FACTORS ASSOCIATED WITH SEVERE RHEUMATIC HEART DISEASE AMONG PATIENTS ATTENDING MOI TEACHING AND REFERRAL HOSPITAL, UASIN GISHU COUNTY, KENYA

BY

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THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF DEGREE OF MASTER OF SCIENCE IN FIELD EPIDEMIOLOGY AND LABORATORY AT MOI UNIVERSITY

DECLARATION

This thesis is my original work and has not been presented to any other University/Institution for an award of a degree.

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DEDICATION

This study was inspired by my loving sister Mitchelle, hoping that this work contributes to unveiling challenges faced by patients living with Rheumatic Heart Disease, with the intent of prolonging life and preventing new cases.

ABSTRACT

Background: Rheumatic Heart Disease (RHD) is a preventable type of cardiovascular disease, most common among children and young, working adults, with twice the risk of developing RHD among females. There are over 15 million cases globally, with 282,000 new cases and 288,348 deaths annually, the majority being in low and middle-income countries. Africa experiences a more malignant course of RHD, with sub-Saharan Africa having a higher burden, reporting a loss of 10.7 million Daily Adjusted Life Years (DALYs). In Kenya, the Moi Teaching and Referral Hospital (MTRH) hosts the largest outpatient cardiac clinic in the Western region. Among its cardiac patients under the age of 50, Rheumatic Heart Disease (RHD) is the most common cardiovascular disease, affecting over 64% of these patients. Most of these patients are younger, with a mean of 26 years, 70% being female. The high number of patients with severe disease in MTRH means that they suffer a significantly higher economic burden compared to other patients with less severe disease.

Objectives: To determine the epidemiologic factors associated with the severity of RHD and assess various co-morbidities among RHD patients attending the Cardiology Clinic at MTRH.

Methods: A case-control study, with the definition of cases being patients with severe valvular disease or having mechanical prosthetic valves/valve repairs done, and controls being diagnosed with either moderate, mild or inactive RHD, both confirmed by echocardiography. A total of 110 participants were sampled, out of the 976 patients with RHD attending MTRH cardiac clinic. Data was collected using both face-to-face questionnaires and patient records. Dependent variables were either a case or control, and independent variables included socio-demographic data and epidemiologic characteristics associated with RHD. Continuous variables were analyzed using measures of central tendency and dispersion while categorical variables were analyzed using frequencies and proportions. Bivariate analysis was done using odds ratios (OR) at a confidence interval of 95%, and a p-value of ≤ 0.05 being considered a significant factor. Factors with a p-value of ≤ 0.2 were subjected to a multivariate analysis using unconditional logistic regression and significance was considered on factors with a p-value of ≤ 0.05.

Results: The mean age among the cases was 35 (SD±11.4), and 27 (SD±11.3) among the controls, with the female cases and controls being 72.5% and 68% respectively (OR=1.3; p=0.34). Most of the cases did not practice regular physical exercise (69%) (OR=2.3; p=0.0344), while 51% of the controls practiced regular physical exercise (OR= 0.43; p= 0.0215). The Body Mass Index (BMI) of overweight and obese ranges among the adult cases, were 43.7%, with 90% of them being females. The proportion of cases with a family history of chronic illness was 78.2% (OR=8.02; p=<0.0001), heart disease being the most common form of chronic illness in their family history. The participants' socioeconomic status showed that 11.6% of the cases were unemployed, with only 2.4% of the controls being unemployed (OR= 6.61; p=0.05). The cases and controls with a previous history of alcohol intake were 20% and 1.8% respectively (OR=13.6; p=0.0144). Among the cases, 25% had comorbidities, while 12.7% of the controls had comorbidities (OR=2.342; p=0.0949). The most common comorbidities were stroke and hypertension, with over 50% having either of the two. Among the cases, participants with high blood pressure (systolic $\geq$140mmHg) were 16%, with 10% among the controls (OR= 1.6; p=0.04). Of the female participants who were on contraceptives, 23% of them were cases while 20% were controls (OR=1.24; p=0.04). Multivariate analysis revealed that occupation, alcohol use and lack of regular exercise remained significant with p-values of 0.000217, 0.000007, and 0.021, respectively.

Conclusion: Severe RHD is common in the younger population and females. Low socioeconomic status and harmful use of alcohol were major drivers in increasing progression to severity. Regular physical exercise was a protective factor in preventing severe RHD.

Recommendations: Patients attending the cardiac clinic at MTRH should receive education on the adverse effects of alcohol consumption, undergo regular hypertension screenings, and be encouraged to engage in consistent physical exercise. Additionally, educational initiatives and awareness campaigns should be conducted in schools and among populations with low socioeconomic status.

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ABBREVIATIONS, ACRONYMS, DEFINITION OF TERMS

AF	Atrial Fibrillation
ARF	Acute Rheumatic Fever
ASOT	Anti Streptolysin O Antigen
BMI	Body Mass index
BPG	Benzathine Penicillin G
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
CRP	C- reactive Protein
CVDs	Cardiovascular Diseases
DALYs	Daily Adjusted Life Years
ESR	Erythrocyte Sedimentation Rate
GAS	Group A Streptococcus
HLA	Human Leukocyte Antigen
IREC	Institutional Research and ethics Committee
KFELTP	Kenya Field Epidemiology and Laboratory Training Program
LMIC	Low- and Middle-Income Countries
MHC	Major Histocompatibility Complex
MTRH	Moi Teaching and Referral Hospital

NACOSTI	National Commission for Science, Technology and Innovation
NCDs	Non- Communicable Diseases
OR	Odds Ratio
RHD	Rheumatic Heart Disease
SDG	Sustainable Development Goals
WHF	World Heart Federation
WHO	World Health Organization

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CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Cardiovascular diseases (CVD) accounted for 17.9 million deaths worldwide in 2017 (WHO Report, 2019), with low and middle-income countries reporting over three-quarters of these deaths. Kenya estimates about 25% and 13% of hospital admissions and autopsy reports respectively, are due to CVDs, (the second highest cause of death). Most CVDs can be prevented by employing various population-level strategies mitigating the different epidemiologic characteristics linked to CVDs. Rheumatic heart disease is one of the preventable types of cardiovascular diseases. There are several documented factors which have been attributed to the occurrence of Rheumatic heart disease and imposition of severe RHD, where early and effective intervention can prevent its morbidity and premature mortality (Beaton et al., 2017).

Rheumatic heart disease (RHD) is a post-infectious chronic cardiovascular disease that comes about as a sequela of Acute Rheumatic Fever (ARF). Acute rheumatic fever is an inflammatory disease that usually develops due to untreated or inadequately treated sore throat caused by an infection with group A streptococcus (GAS) (Okello et al., 2013).

There is immunologic evidence that shows the pathogenic mechanisms that lead to ARF, following GAS infection may include molecular mimicry, which occurs when the antibodies directed against the GAS antigens cross-react with the host antigens. The immune reaction then leads to the destruction of heart muscles and valves, leading to the

narrowing or leaking of the heart valve making it harder for the heart to function normally (Beaton Andrea et al., 2017). Acute rheumatic fever manifests in approximately 3 weeks following GAS infection and presents as carditis, arthritis, chorea, subcutaneous nodules and erythema marginatum. The feature that poses a severe life-threatening state of disease is carditis, and RHD is the disease that evolves from carditis (Beaton Andrea et al., 2017).

Rheumatic heart disease can be present at any age, but it is most common among children (aged 5-15 years) and young, working adults in low-income countries. It disproportionately affects girls and women, having twice the risk of developing RHD among females than males (RHD Global Status Report 2015). In 2015, there were 33.4 million cases of rheumatic heart disease globally, with 319,400 deaths and 10.5 million disability-adjusted life years due to RHD (Watkin et al., 2015).

Rheumatic heart disease has a significant burden of disease in Sub-Saharan Africa (SSA), experiencing the greatest CVD-related loss of DALYs (10.7 million), due to the higher involvement among the young population and associated barriers to surgical treatment throughout SSA and a prevalence of 5.7/1000 in children from 5-14 years in 2005. In Soweto, South Africa, the incidence of RHD was reported to be 30 per 100,000 per year (Zühlke et al., 2015).

In Kenya, a review of 11,654 hospital records for selected cardiovascular diseases dating back three years from 2020 revealed that 9% of the captured records had a diagnosis of RHD. In 2016, a hospital-based study found that 64% of the cardiac patients in the cardiac clinic had RHD (Lumsden et al., 2016).

Heart disease was identified as the second most common cause of indirect maternal deaths in South Africa among pregnant women. In areas where rheumatic fever and RHD are endemic, it emerged as the principal type of heart disease that is seen in pregnant women (Karthikeyan & Mayosi, 2018). There is also high morbidity and mortality among pregnant women with RHD in South Africa, and a high rate of associated fetal loss among women with RHD (Engel et al., 2015). Pregnant women with RHD tend to have a higher risk of preeclampsia, preterm premature rupture of membranes, gestational diabetes and urinary tract infections, causing significant maternal and perinatal morbidity and mortality (Australian RHD guideline, 2nd edition, 2016).

In the past, diagnosis of RHD had been done mostly through auscultation, but this led to very low detection rates; and the addition of echocardiography in the diagnosis proved it to be more sensitive and specific (Reményi et al., 2012). In 2004, the World Health Organization and the National Institute of Health (WHO/NIH) recommended criteria to include echocardiography. This was further revised in 2012, by the World Heart Federation (WHF), to rapidly identify RHD patients, evaluate interventions and facilitation of epidemiological studies, through an evidence-based guideline for RHD diagnosis; on surgical, pathological and echocardiography changes, therefore the classification of RHD based on the severity at presentation (Reményi et al., 2012)

This criterion identified RHD patients as Severe, Moderate, Mild or Inactive. Severe RHD has severe valvular disease/moderate to severe lesion with symptoms/mechanical prosthetic valves and valve repairs including balloon valvuloplasty. Moderate RHD has any moderate valve lesion in the absence of symptoms with normal left ventricular function/mild mitral regurgitation PLUS mild aortic stenosis/mild to moderate mitral or

aortic stenosis/any pulmonary or tricuspid valve lesion co-existing with a left-sided valve lesion. Mild RHD has ARF with no evidence of RHD/Trivial to mild valvular disease and Inactive RHD are patients with a history of ARF (no RHD) for whom secondary prophylaxis has been stopped (Reményi et al., 2012).

Several studies on the natural history of acute rheumatic fever and rheumatic heart disease have been done. A fifteen-year follow-up (1983–1998) of patients diagnosed with ARF in Brazil, showed that 72.1% of them developed chronic valvular disease at least two years after the first attack (Meira et al., 2005).

Another follow-up study (1952–1966), on the progression of RHD patients, who had Aortic regurgitation, showed that 33% of the 174 patients on follow-up died of heart failure or angina within the first year, 48% died after 2 years, 65% died after 3 years and 87% died after 6 years (Spagnuolo et al., 1971). In Germany, a study on the natural history of RHD with mitral valve stenosis showed that the progression of mild to severe RHD among 159 ARF patients was 9.2±4.3 years. After indication, those who refused surgery had a survival average of 0.44±0.06 years after 5 years (Horstkotte et al., 1991).

Rheumatic heart disease is a major risk factor for Atrial Fibrillation (AF), which is a common arrhythmia affecting over 33 million people worldwide. In every five patients with AF, at least one of them has RHD. In a 12-month follow-up study on the clinical characteristics of patients with valvular and non-valvular atrial fibrillation (AF) in Kenya, at the Moi Teaching and Referral Hospital; mortality, hospitalization and stroke rates for valvular AF patients were high, at 10%, 34% and 5% respectively, and were similar to the rates in the non-valvular AF patients 15%, 36%, and 5%, respectively (Temu et al., 2017).

There is a rare diagnosis of acute rheumatic fever in Africa, therefore, we find late presentations of RHD (a complication of untreated or undertreated ARF). It is seen to have a more malignant course in its natural history in Africa, compared to North America and Europe. This variation in natural history and severity remains unexplained. Uncovering epidemiological patterns of disease is critical to finding target populations for early intervention and informing public health strategies to prevent disease progression to severity.

Studying the factors associated with severe rheumatic heart disease is essential for improving patient outcomes by having tailored treatment approaches whereby patients identified with high-risk characteristics can receive more aggressive or targeted therapies, potentially slowing the disease's progression and reducing complications. Furthermore, by understanding the factors that drive disease severity, healthcare systems can allocate resources more efficiently, focusing on those at greatest risk and reducing overall healthcare costs. Studying these factors can lead to the identification of modifiable risk factors which can be addressed and potentially reducing the mortality and disability associated with severe forms of the disease.

1.2 Problem Statement

Despite the declining incidence of RHD in developed countries, it remains a priority disease in global health and one of the leading causes of cardiovascular morbidity and mortality in middle and low-income countries. A multi-state analysis of RHD status in Africa revealed that 63.9% of the RHD patients in the study had moderate to severe disease.

Furthermore, the study conducted in sub-Saharan Africa, reviewing active surveillance studies in several studies showed that 65% of the children and adolescents had mitral valve regurgitation, with clinical symptoms, classifying them as moderate-severe RHD, with 21% of them having atrial regurgitation and 15% had mitral valve stenosis. Active surveillance, where 23 patients were screened with cardiac auscultation and an echocardiogram revealed an incidence of 2.9/1000 people with rheumatic heart disease by cardiac auscultation and 12.9/1000 people by echocardiogram.

In Kenya, comparable results are shown by a study on clinical and geographical patterns of Rheumatic Heart Disease, done at Moi Teaching and Referral Hospital (MTRH), which has the largest outpatient cardiac clinic in the Western region of Kenya. RHD is the most common CVD in cardiac patients, who are less than 50 years old attending the cardiac clinic at MTRH, having over 64% of their cardiac patients with RHD most of whom are young (averaging 26 years) and predominantly female, implicating a significant disease burden. This disproportionality seen in female patients places them in a vulnerable state as they tend to have more severe disease propagated by the cardiovascular changes that accompany pregnancy and the perceived effect of contraception on hemodynamics. They also tend to have a higher mortality rate and pregnancy-related complications associated with heart disease.

According to the World Heart Federation's classification of Rheumatic Heart Disease, severe heart disease with the highest priority includes patients with valvular disease, or valvular lesions with symptoms or having mechanical prosthetic valve replacement and valve repairs including ballon valvuloplasty. The most common valvular disease involvement in MTRH was a combination of mitral and aortic valves, at 51% (n=298),

those with mitral valve involvement alone were 38%, with 8% (n=76) of them having had cardiac surgery done, where 69% had valve replacement surgery and 29% had valve repair done. Patients who had a concurrent cardiac diagnosis of arrhythmia were 20%, with 19% of them having systolic heart failure and 7% with infective endocarditis. In general, showing that over 30% of the RHD patients at MTRH had a moderate-severe form of the disease, with one-third of patients having some form of comorbidity commonly hypertension. The significant severe disease prevalence among rheumatic heart disease patients in MTRH maintained the high morbidity seen in the cardiac clinics, hence high mortality expected from the patients.

Rheumatic heart disease diagnosis and management bear significant costs, which might be difficult to meet among LMIC populations, thus leading to premature death among the most productive individuals in the household and society. The high number of patients with severe disease in MTRH means that they suffer a significantly higher economic burden compared to other patients with less severe disease. Among the RHD patients, 82% were on secondary prophylaxis with Benzathine Penicillin G, and 104 were not receiving any secondary prophylaxis, exposing them to recurrent infections hence more damage to their heart valves leading to a more severe disease.

