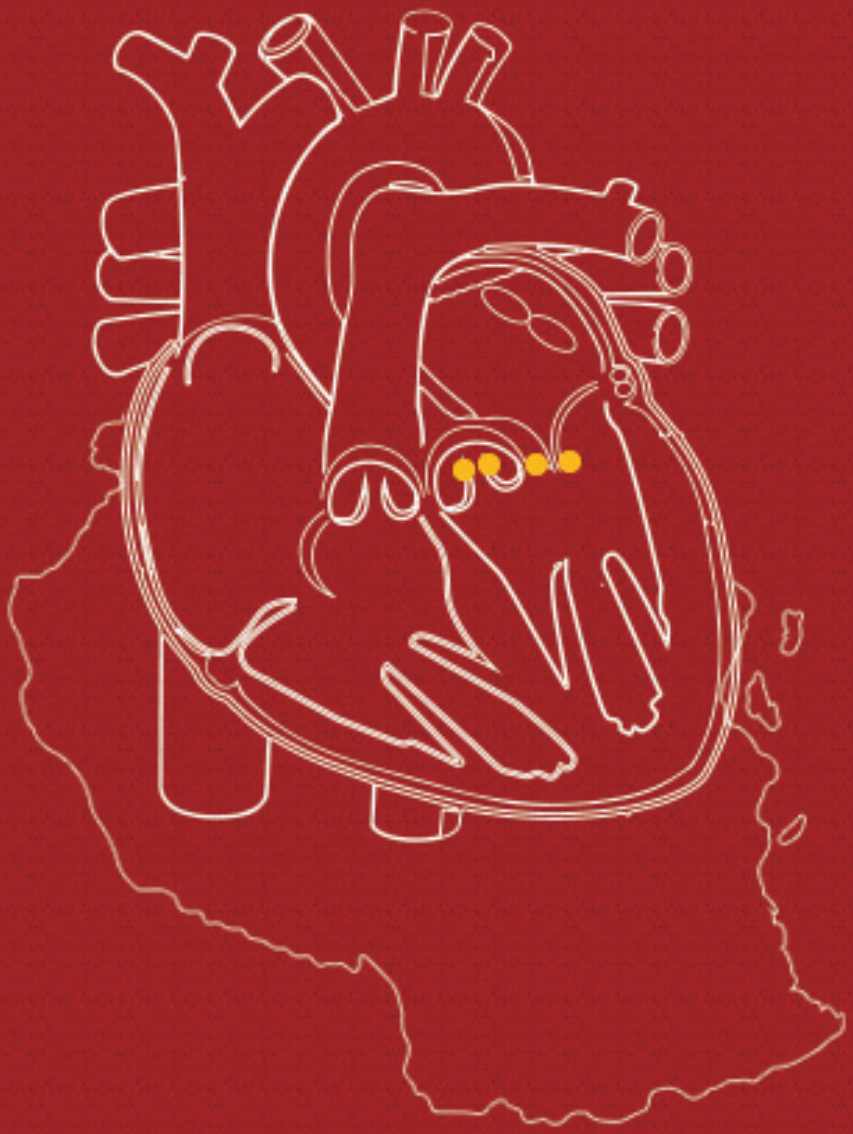
RHEUMATIC HEART DISEASE IN TANZANIA:
Insight in Clinical Aspects and Outcome



Reuben K. Mutagaywa

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Rheumatic heart disease in Tanzania: insight in clinical aspects and outcome

Reumatische hartziekte bij Tanzania: inzicht in klinische aspecten en resultaat

(met een samenvatting in het Nederlands)

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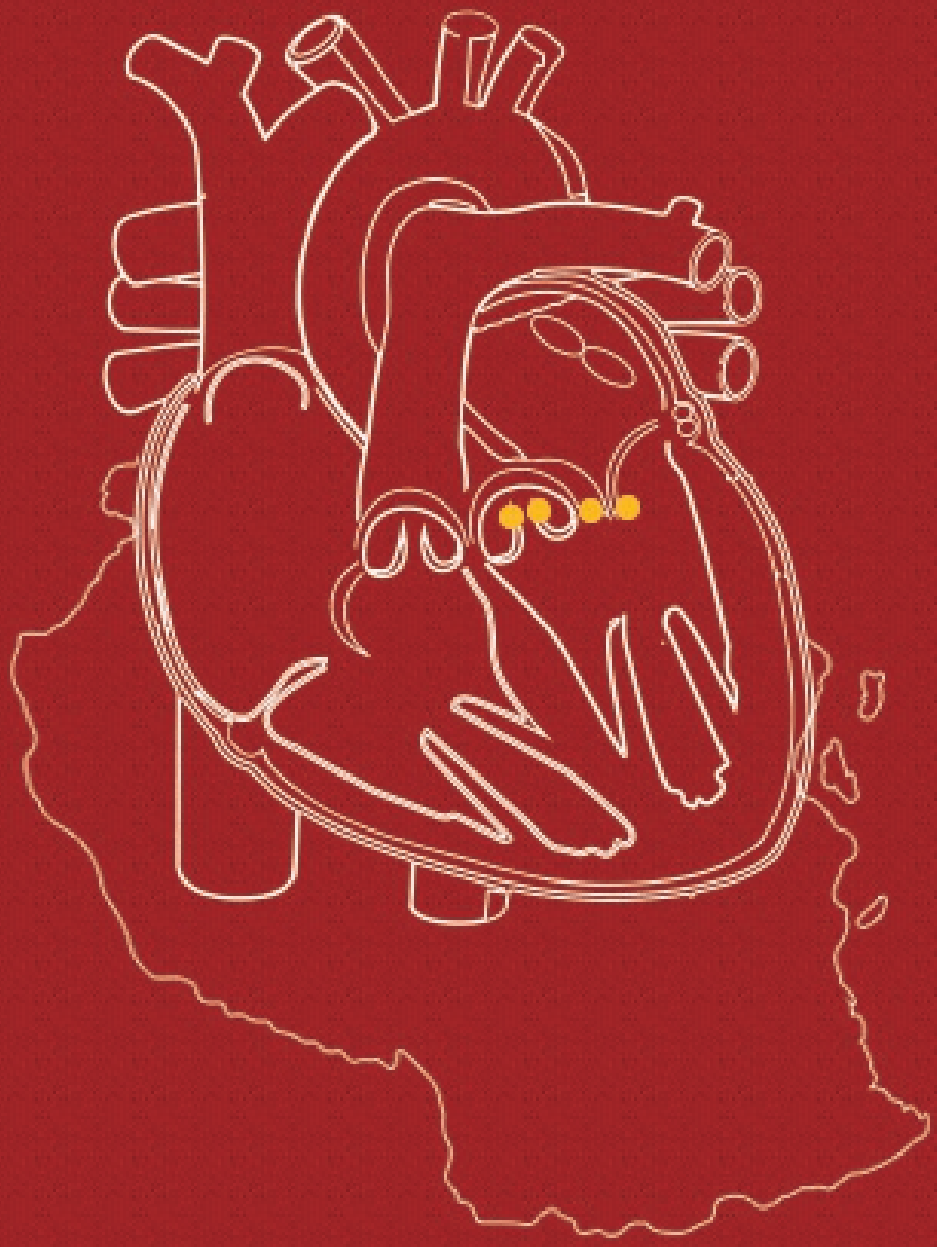
TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ARF	Acute Rheumatic Fever
ACC	American College of Cardiology
AHA	American Heart Association
AU	African Union
CD	Cruster of Differentiation
CRP	C-Reactive Protein
ESC	European Society of Cardiology
GAS	Group A Streptococcus
HIC	High Income Country
HRQoL	Health Related Quality of Life
IE	Infective Endocarditis
LMIC	Low-Middle Income Country
MNH	Muhimbili National Hospital
MS	Mitral Stenosis
NCDs	Non-Communicable Diseases
NYHA	New York Heart Association
PBMV	Percutaneous Balloon Mitral Valvuloplasty
RHD	Rheumatic Heart Disease
SSA	sub-Saharan Africa
WHF	World Heart Federation
WHO	World Heart Organization



CHAPTER 1

General introduction

THE GLOBAL BURDEN OF RHEUMATIC HEART DISEASE

Rheumatic heart disease (RHD) affects an estimated 40.5 million people worldwide, [1] and is responsible for up to 300,000 deaths each year. [1–4] In Tanzania, the prevalence of subclinical RHD among school children is about 21 to 34 per 1,000 population. [5,6] To the rest of African countries, up to 30 for every 1,000 school-aged children (5 – 10 years) are affected by RHD as detected by echocardiography and about 5.7/1,000 by auscultation (**Figure 1**). [7–12] For this reason, since 2021, the World Heart Federation (WHF) has included echocardiography for early detection of RHD owing to its high sensitivity of about 91.06%. [12–16] However, the epidemiological data from many developing countries are of poor quality subjecting this prevalence more likely to underestimate the burden of the disease.

For easier coordination of health services, Tanzania is divided into 8 health zones which includes eastern, northern, southern, central, western, lake, southern highlands, and Zanzibar. Zonal distribution of RHD surgical patients (Jakaya Kikwete Cardiac Institute in 2016) in Tanzania are as shown in **Figure 1**. [17]

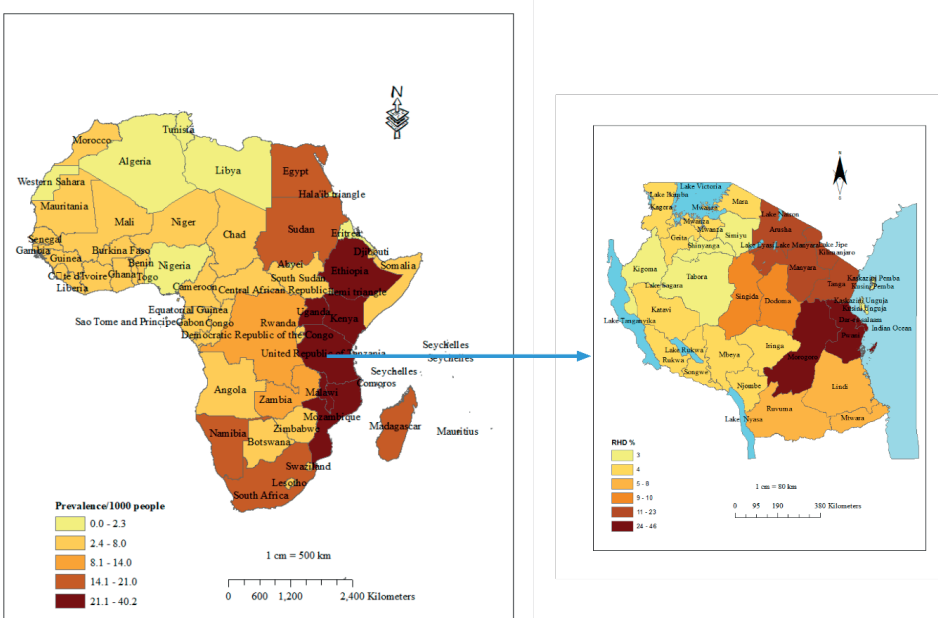


Figure 1. On the left is the map of Africa showing the prevalence of RHD (redrawn from Mocumbi [9] and Muhamad et al [10]). On the right is a map of Tanzania showing the percent of surgical patients contributed by each zone, n = 142 (free internet source).

Other affected areas are south-central Asia, the Pacific and indigenous populations of Australia and New Zealand. [2] For example, in Indonesia the prevalence of RHD is about 2.52 per 1,000 people. [18,19] Although reportedly eradicated in Western Europe and North America, a recent report has shown increased incidences of invasive Group A streptococcus (GAS) throat infection, the agent implicated in acute rheumatic fever (ARF), in the United Kingdom. [20] In high income countries, there is a tremendous decrease (from the year 1990- 2019) in the prevalence of RHD with estimated annual percentage change of-2.15 (95% CI-2.26 to-2.04). [1,4]

Compared with other common sub-types of rheumatic valvular lesions i.e. mitral and aortic regurgitation, rheumatic mitral stenosis (MS) has a unique presentations: 1) In developing countries, MS progresses rapidly and is diagnosed late leading to severe disability at early age; [21] 2) It is the only valvular lesion which is predominantly (99%) rheumatic in origin; 3) It shows a female gender preponderance with possible late diagnosis during pregnancy; and 4) It is the only rheumatic valvular pathology with proven percutaneous intervention. For rheumatic MS, there is a lack of robust data concerning its prevalence from RHD endemic areas such as Tanzania. Most reported screening studies were carried out among school children. Moreover, there is a lack of nationwide screening registries in those areas. Therefore, estimating the true prevalence of MS may be difficult. Available data show that the prevalence of MS in Africa falls in the range of 0.9 to 16.4/1,000. [22,23] MS is the least common valvular heart disease in developed countries with a prevalence of 0.1% in the US population and 9% in the Euro Heart Survey. [24] Because of its peculiarity, our study aimed at exploring the clinical aspects and outcome of RHD in Tanzania with the focus on rheumatic MS (unless specified otherwise).

CLINICAL CHARACTERISTICS OF PATIENTS WITH RHEUMATIC MITRAL STENOSIS

The most common clinical presentations of rheumatic MS are heart failure (usually in New York Heart Association (NYHA) functional class II -III), pulmonary hypertension, infective endocarditis, atrial fibrillation (in 28% of patients), [25] and thromboembolic events (3.2% of patients). [26] All of these factors signify late presentation of patients to health facilities and/or delayed appropriate management. Social-demographically, the affected individuals are from poor family support and poor knowledge about the link between GAS throat infection and RHD. Furthermore, these patients are subjected to providers with ineffective communication and knowledge, and are prone to poor health system design which eventually led for late presentation to health facilities. Only 24.9% of patients are able to recall symptomatic episodes consistent with ARF. [26] Data suggest

the average age of death from RHD is approximately 26 years and that in pregnancy, the outcomes are even worse in whom about 34% will die in the peripartum period. [3]

Generally, physical findings in patients with pure MS include: atrial fibrillation, blood pressure with low pulse pressure, elevated jugular venous pulse, left parasternal lift, and taping apex impulse. Auscultation reveals a low-pitched rumbling diastolic murmur. The loudness of the murmur depends on the level of the trans-mitral gradient. The opening snap (detected by experienced cardiologists) occurs 1.3 – 30ms after the second heart sound- the more the severe the stenosis, the shorter the interval, as increased LA pressure causes earlier opening of the mitral valve. [27,28] Other features are malar flush and signs of pulmonary hypertension.

ECHOCARDIOGRAPHIC FINDINGS IN RHEUMATIC MITRAL STENOSIS

Echocardiography is the preferred method in evaluation of patients with rheumatic MS (**Figure 2**). It is used to confirm the diagnosis, assess severity and assess prognosis of MS. Echocardiography is also used to describe valve morphology, assess valve function, and evaluate the feasibility and indications of a specific intervention. Echocardiography mitral valve area by planimetry is the reference measurement of MS severity. Mean transvalvular pressure gradient and pulmonary pressures are also important and they reflect MS consequences and have a prognostic value. Other strong prognostic factors in MS which should be assessed include size of left ventricle, left ventricular function, and right ventricular function. Left atrial size and left atrium volume should also be determined as well as ruling out left atrium thrombus especially in the left atrium appendages. With echocardiography, an integrated approach including various criteria is strongly recommended instead of referring to single measurements. [27,28] In events where there is a strong suspicion of left atrium thrombus, transesophageal echocardiography is indicated. Mitral stenosis usually presents with other valvular lesions, while 4.7 – 9.5% of cases present only with pure MS. [22,26,29]

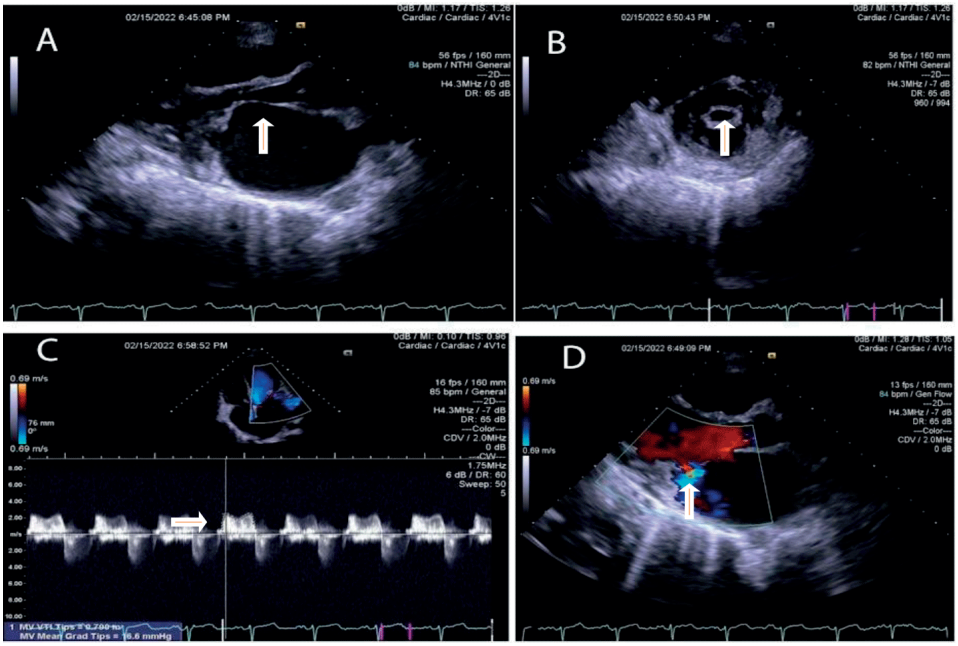


Figure 2. Echocardiographic frames from a 16 years old girl demonstrating hockey stick appearance of the anterior leaflet of mitral valve with enlarged left atrium (A, arrow), severe mitral stenosis (valve area 0.75cm^2) by planimetry (B, arrow) and by the trans-mitral valve pressure gradient (18mmHg) (C, arrow). Panel D shows the associated trivial mitral regurgitation.

MANAGEMENT OF RHEUMATIC MITRAL STENOSIS

MEDICAL THERAPY

Due to limited access to interventional cardiology and cardiothoracic surgery in developing countries where RHD is most prevalent, [25,30,31] the majority of these patients are managed medically. Medical treatment is indicated for all symptomatic patients and is used as a bridge to surgery or interventional procedure, as well as for those with contraindications for open heart surgery. Diuretics are used in most symptomatic patients to treat congestive cardiac failure. They are usually combined with beta blockers, digoxin or heart rate-regulating calcium channel blockers. When mitral stenosis is accompanied with mitral regurgitation Angiotensin Converting Enzymes Inhibitors are added. [32–34]

Anticoagulation (with a target international normalized ratio of 2 to 3) is indicated when there is history of systemic embolism or if thrombus is present in left atrium. Patients may need anticoagulants for prevention of valve thrombosis and/or thromboembolism in severe MS or atrial fibrillation or in less severe MS but left atrium > 50mm diameter / left atrium volume > 60mL/m^2. [27,28] The use of anticoagulants for a pregnant women

or women of childbearing age should be considered as per guidelines. [27,28] Secondary prophylaxis for prevention of recurrent attacks of ARF and progression of valve lesions should be considered as an important aspect of medical management to all patients with RHD. [35] For this purpose, benzathine penicillin G has been the gold standard. The antibiotic is an integral part of patient's management after surgery or percutaneous balloon mitral valvuloplasty (PBMV).

INTERVENTIONAL MANAGEMENT

Guidelines on management of valvular heart disease recommend either PBMV or mitral valve surgery for management of clinically significant MS (mitral valve= 1.5cm^2). [27,28] However, as previously mentioned, most of these patients are likely to be managed conservatively in developing countries. Okello et al [36] found that out of 551 patients evaluated from the Uganda rheumatic heart registry, 398 (72.3%) required invasive intervention, with 332 (60.3%) patients requiring surgery and 66 (12.0%) requiring PBMV. Only 153 (27.7%) required medical management. However, in the registry majority (498, 90.4%) of the patients were on medical treatment. Of the 60.3% requiring surgery, only 44 (8.0%) patients underwent valvular surgery and 12.0% requiring PBMV, only 5(1.0%) underwent successful PBMV. The main problem is that many patients present too late to benefit from surgery. Some of the reasons for the late presentation include, but not limited to, lack of awareness about the disease amongst patients and healthcare workers and the use of traditional medicines. These calls for a need of training and improving communication between healthcare workers and the community at large.

PERCUTANEOUS BALLOON MITRAL VALVULOPLASTY

PBMV is a safe and effective management for rheumatic MS. It is associated with an overall excellent procedural success rate and with a good immediate and long term outcome. [27,28,37] For this reason, PBMV is currently considered the standard of care for selected patients with rheumatic MS such as those with Wilkins score <8 and mild mitral regurgitation. [27,28] However, until recently, it is debatable about what is cut-off Wilkin's score that predict better results post PBMV. While the European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines [27,28] recommend cut-off Wilkins score ≤ 8, several researchers [38–42] recommend Wilkins score of up to 11. This scenario is important in low resource settings where patients come late in hospitals with eventual advanced disease (Wilkins score) and in which some of them cannot afford open heart surgeries (due to the high cost), are pregnant, or have other reasons contraindicating open heart surgery. Outcome after PBMV is dependent on correct patient selection and a number of anatomical and clinical criteria, early and late outcome have been identified. The determinants of procedural success are multifactorial. [37,43,44] Currently, many sub-Saharan Africa countries including Tanzania have access to Catheterization Laboratory capable of facilitating interventional

procedures such as PBMV. However, PBMV services are not fully available in most of African countries owing to several reasons including lack of skilled personnel. Other reasons include: Insufficient health care systems and infrastructure, scarcity of cardiac professionals, skewed budget allocation and lack of prioritization for non-communicable diseases (NCDs) control, and high cost of cardiac treatments and interventions. [45–47] Therefore, there is a need to strengthen PBMV skills and related services in low- and middle-income countries, concentrating on expertise centers.

MITRAL VALVE SURGERY

RHD affects all components of the mitral valve, [48] and these should be systematically dealt with during surgery. Although valve replacement provides good early results, long term outcomes are poorer as the cumulative risk of valve-related complications increases. [49] Hence, valve-conserving restorative operations are now the preferred first-line approach.

In a study by Cohen et al, [50] to compare PBMV, Open Mitral Commissurotomy and Mitral Valve Replacement revealed that the three managements approach produced similar symptomatic improvement and comparable survival in patients with predominant mitral stenosis. PBMV offers the patient a shorter hospital-stay, improve the quality of life and patient prognosis, decreased cost, a short convalescent period, and avoidance of general anesthesia and a surgical incision, all at the price of increased likelihood of further mitral valve procedures or cardiac events. [37,51] Another study that was conducted by Ambari et al [37] reconfirmed that PBMV is non-inferior to mitral valve surgery in survival prognosis, but mitral valve surgery showed better sustained event-free duration than the PBMV arm.

PATHOMORPHOLOGICAL AND HISTOLOGICAL CHANGES IN RHEUMATIC MITRAL STENOSIS

The hallmark of MS includes leaflet thickening, calcification and retraction, peri annular calcification with limitation of annular motion, leaflet fusion, chordal thickening, shortening and fusion as well as papillary inflammation. [52] However, the specific immunologic and inflammatory mechanisms leading to vasculitis is unknown. There is persistent inflammatory process in the heart tissue in the absence of infectious agent. [53] Once the damage has developed on a valve, the altered hemodynamic stresses on the valve perpetuate and extend the damage, even in the absence of a continuing rheumatic process. [54]

Many studies have investigated potential biomarkers to evaluate fibrosis and chronic inflammation process in patients with rheumatic MS. [33,55–57] These biomarkers include the interleukins (ILs), C-reactive protein (CRP), brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), and tumor necrotic factor alpha (TNFα). However, none

of these biomarkers could clearly explain on the disease pathogenesis. The pathological changes in the valvular specimens from patients with RHD have been defined in the past, but these have been either descriptive postmortem studies [58] or retrospective studies of surgically excised mitral valves. [59–61] Excised mitral valve tissue can provide important information of clinical relevance with regards to selection of a particular intervention. For example, presence of calcific deposits in the leaflets of the mitral valve reflects a degenerative component of disease processes. [62] Calcific deposits in stenotic mitral valves are found more frequently and in large amounts in men than in women, in older than in younger individuals, and in patients with higher pressure gradients between left atrium and left ventricle. [62]

Aschoff nodule (bodies) is another histological finding of clinical importance. When present, it signifies that an attack of ARF occurred at some time in the past but does not necessarily indicate an ongoing attack. [62] Different stages of Aschoff nodules have been found to vary in the expression of inflammation cytokines and inflammatory cells. [63] Fibrinoid necrosis in the interstitial tissue implies that the rheumatic process is in its acute phase while presence of histiocytes and giant cells reveals that the disease had occurred about 3 to 6 months ago. The increased production of pro-inflammatory cytokines such as in ARF and in patients with active RHD has been reported. [33,55,56,63,64] These patients also showed increased numbers of $CD4^+$, $CD8^+$ and $CD25^+$ cells suggesting the expansion of activated T CD^+ cells in peripheral blood during the active phase of the disease.

Despite of a significant number of studies done, rheumatic MS remain to be a complex disease with unclear pathogenetic mechanisms. Research on basic science is important in understanding the unexplained susceptibility seen in some people who proceed to develop rheumatic MS. [65] In sub-Saharan Africa, where RHD is most prevalent, one of the publications that have investigated the pathogenesis of RHD was done about three decades ago with the use of basic histopathological techniques. [63,66] Yet, there is no treatment for rheumatic MS that targets the main pathogenesis or to prevent the progression of the disease. [33] Therefore, there is a need for current understanding of the pathophysiological pathways involved in the affected valves, which may provide an insight into disease pathogenesis that in turn can inform new treatments.

ABOUT THIS THESIS

AIM

This overall thesis study aimed at exploring the clinical aspects and outcome of RHD in Tanzania with the focus on rheumatic MS.

The following questions will be addressed in this thesis

- What is the current status of RHD in special populations?
- What is the clinical profile, treatment patterns, and outcomes of patients with rheumatic MS in Tanzania?
- What are the valvular pathology and histological changes of surgically excised rheumatic mitral valves in patients undergoing valvular replacement surgery?.
- What is the valvular suitability or non-suitability for catheter-based interventions in this cohort?
- What is a progress made over time in the management of RHD in Tanzania?

STUDY SETTING

Apart from the two systematic reviews, the studies described in this thesis were conducted at the Jakaya Kikwete Cardiac Institute (JKCI)-four studies, Muhimbili National Hospital (MNH)- one study, and one study from two regions (Pwani and Manyara), Tanzania. JKCI and MNH are national referral hospitals located in Dar es Salaam that receives patients from all over Tanzania. According to the 2022 Census, Tanzania has a population of 61.7 million. [67] Until the year 2012, advanced cardiac services in Tanzania were taking place at MNH. From the year 2012, these services are done at JKCI, which is a specialized cardiac hospital in Tanzania.

THESIS OUTLINE

Following the general introdution in **Chapter 1**, this thesis is divided into three parts illustrated in figure 3. Part one of the thesis provides information about RHD in special populations and consists of chapters 2, 3 and 4. Chapters 2 and 3 are systematic reviews of the current literature of RHD worldwide and Chapter 4 is the original research article. The epidemiology and management of diseases can be influenced by social demographic factors such as sex and migration. In **Chapter 2,** the associations of sex and migration on epidemiology and management of RHD is clarified while **Chapter 3** reports the opportunities and challenges in the management of infective endocarditis in developing countries. In order to set base for the research work comprising this thesis, we conducted a study to determine the burden of RHD in the at a higher risk population i.e the children. In **Chapter 4**, the prevalence of sub-clinical RHD is investigated in a cross sectional study amongst children in a school-based RHD prevention program in Tanzania.

Part two of the thesis mainly explores the clinical aspects in patients with rheumatic mitral stenosis. Despite the high burden of rheumatic MS, there is not enough studies with contemporary data on patient's characteristics, treatment patterns, complications and outcomes. In **Chapter 5,** the clinical profile, treatment and follow-up of 290 patients

with rheumatic MS in Tanzania is described in a prospective study. In this study, the usual standard of care (namely medical/conservative, PBMV, or mitral valve surgery) of the patients with rheumatic MS at the cardiac institute is examined. The primary and secondary outcomes in the three groups are determined and factors associated with the outcomes are explored. Knowledge on the role of inflammatory response in rheumatic MS remains unclearly known. In order to elucidate the ongoing inflammation in patients with chronic rheumatic MS, in **Chapter 6** a prospective study of surgically excised rheumatic mitral valves from patients undergoing mitral valve replacement, by using advanced histopathological and immunohistochemical techniques was conducted. The inflammatory changes were further correlated with patient's clinical presentation, degree of valvular involvement, and management. **Chapter 7** is focusing on the non-surgical interventional management of rheumatic MS by PBMV. In order to achieve successful procedural outcomes, a multidisciplinary approach is advocated by several international guidelines on the management of valvular heart diseases. In this chapter, the role of a heart team is assessed in a prospective study design. Furthermore, an example of a well-planned development that can make significant differences in the diagnosis, treatment, and outcomes of patients with rheumatic MS in low- and middle-income countries is outlined. Lastly, the cut-off Wilkins score that could predict good outcomes post PBMV is investigated.

Part of three of the thesis examines the progress in the management of rheumatic heart disease. In order to assess the progress that has been made in the management of RHD in Tanzania, investigations in terms of surgical outcomes were done over two time period. In **Chapter 8**, the predictors of early operative mortality (May 2008 to December 2012) for RHD at MNH are investigated in a retrospective study. Traditionally, the effectiveness of surgical interventions such as heart valve replacement has been assessed based on morbidity and mortality outcomes. However, the impact of these interventions on the patient's perspective assessed by patient-reported outcome measures (PROMs) is equally important. **Chapter 9** reports on a prospective study (January 2020 to April 2021) on Health-related quality of life of patients following mechanical valve replacement surgery for rheumatic mitral stenosis in Tanzania. The World Health Organization (WHO) recommends screening as an effective way to detect RHD in the early stage when secondary antibiotic prophylaxis can be offered. Finally, **in Chapter 10**, findings from all parts of the thesis are discussed, as well as clinical implications and future directions.

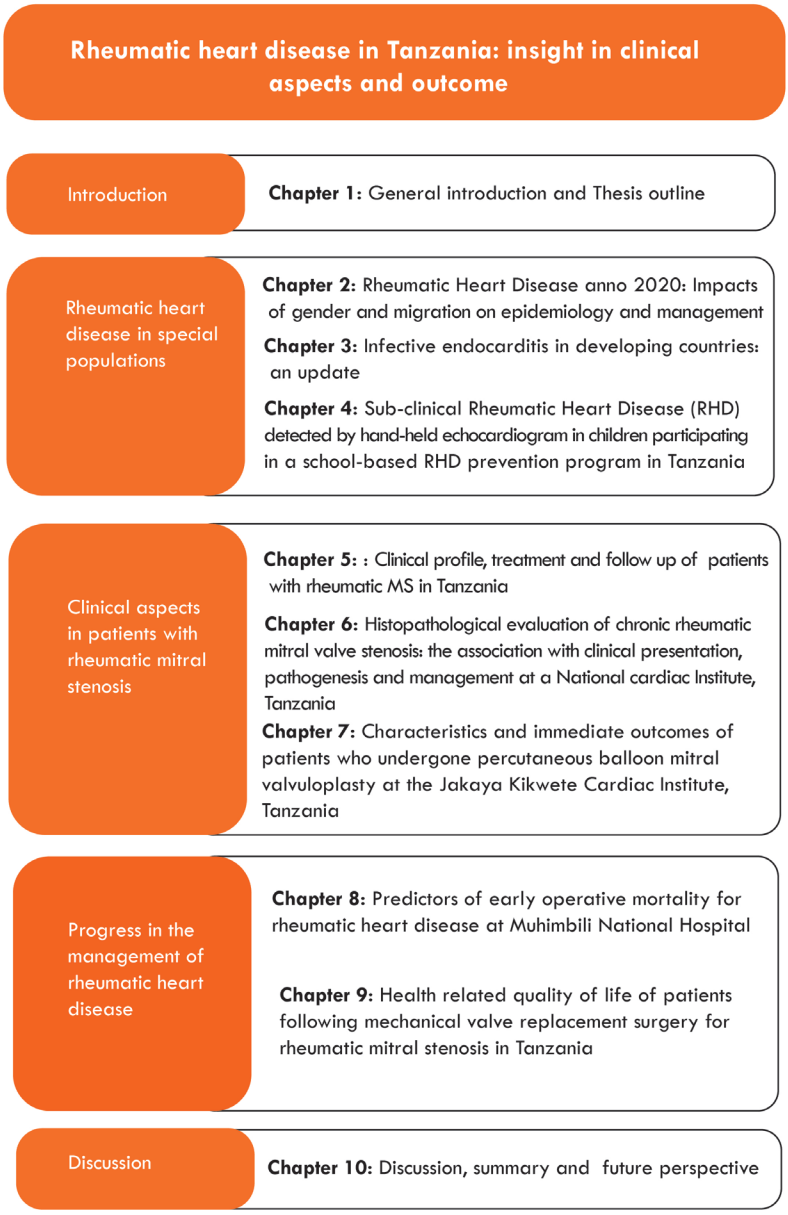


Figure 3. Overview of the thesis

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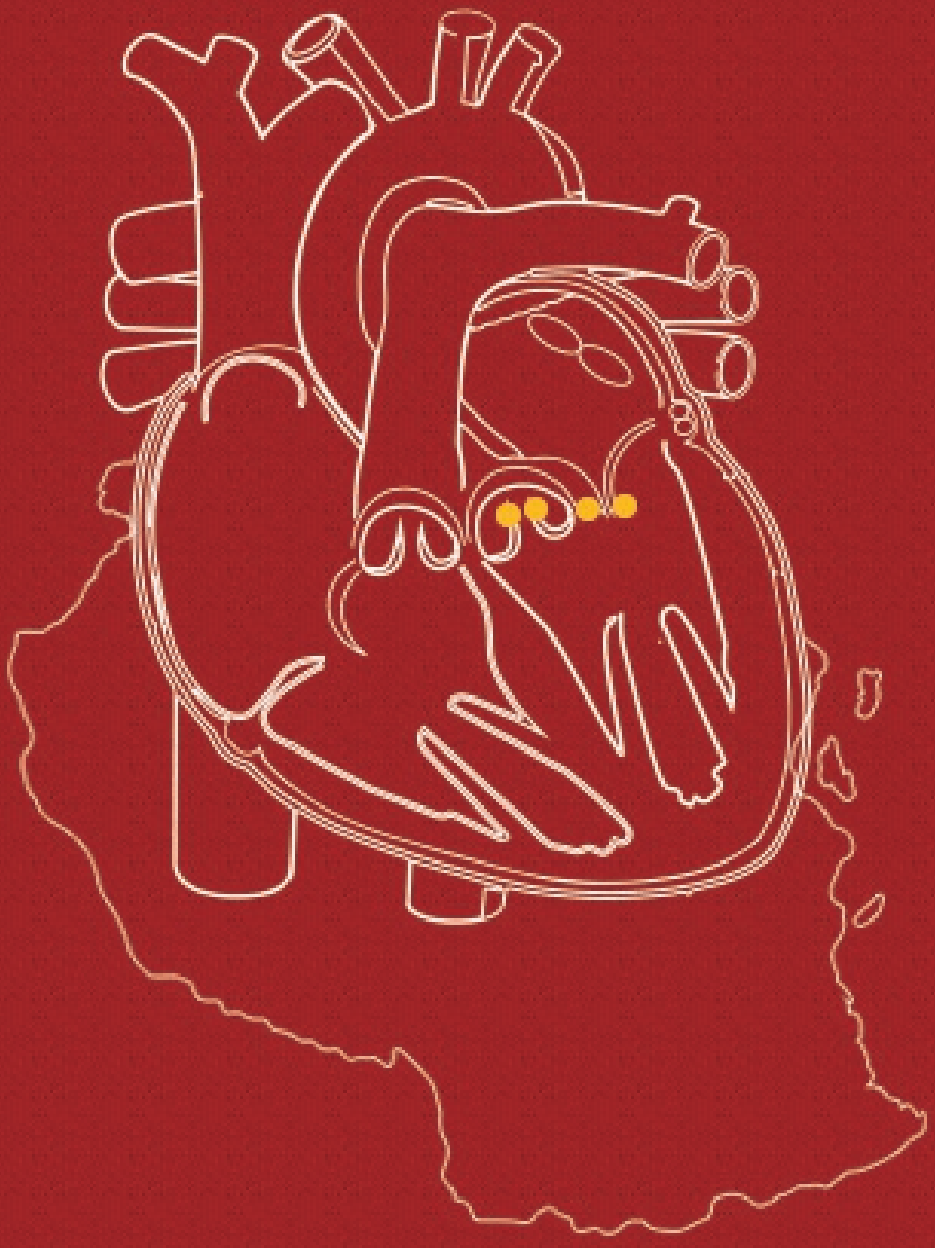
PART I

Rheumatic heart disease in special populations



CHAPTER 2

Rheumatic Heart Disease anno 2020: Impacts of gender and migration on epidemiology and management

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ABSTRACT

BACKGROUND

The epidemiology and management of diseases can be influenced by social demographic factors. Gender and migration are among these factors.

