies have indicated that anemia is one of the most common hematological disorders in patients who are on tuberculosis treatment. It is both common on initiation of treatment and at the time of diagnosis of tuberculosis, with a prevalence of between 9.5% and 96%. Another study in Tanzania has indicated the prevalence of anemia in tuberculosis treatment to be 86% (35)(66). Patients who are anemic are more susceptible to infectious diseases including tuberculosis because of reduced immunity levels. A large proportion (of our study participants had anemia before initiation of the tuberculosis treatment (67). The prevalence of pretreatment anemia of our study was 64.9% while the post treatment anemia was 74.2% this indicated that some patients developed anemia after initiation of tuberculosis treatment and that some patients had already developed anemia even before the initiation of tuberculosis treatment. Studies indicate that the erythropoiesis process is suppressed by the inflammatory mediators caused by tuberculosis infections(68)

Normocytic normochromic anemia induced by antituberculosis treatment has been attributed to be the main source of anemia as a hematological injury in patients receiving tuberculosis treatment(69). The pre- and post-treatment anemia was managed by putting the patients on an iron supplement syrup (Ranferon™)

Thrombocytopenia has previously been reported as a result of anti-tuberculosis treatment, according to a study conducted in Nigeria on tuberculosis medication induced hematological abnormalities(35). Based on our study the post-treatment prevalence of leucopenia was (40%), and the prevalence of leukocytosis was (55.6%) while the prevalence of thrombocytopenia was (6.8%).

Drug induced hematological disorders can affect the whole spectrum of the blood system, affecting the red blood cells, white blood cells, platelets and the blood coagulation pathway. Rifampicin and isoniazid induced leucopenia has been reported in Japan while a study in South Africa reported 87% prevalence of lymphopenia was 87%, 23% thrombocytopenia (23%) and leucopenia (15%) as a result of tuberculosis treatment (35). Out of the 11 patients with leukopenia at baseline, the WBC records for only 10 patients was available. In 40 % of these patients, leucopenia persisted. Persistent leucopenia is often due to myelosuppression. Medications taken by TB patients that cause leucopenia include trimethoprim-sulfamethoxazole. Withholding of the offending agent or dose reduction generally corrects these hematologic abnormalities(70).

Patients on antituberculosis treatment have been reported to develop drug induced liver injury (DILI) with an incidence rate of 2.55% in China. There are several factors that affect the severity of DILI including old age, sex, and alcohol intake. A study found that patients who were put on rifampicin and isoniazid had an incidence rate of 0.8% with an increase to 2.8% on addition of pyrazinamide (71). At baseline, the most prevalent liver injury was alcoholic fatty liver injury, with a prevalence of (31.6%) 24 participants out of 76. After treatment initiation the prevalence of cirrhosis remained relatively constant between 7,9 and 18,2%. However, using the lowest ALT value, the prevalence of hepatocellular injury almost doubled from 13.2% at baseline to 23.6%.

The prevalence of renal injury was 37.0% after the initiation of tuberculosis treatment and the incidence of kidney injury was 11.6% (n-8). Among the 8 patients, 3 patients were in stage 1 (risk), 3 patients in stage 2 (injury) and 2 patients in stage 3 (failure) as per the RIFLE grading. Those with renal injury were significantly ($p=0.044$) older (43 ±13.4 years) compared to those who didn't have renal injury (36.4 ±13.4 years). Gender, alcohol, intake and smoking status were not statistically associated with pre-treatment renal injury. Out of the 8 cases who developed kidney

injury, 25% were classified to have had failure/stage 3. Most of the elderly patients on tuberculosis treatment are more likely to develop acute renal injury as a result of the continuous use of rifampicin which is one of the most common tuberculosis medications used in the standard antituberculosis regimen. Rifampicin has been known to cause AKI and a study in Taiwan reported a 7.1% incidence of AKI after the initiation of the standard tuberculosis treatment. The mean age of developing AKI was 61 years (72).

Pregabalin was negatively associated with low platelet levels, this drug is mainly used for the treatment of neuropathic pains. Literature shows that pregabalin can cause thrombocytopenia (73). From the study the thrombocyte levels seem to be significantly affected by the concurrent use of other drugs. Older patents were at a lower risk of developing thrombocytopenia because of the week co-relation between the highest platelet levels and age (coefficient of 0.02201).

Unexpectedly paracetamol was positively associated with increased hemoglobin levels, however no previous reports were found that indicated that use of paracetamol may improve hemoglobin levels, although paracetamol has recently been shown to cause endocrine disruption(74). While the bi variable analysis show that corticosteroids were positively associate with increased hemoglobin levels, this was attributed the suppression of the immune mediated hemolytic anemia(75).