1.3 Justification

One of the barriers to prevention and reduction in morbidity and mortality rates of RHD, and reduction in the economic burden, is the lack of sufficient data to enable targeted prevention efforts, being the biggest gap in the control of RHD. With the paucity of information on the factors associated with the severity of RHD in Kenya, there is

inadequate evidence-based data, to help direct interventions. Using a systematic approach of identifying the burden of disease, expounding on the modifiable risk factors and setting up strategies to address these risk factors and achieve this reduction, we need to carry out more studies on RHD in the Kenyan population dynamics.

MTRH, being the center of cardiac healthcare in the better part of the Western region in Kenya serves as the best place to implement strategic interventions towards the improvement of management and control of heart diseases and serves as the epicenter of community involvement and health education due to the high patient flow from the surrounding three regions. This study will be a source of additional knowledge based on the disease's interaction between factors associated with RHD severity, their comorbidities and changing epidemiologic traits which will help in targeted public health intervention towards prevention and control of RHD, aligning with WHO and WHF's aim of eliminating ARF and RHD control by a 25% reduction for those <25 years by 2025. The recommended interventions are targeted to MTRH but can be embedded in any other health facility within the country.

1.4 Anticipated use of the study

The National Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2020-2026 has prioritized and focused on rheumatic heart disease, due to its preventable attribute, and the endemicity in the country. Therefore, the Ministry of Health advocates for interventions such as strengthening health systems, prevention of biological risk factors, strengthening of data through surveillance, advocacy, awareness creation and

implementation of evidence-based strategies or interventions for the prevention and control of RHD.

Insufficient data prevents targeted prevention efforts towards the prevention of modifiable risk factors associated with RHD and related premature deaths. The study will therefore add to the data and scientific information to guide interventions thus reducing the advancement of RHD, morbidity and mortality. It will also give a background on the plans of setting up surveillance systems, and registries, strengthening national programs for monitoring RHD disease status, moreover, expanding national training hubs, especially on early diagnosis and classification of RHD through echocardiography.

Specifically for Moi Teaching and Referral Hospital, this study will guide the cardiac clinic on ways of tackling the high numbers of Rheumatic Heart Disease patients' health needs aiming to prevent the progression of RHD to severe forms. The study will also guide as an initial basis for beginning a facility-based RHD program, with an end goal of guiding the Ministry of Health on how to initiate an establishment of a register-based National RHD Control Program.

1.5 Broad Objective

To describe factors associated with severe RHD among patients attending Moi Teaching and Referral Hospital Cardiology Clinic.

1.6 Specific Objectives

1. To determine the demographic characteristics, nutritional status, lifestyle characteristics, family history of chronic illness, obstetric & gynecological history,

and medical history associated with severe RHD among patients attending the Cardiology Clinic at MTRH.

2. To assess various co-morbidities with RHD among cardiac patients in MTRH.

CHAPTER TWO

2.0 LITERATURE REVIEW

Rheumatic heart disease (RHD) is a post-infectious chronic cardiovascular disease that comes about as a sequela of Acute Rheumatic Fever (ARF). Acute Rheumatic Fever is an inflammatory disease that usually develops due to untreated or inadequately treated sore throat caused by an infection with group A streptococcus (GAS) (Okello et al., 2013), typically following strep throat or scarlet fever.

Many systems are affected by ARF, including the joints, heart, brain, and skin. Jones criteria is used for ARF diagnosis, using different criteria, that is carditis, arthritis, chorea, erythema marginatum, and subcutaneous nodules, and the use of various laboratory tests including throat culture, rapid strep test, and elevated anti-streptolysin O (ASOT) titers. Treatment of acute Rheumatic fever usually involves antibiotics, anti-inflammatory medications and additional care and medication if heart failure is present. Rheumatic heart disease, as a sequela of ARF results from damage to the heart valves.

Damaging heart valves leads to various complications like heart valve stenosis (narrowing), regurgitation (leakage), heart failure, and arrhythmias. Signs and symptoms of RHD include shortness of breath, generalized tiredness due to a decrease in the cardiac output, irregular heartbeat, and chest pain. Various imaging can be done to diagnose RHD, including echocardiogram which detects abnormalities and assesses the valve function, electrocardiogram which identifies rhythm abnormalities, and chest X-ray, which detects lung congestion.

Early diagnosis and treatment of RHD prevents premature mortality and reduces the morbidity experienced with RHD. Medical management includes the use of diuretics, beta-blockers and other medications used to manage the various symptoms accompanying individual disease diagnosis. Surgical intervention is incorporated in severe valvular damage. Prevention of RHD is divided into primary prevention, that is prompt treatment of strep throat, and secondary prevention through the regular use of antibiotics in patients with a history of ARF to prevent recurrence and progression to RHD.

2.2 Epidemiology

The sudden change in the cardiovascular disease picture in terms of morbidity and mortality in Africa is directly associated with the epidemiologic transitions and the population surges seen in the continent, and mostly in the most vulnerable areas and communities globally. Sub-Saharan Africa serves as the epicenter of the highest proportion of the poorest communities worldwide, which includes other countries found along the central belt, stretching from the Western to the Eastern part of Africa. Based on these sudden epidemiological transitions and population increase factors, it is paramount that they influence the health picture of individuals residing in the most vulnerable regions, therefore, these factors cannot be sidelined in the attempt to provide optimum prevention and control measures against cardiovascular diseases. Understanding and acknowledging these factors, and identifying the gaps associated with the challenges faced in Sub-Saharan Africa, on CVD management has been the epitome of interventions and actions, especially on preventable cardiovascular diseases.

Rheumatic Heart Disease, as one of the most preventable forms of CVDs has been the center of action against the growth of CVD morbidity and mortality in Sub-Saharan Africa, and epidemiological transition has been described as the first step in the actions set towards redirecting the balance of human life worldwide (Keates et al., 2017).

Cardiovascular diseases (CVDs) have been responsible for over half of the deaths every year, globally, with the low- and middle-income countries being the most affected as almost 80% of these deaths occur in the LMICs. Africa alone contributes to over 50% of these cases, with attribution of about 1 million deaths directed to Sub-Saharan Africa, which amounts to about 5.5% of all CVD-related deaths globally and about 11.3% of all CVD-related deaths in Africa. Cardiovascular diseases are the most common type of non-communicable diseases in the world, with about 70% of hospital admissions connected to heart diseases and cardiovascular health while 38% of all deaths are attributed to CVDs. There has been a growing threat of CVD-related mortalities in Africa, where communicable diseases have been predominantly taking the forefront causes of death in the past, and with over 10%differences in the morbidity and mortality of CVDs between women and men (women being more affected) (Keates et al., 2017).

Previously, hypertension had been the main talk of cardiovascular health in Africa before the prevalence and incidences of other CVDs were more studied and pronounced. Hypertension prevalence has been said to be between 15-70% all over Sub-Saharan Africa from 1999-2013. During this systematic review in figuring out the prevalence of hypertension in SSA, it also revealed that hypertension awareness was lacking, with poor treatment and control modalities. Currently, it is stated that not only hypertension serve as the main cause of CVD morbidity in Sub-Saharan Africa, but also other CVDs are said to

contribute significantly to cardiovascular events in the future, hence the more revelation of other preventable cardiovascular diseases, like Rheumatic Heart Disease (Keates et al., 2017).

Rheumatic heart disease is relatively rare in the developed world but remains a leading cause of cardiovascular mortality in developing countries, (which are inhabited by 80% of the world's population) (Watkins et al., 2015). It affects 33.4 million people worldwide, with 470,000 new cases every year and accounts for over 319,400 deaths annually with 10.5 million disability-adjusted life years (Lumsden et al., 2016; Watkins et al., 2015).

The Epidemiology of Rheumatic heart disease serves as the most fundamental and easiest way of studying the factors that have led to the development of RHD, as it is a chronic illness, with a prolonged natural history. The previously accumulated knowledge has been forthcoming in guiding the management and control of RHD, proving that research and epidemiology teamwork are effective in guiding interventions towards heart health. Previous studies have shown that (Hennekens & Buring, 1987) Rheumatic Heart Disease is believed to be a "disease of poverty" because socioeconomic status has been seen as an impact associated with the presence of RHD in studies done in different parts of the world. An example is a study done in Kinshasa on the prevalence of RHD based on clinical examination, they found that 22.2 per 1000 children who lived in the slums had RHD, compared to 4 per 1000 among children attending city schools (Damasceno et al., 2012). Presentation of RHD can be at any age but it is most common among children (aged 5-15 years) and young, working adults in low-income countries.

Females have twice the risk of developing RHD than males (WHO RHD Global Status Report, 2015), bearing an unproportioned burden compared to men, because of pregnancy-related complications that are experienced with rheumatic heart disease. Uganda and India conducted a study, using a model to simulate the natural history of rheumatic heart disease and in comparison to men, women accounted for much of the disability-adjusted years at 71-80% in Uganda, and 75% in India, of the total cost of economic burden in the two countries. This suggests that early screening and prevention strategies targeted at populations at higher risk in the community, such as women of reproductive age, is a viable and effective way of investing on rheumatic heart disease control and prevention of acute rheumatic fever. (Sandhu Alexander T et al., 2014).

Hemodynamic changes during pregnancy have been shown to have significant exposure towards the development of RHD, and the progression of disease states to more severe forms. In Newcastle General Hospital studies running from 1960 to date have revealed a continued decrease in the diagnosis or identification of rheumatic heart disease found within their antenatal clinics, and further decline in the severity of RHD among the pregnant women already diagnosed with RHD. Consequently, the complications associated with severe rheumatic heart disease such as heart failure, atrial fibrillation, and pulmonary edema, among others, which were predominantly seen in the past, have drastically declined. Moreso, the recorded natural history of RHD among pregnant women shows fewer morbidity states due to improvement of the medical treatment modalities, and the adoption of more cardiac surgery among the cases (Szekely et al., 1973).

This is however not the case in Sub-Saharan Africa, as pregnant women still tend to present with severe symptoms, and progression of RHD to severe forms occurs mainly during

pregnancy and postnatally. Even though each maternal death from RHD has been stated as having a high potential for prevention, Sub-Saharan Africa still reports significantly higher numbers of maternal mortality from RHD and other CVDs.

Management of carditis through early intervention with appropriate prophylaxis and therapeutic regimens, with routine medical check-ups and follow-ups has significantly assisted developed countries to manage pregnancy safely among rheumatic heart disease patients (Szekely et al., 1973). In SSA, this is still a challenge that needs significant and efficient strategies to curb the heavy RHD morbidity associated with pregnancy.

Africa's most recent studies show the prevalence of RHD among asymptomatic school-going children (who are the most at risk) to be at 30.2 per 1000 in Mozambique in 2007, and 15/1000 in Uganda in 2012. In 2013, Cameroon reported 62% of their heart disease patients between 10-19 years to have had RHD whereas the prevalence among school-going children in Malawi was 22.4/1000 in 2013 (*A M Cilliers, 2015, Paediatric Cardiology Unit, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa, and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, S Afr Med J;105(5):361-362. DOI:10.7196/SAMJ.9433 - Google*).

Among the younger population in Africa, RHD is among the leading causes of premature deaths. The prevalence of RHD at 2.9 per 1,000 after cardiac auscultation and 12.9 per 1,000 after echocardiography (Rothenbühler et al., 2014), after a meta-analysis study in 6 African countries from 1993 to 2014.

This has increased with an increase in the ages of patients, from 4.7 per 1000 at 5 years of age to 21 per 1000 at 16 years. This study also found that 63.9% of the RHD patients had moderate to severe multi-valvular disease (Zühlke et al., May 2015).

Sub-Saharan Africa is described as a hotspot for RHD in Africa, with a prevalence of 5.7/1000 in children from 5-14 years in 2005. In Soweto, South Africa, the incidence of RHD was reported to be 30 per 100,000 per year (Engel et al., 2015). Still, in South Africa, a systematic review of the incidence, prevalence and outcomes of RHD patients reported a 60-day mortality period in 24.8% of those who presented with acute heart failure due to a complication of severe RHD, 180-day mortality period in 35.4% and 2% had a 30-day mortality post mechanical valvular surgery (Zühlke et al., November 2015). In Kenya, a study done in 1989, reported the prevalence of RHD to be estimated at 62 per 1000, with a point prevalence of 40 per 1000 in school-aged children in Kenya (Anabwani et al., 1989).

Globally, several risk factors have been implicated in RHD, and most of them involve environmental conditions such as unclean water and improper sanitation, which pose a higher risk of infection by group A streptococcus. Overcrowding, poor housing, undernutrition and lack of access to health care encourage the persistence of the disease in developing countries. Genetic susceptibility has also been implicated as a risk factor for RHD (Watkins et al., 2015).

In Africa, ARF is rarely diagnosed, thus we find late presentations of RHD (Mocumbi et al, 2015). The severe and virulent forms of RHD are seen mainly in the early ages of life, thus leading to high mortality and morbidity in the young population. Rheumatic heart disease has been seen to have a more malignant course in its natural history in Africa,

compared to North America and Europe. In as much as the pathogenesis of RHD is well understood, this variation in natural history and severity remains unexplained (Mocumbi et al, 2015).

2.3 Economic Burden

There is a persistently high incidence of Rheumatic heart disease in low and middle-income countries, and among young adults who were at their highest peak of productivity in these financially struggling nations. This led Uganda and India to conduct a study on the economic burden of rheumatic heart disease in low-income nations, expounding on the economic burden to encourage prevention strategies and research, and to guide on ways of reducing the medical costs accrued with RHD morbidity, finally reducing the incidence especially among the young adults. This study showed that in 2012, rheumatic heart disease generated 6.1 million disability-adjusted years in India, costing them 10.7 billion dollars in medical management of the disease. Uganda on the other hand, accrued a medical cost of rheumatic head disease of 414 million dollars at 216,000 disability-adjusted years (Sandhu Alexander T et al., 2014).

There is a significant economic cost towards its treatment and management, to sustain or improve the status of living for patients (Wyber et al., 2014). It has been attributed to 11.5 million disability-adjusted life years lost. Globally, the cost of deaths due to rheumatic heart disease, in 2010, was estimated at a discounted cost of US$ 2200 billion, and an undiscounted cost of US$ 5400 billion (Watkins & Daskalakis, 2015).

An increase in the severity of RHD increases the costs needed in the day-to-day management of the patient, with little income generated by the working class RHD patients

due to their effective work limitations, causing a higher economic burden to the patients, families and government. The economic burden of RHD can be divided into direct costs, indirect costs and government costs.

Direct costs include symptomatic management of the disease such as medication, dental care, laboratory work, outpatient and inpatient costs, transport to appointments and surgery (RHD Action, 2015). Indirect costs include loss of jobs, inability to complete studies due to severe disease states, and parents taking time off from work to take care of children with RHD. There are many reports of school absenteeism, drop-outs and lost wages, due to having RHD all over the world, a study in Brazil showed that RHD cost affected families approximately US$97 per patient and society US$ 320 annually, on the flip side, if they implement a prevention program, it will cost US$23 per patient annually (Watkins & Daskalakis, 2015).