METHODS

We aimed at reviewing the impacts of gender and migration on Rheumatic heart disease (RHD) epidemiology and management by a non-systematic literature review of published studies on RHD worldwide. Our PubMed search terms included RHD pathophysiology, diagnosis, complications, management or prevention, combined with words 'rheumatic mitral stenosis (MS)', 'outcomes after percutaneous balloon mitral valvuloplasty (PBMV)', 'gender or sex difference', and 'migration'. The reporting of this study conforms to SANRA (the Scale for Assessment of Narrative Review Articles) guidelines.

RESULTS

We retrieved eight studies about the impact of sex on outcomes after PBMV. All of these studies showed a female predominance for RHD. Two studies showed that there is no impact, three studies showed female sex as a predictor of poor outcomes, and the other three showed male sex a predictor of poor outcomes. Although RHD is reported to be eradicated in the developed countries, 2.1% of refugees recently screened for RHD in Italy were found to have subclinical RHD. This prevalence is similar to those found in India (2.0%), Cambodia (2.2%), and Mozambique (3%).

CONCLUSIONS

There are contradicting results for outcomes after PBMV between males and females. It is not clear whether sex difference plays a role in pathophysiology, diagnosis, management and prognosis of MS. Migration has impacts on epidemiology and management of RHD. Further studies are required in these two fields to explore their relationship to RHD.

KEY WORDS

Gender; sex; migration; rheumatic mitral stenosis; impact; review

1. INTRODUCTION

Rheumatic heart disease is an important cause of cardiac morbidity and mortality among children and young adults. Worldwide, RHD affects 15.6 million people yearly, and it is responsible for about 300,000 deaths each year.[1,2] RHD has been eradicated in developed countries mainly attributed to improved living standards and widespread use of antibiotics.[3] However, recent studies have shown that globalization, migration and refugee crises have led to evolving of RHD in developed countries making RHD a global health problem.[4,5] Antonio and colleagues[6] reported that cardiovascular diseases (CVDs) are major health problems among immigrants in developed nations with RHD being a major reason for hospitalization for cardiac operation. Moreover, RHD has been reported in middle-class children in Utah, United States of America[7–9] and outbreaks have been recently reported in Trieste, Italy.[10] More recently, in a study done by Condemi et al[11] in Italy, it was found that the prevalence of RHD was similar to that found in resource-limited countries. Indeed, Marijon[12] warned that ''the affluent world cannot afford complacency; large population movements and refugee crises can displace persons with RHD to developed nations''. RHD is not confined to low income or tropical nations, but it should raise concern in middle- and high-income countries.

RHD is still prevalent in many parts of developing countries, including Sub Saharan Africa where the prevalence is 1 – 3 for every 1,000 school children.[2] In these countries, RHD is seen in people with poor socioeconomic status, living in overcrowded conditions, with limited access to health care.[13,14] Patients present late to tertiary facilities when they have indications for invasive interventions due to the distal sequelae of RHD.[13] For situations in which open heart surgery (OHS) cannot be performed, procedures like PBMV can be performed for MS.

The pathogenesis of acute rheumatic fever (ARF) and its sequelae RHD remains incompletely understood. Evidence supports the view that ARF is the result of an autoimmune response to pharyngeal infection with Group A Streptococcal (GAS) in a genetically susceptible individual, which is mediated through molecular mimicry.[15] Poverty and social disadvantages are among the strongest predisposing factors for developing ARF.[16] Patients with ARF present with a combination of fever, joints pain, carditis, chorea, and skin manifestations (the Jones criteria).[17] Carditis commonly involves the mitral (35%) and aortic valves (12%) while tricuspid and pulmonary valves are rarely involved.[18] In regions with a high prevalence of RHD, it is common to see patients in whom more than one valve is affected. Complications of RHD include atrial fibrillation, stroke, heart failure, pulmonary hypertension, and infective endocarditis.[13] Treatment of ARF includes treatment of GAS infection[19] and arthritis as well as preventing recurrent attacks of ARF with a monthly injection of Benzathine penicillin G.[20]

Therapeutic strategy in RHD involves the management of its associated complications by medications and/or OHS or PBMV (for MS) as per available guidelines.[21,22]

PBMV is a safe and effective management for rheumatic MS. It has excellent procedural success rate {defined by the composite endpoint of a final mitral valve area $\geq 1.5cm^2$ without mitral regurgitation (MR) of more than grade 2} of 90% to 95%[23–25] with good immediate[26] and long term outcomes;[21,22] event-free survival rate of 90% at 5 to 7 years,[27] 61% to 96% at 10years[28–30] and 43% to 79% at 15 years.[25,28] For this reason, PBMV is considered standard of care for selected patients with rheumatic MS with Wilkins score <8 and mild MR.[21,22] Wilkins score[31] is an echocardiographic method used to predict the success of PBMV in the setting of rheumatic MS. The score has four components: leaflet mobility, thickness, calcification, and sub-valvular thickening each of which is graded from 1 to 4 with a total score being the sum of the items and ranging from 4 to 16. The determinants of procedural success are multifactorial depending on correct patient selection and some anatomical and clinical criteria.[32,33] The influence of sex on diagnosis, management, the progression of MS and on short and long-term post-PBMV results remain unclear.[34,35] While a study by Palacios et al[32] reported sex as an independent predictor of PBMV success, other studies[33,36] did not confirm that observation. Indeed, the limited data available in the literature are inconsistent. Moreover, the recent European Society of Cardiology and the American Heart Association guidelines in the management of valvular heart disease did not mention sex as a predictor of outcomes post interventions.[21,22,37,38]

This article aimed at reviewing the impacts of gender and migration on Rheumatic heart disease (RHD) epidemiology and management, with emphasis on rheumatic MS by a non-systematic literature review of PubMed published studies on RHD worldwide. Additional searches were done in Google Scholar for categories that yielded few results in PubMed. This review article adhered to SANRA guidelines, a brief critical appraisal for the assessment of non-systematic articles.[39]

2. SEX DIFFERENCES IN RHEUMATIC HEART DISEASE: FOCUSING ON MITRAL STENOSIS

2.1. EPIDEMIOLOGY AND RISK FACTORS

Sex differences are frequently encountered in RHD as shown by the female predominance in a ratio of 2:1 in studies concerning PBMV.[32,35,40,41] There is a difference in the epidemiological presentation of MS according to regions. In Africa, the prevalence of MS is up to 26% among children with RHD aged 6 to 10 years and shows female predominance with an early presentation in life (mean age of 28 years in male, 31 years

in female) but with already advanced disease mostly in New York Heart Association (NYHA) functional class II-III.[13,14] For South Asia, MS also shows female predominance and clinical presentation similar to Africa but with a higher mean age of 39 years, similar to that seen in western countries.[42] According to the Euro Heart Survey, the prevalence of MS in the Mediterranean and Eastern European countries is high, accounting for 12% of valvular diseases in Europe.[43] In these countries, MS exhibits female predominance but the age at presentation is late, with only 4.7% presenting before 40 years.[44] These patients had low mean NYHA class (1.5) but they deteriorate with age and with the presence of co-morbidities. The incidence of Atrial fibrillation (AF) is higher (72%) than that seen among patients from Africa (28%)[13,14] and Asia (32%).[42] Thromboembolic events occur in 3.2%[45] and 12.3%[42] of patients in Africa and Asia respectively.

2.2. MITRAL VALVE ANATOMY AND ITS EFFECTS ON MANAGEMENT

Although the pathophysiology of rheumatic MS has long been known, its clinical presentation is known to vary significantly by sex. In females, isolated MS is more common, while mixed mitral valve (i.e. MS and mitral regurgitation) is common in males.[35,43] In a study done by Cruz-Gonzalez et al,[46] females had good anatomy for PBMV based on Wilkins score but short term post-PBMV outcomes were worse among females compared to males (success rate of 69% vs. 83%). They speculated that this may be related to an increased incidence of post-PBMV MR among females (9.4% vs. 4%) that in turn may reflect the slightly higher effective balloon dilatation to body surface ratio in females. Moreover, it has been reported that morphology and severity of mitral valve (MV) prolapse vary by sex.[47] It can be postulated that morphology and outcomes of MS also vary by sex.[46] However, the mechanisms of these differences need to be explored.

2.3. DISEASE PRESENTATION, DIAGNOSIS AND MANAGEMENT

MS presentation differs between different geographical settings. In Africa and Asia patients present with advanced stages of heart failure (HF) with paroxysmal nocturnal dyspnea and pulmonary edema being present in 30.5% and 16.7% of patients respectively. In developed countries, patients present mainly in a lower class of HF, NYHA class II.
Recently, gender medicine has attracted attention in the way CVDs are managed, as several studies[47–50] have shown differences between males and females in terms of disease presentation, response to treatment, and prognosis. However, it remains unclear whether this gender difference is a true biological sex difference or due to sex bias in medical care, in which females are less likely to get correct screening and prevention strategies, early diagnosis, and evidence-based medicine like for instance indications for PBMV for rheumatic MS.

According to Kislitsina et al,[48] a significant sex difference remains in MV pathology in which females have more RHD than males. When compared to males, females are: older,

have more symptoms, have more comorbidities, lately referred for intervention and therefore presenting with advanced disease. The reasons for late referral could be that females are well known to have a different presentation (higher prevalence of preserved left ventricular function[49,51]) and less clear symptoms (women with cardiac failure are likely to report symptoms of dyspnea more vaguely[50]) and have poor socioeconomic status.

A study of 3761 patients by Seeburger et al,[52] revealed that females had more MS and MV leaflet calcification than males. The authors postulated that higher MV calcification in females could be explained by differences in calcium metabolism and bone resorption among postmenopausal females.

The diagnostic approach for rheumatic MS is similar in males and females. An exception is in pregnant women in which an expert professional should be involved to make a risk prediction, if possible before pregnancy because pregnancy increases risk of HF and death.[53]

Management of clinically significant MS is as shown in figure 1.[21,22] As the figure shows, the only sex difference to take into consideration during management is the presence of pregnancy.

2.4. IMAGING CONSIDERATIONS

There are no sex-specific differences in the aspect of imaging in a patient with rheumatic MS. Management of patients with rheumatic MS requires the use of echocardiography and multimodality imaging to ensure a thorough assessment of the MV morphology and MS severity.[54] Usually, 2-Dimension echocardiography (2DE) by transthoracic (TTE) or transesophageal (TEE) is the imaging of choice. Due to its limitations like poor acoustic window and the effects of hemodynamic conditions on doppler studies, 3-Dimension echocardiography (3DE) is implicated. TEE is useful for the assessment of left atrial appendage for thrombi and for guiding interventions like PBMV. Multidetector computed tomography (MDCT) can be used as an alternative or complementary method in patients with poor acoustic windows. Cardiovascular magnetic resonance (CMR) is the third choice if echo and MDCT are inconclusive.[54] However, particular attention should be paid to pregnant women in whom echocardiography and CMR appear to be safe and are not associated with adverse fetal effects owing to lack of radiations.[53]

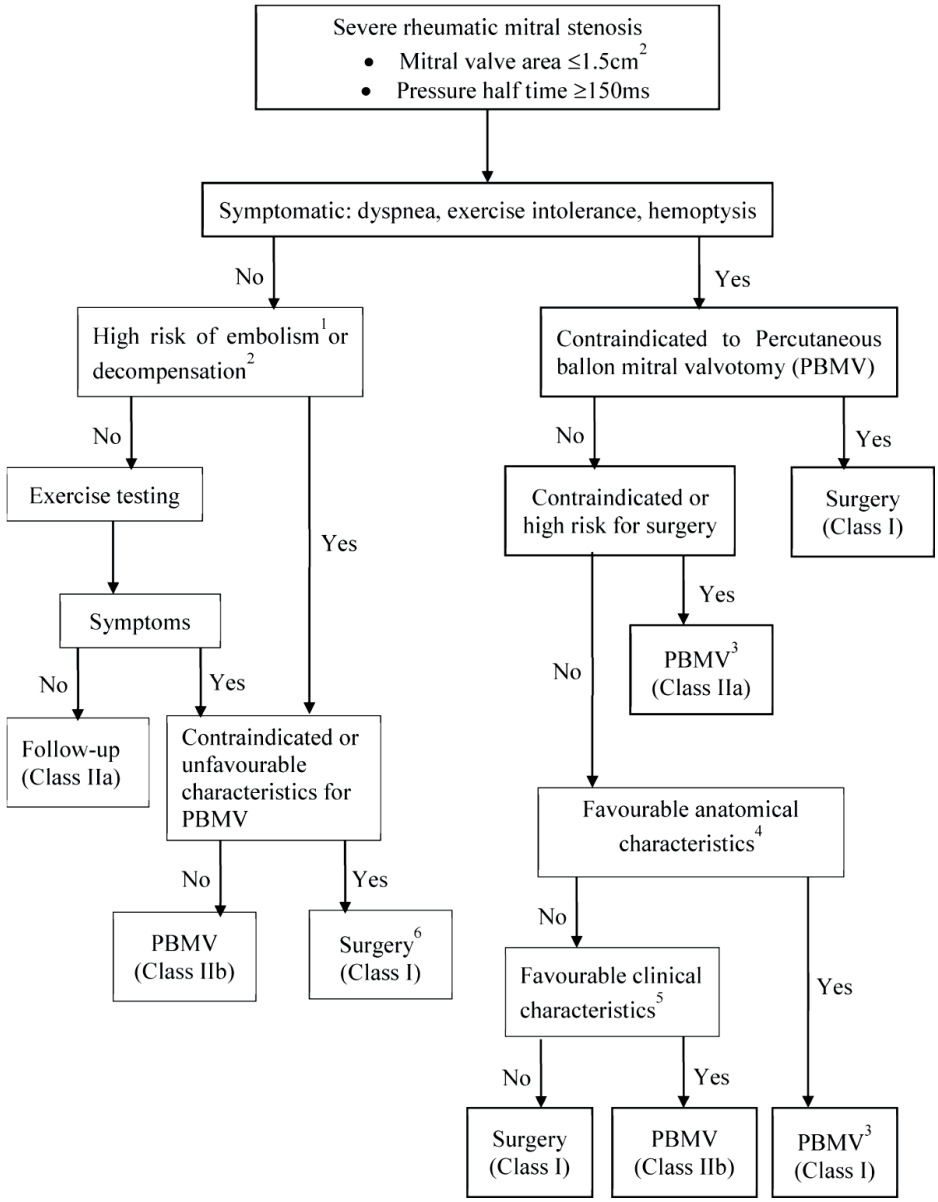

Figure 1. Management of clinically significant MS.

[1]Thromboembolism: past embolism, atrial fibrillation, dense echo in leftatrium; [2]decompensation: pulmonaryhyper tension > 50mmHg, major noncardiac operation, intention for pregnancy; [3]Consider commissurotomyby experienced surgeons or in patients contraindicated for PBMV; [4]Mitral valveorifice <1.5 cm2, no left atrium clots, MR< grade 2, mild calcification, no fused commissures; [5]PBMV for symptomatic patients contraindicated to operation, mitral valve operation for symptomatic patientsun suitable for PBMV; [6]Surgeryif symptomatic at less physical activity and low surgical risk. For the strength of recommendation: class I means the procedure should be performed, classIIa means it is reasonable to perform the procedure, and class IIb means the procedure may be considered (Redrawn from: Baumgartner et al[21] and Nishimuraet al[22]

2.5. APPROACH TO INTERVENTIONAL MANAGEMENT

2.5.1. Percutaneous balloon mitral valvuloplasty

Historically, chronic RHD was being treated with surgical interventions. The balloon for MS was introduced in the early 1980s, became the treatment of choice and offered superior results over open commissurotomy in patients with severe MS and conditions suitable for valvotomy.[55] PBMV is important in developing countries where hemodynamically severe MS presents earlier in life, and young patients have thickened valve leaflets presenting with or without concurrent regurgitation.[56] It is also a bridging therapy to OHS of MS patients during pregnancy, postponement of valvular replacement for females to finish their childbearing time (in avoidance of anticoagulation), or in patients who cannot tolerate OHS.[33,55] Other advantages are those related to its lower cost, lower morbidity, and lower procedure-related mortality.[40]

2.5.2. Surgery

The higher rate of mitral calcification among females lead to many of them to undergo MV replacement than males.[52] Also, a study done by Cruz-Gonzalez[46] showed that females have lower post-PBMV mitral valve area (MVA) and a higher incidence of post-PBMV mitral regurgitation the factors which predispose them to MV replacement.

2.6. THE IMPACTS OF GENDER ON IMMEDIATE AND/OR LONG-TERM OUTCOMES POST PBMV FOR RHEUMATIC MS

Several studies (Table 1) have been conducted to determine the impacts of sex on outcomes after PBMV.

2.6.1. Studies showing that sex is not a predictor of outcomes after PBMV

Older studies[35,40] reported that sex is not a predictor of long term outcomes after PBMV. Hernandez et al[35] did a univariate analysis of several variables (age, sex, cardiac rhythm, previous commissurotomy, Wilkins score, balloon size, and post-procedural mitral valve area and MR) as predictors of event-free survival and found that there was no significant difference between male and female (relative risk for female 1.22, 95% CI 0.67-2.22, p=0.1213) on outcomes after PBMV. Only Wilkins score was an independent predictor of outcomes on multivariate analysis.

2.6.2 Studies showing that male sex is a predictor of poor outcomes after PBMV

Yetkin and colleagues[34] found that the restenosis rates in males were higher than in females at 20% and 9% respectively ($p<0.05$). Males were older, had high Wilkins, low pre-PBMV MVA. Generally, males had unfavorable pre-procedural clinical and anatomical characteristics except for pre-PBMV pulmonary arterial pressure (PAP). Authors argued on their findings of the effect of male sex on outcomes that could be due to: smaller sample, the study was limited to patients who underwent successful PBMV,

and evaluation of different outcome measures.

Bouleti et al[57] found that 20 years after successful PBM**V,** 30% of patients still had good functional results (survival without cardiovascular death, MV surgery and repeat PBMV). Interaction between male sex and valve calcification was found to be among the predictors of poor late functional results (adjusted hazard ratio (HR) 2.3, 95% CI 0.6-3.2, P<0.0001) showing that the impact of valve anatomy is stronger in men. Other predictors were higher final trans-mitral mean pressure gradient, the interaction between age and final MVA, interaction between AF and NYHA class.

In a study done by Fabrizio Tomai et al[58] among 439 patients for a mean follow up of 11 years after successful PBMV with primary endpoints of major adverse cardiovascular events (MACE) including cardiovascular death and need for MV surgery or repeat PBMV; predictors of the primary endpoint were: male sex (HR 1.65, 95% CI 1.17-2.32, p=0.004), AF, Wilkins > 8, and post-PBMV MVA <1.75cm^2.

2.6.3 Studies showing that female sex is a predictor of poor outcomes after PBMV

Palacio et al,[32]showed that when compared to females, male sex was among the predictors of immediate PBMV success (71.7% for the overall group) both on univariate analysis (p=0.002) and on multivariate analysis (odds ratio 1.92 and 95% confidence interval 1.19 – 3.13, p=0.008). However, male sex was not among the independent predictors of long-term mortality. Male comprised 19.5% (n=182) of the study population therefore results could be affected by their smaller number.

Ignacio Cruz-Gonzalez et al[59] used a multifactorial score to predict success and long term outcomes of PBMV. Independent predictors of poor PBMV outcomes were age >55 years, female sex, NYHA classes ≥III, pre-PBMV MVA < 1cm^2, pre-PBMV MR grade > 2, and Wilkins ≥ 8.

Ignacio et al[46] showed that when compared to men and despite lower Wilkins scores, women who underwent PBMV had lower procedural success (69% Vs 83%, OR 0.04, 95% CI 0.19-0.74, p=0.02), achieved a smaller post-procedural MVA (73.7% Vs 86.9%, OR 0.14, 95% CI 0.23-0.72, p=0.002), and had higher incidence of post-procedural MR (9.4% Vs 4%,OR 2.41, 95% CI 1.0-5.83, p=0.05). However, the difference between the two sexes was not observed for long-term outcomes (mortality, need for repeat PBMV or composite adverse outcome endpoint of mortality). Male comprised 17% (n=176) of the study population therefore results could be affected by their smaller proportion.

Table 1. Studies reporting an association between sex and outcomes after PBMV

Author	Year	Study design	PBMV measure (follow-up)	Outcome
Cohen et al[40]	1992	Prospective observational study of 147 patients (77% female) who underwent PBMV	Predictors of long-term event-free survival (patients without MVR, repeat PBMV or Death) (36±20months)	Sex, cardiac rhythm, previous commissurotomy, baseline PAP/LAP, and MPG were not significant multivariate predictors of long-term outcome
Hernandez et al[35]	1999	Longitudinal observational study of 561 patients (82% female) who underwent PBMV	Long-term clinical and echocardiographic follow-up (39±23months)	Sex, age, cardiac rhythm, MVA pre-PBMV were not significant multivariate predictors of long-term outcome
Yetkin et al[34]	2001	Longitudinal observational study of 156 patients (78% female) who underwent PBMV	Comparison of pre- and post-PBMV characteristics and outcome of male and female patients, 38 months follow-up	Restenosis rates were significantly higher among male than female
Palaciao et al[32]	2002	Prospective observational study of 765patients (81.5% female) who underwent PBMV	Immediate and long-term clinical follow-up (4.2 ± 3.7 years)	Male sex, young age, pre-PBMV MVA, less degree of pre-PBMV MR, absence of prior-commissurotomy, Wilkins score ≤ 8 were independent predictors of immediate PBMV success
Ignacio Cruz-Gonzalez et al[59]	2009	Prospective observational study of 1085 patients who underwent PBMV	Immediate and long-term clinical follow-up median 3.097years (interquartile range 1.01 – 5.65 years)	Predictors of PBMV success were age <55 years, male sex, NYHA classes I and II, pre-PBMV MVA ≥ 1cm^2, pre-PBMV MR grade < 2, and Wilkins score ≤ 8
Ignacio Cruz-Gonzalez et al[46]	2011	Prospective observational study of 1015patients (83% female) who underwent PBMV	Immediate and long-term clinical follow-up (median 3.1 years)	When compared to men and despite lower Wilkins scores, women who underwent PBMV had lower procedural success.
Bouleti et al[57]	2012	Prospective observational study of 848 patients (85% female) who underwent PBMV	Immediate and long-term clinical follow-up median 10.7years (interquartile range 4.6 – 15.8years)	Predictors of poor late (after good immediate) results post PBMV were (among other factors) interaction between male sex and valve calcification.
Fabrizio et al[58]	2014	Prospective observational study of 439patients (83.3% female) who underwent PBMV	Immediate and long-term clinical follow-up (11.7 ± 4.9 years)	Predictors of primary end point (the 20 years incidence of MACE) were: male gender, atrial fibrillation, Wilkins >8, and post PBMV MVA <1.75cm^2

Abbreviations: LAP, left atrium pressure; MACE, major adverse cardiac events; MR, mitral regurgitation; MVA, mitral valve area; MVR, mitral valve replacement; NYHA, New York Heat Association; PAP, pulmonary artery pressure; PBMV, percutaneous balloon mitral valvuloplasty.

3. MIGRATION AND ITS EFFECTS ON DISEASE EPIDEMIOLOGY

3.1. EFFECTS OF MIGRATION ON THE EPIDEMIOLOGY OF CVD

It is estimated that 68.5 million people worldwide have been driven from their homes due to either conflict, war, persecution or as asylum seekers[60] It is known that globalization, urbanization and migration affect the epidemiology of CVDs.[61] Therefore, it is important to elucidate how they influence the burden and distribution of CVDs and to modify health systems and health service delivery to changing needs. In their review, Anna et al[62] argued that there are three factors influencing CVD burden in migrant populations: conditions in the country of origin, the migration process, legal status in the host country.

Migration requires new strategies to be implemented to health policy and practice, informed by evidence derived from relevant research to support them. Anna et al[62] proposed an approach that includes components which should be introduced in welfare and health systems to bring an effective response to the challenges of migration, specifically the changing pattern of CVD. Since immigrants exhibit variations,[63] CVD care services should be designed and implemented in ways that respond to certain requirements of immigrants, the variations should also be considered when assessing CVD risk profiles and when designing health services which should be culturally and religiously appropriate, accessible[63] and acceptable. Health services for migrants should be medically and culturally appropriate and should be integrated into the hosting national health system.[64] There is a need for enhanced cross-border surveillance, clinical data sharing, and the ability to share cross-country experience and best practices. The authors named these components as “responding-integrating and sharing” formula. [62] They proposed, for them to be in use they should be supported by international commitment, training and education of workforces, information and technology, and by research for filling evidence gap.[62]

3.2. EFFECTS OF MIGRATION ON EPIDEMIOLOGY AND MANAGEMENT OF RHD

About a third of the 68.5 million people who have been forced from their homes worldwide are refugees, over half of them being under the age of 18 years, putting them at high risk of acute rheumatic fever (ARF).[65]

The exact prevalence of RHD among migrant and refugee populations worldwide is difficult to ascertain, however, it is believed to be high. A recent review on the impact of migration on CVD focused on ischemic heart disease, its risk factors and consequences[62] but also appreciated on the high burden of RHD in many parts of the world.[13]

Gianfranco De Maio et al[66] when they screened refugees aged 10 – 25 years for RHD in

Rome, Italy they found that 1.7% of these refugees had definitive RHD. The prevalence of subclinical RHD was 2.1% similar to that found in other parts of the world[13] such as India (2.0%), Cambodia (2.2%) and Mozambique (3%). Similarly, Condemi et al[11] have recently screened refugees aged 13 – 26 years and found a prevalence of 'definitive RHD' of 2.6% while that of ' borderline RHD' was 18.6%. The burden of borderline cases was markedly higher than that reported elsewhere. It is being reported that of the more than 1 million asylum seekers who moved to Europe in 2015, approximately 1% of them could have RHD.[67]

Since refugee camps and informal settlements are overcrowded, there is a great likelihood for the streptococcus infections which cause ARF and subsequent RHD to spread more easily.[67] When refugees settle in places where RHD is uncommon or under-recognized, this may lead to late diagnosis and eventually poor care associated with disease complications.

The effect of migration on RHD goes beyond disease distribution because it also affects disease management. Antibiotic injections to prevent recurrent ARF and sequela of valve damage must be given monthly, necessitating a stable and supportive health service, something which is unlikely among the migrant populations.[67] The impact of disorganized health services on disease prevalence in vulnerable communities has been reported before: during the breakdown of the Union of Soviet Socialist Republics, RHD prevalence increased tremendously in association with social and economic disruption.[68] Besides, migrants have a high burden of non-communicable diseases which may contribute to other heart diseases in the elderly.

4. CONCLUSION AND FUTURE PERSPECTIVES

This review showed a female predominance for RHD and contradicting results for outcome after PBMV among the two sexes. It is not clear whether sex difference plays a role in diagnosis, management and prognosis of MS: i) Is it a true sex biological difference or a sex bias in medical care, in which female are less likely to get correct screening and prevention strategies due to socioeconomic status? (ii) Is there a difference in mitral valve calcification between sexes. Further studies need to be done to explore the mechanisms for the differences.

Migration has impacts on RHD: i) among immigrants in developed nations, RHD is a major reason of admission and cardiac surgery, ii) migration requires new strategies to be implemented to health policy and practice, evidenced by relevant research, iii) a call for developed nations to revive their medical education programs to include RHD

because clinicians and health systems have become unfamiliar with the condition. Further studies are required to explore more on the impacts of migration on RHD.

Conflict of interest

The authors declare no conflict of interest.

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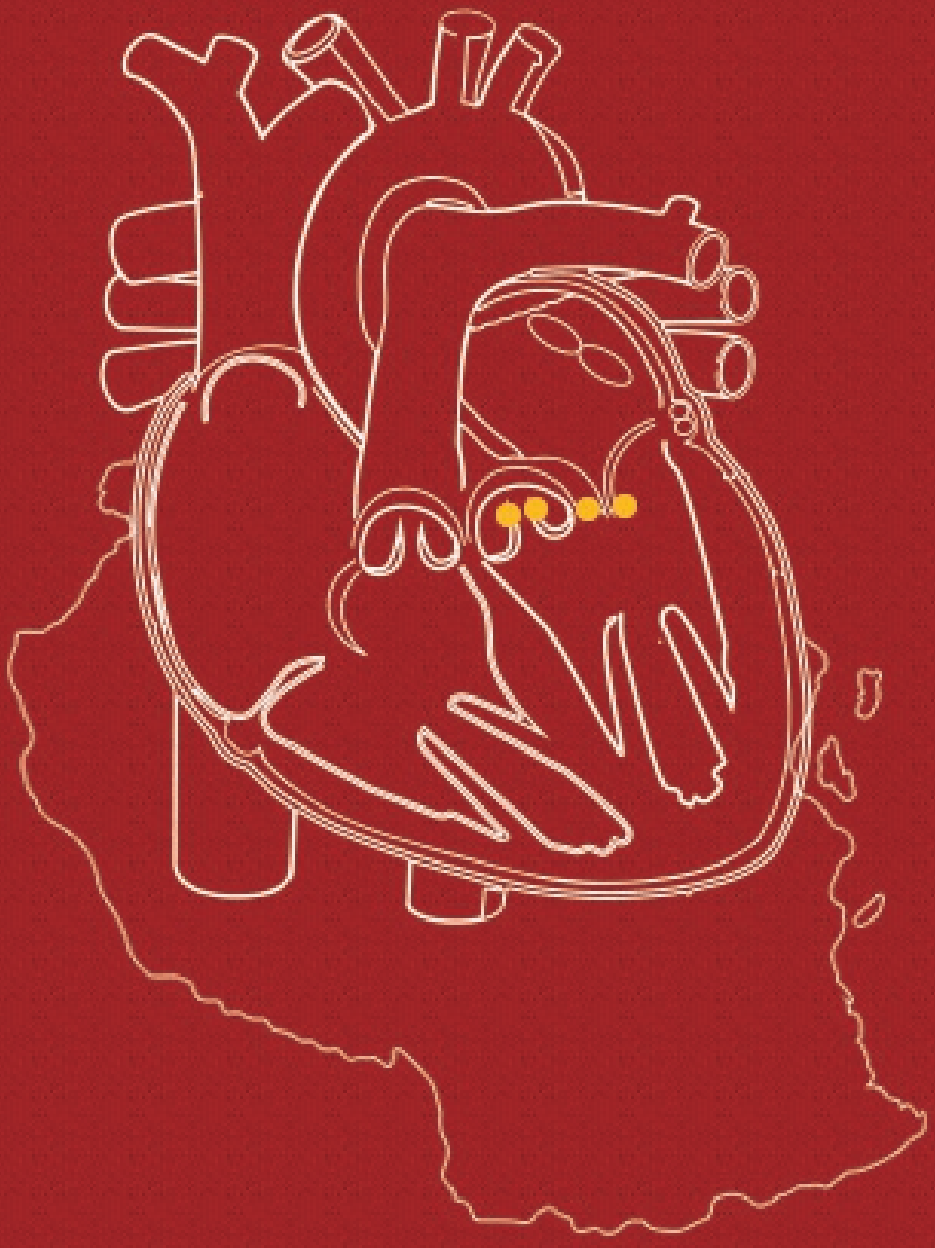

CHAPTER 3

Infective endocarditis in developing countries: an update

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ABSTRACT

INTRODUCTION

Despite advances in diagnostic and treatment, morbidity and mortality due to infective endocarditis (IE) has not decreased. There is a discrepancy in epidemiology of IE between developed and developing countries. Over the last years, increased early detection and consequently prevalence of rheumatic heart disease (RHD) and congenital heart disease (CHD) which are considered predisposing conditions for IE, is noted. Here, we present a review of literature on IE in developing countries.