Study Strengths and limitations

One strength of this study was the ability to collect baseline data on the status of the patients before TB therapy. However, during the study a number of challenges were encountered. Causality assessment was not done. The study also focused on inpatients yet it is known that a majority of TB patients are treated as outpatients. Most potential participants were coinfected with HIV which

made them ineligible to participate in the study. There was also missing patient data on the initial laboratory tests before the initiation tuberculosis as most of the patients did not have their weight recorded. A number of patients had history of self-medication and were on other forms of treatment prior to tuberculosis treatment while others were admitted due to other comorbidities. Renal classification using the urine output parameter was difficult since most of the patients were not put on catheter making it difficult to measure the urine output.

CHAPTER SIX: CONCULUSION AND RECOMMENDATIONS

6.1 Conclusion

This study was able to highlight that a number of tuberculosis patients exhibit more than one adverse drug reaction prior to diagnosis and initiation of tuberculosis treatment. Diabetes mellitus and hypertension also emerged as the most common comorbidities in patients on antituberculosis treatment. Anemia was the most common hematological injury in both the pre and post treatment period with more severer cases of anemia being reported in the post treatment. Pregabalin was implicated as a cause of thrombocytopenia post treatment while fluoroquinolone use was implicated as a cause of elevated ALT levels.

6.2 Recommendations

6.2.1 Recommendations for future research

The high pre-treatment anemia brings about the need for a research study establish the reason as to why most of the tuberculosis patients developed anemia before being the initiation of tuberculosis treatment and also establish the exact association of diabetes and hypertension in tuberculosis patients.

The role of corticosteroids in the elevation of hemoglobin should be investigated as they seemed effective in the prevention of immune mediated hemolytic anemia.

6.2.2 Recommendations for policy and practice

Generally, men should be considered as being a high-risk group when it comes to tuberculosis infection and policies should be made that actively target their screening and diagnosis, this will help in early detection and prevent the spread of tuberculosis. Anemia is significantly associated with the infection of tuberculosis and therefore the government should introduce anemia screening,

treatment and diagnosis at all the primary health care levels for early detection and to reduce the tuberculosis burden at the community.

Since corticosteroids were positively associated with elevated hemoglobin levels as a result of suppression of the immune mediated hemolytic anemia, this suggest that patients who responds poorly to iron supplementation may be treated with corticosteroid for a positive outcome.

Fluoroquinolones and mostly levofloxacin were significantly associated with the liver injury, although it is he preferred drug in the treatment of multi drug resistance tuberculosis it should possible be avoided. pregabalin should also be avoided as it can cause severe thrombocytopenia.

KNH should put in place measure to ensure that patients on tuberculosis treatment are monitored for adverse drug rection as a result of tuberculosis treatment as this group of patients are at risk of developing renal, hematological and liver injuries that will need more expensive interventions for best treatment outcome.