South Korea reported the cost of RHD in 2008 at 67.25 million USD, where 39.04% of it was indirect cost (Seo et al., 2013). Uganda reported the cost attributed to RHD to be approximately 414 million USD in 2018, where 88% of it was indirect costs (Sandhu et al, 2014). In general, developing countries impacted the cost of ~222,000 deaths from RHD in 2010 to be at 2.2 trillion discounted or 5.4 trillion undiscounted (Watkins & Daskalakis, 2015), whereas costs to the government in terms of premature mortality in low and middle-income countries were about 56 billion USD in 2013 (RHD Action, 2015).

2.3.1 Causes

Infection by Group A Streptococcus leads to acute rheumatic fever, and after 3 weeks, with no antibiotic treatment, complications occur, including carditis. This evolves causing RHD,

and year after year, with frequent attacks, the severity of Rheumatic Heart Disease increases (Watkins et al., 2015).

Predisposition to GAS infection is attributed to several factors including overcrowding, unhygienic living conditions and reduced access to medical care (Watkins et al., 2015).

A case-control study on socio-economic and environmental risk factors among RHD patients in Uganda; to well describe this subject matter, investigated factors such as income status, employment status, distance from the nearest health Centre, number of people per house and space area per person (Okello et al., 2013). The major findings of this study were that there was a trend toward increased risk of rheumatic heart disease in association with overcrowding and unemployment. This study revealed the importance of assessing these risk factors, concerning the severity of the disease in Uganda (Okello et al., 2013).

In developed countries, new cases of acute rheumatic fever have drastically decreased, leading to a further decrease in the incidence of rheumatic heart disease, but this is not the case as seen by Kheir and Ali in Sudan, a developing country in the Sub- Saharan Africa region. Furthermore, the other countries in SSA experience increased acute rheumatic fever cases, and the diagnosis of RHD while it has reached a more severe state. Developed countries also see a drastic decline in incidence, which is largely attributed to the initial antibiotic prescription to treat bacterial pharyngitis and their vastly improved medical care services, to have improved cardiac care.

Although there is a persistence of debilitating morbidity and mortality in SSA, having integrated Rheumatic Heart Disease programs has proven to be of great service in decreasing the new cases of rheumatic fever thus decreasing the incidence of RHD. This

has evolved from their previous dependence on secondary prophylaxis using benzathine penicillin G, which was seen to be ineffective in controlling the morbidity and mortality of RHD. Therefore, adoption of control programs which apply both primary interventions, secondary prophylaxis and tertiary interventions, intending to achieve a decrease in mortality by 25% in people who are less than 25 years old by the year 2025.

The programs also utilize increased education and awareness among the populations, especially the most exposed groups of persons including the young, women and people who live in unsanitary environments. The programs also embrace surveillance to monitor the trends of ARF and RHD in the region. Sudan has adopted such a program, which has been shown to assist in reducing ARF and RHD incidence since 2012 (Kheir & Ali, 2014).

2.4 Pathogenesis

A study on rheumatic fever stated various M serotypes, which are 3, 5,6,14,18,19,24 and 29 have been implicated in an outbreak of pharyngitis, leading to rheumatic fever in the United States in the mid-80s. This revealed a rheumatogenic cause of specific strains, leading to a further study ‘on serological surveillance to compare these M types, but a resolution was never reached, it was concluded that a strain with the potential of causing pharyngitis leads to the development of rheumatic fever (Stollerman et al., 1997).

The exact pathogenic mechanisms leading to the development of RHD are still not understood, but epidemiologic and immunologic evidence shows the certainty of the requirement of pharyngeal streptococcal infection. Genetic susceptibility may also be required for its occurrence (Katzenellenbogen et al., 2017).

Molecular mimicry plays a significant role in explaining the pathogenesis of ARF and RHD. Molecular mimicry occurs when the antibodies directed against the GAS antigens cross-react with the host antigens. GAS antigens (Streptococcal M protein and N-acetyl beta-D glycosamide (NABG), which is the immunodominant carbohydrate antigen of GAS) share epitopes with myosin (an essential component of the heart) (Beaton et al., 2017). An immune reaction occurs, leading to the destruction of heart muscles and valves, and the narrowing or leaking of the heart valve making it harder for the heart to function normally.

Acute Rheumatic Fever may also affect other parts of the body like the joints, skin and central nervous system. Patients with ARF have at least one of these three antibody titers to antistreptococcal antibodies elevated: hyaluronidase, streptokinase and streptolysin “O”, regardless of remembering the precedent of sore throat. However, the isolation of GAS from the oropharynx is generally very low (Beaton et al., 2017).

A study done on the collection of GAS following pharyngitis was higher in older children and young adults, at 70% but only 20% in younger children, who are the most at risk with a higher incidence of RHD. This shows that we should have a high index of suspicion of ARF especially in younger children presenting with arthritis or carditis, with the absence of preceded pharyngitis (Stollerman et al., 1997).

There are five chromosome patterns of Emm genes, which code for M and M-like surface proteins, which have been identified and coded A-E. Of these codes, pharyngeal strains have patterns A-C, and D-E are classified as impetigo strains (Stollerman et al., 1997).

2.5 Genetic Susceptibility

There have been suggestions that the disease is transmitted in an autosomal dominant manner or as an autosomal recessive, or through genes, which usually determine the blood group secretor status. Studies have shown the presence of MHC class II alleles, HLA-DR4 and DR2 in Caucasian and black Americans with Rheumatic Heart Disease (Ayoub et al., 1986).

In South Africa studies have exposed DR1 and DRW6 as susceptibility factors in RHD patients (Maharaj et al., 1987), whereas HLA-DR7 and DW53 have been found in Brazil (Guilherme et al., 1991). Further studies have associated some genes to be linked with specific clinical signs. A study done on the primary prevention of Rheumatic Fever in the Control of Rheumatic Heart Disease in Africa found that patients who have had carditis in the past are more likely to develop carditis during recurrences and, presumably, suffer cumulative valve damage (Karthikeyan Ganesan & Mayosi Bongani M., 2009).

2.6 Clinical Features

Clinical features of ARF are grouped into major and minor criteria, the five major criteria include Migratory arthritis (predominantly involving the large joints), Carditis and valvulitis (e.g., pancarditis), and Central nervous system involvement (e.g., Sydenham chorea), Erythema marginatum and Subcutaneous nodules. The four Minor criteria include Arthralgia, Fever, Elevated acute phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], and Prolonged PR interval. The presence of GAS infection preceding two major manifestations or one major and two minor manifestations increases the probability of ARF (Stollerman et al., 1997).

RHD includes a spectrum of lesions from pancarditis (pericarditis, epicarditis, myocarditis, and endocarditis) and valvulitis, to chronic valvular lesions that evolve over years following one or more episodes of acute rheumatic fever (Reményi et al., 2012). This causes structural dysfunction of the heart, and the most common valvular structural manifestation is mitral regurgitation, which may be accompanied by aortic regurgitation. Aortic stenosis and mitral stenosis are typically late manifestations of scarring and calcification of damaged valves. All of this may cause complications like heart failure, arrhythmias and thromboembolism, thus may lead to death (Lumsden et al., 2016). Circumstances in which ARF can be diagnosed presumptively include the presence of Chorea alone; indolent carditis alone; and recurrent rheumatic fever in a patient diagnosed with RHD (Lumsden et al., 2016).

2.7 Diagnosis

Diagnosis involves the identification of GAS infection, (through a positive throat culture for group A beta-hemolytic streptococci, positive rapid streptococcal antigen test, elevated or rising antistreptolysin O antibody titer), evaluation of acute-phase reactants, and assessing the cardiac function (Reményi et al., 2012).

In about 75% of patients, by the time of the appearance of ARF, throat cultures come back negative. Anti-streptolysin O titers (ASOT) vary with age, season, and region. Documents show that about 80% of patients have a rise in ASOT, and a negative ASOT should prompt further tests for the other antistreptococcal antibodies, and 90% of patients usually demonstrate positive tests for 2 of the antigens tested (Stollerman et al., 1997).

Serum C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) are elevated during the acute process, but no changes are seen if a patient has been subjected to antirheumatic drugs. CRP usually normalizes after an acute phase, but ESR will stay elevated even up to two months after. Diagnosis of carditis using echocardiographic evidence may be non-specific, however, with the clinical features and auscultation, with the backup of echocardiography, RHD diagnosis is more accurate (Stollerman et al., 1997).

The World Heart Federation (WHF) set up guidelines aimed at enabling rapid identification and staging of RHD in patients, to allow for consistent and reproducible reporting of RHD worldwide which would then facilitate epidemiologic studies and evaluation of interventions, aimed at reducing the worldwide burden of RHD (Remenyi et al, 2013).

The 2012 WHF criteria for echocardiographic diagnosis of RHD classified it as Definite RHD, Borderline and normal echocardiographic findings, with specific sub-classifications in all the groups as definite mild RHD, definite moderate RHD and definite severe RHD as follows (Remenyi et al, 2013)

Table 1: World Heart Foundation criteria for the diagnosis of RHD

Classification	Criteria
Priority 1 (Severe)	Severe valvular disease or Moderate/severe lesion with symptoms or Mechanical Prosthetic valves and valve repairs including balloon valvuloplasty
Priority 2 (Moderate)	Any moderate valve lesion in the absence of symptoms with normal left ventricular function or Mild mitral regurgitation PLUS mild aortic stenosis or Mild or moderate mitral or aortic stenosis or Any pulmonary or tricuspid valve lesion co-existing with a left-sided valve lesion
Priority 3 (Mild)	ARF with no evidence of RHD or Trivial to mild valvular disease
Priority 2 (inactive)	Patients with a history of ARF (no RHD) for whom secondary prophylaxis has been ceased

2.8 Treatment

The three ways of preventing it are by reducing the risk factors of rheumatic fever (primordial prevention); primary prevention of rheumatic fever and rheumatic heart disease; and secondary prevention of reinfection, through antibiotic prophylaxis (WHO report, 2018).

Primary prevention methods include prevention of GAS infection and treatment of pharyngitis caused by GAS with penicillin, amoxicillin, azithromycin or erythromycin. Secondary prevention includes giving monthly benzathine penicillin prophylaxis, this helps prevent recurrent attacks. Patients with permanent structural damage may undergo surgery, and the complications that arise as a result of RHD should be managed appropriately (Beaton et al., 2017).

There are no proven treatments that alter the natural history of RF; therefore, prevention is the key to reducing the burden of disease in the community. Nevertheless, with the patients who already have the disease, there is secondary and tertiary prevention, which becomes difficult to access in low socio-economic countries. Patients with severe RHD are at high risk for death and require consideration for definitive therapy such as surgical intervention. In countries where surgical and catheter intervention is available, timely referral and intervention are important.

Most African countries do not have this capacity, even though surgical services have recently been identified by the World Health Organization at the 68th World Health Assembly as a critical element of global health systems (Zühlke et al., 2015).

Most individuals with severe RHD do not have access to expensive life-saving cardiac surgery. Access to open-heart surgery in Africa is poor, where 18 such procedures per million of the population are performed compared to 1,222 per million in the USA. Travelling abroad for cardiac surgery is expensive and often unsustainable at a national level (Watkins & Daskalakis, 2015). However, most of the low-income countries with geographically dispersed populations rely on centralized health facilities with specialists to get the best management. Access to these facilities and services becomes a major hurdle, as the aspect of the cost of transport to the facilities, medication and tests sets in and is more of a burden to patients with severe diseases. The result is often suboptimal therapeutic monitoring and management of the disease (Watkins & Daskalakis, 2015).

2.9 Severity

To understand various aspects of what drives Rheumatic Heart Disease's progression to severity, several studies with different approaches have been conducted in different parts of the world. In Ethiopia, 1995-2001, a retrospective study on the severity of RHD at a teaching hospital collected information on the age at the time of death, sex, immediate causes of death, length of duration of follow-up in the health facility, presence of co-morbid illness, type of lesion, and status of secondary prophylaxis. Out of 457 cardiovascular deaths, 121 (26.5%) had RHD (Oli K., Asmera, J, 2004).

The investigators went further to review records for 115 of the RHD patients, and the mean age at the time of death was 25+/- 11years, of which 57.4% were female. The main causes of death were systemic embolism and co-morbid conditions. With this, they concluded that RHD takes a more aggressive course at a younger age in Ethiopia, and recommended on

the urgent need to investigate and address factors associated with the rapid course of RHD in Ethiopia (Oli K., Asmera, J, 2004).

Newcastle General Hospital, in the United Kingdom and Western General Hospital in Edinburgh, did a 28-year and 25-year period study, respectively, on the clinical aspects of RHD, concerning pregnancy.

In this study, they found that from 1942 to 1969, pregnancy posed one of the main factors that increased the severity of RHD, with the main complications including pulmonary congestion, pulmonary oedema, Right Heart Failure, dysrhythmias and embolism. Since 1969, there has been a progressive decrease in the number of patients with RHD found in antenatal clinics and its severity. The factors thought to be responsible for this decrease were improved medical care during pregnancy and the years preceding the childbearing age, antistreptococcal prophylaxis, surgical relief of severe mitral valve obstruction, and also the natural decline in the severity of rheumatic heart disease (Szekely et al., 1973).

South Africa conducted a retrospective analysis (1993-1995) of the geographical regions of pediatric patients, looking at the geographical area as one of the factors that influence the severity of RHD, classifying severity as those requiring surgery. More severe cases were from Northern Province; KwaZulu- Natal and Mpumalanga, and less severe from Gauteng (32.9%). The Northern Province was then referred to as a high-risk area for RHD, known to have had the highest rural populations in South Africa, in 1995. Over 9 million children were living in poverty in South Africa in 1994, and the unemployment rate was 32.6%, with the highest figure of 47% in the Northern Province (Clur, 2006).

A closer look at the frequency and severity of Rheumatic heart disease in the catchment area of Gauteng, South Africa, there is a revelation of a special situation, having equipped facilities offering tertiary care, against conditions that promote acute rheumatic fever and rheumatic heart disease. The prevalence of acute rheumatic fever and rheumatic heart disease is seen mainly among people in the black communities in South Africa, those who had a deprivation of socio-economic and human rights, attributed to apartheid. Frequent reinfection of group A streptococcus, resulting in relapses of acute rheumatic fever, prolonged hospitalization and surgery due to increasing severity of RHD is heavily expounded among young children in the rural parts of South Africa.

The vulnerable pediatric patients were seen too often present in a severe state of rheumatic heart disease, with cardiac failure, requiring immediate intervention, usually surgical. In the acute phase of the disease, conservative surgery is not advised, although mechanical valve replacement and anticoagulant therapy are necessitated. This requires professional expertise, and well-equipped tertiary centers, which a few developing countries can offer, guaranteeing lifelong anticoagulation therapy, prophylaxis and continuous surveillance after surgery. This is because the cost implications of surgery, antifailure and anticoagulation therapy are substantial among the rural patients, promoting the higher prevalence of severe rheumatic heart disease among communities of low socio-economic status.