METHODS

We conducted a systematic literature search of IE studies in developing countries through PubMed and Embase. We have divided the studies into two groups: studies published before 2015 (group 1) and studies ≥ 2015 (group 2). The outcome was defined as a difference in epidemiology, microbiology, treatment, and mortality over time. The Scale for Assessment of Narrative Review Articles guidelines was applied.

FINDINGS

In total, 16 studies were included. The total number of IE cases was 1,098 and 1,505 in groups 1 and 2 respectively. We compared 4/7 cohorts from group 1 (n = 789) with 5/9 cohorts from group 2 (n = 636). Six studies were not included in the comparison because they were interacting between the two cohorts. Males predominated in all studies. RHD was higher in group 1 than in group 2 (42.3% vs 30.3%, p<0.001) while for CHD there was no change (17.6% vs 16.7%, p = 0.672). Streptococci infections was lower in group 1 than group 2 (26.2% vs 37.7%, p<0.001). The proportion of *Staphylococcus aureus* was 15.3% in group 1 and 23.6% in group 2, p<0.001. Negative blood culture (NBC) was higher in group 1 than in group 2 (42.2% vs 34.1%, p=0.002). Patients in group 1 received more surgery than in group 2 (38.8% vs 28.8%, p<0.001). Mortality was similar in the two groups (20.9% vs 22.3%, p = 0.518).

CONCLUSION

This review shows a scarcity of studies on IE in developing countries. RHD and CHD are common predisposing conditions. Other risk factors are prosthetic valves, degenerative valve disease, intravenous drug use, and human immunodeficiency virus infection. While the proportion of IE cases caused by *Streptococcus* and *Staphylococcus* has increased, the number of NBC and patients getting surgery has decreased. Mortality has not changed over time. Timely diagnosis and management of patients with RHD and CHD and comprehensive management of IE are warranted.

KEYWORDS

Infective endocarditis, morbidity, mortality, developing countries, rheumatic heart disease.

INTRODUCTION

Infective endocarditis (IE) is a complex disease associated with a burden on the healthcare system due to its imposing prolonged hospitalization, a high mortality rate of about 20-25%, and high morbidity. [1–4] Worldwide the incidence of IE is still rising, despite the improvement in diagnostics and treatment options. The risk factors for developing IE have been evolving over the last decade. [5] In high-income countries (HIC), advances in interventional cardiology with devices came at the cost of increased device-related infections. Prosthetic valve endocarditis now accounts for approximately 20% of all endocarditis cases in HIC. [6] Advances in diagnostic tools like positron emission tomography (PET) scan and transesophageal echocardiography (TEE), availability of modern treatment options, and the creation of 'endocarditis team' have improved the management and outcomes of IE in HIC. [7–11]

To the best of our knowledge, little is known about IE in developing countries due to a lack of adequate studies in this area. Rheumatic heart disease (RHD) and congenital heart disease (CHD) have been reported as the most common cause of IE. [3,12] Studies have shown that, in developing countries, optimal medical and surgical management is limited. [12] In these countries, microorganisms are reported to be unidentified due to poor diagnostic capacity. [3] Moreover, studies have shown that patients have more complications due to delays in diagnosis and late hospital presentation. [3,12]

Recently, in developing countries, there has been an increase in the use of prosthetic and intra-cardiac devices which are other risk factors of IE. [12] Patients who are at risk of developing IE also include those who visit the healthcare system for other comorbidities, for example, immunosuppressed patients. [1,5] The microbiological spectrum of IE has also been changing field. [3,12] Some studies report that *S. aureus* is now the most common organism, especially due to the healthcare-associated IE. [3,12–14] However, other studies show that streptococci still predominates. [15,16] Furthermore, the proportion of cases of IE that are caused by coagulase-negative staphylococci (CoNS) are rising concurrently with the decrease of *Streptococcus viridians* and *Enterococcus*. [3,12]

In the present study, we are summarizing the current state of IE in developing countries and to investigate whether there is a change over time in the presentation of IE. We have assembled information about the epidemiology, diagnosis, treatment, and mortality of IE in these developing countries. Our review includes publications of studies from the year 2000 to 2020 with two predefined groups: studies published before the year 2015 (group 1, the 'early' cohorts) and the year ≥ 2015 (group 2, the 'late' cohorts). In the end, we have highlighted the future perspectives toward comprehensive management of IE in developing countries.

METHODS

SEARCH STRATEGY

A systematic literature search was performed through PubMed and Embase using the keywords "endocarditis", "developing country", "poverty" and "low- and middle-income country". The identified records were entered in Rayyan QRCI and were independently screened by two blinded reviewers (JV & RM). Subsequently, a full-text review of the remaining studies was performed, and studies were selected if eligibility criteria were fulfilled. Disagreements were resolved by consensus. The detailed search queries are Pubmed: *(((endocarditis [MeSH Terms]) OR "endocarditis"[Title/Abstract])) AND (((((developing countries [MeSH Terms]) OR developing country [MeSH Terms]) OR low-income population [MeSH Terms]) OR "developing countries"[Title/Abstract]) OR "low income countries"[Title/Abstract])* and Embase: *'endocarditis': ti, ab, kw AND ('developing country': ti, ab, kw OR 'low income country': ti, ab, kw OR 'low middle income country': ti, ab, kw OR 'lowest income group': ti, ab, kw)*

STUDY ELIGIBILITY AND DEFINITIONS

Any study which reported detailed information about the IE population from developing countries was considered eligible for this research. The inclusion criteria were English language and publication date from the year 2000 to 2020. Exclusion criteria comprised studies that entirely included children only and studies in which full text was not available. Developing countries were defined according to the International Monetary Fund definition. [17,18] Our study population was defined as patients diagnosed with possible or definite endocarditis by using the revised Duke criteria. [19] All studies had to report on the number of IE subjects included in that particular study, age, and sex of the study population and it was required to describe data on numbers of antibiotic and surgical treatment and (in-hospital) mortality. Besides, data concerning predisposing conditions and microbiology was mandatory. For the sake of determining the trends in different parameters concerning IE and for comparison purposes, we have divided our study population into two groups namely studies published before the year 2015 (group 1, 'early' cohorts) and studies published in the year ≥ 2015 (group 2, 'late' cohorts). 'Early' cohorts are studies that entirely recruited patients from the year 1986 – 2005 while 'late' cohorts are studies that entirely recruited patients from the year ≥ 2005 - 2017. The reporting of this study conforms to SANRA (the Scale for Assessment of Narrative Review Articles) guidelines. [20]

DATA ANALYSIS

Descriptive summaries of the data are presented. Continuous parameters are reported as mean and standard deviation or median and interquartile range. Discrete variables are presented in percentages. The Chi-square and Fisher's exact tests were used to

compare categorical data. SPSS (v.28) was used for analysis. P value <0.05 was considered statistically significant.

RESULTS

Our search resulted in 145 articles of which 12 studies eventually are included. All of the included studies were Google searched and cross-referenced for an additional of four relevant articles which brought a total of 16 studies from 9 countries (Figure 1).

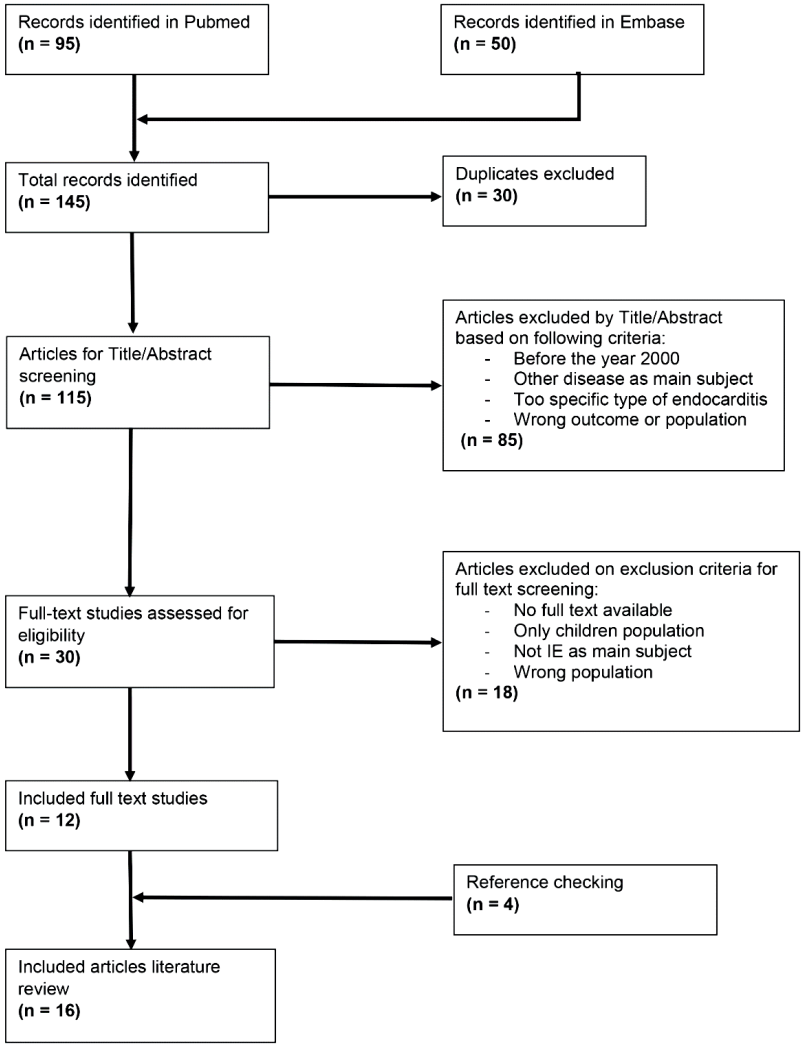

Figure 1. A flowchart showing a literature search of included studies

STUDY CHARACTERISTICS AND DEMOGRAPHICS

All study characteristics are shown in Table 1 and Table 2**.** We retrieved 7 studies for group 1 and 9 studies for group 2.

In the first group, the total number of IE cases was 1,098 whereas in the second group it was 1,505. The lowest mean age was 23.5 (interquartile range, 9 - 38) years while the highest was 59 ± 17.8 years. In all studies except one, there were more males than females. The clinical case definition used for diagnosing IE was reported in 12 (75%) studies of which 100% of definite diagnosis was only in 3 studies.

We performed a detailed comparison of four studies (cohorts by Kanafani et al, [21] Tariq et al, [22] Garg et al, [23] and Letaief et al [24]) from group 1 with five cohorts (by Mirabel et al, [15] Xu et al, ([26] Subbaraju et al, [30] Villers et al, [14] and Sunil et al [32]) from group 2 for several parameters. The remaining cohorts were either interacting between the two groups or had missing data and therefore they were not considered for comparison but were described accordingly. The prevalence of males was lower in group 1 than in group 2 (62.0% vs 65.6%, p=0.167) as shown in Table 3. The proportion of native valves affection was lower in group 1 than in group 2 (84.9% vs 90.3%, p=0.003). The proportion of IE on prosthetic valves was higher in group 1 than in group 2 (15.1% vs 7.4%, p<0.001) as depicted in Table 3.

Table 1. Characteristics of the study population of group 1, publications before 2015

Year	Author	Cohort	Country	Study design	IE cases	Definite vs Probable (%)	Native vs PHV (%)	Mean age ± SD (yrs)	Male (%)	Predisposing condition (%)	Microbiology (%)	Antibiotics (%)	Surgery (%)	In-hospital mortality (%)
2002	Kanafani et al(21)	1986-2001	Lebanon	Retrospective	91	82 vs 17	80 vs 20	48 ± 19	64	RHD (33) CHD (13) DVD (NR) IVD (0) HIV (0)	NBC (23) *Strept* (51) *S. viridans* (28) *Staph spp* (36) *S. aureus* (26) enteroc (4) CoNS (10)	100	32	18
2004	Tariq et al(22)	1997-2001	Pakistan		66	50 vs 50	92 vs 8	Mean 28.8 Median 24	60	RHD (23) CHD (50) DVD (2) IVDA (NR) HIV (NR)	NBC (48) *Strept* (59) *Staph spp* (24) enteroc (3) Gramneg (15)	100	12	27
2005	Garg et al(23)	1992-2001	India	Retrospective	192	100 vs 0	90 vs 10	27.6 ± 12.7	73	RHD (47) CHD (29) DVD (3) IVD (NR) HIV (NR)	NBC (32) *Strept* (23) *Staph spp* (20) *S. aureus* (15) CoNS (5) enteroc (8) Gramneg (13)	100	23	21
2007	Letaief et al(24)	1991-2000	Tunisia	Retrospective	440	NR	83 vs 17	32.4 ± 16.8	56	RHD (45) CHD (9) DVD (6) IVDA (0) HIV (NR)	NBC (50) *Strept* (18) *Staph spp* (18) *S. aureus* (12) CoNS (6) enteroc (4)	100	51	21
2008	Trabelsi et al(25)	1997-2006	Tunisia	Retrospective	134	93 vs 7	100 vs 0	Mean 34.2 (IQR 4 - 73)	58	RHD (45) CHD (16) DVD (8) IVDA (NR) HIV (NR)	NBC (49) *Strept* (24) *Staph spp* (22) *S. aureus* (18) CoNS (4) Bartonella (8) enteroc (1)	100	51	19

Table 1. Continued.

Year	Author	Cohort	Country	Study design	IE cases	Definite vs Probable (%)	Native vs PHV (%)	Mean age ± SD (yrs)	Male (%)	Predisposing condition (%)	Microbiology (%)	Antibiotics (%)	Surgery (%)	In-hospital mortality (%)
2011	Math et al[16]	2004-2006	New Delhi, India	Prospective	104	100 vs 0	30 vs 20	Mean 23.5 (IQR 9- 38)	71	RF (5) CHD (39) IVDA (0) HIV (NR)	NBC (59) *Strep*t (8) *S. aureus* (7) enteroc (5)	100	15	26
2014	Damasco et al[13]	2009–2013	Brazil	Retrospective	71	79 vs 21	90 vs 10	49.8 ± 2.4	58	NR	NBC (15.5) *Strept* (25) *S. aureus* (30) enteroc (27) CoNS (8)	NR	NR	46

RHD, rheumatic heart disease; CHD, congenital heart disease; DVD,degenerative valve disease; RF, Rheumatic fever; NR, not reported; PHV, prosthetic heart valve, IE, infective endocarditis, NBC, negative blood culture, CoNS, coagulase negative staphylococci, IVDA, intravenous drug abuse; HIV, human immunodeficiency virus; Staph spp, *Staphylococcus spp;* Strept, *Streptococcus spp;* enteroc, enterococci; Gramneg, Gram negative

Table 2. Characteristics of the study population of group 2, publication ≥ 2015 to 2019

Year	Author	Cohort	Country	Study design	IE cases	Definite vs Probable (%)	Native vs PHV (%)	Mean age ± SD (yrs)	Male (%)	Predisposing condition (%)	Microbiology (%)	Antibiotics (%)	Surgery (%)	In-hospital mortality (%)
2015	Mirabel et al[15]	2006-2012	Lao PDR	Retrospective	36	31 vs 69	83 vs 17	25 (IQR 18- 42)	42	RHD (33) CHD (19) DVD (8) IVDA (NR) HIV (NR)	NBC (61) *Strept* (19) *Staph spp* (6) *E. coli* (6) enteroc (6) *S. aureus (3)* CoNS (3)	69	0	39
2016	Xu et al(26)	2008-2011	East China	Retrospective	66	73 vs 27	96 vs 4	46.3 ± 16.1	61	RHD (33) CHD (19) DVD (8) IVDA (1)	NBC (39) *Strept* (56) *Staph spp* (26) enteroc (3)	100	32	10
		2012- 2015			108	81 vs 19	93 vs 7	48.7 ± 15.5	69	RHD (27) CHD (12) DVD (33) IVDA (0)	NBC (41) *Strept* (65) *Staph spp* (21) enteroc (6)	100	51	12
2017	Fernandes et al(27)	2000- 2012	West Indies	Retrospective	201	100 vs 0	90 vs 10	Median 48	67	BHD (54) CHD (NR) DVD (NR) IVDA (2) HIV (27)	NBC (21) *Strept* (30) *Staph spp* (29) *S. aureus* (23) CoNS (6) enteroc (5)	100	53	19

Table 2. Continued.

Year	Author	Cohort	Country	Study design	IE cases	Definite vs Probable (%)	Native vs PHV (%)	Mean age ± SD (yrs)	Male (%)	Predisposing condition (%)	Microbiology (%)	Antibiotics (%)	Surgery (%)	In-hospital mortality (%)
2017	Chakhtoura et al(28)	1989- 2001	Lebanon	Retrospective	86	80 vs 20	80 vs 20	48 ± 18.2	62	RHD (15) CHD (8) DVD (NR) IVDA (0) HIV (0)	NBC (26) *Strept* (40) *Staph spp* (26) *S. aureus* (20) CoNS (6) enteroc (4)	NR	33	15
		2001- 2014			80	80 vs 20	70 vs 30	59 ± 17.8	75	RHD (16) CHD (9) DVD (NR) IVD (1) HIV (1)	NBC (16) *Strept* (26) *Staph spp* (31) *S. aureus* (20) CoNS (11) Enteroc (15)	NR	31	16
2017	Tran et al(29)	2005- 2014	Vietnam	Retrospective	189	NR	87 vs 12	38 ± 18	64	VHD (66) CHD (19) DVD (NR) IVDA (1) HIV (NR)	NBC (30) *Strept* (75) *Staph spp* (10) Gramneg (5) enteroce(4)	NR	NR	7
2018	Subbaraju et al(30)	2007- 2013	South India	Retrospective	139	68 vs 32	96 vs 4	47.9 ± 15.8	68	RHD (31) CHD (16) DVD (23) IVDA (0)	NBC (30) *S. pyogen* (31) *S. aureus* (11) enteroc (13)	100	4	17
2019	Ren et al(31)	2001- 2009	South China	Retrospective	97	NR	97 vs 3	36.5 ± 15.2	72	BHD (49) CHD (21) RHD (23) DVD (4) IVDA (26)	NBC (53) *Strept* (37) *S. aureus* (41) enteroc (2)	100	59	13
		2010- 2018			216	NR		44.9 ± 15.4	72	BHD (44) CHD (15) RHD (18) DVD (9)	NBC (38) *Strept* (44) *S. aureus* (20) enteroc (10)	100	60	10

Table 2. Continued.

Year	Author	Cohort	Country	Study design	IE cases	Definite vs Probable (%)	Native vs PHV (%)	Mean age ± SD (yrs)	Male (%)	Predisposing condition (%)	Microbiology (%)	Antibiotics (%)	Surgery (%)	In-hospital mortality (%)
2019	Villiers et al[14]	2009– 2016	Cape Town	Retrospective	105	65 vs 35	84 vs 16	Median 39 (IQR 29- 51)	62	RHD (34) CHD (11) IVDA (14) HIV (23)	NBC (41) *Strept* (17) *S. aureus* (19) enteroc (7)	100	42	19
2019	Sunil et al(32)	2005- 2017	Malaysia	Retrospective	182	84 vs 16	94 vs 6	50.0 ± 17.6	70	RHD (42) CHD (8) DVD (NR) IVD (5) HIV (3)	NBC (22) *Strept* (36) *S. viridans* (29) *S. aureus* (41) enteroc (9)	100	32	37

RHD, rheumatic heart disease; CHD, congenital heart disease; BHD, basic heart disease; DVD, degenerative valve disease; VHD, valvular heart disease; NR, not reported; PHV, prosthetic heart valve; IE, infective endocarditis; NBC, negative blood culture; IVDA, intravenous drug abuse; HIV, human immunodeficiency virus; Staph spp, *Staphylococcus spp;* Strept, *Streptococcus spp;* S. pyogen, *Streptococcus pyogenes;* enteroc, enterococci

Table 3. Comparison of the two IE cohorts in respect to several parameters

Variable	< 2005 (N = 789) n (%)	≥ 2005 (N = 636) n (%)	Difference (95% CI)	P - value
Sex (Male)	489 (62.0)	417 (65.6)	-0.04 (-0.09, 0.01)	0.167
Native	670 (84.9)	574 (90.3)	-0.05 (-0.09,-0.02)	0.003
Prosthetic	119 (15.1)	47 (7.4)	0.08 (0.04, 0.11)	< 0.001
RHD	334 (42.3)	193 (30.3)	0.12 (0.07, 0.17)	< 0.001
CHD	139 (17.6)	106 (16.7)	0.01 (-0.03, 0.05)	0.672
Streptococcus	207 (26.2)	240 (37.7)	-0.12 (-0.16,-0.07)	< 0.001
Staphylococcus	121 (15.3)	150 (23.6)	-0.08 (-0.12, 0.04)	< 0.001
Culture negative	333 (42.2)	217 (34.1)	0.08 (0.03, 0.13)	0.002
Surgery	306 (38.8)	183 (28.8)	0.10 (0.05, 0.15)	< 0.001
Mortality	165 (20.9)	142 (22.3)	-0.01 (-0.06, 0.03)	0.518

PREDISPOSING CARDIAC CONDITIONS

Tables 1 and 2 show a wide range of rheumatic (23% - 46.9%) and congenital heart disease (7.7% - 50%), the two conditions were reported in 13 (18.25%) of the reviewed studies. As shown in Table 3, the prevalence of RHD was significantly higher in group 1 than in group 2 (42.3% vs 30.3%, 0<0.001). Congenital heart disease occurred with a similar magnitude between groups 1 and 2 (17.6% vs 16.7%, p=0.672). Tables 1 and 2 depict that the prevalence of degenerative valve disease (DVD) was ranging from 4% – 33%, being reported in half of the reviewed studies. The proportion of intravenous drug use and HIV infections were raging from (0 – 25.8%) and (0 – 27%) respectively but they were rarely reported as shown in tables 1 and 2. Overall, there was under-representation of Africa where many developing countries belongs. Figure 2 exemplifies countries that were recruited in this review with a reference to the prevalence of RHD as the common predisposing cardiac condition of IE.

MICROBIOLOGY

As depicted in Table 3, the proportion of streptococci spp was lower in group 1 than in group 2 (26.2% vs 37.7%, p<0.001) with the common isolates being *Streptococcus pyogenes* and *Streptococcus viridans*. Similarly, the presence of staphylococci spp in the early cohorts was less common than in the late cohorts (15.3% vs 23.6%, p<0.001) with the common isolates being *S. aureus*. The proportion of coagulase-negative *Staphylococcus* occurred in the range of 2.8% - 11.3% while that of enterococci was ranging from 1% – 26.7% (Table 1 and 2). The proportion of negative blood culture (NBC) was significantly higher in group 1 than in group 2 (42.2% vs 34.1%, p=0.002) as shown in Table 3.

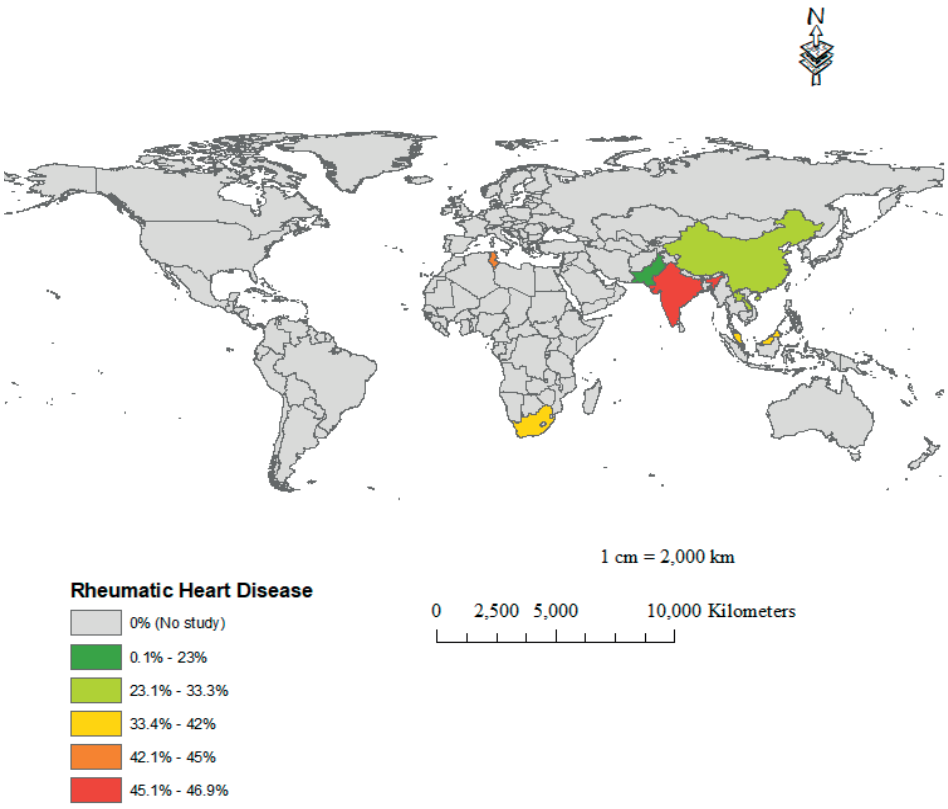

Figure 2. A map showing the prevalence of rheumatic heart disease as a predisposing condition of IE in the reported IE studies

MEDICAL TREATMENT

As shown in Tables 1 and 2, antibiotics were prescribed by 100% in all of the reported studies except one. Penicillin with or without aminoglycosides was the most used antibiotic across all cohorts. Of the aminoglycosides, gentamicin was the most commonly used antibiotic. Ceftriaxone and vancomycin were also regularly used. In group 1, Letaief et al [24] and Trabelsi et al [25] did not report on the antibiotic used and only Math et al [16] mentioned larger combinations of therapy in addition to fluoroquinolones. In group 2, Xu et al [26] often used glycopeptides and cephalosporin, Subbaraju et al [30] mostly used gentamicin and ceftriaxone, and Sunil et al [32] most frequently used ceftriaxone, with or without benzylpenicillin. Fernandes et al, [27] Tran et al, [29] Ren et al, [31] and Villiers et al [14] did not report on the kind of antibiotics used.

SURGERY

Fifteen (93.8%) of 16 studies reported surgical treatment of infective endocarditis. The

rate of surgery performed varied across the reviewed studies from 0% in Lao to 60.2% in China (Tables 1 and 2). Among the compared groups, the proportion of patients who underwent surgery was higher in group 1 than in group 2 (38.8% vs 28.8%, p<0.001) as shown in Table 3. Damasco et al [13] and Tran et al [29] did not report on surgical intervention. In a report by Mirabel et al, [15] no surgical intervention was offered to patients with IE in Lao People's Democratic Republic.

MORTALITY

Mortality data were reported in all of the studies (Tables 1 and 2). As shown in Table 3, the in-hospital mortality did not significantly differ between group 1 and group 2 (20.9% vs 22.3%, p=0.518). This signifies that mortality as a result of infective endocarditis (IE) has not changed over the past four decades of the reviewed cohorts i.e. 1986- 2017.

DISCUSSION

The epidemiology of IE in developing countries has been reported in a few studies some of which give inconsistent results. [3,12] In the past, the epidemiology of IE in developing countries was reported to be similar to that of HIC. [3,4] Anecdotal evidence shows that in developing countries IE is not an uncommon condition although some hospital records report that IE accounts for < 0.5% of admissions due to cardiovascular conditions. [33,34] It is challenging to make a diagnosis of IE in areas where causes of fever are plenty and therefore high expertise in clinical suspicion complemented by appropriate laboratory investigations is needed. This is further hampered by the poor health infrastructures and patients' financial constraints in which most of these patients do not own health insurance. This review was undertaken to summarize the current state of IE in developing countries and to investigate whether there is a change over time in the presentation of IE. The review had a main focus on epidemiology, diagnosis, treatment, and mortality of IE in these developing countries. However, suffice it to say we know little about IE in most parts of sub-Saharan Africa.

In this review, the lowest mean age of patients was 23.5 (interquartile range, 9 - 38) years while the highest was 59 ± 17.8 years. This is similar to the mean age of 47 years reported by Njuguna et al [3] and the mean age of fewer than 40 years in a systematic review done by Noubiap et al. [12] These findings imply that IE in developing countries affects the young and this is probably due to the common predisposing conditions in these areas which are RHD and CHD. On the contrary, native valve IE in the HIC commonly affects the old population of which degenerative valve disease is the major underlying cardiac disease. [6,35,36] Our review showed a male predominance in all except one study. Similarly, previous studies have reported a high prevalence of males in IE studies. [3,12] The

reason for the increased proportions of males in these studies has not been elucidated, although estrogen is implicated in protection against endothelia damage. [37]

This review showed that the proportion of patients with native valve IE was significantly lower in group 1 (84.9%) than in group 2 (90.3%). The higher proportion of patients with native valve IE in the second cohort could be explained by the fact that awareness and diagnostic tests have probably increased in the latest decades hence increasing the detection rate. Similarly, a recent systematic review has reported that Native valves were involved in 81.1% of patients with IE. [12] The same observation has been reported in a study from HIC in which native valve IE accounted for 72%. [6] On the other hand, the proportion of patients with prosthetic valve IE was significantly higher in group1 (15.1%) than in group 2 (7.4%). This could probably be due to improved care of patients with prosthetic valves in recent decades. In contrast, Noubiap et al [12] reported that 18.2% of patients with IE had prosthetic valves. The authors argued that this could be due to increased access to cardiac surgery and/or a reporting bias because these patients are likely to receive regular medical follow-up with subsequent early detection of IE if occurs. On the other hand, native valve IE commonly go undiagnosed until when it has resulted into complications.

Predisposing conditions

The current review showed that RHD was the leading predisposing condition for IE followed by CHD. Similarly, previous studies have reported the same findings, [3,12] implying the endemicity of RHD in developing countries. In contrast, in high-income countries, RHD accounts for 3% of patients with IE. [6] However, with migration, RHD is evolving in the HIC [38] and hence the prevalence of IE in HIC may also increase. The prevalence of RHD as a predisposing condition for IE was statistically significantly higher (42.3%) in the first group than in the second group (30.3%). The reasons for a decrease in the prevalence of RHD as a predisposing condition for IE in group 2 as compared to group 1 could probably, among other reasons, be due to improved hygiene and the use of prophylactic antibiotics when patients are undergoing risky procedures. The prevalence of CHD as a predisposing condition of IE in group 1 and group 2 was similar (17.6% vs 16.7%, p=0.672). The reason for the similarity in the proportion of CHD in the two groups is possible because no interventions have been provided over time given the fact that adult CHD are less likely to be predisposed to IE. In contrast, a recent review of previous studies which were mostly performed in adults have reported that IE occurred in only 8% of patients with CHD.[12] The observed differences between the two reviews are due to the fact that some of our reviewed studies comprised children. Congenital heart disease is a common risk factor for IE in children accounting for about 50% in several studies. [3,12]

Our review showed that degenerative valve disease was rare in patients with IE, this is contrary to findings from HIC where it is the commonest predisposing cardiac condition in native valve IE.[6] The reason for this observation is probably because in developing countries IE affects the younger patients as was seen in our reviewed studies. Similarly, both intravenous drug use and human immunodeficiency virus were rare predisposing conditions for IE. However, our findings should be interpreted with caution because most of the reviewed studies did not report on these conditions. Indeed, several reports have shown that intravenous drug use is not uncommon in developing countries, [12,39] but lower than what has been reported in HIC. [40] Moreover, several studies have reported human immunodeficiency virus as a predisposing factor for HIV-associated cardiac disease including IE. [13,14,41]

MICROBIOLOGY

It is important to identify the causative microorganisms of IE to offer targeted antimicrobial therapy. Unfortunately, in our review nearly half of the patients with IE in group 1 no microorganism was detected, opposing to HIC where microorganisms are identified in 95% of cases. [4] Possible explanation for such a low detection rate observed in our review could be due to the use of antibiotics before the collection of blood, poor infrastructures for laboratory tests, and unavailability of standard operating procedures for blood collection and processing. [3,4,12] Due to financial constraints, it is likely that very few blood cultures are done in developing countries. [32] This in turn, has a consequence in the overall management of IE. Our review showed a decrease in the number of NBC in the late cohorts probably be due to the overall improvement in the standard of health care observed over time. Failure to do blood culture in patients with IE in developing countries is a concern when one suspect fastidious organism. With the use of newer blood culture techniques (mass spectrometry) which allow direct detection of bacterial species, the incidence of NBC infective endocarditis may drop significantly. [42]

Our review revealed that Streptococcus spp continues to be the leading cause of IE, followed by staphylococci spp and that both of the two species have increased over time. Our findings are similar to what has been reported in previous studies. [3,43] On the contrary, Noubiap et al [12] has reported in their review that *Staphylococcus* is the leading cause of IE in Africa, same as it is in HIC. [6,36] The difference observed between our review and that of Noubiap et al could be due to the difference in the studied populations, we recruited studies across many developing countries and mostly adults while they reviewed African studies with a large proportion of children. The observation that both of the two genera have increased over the compared two time period, is a concern. Infective endocarditis due to *Staphylococcus* is relatively fatal and is associated with antimicrobial resistance, recently methicillin resistance *S. aureus* (MRSA) has been reported to be a global health problem. [4] This scenario is particularly

important in developing countries where susceptibility tests are not routinely done. Of the common *Streptococcus spp* reported in our review were *S. pyogenes* and *S. viridans* similar to what has been reported in previous studies. [3,12] It is worth to mention that *S. pyogenes* is uncommon as a cause of IE in HIC. [44,45] Our postulation is that there could be problems in species determination in developing countries in which any beta-hemolytic *Streptococcus* is reported as *S. pyogenes* despite that S. *dysgalactiae* and *S. agalactiae* are much more common beta-hemolytic *Streptococcus* IE. The presence of S. viridans recall a need for antibiotic prophylaxis among patients with structural cardiac disease such as RHD when undergoing procedures that involve gingival manipulation. The other category of microorganisms reported as a cause of IE is coagulase-negative staphylococci and enterococci. The proportion of CoNS was 7.3% in group 1 and 8.6% in group 2 while the proportion of enterococci was 6.3% in group1 and 5.9% in group 2.