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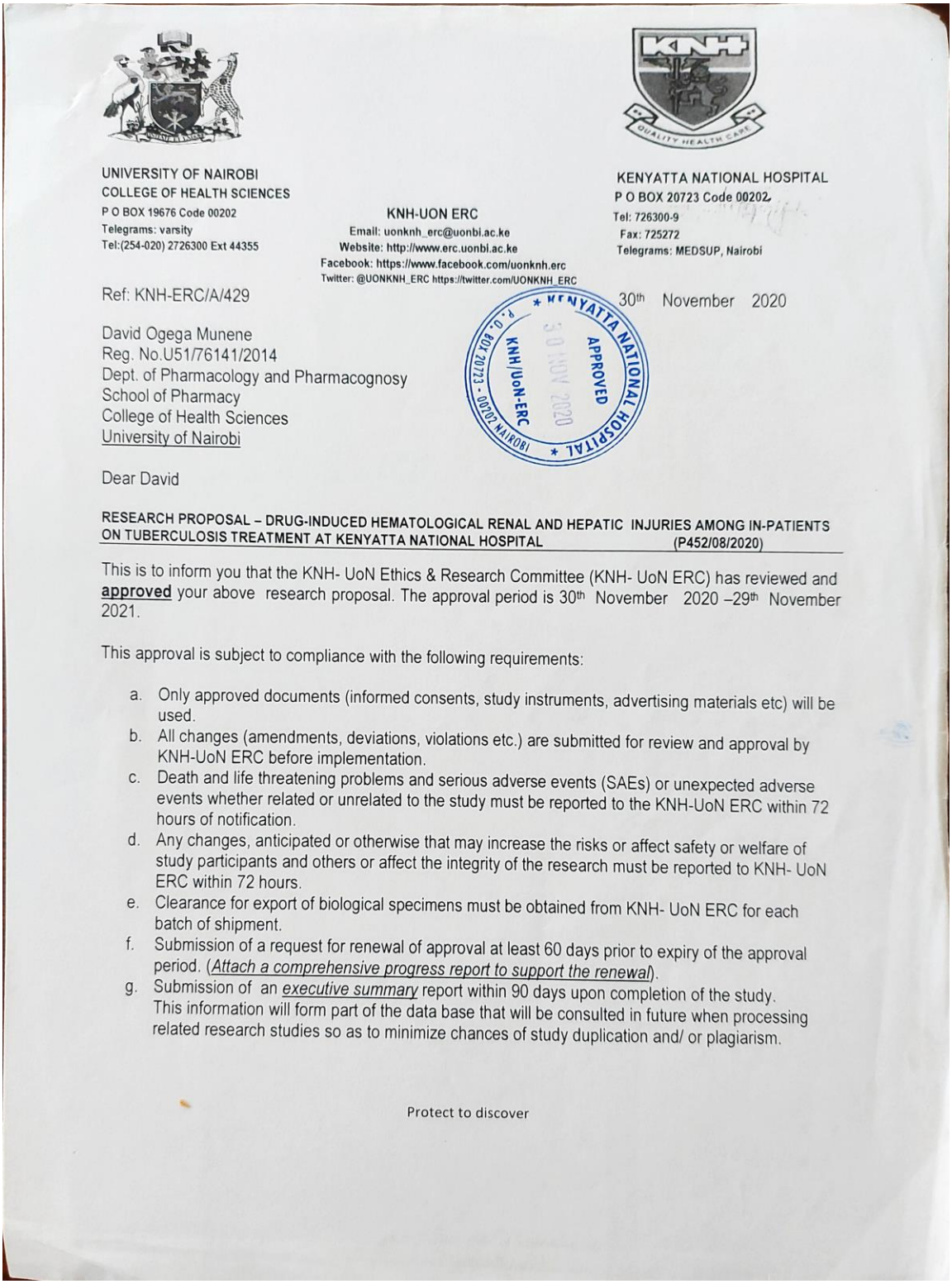
APPENDICES

APPENDIX A: KNH-UoN ERC APPROVAL



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30th November 2020

KENYATTA NATIONAL HOSPITAL P.O. BOX 20723 - 00202 NAIROBI KNH/UoN-ERC APPROVED 30 NOV 2020

David Ogega Munene
Reg. No.U51/76141/2014
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear David

RESEARCH PROPOSAL – DRUG-INDUCED HEMATOLOGICAL RENAL AND HEPATIC INJURIES AMONG IN-PATIENTS ON TUBERCULOSIS TREATMENT AT KENYATTA NATIONAL HOSPITAL (P452/08/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 30th November 2020 –29th November 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
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Dr. Eric M.Guantai, Dept.of Pharmacology and Pharmacognosy, UoN
Prof. Faith Okalebo, Dept. of Pharmacology and Pharmacognosy, UoN

APPENDIX B: DATA EXTRACTION FORM

A: Identification details

Date ……. (dd/mm/yyyy) Serial number ……

Patient code …….

B: Socio-demographic and clinical characteristics

1. Age …….
2. Gender
   a) Male
   b) Female
3. Marital status
   a) Single
   b) Married
   c) Separated
   d) Divorced
4. Alcohol intake
   a) Yes
   b) No
5. Cigarette smoking
   a) Yes
   b) No
6. Anti-tuberculosis regimen …….

   ……

   ……

   ……

   ……
7. Other medications …….

   ……

   ……

……

……

8. Comorbidities …….

……

……

……

……

Baseline values at admission point (if available)

C: <u>Hematological profile</u>

9. HB levels (g/dl) …….
10. Platelets count ……
11. White blood cells count …….
12. Creatinine levels…….

D: <u>Renal function test</u>

13. Urea levels …….
14. Potassium levels ……
15. Sodium levels……

E: <u>Liver function test</u>

16. ALT ……
17. AST …….
18. Direct bilirubin …….

Highest and lowest values documented after treatment initiation

C: <u>Hematological profile</u>

19. HB levels (g/dl) …….

20. Platelets count ……

21. White blood cells count …….

22. Creatinine levels…….

D: <u>Renal function test</u>

23. Urea levels …….

24. Potassium levels ……

25. Sodium levels……

E: <u>Liver function test</u>

26. ALT ……

27. AST …….

28. Direct bilirubin …….