South Africa listed rheumatic heart disease among the top ten causes of death in the 15–24-year age group. In the year 1973, RF/RHD was listed among the top 10 causes of death in the 15 - 24-year age group in South Africa. The disease accounts for about 15% of the pediatric cardiac patients admitted to South African hospitals. The need for a

comprehensive preventive campaign on rheumatic fever prophylaxis and socio-economic upliftment was recognized over 30 years ago. In 1983 it was suggested that a national register of RF/RHD patients be instituted along with patient identity/record cards to help the situation. An effective national campaign on the prevention of RF/RHD is long overdue. This study was conducted to identify areas with a high frequency and severity of RF/RHD within the referral range of the three pediatric teaching hospitals of the University of the Witwatersrand. Such information would identify geographical areas and communities for priority preventive action.

In India, a study looking into children <12 years as a factor influencing the progression of RHD to severity. Following Rheumatic Fever, children, mostly below 6 years of age rapidly developed mitral stenosis, severe enough to require operative treatment. Moderate to severe pulmonary venous and arterial hypertension was found in ¾ of the patients (Shrivastava & Tandon, 1991).

The journal of the American Heart Association conducted a multi-state model of residents diagnosed with RHD between 5-24 years of age, Rheumatic heart disease (RHD) is still a disease of international importance, yet little has been published about disease progression in the contemporary patient cohort. Multi-state models provide a well-established method of estimating the rates of transition between disease states and can be used to evaluate the cost-effectiveness of potential interventions. We aimed to create a multi-state model for RHD progression using serial clinical data from a cohort of Australian patients.

The Northern Territory RHD register was used to identify all Indigenous residents diagnosed with RHD between the ages of 5 and 24 years in the period 1999 to 2012.

Disease severity over time, surgeries, and deaths were evaluated for 591 patients. Of 96 (16.2%) patients with severe RHD at diagnosis, 50% had proceeded to valve surgery by 2 years, and 10% were dead within 6 years.

Of those diagnosed with moderate RHD, there was a similar chance of disease regression or progression over time. Patients with mild RHD at diagnosis were the most stable, with 64% remaining mild after 10 years; however, 11.4% progressed to severe RHD and half of them required surgery.

2.10 Effect of COVID-19 on RHD

A global pandemic of coronavirus disease (COVID-19) occurred between December 2019 to 2022, with some cases being reported to date, with over 210, 000 fatalities. Covid-19 is a type of severe acute respiratory syndrome (SARS) caused by coronavirus 2, where the first outbreak was reported in China, and is believed to have a zoonotic origin, with rapid rise of cases globally increasing by March 2020. This disease has proven to be an extremely fatal disease therefore it has become a disease of massive public health concern worldwide. It is highly transmissible from one person to another through several mechanisms, leading to the isolation of patients showing symptoms and testing positive to the coronavirus. Although stringent measures have currently been explored in various countries, to reduce this person-to-person transmission, it remains a significant challenge, especially among the most susceptible groups such as children, the elderly and the healthcare providers (Rothan & Byrareddy, 2020).

Covid 19 has proven to have a higher transmissibility and its effect on the body has a higher severity compared to the other SARS outbreaks. It also has more susceptibility to infection

with more severe effects and higher chances of death among patients with underlying chronic conditions such as cardiovascular diseases, and diabetes ("COVID-19 and CVD," n.d.). The cardiovascular system was the most affected in most cases, with affected viscosity of blood within the vessels, increasing the chances of acute cardiac events, and increased myocarditis, myocardial infarction and cardiac dysfunction especially on patients who have already been diagnosed with heart disease. This rendered CVDs the most common comorbidity among patients diagnosed with a positive Covid test, with higher numbers of admissions being patients with CVDs, hence more of them having severe morbidity and mortality. This was reported in China where about a quarter of the 138 patients admitted at the beginning of the pandemic had some form of cardiovascular disease, with 36% of those intubated or died having CVDs (Clerkin Kevin J. et al., 2020).

This has posed intense difficulty in the management of patients with CVDs who also get infected with coronavirus due to the limited management guidelines and strategies currently available. There has been a main challenge that scientists have debated upon in the management of CVDs, which is the use of Angiotensin- converting enzyme 2 (ACE2) in patients with covid 19. ACE2 is a widely used group of medications on patients with cardiovascular diseases and some current studies have revealed it as a functional receptor for covid 19, where infectivity begins by the attachment of the covid-19 protein spikes to the angiotensin-converting enzyme 2. Although this study has been published and letters written to this effect, the research has been limited on the decision on whether to continue the use of angiotensin converting enzyme inhibitors and angiotensin-receptor blockers, due to their presumed risk or benefits in some cases (Perel & Grobbee, n.d.).

Coronavirus disease has posed significantly increased negative effects and challenges for heart transplantation, and heart surgeries, affecting donor selection, reduced immunity and management of post-surgical and post-transplant patients.

2.11 Prognosis

The search of risk factors and comparison of progression-free survival between patients who did and did not receive penicillin, led to a prospective natural history study on children with latent RHD. It revealed that children had the earliest forms of RHD are at substantial risk for the progression of the disease (Beaton Andrea et al., 2017). Few patients die after the first attack (about 4%), and those who die usually have pericarditis (Keith et al., 1941).

The natural history of Acute Rheumatic Fever and Rheumatic heart disease f shows that a fifteen year follow up (1983–1998) of patients diagnosed with ARF in Brazil, 72.1% of them developed chronic valvular disease at least two years after the first attack (Meira et al., 2005). In Germany, the progression of mild to severe RHD among 159 ARF patients was 9.2±4.3 years and those who refused surgery after indication had a survival average of 0.44±0.06 years, after 5 years (Horstkotte et al., 1991).

2.12 Rheumatic Heart Disease Programming

The World Health Organization recommended the reduction of Rheumatic Heart Disease by 25% in persons 25 years and below by the year 2025. This recommendation was guided by the adoption of control programs worldwide, as the main driver to the reduction of Rheumatic heart disease burden in both developed and developing countries. These programs are to be designed and set up within surveillance and registries of persons living with rheumatic heart disease, to help support the primary, secondary and tertiary

interventions directed towards the patients and the large public within the most susceptible areas. These programs have been referred to as ‘Register-Based RHD control Programs’, which have been successfully set up in Australia, Fiji, New Zealand, and other Pacific Island nations, but rarely seen in African countries, India and South America, where reports of the high numbers of people living with rheumatic heart disease are recorded worldwide in these regions (Wyber & Kado, 2021).

Rheumatic heart disease, being a preventable type of CVD can be well controlled and eliminated worldwide, through proper set-up of the Register-based RHD programs, there are however basic components which should be implemented before setting up these programs, which are more than just provision of clinical care to patients living with RHD. The unique natural history of RHD of having an infectious period preluding to the occurrence of rheumatic heart disease, exposing an opportunity for involvement of different levels of health care, offering a broad range of services from community prevention of communicable diseases to prevention and control of non-communicable diseases, including conducting of open-heart surgeries and post-surgical care. It also exposes the need to integrate the different domains of RHD programming into the normal healthcare delivery routine in our countries.

The needed stakeholder engagement among the healthcare workers, communities and policymakers involved in the program tends to strengthen the support of all the six tiers of health system delivery. However, it is paramount that the baseline elements of initiating a Register-based RHD program are adhered to, including conducting an initial survey or study to determine the exact burden of disease that the country faces, setting up a sustainable governance structure, and inclusion in the wider health budget for proper

financing of the program activities. These baseline elements should however not hinder the setting up of an RHD program, as these elements can be updated or revised to strengthen the program. It is important to include the training component, laboratory, pharmaceutical, disease surveillance, health information systems, and primary healthcare as part of the register-based RHD program (*TIPS Handbook: Tools for Implementing Rheumatic Heart Disease Control Programmes (Second Edition) | RHD Action*, n.d.).

Countries exhibit different ways or methods of integrating data collection within their health systems. This is also important in the collection of the required variables within the registers in these RHD control programs, as it enhances cohesion within the health system reduces duplication of entries, and avoidance in overstretching the human resource. This eventually ensures that quality data is entered into the information systems, within the recommended levels of quality control.

There is an already increased awareness of the effect of rheumatic heart disease among different populations, and its chances of prevention which if not met leads to increased financial burden among the patients and their families, and increased morbidity and mortality. This has been the guidance to support its inclusion into conditions of public health importance and be part of the diseases of higher priority in the countries. Therefore, it is critical to have proper and sustainable governance within the RHD control programs that set up positive policy regulations, involving the community and people living with RHD and initiate implementation projects to help in the application of interventions. The inclusion of community and patients within governance helps the government understand the importance of allocating funds to run the programs, and long-term funding has been the mainstay of population-level impact felt from the already established register-based

RHD control programs in terms of a reduction in disease burden and incidence. It is also critical to carry out a cost-benefit analysis frequently within the RHD control program, to always support the need for budget inclusion.

Rheumatic heart disease can be widely prevented at the primary level by preventing the sequelae of acute rheumatic fever through proper diagnosis. Therefore, access to laboratory services is important during the setting up of these register-based rheumatic heart disease control programs. Facilities are encouraged to set up laboratories and hire well-trained human resources to offer simple and basic microbiology services, which help in the early diagnosis of group A streptococcus (GAS) infection, and guide on proper clinical management.

To have continued and sustainable healthcare services within health systems, the World Health Organization recommends integrating care services across all levels of care. In Rheumatic heart disease control programming, this can be done either through a vertical approach where there are RHD-specific clinics, with their staff, and the register embedded within these clinics, or a horizontal approach where the RHD control program is embedded within a universal health coverage, improving the laboratory and health systems to incorporate RHD care from prevention to surgical services needed to assist in the provision of proper, quality management (*TIPS Handbook: Tools for Implementing Rheumatic Heart Disease Control Programmes (Second Edition)* | *RHD Action*, n.d.).

Monitoring and evaluation of the effectiveness of these programs is required through the running of the RHD care services, advocacy, awareness creation and education are at the central point of maintenance of the program’s activities to maintain the government's

engagement and have multiple funding sources for the program activities. This should encompass the utilization of support from community leaders, people living with rheumatic heart disease, clinicians and researchers.

Furthermore, RHD must be included in the list of diseases that need notification as it has been proven to have components that call for its inclusion. These include RHD being a recognizable disease through its detailed diagnosis by the Jones criteria, therefore having a specific case definition. it is also a preventable type of disease, where we have primary prevention through proper management of GAS infections, and secondary prevention by provision of secondary prophylaxis through administration of benzathine penicillin G. Rheumatic heart disease's natural history presents different levels of action that can be taken to reduce the risk of increased severity and mortality. Rheumatic heart disease is highly susceptible to females, therefore, interventions can be targeted to the highly affected. The data collected from notification of RHD will serve as a central point in further understanding the disease burden and assist in making targeted interventions in reducing morbidity and premature mortality, and halting the disease incidence. (*TIPS Handbook: Tools for Implementing Rheumatic Heart Disease Control Programmes (Second Edition) | RHD Action*, n.d.)

2.13 Conceptual Framework

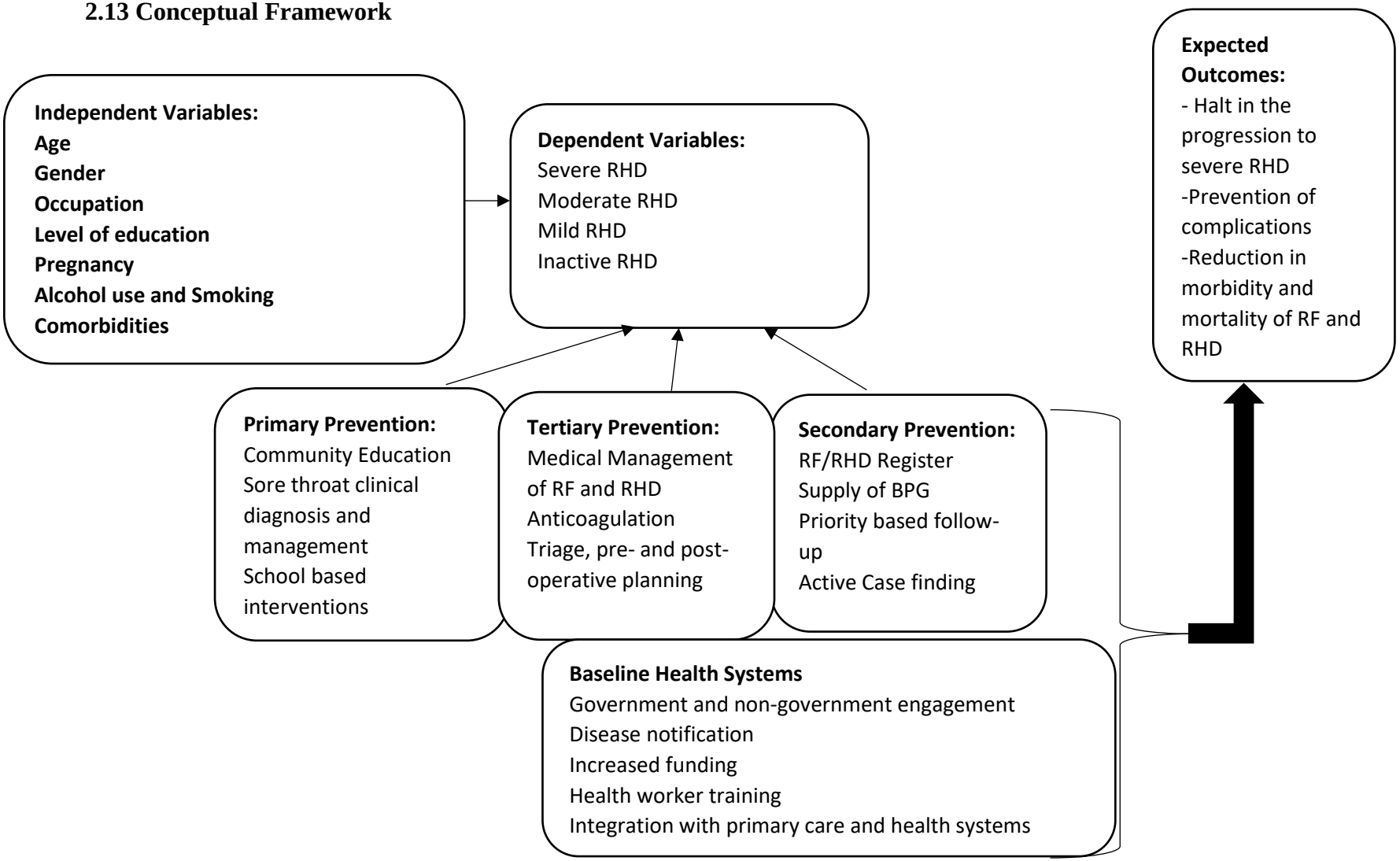

Figure 1: World Heart Federation for Rheumatic Heart Disease, Evidence, Advocacy, Communication and Hope (Wyber et al., 2014)**,** (Okello et al., 2013), (Damasceno et al., 2012) (Oli K., Asmera J., 2004)**,** (Szekely et al., 1973) (Shrivastava & Tandon, 1991)**,** (Clur, 2006)

In this conceptual framework, various factors (independent variables) contribute to the severity of rheumatic heart disease. For instance, demographic factors like age and gender might inherently predispose individuals to more severe disease forms, while behavioral factors such as smoking could exacerbate symptoms. Moderating factors, like healthcare access and disease management practices, can affect the extent to which these risk factors impact disease severity. Alcohol use and smoking is shown to increase the speed of conversion of RHD to severe cases, and co-existence with other chronic illnesses enhance the symptoms of RHD and may increase susceptibility to having more severe cases.