MEDICAL TREATMENT

In developing countries, medical treatment is the most common treatment of infective endocarditis owing to the limited availability of cardiac surgery. However, due to the unavailability of appropriate blood culture tests and susceptibility testing, empirical antibiotic therapy remains the mode of treatment. In our review, penicillin was used most frequently, with or without aminoglycoside. Of the aminoglycosides, gentamicin was the most common antibiotic used. Ceftriaxone and vancomycin were also being used regularly. Another reason for empirical antibiotic therapy in developing countries is the absence of local guidelines (informed by local data) on common microorganisms and on antibiotic resistance. [46] Lastly, financial constraint is limiting access to expensive medications that may be required for antibiotic resistant bacteria. [47] In developed countries, the use of partial oral treatment of infective endocarditis is reported to offer early discharge out of the hospital and hence would reduce hospital complications and costs. [8,48,49] However, this practice has not been reported in developing countries.

SURGERY

This review showed a wide range of proportions of patients who underwent surgery for infective endocarditis, ranging from 0% in Lao [15] to 60.2% in China. [31] The higher numbers in this range (42.3% - 60.2%) come from upper-middle-income countries. [14,24,25,27,31] Similarly, previous studies have reported a wide variation in cardiac surgical interventions for infective endocarditis in developing countries. [3,12] In contrast, in developed countries 50% – 75% of infective endocarditis patients receive surgery. [6,8,35,36,50] However, these figures may reflect a selection biased population done from tertiary centres. Indeed, studies from the Nordic countries have shown that surgery is performed in a smaller proportion of cases. [51,52] In the current review, the number of patients receiving surgery was significantly higher (38.8%) in the early cohorts compared to the late cohorts (28.8%). The reason for a smaller number of surgeries in the late

cohort is that the proportion of surgeries were higher in the cohort with Letaief et al study. [24] However, in our reviewed studies we did not include complications imposed by IE but we assume that since many patients in developing countries attend late hospital, the complications are many and hence these figures are low. Indeed, two previous reviews have reported that the rates of surgery among patients with IE in developing countries are low. [3,12] There are several reasons for the low uptake of surgery for infective endocarditis in developing countries. Firstly, in developing countries, there is limited access to cardiovascular surgery. [22,53,54] There are very few countries with independent cardiac surgery programs, [53] with one cardiac surgeon serving about 14 million persons in sub-Saharan Africa. [55] Unlike in HIC countries like the USA where there is one cardiac centre per 120,000 people, in Africa, there is one centre per 33 million people. [56] Secondly, even in countries where there is the availability of facilities capable of surgical interventions, the high costs of procedures are another obstacle considering that most of these patients do not have health insurance. [22] Thirdly, the optimal timing for surgical intervention among patients with complications that require emergency surgery is debatable. [57] Early surgery is recommended (and decreases mortality) in the setting of infective endocarditis with complications such as embolic events, congestive cardiac failure, and valvular abscess. [3,35,57–59] These complications are common among most patients with infective endocarditis in developing countries because these patients are usually diagnosed late and therefore present late in the hospital. However, the observed difference among the two cohorts should be interpreted cautiously owing to a wide range of surgeries performed in the reviewed studies with Letaief et al [24] reporting higher figures than others.

MORTALITY

The current review showed that over the last four decades the in-hospital mortality imposed by IE has not significantly changed, in the early cohorts the mortality was 20.9% while in late cohorts it was 22.3%. Similarly, other studies by [3,12] have reported a relatively similar in-hospital mortality due to IE with an in-hospital mortality rate of 22.6% (11.2% - 31.2%). Surprisingly, the observed mortality is similar to the 20% that is reported in HIC. (6,35,36) In HIC patients present early and get diagnosed early. [6,36] As could be expected, in resource-constrained countries the management of severe diseases like IE is challenging and hence mortality could be higher than that observed in HIC. [1,4,35] There are several reasons for the observed relatively lower mortality in our review. Firstly, the most common pathogen is *Streptococcus spp* rather than *Staphylococcus spp* which is fatal. Secondly, could be due to the use of cardiac surgery on patients with guideline-recommended indications such as congestive heart failure. Thirdly, in developing countries patients with IE are young and with few comorbid conditions compared with patients in HIC. [35,60] It is known that old age and comorbid conditions are important predictors of increased mortality in IE patients. [4]

STRENGTHS AND LIMITATIONS OF THE STUDY

This review has several strengths. Firstly, we covered several decades of cohorts of IE studies (1986- 2017). Secondly, we did a comparison of two cohorts to assess the trends in the changing of several parameters affecting/related to IE. Thirdly, we excluded studies that entirely recruited children to avoid skewness of our findings to one population. However, our review has several limitations. First, there was under-representation of Africa where many developing countries belongs. Second, most of the included studies were retrospective and hence subjective to all of the inherent shortcomings of retrospective studies. Third, we could not assess for determinants of mortality because the included studies were retrospective and most of the studies could not report outcome data. Fourth, many of the reviewed studies were tertiary level hospital-based and therefore the results could not be representative of the general population. Lastly, because the Letaief study comprised a very large proportion of patients in the early cohort it means that the results from this single study made a large contribution to the overall conclusions.

CONCLUSIONS

This review is a wake-up call for addressing a scarcity of studies on IE in developing countries. RHD and CHD are still the most common underlying cardiac conditions of IE. Prosthetic heart valve, degenerative valve disease, intravenous drug use, and HIV are risk factors also. While the proportion of streptococci and *S. aureus* has increased, the number of negative blood cultures and patients getting surgery has decreased over time. In the reviewed cohorts, mortality caused by infective endocarditis has not changed over the past four decades.

RECOMMENDATIONS

It is essential to identify the causative bacteria to offer the proper medical treatment in patients with IE. To improve outcomes of IE in developing countries, access to cardiac surgical intervention should be scaled-up. Well-designed research such as prospective cohort studies are needed and programs (such as RHD control) aiming at the reduction of morbidity and mortality caused by IE in developing countries are encouraged. A conceptual framework comprising of required baseline information (such as data on disease burden, human resources, and treatment protocols) and requirements for executing primary, secondary, and tertiary preventions has been advocated as a best model for RHD control. [61] With primordial prevention and research agenda being an integral part of the program.

LIST OF ABBREVIATIONS

CHD: Congenital Heart Disease

CoNS: Coagulase Negative *Staphylococcus*

DVD: Degenerative Valve Disease
HIC: High Income Countries
HIV: Human Immunodeficiency Virus
IE: Infective Endocarditis
IVDA: Intravenous Drug Abuse
NBC: Negative Blood Culture
PHV: Prosthetic Heart Valve
RHD: Rheumatic Heart Disease
USA: United States of America

Author contribution

RKM and SAJC conceptualized the idea. RM and JV performed literature search and wrote the first draft of the manuscript. MJC, PC, AK, GK, JM, AW, PK, and LF critically reviewed the manuscript. All authors contributed to the manuscript and approved the final version.

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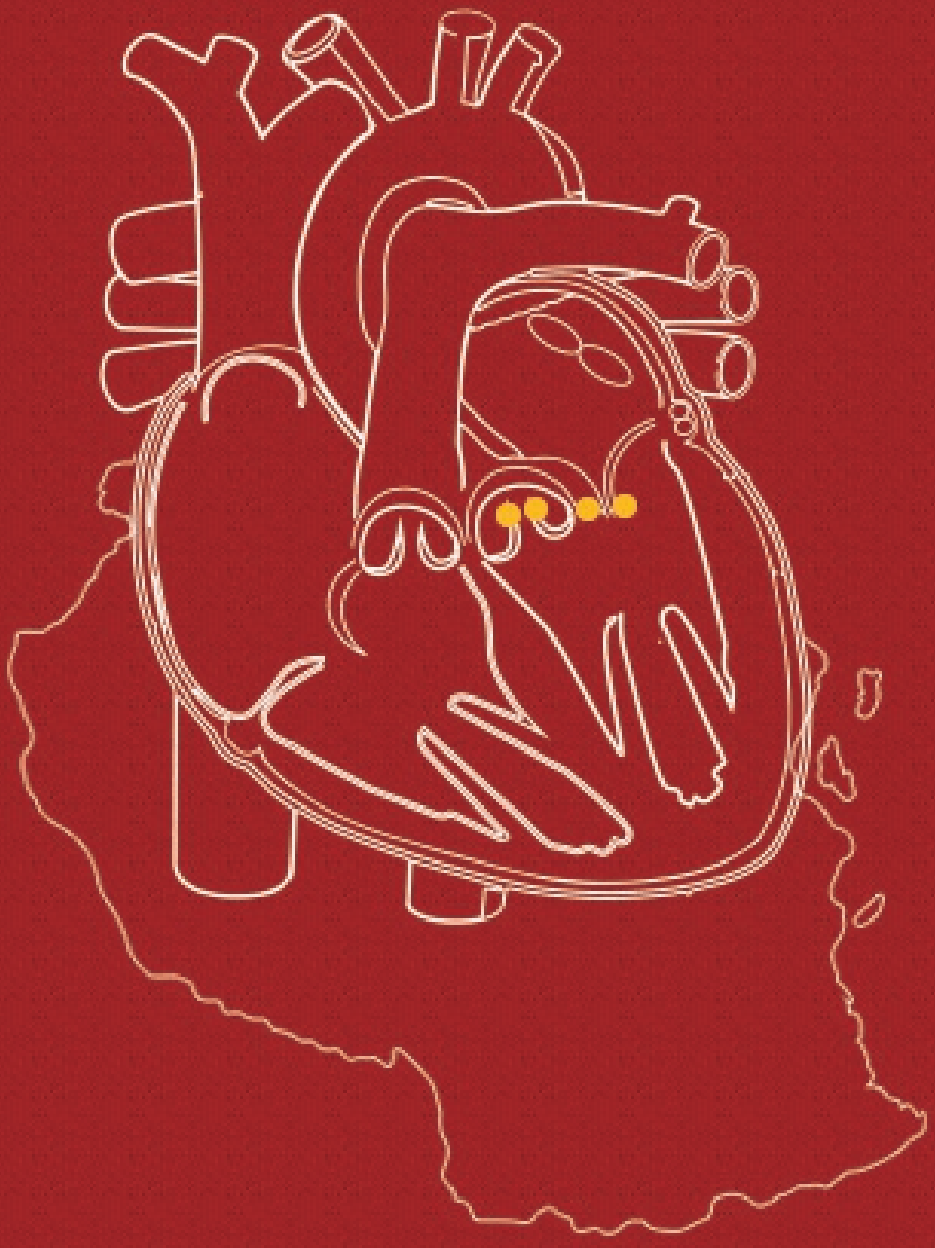

CHAPTER 4

Sub-clinical Rheumatic Heart Disease (RHD) detected by hand-held echocardiogram in children participating in a school-based RHD prevention program in Tanzania

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ABSTRACT

BACKGROUND

Rheumatic Heart Disease (RHD) continues to cause suffering and premature deaths in many sub-Saharan Africa (SSA) countries, where the disease is still endemic. RHD is largely preventable and determining its community burden is an important critical step in any RHD prevention program.

METHODS

We conducted a cross-sectional study of 5-16 years old pupils from 11 primary schools participating in an RHD prevention program in 4 districts in Tanzania, between 2018 and 2019. At the school, all children were invited to participate after receiving consent from their parents/guardians. Participating children filled a questionnaire and were auscultated for cardiac murmurs. Echocardiographic screening was done by two experienced cardiologists, using a hand-held machine (V-Scan, GE®). All positive screening tests were stored for further examination by the same two cardiologists to reach to a consensus of definite, borderline or no RHD, using a modified World Heart Federation (WHF) criterion.

RESULTS

Of the 6895 children invited, 4738 (68.7%) were screened and 4436 (64.3%) had complete data. The mean (SD) age was 10.04 (2.43) years, and 2422 (54.6%) were girls. Fifty three (1.2%) children were found to have a murmur. The proportion of children with trace or mild valvular regurgitation, sub-valvular/chordal thickening and valvular thickening/deformity were 8.3%, 1.3%, and 1.0%, respectively. Sub-clinical RHD was found in 95 children (59 definite and 36 borderline), giving a prevalence of 2.1%, [95% CI 1.7% – 2.6%]. Sub-clinical RHD was independently associated with female sex (aOR 1.83, 95% CI 1.18 – 2.85, p = 0.007), older age groups (aOR 1.73, 95% CI 1.10 – 2.72, p = 0.018 for age group 11-14 years; and aOR 3.02 95% CI 1.01 – 9.05, p = 0.048 for age group 15-16 years), as well as presence of a cardiac murmur, aOR 5.63 95% CI 2.31 – 13.69, p < 0.0001. None of the studied socio- or economic factors was associated with the presence of sub-clinical RHD in this study.

CONCLUSION

The prevalence of sub-clinical RHD among primary school children in Tanzania is 2.1%, similar to previous reports in SSA. Efforts to prevent and control RHD in our communities are highly warranted.

KEY WORDS

Rheumatic heart disease; sub-clinical rheumatic heart disease; sub-Sahara Africa; Tanzania; rheumatic fever.

INTRODUCTION

Rheumatic heart disease (RHD) is the most common acquired heart disease in children and young adults. According to the most recent Global Burden of Disease estimates, RHD affects an estimated 40.5 million people [1] and globally up to 80 million people may have .asymptomatic RHD. [2] The disease accounts for approximately 275,000 deaths annually, and although almost eradicated in developed countries, RHD continues to affect many children and young adults in sub-Saharan Africa (SSA) countries, including Tanzania. [3,4] RHD can largely be prevented when appropriate control programs are implemented focusing on community awareness, appropriate diagnosis and treatment of its precursors, namely streptococcus sore throat, acute rheumatic fever (ARF) and sub-clinical RHD. [5]

Gathering data on the community burden of RHD is an important critical step before any RHD prevention program is initiated [6] Globally, there is currently an increased interest to control or where possible eradicate RHD, resulting from an intensified advocacy in regions where RHD is still endemic. [7,8] In SSA, several recent screening surveys on community burden of RHD have been published. [9–17] and the findings show that subclinical RHD occurs in 1 – 3% of 5 – 17 years old children in the region. [9–18] Of these, only a few studies have reported the screening to be part of an ongoing RHD prevention program. [11,13]

In its natural history form, sub-clinical RHD occurs 5-15 years before the clinical manifestations of RHD ensues. [19] The long latent phase of RHD offers an opportunity for prevention before the disease becomes clinically overt. The World Health Organization (WHO) recommends screening as an effective way to detect the disease in early stage when secondary prophylaxis can be offered in those who would benefit the most. [20] Indeed, a recent clinical trial from Uganda confirmed that secondary prophylaxis given to children with sub-clinical RHD prevents disease progression. [21] Screening is also a way of raising awareness to policy makers who need to be on board in any RHD prevention program.

Traditionally, auscultation was used to screen for subclinical RHD. [22,23] This method has however been superseded by screening using a portable echocardiography, which has shown to be up to 10 times more sensitive than auscultation. [11,13] Therefore, portable echocardiography has been the mainstay of subclinical RHD screening. [24] However, increasing evidence suggests that the more compact hand-held echocardiogram may be as sensitive as the conventional portable echocardiogram, especially when used by experts. [25–28] The relatively low cost of the hand-held echocardiogram has an added advantage by permitting widespread RHD screening, especially in low resource settings where the use of the more expensive portable echocardiogram is a limiting factor. [29]

As part of the research agenda for the establishment of the East African Centre of Excellence for Cardiovascular Sciences (EACoECVS) within the Muhimbili University of Health and Allied Sciences, [30] RHD was identified as a priority disease due to its persistent high morbidity and mortality in Tanzania. [23,31,32] Beginning in 2018 the EACoECVS has been implementing a community based RHD prevention program which has several components including: obtaining community prevalence and risk factors of RHD, developing RHD health education and awareness materials for Tanzanian primary health care workers, pupils and teachers as well as delivering health education on prevention of RHD in these population groups. The project involves 11 schools in 4 districts (Bagamoyo, Kisarawe, Babati and Kiteto) in Tanzania representing semi-urban and rural populations. Here we present findings of an RHD screening survey we conducted between 2018 and 2019 that aimed at determining the community burden and associated risk factors of RHD in these communities.

MATERIALS AND METHODS

STUDY DESIGN, POPULATION AND AREA

This was a cross-sectional school-based survey conducted among public primary school children between the ages 5-16 years. The survey was conducted in Mainland Tanzania. In the 2012 census, Mainland Tanzania had a total population of 46.3 million, of which young population 0 – 17 years was 21.8 million (47.1%). The country has 25 administrative regions which are grouped into seven geographical zones. This study was conducted in two regions Pwani (Eastern zone) and Manyara (Northern zone), Figure 1.

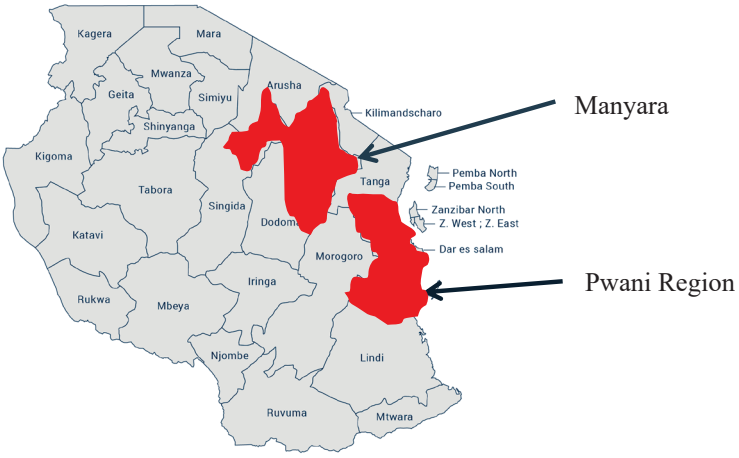


Figure 1. Map of Tanzania showing study area

SAMPLE SIZE CALCULATION

Sample size calculation was based on reported prevalence of RHD using echocardiography screening in school children in SSA of 1 – 3%. The sample size was calculated to be 4,000 school children between the ages 5 – 16 years with type 1 error of 0.05 and a power of 80% for an expected diagnosis rate of 2 cases per 100 school children screened.

SAMPLING PROCEDURE

A multi-stage sampling procedure was used. Two zones were randomly selected from the list of the seven geographical zones in Tanzania Mainland, and a further simple random selection was applied to obtain one region from each zone. At the region, all districts were listed in alphabetical order and then two districts were randomly chosen from each region.

At the district level, a list of all public primary schools was obtained from the District Administrative Office. Schools were then stratified as semi-urban or rural depending on their locations, and from each district, primary schools representing semi-urban and rural (in 1:2 ratio) were randomly selected to obtain schools included in the program. In one of the districts (Kiteto) only 1 rural school was surveyed due to logistical problems. In total, 11 public primary schools were included in the survey as summarized in Table 1.

Table 1. List and distribution of Primary Schools involved in the study

Region	District	Selected schools	
		Semi-urban	Rural
Manyara	Kiteto	Kaloleni	Osteti
	Babati	Magugu	Mbugwe, Dareda Kati
Pwani	Bagamoyo	Kiromo	Buma, Kondo
	Kisarawe	Mloganzila	Masaki, Masanganya

DATA COLLECTION

Socio-demographic and economic data

A structured questionnaire was used to acquire data on socio-demographic background and selected socio-economic indicators. Socio-demographic indices of age, sex, parents' or head of household education and occupation were asked. Furthermore, details of household characteristics including roofing, floor, and wall materials were asked. Children were also asked in the medical history if they have been on any regular monthly injections (as a proxy for secondary prophylaxis of RHD). All children were asymptomatic at screening.

Screening for subclinical rheumatic heart disease

Auscultation procedure: All study participants underwent a clinical examination by auscultation. Auscultation was done in a quiet room or outside in an enclosed screen with participants having bear-chest and rested in a 45^0 inclined examination bed. Privacy was ensured. Cardiac auscultation was done by two trained final year medical students using standard procedures. They auscultated all the 4 auscultatory areas namely the mitral area, the tricuspid area, the aortic area and the pulmonary area. The 1^{st} and 2^{nd} heart sounds were firstly determined and noted if these were normal. Any additional sound was noted as a positive auscultation finding. Murmurs were then defined as systolic or diastolic and where they were best heard.

Echocardiogram examination procedure: After auscultation, all children underwent echocardiogram examinations using a hand-held echocardiogram machine (V-Scan, General Electric, Milwaukee WI, USA). All echocardiogram examinations were performed by two experienced Cardiologists (PC and RM) following a standard procedure, in a quiet room (Figure 2) or outside under enclosed screen. Morphological and functional valvular lesions consistent with RHD were recorded. Morphological lesions recorded included valvular/subvalvular thickening, as well as valve deformities, including restricted valve motion, and excessive leaflet mobility. Functional lesions of any regurgitation (by color Doppler) and limited valvular opening (stenosis) were noted and recorded. At the end of each examination, the senior cardiologist determined whether the screening was "positive" or negative, and all "positive tests" were stored in the V-scan, for further scrutiny.

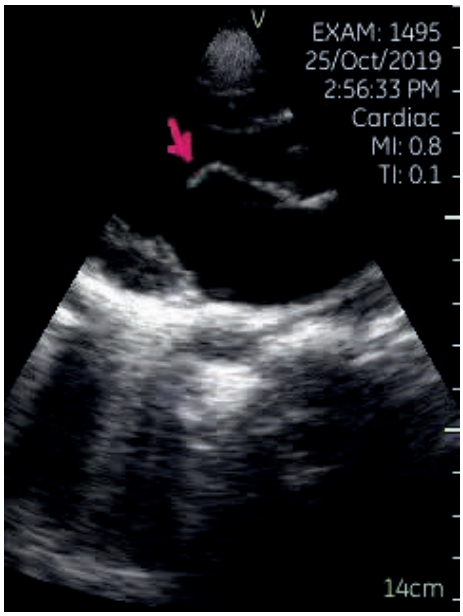
DEFINITION OF A POSITIVE SCREENING TEST

The modified World Heart Federation (WHF) criteria for defining RHD for individuals ≤20 years was used as previously described. [24,25] Definite RHD was considered present when there was either of the following echocardiogram findings: 1) pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve, 2) pathological aortic regurgitation and at least two morphological features of RHD of the aortic valve or 3) borderline disease of both the aortic valve and mitral valve. Borderline RHD was considered present when there was either of the following: 1) at least two morphological features of RHD of the mitral valve without pathological mitral regurgitation or mitral stenosis, 2) presence of pathological mitral regurgitation or 3) presence of pathological aortic regurgitation.

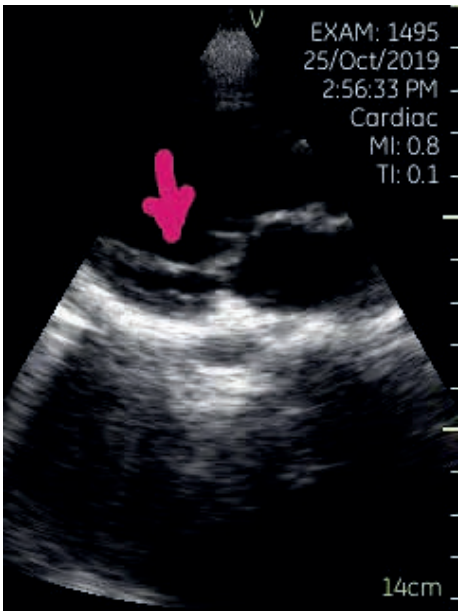
Using the same criteria, pathological mitral regurgitation was defined as mitral regurgitation seen in two echocardiographic views and in at least one view, the jet length is ≥2cm, while pathological aortic regurgitation was defined as aortic regurgitation seen in two views and in at least one view the jet length is ≥1cm. Morphologic features include mitral valve (MV): anterior leaflet thickening, chordal thickening, restricted

leaflet motion, excessive leaflet tip motion during systole; and aortic valve (AV): irregular or focal thickening, coaptation defect, restricted leaflet motion, prolapse. Examples of definite and borderline echocardiogram findings are shown in figure 3 and 4, respectively.

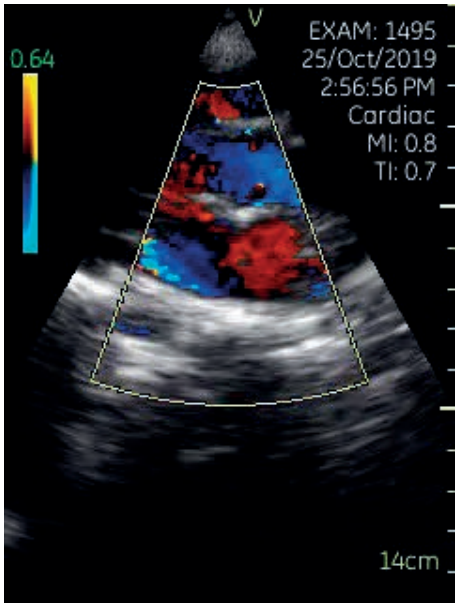
Figure 2. Screening using a hand-held V-Scan



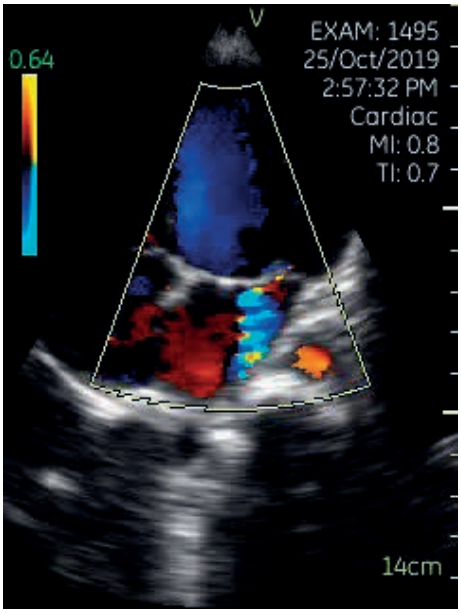
Deformity of the anterior mitral leaflet



Sub-valvular (chordal) thickening

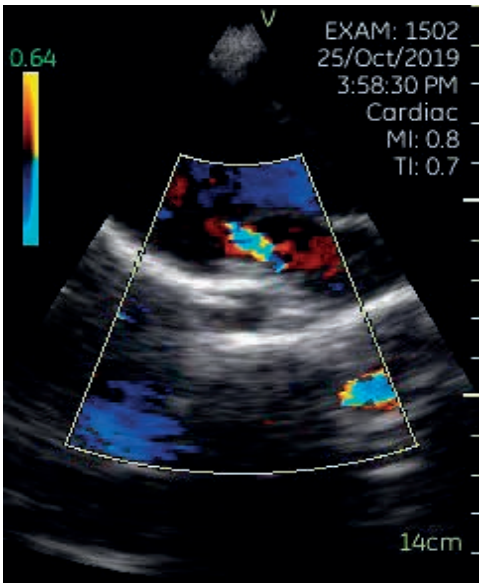


Pathological mitral regurgitation

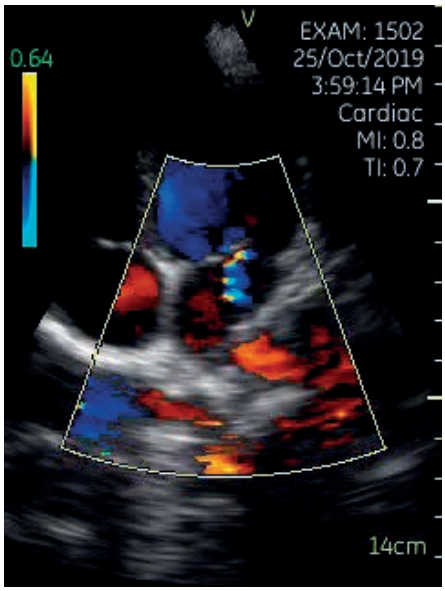


Pathological mitral regurgitation

Figure 3. Echocardiographic findings in a child with definite RHD



Pathological mitral regurgitation without mitral deformity



Pathological mitral regurgitation without mitral deformity

Figure 4. Pathological mitral regurgitation in a child with borderline RHD

Data management and analysis

Data entry and analysis was done using SPSS Version 23. All data was checked for completeness and plausibility before being entered into the data entry system. For echocardiogram findings, first all findings (morphological and functional) were recorded in data collection forms on site. Then, for the second scrutiny of the initial "positive" echocardiograms, data was included in the data collection forms within 24 hours after agreement as definite, borderline or normal findings between the two senior cardiologists.

Prevalence rates (with 95% confident interval, CI) of RHD were estimated in the total population and separately according to socio-demographic characteristics and according to regions, districts and the schools participated in the survey. Differences in prevalence between groups were compared using the Chi square test. Factors found to have association with RHD diagnosis in univariate analysis were entered into logistic regression model to determine independent factors associated with RHD in this study population. Then, factors known to be associated with RHD (from previous studies in the region) including maternal education, distance to the health facility, as well as number of people in the household [9,13,33] were forced into the model to determine their influence.

DISPOSAL OF POSITIVE SCREENING TESTS

Parents/guardians of all children who participated in the study were notified of the results of their children's screening test. Those whose children were found to have sub-clinical RHD were given further details including information about ARF prophylaxis, and were referred to the nearby health facility to continue with usual care and follow-up.

RESULTS

In total 6,895 children were invited to participate in the echocardiographic screening study, but only 4,738 (68.7%) were screened and 4,436 (64.3%) had complete data including the echocardiogram screening findings. Details of invited, screened and with echocardiogram examination per each school are shown in Table 2.

Table 2. Response rate for echocardiogram screening survey

School	Total number invited at the school	Number surveyed	Echocardiogram performed	Percent of total studied (%)
Kiromo	815	590	564	12.7
Buma	410	308	278	6.3
Kondo	340	190	178	4.0
Mloganzila	850	580	552	12.4
Masaki	526	319	274	6.2
Masanganya	330	212	188	4.2
Kaloleni	869	650	627	14.1
Mbugwe	810	545	518	11.7
Dareda Kati	750	513	458	10.3
Osteti	530	350	346	7.8
Magugu	665	481	453	10.2
TOTAL	**6,895**	**4,738**	**4,436**	**100%**

PREVALENCE OF SUB-CLINICAL RHD

Using auscultation, 53 children (out of the 4426 pupils with reported findings) were found to have a cardiac murmur, giving a prevalence of positive auscultation of 1.2% (95% CI 0.9 – 1.6). On screening echocardiogram, the findings showed 367 children had trace to mild valvular regurgitation, 56 had valvular or sub-valvular thickening and 45 showed valvular deformity, Table 3. Majority of the abnormalities were detected on the mitral valve and its sub-valvular structures, while aortic abnormalities were detected in only two children (both with aortic valve thickening), and in both children the mitral valve was also involved. No child was diagnosed with congenital heart disease during the screening echocardiogram. On second analysis of the recorded V-Scan loops, 95 children were found to have sub-clinical RHD, giving a prevalence of 2.1% (95% CI 1.7 – 2.6). Of

these 59 were definite and the remaining 36 had borderline RHD.

Table 3. Findings of hand-held echocardiogram screening

Finding	Frequency*	Prevalence (95% CI)
Valvular regurgitation**	367/4433	8.3 (7.5 – 9.1)
Valvular and/or chordal thickening	56/4434	1.3 (1.0 – 1.6)
Valvular deformity	45/4433	1.0 (0.7 – 1.4)
Sub-clinical RHD	95/4436	2.1 (1.7 – 2.6)

* The denominator is not uniform as there were some few missing reports of the variables

** Any regurgitation, i.e. trace and mild regurgitation included

The prevalence of sub-clinical RHD by region and school is shown in Table 4. The highest prevalence was seen in Osteti primary school in Kiteto district and the lowest was in Dareda Kati primary school in Babati district, both are rural schools in Manyara region. The differences in prevalence between schools were not statistically significant, p = 0.951.

Table 4. Prevalence of sub-clinical RHD by schools

District	School	School category	Prevalence (95% CI)
Bagamoyo	Kiromo	Semi-urban	2.3 (1.23 – 3.91)
	Buma	Rural	1.8 (0.59 – 4.15)
	Kondo	Rural	2.2 (0.62 – 5.65)
Kisarawe	Mloganzila	Semi-urban	2.0 (1.00 – 3.54)
	Masaki	Rural	2.2 (0.81 – 4.70)
	Masanganya	Rural	2.1 (0.58 – 5.36)
Babati	Kaloleni	Semi-urban	2.4 (1.35 – 3.93)
	Mbugwe	Rural	2.3 (1.20 – 4.01)
	Dareda Kati	Rural	1.1 (0.36 – 2.53)
Kiteto	Magugu	Semi-urban	2.2 (1.06 – 4.02)
	Osteti	Rural	2.9 (1.39 – 5.25)

FACTORS ASSOCIATED WITH SUB-CLINICAL RHD

Of the socio-demographic and economic indices studied, only sex and age showed significant differences in the prevalence of sub-clinical RHD. Females were more likely to have sub-clinical RHD (2.7%) when compared to males (1.5%), and older children aged 15-16 years were more likely to have sub-clinical RHD (4.8%) than younger children aged 10-14 years (2.6%) and those aged 5-9 years (1.6%). Furthermore, children with a cardiac murmur were more likely to have sub-clinical RHD (11.3%) when compared to those without a murmur (2.0%), (Table 5). We did not find any child on long-term prophylaxis against ARF.

Table 5. Socio-demographic, economic and clinical characteristics of children in relation to sub-clinical RHD findings

Variable	Number in group	Number (%) with RHD in the group	p-value
Sex			
Males	2014	30 (1.5)	0.006
Females	2422	65 (2.7)	
Age groups, (years)			
5 – 9	1855	29 (1.6)	0.023
10 – 14	2429	62 (2.6)	
15 – 16	84	4 (4.8)	
Missing	68		
School setting			
Semi-urban	2196	49 (2.2)	0.683
Rural	2240	46 (2.1)	
Living with parents			
Yes	3733	79 (2.1)	0.732
No	689	16 (2.3)	
Missing	14		
Head of house occupation			
Farmer/peasant	2050	49 (2.4)	0.625
Government employed	359	5 (1.4)	
Self employed	1035	23 (2.2)	
Petty business	738	12 (1.6)	
Other occupations	206	5 (2.4)	
Missing	48		
Mother education			
No formal education	391	6 (1.5)	0.254
Primary education	2546	60 (2.4)	
Secondary education	878	12 (1.4)	
Above secondary	281	9 (3.2)	
Not applicable/deceased	255	6 (2.4)	
Missing	85		
Father education			
No formal education	258	3 (1.2)	0.414
Primary education	2390	57 (2.4)	
Secondary education	1001	17 (1.7)	
Above secondary	370	10 (2.7)	
Not applicable	325	5 (1.5)	
Missing	99		
Head of household education			
No formal education	326	5 (1.5)	0.580
Primary education	2468	60 (2.4)	
Secondary education	938	16 (1.7)	
Above secondary	390	8 (2.1)	
Not applicable	203	3 (1.5)	
Missing	111		

Table 5. Continued.

Variable	Number in group	Number (%) with RHD in the group	p-value
Roofing materials			
Iron sheets	4111	87 (2.1)	0.862
Tiles	11	0 (0.0)	
Grass	252	7 (2.8)	
Mud	51	1 (2.0)	
Missing	11		
Wall materials			
Bricks	3230	70 (2.2)	0.993
Mud	1011	21 (2.1)	
Wood	101	2 (2.0)	
Iron sheets	73	2 (2.7)	
Others	4	0 (0.0)	
Missing	17		
Floor materials			
Cement	2876	67 (2.3)	0.675
Mud	1359	25 (1.8)	
Tiles	159	3 (1.9)	
Others	19	0 (0.0)	
Missing	23		
Number in the household			
2-5	2088	40 (1.9)	0.375
6-10	2031	52 (2.6)	
>10	138	3 (2.2)	
Missing	179		
Number in same room			
1-4	4240	91 (2.1)	0.784
≥5	116	3 (2.6)	
Missing	80		
Distance to health facility			
Within 1 km	3006	71 (2.4)	0.527
1-5km	1223	22 (1.8)	
>5km	45	1 (2.2)	
Missing	162		
Cardiac murmur			
Yes	53	6 (11.3)	<0.0001
No	4473	88 (2.0)	
Missing	10		

In a multivariate logistic regression analysis including sex, age groups and presence of a murmur in auscultation, all variables were found to be independently associated with the diagnosis of sub-clinical RHD, Table 6. Adding variables that were previously reported to be associated with RHD (maternal education, distance to the health facility or number of people in the household) did not alter the findings.

Table 6. Independent factors associated with sub-clinical RHD

Variable	Un-adjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex				
Males	Constant			
Females	1.82 (1.18 – 2.82)	0.007	1.83 (1.18 – 2.85)	0.007
Age groups, (years)				
5 – 10	Constant			
11 – 14	1.65 (1.06 – 2.57)	0.028	1.73 (1.10 – 2.72)	0.018
15 – 16	3.15 (1.08 – 9.18)	0.036	3.02 (1.01 – 9.05)	0.048
Murmur on auscultation				
No	Constant			
Yes	6.22 (2.59 – 14.91)	< 0.0001	5.63 (2.31 – 13.69)	<0.0001

SENSITIVITY OF CARDIAC AUSCULTATION TO DETECT SUB-CLINICAL RHD

Of the 95 children with echocardiographically diagnosed sub-clinical RHD, only 6 were also found to have a cardiac murmur, giving a sensitivity of clinical auscultation to detect sub-clinical RHD of only 6.3%. Of note, echocardiogram in this study was about 15 times more sensitive in detecting sub-clinical RHD when compared to cardiac auscultation.

DISCUSSION

Both the World Health Organization (WHO) and the World Heart Federation (WHF) are supporting screening for sub-clinical RHD as a critical initial step when planning for a comprehensive RHD control program in order to obtain data on the community burden of the disease. [6–8] We found the prevalence of RHD in this large representative sample of school children in Tanzania to be 2.1%. This prevalence lies within the reported RHD prevalence in SSA of 1 – 3%; [9–18] underlining similarities of the populations across our region.

Although the schools we studied were either semi-urban or rural located, we did not find significant different prevalence of RHD between these schools, indicating similar occurrence of the disease burden in this age group, independent of location. In fact, in a similar screening survey involving school children in Dar es Salaam (the most urbanized city in Tanzania), the prevalence of sub-clinical RHD was higher (3.4%) than the current study. [14] Moreover, our results showed no difference in prevalence between Manyara and Pwani Regions. This observation is in contrast to our anecdotal hospital data at the National Cardiac Referral Hospital (the Jakaya Kikwete Cardiac Institute) which suggests that majority of the RHD cases come from the Northern Zone (including Manyara region). Of note though, the prevalence of sub-clinical RHD was highest (2.9%) in the most remote school screened (Osteti) – a predominantly pastoralist Maasai community

in Manyara region. Recently, Beaton and colleagues found that without prophylaxis, 12% of children with latent RHD in neighboring Uganda progressed to having more RHD changes within 2 years, but also 34% of these children had their RHD changes regressed to normal within the same period of follow-up. [21] It is therefore worth noting that several other factors (apart from prophylaxis) play role in determining regression as well as progression of RHD. Further research including genetic studies are therefore needed to determine these other factors which may add to our understanding of the mechanisms of progression or regression of sub-clinical RHD, and therefore add more insight to appropriate prevention strategies.

We found RHD to be more likely diagnosed in the older age groups as previously reported. [9,11,13,14] This is an expected occurrence as in these older children several episodes of ARF may have occurred, therefore the fibrosis, valve deformity and valve dysfunction accompanying RHD is more likely to be detected at this age. [19] Here we draw an important observation that if performed among older children and adolescents, echocardiographic screening will likely yield more positive findings, and therefore making this approach more cost effective. However, reaching out to older children and adolescents may need special efforts in a country like Tanzania, because only around 50% of adolescents proceed to secondary school education, [34] therefore any school-based screening may miss half of the target population.

In this study, female children were 83% more likely to have a positive screening test for RHD when compared to male children. This finding is similar to many previous studies. [9–11,13,14,35] The reasons of higher RHD among females are not well understood, [35–37] although it is generally known that most of autoimmune diseases affect females more than males. [38] A recent study has however shed light on the possible reasons for female predominance in RHD, implicating Prothymosin alpha as a potential regulator of sex predisposition in RHD. [39] It has also been postulated that probably the difference seen is related to socio-cultural issues whereby males are given priority when they fall sick than females, considering the devastating household economic consequence of RHD which necessitates coping mechanisms in those at the lowest end of the socio-economic ladder. [40] The higher prevalence of RHD among girls indicate that screening for adolescent girls or young women is another strategy that may yield better cost effective measures, taking advantage that women can be screened during pregnancy. This can answer an important question on the burden of sub-clinical RHD among women but also may serve to detect potentially significant RHD lesions, which if left unchecked can result into poor outcomes to the mother and the baby in utero. [41]

In our study, the presence of a cardiac murmur was 5 times more likely to be associated with sub-clinical RHD, independent of age or sex of the child. Although this was an

impressive association, the actual sensitivity of clinical auscultation to detect sub-clinical RHD in this study was very low at only 6.3%, supporting previous findings that clinical auscultation is up to 10 times less sensitive as compared to echocardiography screening. [13,25,42] The cardiac auscultation sensitivity was lower in our study compared to that reported by Gordon et al in Uganda (16.4%) [25] and by Marjon et al in Mozambique (10%), [13] most likely due to use of non-professionals (medical students) to perform auscultation in our study.

Most of the previously studied factors associated with RHD were negative in this study. Previous studies found maternal education, low socio-economic status, distance from the hospital and rural residency to be associated with RHD. [9,13,33,36] We studied all these factors and none showed significant association with RHD. It is possible that the population of the current study was more homogenous and that these factors were somehow equally distributed in the studied population.

Strengths and limitations

This study is the largest on RHD prevalence in Tanzania and is among the few studies that estimated the prevalence of RHD in East Africa. [11,12,14] Being part of an on-going program, [43] this study is unique due to the fact that it will generate longitudinal data. Moreover, due to its programmatic nature involving different stakeholders, we believe this screening exercise has already raised awareness of RHD among Tanzanian government officials, healthcare workers as well as pupils, their parents and teachers in the schools that were involved. The on-going training component which involves health education on sore throat, ARF and RHD [43] is expected to be beneficial beyond the echocardiographic screening data alone.

We used a hand-held echocardiogram machine to detect sub-clinical RHD. The hand-held echocardiogram machine lacks the capability to perform continuous Doppler studies and therefore necessitated our use of the modified WHF to diagnose sub-clinical RHD. This may have slightly under- or over-estimated the prevalence of sub-clinical RHD. However, as previously reported by other investigators, the hand-held echocardiogram is almost as sensitive as the conventional portable echocardiogram, especially when used by experts. [25–28] Our finding of more definite RHD cases than borderline RHD cases is likely due to the fact that in this study screening and diagnoses were done by specialist Cardiologists only. Cardiologists are more likely to recognize and therefore exclude most of the false positive echocardiogram findings which could have otherwise been diagnosed as borderline disease, especially those with trace to mild mitral regurgitation (which was found in 8.3% children in this study). We therefore believe that the prevalence obtained is closely the true prevalence of sub-clinical RHD in this population.

Conclusion

The prevalence of sub-clinical RHD among primary school children in Tanzania is 2.1%, similar to previous reports in SSA. Female sex, older age and the presence of a cardiac murmur were independently associated with the diagnosis of sub-clinical RHD in this population. Efforts to prevent and control RHD in our communities are highly warranted.

Abbreviations

ARF	Acute Rheumatic Fever
EACoECVS	East African Centre of Excellence for Cardiovascular Sciences
RHD	Rheumatic Heart Disease
SSA	Sub Saharan Africa
WHF	World Heart Federation
WHO	World Health Organization

Acknowledgements

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Authors' contributions

PC, RM, FK, GK, and AK conceptualized and planned the study. PC and RM participated in data collection and led in the manuscript writing. DN, MN, and VK contributed to the development of specific sections of the protocol and the manuscript and substantially revised the manuscript. All authors read and approved the final version of the manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due on-going follow-up study but are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

The study was done in accordance with the Helsinki Declaration on studies involving

human subjects. Ethical approval to conduct the study was obtained from the Muhimbili University of Health and Allied Sciences Institutional Review Board. Permission to conduct the study was also obtained from the Tanzanian Ministry of Education. All parents/guardians of the children were informed by a letter distributed through their children; outlining the study details and indicating a contact address and telephone number should there be any questions or queries from the parents/guardians. Informed written consent was obtained from parents/guardians of all children who participated in this study. All children gave a verbal assent to participate in the study. Children were free to participate or not, and assurance was given for those not participating to have no punishment.

Consent for publication

Informed consents were obtained from the doctor as well as from the child's parent to publish the image (in figure 2) in an online open-access publication.

Competing interests

The authors declare that they have no competing interests

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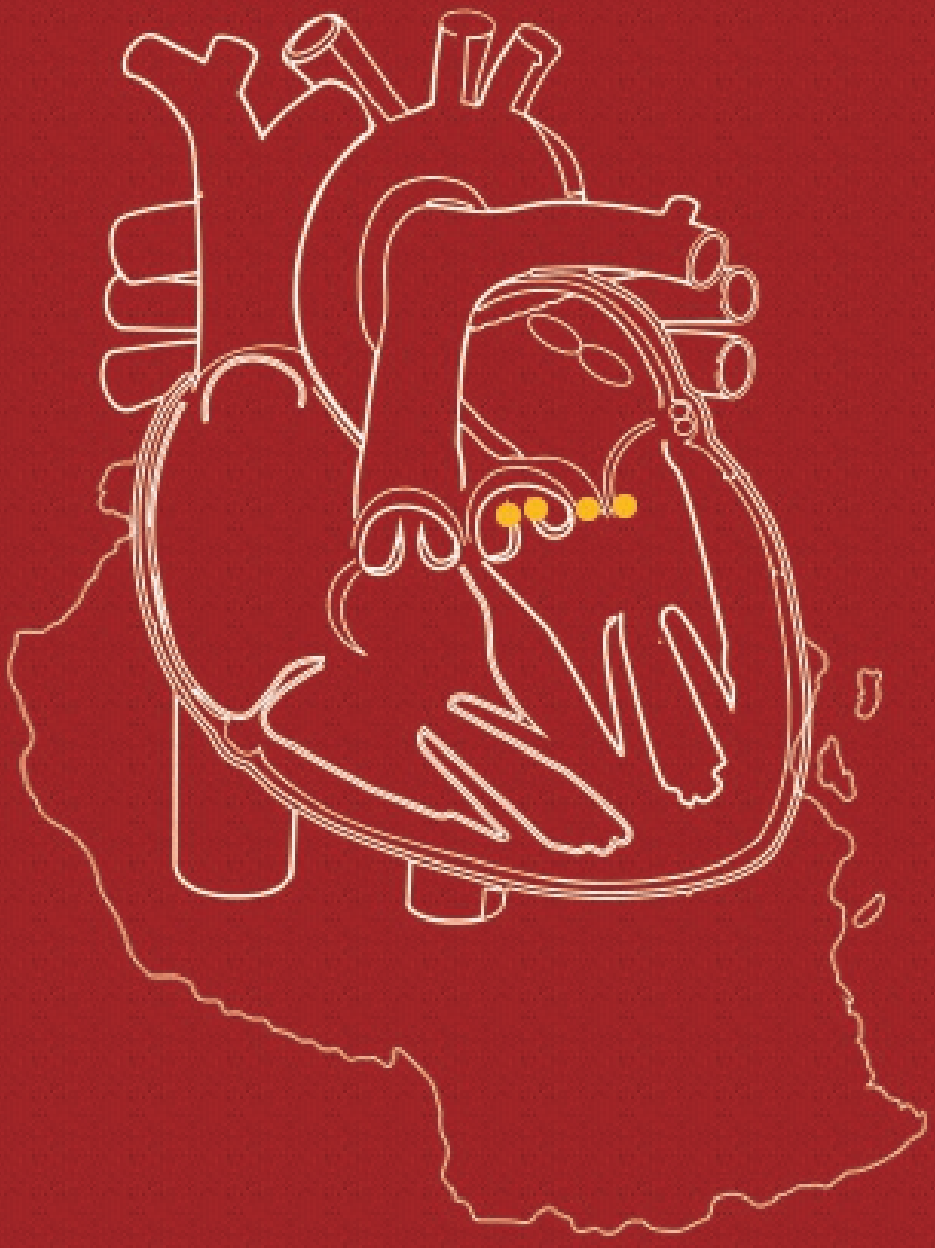
PART II

Clinical aspects in patients with rheumatic mitral stenosis



CHAPTER 5

Clinical profile, treatment and follow-up of patients with rheumatic mitral stenosis in Tanzania

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ABSTRACT

BACKGROUND

Worldwide, rheumatic heart disease (RHD) remains the most common cardiovascular disease in children and young adults. There is dearth of data on contemporary characteristics of disease presentation and the use of evidence-based interventions from disease-endemic countries.

OBJECTIVES

To provide contemporary data on the clinical profile, treatment and follow-up of patients with rheumatic MS attended at Jakaya Kikwete Cardiac Institute (JKCI) in Tanzania.

METHODS

A prospective study of consecutively enrolled inpatients and from outpatient clinics. Their medical history and physical findings were obtained. Imaging, laboratory and treatment data were recorded. Patients were followed up for outcomes for a minimum of six months and a maximum of 2 years. Kaplan – Meier curves were used for survival analysis. Risk factors associated with outcomes were determined by using Cox proportional hazards model. P-value < 0.05 was considered statistically significant.

RESULTS

This study enrolled 290 patients. The patients were young (median age 36 years), predominantly females (68.3%), and had monthly income < 42$ (55.5%). Pure MS was found in 27 (9.3%) patients, atrial fibrillation (31.4%), stroke/transient ischemic attack (18.9%), and New York Heart Association class III–IV (44.1%). The median duration of disease was 3 years and there was low use of secondary antibiotic prophylaxis (27.7%). Interventions were done in half of the patients (46.2% surgical and 3.8% PBMV). Mortality was higher in the medical than surgical treatment group (10.4% vs 4%, log-rank p = 0.004). In multivariable analysis, the risk of death among patients on medical treatment was 3.12 times higher than those on surgical treatment (crude HR 3.12, 95% CI 1.50 – 6.49, p = 0.002) and 2.44 times higher among patients with arrhythmias vs without arrhythmias (crude HR 2.44, 95% CI 1.19 – 4.49, p = 0.015).

CONCLUSIONS

In Tanzania, rheumatic MS affects young people, predominantly females, and with low income. Patients present late in the hospital and there is a low uptake of secondary prophylaxis. The mortality is comparable with previous studies; surgery is carrying low mortality and arrhythmias are associated with high mortality. We recommend optimization of surgical services, controlling arrhythmias, and increasing the uptake of secondary prophylaxis.

KEYWORDS
Rheumatic mitral stenosis; Treatment; Predictors; Mortality, Outcomes; Tanzania

1. INTRODUCTION

1.1. GLOBAL EPIDEMIOLOGY

Rheumatic heart disease (RHD) is amongst the common non-communicable diseases (NCDs) in developing countries. It is estimated to be responsible for up to 1.4 million deaths per year and over 10 million disability-adjusted life-years globally. [1–3] Despite the high burden of the disease, there are not enough studies with contemporary data on patient characteristics, treatment patterns, complications and outcomes. [4] The World Heart Federation (WHF) has since 2013 prioritized RHD as an important public health problem. [5] Several low-and middle-income countries have implemented the strategies that were proposed by WHF to reduce and eradicate RHD. [6] However, the proposed strategies need an understanding of the contemporary characteristics of disease presentation and the use of evidence-based interventions in patients residing in endemic areas of RHD. [5]

1.2. SITUATION IN TANZANIA

Despite of high prevalence of RHD in Tanzania, [7] for unknown reasons the country was not involved in the two large multicentre RHD registries that have been developed in the last two decades which covered most of the African countries. The VALVAFRIC registry [8] covered eight Western and Central African countries while the REMEDY registry [1] covered twelve African countries. Registry-based control strategies have been reported to be the best framework for delivering secondary prophylaxis and for the establishment of a countrywide RHD control program. In Tanzania, RHD was not part of national health (research) agendas or strategies despite its intersection with priorities like child and adolescent health, maternal health, and NCDs. However, the Ministry of Health has recently initiated special programmes to deal with NCDs including RHD mainly aiming at research, training, and treatment. [9]

Mitral stenosis (MS), one of the common forms of RHD, has a peculiar presentation compared with other sub-types of the disease i.e. mitral and aortic regurgitation. In developing countries, MS progress rapidly and is diagnosed lately leading to severe disability at an early age; [10] it is the only valvular lesion which is predominantly (99%) rheumatic in origin; it shows a female gender preponderance with possible late diagnosis during pregnancy; and it is the only rheumatic valvular pathology with proven percutaneous intervention. In developing countries, patients with MS present with

complications such as heart failure, atrial fibrillation (AF), thromboembolic events, and infective endocarditis. [11] Ideally, timely surgery or percutaneous mitral valvuloplasty (PBMV) is needed for symptomatic severe MS, but these services are rarely available in most developing countries. Therefore, medical treatment is what is commonly initially offered mainly targeting the consequences of the disease such as heart failure and AF. The medicines include diuretics, beta-blockers, digoxin (if in AF), ivabradine (if in sinus rhythm), warfarin for patients with significant rheumatic MS with AF, and non-vitamin K antagonist oral anticoagulants for patients without significant MS with AF. [12] Secondary prophylaxis of ARF and RHD is recommended with a monthly intramuscular benzathine penicillin G (BPG) injection for low-risk patients and twice-a-day oral penicillin V for high-risk patients. [12,13] PBMV is a treatment of choice for suitable candidates offering symptomatic relief lasting up to twenty years, [14] and a success rate of about 95% in pregnant patients. [15] Surgery, individualized based on the patient's health status, surgical capabilities, the extent of valve damage, patient preferences, geographic background, and socio-cultural and economic background should be performed for patients who are not suitable for PBMV. [12]

Prospective RHD studies have shown that univariate predictors of mortality were heart failure, New York Heart Association (NYHA) functional class, and prescription for penicillin; however, penicillin prophylaxis did not persist in multivariable models. [1,11] These studies also showed that males had a higher risk of mortality than females. The current study was conducted to provide contemporary data on the clinical profile, treatment and follow-up of patients with rheumatic MS attended at Jakaya Kikwete Cardiac Institute (JKCI) in Tanzania. Results from this study are expected to inform policymakers/clinicians and the community at large on the presentation of patients with RHD in Tanzania. With that information, appropriate interventions such as preventive measures, management approaches and the development of a country-wide RHD registry could be executed. The lessons learnt might be of interest to the global health community because RHD is now identified as a global health problem.

2. MATERIAL AND METHODS

2.1. STUDY DESIGN AND SETTING

This was a prospective, single-centre, hospital-based cross-sectional study of Tanzanian patients with rheumatic MS that were attended at the JKCI from August 2019 to May 2022. Symptomatic patients were enrolled consecutively from outpatient clinics and inpatients until the sample size was attained. We excluded patients with pure MR, no MS, prosthetic valves, and those with other forms of non-rheumatic valvular heart disease or other cardiac diseases.

2.2. SAMPLE SIZE ESTIMATION

Two methods for sample size calculation were used: (a) prevalence formula for answering two objectives: i) to describe the clinical characteristics of patients with rheumatic MS and ii) to determine the proportion of patients on PBMV, surgery and medical treatment at JKCI. A study done by Makubi et al [16] found the prevalence of rheumatic MS to be 15%. So, the sample size was calculated from the formula: $\mathbf{n=z^2p\ (1-p)/\varepsilon^2}$

Where:

n = minimum sample size required,
P = Prevalence of MS among RHD patients (estimated at 15%according to a study quoted above)
ε = margin of error; set at 5% (0.05) and
Z = z-score (1.96 at 95% confidence level)

The estimated sample size was 196. Adjusting (10%) for non-response estimated sample size was ≈216 patients.

and (b) the proportional formula for the objective: to assess the effects of baseline clinical characteristics, cardiac morphology and treatment modality (PBMV, surgery, or medical treatment) on patients' outcomes. A study conducted by Cohen and co-workers [17] found that the proportion of patients who underwent operative procedures compared to those who underwent PBMV was 60/64 (93.7%). The sample size was calculated from the formula: $\mathbf{n=z^2p\ (1-p)/\varepsilon^2}$. The estimated sample size was 90. Adjusting (20%) for loss to follow-up and non-response, the estimated sample size is ≈110 patients.

2.3. DATA COLLECTION

The patient's history was obtained. This included age (6 years and above), residence, sex, education level, occupation and monthly income, date of diagnosis, presenting symptoms, associated comorbidities, medications, and interventional history. Physical examination including anthropometric measurements and systemic examination was performed. All patients were clinically evaluated for evidence of rheumatic MS according to recognized clinical and echocardiographic criteria. [18,19] The severity of mitral stenosis was graded as mild (valve area > 1.5cm^2), moderate (valve area 1.0 – 15cm^2) and severe (valve area < 1.0cm^2). Several echocardiographic (SC 2000 Siemens Echo machine, Germany), electrocardiographic (General electronic Mac 400, United States of America), and roentgenogram data were collected. The echocardiogram examination followed the American Society of Echocardiography (ASE) guidelines. [20,21] Two-dimensional and M-mode images were used to obtain chamber dimensions and ejection fraction quantification. A venous blood sample was collected for haematological, serological, and biochemistry analyses.

2.4. TREATMENT STRATEGY

The treatment of patients recruited in this study was following the usual standard of care as per the institute protocol. Patients could either belong to the PBMV, surgery or medical treatment. The definite treatment strategy for patients with severe MS, either PBMV or surgery, was determined during the pre-surgery conference attended by the heart team and was based on echocardiographic data, patient age, and comorbidities. Details about PBMV and surgical treatment strategies can be found in our previous publications. [22,23]

2.5. FOLLOW UP

Patients were followed-up at different time intervals for a minimum of six months to determine the primary and secondary outcome measures namely mortality and different complications respectively. The data were obtained either during patient visits to the outpatient clinic or during hospitalization or by telephone interviews. We defined loss to follow-up as a failure to show up /not being able to be contacted 6 months after enrollment and only seen on the initial visit.

2.6. STATISTICAL ANALYSIS

The data obtained from collection tools were entered into the computer and analyzed using Statistical Package for Social Sciences (IBM SPSS Statistics) version 28.0 and STATA (StataCorp) version 13. Categorical variables are summarized as numbers and percentages and were compared by Chi-square or Fisher's exact test. Mean (standard deviation) and median (interquartile range) were employed for continuous variables and were compared by Student's t-test. Kaplan – Meier analysis was used to ascertain the incidence of survival probability at the end of follow-up. Differences between curves were described using log-rank tests. Risk factors (hazard ratios with 95% confidence intervals) associated with different outcomes were determined by using the stepwise method of the Cox proportional hazards model. Covariates with $p < 0.2$ in the univariate analysis were added to a multivariable model. Model goodness of fit was assessed using likelihood ratio tests (LRTs). For laboratory variables (not done to all patients) we calculated the incidence rates of mortality as the number of events per 1000 patient-years of follow. P-value < 0.05 was considered statistically significant.

2.7. ETHICAL CONSIDERATION

Written informed consent was obtained from all participants ≥ 18 years. Assent was obtained from minors > 13yrs of age in the presence of the adult witness. For < 13yrs, oral consent was provided by the guardian of the minor. The study was approved by the Directorate of Research and Publications of the Muhimbili University of Health and Allied Sciences (P. MUHAS – REC-9-2019-059). Permission to conduct this study was obtained from JKCI (AB.157/334/01'A).

3. RESULTS

Two hundred and ninety (290) patients were consecutively enrolled in the Tanzania Mitral Stenosis (TAMS) study. Their baseline sociodemographic and clinical characteristics are shown in Table 1. There were more females than males and the median (IQR) age of enrollment was 36 (27) years. More than half of the patients attained primary education (55.9%), employed (54.1%), and had a monthly income of < 42$ (55.5%). Patients owning national health insurance were 131 (45.2%). The median (IQR) duration of the disease was 36 (48) months. A history of ARF was reported by one-fifth of the patients. The most common symptoms were dyspnea (97.2%), palpitations (90.3%), and orthopnea (80.7%). Cardiomegaly was found in 215 (74.1%) patients. At the time of presentation, 128 (44.1%) patients were in heart failure NYHA functional class III – 1V, 55 (18.9%) had a previous stroke/transient ischemic attack, 26 (8.9%) had infective endocarditis, 56 (19.3%) were hypertensive, and 5 (2.5%) were pregnant. A majority, 185 (63.8%) seek medical attention at a modern health facility when they initially experienced symptoms. The commonly prescribed medicines were loop diuretics (85.2%), spironolactone (73.1%), and beta blockers (65.9%). Benzathine penicillin prophylaxis was prescribed in 46 (27.7%) of eligible patients. Half of the patients were on medical treatment.

Table 1. Socio-demographic and clinical characteristics of the patients with rheumatic mitral stenosis, N= 290

Variable	Category	Frequency (%)
Age group (years)	< 20	50 (17.2)
	20- 40	121 (41.7)
	≥ 40	119 (41.0)
Sex	Male	92 (31.7)
	Female	198 (68.3)
Level of education	Primary	181 (62.4)
	Secondary/college	109 (37.6)
Occupation	Employed	157 (54.1)
	Not employed	133 (45.9)
Mode of payment	National insurance	131 (45.2)
	Public/others	159 (54.8)
Monthly income (TShs)	< 100,000	161 (55.5)
	100,001 +	129 (44.5)
Duration of symptoms (months)	< 60	192 (66.2)
	60 +	98 (33.8)
Proportion with past history of acute rheumatic fever		62 (21.4)
Symptoms and signs at enrolment	Dyspnoea	282 (97.2)
	Fatigue	202 (69.7)
	Ascitis	31 (10.7)
	Cardiomegaly	215 (74.1)

Table 1. Continued.

Variable	Category	Frequency (%)
Cormobidities	Stroke/Transient ischemic attack	55 (18.9)
	Infective endocarditis	26 (8.9)
	Hypertension	56 (19.3)
	Pregnant	5 (2.5)
NYHA functional class	I & II	162 (55.9)
	III & IV	128 (44.1)
Attended at a modern health facility when experienced symptoms		185 (63.8)
Attended traditional medicine when experienced symptoms		79 (27.2)
Medications	Loop diuretics	247 (85.2)
	Beta blockers	191 (65.9)
	ACEIs	120 (41.4)
	Benzathine penicillin for prophylaxis	46 (27.7)
Treatment arm	Medical	145 (50)
	Surgical	134 (46.2)
	PBMV	11 (3.8)

Key: NYHA = New York Heart Association; ACEIs = Angiotensin Converting Enzyme Inhibitors; PBMV = Percutaneous Balloon Mitral Valvuloplasty

As per valvular lesions, 27 (9.3%) patients had pure mitral stenosis (MS). Thirty-six (12.4%) patients had mixed mitral valve disease. The remaining patients had MS in combination with other valvular pathologies as expressed in Figure 1.

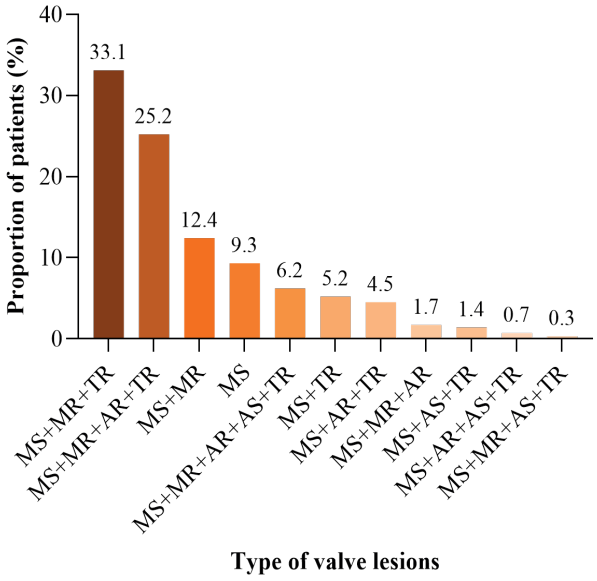

Figure 1. Categories of primary pathology of the valves.

As depicted in Table 2, the left ventricular diastolic diameter was normal in the majority, 252 (86.9%) of the patients while the left atrium diameter was dilated in 280 (96.6%) patients. A majority, 234 (80.7%) had normal left ventricular ejection fraction. The majority (72.4%) of the patients had a severe form of mitral stenosis. The right ventricular systolic pressure was elevated in 255 (87.9%) patients and the right ventricular function was depressed in 117 (40.3%) patients. Arrhythmias were detected on ECG in 148 (51%) patients. AF was found in 91 (31.4%) patients, representing 61.5% of all arrhythmias. On chest x-ray, cardiomegaly was reported in 234 (90%) patients and lung congestion in 27 (10.5%) patients. ASOT was elevated in 23 (27.4%) patients, 4 (1.9%) patients had HIV infection, and 8 (5.4%) patients were VDRL positive. Haemoglobin level was low in 44.6% of patients.

Table 2. Echocardiographic, Electrocardiographic, Roentgenogram, and Laboratory data of patients with rheumatic MS attended at Jakaya Kikwete Cardiac Institute

Variable	Category	Number (%)
Echocardiography	Proportion of dilated LV diastolic diameter	38 (13.1)
	Proportion of dilated left atrium diameter	280 (96.6)
	Proportion of reduced LV ejection fraction	56 (19.3)
	Proportion of severe mitral stenosis	211 (72.7)
	Proportion of severe trans-mitral gradient	235 (81)
	Proportion of elevated RV systolic pressure	255 (87.9)
	Proportion of depressed TAPSE	117 (40.3)
Electrocardiography	Proportion with arrhythmias	148 (51.0)
	Proportion with atrial fibrillation	91 (31.4)
Chest X-ray	Cardiomegaly	234 (90)
	Infiltrates /consolidation	32 (12.5)
	Lung congestion	27 (10.5)
Laboratory	Proportion of elevated ASOT	23 (27.4)
	Proportion of HIV positive	4 (1.9)
	Proportion of Hepatitis B positive	1 (0.6)
	Proportion of VDRL positive	8 (5.4)
	Proportion of elevated WBC	54 (23.4)
	Proportion of low haemoglobin	108 (44.6)
	Proportion of elevated Creatinine	14 (6.3)
	Proportion of elevated ALT	43 (25.3)

Key: RV = Right Ventricle, LV = Left Ventricle, TAPSE = Tricuspid Annular Plane Systolic Excursion, ASOT = Anti-streptolysin O titre, HIV = Human Immunodefiency Virus, VDRL = Veneral Disease Reseacrh Laboratory, White Bllod Cells = White Blood Cells, ALT = Alanine Transaminase

Nineteen (6.6%) patients were lost to follow-up. Thus, outcomes data is determined by the remaining 271 patients. These were seen at least for more than one visit with a minimum of 6 monhts and a maximum of 24 months i.e varying duration of follow-up. The median (interquartile range) duration of follow-up was 23.5 (26) months.

Morbidity

Complications which occurred at any time of follow-up were stroke which happened in 2 (0.7%) patients, 6 (2.2%) patients who developed infective endocarditis, and 3 (1.1%) patients who developed AF. Bleeding due to warfarin toxicity occurred in 10 (3.7%) patients. One patient who previously underwent PBMV was operated on 2 years later due to progressive symptoms of heart failure.

Mortality

There were a total of 39 (14.4%) deaths, 11 (4 %) in the surgical treatment arm and 28 (10.4%) in the medical treatment arm. No death occurred in the PBMV treatment arm. As Figure 2 shows, there was a statistically significant difference in deaths between the surgical and medical treatment arm (log rank p-value = 0.004). The mean (SD) age of death was 40.46 (20.09) years. More deaths occurred in females than males (74.4% vs 25.6%). Most deaths occurred within the first 6 months of presentation.