Other factors that increase susceptibility to Group A Streptococcus (GAS) infection and the subsequent development of acute rheumatic fever (ARF) include overcrowding, poor living conditions, malnutrition, limited access to healthcare, and poor hygiene. These conditions exacerbate the spread of infections and contribute to the persistence and severity of rheumatic heart disease in vulnerable populations.

This framework supports the study by highlighting key areas where interventions could be applied, either by targeting risk factors to prevent severe disease or by enhancing moderating variables to improve disease outcomes and quality of life.

CHAPTER THREE

3.0 METHODS

3.1 Study area

Moi Teaching and Referral Hospital is a national referral hospital in Kenya, located in Eldoret town, Uasin Gishu County.

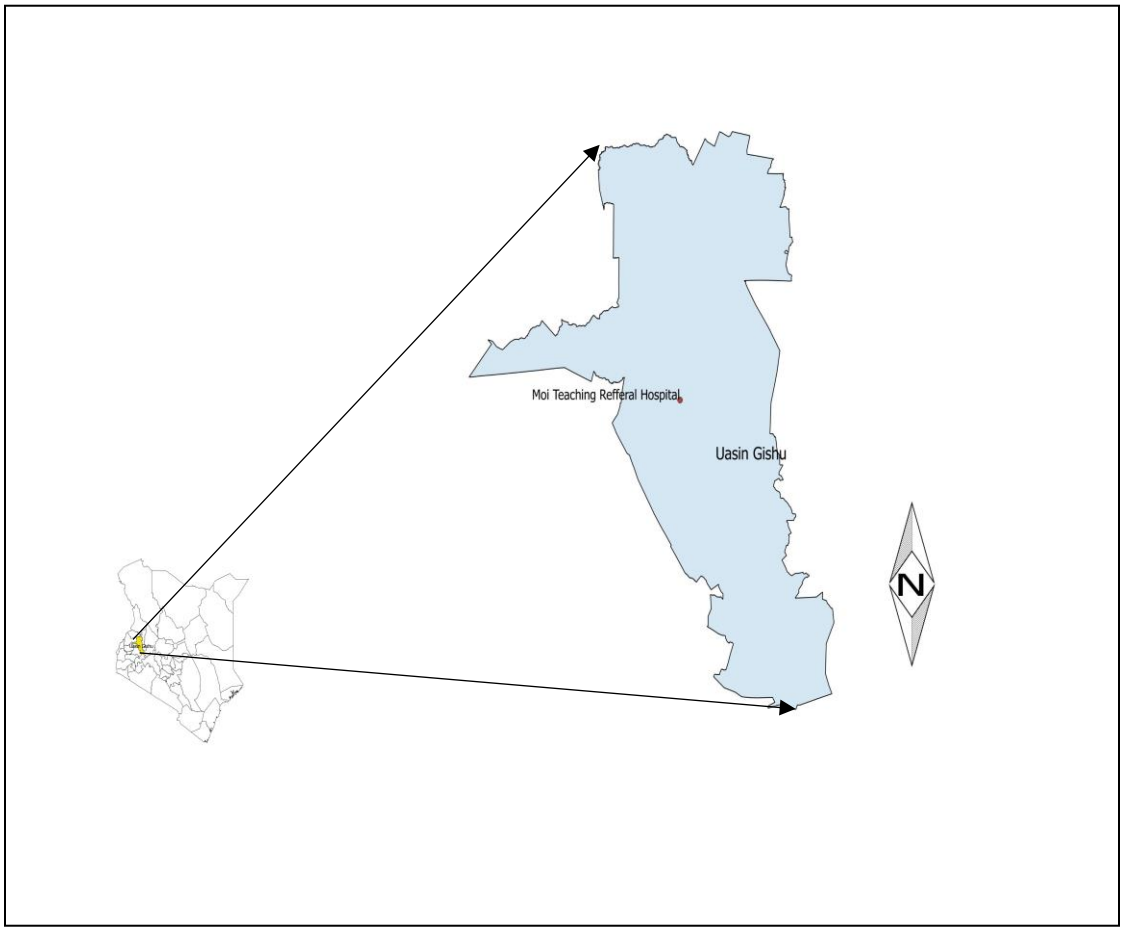

Figure 2: Map of Uasin Gishu County in Kenya, showing the location of Moi Teaching and Referral Hospital

Moi Teaching and Referral Hospital), serves the Rift Valley, Western and Nyanza regions in Kenya, offering a wide range of specialized care to cardiac disease patients in their active cardiac unit. It reported that a majority (64%) of their cardiac patients have RHD (Lumsden

et al., 2016). The large pool of RHD patients at MTRH, with distinctive characteristics, is essential in this study, as it reflects more generalizable findings on their dynamic of factors

3.2 Target Population

Patients seeking services at MTRH outpatient cardiac clinics during the study period.

3.3 Study Population

The study population included patients with Rheumatic Heart Disease, attending the cardiology outpatient clinic at Moi Teaching and Referral Hospital.

3.4 Study Design

This was an unmatched case-control study. Rheumatic heart disease has a long latent period between exposure and disease manifestation. This chronic aspect of RHD makes the use of a case-control type of study design most beneficial and advantageous for the identification of factors associated with the severity of RHD. It is also preferrable in studying several exposures and giving a risk approximation by the calculation of the odds ratio, thus identifying sub-groups with lower or higher risk.

A Case is defined as a patient who has been diagnosed with severe RHD as per the World Heart Federation's standardized and evidence-based criteria for echocardiographic diagnosis of RHD (Reményi et al., 2012). Severe RHD; patients have severe valvular disease/moderate/severe lesion with symptoms/ mechanical prosthetic valves and valve repairs including balloon valvuloplasty.

A control was defined as a patient who has been diagnosed with either moderate or mild RHD or inactive RHD. Moderate RHD were those patients who have any moderate valve lesion in the absence of symptoms with normal left ventricular function/mild mitral regurgitation and mild aortic stenosis/mild or moderate mitral or aortic stenosis/any

pulmonary or tricuspid valve lesion co-existing with a left-sided valve lesion. Mild RHD, have ARF with no evidence of RHD/trivial to mild valvular disease. Inactive RHD; patients with a history of ARF (no RHD) for whom secondary prophylaxis has been ceased (Reményi et al., 2012)

3.5. Inclusion Criteria

Any patients with rheumatic heart disease in the cardiac outpatient clinics at MTRH, after receiving their initial care during the study period, was classified by the principal investigator as a case or a control.

3.6 Exclusion Criteria

Any patient with rheumatic heart disease at the outpatient clinic in MTRH who is critically ill and needs emergency intervention during the visit.

3.7 Sample Size Determination

The sample size was calculated from the Fleiss, J.L formula (Fleiss et al., 1980) with an assumption of 80% power, an equal number of cases and controls, and we set to detect an odds ratio of ≥ 3 with a significance level of $P \leq 0.05$.

A study done in Brazil, on a long-term follow-up on RHD progression to severity found that a low level of education (for the mother or adult patients) was a significant risk factor for the level of RHD severity, whereas those with <4 years of education had 4 times the risk of developing a severe form of the disease (Meira et al., 2005). Based on this study, the level of education was a major exposure to the progression of RHD to severity. In Kenya, from the national adult literacy survey report, 38.5% of Kenyan adults were found to have a low level of education (Kenya National Adult Literacy Survey report, 2009), therefore, we assumed the exposure (the low level of education) among the controls to be

estimated at 40%. These assumptions will give the odds ratios that are significant to the researchers in this study.

$$n = \left(\frac{r+1}{r}\right)\frac{(\bar{P})(1-\bar{P})(Z_{\beta}+Z_{\alpha/2})^2}{(P_1-P_2)^2}$$

Where.

- *n*= Sample size in the case group
- *r*= ratio of controls to cases (r =1)
- $\bar{P}$= A measure of variability
- P_1-P_2= Effect size (the difference in proportions
- Z_{β} = The desired power (80%)
- $Z_{\alpha/2}$ = The desired level of significance, typically 1.96 for 0.05 significance level

To get the proportion of the cases exposed:

$$p_{case\exp} = \frac{ORp_{controls\exp}}{p_{controls\exp}(OR-1)+1}$$

$$p_{case\exp} = \frac{3.0(.40)}{(.40)(3.0-1)+1} = \frac{1.2}{1.80} = .667$$

$$n = 2\frac{(0.533)(1-0.533)(0.80+1.96)^2}{(0.667-0.40)^2}$$

n= 54.8 therefore, ~55 cases and 55 controls, a total of 110 participants

3.8 Sampling Technique

Probability sampling, using the systematic sampling technique was used, where we divided the sample size by the number of expected working days (20 days). Therefore, n= 110/20= 6 participants per day, as the ratio of cases to controls, is 1:1. With 30 patients scheduled for each clinic day, the selection of the consecutive participant was after every 5 patients, at the waiting bay after checking vitals.

Based on the inclusion criteria of the cases and controls, the first case to be seen in the clinic was the first participant in the study, after receiving initial care and consenting to be included in the study. For each case, one consecutive control was selected, this process continued until the expected participants were included per day (6 participants), and the total sample size was calculated for the period of data collection of 20 days (110 participants, with 55 cases and 55 controls) was attained. If a participant was sampled for the study but did not consent, he or she was replaced by the consequent participant. Participants under 18 years of age would verbally assent to the interview, and the parent/guardian accompanying them signed the written consent. Those who were not accompanied by either a parent or a guardian were not allowed to participate in the study, therefore replaced by the next consenting participant.

3.9 Data Collection

A structured questionnaire was used to collect information from the face-to-face interviews, of the cases and controls, and their patient files. This was done at a room next to the consultation room. The questionnaire was divided into dependent variables, which is a diagnosis of rheumatic heart disease as either a case or a control based on the case definition.

The independent variables, which included demographic variables (age, sex, residence and occupation); weight and height, to get the body mass index to information on obesity or malnutrition/ undernutrition; history of smoking and alcohol use; a period in which the patient has lived with the diagnosis; comorbidities, allergies; lifestyle focusing on diet and exercise; where healthy diet was described as a diet that has a balance of macronutrients (carbohydrates, proteins and fats) and micronutrients, while average diet was described as

one that may lack essential nutrients like vitamins, minerals or fiber. Exercise included incorporation of a regular exercise regimen including walking and sport activities . We inquired about the family's medical history of heart disease and other comorbidities. The female respondents were questioned about their history of use of contraception, pregnancy or if they were in their postpartum period.

The echocardiogram information on the diagnosis, which is done and reported by echocardiographic technicians was sought from the patient's file after they received their initial medical care. From this echocardiogram, and using the WHF criteria for diagnosis of RHD, severe RHD was classified as cases and mild and moderate RHD as controls. The diagnosis and severity of RHD were determined from the latest echocardiogram and clinical presentation at the interview. The echocardiogram must have been performed within 6 months for cases and within 1 year for controls.

Severe RHD were those with severe valvular disease/ moderate/severe lesion with symptoms/mechanical prosthetic valves and valve repairs including balloon valvuloplasty. Moderate RHD had any moderate valve lesion in the absence of symptoms with normal left ventricular function/mild mitral regurgitation and mild aortic stenosis/mild or moderate mitral or aortic stenosis/any pulmonary or tricuspid valve lesion co-existing with a left-sided valve lesion. Mild RHD had ARF with no evidence of RHD/trivial to mild valvular disease and inactive RHD were patients with a history of ARF (no RHD) for whom secondary prophylaxis has been ceased (Reményi et al., 2012). The height and weight measurements were done using a two-in-one stadiometer and weighing scale, which was calibrated every morning before the commencement of data collection.

The principal investigator coded the severity of the RHD cases by the grading proposed by the World Heart Federation (Reményi et al., 2012), and the questionnaire was translated into Kiswahili for effective communication with the participants. Training of research assistants who administered the face-to-face interviews using tablets was done a week before the pilot study.

Piloting and pretesting of the questionnaire were done two weeks before the study, this helped to check the feasibility of the study in terms of the process of collecting and management of the data, and the general process expected for the study. It also aided in removing ambiguity from the questionnaire and clarifying response categories, and the validity and reliability of the questionnaire were ensured.

The pilot study site was at MTRH cardiac clinics; this gave a clear expectation of the cost, accessibility, methods and tools for the main study. The sample size for the pilot study was determined based on the Rules of Thumb for scientific studies: Rule of 10, which is specific for a binary outcome (case and control) (Belle, 2011), where 10 participants each from the outcome of interest were selected, therefore, 10 cases and 10 controls were the sample size for the pilot study. Written informed consent was obtained, and the interview was done after the participants received initial medical care. To mitigate the chances of encountering a pilot participant, a screening question was administered before commencement of each interview during the main data collection period, asking whether the participant took part in any recent similar study.

3.10 Data Analysis

Data was validated, cleaned, and analyzed using Microsoft® Excel 2016 and Epi Info™ version 7.2 statistical software. Descriptive analysis of continuous variables was done by calculation of measures of central tendency (mean and medians) measures of dispersion (standard deviation and range), and categorical variables were analyzed using frequencies and proportions. The cases (severe RHD) were coded as 1 and controls (mild and moderate RHD) as 0.

Bivariate analysis of continuous variables was compared using the student's T-test, and categorical variables of factors associated with severity were done by calculation of odds ratios (OR) at a 95% confidence interval and p-value <0.05 being used as a measure of association. An OR of >1 was considered a significant risk factor, <1 a protective factor and an OR of 0 was considered as not having any effect on the severity of RHD. A confidence interval of 95% and p-values were used to assess the variability and significance of the OR. A p-value of ≤0.05 was considered significant.

Multivariate analysis was done using unconditional logistic regression, using backward elimination. The significant factors, with a p-value of ≤0.2 were subjected to an unconditional logistic regression model and a variable with a p-value of ≤0.05 was considered statistically significant. Factors included in the model include unemployment, being obese and overweight, having comorbidities, a current or previous history of alcohol use, lack of regular exercise, and having a family history of chronic illness.

3.11 Ethical Considerations

Permission was granted by the Institutional Research and Ethics Committee (IREC), with approval number 0003520, and approval was sought from Moi Teaching and Referral

Hospital through the Chief Executive Officer. Clearance to conduct my studies was also sought from the Kenya Field Epidemiology and Laboratory Training Program, and the National Commission for Science, Technology & Innovation (NACOSTI).

Written informed consent was sought from the eligible participants or a responsible adult and assent for the minors with a written consent from the parent or guardian. Recruitment was conducted after receiving initial care.

Confidentiality of the study participants was observed, no personal identifiers were used and there were no incentives given nor coercion done to participate. Respondents were informed of their freedom to withdraw from the study at any point during the study if they wished. There were no direct benefits to individuals who participated, and no risks for participating, without any penalty for refusal.

Information that was obtained was stored in a password-protected computer at the principal investigator's office, only she has the passwords to access the data, and the confidentiality of questionnaires was maintained and stored in storage cabinets.

CHAPTER FOUR

4.0 RESULTS

4.1 Introduction

This study was conducted and analyzed between September 2019 to November 2020.

The total number of respondents was 110, with 55 cases and 55 controls. The non-respondents encountered were replaced systematically. Total mean age was 35 among the cases, with a standard deviation of 11.4, and 27 among the cases, with a standard deviation of 11.3.