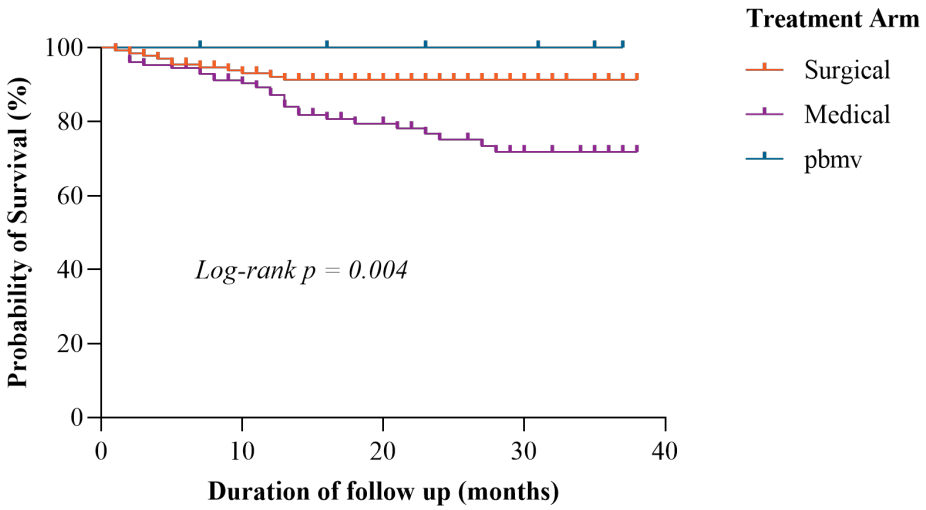

Figure 2. Kaplan - Meir curves of participant survival stratified by treatment arm

Table 3 shows the univariate analysis of factors associated with mortality. Mortality was higher among self-employed patients (crude HR 8.66, 95% CI 1.16 – 64.68, p = 0.035) and not employed (crude HR 7.73, 95% CI 1.03 – 57.76, p = 0.046) compared with the employed patients; and among patients with a monthly income of < 100,000 Tshs (crude HR 8.55, 95% CI 1.16 – 62.84, p = 0.035) compared to patients with income of > 300,000 Tshs. Note a wide 95% CI due to a small number of deaths in the particular groups. The mortality was high among patients who presented with fatigue (crude HR 2.53, 95%

CI 1.06 – 6.04, p = 0.037), ascites (crude HR 2.43, 95% CI 1.12 – 5.29, p = 0.025), and hepatomegaly (crude HR 2.12, 95% CI 1.01 – 4.46, p = 0.048) compared with patients who did not present with those symptoms/signs. There was a higher mortality among patients on Angiotensin Converting Enzyme Inhibitors (ACEIs) {crude HR 2.37, 95% CI 1.24 – 4.52, p = 0.009} compared with the ones not on ACEIs. Mortalities were higher among patients on medical vs surgical treatment (crude HR 2.91, 95% CI 1.45 – 5.84, p = 0.003) and among patients with arrhythmias vs without arrhythmias (crude HR 2.41, 95% CI 1.25 – 4.68, p = 0.036).

Table 3. Univariate analysis of factors associated with mortality among patients with rheumatic MS

Variable	Category	cHR	95% CI of cHR	P - Value
Age (years)	≥ 41	1.14	0.48 – 2.72	0.763
	20- 40	0.75	0.30 – 1.87	0.530
	< 20	Ref		
Sex	Female	1.33	0.65 – 2.73	0.436
Level of education	No formal education	3.11	0.74 – 13.01	0.121
	Primary	1.68	0.51 – 5.55	0.392
	Secondary	0.46	0.10 – 2.04	0.305
	College / University	Ref		
Occupation	Not employed	7.73	1.03 – 57.76	0.046
	Self employed	8.66	1.16 – 64.68	0.035
	Employed	Ref		
Monthly income (Tshs.)	< 100,000	8.55	1.16 – 62.84	0.035
	100,000 – 300,000	5.33	0.68 – 41.69	0.111
	>300,000	Ref		
Symptoms and signs	Dyspnea	1.12	0.15 – 8.14	0.913
	Fatigue	2.53	1.06 – 6.04	0.037
	Ascitis	2.43	1.12 – 5.29	0.025
	Hepatomegaly	2.12	1.01 – 4.46	0.048
Medications	Loop diuretics	2.18	0.67 – 7.08	0.195
	Spironolsctone	2.41	0.94 – 6.15	0.067
	Beta blockers	0.66	0.35 – 1.24	0.197
	ACEIs	2.37	1.24 – 4.52	0.009
	ARBs	0.39	0.09 – 1.62	0.196
Electrocardiography	Arrhythmias	2.41	1.25 – 4.68	0.036
Echocardiography	Dilated LV in diastole	1.22	0.51 – 2.91	0.655
	Dilated left atrium	0.89	0.12 – 6.56	0.916
	Reduced LV ejection	1.51	0.74 – 3.09	0.262
	Depressed TAPSE	1.65	0.88 – 3.09	0.121
Treatment arm	Medical	2.91	1.45 – 5.84	0.003

Key: cHR: crude Hazard Ratio, Ref: Reference category, CI: Confidence Interval, Tshs = Tanzania Shillings; ACEIs = Angiotensin Converting Enzyme Inhibitors; TAPSE = Tricuspid Annular Plane Systolic Excursion, LV = left ventricle, ARBs= Angiotensin Receptor Blockers

To control for confounding variables, a multivariable analysis was conducted. The independent predictors of mortality were being on medical treatment and presence of arrhythmias as shown in Table 4. The risk of death among patients on medical treatment was 3.12 times higher than those on surgical treatment (crude HR 3.12, 95% CI 1.50 – 6.49, p = 0.002) and 2.44 times higher among patients with arrhythmias vs without arrhythmias (crude HR 2.44, 95% CI 1.19 – 4.49, p = 0.015).

Table 4. Multivariable analysis of the factors associated with mortality among patients with rheumatic MS

Variable	Category	aHR	95% CI of aHR	P - Value
Monthly income (Tsh/=)	< 100,000	5.83	0.77 – 44.11	0.088
	100,000 – 300,000	6.29	0.79 – 50.32	0.083
	≥ 300,000	Ref		
Fatigue	Yes	1.04	0.39 – 2.74	0.938
	No	Ref		
Ascitis	Yes	1.18	0.53 – 2.66	0.674
	No	Ref		
Treatment arm	Medical	3.12	1.50 – 6.49	0.002
	Surgical	Ref		
Loop diuretics	Yes	1.56	0.39 – 6.13	0.525
	No	Ref		
Spironolactone	Yes	2.08	0.74 – 5.83	0.163
	No	Ref		
Beta blockers	Yes	0.54	0.26 – 1.11	0.176
	No	Ref		
ACEIs	Yes	1.68	0.83 – 3.43	0.104
	No	Ref		
ARBs	Yes	0.49	0.11 – 2.18	0.429
	No	Ref		
TAPSE (mm)	Depressed	1.29	0.65 – 2.55	0.694
	Normal	Ref		
Presence of arrhythmias on ECG	Yes	2.44	1.19 – 4.99	0.015
	No	Ref		

Key: aHR: adjusted Hazard Ratio, Ref: Reference category, CI: Confidence Interval, ACEIs = Angiotensin Converting Enzyme Inhibitors; TAPSE = Tricuspid Annular Plane Systolic Excursion, ECG = Electrocardiography, ARBs= Angiotensin Receptor Blockers

Table 5 shows that the incidence rate of deaths were statistically significant higher among patients with elevated Anti-streptolysin O titres, abnormal white blood cells, low haemoglobin level, elevated C-reactive protein, elevated creatinine, low sodium, and elevated alanine transaminase compared to patients with normal values. Note a wide 95% CI due to small number of deaths in the particular groups.

Table 5. Mortality rate stratified by laboratory parameters of the patients with rheumatic MS

Variable		Total (N)	Person time	Death (n)	Incidence rate per 1,000 patients	95% CI of Incidence
ASOT (units/mL)	Normal	61	1685	5	2.97	1.24 – 7.13
	High	23	549	7	12.75	6.08 – 26.75
WBCs	Normal	178	4069	19	4.66	2.97 – 7.31
	Abnormal	54	954	11	11.51	6.37 – 20.78
Haemoglobin (g/dl)	Low	103	2248	19	8.43	5.38 – 13.22
	Normal	122	2685	11	4.10	2.27 – 7.40
CRP (mg/L)	Normal	62	1445	9	6.23	3.24 – 11.97
	High	124	2721	19	6.98	4.45 – 10.95
Creatinine (µmol/L)	Normal	211	4630	27	5.83	4.00 – 8.50
	Elevated	14	240	4	16.67	6.26 – 44.41
Sodium (mmol/L)	Normal	80	1859	15	8.07	4.86 – 13.38
	Low	123	2659	13	4.89	2.84 – 8.42
ALAT (U/L)	Normal	128	3066	17	5.54	3.45 – 8.92
	Elevated	43	830	6	7.23	3.25 – 16.09

Key: ASOT = Anti-streptolysin O titre, White Bllod Cells = White Blood Cells, CRP = C-Reactive Protein, ALT = Alanine Transaminase

4. DISCUSSION

This is the first follow-up study on the outcomes of rheumatic mitral stenosis in Tanzania. The study has seven main findings. First, patients were young (median age 36 years), predominantly females (68.3%), and had a monthly income < 42$ (55.5%). Second, patients presented with a long duration of disease (median duration 3.8 years) and there was low use of secondary antibiotic prophylaxis (27.7%). Third, interventions were done in half of the patients (46.2% surgical and 3.8% PBMV). Fourth, there were 11 (4%) deaths in the surgical treatment and 28 (10.4%) in the medical treatment group. Fifth, the independent predictors of mortality were being on medical treatment and presence of arrhythmias (predominantly AF).

The current study has shown that rheumatic MS affects young patients (median age of 36 years). Similarly, In REMEDY [1] and VALVAFRIC registries, [8] the median age of the patients was 28 years. The relatively higher median age in our study compared with the two registries is because we recruited patients aged 6 to 80 years while the registries recruited patients aged 5 to 65 years. Female predominance is a well-recognized finding in RHD studies. [1,8,11,24,25] It is not uncommon for women to be diagnosed with RHD for the first time when they become pregnant. In the current study, five women were pregnant when they were diagnosed with RHD for the first time. In RHD, the risk of pregnancy is increased - management of a pregnant patient with RHD is complicated and there is an associated increase in maternal death. [1,2] We have recently published from our RHD hospital cohort that, the majority of women of reproductive age are at

the highest pregnancy risk based on the modified WHO classification and few of them are on contraception. [26] This calls for strategies aiming at reducing these risks that include the provision of family planning and pre-pregnancy advice for women with RHD.

Our study showed that patients had a long duration of disease before presenting to the hospital indicating that they present for care at a very late stage of the disease. At presentation, 97% reported dyspnea of any severity, AF (31%), NYHA class III – 1V (44%), stroke/TIA (19%), infective endocarditis (9%), severe MS (75%), and multivalvular disease in a majority. These results are similar to those reported in previous studies. [1,11,25] Interestingly, 64% of the patients seek medical attention at a health facility when they initially experienced symptoms highlighting that probably the delay is at lower healthcare facility levels. This informs that there is a need for capacity building by ensuring proper training to healthcare workers for early detection of the disease at lower levels. In the current study, secondary antibiotics prophylaxis was prescribed in a minority (28%) of the patients. Some of the reasons for the low uptake were lack of BPG prescription, believing not in need of BPG, painful injection and lack of knowledge about the disease and prevention. In contrast, the intake of prophylaxis in Ugandan and REMEDY registries were 67% and 60% respectively. Recently, a trial has shown that secondary prophylaxis retards the progression of the disease. [27] Low uptake of secondary prophylaxis has been reported in several LMICs [1,28,29] underscoring the need to identify barriers and enhance its access within the framework of RHD control programs in endemic areas. [30]

In the current study, half of the patients received interventions (surgery and PBMV). Outcomes of patients who have undergone PBMV [23] and surgery (31) in RHD hospital cohort have been recently published. This is a very interesting and encouraging finding given the fact that in many Low-Middle-Income Countries (LMICs) most of these patients are likely to be managed conservatively due to the inadequacy of these services. It should be noted that even though the remaining half of the patients were on medical treatment, not all of them required interventions due to several reasons, implying that the uptake of interventions in this cohort was satisfactory. In REMEDY, [1] and VALVAFRIC [8] registries, although most the patients were likely to require intervention, only 10.3% of them received the interventions. Similarly, in South Africa [32] and Uganda, [33] interventions were provided in 22% and 9% of the patients who required it respectively. Timely provision of these interventions might improve outcomes. [19,34] There is a need of implementing strategies for providing high quality care at tertiary-level facilities for RHD patients in Africa. [35]

In our study, the mortality of 14.3% is somewhat similar to the 11% observed in REMEDY but lower than the 18% reported in the Ugandan [11] and 16% in VALVAFRIC [8] cohorts. The high mortality in the current study is mainly contributed to the patients who were

on medical treatment, an independent predictor. Similarly, studies have shown that if left untreated the prognosis of RHD is worse – imposing death at an early age with a mean age of death of 26 years. [36] The mean (SD) age of death in our study was 40.46 (20.09) years because we recruited patients ranging from 6 – 80 years. Reasons why half of the patients were on medical treatment include patients not coming back when booked for surgery, being on the waiting list for surgery, not meeting criteria for surgery, and financial constraints among others. In fact, the 4% mortality seen in patients who undergone surgery is similar to those reported in previous studies: 3.8% by Akhtar et al, [37] 4% by Panda et al, [38] and Sharma et al, [39] and 4.4% by Debel et al. [40] Interestingly, a tremendous improvement in surgical outcomes is observed when compared with the 14.1% from the same institution 10 years ago. [25] These findings underscore a need of improving access to cardiac care services for RHD in Africa. [6,41,42]

This study showed that arrhythmias (predominantly AF) were an independent predictor of mortality. In MS there is a decreased LV filling, end diastolic volume and LV stroke volume. Arrhythmias further decreases diastolic filling time resulting in worsening of symptoms ± death. In our study, the mortality was 2.44 times higher in patients with arrhythmias compared with patients without arrhythmias. Similarly, in REMEDY registry, the mortality was 1.4 times higher in patients with AF compared with patients without AF. [1] Several other studies conducted in sub-Saharan Africa (SSA) had consistently shown that arrhythmias, particularly AF, are a major public health problem and a common cause of morbidity and mortality. [43,44] In the current study, the prevalence of AF was 31% comparable with those reported from other studies in SSA, [1,43,44] but lower compared with the reported 40% from high-income countries. [45] The postulated reasons for the difference in prevalence are: patients from developed countries have a higher life expectancy and higher chronicity of heart failure and patients from SSA are young. Recently, we have published from our hospital RHD cohort that arrhythmias were detected on 12-lead ECG in 49.5% of RHD patients highlighting a need for its early detection and management. [46] Indeed, we had previously reported that there is unmet need in management of arrhythmias among heart failure patients in Africa. [47]

Lastly, previous studies had found that age, sex, education level, heart failure, New York Heart Association (NYHA) functional class and left ventricular diastolic diameter were independent predictors of mortality. [1,11] None of these factors showed significant association with mortality in our study. It is possible that this could be due to the diffence in studied population. While the referenced studies recruited patients with RHD regardless of the nature of valve lesions, we recruited patients with a predominant mitral stenotic lesion. Moreover, the median age of our study population (36 years) differed from the reported in those studies (28 years). In this study, there was no difference in mortality between males and females. Similarly, while some studies have shown that

females had a higher risk of mortality than males, [48,49] others [1,11] reported the opposite. Indeed, in our previous review, we concluded that it is not clear whether sex plays a role in the diagnosis, management and prognosis of MS and hence a need for research to explore the mechanisms for the differences. [24] Our study showed that patients who were self/not employed and those with low income had a higher risk of death compared with employed patients and patients with better income. Similarly, studies that correlated socioeconomic status with RHD outcomes had reported lower mortality among civil servants. [1,8,11] Improved socioeconomic status has been recommended in RHD control programs. [30] Our study have shown that presenting with fatigue, ascites and hepatomegaly were univariate predictors of mortality similar to what have been reported from previous studies indicating initial presentation with advanced disease. [1,8,11] In this study, the incident rates of death were higher among patients with elevated ASOT and elevated CRP compared to patients with normal values. Similarly, in a study done by Okello et al, elevated ASOT and CRP were predictors of mortality. [11]

5. STRENGTHS AND LIMITATIONS

Our study has several advantages. Firstly, it is a prospective study with a reasonable follow-up period for ascertaining outcomes of interest. Secondly, it provides contemporary baseline data for future comparisons/planning. Thirdly, it has an adequate sample size with the power to allow satisfactory statistical findings. Despite the fact that JKCI receives cardiac patients from all regions of the country, it is necessary that our results may not be generalized for the entire country because there may be factors associated with the way patients access the cardiac services that may hinder representation of patients based on probability samples.

6. CONCLUSION AND RECOMMENDATION

In Tanzania, rheumatic MS affects young people, predominantly females, and with low income. Patients present late in the hospital and there is a low uptake of secondary prophylaxis. The mortality observed in our study is comparable with others reported in previous studies. Surgery carries low mortality and arrhythmias are associated with high mortality. We recommend early detection of the disease, optimization of surgical services, controlling the arrhythmias, and increasing the uptake of secondary prophylaxis in patients with rheumatic MS.

CONTRIBUTORS
RKM, PC, SC conceptualised and planned for the study. RKM, HM, EK, ME, PK, TS, EN

took charge of the data collection and data processing. RKM, PPK, AB, SC, AK, PC, GK, MC supported the analysis, write-up and review of the manuscript. All authors approved the final manuscript for submission

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COMPETING INTERESTS

No conflict of interest.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL

The study was approved by the Directorate of Research and Publications of the Muhimbili University of Health and Allied Sciences (P. MUHAS – REC-9-2019-059). Permission to conduct this study was obtained from JKCI (AB.157/334/01'A).

DATA SHARING STATEMENT

Data used in this paper are available on request from the corresponding author.

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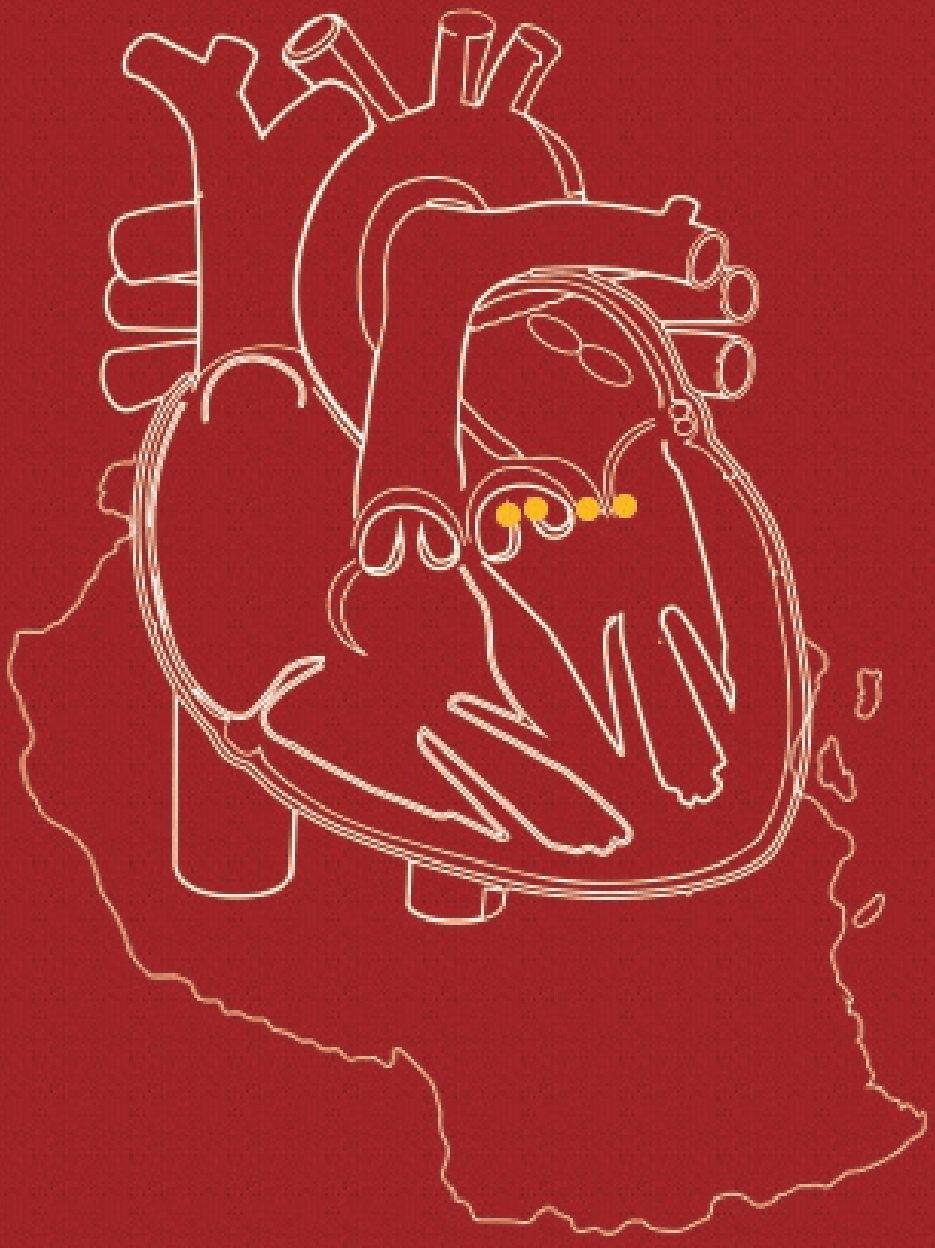

CHAPTER 6

Histopathological evaluation of chronic rheumatic mitral valve stenosis: the association with clinical presentation, pathogenesis and management at a National cardiac Institute, Tanzania

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ABSTRACT

AIMS

The histopathology of mitral valve (MV) tissues have been reported in necropsy and retrospective studies. We prospectively studied the histopathological changes in rheumatic mitral stenosis using advanced techniques and corroborated these with clinical presentation, pathogenesis, and management.

METHODS

Surgically excised rheumatic stenotic MV from 54 Tanzanian patients were studied. These were examined using hematoxylin-eosin, von Kossa staining, and immunohistochemistry.

RESULTS

Their median (range) age was 39 (14 – 57) years with 34 (63%) females. Secondary prophylaxis was given in 7 (13%) patients and 2 (3.7%) had evidence of rheumatic fever (RF). With hematoxylin-eosin, 37 (68.5%) specimens showed fibrinoid degeneration (FD), 44 (81.5%) polymorphonuclear leucocytes (PMNL), 6 (11.1%) Aschoff nodules, 30 (55.6%) calcification, and 39 (72.2%) fibrosis. Thirty-five (64.8%) specimens were positive to von Kossa. The proportion of specimens positive for CD3, CD20, CD68, and CD8 were 46 (85.2%), 35 (64.8%), 39 (72.2%), and 8 (14.8%) respectively. Valvular calcium was high among older patients, males and with a higher trans-MV gradient. The degree of inflammatory cellular infiltration was associated with valvular calcification, FD with ARF, PMNL with disease duration < 10 years, and fibrosis with the absence of atrial fibrillation. C-reactive protein and anti-streptolysin titres were high in CD20 and CD8 staining cells.

CONCLUSIONS

This study confirms that high MV calcium are found in patients who are old, male, and with severe mitral stenosis. The association between clinical parameters with histopathological-immunohistochemical studies observed in our study provides new insight to disease presentation. We found a low rate of secondary prophylaxis and two patients with ARF. Our findings compare with those from other countries suggesting similar pathogenesis and thus intervention modalities. This is the first study on mitral valve histopathology to be reported from Africa.

1. INTRODUCTION

Rheumatic heart disease (RHD), an important cause of cardiac morbidity and mortality among children and young adults affecting an estimated 15.6 million people yearly and annually responsible for 300,000 deaths worldwide,[1] has a sub-Saharan Africa prevalence ranging from 5.7 – 21.0 per 1,000 school children.[2–5]

Surgically excised mitral valve (MV) tissue provides information related to the severity of disease, clinical presentation, and insight into pathogenesis and management.[8–11] For example, higher amounts of calcium are commonly found in men, in older patients and patients with higher transmitral pressure gradients.[11–13] In addition, there is higher correlation between the degree of valvular calcification and the extent of inflammatory response.[9,10,14]Neoangiogenesis, calcific deposits, and inflammation play a role in the formation of valvular calcification. [9,14] The Aschoff granuloma, when present, signify acute rheumatic fever (ARF) but do not necessarily indicate an active attack.[11,15–19] On the other hand, finding fibrinoid degeneration (FD) implies an acute phase while the histiocytes and giant cells indicate the chronic phase of the disease. [11,18]

Heart valves from RHD patients reveal marked inflammatory cellular infiltrates. These cells are capable of producing cytokines and soluble molecules that affect valvular interstitial and endothelial cell activities.[16,20,21] Macrophages are plenty and play a key role in the production of inflammatory mediators that are implicated in the remodelling of extracellular matrix and fibrosis.[8,22] Similarly, B- and T-lymphocytes have been found in abundance. Furthermore, in ARF/active RHD, pro-inflammatory cytokines have been reported[20] and co-occur with increased numbers of $CD4^+$, $CD8^+$ and $CD25^+$ cells.[8,23,24]

The histopathological findings in the valvular tissues from RHD patients have been previously reported.[6,9,16–19,23,25,26] However, these studies are: descriptive necropsy,[17,25] retrospective,[6,17,18,27] used conventional histology,[6,9,17,18,25]were done outside Africa[9,16,17,19,23,25,27] and more than a decade ago.[9,17,19,23,25] We aimed to conduct a prospective study relating the histopathological changes with clinical presentation, disease pathogenesis, and management.

2. MATERIAL AND METHODS

2.1. STUDY DESIGN AND SETTING

This was a prospective study on surgically excised rheumatic MS (rMS) valves from Tanzanian patients. All consecutive patients who were accepted for mitral valve replacement (MVR) due to moderate-severe rMS (from January 2020 to February 2021)

were enrolled. We excluded patients with other forms of valvular heart disease or other cardiac diseases. The specimens were collected from patients admitted and operated on at the Jakaya Kikwete Cardiac Institute (JKCI), Dar es Salaam. The specimens were submitted to the histopathology unit at Muhimbili National Hospital (MNH). Clinical and surgical information of each specimen was provided to two pathologists who performed all histopathological evaluations independently and/or by consensus.

2.2. CLINICAL EVALUATION

The past medical and comorbidity history was obtained from all patients. Patients were clinically evaluated for the evidence of moderate to severe MS according to recognized clinical and echocardiographic criteria.[28]Preoperatively, Doppler echocardiography was used to make a diagnosis. The diagnosis of ARF was made based on the recognized criteria.[29] The diagnosis of atrial fibrillation was made on a clinical basis and confirmed by electrocardiogram.

2.3. HISTOPATHOLOGICAL STUDIES

2.3.1. Biopsies

The excised MV tissues were grossly evaluated and fixed in 10% well-buffered neutral formalin and then paraffin-embedded. Subsequently, a critical gross examination of the valves was performed at the histopathology unit by a cardiologist and a pathologist following established macroscopic criteria for rheumatic carditis.[6,30,31] Eventually, representative MV specimens were photographed. Tissue processing, sectioning and staining were done by specialist histotechnologists using the Sakura Tissue processor and sectioning (4μm) by using Sakura Rotary Microtome 200.

2.3.2. Routine staining

Hematoxylin-eosin (H & E) staining was done on formalin-fixed and paraffin-embedded (FFPE) biopsies after tissue processing and microtomy as previously described.[32] Briefly, FFPE sections were dewaxed in two changes of xylene for five minutes in each and rehydrated to water through descending grades of ethanol (100%, 95%, 80% and 70%) ten dips in each followed by staining in Harris' hematoxylin for ten minutes. Thereafter, slides were briefly rinsed in tap water and differentiated in 1% acid-alcohol for 30 seconds. Bluing of slides was done in running tap water for ten minutes and then counterstained in 1% aqueous eosin for 4 minutes. Slides were then washed in tap water, dehydrated in ascending grades of ethanol (70%, 80%, 95%, and 100%) ten dips in each and cleared in two changes of xylene for ten minutes and mounted by using an automated Sakura TCA 200 coverslipping and labelled accordingly.

2.3.3. Histopathological microscopic evaluation

The H & E-stained sections of MV were evaluated for the presence of FD in leaflets

or annular tissue, polymorphonuclear leucocytes (PMNL) infiltrates, oedema, neovascularization, Aschoff nodules, calcification and fibrosis. These were either noted for presence or absence.

2.3.4. Histochemistry

The von Kossa histochemical staining was done according to the protocol previously described.[32] Briefly, the 4 µm thick tissue sections were allowed to float in a distilled water bath at 45 ^{0}C and mounted on frosted glass slides, dried and then incubated in a hot air oven for 30 minutes at 60 ^{0}C followed by dewaxing in two changes of xylene for 3 minutes in each and rehydrated to distilled water. Slides were then placed in 10% silver nitrate solution and exposed directly underneath a 100W electric light bulb for one hour. Thereafter, slides were rinsed in two changes of distilled water followed by immersing in 5% sodium thiosulphate solution for five minutes and then counterstained in 1% neutral red for 1 minute, blot dried, dehydrated in ascending grades of alcohol, cleared in xylene and mounted.

2.3.5. Histochemical microscopic evaluation

Trephine biopsy and tissue without calcium were used respectively as positive and negative controls and were included in each batch of staining. A semi-quantitative grading system was used as described by Subramanian et al[33] and Lars et al.[16] The extent of valvular calcification was graded as: absent, mild, moderate, severe and the degree of microcalcification as 0 = absent, trace/mild = scattered/dense deposits covering ≤ 2 HPF, moderate = dense deposits in 3- 6 HPFs, or severe = dense deposits in ≥ 6 HPFs.

2.3.6. Immunohistochemistry (IHC)

Immunohistopathological studies for B-lymphocyte (CD20), T-lymphocyte (CD3), macrophage (CD68), CD 4, CD 8, and CD 25 markers were performed as previously described.[32] Briefly, the 3 µm thick tissue sections were labelled with respective antibodies and incubated in a hot air oven overnight at 40 ^{0}C. The next day the slides were deparaffinised using two changes of xylene for eight minutes, then rehydrated using decreasing grades of ethanol. Sections were first blocked with peroxidase blocking reagent (Dako Carpentaria, CA) for 15 minutes followed by antigen retrieval with citrate buffer pH 6.0 in a pressure cooker for 20 minutes at 100 ^{0}C. The plastic container with retrieval solution and slides was placed into the pressure cooker with the lid being tightened then heating the tap water for 20 minutes. Sections were then stained with antibodies for CD3 (clone polyclonal, RTU, Dako), CD4 (clone 4B12, RTU, Dako), CD8 (clone C8/144B, RTU, Dako), CD 20 (clone L26, RTU, Dako), CD25 (clone EP 218, RTU, USA) and CD68 (clone PG-MI, Dako; 1:10) for 30, 25, 32, 28, 32, and 35 minutes respectively. Thereafter, sections were incubated with secondary antibody for 25 minutes [horse-raddish peroxidase (HRP) detection system, Dako Carpentaria, CA]

and visualized by 3, 3'Diamino Benzidine (DAB by Dako). Slides were then washed in three changes of wash buffer for nine minutes to make sure HRP is completely removed. Sections were then incubated with DAB for 10 minutes followed by rinsing in water for 2 minutes then counterstained with hematoxylin for 1 minute, briefly differentiated in 1% acid alcohol and blued for five minutes. Sections were dehydrated in the ascending grades of alcohol and then cleared in two changes of xylene for 5 minutes in each and covered by using a cover slipper.

2.3.7. Microscopic IHC evaluation

Normal tonsil tissue was used as a positive control for the antibodies, and the negative control; the primary antibody incubation step was replaced by a phosphate buffer solution (PBS) as previously described.[32] Non-staining parts/cells within the same tissue were used as internal negative controls as previously described.[32] A semi-quantitative grading system was applied for the degree of mononuclear inflammatory cell infiltration as previously described[34] as 0, 1+, 2+, or 3+.

2.4. STATISTICAL ANALYSES AND ETHICAL CONSIDERATION

Data analysis were done by using Prism V.8.0.1 and SPSS V.27. Continuous data was presented as median or mean and discrete data as counts. The Chi-square and Fisher's exact tests were used for the of the histopathological findings of the excised MV with the clinical findings and results for complex data were presented by the heat map charts. Kappa statistics were used to test the reliability and agreement between the two tests. A p-value of ≤ 0.05 was considered statistically significant. We obtained written informed consent from all participants. The study was approved by the institutional review board through the Directorate of Research and Publications of Muhimbili University of Health and Allied Sciences (P. MUHAS - REC-9-2019-059). Permission to conduct study was obtained from Jakaya Kikwete Cardiac Institute authority (AB.157/334/01'A).

3. RESULTS

Fifty-four Tanzanian patients, who were consecutively accepted for MVR at JKCI due to moderate to severe rMS were enrolled in the study. There was a female 34(63%) predominance. Their median (range) age was 39 (14 – 57). Twenty-nine (53.7%) patients had severe MS, 18 (33.3%) had disease duration of > 10 years, 2 (3.7%) ARF, 7 (3.7%) on secondary prophylaxis and 24 (44.4%) had atrial fibrillation. Their mean Wilkins' score was 11.76 ± 1.74 (Table 1). Seventeen (31.5%) patients had elevated anti-streptolysin titres (ASOT), 5 (9.3%) had prolonged PR interval on electrocardiogram, and 33 (61.1%) had elevated C-reactive protein (CRP).

Table 1. Baseline characteristics of patients operated for Rheumatic MS at JKCI from January 2020 to February 2021 (N=54).

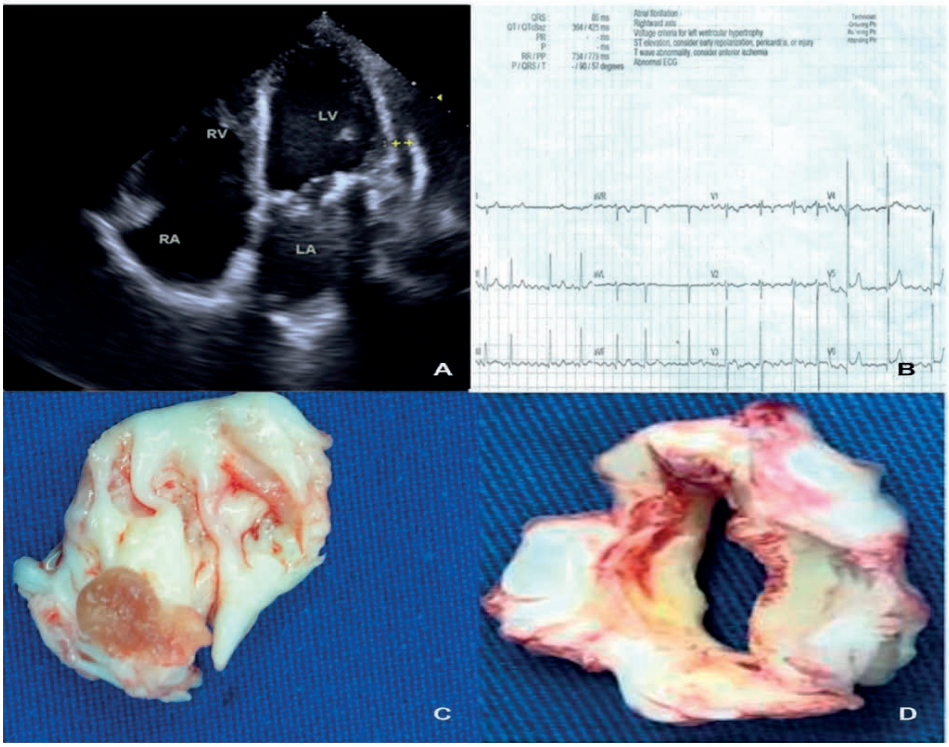
Variable	Mean (±SD)/Frequency (%)
Age (years)	37.9 ± 12
Female sex	34 (63)
Mean duration of symptoms (years)	6.83 ± 5.51
Duration of symptoms categories (years)	
< 10	36 (66.7)
≥ 10	18 (33.3)
Diagnosis	
Pure MS	19 (35.2)
Mixed mitral valve disease	35 (64.8)
Proportion with RF	2 (3.7)
Proportion with atrial fibrillation	24 (44.4)
Proportion with NYHA class III-IV	15 (27.8)
Proportion received Benzylpenicillin	7 (13.0)
Proportion with stroke	9 (16.7)
Proportion with hypertension	6 (11.1)
Proportion with infective endocarditis	2 (3.7)
Proportion with anaemia	1 (1.9)
Proportion with diabetes	1 (1.9)
Proportion with HIV	1 (1.9)
Mean Wilkins' score	11.76 ± 1.74
Mean mitral valve area (cm^2)	1.14 ± 0.39
Mean transmitral pressure gradient (mmHg)	12.54 ± 3.57
Mean Left atrium volume index (ml/m^2	90.46 ± 30.62

Legend: MS = mitral stenosis, RF = rheumatic fever, NYHA = New Heart Association, HIV = human immunodeficiency virus

Supplementary figure 1 shows the echocardiogram (A) and electrocardiogram (B) of a patient with severe MS and a photographic gross appearance of the excised MV (C and D).

The proportion of specimens that stained on H & E showed Aschoff nodules (Fig. 1A&B) and Anitschkow cells (Fig. 1C) in 6 (11.1%) specimens, 44 (81.5%) showed PMNL (Fig. 1&E), 18 (33.3%) neovascularization (Fig. 1D), 37 (68.5%) edema (Fig. 1D&E), 28 (51.9%) haemorrhage (Fig. 1F), 30 (55.6%) calcification (Fig. 1G&H), 37 (68.5%) FD (Fig. 1I), and 39 (72.2%) fibrosis.

With von Kossa stain, 35 (64.8%) of the tissues showed evidence of calcification (figure 2A). The proportion of tissues stained with immunohistochemical markers were: 39 (72.2%) with CD68, 46 (85.2%) with CD3, 35 (64.8%) with CD20 (figures 2B-D respectively), and 8 (14.8%) tissues with CD8. None of the tissues were stained with markers for CD4 and CD25.



Supplementary figure 1. Example of echocardiogram showing severe MS and heavy calcification (A) and the electrocardiogram showing atrial fibrillation (B) from the same patient, and examples gross appearance of an inflamed and thickened (C) and an inflamed, thickened and calciefied (D) surgically excised MV.

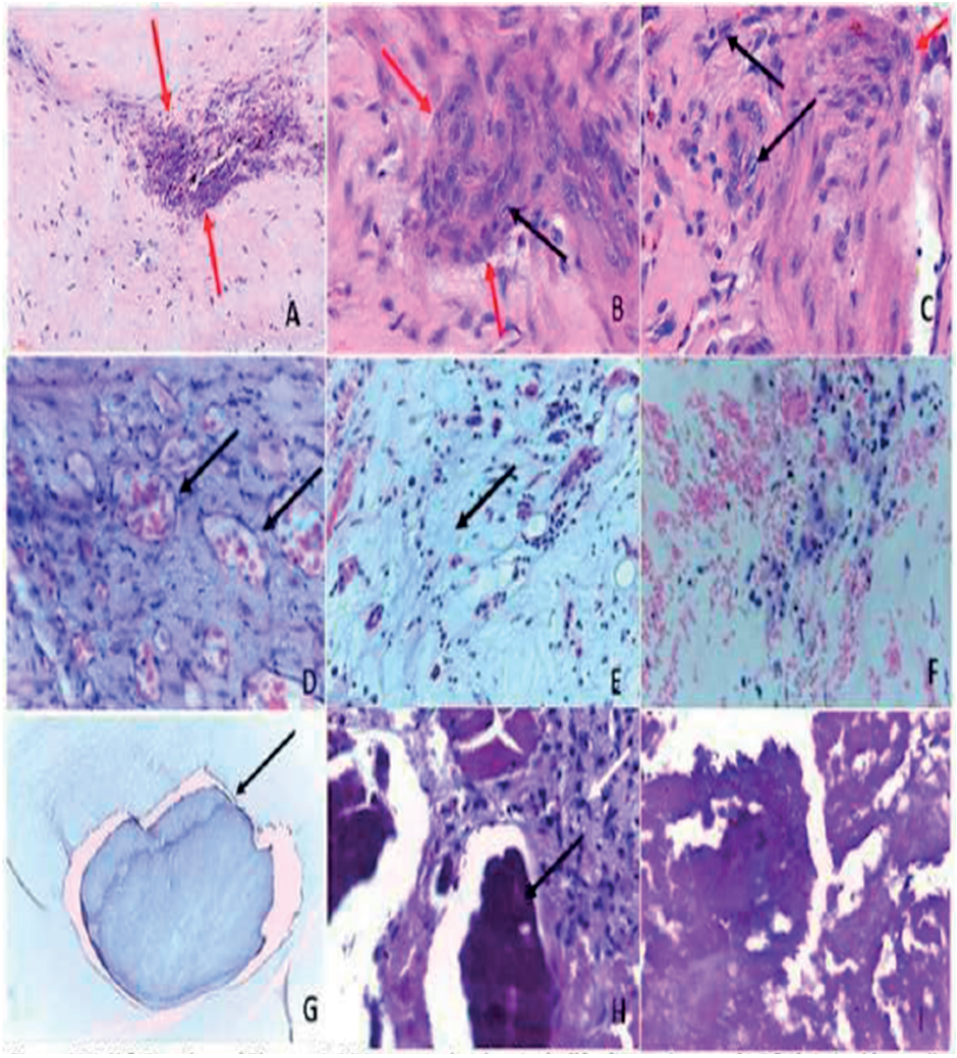


Figure 1A-I. H & E sections of rheumatic MV stenosis showing: **Aschoff bodies**; arrows **[A & B]; Anitschkow cell**; note the caterpillar-like chromatin **[C]; Valvulitis [D & E]** with **Neoangiogenesis [D] Granulation tissue [D & E]** figures **[D & E]** also shows valvular **Oedema;** Aschoff body (black arrow) **[F]** with **Haemorrhage** (white arrow) **[E]** high power; **Macrocalcification [G & H];** valvulitis (white arrow) and calcification (black arrows) **[H]; Fibrinoid degeneration/necrosis [I].**

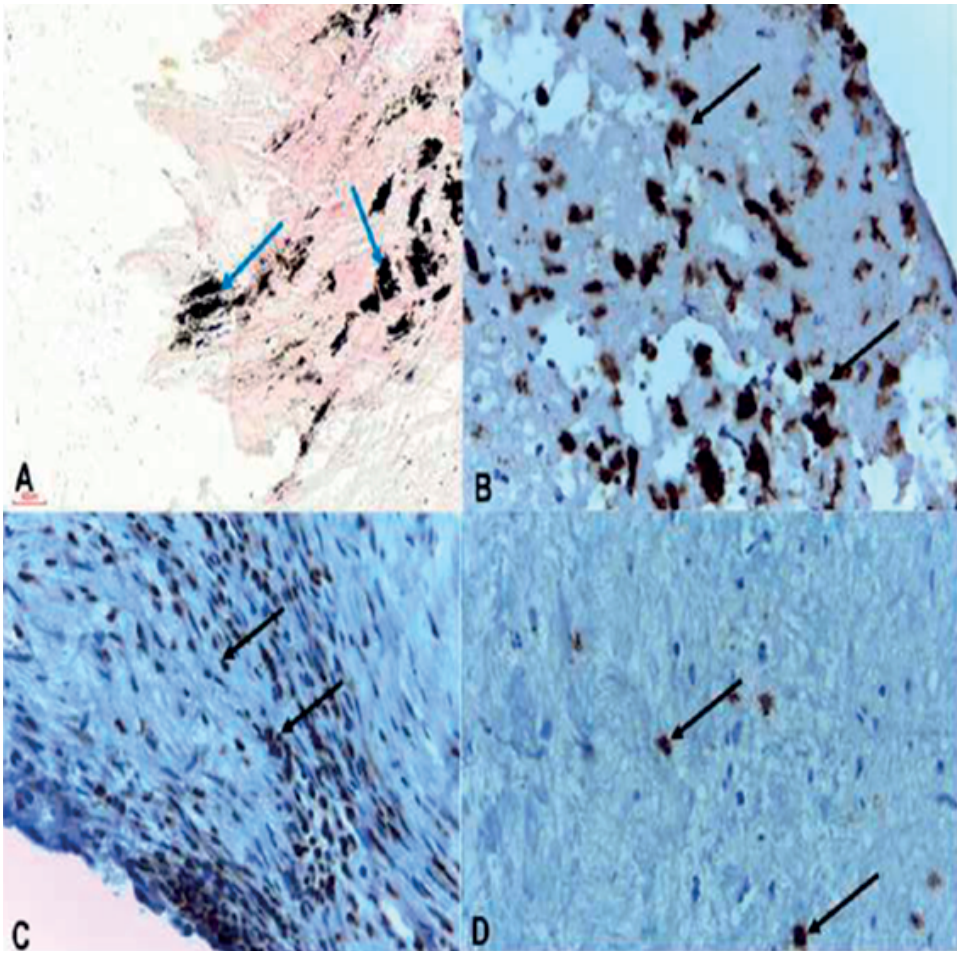


Figure 2. Von Kossa stained MV tissue specimen (2A) showing intense calcification and photomicrographs of excised MV tissues stained by immunohistochemistry with anti-CD 68 (2B), anti-CD 3 (2C), and anti-CD 20 (2D) monoclonal antibodies.

Table 2 shows statistically non-significant higher MV calcium levels among patients with age >30 years, males, and with a higher trans-MV pressure gradient. Patients with a duration of symptoms < 10 years had higher MV calcium than those with duration ≥ 10 years. When present, valvular calcification was more likely to be detected by echocardiography than not to be detected. The percentage in agreement for detecting valvular calcification between echocardiography and von Kossa stain was 66.6% (kappa value 0.269, p= 0.048). The mean Wilkins' score among patients without valvular calcium was higher than those with calcium.

Table 2. Association between presence of valvular calcium with clinical variables among the operated patients (N=54).

Variable	Category	Presence of valvular calcium		P - value
		Yes n (%)	No n (%)	
Age (years)	≤ 30	10 (62.5)	6 (37.5)	0.817
	>30	25 (65.8)	13 (34.2)	
Sex	Male	16 (80.0)	4 (20.0)	0.073
	Female	19 (55.9)	15 (44.1)	
Mean PG	Moderate	5 (50.0)	5 (50.0)	0.277
	Severe	30 (68.2)	14 (31.8)	
Duration of disease (years)	< 10	27 (75.0)	9 (25.0)	**0.027**
	≥ 10	8 (44.4)	10 (55.6)	
Atrial fibrillation	Yes	15 (62.5)	9 (37.5)	0.750
	No	20 (66.7)	10 (33.3)	
ECHO calcification	Yes	26 (74.3)	9 (25.7)	**0.048**
	No	9 (47.4)	10 (52.6)	
Mean Wilkins' score		11.40 ± 1.61	12.42 ± 1.81	**0.038**
Mean MVA		1.07 ± 0.35	1.26 ± 0.43	0.082

Legend: PG = pressure gradient, ECHO = echocardiography, MVA = mitral valve area

Table 3 depict a statistically significant association (and a trend towards the increase) between the extent of calcification and the degree of cellular infiltrations as marked by CD3, CD20, and CD68 staining. For CD 8 marker the association was statistically not significant.

Table 3. Association between the extent valvular calcification and the degree of inflammatory cell infiltrations among the operated patients (N=54)

Variables		Extent of valvular calcification				P - value
		Absent (%)	Mild (%)	Moderate (%)	Severe (%)	
CD 3						
	Absent	6 (31.6)	2 (8.3)	0 (0.0)	0 (0.0)	**0.002**
	Occasional	8 (42.1)	3 (12.5)	0 (0.0)	0 (0.0)	
	Several groups	2 (10.5)	9 (37.5)	1 (100)	3 (30.0)	
	Many groups	3 (15.8)	10 (41.7)	0 (0.0)	7 (70.0)	
CD 20						
	Absent	13 (68.4)	5 (20.8)	1 (100)	0 (0.0)	**< 0.001**
	Occasional	5 (26.3)	9 (37.5)	0 (0.0)	4 (40.0)	
	Several groups	1 (5.3)	3 (12.5)	0 (0.0)	0 (0.0)	
	Many groups	0 (0.0)	7 (29.2)	0 (0.0)	6 (60.0)	
CD 68						
	Absent	14 (73.7)	0 (0.0)	0 (0.0)	1 (10.0)	**< 0.001**
	Occasional	1 (5.3)	2 (8.3)	0 (0.0)	0 (0.0)	
	Several groups	3 (15.8)	3 (12.5)	1 (100)	0 (0.0)	
	Many groups	1 (5.3)	19 (79.2)	0 (0.0)	9 (90.0)	
CD 8						
	Yes	3 (15.8)	4 (16.7)	0 (0.0)	1 (10.0)	1.000
	No	16 (84.2)	20 (83.3)	1 (100)	9 (90.0)	

Table 4 shows a statistically significant association (and a trend towards severity) between calcification and the degree of cellular infiltrations as marked by CD3, CD20, and CD68 staining. For CD 8 marker, the association was not statistically significant.

Table 4. Association between the degree of microcalcification and markers of inflammatory cells among the operated patients (N=54)

Variables	Degree of microcalcification				P - value
	Absent (%)	Trace/mild (%)	Moderate (%)	Severe (%)	
CD 3					
Absent	6 (31.6)	1 (5.9)	0 (0.0)	1 (10.0)	**0.005**
Occasional	8 (42.1)	1 (5.9)	1 (12.5)	1 (10.0)	
Several groups	2 (10.5)	5 (29.4)	5 (62.5)	3 (30.0)	
Many groups	3 (15.8)	10 (58.8)	2 (25.0)	5 (50.0)	
CD 20					
Absent	13 (68.4)	1 (5.9)	2 (25.0)	3 (30.0)	**0.016**
Occasional	5 (26.3)	7 (41.2)	3 (37.5)	3 (30.0)	
Several groups	1 (5.3)	2 (11.8)	1 (12.5)	0 (0.0)	
Many groups	0 (0.0)	7 (41.2)	2 (25.0)	4 (40.0)	
CD 68					
Absent	14 (73.7)	0 (0.0)	0 (0.0)	1 (10.0)	**< 0.001**
Occasional	1 (5.3)	0 (0.0)	1 (12.5)	1 (10.0)	
Several groups	3 (15.8)	2 (11.8)	1 (12.5)	1 (10.0)	
Many groups	1 (5.3)	15 (88.2)	6 (75.0)	7 (70.0)	
CD 8					
Yes	3 (15.8)	3 (17.6)	1 (12.5)	1 (10.0)	1.000
No	16 (84.2)	14 (82.4)	7 (87.5)	9 (90.0)	

Figure 3 shows a statistically significant difference in presence of: FD in patients with ARF Vs without (91.3% Vs 51.6%, p = 0.003); PMNL infiltration among patients with disease duration < 10years Vs ≥ 10 years (91.7% Vs 61.1%, p=0.011); and fibrosis in patients without Vs with atrial fibrillation (86.7% Vs 54.2%, p=0.014). The remaining histopathological findings did not reveal a statistically significant association with the analysed parameters.

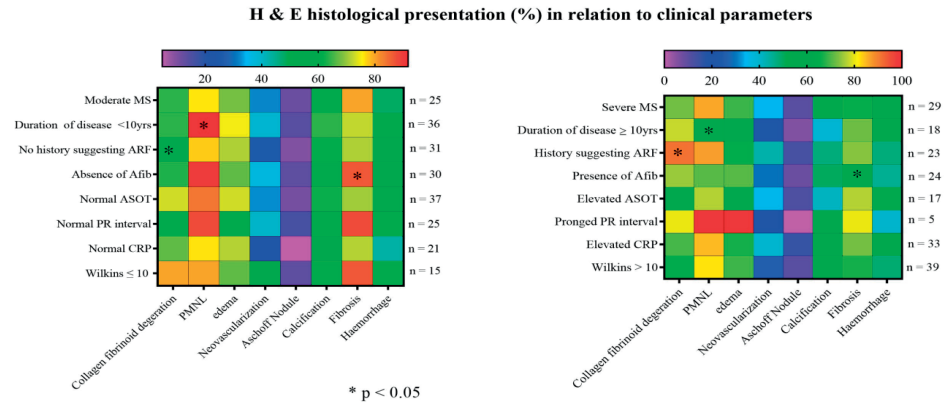


Figure 3. A heat map showing the association of several mitral valvular H&E histopathological findings with clinical parameters. ARF= acute rheumatic fever; Afib=atrial fibrillation; ASOT= antistreptolysin titre; CRP= C-reactive protein; PMNL= polymorphonuclear leucocytes.

Figure 4 depicts a statistically significant difference in presence of: CD20 staining cells among patients with normal Vs elevated CRP (47.6% Vs 75.8%, p = 0.035) and CD8 staining cells among patients with normal Vs elevated ASOT (8.1% Vs 29.5%, p=0.041). The remaining CD staining cells did not show a statistically significant association with the analysed parameters.

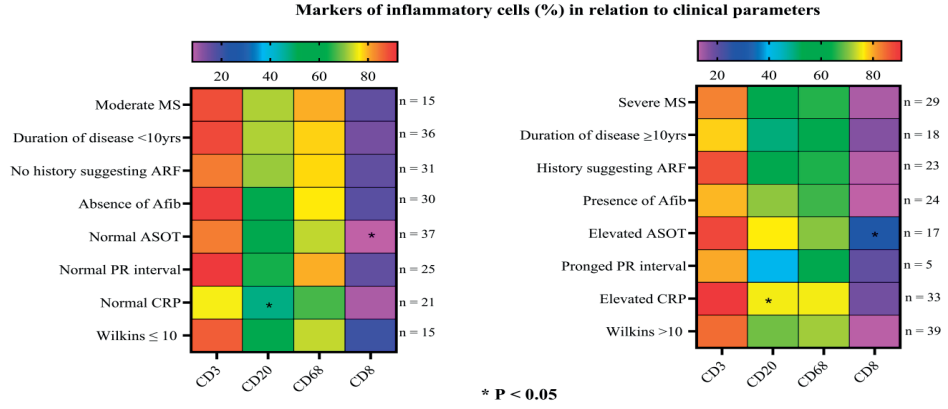


Figure 4.A heat map showing the association of inflammatory cell infiltrates with clinical parameters. ARF= acute rheumatic fever; Afib=atrial fibrillation; ASOT= antistreptolysin titres; CRP= C-reactive protein; PMNL= polymorphonuclear leucocytes.

4. DISCUSSION

The present single-centre prospective study interpreted the histological findings observed in surgically excised rMS valves and explored how those findings correlate to the clinical presentation, disease pathogenesis and management. Our study showed higher MV calcium levels in individuals of >30 years, male, and with higher trans-MV pressure gradients. The degree of inflammatory cell infiltration was associated with the extent of valvular calcification and the degree of microcalcification. ARF and shorter duration of disease were associated with the of cells of acute inflammation.

The median (range) age of the patients was 39 (14 – 57) years and female 34 (63%) predominance is similar to other rMS studies which indicate that, in Africa, MS presents at an early age with rapid progression and severe disability at an early age.[35] Moreover, other studies report RHD to be more common in females than males in the ratio of 2:1.[2,12,13,36]

Our study showed that with H & E staining, 37 (68.5%) specimens had FD, 44 (81.5%) PMNL, 37 (68.5%) edema, 18 (33.3%) neovascularization, 6 (11.1%) Aschoff nodules, 30 (55.6%) interstitial calcification, 39 (72.2%) fibrosis and 28 (51.9%) revealed fresh haemorrhage. These findings are similar to those reported by Rashed et al[18] and Suresh et al[10] implying a similar pathogenesis.

Our study revealed a higher MV calcium level among males than females, patients with > 30 years than with ≤ 30 years and those with higher trans-MV pressure gradients. Similarly, other studies reported that stenotic MV calcium occur more frequently and in huge amounts in men than women, in older than younger individuals, and in patients with severe MS.[11,12]

In this study, there was a fair agreement between echocardiography and von Kossa stain (gold standard) for valvular calcification detection. Valvular calcium is a known predictor of poor outcomes after percutaneous balloon mitral valvuloplasty (PBMV) in both immediate and long term.[12,13,37] In circumstances where echocardiography is not confirmatory, fluoroscopy or computed tomography could be used to assess the severity and location of calcification. Alternatively, other methods for predicting outcomes following PBMV apart from Wilkin's score[38] can be used, for example, the ECHO score revisited[39] and the Cormier score.[40]

Similar to previous studies,[9,10,14] our study showed a highly statistically significant association between the extent and distribution of valvular calcification with the severity of inflammatory cellular infiltrates. These inflammatory cells, calcific deposits and

neovascularization has been postulated to be involved in calcification formation. Ambari and his colleagues[41,42] are investigating the role of angiotensin converting enzyme inhibitor (ACEI) ramipril in the reduction of fibrosis in rMS. In RHD, fibrosis is induced by Angiotensin II through the stimulation of transforming growth factor-β (TGF-β), which eventually increases the binding of interleukin (IL)-33 to a soluble decoy receptor (sST2) instead of its natural receptor (ST2L). The overall effect is upregulation of Angiotensin II and progression to fibrosis.

Similar to previous studies,[9,14] this study showed that the extent of valvular calcification and degree of microcalcification has a strong association with the severity of inflammatory cellular infiltration. As postulated,[43–45] there is a resemblance between diseases involving lipid deposition, inflammatory cell infiltrations and calcification with that of atherosclerotic diseases. Indeed, as reported by Soini et al,[46] patients administered with statin medications revealed a significantly lower tendency for neo-vessels formation.

Previous studies have shown that in ARF and patients with active RHD, the increased production of pro-inflammatory cytokines has been reported[20] and co-occurs with increased numbers of $CD4^+$, $CD8^+$ and $CD25^+$ cells.[8,23,24]Interestingly, in the current study C-reactive protein and anti-streptolysin titres were statistically significantly high in both CD20 and CD8 staining cells but none of the tissues stained with markers for CD4 and CD25.

In developing countries, patients' selection and the type of valvular surgery are among the important issues to be considered because patients come late with complications of the disease. There are no local guidelines in our setting that could probably fit our patients' presentation with treatment outcomes. Ideally, there should be no active inflammatory process when these patients are sent for surgery. However, it is challenging to make a diagnosis of ARF in areas where causes of fever and/or joint pain/swelling are plenty and therefore high expertise clinical suspicion complemented by appropriate laboratory investigations is needed.

Our study showed that secondary prophylaxis against recurrent attacks of ARF was given in 7 (13%) patients. Unfortunately, of the 2 (3.7%) patients diagnosed to have ARF, none of them had received the prophylaxis despite being eligible. Appropriate use of secondary prophylaxis is a cost-effective approach for preventing morbidity and mortality associated with ARF.[47]Low uptake of benzathine penicillin G has been documented in several countries[48–50] highlighting for a need to identify barriers and enhance its access within the framework of care for chronic diseases in countries affected by RHD.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our study was conducted at the country sole hospital performing valvular surgeries making the study a representative of the country. The small sample size of this study limited further analysis. However, by utilizing three advanced histopathological techniques important analyses were done.

5. CONCLUSIONS

This study confirms that high MV calcium are found in patients who are old, male, and with severe mitral stenosis and that valvular calcification is associated with cellular infiltration. We found a low rate of secondary prophylaxis and two patients with ARF. Our findings compare with those from other countries suggesting similar pathogenesis and thus intervention modalities. We recommend: i) rigorous pre-operative workup to rule out active inflammation, ii) increased uptake of secondary prophylaxis for recurrent attacks of acute rheumatic fever, and iii) the use of anti-inflammatory and antibiotic prophylaxis post-surgery.

FUNDING

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CONFLICTS OF INTEREST

None

ETHICS APPROVAL STATEMENT

This study was approved by the institutional review board of the Muhimbili University of Health and Allied Sciences

AUTHORS' CONTRIBUTIONS

Conceived and designed the study: RKM, PC, SC, AK; **Data collection**: RKM, MB, AN, AM; **Analysed the data**: RKM, AM, AN; RKM wrote the first draft of the paper and subsequent drafts in collaboration with PC, AM, MJC, GK, AK, LF and SC. All authors have given final approval of the version to be published.

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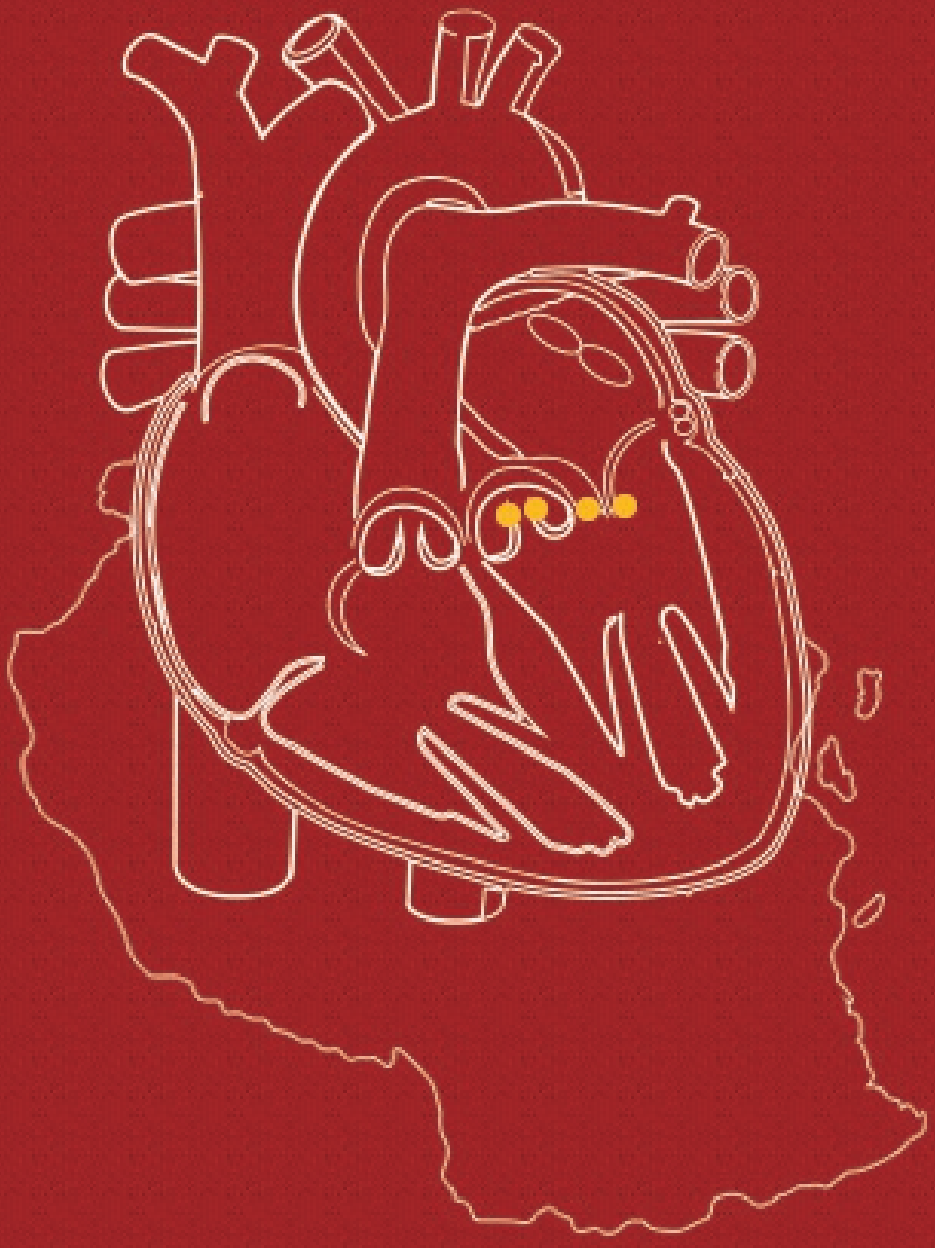

CHAPTER 7

Characteristics and immediate outcomes of patients who undergone percutaneous balloon mitral valvuloplasty at the Jakaya Kikwete Cardiac Institute, Tanzania

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ABSTRACT

BACKGROUND

For rheumatic mitral stenosis (MS), a multidisciplinary evaluation is mandatory to determine the optimal treatment: medical, percutaneous balloon mitral valvuloplasty (PBMV) or valve surgery. Clinical and imaging evaluations are essential for procedural risk assessment and outcomes. PBMV interventions are increasingly available in Africa and are feasible options for selected candidates. Enhancing PBMV training/skill transfer across most of African countries is possible.

OBJECTIVES

To provide insight into the clinical practice of patients with rheumatic MS evaluated for PBMV in a Tanzania teaching hospital and to define the role of imaging, heart team, training/skill transfer in PBMV interventions.

METHODS

From August 2019 to May 2022, 290 patients with rheumatic MS were recruited consecutively in the Tanzania Mitral Stenosis (TAMS) study. In total, 43 (14.8%) patients were initially evaluated for eligibility for PBMV by a heart team. We did the clinical assessment, laboratory investigations, trans-thoracic/oesophageal echocardiography (TTE/TEE), and electrocardiography.

RESULTS

The median age was 31 years (range 11- 68), two-thirds females (four diagnosed during pregnancy). Two patients had symptomatic MS at 6 and 8 years. Nine patients had atrial fibrillation with left atrial thrombus in three, two detected by TEE. Nine patients in normal sinus rhythm had spontaneous echo contrast. The mean Wilkins score was 8.6 (range 8 – 12). With re-evaluation (by the local and visiting team), seventeen patients were found to have unfavourable characteristics: bi-commissural calcification (4), ≥ grade 2/4 mitral regurgitation (6), high scores and left atrial thrombus (3), left atrial thrombus (2), and severe pulmonary hypertension (2). Three patients died before the planned PBMV. Eleven patients were on a waiting list. We performed PBMV in 12 patients with success in 10 and good short-term outcomes (mean pre-PBMV 16.03 ± 5.52 and post-PBMV gradients 3.08 ± 0.44 mmHg, $p < 0.001$). There were no complications.

CONCLUSIONS

PBMV has good outcomes for selected candidates. TEE is mandatory in pre-PBMV screening and for procedural guidance. In our cohort, patients with Wilkins score of up to 11 underwent successful PBMV. We encourage PBMV skills expansion in low- and middle-income countries, concentrating on expertise centres.

KEYWORDS
Rheumatic heart disease; percutaneous mitral valvuloplasty; Wilkins score; outcome; thrombus

HIGHLIGHT
Our findings are an example of well-planned development that, if sustained, can make significant differences in the diagnosis, treatment, and outcomes of patients with rheumatic MS in low- and middle-income countries.

1. INTRODUCTION

Rheumatic heart disease (RHD) is endemic in Tanzania; recently published data states the prevalence is around 17.9 per 1,000 population. [1] In Tanzania, RHD is the third most common cause of heart failure after hypertension and cardiomyopathies, including idiopathic dilated cardiomyopathy, peripartum cardiomyopathy, and endomyocardial fibrosis. [2] Rheumatic mitral stenosis (MS) in Africa shows a female predominance with early presentation in life. [3,4] Patients usually present in New York Heart Association (NYHA) functional class II - III, atrial fibrillation (28%), and thromboembolic events (3.2%). [4,5] Clinically, patients may present with an irregular pulse, normal blood pressure, elevated jugular venous pulse, left parasternal lift, and normal apex impulse. Auscultation reveals a low-pitched rumbling diastolic murmur.