4.2 Descriptive Analysis

The mean age among the male and female cases was 35 (SD±11.4), and the mean age of controls was 27 (SD±11.3). The age group with the highest number of cases was 24-28 years at 17.4%, and 14-18 years was the highest among the controls at 29.3%. A cumulative percentage of 58% and 70.8% of cases and controls respectively are within the age groups of below 33 years.

The most common age group of cases among the female is between 24 and 38 years of age, and among 14-28 years old in male. Among the controls, the most common age-group among the females in 14-28-year-olds, and 14–23-year-olds among the males.

Table 2: Table 2. Age Distribution Among RHD Male and Female Patients at MTRH Cardiac Clinic, 2020 (N=110)

			Cases (n=55)	**Controls (n=55)**
	Age(All Cases):	Mean= 35(SD±11.4)		
		Median= 31		
	Age (All Controls):	Mean= 27(SD±11.3)		
		Median= 24		
	Age-Group (All):		**Percentage**	**Percentage**
		24-28	17.4	17.1

		14-18	13.1	29.3
		19-23	14.5	19.5
		29-33	13	4.9
		34-38	14.5	7.3
		39-43	7.2	12.2
		44-48	11.6	2.4
		49-53	2.9	7.3
		54-58	5.8	0
Age-Gender Frequency Distribution of Cases and Controls				
	Female		**Male**	
Age-group:	**Cases (frequency)**	**Controls (frequency)**	**Cases (frequency)**	**Controls (frequency)**
14-18	5	6	4	6
19-23	7	4	3	4
24-28	8	6	4	2
29-33	6	1	1	2
34-38	7	3	1	2
39-43	2	5	0	3
44-48	4	1	0	3
49-53	1	2	0	2
54-58	2	1	0	2
Total	**42**	**29**	**13**	**26**

The female cases were 72.5%, with 68% female controls. The most common occupation in both genders was farming at 37.7% among the cases and students and farmers tied in numbers among the controls at 31.7%. The number of unemployed among the cases was 11.6%, with only 2.4% of the controls being unemployed.

Table 3: Gender and Occupation Distribution Among RHD Patients at MTRH Cardiac Clinic, 2020 (N=110)

			Cases (n=55)	**Controls (n=55)**
	Gender:		Percentage	Percentage
		Female	72.5	68
		Male	27.5	32
	Occupation (Top 5) (M&F)			
		Farmer	37.7	31.7
		Business Owner	20.3	9.8
		Students	17.4	31.7
		Unemployed	11.6	2.4
		Casual laborer	2.9	17.1

Women of childbearing age among the cases were 78.2% with 30.2% of them being in some form of contraception, while among the controls 45.4% were of childbearing age while 20% of them were in current use of contraception, none of the females in the control group was pregnant at the time of the interview.

The most usual form of contraceptive in use among the cases was intra-uterine copper device and oral contraceptive pills at 30.8%, and the three-month injection was the most usual form among the controls. Participants who were pregnant were 2.3% (1), who was classified as a case (severe RHD), while one had hysterectomy done.

Table 4: Distribution of Women of Child-Bearing Age Among RHD Patients at MTRH Cardiac Clinic, 2020 (N=68)

Women of Child-Bearing Age			**n=43 (78.2)**	**N=25 (45.4)**
		Age-Group	Percentage	Percentage
		15-19	0	0
		20-24	25	9.1
		25-29	16.7	36.4
		30-34	25	9.1
		35-39	8.3	27.3
		40-44	16.7	18.2
		45-49	8.3	0
Current use of contraception:			**n=13(30.2%)**	**n=11(44%)**
	3-month Injection		7.7	27.3
	Bilateral Tubal Ligation		7.7	9.1
	Condom		7.7	9.1
	Herbal		7.7	0
	Implant		30.8	18.2
	Intra-Uterine Copper Device		30.8	18.2
	Oral Contraceptive Pills		7.7	18.2
	Women of Childbearing Age		**n=43 (f)**	**N=25**
		Hysterectomy	2.3 (1)	0
		Pregnant	2.3 (1)	0

Type of diet among the cases, 69.5% of both male and female had a relatively average diet, and only 26.1% reported having a healthy diet. On the type of diet among the controls

(M&F), 61% of them had a relatively average diet, and only 29.3% reported having a healthy diet.

Table 5:Diet Among RHD Patients at MTRH Cardiac Clinic, 2020 (N=110)

			Cases (n=55)	**Controls (n=55)**
	Diet:	Healthy Diet	26.1	29.3
		Average Diet	69.5	61
		Low Fat	55.1	39
		Low Salt	66.7	56.1

Body Mass Index (BMI) of overweight and obese ranges among all the adult cases, were (21) 43.7%, where 90% of them were female cases. All the obese participants were females, (15.6% cases and 12.9% controls), none of the male participants were obese. We found 43.7% overweight females cases compared to 12.5% male cases, and 9.7% overweight female controls with no overweight male controls.

Table 6: Body Mass Index Among Rheumatic Heart Disease Patients ≥18 Years at MTRH Cardiac Clinic, 2020

	Cases (%), n=32	**Controls (%), n=31**
Female		
Obese	5 (15.6)	4 (12.9)
Overweight	14 (43.8)	3 (9.7)
Underweight	6 (18.7)	5 (16.1)
Normal	7 (21.9)	19 (61.3)
Male	**Cases (%), n=16**	**Controls (%), n=15**
Obese	0	0
Overweight	2 (12.5)	0
Underweight	6 (37.5)	3 (20)
Normal	8 (50%)	12 (80%)

In the period in which all the cases lived with RHD (M &F), 42% of them lived with RHD for 10 years or more, with an average of 9.1 years. While 34% of the controls had RHD for 10 years or more, with an average of 7.4 years.

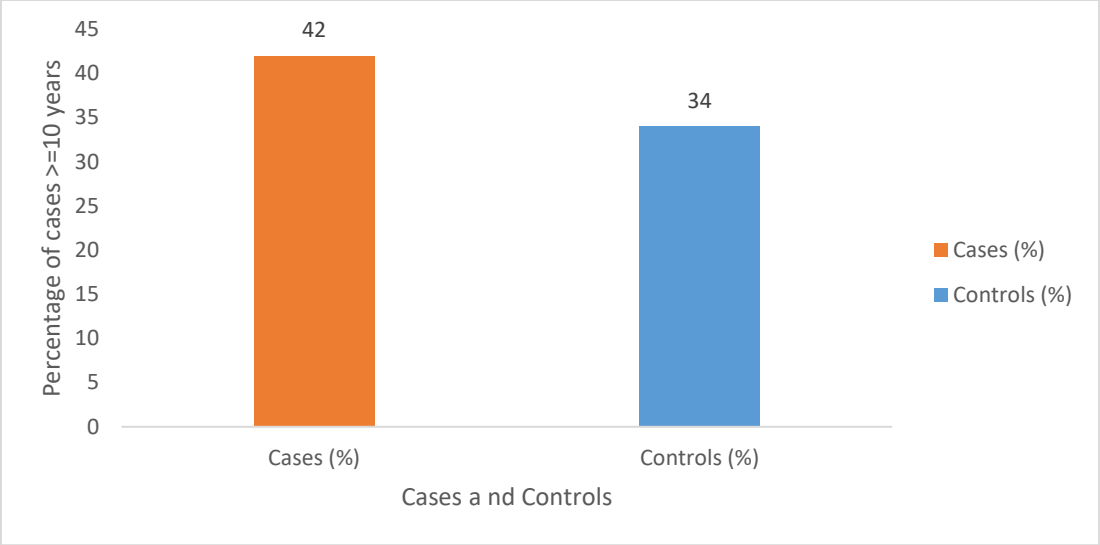

Figure 3: Proportion of all Cases and Controls who have been living with RHD for ten years or more, MTRH, Kenya 2020

The proportion of male and female cases with comorbidities was 25% (14), and 12.7% (7) of the controls had comorbidities. The most common comorbidity among the cases was stroke, and hypertension was the most common comorbidity among the controls.

*One control had Anemia, 2 cases with HIV and one case with cancer.

Table 7:Comorbidities Associated with Rheumatic Heart Disease among Male and Female Patients at MTRH Cardiac Clinic, 2019

Variables	Cases% (f) (n=14)	Controls% (f) (n=7)
Stroke	28.6 (4)	0.0
Hypertension	21.4 (3)	42.9 (3)
Epilepsy	7.1 (1)	14.3 (1)
*HIV	14.3 (2)	0.0
*Cancer (Specify Type)	7.1 (1)	0.0
Asthma	0.0	14.3 (1)
Chronic Kidney Disease	14.3 (2)	0.0
Rheumatoid Arthritis	0.0	14.3 (1)
Hyperthyroidism	7.1 (1)	0.0
*Anemia	0.0	14.3 (1)
Total	100.0	100.0

Tobacco use, both previously and currently was at 5.4% (3) among all the participant cases, while 1.8% (1) of the controls had a history of smoking. On the participants who had a previous history of alcohol intake, and those currently taking, 20% (11) were cases, and 1.8% (1) were controls.

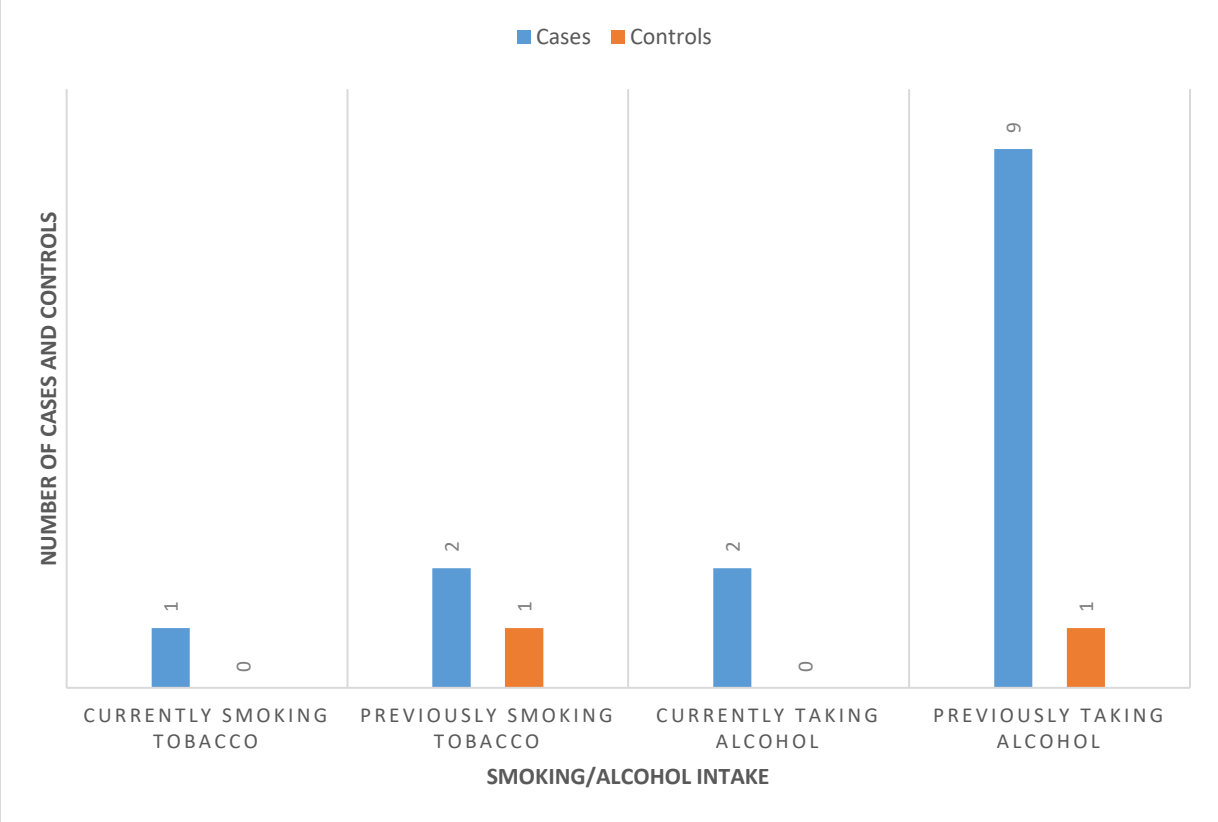

Figure 4: Number of cases and controls smoking tobacco and taking alcohol among the RHD Male and Female patients, MTRH, Kenya, 2020

The proportion of all cases with a family history of chronic illness was 78.2%, whereas 30.9% of the controls had a family history of chronic illness.

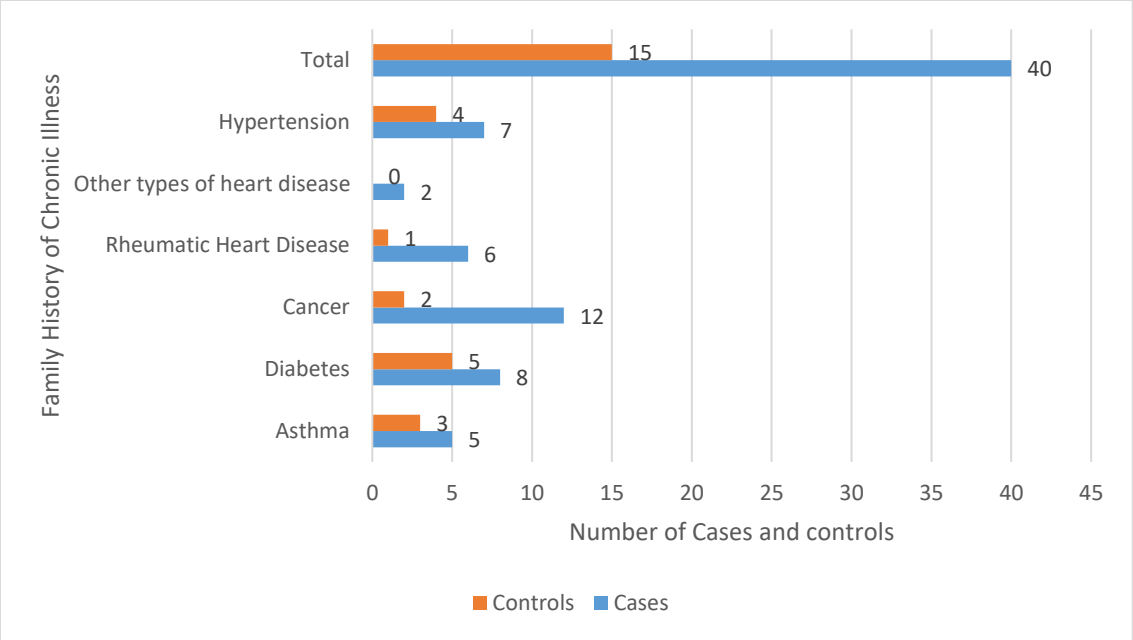

Figure 5: Number of Cases and Contols among RHD Male and Female patients with a family history of chronic Illness, MTRH, Kenya, 2020

Male and Female cases with systolic blood pressure at or above 140 mmHg at the time of the interview were 16.4% and 10.9% of the controls had blood pressure at or above 140 mmHg. Diastolic blood pressure was increased (at or above 90 mmHg) in 18.1% of the cases, and 5.4% of the controls.

Table 8:Blood Pressure Analysis Among RHD Male and Female Cases and Controls in MTRH, Kenya 2020

Blood Pressure	Method	Cases (%)	Controls (%)
Systolic Blood Pressure (>=140mmHg)	Digital Blood Pressure machine	16.4	10.9
Diastolic Blood Pressure (>=90)	Digital Blood Pressure machine	18.1	5.4

4.3 Risk Factor Analysis

4.3.1 Bivariate Analysis

The significant risk factors revealed among the male and female participants in this study included unemployment, overweight/obesity, and the presence of comorbidities with ORs of 6.612 (p<0.0001), 4.24 (p=0.0022) and 2.34 (p<0.0001) respectively. Previous and current use of alcohol and smoking was also a significant risk factor (OR=13.5; p<0.0001 and 3.12 ; p=<0.0001 respectively) with a higher chance of exposure to severe RHD seen in participants who were not doing any regular physical exercises, with an OR of 2.318 (p=0.17). Doing regular exercises was found as a protective factor to developing severe RHD (OR=0.43; p=0.0215).

The higher blood pressure measured during the interview was also picked as a slightly significant risk factor to having severe RHD, with an OR of 1.598 (p=0.0407). Male and Female patients who had a family history of chronic illness, as an exposure, had an OR of 8.02 (p=<0.0001). Among the female participants, significant association was seen with those using some form of contraceptive, with an OR of 1.24 (p=<0.0001). Factors with p-values of ≤0.2 and OR of >1 were subjected into an unconditional regression model with backward selection.

Two by Two Tables showing the variables Assessed for Association

Table 9: Two by Two table of Age-Group, <18years Vs >18 Years

Exposure (<18years)	**Outcome**		
	Cases	Controls	Total
Yes	7	16	23
No	48	39	87
Total	55	55	110
OR= 0.36 (0.13- 0.95)			
P value= 0 (0.05- 0.25)			

Table 10: Two by Two table of Female Vs male

Exposure (Female)	**Outcome**		
	Cases	Controls	Total
Yes	40	37	77
No	15	18	33
Total	55	55	110
OR= 1.3 (0.57-2.94)			
P value= 0 (0.59- 0.85)			

Table 11: Occupation, Unemployment Vs Employed

Exposure (Unemployment)	**Outcome**		
	Cases	Controls	Total
Yes	6	1	7
No	49	54	103
Total	55	55	110
OR= 6.61 (0.77- 56.88)			
P value= <0.0001 (0.05- 0.22)			

Table 12: Overweight and Obese Vs other BMI

Exposure (Overweight & Obese)	**Outcome**		
	Cases	Controls	Total
Yes	21	7	28
No	34	48	82
Total	55	55	110
OR= 4.24 (1.62- 11.08)			
P value= <0.0001 (0.25- 0.5)			

Table 13: Underweight Vs other BMI

Exposure (Overweight & Obese)	**Outcome**		
	Cases	Controls	Total
Yes	12	8	20
No	43	47	90
Total	55	55	110
OR= 1.64 (0.61- 4.39)			
P value= <0.0001 (0.12- 0.35)			

Table 14: Comorbidities Vs. No comorbidities

Exposure (With Comorbidities)	**Outcome**		
	Cases	Controls	Total
Yes	14	7	21
No	41	48	89
Total	55	55	110
OR= 2.34 (0.86- 6.36)			
P value= <0.0001 (0.15- 0.40)			

Table 15: Smokers Vs Non-Smokers

Exposure (Smoking)	**Outcome**		
	Cases	Controls	Total
Yes	3	1	4
No	52	54	106
Total	55	55	110
OR= 3.12 (0.31- 30.92)			
P value= <0.0001 (0.001- 0.15)			

Table 16: Alcohol Vs Not taken Alcohol

Exposure (Alcohol)	**Outcome**		
	Cases	Controls	Total
Yes	11	1	12
No	44	54	98
Total	55	55	110
OR= 13.5 (1.68- 108.65)			
P value= <0.0001 (0.1- 0.35)			

Table 17: Not doing Regular Exercise Vs Doing regular Exercise

Exposure (Not Doing Regular Exercise)	**Outcome**		
	Cases	Controls	Total
Yes	38	27	65
No	17	28	45
Total	55	55	110
OR= 2.32 (1.06- 5.05)			
P value= 0.17 (0.55- 0.8)			
Exposure (Doing Regular Exercise)	**Outcome**		
	Cases	Controls	Total
Yes	17	28	45
No	38	27	65

Total	55	55	110
OR= 0.43 (0.2- 0.94)			
P value= 0.21 (0.098- 1.271)			

Table 18: Family history of chronic illness Vs. No family history of chronic illness

Exposure (Family history of chronic illness)	**Outcome**		
	Cases	Controls	Total
Yes	43	17	60
No	12	38	50
Total	55	55	110
OR= 8.01 (3.4- 18.9)			
P value= 0.4576 (0.5- 0.9)			

Table 19: Use of Contraceptives among women of fertile ages Vs. Not using contraceptives

Exposure (Use of Contraceptives)	**Outcome**		
	Cases	Controls	Total
Yes	13	11	24
No	42	44	86
Total	55	55	110
OR= 1.24 (0.5- 3.07)			
P value= <0.0001 (0.14- 0.37)			

4.3.2 Multivariate analysis

Factors included in the model include unemployment, being obese and overweight, having comorbidities, current or previous history of alcohol use, lack of regular exercising, having a family history of chronic illness, current systolic blood pressure measurement of >140mmHg, length of period with the diagnosis and current use of contraceptives.

Table 20: Multivariate Analysis of Factors Associated with the Severity of RHD among Patients at MTRH, Kenya, 2020

Variables (Exposure)	P- Value	95%C.I
Occupation (Unemployment)	**0.000217**	**4.89-10.45**
BMI (Overweight and Obese)	0.082042	0.0203- 0.151

Comorbidities	**0.009531**	**1.3150 - 12.476**
Alcohol (Previous and current smokers)	**0.000007**	**8.4-13.88**
Not doing Regular Physical Exercises	**0.021**	**1.8-17.69**
Family History of Chronic Illness	0.979	1.0459- 1.709
Current systolic blood pressure measurement >140mmHg	0.170	0.66- 0.995
Length of period living with the diagnosis	0.286	0.075- 3.97
Current use of contraceptives (Female)	0.44	0.035- 0.115

In multivariate analysis, occupation, comorbidities, alcohol use and lack of regular exercise remained as significant in the first round with P values of 0.000217, 0.009531, 0.000007, and 0.021, respectively.

CHAPTER FIVE

5.0 DISCUSSION

The WHO RHD Global Status Report states that RHD is common between the ages of 5-15 years but can generally be present at any age. This study shows a similar finding, as more than a quarter of the controls are in the ages 14-18 years, which aligns with the status report, but among the cases, most of them are between 19-28 years of age with many of them reporting the onset of RHD being when they were between the ages 5-12 years. This can be explained by the fact that these are the school-going children, who are more susceptible to upper respiratory tract infections (URTIs) or pharyngitis due to their expected poor hand washing practices, questionable hygiene, and sharing toys or school materials with a propensity of putting them in their mouths. The untreated pharyngitis, which is caused by GAS leads to ARF, eventually RHD becomes a sequela of this infection. Furthermore, these children are still developing their immunity, and balancing their responses to organisms, therefore making them prone to recurrent infections leading to severe forms of Rheumatic Heart Disease.

The WHO report also states that females have twice the risk of developing RHD than males, which aligns with this study as many of the patients selected, both cases and controls, were females, and further analysis shows that being female is a significant exposure to getting severe RHD. Some studies show that women have a stronger immune response to infections and a higher autoimmune response compared to men, and RHD occurs as an autoimmune mimicking effect of group A streptococcus on the heart valves, making them more prone to RHD than men. Women are also at a higher risk of upper

respiratory tract infections and pharyngitis, as most of them are the primary caregivers of children, who are more prone to infections, and in turn, pass them on to their mothers. The women who already have RHD are still susceptible to recurrent infections, therefore causing more severe disease. Women especially in their child-bearing ages undergo numerous hormonal and environmental changes, which may be mistaken for other illnesses, therefore leading to late or misdiagnosis of acute rheumatic fever and Rheumatic heart disease.

Globally, the areas with RHD endemicity, it is the principal type of heart disease in pregnant women. There is a high morbidity and mortality among pregnant women with RHD in South Africa. In this study, there was only one woman who was pregnant had severe Rheumatic Heart Disease. Pregnancy is a low immunity state, which promotes higher chances of infections, therefore having a higher chance of acquiring acute rheumatic fever. Most pregnant women may have the symptoms of ARF mistaken or misdiagnosed as other conditions, thus increasing their chances of getting RHD, more so being at a higher risk of severe disease due to late interventions. Pregnant women with RHD tend to have recurrent pharyngitis due to their low immunity state, therefore more damage to the heart valves, causing more severe disease.

Research has shown that birth control pills compound the risk of complications among patients with RHD. We found out that women of reproductive age who are on some form of contraception are significantly exposed to having severe RHD, but the use of oral contraceptives as a form of contraception was not a significant risk factor to progression of disease to severity. This might be explained by the correlation of the use of oral

contraceptives to a reduced level of immunity, but this assumption needs to be further studied or researched upon.

Poverty has been highly linked to the presence and increase in severity of RHD, as depicted in Kinshasa, where a higher incidence of RHD was seen in the slums, as compared to children in city schools. This is like MTRH, looking at the differences in the socio-economic status between cases and controls, where being unemployed was a significant risk factor for the presence of severe RHD. Low socioeconomic status exposes people to harsh living conditions in overcrowded places with poor sanitation, poor housing, and unclean water. These factors increase the chances of getting acute rheumatic fever, if untreated, or poorly managed, leading to rheumatic heart disease. In 2016, a study was done in MTRH, on the geographical and physical residences of patients with rheumatic heart disease, which showed that most of the patients lived in informal settlements in and around the towns surrounding Uasin Gishu County. Knowing that these environmental factors are the main drivers to getting RHD, a preventable heart disease, the residents of these poor and informal settlements were very susceptible to not only acute rheumatic fever but also other infectious diseases. Those patients with RHD who continue residing in these informal settlements have a propensity of acquiring recurrent infections, which has been proven to increase the damage of the heart valves, causing more severe disease.

A case-control study on socio-economic factors in Uganda such as income status and employment status showed that there was a trend toward increased risk of rheumatic heart disease in association with unemployment leading to poor management of ARF and RHD, predisposing the patients to the progression of RHD to severity. This study has the same finding, in that, the comparison of cases and controls on unemployment shows a significant

effect on having a severe form of RHD rather than a moderate or mild form. The insights on the financial burden of RHD by Watkins & Daskalakis show that there is a significant economic cost towards its treatment and management, to sustain or improve the status of living for patients with RHD. Uganda reported that the cost attributed to RHD was approximately 414 million USD in 2018. This is an expensive uptake in families in the low and middle-income countries, where the patients may find it hard to meet their medical needs due to a lack of enough income. Furthermore, the economic burden of diagnosis of rheumatic heart disease and follow-up treatment or management limits low socio-economic patients from proper control and prevention to severe disease and adds to their continued exposure to poor sanitation and crowded living conditions causing recurrent infections thus a higher chance of progression to severe rheumatic heart disease.

Non-communicable diseases in general, have been on the rise both globally and in Kenya. There are five main risk factors attributed to the occurrence of NCDs and these include harmful use of alcohol, tobacco smoking, physical inactivity, unhealthy diets, and air pollution. We found that almost a quarter of the cases were either currently taking alcohol or had a previous history of heavy alcohol intake, revealing it as a highly significant risk factor for progression to severe RHD compared to the controls. Alcohol use is known to lead to poor nutrition or undernutrition, therefore leading to reduced immunity thus increased susceptibility to infections. In addition, alcoholics are environmentally exposed to allergens that promote the occurrence and development of pharyngitis and other upper respiratory tract infections, leading to an increased chance of acquiring acute rheumatic fever, which, if mismanaged or left untreated, causes RHD. Patients with RHD and

alcoholics are also exposed to these conditions continuously, causing recurrent infections and damaging the heart valves more, causing an increase in the severity of RHD.

Smoking also showed a slight difference between the cases and controls, therefore playing a significant role in the progression to severity in patients with RHD. Smoking affects the healing process of the body as it promotes organism growth since it reduces oxygen perfusion in the tissues. This may sustain an infection by GAS and promote autoimmunity to mimic the immune response/effect on the heart, causing severe damage to valves, or more damage to patients already diagnosed with rheumatic heart disease.

Hypertension is known as a major risk factor for the development of other cardiovascular diseases. A considerable number of our participants categorized as cases (severe RHD), had increased systolic blood pressure of above 140 mmHg during the interview. This can be explained as hypertension reduces blood perfusion to vital areas in the body, hence, may promote the presence of disease or infection in the heart valves, causing more damage thus severe RHD. Hypertension increases due to several factors in the body, including increased blood volume, and blockage of the arterial diameter either through cholesterol accumulation or restrictive arterial walls.

Most of the cases were not doing regular physical exercises and this was a significant risk factor in the progression of RHD to the severity in comparison with the controls, where more than half were doing regular physical exercises, and this was found to be a protective factor to developing severe RHD. Performing regular exercises improves cardiovascular health in several ways. It strengthens the heart muscles, improves blood circulation, and

lowers blood pressure, therefore promoting healthy heart functions. It also increases the flexibility of the arteries, improving vasodilation thus reducing chances of hypertension.

Hypertension is known to worsen the damage of the valves caused by rheumatic heart disease, through its debilitating effect on the blood volume and heart functions. One of the other positive effects of exercise includes the reduction of bad cholesterol (Low-density lipoproteins (LDL)) which, when it builds up in the arterial walls, reduces the sizes of the arteries, making them more constricted thus leading to high blood pressure, causing more severe disease. Exercise also assists in removing LDL from the arteries, increasing the absorption of good cholesterol (High-Density Lipoproteins (HDL)) and promotes a healthy weight through the burning of calories from the body. Individuals who exercise also tend to promote their healthy lifestyle choices of not smoking, not taking alcohol and eating a balanced diet, with regular health check-ups to properly manage rheumatic heart disease.

This study looked at the nutritional status of the participants, finding that almost half of the cases were obese or overweight, with most of them being female. Exposure to being overweight or obese was found to be a significant risk of having severe RHD. Poor nutrition or undernutrition leads to poor immunity, therefore having a higher chance of recurrent infections among the patients with RHD, leading to more damage to the heart valves, and more severe disease.

The length of duration of having RHD (an average of more than 10 years), and the presence of comorbid illness, are some of the aspects which drive rheumatic heart disease into progression to severity. We found a similarity, as a quarter of the cases had a comorbid disease, which is a significant risk factor to the progression of RHD to severity in

comparison to the controls. Looking at the length of duration, the patients had RHD, almost half of the cases had RHD for more than 10 years, with further analysis showing a slight sign of the increase of duration to increase the chances of progression to severe RHD. It is assumed that the patients who have had rheumatic heart disease for most of their lives have had several chances of getting pharyngitis or upper respiratory tract infections, leading to more damage of the heart valves thus most of them tend to have severe RHD.

Patients who had a family history of heart disease or rheumatic heart disease were mainly the cases with severe RHD. The correlation of RHD and genetics was however not further investigated but it can be related to several genetic factors. Firstly, familial hypercholesterinemia leads to high bad cholesterol (LDL) from an early age and increases the chances of getting hypertension and heart disease. This can be explained by the changes in the DNA sequence, and more studies are needed to answer these questions. Another reason may be gene-environmental interaction, where the lifestyle choices are affected due to genetic chances/ mutations.

This study has revealed that the major risk factors for the presence of severe RHD unemployment; which plays a part in late diagnosis, and lack of access to immediate interventions to prevent the progression of the disease, being obese and overweight, current or previous history of alcohol use, lack of regular exercising; which increase the chances of getting hypertension and stroke as a comorbidity; and having a family history of chronic illness which correlates to genetic predisposition.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusions

- Rheumatic heart disease affects the young population more than the older population in MTRH, with severity increasing with age, and this is attributed to several other risk factors.
- More females tend to have a severe form of Rheumatic Heart Disease, having three times the risk of developing RHD than males, both moderate and severe forms of the disease. From this study, we can also conclude that being female is a significant exposure to the development of severe Rheumatic Heart Disease.
- The increased susceptibility of women may lie in the hormonal changes during their child-bearing years, and the use of hormonal contraceptives. The hormonal effects of women and their predisposition to getting acute rheumatic fever or rheumatic heart disease needs further studies to make more scientifically acceptable conclusions.
- A higher incidence of Rheumatic heart disease has been reported in low-settlement areas in the Sub-Saharan region. Around MTRH, where the study took place, earlier studies on the geographical and physical locations of the RHD patients in the cardiac clinic in Moi Teaching and Referral Hospital showed quite a substantial number of their patients coming from low settlement areas within the major towns surrounding MTRH.
- This study cements this finding by exposing the socio-economic status of the patients and caregivers of students who were part of the participants.

- We concluded that low socioeconomic status is a major drive to poor management of RHD patients, therefore increasing the speed of progression to severity, where unemployment remained a significant risk factor for the presence of severe RHD.
- Harmful use of alcohol and tobacco smoking is still a significant problem in the occurrence of non-communicable diseases. This study fundamentally supports these risk factors in alignment with the progression of rheumatic heart disease to severe forms, with the use of alcohol currently or previously being significantly linked to the development of severe rheumatic heart disease.
- Tobacco Smokers are also exposed to developing severe RHD, as smoking reduces tissue perfusion, increasing the damage from pathogens, leading to severely damaged valves thus more severe RHD among smokers.
- This study proved that doing regular physical exercise is a protective factor in the prevention of the progression of severity among RHD patients.
- Hypertension, as a comorbidity in this study, remains a significant risk factor for the progression of RHD to severe forms, and having a history of heart disease in the family is significantly linked to developing Rheumatic Heart Disease.
- Proper nutritional status prevents undernutrition, overweight and undernutrition, which negatively affects the prevention of complications that come about through the conversion of RHD from mild to severe forms.
- Participants who have been with rheumatic heart disease for ten years or more had the presence of comorbid disease, and most of them had severe disease. This study showed a propensity to development of severity with time, hence posing the question of management both on the prevention of reinfections, and acquisition of

medicines regularly to cope with the symptoms that accompany rheumatic heart disease.

- Finally, this study concluded that the familial history of heart disease (including rheumatic heart disease), was mainly associated with the cases (those with severe RHD). However, we did not ascertain the genetic connection between heart disease and the progression of rheumatic heart disease to severe forms. Further genetics study is needed to link the two.

6.2 Recommendations

- Creation of awareness and health education among schools surrounding MTRH and major towns encompassing the high-level facility.
    - This will be targeting the younger generation on what rheumatic heart disease is, how it develops, ways of preventing acute rheumatic fever, and how to manage pharyngitis.
    - The creation of awareness can be done through collaboration with community-led programs and school health programs in providing health education to all levels of school-going children.
- Rheumatic Heart Disease should be incorporated into the Antenatal profile in terms of screening through cardiac auscultation, and selection of questionable cases to conduct echocardiography.
    - The World Heart Federation has developed a guide on screening which can aid the cardiac clinic, and the antenatal clinic in MTRH in conducting this screening for every pregnant woman visiting the facility.

- Patients visiting the cardiac clinic in MTRH should be educated on the negative effects of alcohol use and tobacco smoking on their heart conditions.
    - This can be done through weekly health talks before the cardiac clinic begins. During these health talks, the benefits of exercising should also be emphasized, guiding the patients on ways of incorporating regular physical exercises into their daily lives.
    - The weekly health talks should also guide the cardiac patients on healthy foods and portions, to help support the reduction of overweight and obesity.
- Hypertension, being one of the major comorbidities should be monitored diligently among all cardiac patients visiting the facility, and proper advice and management given to the patient on ways of preventing and controlling it.
    - This can be done by ensuring that the correct measurement of blood pressure is done for all cardiac patients visiting the facility.
- The government should support the management of rheumatic heart disease by proper allocation of treatment modalities to all indigent people, for easy accessibility and affordability of health care to all.

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Appendices

Appendix 1: Budget

Activity	Unit Cost (Ksh)	Total Cost (Ksh)
Pilot Study:		
Research Assistants	1000*2*2 days	4,000
Materials and equipment:		
Tablets	30,000*3	90,000
Weighing Scales	5000*3	15,000
Transport	5,000*3	15,000
	Sub Total	**124,000**
Research Assistants	1000*2*35 days	70,000
Printing costs	20,000	20,000
Transport	15,000*3	45,000
Allowance	3000*35 days	105,000
	Total	**364,000**
Contingency	10% of Total	36,400
	Grand Total	**400,400**

***Tablets and materials bought for the pilot study were still the ones in use for the main study**

Appendix 2: IREC Informed Consent Form

MOI UNIVERSITY COLLEGE OF HEALTH SCIENCES / MOI TEACHING AND REFERRAL HOSPITAL
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC) INFORMED CONSENT FORM (ICF)

dy Title: [Factors Associated with the Severity of Rheumatic Heart Disease Among Patients in Moi Teaching and erral Hospital, Kenya, 2019]

ne of Principal Investigator(s): [Dr. Nasirumbi Anne Magero]

Investigators: [Prof. Owino Ong'or and Dr. Zeinab Gura]

ne of Organization: [Kenya Field Epidemiology and Laboratory Program, P.O Box, 22313-00100, Kenyatta Hospital unds, Tel No.+254700752546]

ne of Sponsor: [Kenya Field Epidemiology and Laboratory Program]

ormed Consent Form for: [Any patient with Rheumatic Heart Disease in the cardiac outpatient clinics at MTRH, after eiving their initial care during the study period, who will then be classified as a case or a control]

s Informed Consent Form has two parts:

- Information Sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you choose to participate)

will be given a copy of the signed Informed Consent Form

t I: Information Sheet

oduction:

are being asked to take part in a research study. This information is provided to tell you about the study. Please read form carefully. You will be given a chance to ask questions. If you decide to be in the study, you will be given a copy his consent form for your records.

ing part in this research study is voluntary. You may choose not to take part in the study. You could still receive other atments. Saying no will not affect your rights to health care or services. You are also free to withdraw from this study at time. If after data collection you choose to quit, you can request that the information provided by you be destroyed er supervision- and thus not used in the research study. You will be notified if new information becomes available ut the risks or benefits of this research. Then you can decide if you want to stay in the study

Appendix 3: Questionnaire

☐I CONSENT (*Napatiana Ihini*)

☐I DO NOT CONSENT (*Sipatiani Idhini*)

Personal details:

Identification Number: …….
(*Nambari*)

Date of Birth: Day/Month/Year …….
(*Siku ya Kuzaliwa*) (*Siku/Mwezi/Mwaka*)

Age (*Miaka*): …….

Gender (*Jinsa)*: …….

Permanent Residence (estate and county) (*Makazi*): ……..

Occupation (*Kazi*) (if under 16, please give parent's occupation/s):
…….

Past Medical History (*Historia ya hali ya afya*)

Clinical Diagnosis (*Utambuzi wa Kliniki*)……..

History of any other chronic illnesses (Co-morbidities) (*Historia ya magonjwa Mengine*)

Chronic Disease (*Ugonjwa Sugu*)	Yes/No (*Ndio/La*)
Asthma (*Ugonjwa wa Pumu*)	
Chronic Kidney Disease (*Ugonjwa Sugu wa Figo*)	
Chronic Obstructive Pulmonary Disease (*Ugonjwa Sugu wa Mapafu*)	
Diabetes (*Ugonjwa wa Sukari*)	
Epilepsy (*Kifafa*)	

Hypertension (*Uwingi wa Shinikizo la damu*)	
Hypothyroidism (*Ugonjwa wa tezi*)	
Hyperthyroidism (*Ugonjwa wa tezi- ufumbuzi*)	
Rheumatoid Arthritis (*Ugonjwa wa Viungo*)	
Stroke/Transient Ischemic Attack (*Ugonjwa wa Kiharusi*)	
Other (Specify) (*Mengine*)	

Lifestyle (*Mtindo wa Maisha*)

Are you: a smoker □ (*mvutaji wa sigara*) — If yes, how many days in a week and how many years……. (*Kama ndio, siku ngapi kwa wiki*)

an ex-smoker □ (*Umewahi vuta sigara?*) — When did you stop smoking (Years)…… (*Uliwacha miaka ngapi iliyopita*)

never smoked □ (*Sijawahi vuta sigara*)

Do not wish to answer……. (*Sitaki Kujibu swali*)

Do you take Alcohol? (*Unakunywa pombe?*)

☐Yes (*Ndio*)

☐No (*La*)

Questions (*Maswali*)	**Scoring system (*Mfumo wa bao*)**				
		1	2	3	4
How often do you have a drink containing alcohol? (*Unachukuwa kinywaji cha pombe mara ngapi?*)		Monthly (*Mara moja kwa mwezi)*	2-4 times per month (*Mara mbili mpaka nne kwa mwezi*)	2-3 times per week (*Mara mbili mpaka tatu kwa wiki*)	4+ times per week (*Kupita mara nne kwa wiki*)

How would you class your diet (healthy/average/low fat/low salt etc.)?

(*Unaweza sema mlo wako ni wa afya bora, wastani, mafuta ya chini, au chumvi ya chini?)*

……
…

Do you take regular exercise? ☐ Yes (*Ndio)* ☐No (*La*)

(*Unafanya mazoezi mara kwa mara?)*

Family History (*Historia ya Familia*)

Have any close family members suffered from below:
(Yes/No)
(*Kuna mtu yeyote kwa familia yako anaugua magonjwa yafuatayo*) (*Ndio au La*)

Asthma (*Ugonjwa wa Pumu*): ……Yes (grandma)…….

Diabetes (*Ugonjwa wa Sukari*): ……

Cancer (*Ugonjwa wa Saratani*) (please specify type): ……

Heart Disease (*Ugonjwa wa Roho*) (Please specify Type): ……

Stroke (*Ugonjwa wa Kiharusi*): …….

High Blood Pressure (*Uwingi wa Shinikizo la damu*): ……

Do any allergies to any medication? **YES/NO** If yes, which ones?

(*Kuna madawa hayaambatani na mwili wako? Ndio/La Kama Ndio, madawa gani?*)
……

……
Do you have any food allergies? **YES/NO** If yes, please detail

(*Ukona Mzio wowote? Ndio/La*) ……....

……
…...

Tribe (*Kabila*)

☐ Bantu (Specify)

□ Nilote (Specify)
□ Cushite (Specify
□ Other

Weight (*Kilo*):

Height (*Urefu*):

Blood Pressure (*Shinikizo la Damu*):

Women – Contraception (*Dawa ya upangaji uzazi*): (Yes/No) (If Yes, Specify)……..

– Pregnancy (*Mja mzito*): (Yes/No) …….. Gestation (*Miezi ngapi*):……..

Filled in by:

Name ……..…….

Sign ……..

Appendix 4: NACOSTI Letter

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Ref No: **271949**

Date of Issue: **11/June/2020**

RESEARCH LICENSE

This is to Certify that Dr.. Nasirumbi Magero of Moi Teaching and Referral Hospital , has been licensed to conduct research in Uasin-Gishu on the topic: Factors Associated with the Severity of Rheumatic Heart Disease among Patients in Moi Teaching and Referral Hospital, Kenya for the period ending : 11/June/2021.

License No: **NACOSTI/P/20/5235**

271949

Applicant Identification Number

Director General
NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Verification QR Code

NOTE: This is a computer generated License. To verify the authenticity of this document, Scan the QR Code using QR scanner application.

Appendix 5: IREC Letter

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2019/222
Approval Number: 0003520
7th May, 2020

Dr. Nasirumbi A. Magero,
Moi University,
School of Medicine,
P.O Box 4606-30100,
ELDORET-KENYA

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
07 MAY 2020
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dear Dr. Magero,

FACTORS ASSOCIATED WITH THE SEVERITY OF RHEUMATIC HEART DISEASE AMONG PATIENTS IN MOI TEACHING AND REFERRAL HOSPITAL, KENYA, 2019

This is to inform you that ***MU/MTRH-IREC*** has reviewed and approved your above research proposal. Your application approval number is ***FAN: 0003520.*** The approval period is **7th May, *2020 – 6th May, 2021.***

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MU/MTRH-IREC***.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MU/MTRH-IREC*** within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MU/MTRH-IREC*** within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. 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.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MU/MTRH-IREC.***

Prior to commencing your study; you will be required to obtain a research license from the National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and other relevant clearances. Further, a written approval from the CEO-MTRH is mandatory for studies to be undertaken within the jurisdiction of Moi Teaching & Referral Hospital (MTRH), which includes 22 Counties in the Western half of Kenya.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix 6: MTRH Permission to Conduct Research Letter

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

4th August, 2020

Dr. Nasirumbi A. Magero,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET- KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Factors Associated with the Severity of Rheumatic Heart Disease among Patients in Moi Teaching and Referral Hospital, Kenya, 2019".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

MOI TEACHING AND REFERRAL HOSPITAL
CEO
APPROVED
04 AUG 2020
SIGN
P. O. Box 3 - 30100, ELDORET

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM

Appendix 7: Introduction Letter from Ministry of Health

MINISTRY OF HEALTH
DIRECTORATE OF PUBLIC HEALTH
FIELD EPIDEMIOLOGY AND LABORATORY TRAINING PROGRAM

Telephone: Nairobi 2724951/ Fax 2724951
When replying please quote:

KENYATTA HOSPITAL GROUNDS
P. O. BOX 22313-00100 NAIROBI

Ref No: MOH/DPH/FELTP/GEN/REG 039

9th June, 2020

Chief Executive Officer;
Moi Teaching and Referral Hospital;
Nandi Road, Uasin Gishu County
P.O. Box 3-30100;
ELDORET.

Dear sir,

RE: LETTER OF INTRODUCTION: DR. ANNE NASIRUMBI MAGERO (SPH/PGH/FE/017/17)

The above subject matter refers. Dr. Anne Magero is a Moi University student undertaking a Master of Science degree course in Field Epidemiology. This training is a collaboration between Kenya Field Epidemiology and Laboratory Training Program (K-FELTP) and Moi University. Her thesis project is titled "*Factors Associated with the severity of Rheumatic Heart Disease among Patients in Moi Teaching and Referral Hospital*". The protocol for the thesis project has been approved (IREC Approval No 0003520). She wishes to begin data collection for this project.

This letter therefore serves to introduce Dr. Anne Magero and to request for support as she begins data collection for her thesis project.

Yours Sincerely