Transthoracic echocardiography (TTE) is used to confirm the diagnosis, and assess the severity and prognosis of MS. It is used to describe valve morphology, assess valve function, assess cardiac chambers, and evaluate the feasibility and indications for intervention. [6] Transesophageal echocardiography (TEE) is done to complement TTE pre-intervention, and specifically to rule out left atrial (LA) or left atrial appendage thrombus that may not be visible by TTE. Several 2-dimensional echocardiography scoring systems have been created for evaluation of mitral valve anatomy and suitability for percutaneous balloon mitral valvuloplasty (PBMV) without demonstrating superiority, [7] including the most commonly used Wilkins score, [8] Echo Score Revisited, [9] and Cormier score. [10] Limitations of the Wilkins score are the inability to differentiate fibrosis from calcification and the underestimation of commissural/sub valvular involvement. [11,12] However, the decision to perform PBMV is not solely dependent on the mitral valve score but also on clinical judgment. Studies have shown that in young patients or patients with fewer comorbidities, PBMV gave a better survival rate despite a mean Wilkins score of 9.5. [13]

Guidelines recommend PBMV or mitral valve surgery for the management of clinically significant MS. [14,15] However, due to limited access to interventional cardiology

and cardiothoracic surgery in low-and-middle-income countries (LMICs), most of these patients are likely to be managed conservatively. [16] In Uganda, Okello et al [17] demonstrated only 8% of patients requiring surgery and 1% requiring PBMV received those services. Instead, only medical therapy including diuretics, beta-blockers, digoxin, calcium channel blockers, and Angiotensin Converting Enzymes Inhibitors were prescribed. However, most of these medications only alleviate some of the symptoms but do not resolve the obstructive valve pathology. [18] Additional medical therapy includes anticoagulation, indicated for the history of systemic embolism, thrombus in the left atrium, atrial fibrillation, dilated left atrium (diameter > 50mm / indexed volume> 60mL/m^{2}), and those that receive a prosthetic heart valve. [6,19] Secondary antibiotic prophylaxis for prevention of recurrent attacks of acute rheumatic fever and progression of valve lesions is important. [20]

To optimize the evaluation and management of rheumatic MS, a heart team including cardiology, anaesthesiology, interventional cardiology and cardiothoracic surgery is a necessity. [14,15] To guide the choice of intervention (PBMV or Surgery), this multidisciplinary approach incorporates clinical assessment, detailed imaging evaluation, procedural risk assessment, and scoring systems. PBMV is a safe and cost-effective procedure, and provides excellent short- and long-term outcomes with improved hemodynamics, and symptomatic improvements in appropriately selected patients. [6,19,21,22] Currently, most sub-Saharan African countries including Tanzania, have access to a cardiac catheterization laboratory and therefore PBMV is a feasible option. In August 2019, visiting teams from the United States started a mission in Tanzania to initiate, enhance and consolidate PBMV skills in the local cardiac interventional team. This study was conducted to determine the profiles of patients evaluated for PBMV due to rheumatic MS at Jakaya Kikwete Cardiac Institute (JKCI) during those workshop missions.

2. MATERIAL AND METHODS

2.1. STUDY DESIGN AND SETTING

This was a prospective, single centre, hospital-based cross-sectional study of Tanzanian patients who were screened for PBMV at JKCI, the only institute offering the intervention in the country. All consecutive patients who were planned for PBMV due to severe rheumatic mitral stenosis (from August 2019 to May 2022) were enrolled in the study. We excluded patients with unfavourable clinical and mitral valve morphology characteristics and those with other forms of non-rheumatic valvular heart disease or other cardiac diseases.

2.2. DATA COLLECTION

The sociodemographic, medical and comorbidity history were obtained from all patients. New York Heart Association (NYHA) functional class, Wilkins score, and mortality information were also collected. All patients were clinically evaluated for the evidence of severe MS according to recognized clinical and echocardiographic criteria. [14,15,23] Several echocardiographic (SC 2000 Siemens Echo machine), electrocardiographic (General electronic Mac 400) and laboratory parameters were documented.

2.3. ELIGIBILITY ASSESSMENT OF PBMV

All of the echocardiographic images were reviewed by a heart team which comprised of the local team and respective members of the visiting team. All TTE were done with the patient on left lateral decubitus and with conventional views (parasternal long axis, short axis and apical four chamber view). Two-dimensional and Doppler echocardiographic studies were performed according to the American Society of Echocardiography guidelines. [24] TEE was also performed as previously described. [25] The team took into consideration the following factors (on top of MVA ≤ 1.5cm^2) when reaching a consensus on management strategy: clinical assessment (e.g. symptomatic severity and comorbidities), scoring systems (by Wilkins score) and procedural risk assessment (e.g. anatomical favourability and clinical favourability {pulmonary hypertension}). We used the European Society of Cardiology (ESC) and the American Heart Association/ American College of Cardiology (AHA/ACC) [14,15] definition of unfavourable anatomical characteristics: left atrial thrombus, Wilkins > 8, mitral regurgitation > grade 2, and bilateral commissural fusion to guide our decision. For unfavourable clinical characteristics the definition is: old age, NYHA functional class IV, severe pulmonary hypertension, atrial fibrillation, and history of commissurotomy. [14,15] In this study, severe pulmonary hypertension was defined as a right ventricular systolic pressure >70mmHg measured from the maximum tricuspid regurgitation jet velocity as previously described. [26]

2.4. PBMV APPROACH

A TEE was done on the day of PBMV to rule out LA or LA appendage thrombus. In four patients, the procedure was performed under local anaesthesia and moderate sedation, utilizing TTE and fluoroscopy. In eight patients, TEE was used while the patient was under general anaesthesia and mechanical ventilation. While recognizing that TEE adds to procedure time and complexity, the aim was to expose the local team to the two methods i.e fluoroscopy and TEE guided approach. Vascular accesses were right femoral vein with 8F sheaths upsized to 12F for the Inoue balloon, left femoral vein with 7F sheath for the Swan-Ganz catheter, and left femoral artery with 5F sheaths for angiographic pigtail catheter. Trans-septal puncture was done by an anterograde approach using a Brockenbrough needle via the Trans-septal sheath and at AP projection. Intravenous heparin at a dose of 100IU/Kg body weight was given immediately after septal

puncture. The Inoue balloon stepwise technique was used in all patients and performed as previously described. [27] Balloon sizing was based on patient height as previously described. [28] The hemodynamic parameters were recorded before and after PBMV. A successful PBMV was defined as improvement in mitral valve area (MVA) to ≥ 1.5cm^2 without complications, including mitral regurgitation of > 2/4 grade. One day after the procedure, echocardiography was done to evaluate the MVA and mitral regurgitation (MR). **Figure 1** shows the local team performing trans-oesophageal echocardiography (TEE) before PBMV as part of pre-procedural patient preparation.

Figure 1: A photograph showing pre-procedural trans-oesophageal echocardiography (TEE).

2.5. STATISTICAL ANALYSIS

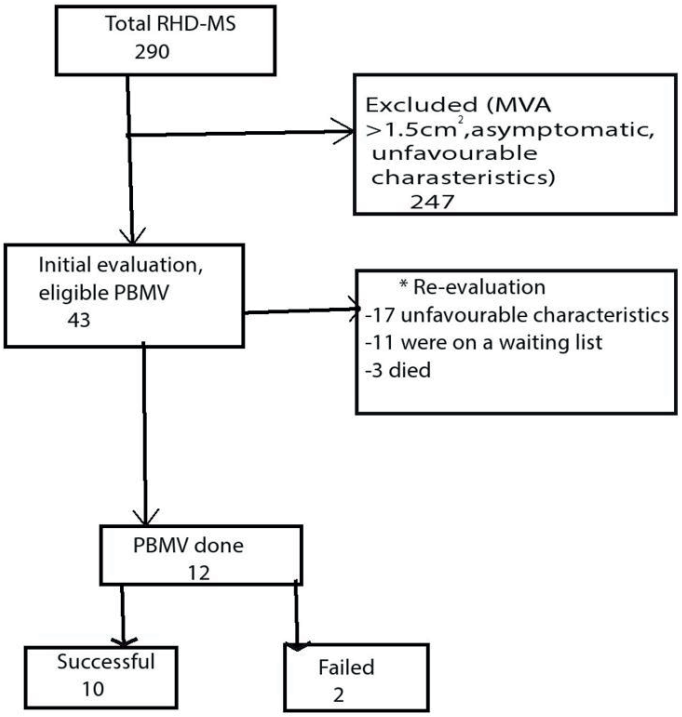
The collected data was checked for quality. Coding was done before entry. The analysis was done using Statistical Package for Social Sciences (SPSS) version 28.0. Continuous data were presented as mean with standard deviation (SD) when distributed normally and as median with range when skewed. Categorical data were reported as counts and percentages. The Chi-square and Fisher's exact tests were used to compare categorical data. T-Test was used to compare the difference between continuous variables. P value <0.05 was considered statistically significant.

2.6. ETHICAL CONSIDERATION

Written informed consent was obtained from all participants ≥ 18 years. Assent was obtained from minors > 13yrs of age in the presence of adult witness. For < 13yrs, oral consent was provided by the guardian of the minor. The study was approved by the Directorate of Research and Publications of Muhimbili University of Health and Allied Sciences (P. MUHAS – REC-9-2019-059). Permission to conduct this study was obtained from JKCI (AB.157/334/01'A).

3. RESULTS

Forty-three (14.8%) out of 290 patients enrolled in the Tanzania Mitral Stenosis (TAMS) study were evaluated for eligibility for PBMV at JKCI (from August 2019 to May 2022, **Figure 2**). The interventions were done in August 2019 and May 2022, skipping the years 2020 and 2021 due to restrictions on travelling because of the COVID-19 pandemic.



*These patients were excluded from PBMV due to technical and logistical reasons.

Figure 2. A flow chart diagram showing patients recruitment
Legend: RHD-MS = rheumatic heart disease - mitral stenosis, MVA = mitral valve area, PBMV= percutaneous balloon mitral valvuloplast

Figure 3 is the map of Tanzania showing the residence of 290 patients enrolled in the Tanzania Mitral Stenosis (TAMS) study. Most of the patients were residing from the northern zone of the country.

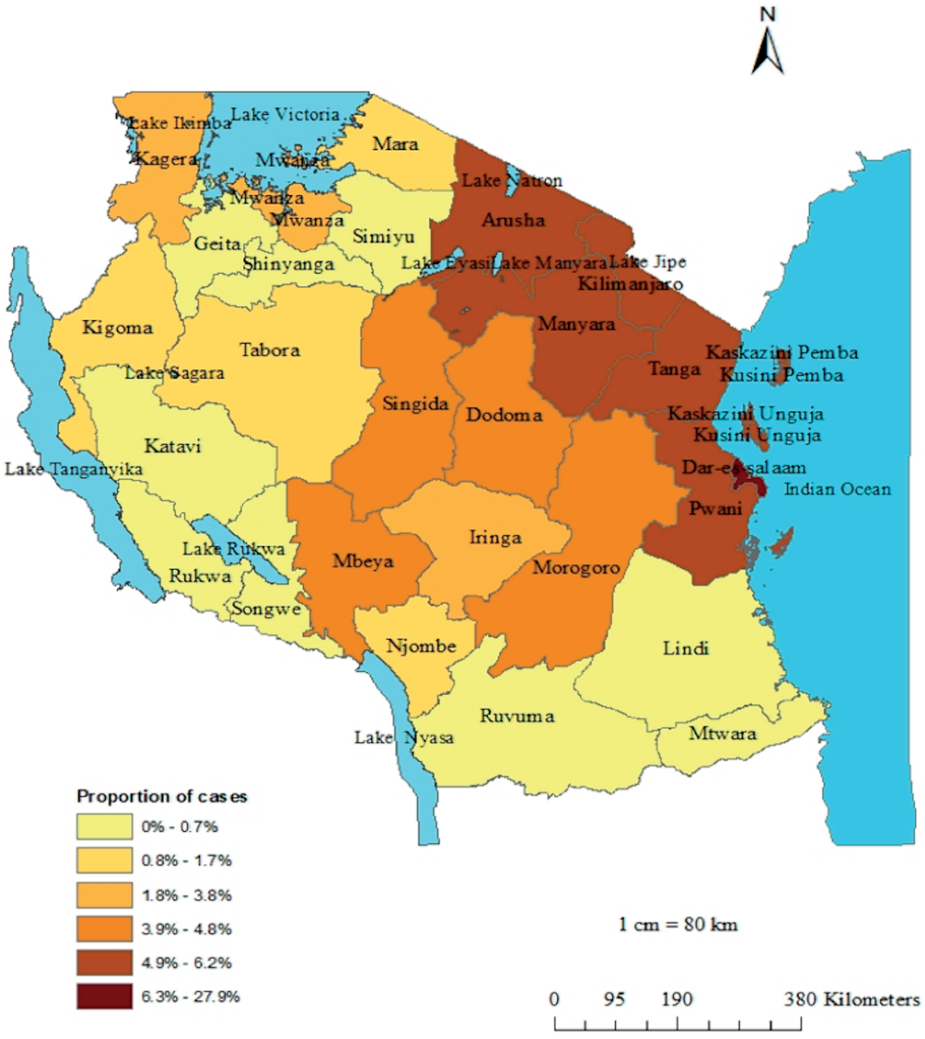


Figure 3: The map of Tanzania showing residence of 290 patients enrolled in the Tanzania Mitral Stenosis (TAMS) study

As shown in Table 1, there was a female 32 (74.4%) predominance. The median age of the patients was 31 (range 11 – 68) years. Twenty-five (58.1%) patients were single, 21 (48.8%) had primary education, 23 (53.5%) were not employed, 38 (88.4%) were from outside of Dar es Salaam, 24 (55.8%) had income < 42$ per month, 25 (58.1%) had a national health insurance, and 34 (79.1%) lived in the clean environment during childhood. Four (9.3%) patients were firstly diagnosed with RHD during pregnancy. The mean duration of symptoms before diagnosis was 43.26 ± 30.03 months. Two patients presented with symptomatic MS at the age of 6 and 8 years respectively. Nine (20.9%) patients had AF (all were on anticoagulants), 4 (9.3%) patients had a stroke, and 7 (16.3%) had hypertension. The mean right ventricular systolic pressure derived from the tricuspid regurgitation velocity jet was 56.37 ± 21.60. About a quarter were in NYHA functional class III – IV and 9 (16.7%) had reduced LVEF. The mean mitral valve area was 0.89 ± 0.19 cm^2 and the mean transmitral pressure gradient was 15.66 ± 4.25 mmHg. The mean Tricuspid Annular Plane Systolic Excursion (TAPSE) was 16 ± 2.93 (Table 1).

Table 1. Sociodemographic and clinical characteristics of patients evaluated for percutaneous mitral balloon valvuloplasty at JKCI from August 2019 to May 2022 (n=43).

Variable	Mean (±SD) or Median (range)/Frequency (%)
Median age (years)	31 (11- 68)
Female sex	32 (74.4)
Mean duration of symptoms (months)	43.26 ± 30.03
Proportion residing outside of Dar Es Salaam	38 (88.4)
Proportion of not married	25 (58.1)
Proportion without health insurance	25 (58.1)
Proportion with monthly income < 42$	24 (55.8)
Proportion with primary education	21 (48.8)
Proportion with stroke	4 (9.3)
Proportion with hypertension	7 (16.3)
Proportion with atrial fibrillation	9 (20.9)
Proportion with NYHA class III-IV	12 (27.9)
Proportion on anticoagulants	11 (25.6)
Mean LVEF (%)	60.67 ± 8.73
Mean Wilkins score	8.63 ± 0.93
Mean RVSP (mmHg)	56.37 ± 21.60
Mean LA diameter (mm)	51.39 16 ± 8.98
Mean mitral valve area (cm^2)	0.89 ± 0.19
Mean transmitral pressure gradient (mmHg)	15.66 ± 4.25
Mean TAPSE	16 ± 2.93

NYHA = New York Heart Association, LVEF = Left ventricular ejection fraction, TAPSE = *Tricuspid Annular Plane Systolic Excursion,* ***LA = left atrium***

TTE was done in all patients while TEE was done in 29 patients (Table 2). Nine patients were in AF out which 3 patients had LA thrombus. Only 1 of these patients had detectable LA thrombus on TTE while the other 2 patients required TEE for detection. **Figure 4** shows the echocardiography of a patient with an LA thrombus in atrial fibrillation.

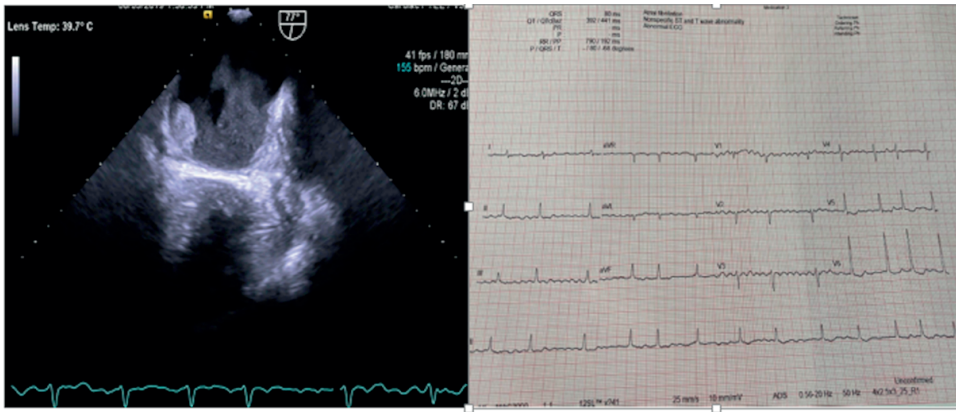


Figure 4. Echocardiographic and electrocardiographic images taken from a patient with left atrial thrombus (left) in atrial fibrillation (right)

As depicted in Table 2, thirty-four patients were in normal sinus rhythm out of which 2 patients had LA thrombus on TEE but not on TTE. These two patients with normal sinus rhythm had LA volume index (LAVI) of 88ml/m^2 and 90ml/m^2 respectively. Nine patients in normal sinus rhythm had left atrial spontaneous echo contrast (LASEC) of moderate to severe intensity (**Figure 5**). The mean LA size for the occurrence of spontaneous echo contrast was 55.34 ± 11.24mm. All patients with LA thrombus had associated LASEC.

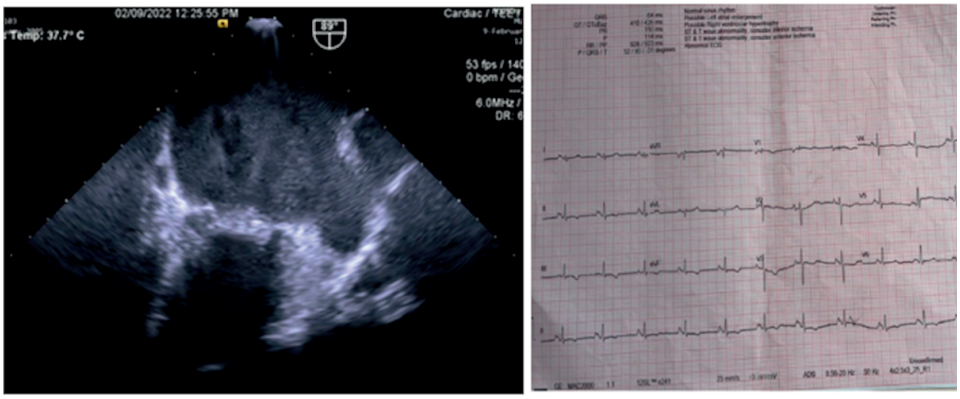


Figure 5. Echocardiographic and electrocardiographic images taken from a patient with left atrial severe spontaneous echo contrast 'smoke' (left) in normal sinus rytthm (right)

A careful evaluation revealed that 15 patients had unfavourable anatomical characteristics characterized by: bi-commissural calcification (4 patients), ≥ grade 2/4 mitral regurgitation (6 patients), high scores and left atrial thrombus (3 patients), and left atrial thrombus (2 patients). Two patients had unfavourable clinical characteristics (severe pulmonary hypertension). Among these, 10 underwent mitral valve replacement (MVR), five were on schedule for MVR, and two (with LA thrombus) were re-scheduled for PBMV. Three patients died before the planned PBMV, presumably due to progressive heart failure. Eleven patients were on a waiting list for PBMV (Table 2).

Table 2. Characteristics of the patients evaluated for PBMV (n=43)

Case no	Age	Sex	Wilkins score	ECG rhythm	TTE LA thrombus	TEE LA thrombus	Spontaneous echo contrast	Disposal	Status
1	16	F	8	Sinus	No	No	No	PBMV	Done
2	62	F	8	AF	Yes	-	Yes	PBMV	†Re-scheduled
3	42	F	8	AF	No	No	No	MVR*	Done
4	28	F	8	Sinus	No	No	No	PBMV	Failed
5	30	F	8	Sinus	No	-	No	PBMV	On waiting list
6	18	F	8	Sinus	No	-	No	PBMV	On waiting list
7	20	F	8	Sinus	No	-	No	PBMV	On waiting list
8	35	F	8	Sinus	No	No	No	PBMV	Done
9	42	F	8	AF	No	Yes	Yes	PBMV	†Re-scheduled
10	43	F	8	Sinus&	No	No	Yes	PBMV	On waiting list
11	19	M	8	Sinus	No	No	No	MVR#	Scheduled
12	25	F	8	Sinus	No	-	No	PBMV	On waiting list
13	35	F	8	Sinus	No	No	No	PBMV	Done
14	49	F	8	AF	No	-	No	PBMV	On waiting list
15	11	F	8	Sinus	No	-	No	PBMV	Died before
16	19	M	8	Sinus	No	-	No	PBMV	On waiting list
17	20	F	8	AF	No	-	No	PBMV	On waiting list
18	62	M	8	AF	No	-	No	MVR*	Scheduled
19	19	M	8	Sinus	No	No	No	MVR*	Done
20	13	F	8	Sinus&	No	No	Yes	PBMV	Died before
21	17	F	8	Sinus&	No	No	Yes	PBMV	Failed
22	33	F	8	Sinus	No	Yes	Yes	MVR*	Done
23	39	F	8	Sinus	No	Yes	Yes	MVR*	Scheduled
24	30	F	8	Sinus	No	-	No	PBMV	On waiting list
25	31	F	9	Sinus	No	No	No	PBMV	Done
26	16	M	9	Sinus	No	-	No	PBMV	On waiting list
27	24	F	9	Sinus	No	No	No	PBMV	Done
28	47	F	9	AF	No	No	Yes	PBMV	Done
29	68	F	9	AF	No	No	Yes	MVR#	Done
30	45	F	9	Sinus	No	No	Yes	PBMV	Done
31	48	F	9	Sinus&	No	No	Yes	PBMV	Died before
32	42	F	9	Sinus&	No	No	Yes	PBMV	Done
33	49	F	9	AF	No	Yes	Yes	MVR*	Scheduled

Table 2. Continued.

Case no	Age	Sex	Wilkins score	ECG rhythm	TTE LA thrombus	TEE LA thrombus	Spontaneous echo contrast	Disposal	Status
34	45	F	9	Sinus	No	No	No	MVR*	Done
35	60	M	9	Sinus	No	-	No	MVR*	Done
36	61	F	9	Sinus	No	No	No	MVR*	Done
37	15	F	10	Sinus	No	-	No	PBMV	On waiting list
38	28	F	10	Sinus[&]	No	No	Yes	MVR*	Done
39	16	F	10	Sinus	No	No	No	MVR*	Done
40	20	M	10	Sinus[&]	No	No	Yes	PBMV	Done
41	17	M	11	Sinus[&]	No	No	Yes	PBMV	Done
42	35	F	11	Sinus[&]	No	No	Yes	MVR*	Done
43	20	M	12	Sinus	No	No	No	MVR*	Scheduled

**Unfavorable anatomy, [#]Unfavorable clinical, [&]Smoke in normal sinus rhythm, [†]LA thrombus alone*

Table 3 shows the individual outcomes of patients who underwent PBMV. The procedure was done in 12 patients out of which 10 (83.3%) were successful. There were no immediate post-procedural complications. Two patients whom the procedure failed had a score of 8 each. Of the two failures, one was a problem in septal puncture while the other one was due to difficulties of crossing the mitral valve orifice.

Table 3. Outcome of patients who underwent PBMV at JKCI from August 2019 to May 2022 (n=12).

Case no	Wilkins score	LA size (mm)	Pre-PBMV Transmitral gradient (mmHg)	Post-PBMV Transmitral gradient (mmHg)	Pre-PBMV MR	Post-PBMV MR	Complications
1	8	44	11	3	Trace	Mild	None
4	8	46	14	-	Mild	-	Failed
8	8	46	14	3.5	Trace	Mild	None
13	8	44	12	3	Trace	Mild	None
21	8	58	16	-	Trace	-	Failed
25	9	60	21.2	3.5	Mild	Mild	None
27	9	46	10.9	3	Trace	Mild	None
28	9	50	10	2	Mild	Mild	None
30	9	47	17	3	Mild	Mild	None
32	9	45	18.2	3	Mild	Mild	None
40	10	42	12	3	Mild	Mild	None
41	11	58	28	3.4	Mild	Mild	None

- = Not done

Table 4 shows the mitral valve area improvement and the hemodynamic changes produced by PBMV. The mean pre-PBMV was 16.03 ± 5.52 mmHg and the mean post-PBMV was 3.08 ± 0.44 mmHg, p < 0.001. PBMV resulted in a significant decrease in mitral gradient, left atrial and pulmonary arterial pressures and an increase in the mitral valve area. There was a significant symptomatic improvement among all patients, attaining NYHA functional class I.

Table 4. Comparison of pre- and post-PBMV parameters of patients who underwent successful PBMV at JKCI from August 2019 to May 2022 (n=10).

Parameter	Pre-PBMV	Post-PBMV	p-value
Mean mitral valve area (cm^2)	0.87 ± 0.16	2.25 ± 0.46	< 0.001
Mean mitral valve pressure gradient (mmHg)	16.03 ± 5.52	3.08 ± 0.44	< 0.001
Mean left atrial pressure (mmHg)	22.66 ± 3.89	8.00 ± 2.31	< 0.001
Mean pulmonary arterial pressure (mmHg)	38.40 ± 13.59	33.50 ± 11.29	< 0.001

PBMV = percutaneous mitral valvuloplasty

With respect to Wilkins score, improvements in mitral valve area by planimetry in the two groups {1.6 (0.88) vs 1.63 (1.88), p = 1.00} and in hemodynamics i.e mitral gradient {8.5 (2.6) vs 14 (16.6), p = 0.117}, left atrial pressure {2 (2) vs 4 (8), p = 0.117}, and pulmonary artery pressure {5 (6) vs 2 (20), p = 0.517} were similar as shown in Table 5.

Table 5. Pre- and post-PBMV median (range) differences in improvement between groups

	Wilkins score		P - value
Variable	≤ 8 (n =3)	9 - 11 (n = 7)	
MVA improvement (cm^2)	1.60 (0.88)	1.63 (1.18)	1.000
MV gradients improvement (mmHg)	-8.50 (2.60)	-14.00 (16.60)	0.117
LAP improvement (mmHg)	-2.00 (2.00)	-4.00 (8.00)	0.117
PAP improvement (mmHg)	-5.00 (6.00)	-2.00 (20.00)	0.517

***Legend: MVA = mitral valve area, MV = mitral valve, LAP = left atrial pressure, PAP = pulmonary artery pressure,* PBMV = percutaneous mitral valvuloplasty**

In the two mission visits, four local interventional cardiologists were supervised in performing PBMV. **Figure 6** shows the local team (left) performing PBMV at JKCI Cath Lab in May 2022. On the right is the balloon inflated across the mitral valve.

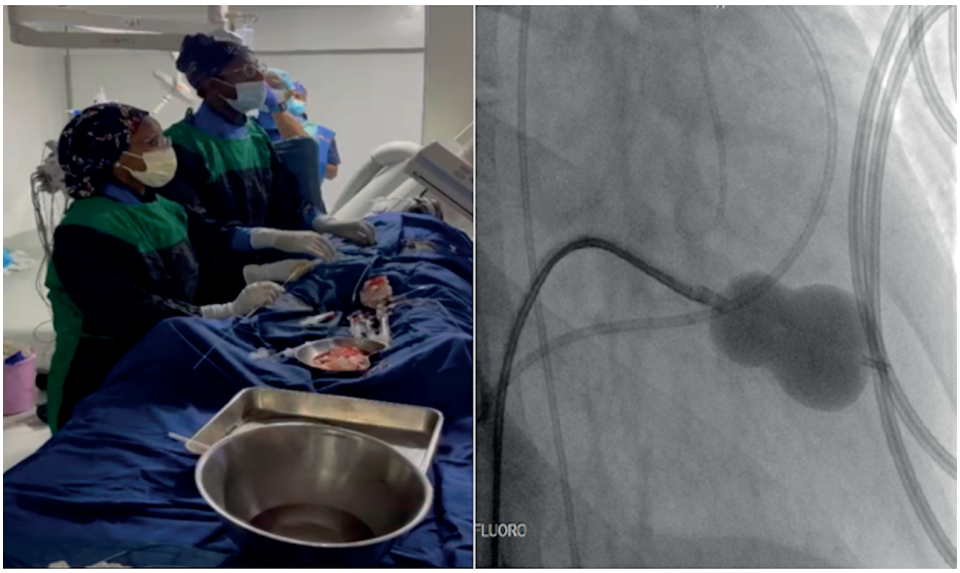


Figure 6. A photograph showing the local team is performing PBMV (left) and the balloon is inflated across a stenosed rheumatic mitral valve (right)

4. DISCUSSION

THE MAIN FINDINGS

This single-centre prospective study reports the first investigation of patients' eligibility for PBMV and the immediate post-PBMV outcomes in Tanzania. The study further defines the role of heart team and training/skill transfer in PBMV interventions. Lastly, we highlight the presentation of female gender in RHD. The main findings are: (1) TEE is mandatory in pre-PBMV screening to rule out LA thrombus as TTE does not always detect it, and for procedural guidance; (2) the ESC and AHA/ACC guidelines [14,15] for a good outcome of PBMV (cut-off Wilkins score ≤ 8) needs reconsideration. In our cohort, patients with Wilkins score of up to 11 underwent successful procedures; (3) PBMV has good short-term outcomes in selected patients that underscores the importance of appropriate patients' selection in a multidisciplinary valvular heart team, and 4) in Tanzania, MS has a female predominance with the early presentation in life. These findings are encouraging and lower the bar for performing PBMV in a large group of RHD-MS given its short procedural time and short recovery period allowing the patient to return to family or work more promptly if needed. Our findings are an example of well-planned development, which if sustained, can make significant differences in the diagnosis, treatment, and outcomes of patients with rheumatic MS in LMICs.

4.1. THE ROLE OF IMAGING IN PATIENT SELECTION

In this study, LA thrombi were present in five patients, four of which could not be detected with a TTE but only with a TEE. This finding highlights the importance of pre-PBMV transoesophageal echocardiography. Similarly, other studies have reported that the sensitivity of TTE in detecting a thrombus in the LA or its appendages (posteriorly located) in patients with RHD was 32%- 50%. [23,29] The sensitivity and specificity of TEE in identifying LA thrombi is 99%. [29] Among patients with LA thrombus, two were in normal sinus rhythm (their left atrial volume indexes were 88ml/m^2 and 90ml/m^2). It is possible that these patients in sinus rhythm may have experienced paroxysmal atrial fibrillation owing to the dilated LA. In this cohort, one patient with LA thrombus had a history of stroke. Similarly, previous studies have shown the risk of arterial-systemic embolism is increased by LA thrombus and LASEC, particularly in LA thrombi with irregular surface and LASEC with moderate to severe intensity. [23,30–33] In our study, all patients with LA thrombus had associated LASEC. Previously, it has been reported that LASEC increases the risk of LA thrombi and hence the expression “when there is smoke, there is fire”. [34,35] In this study, nine patients in normal sinus rhythm had moderate to severe intensity left atrial spontaneous echo contrast (so-called “smoke”). The mean size of the left atrium for the occurrence of LASEC was 55.34 ± 11.24mm. LA thrombus (and ≥ grade 2/4 mitral regurgitation, bilateral commissural fusion) absolutely contraindicate eligibility for PBMV. [14,15] However, depending on certain clinical circumstances, experienced operators may deviate from these guidelines. [23] For example, the approach for patients with LA thrombus is controversial. [11] While most operators agree with the American College of Cardiology/American Heart Association guidelines to avoid PBMV, [14,15] other argues that the risk of dislodging a thrombus is reduced by the low profile and manoeuvrability of the Inoue balloon when done in experienced hands. [36]

4.1.1. Indications for anticoagulation therapy

Indications for anticoagulation are: history of systemic embolism, thrombus in LA, prosthetic heart valve, atrial fibrillation or left atrium > 50mm diameter / left atrium volume > 60mL/m^2. [14,15] However, controversy exists on whether patients with rheumatic MS in normal sinus rhythm based on enlarged LA or LASEC should be anticoagulated. [14,15,37,38] Patients with LA thrombus should be given a 4 – 6 weeks pre-PBMV treatment with warfarin. [11] There is an unmet need for alternative anticoagulation strategies (apart from vitamin K antagonists) in patients with moderate to severe MS and prosthetic heart valves because the new oral anticoagulants are neither safe nor effective as evidenced by the Randomized Evaluation of Dabigatran in Patients after Heart Valve Replacement (RE-ALIGN) trial. [39] Indeed, the INVestigation of rheumatiC AF Treatment (INVICTUS) trial results, which had just been published have shown that Rivaroxaban is outmatched by vitamin K antagonists for rheumatic atrial fibrillation. [40] Findings from the INVICTUS trial underscore a need to improve anticoagulation control in LMICs, for instance, by

ensuring the availability of Point-of-Care International Normalized Ratio (INR) devices at different levels of health facilities, including primary health care. Currently, in sub-Saharan Africa, there are great challenges with anticoagulation, with wide variation in its use and time in the therapeutic range of 27 – 56%. [41,42]

4.2. IMMEDIATE POST-PBMV OUTCOMES

In our study, the mean Wilkins score was 8.6 ± 0.9 with a range of 8 – 12. Seven patients had a score ≥ 10 implying an "unfavourable" Wilkins score. However, we obtained successful results in 10/12 patients with no immediate post-procedural complications. The improvement in the mitral valve area and hemodynamics were similar between patients with Wilkins scores ≤ 8 and those with scores of 9 – 11. Similarly, previous studies [13,43,44] have shown that in a population of young patients or those with fewer co-morbidities, PBMV gave a better survival rate despite an unfavourable Wilkins score (mean score of 9.5). In our cohort, the patients were young and with no co-morbidities. That is an important observation in selecting a candidate for PBMV, as it should not solely rely on Wilkins score. In addition, Almeida et al [45] have reported that PBMV is safe and effective in patients with rheumatic MS in both patients with Wilkins scores ≤ 8 and 9 – 11; and with similar improvement in the MVA. Recently, Carvalho et al [46] reported no difference in all-cause/composite of all-cause mortality between the two groups after a follow of 10 years. Another study from Khartoum by Suliman et al [47] that comprised of patients with average Wilkins score of 9 showed good immediate PBMV outcomes similar to our findings. In its original description, a Wilkins score ≥ 12 predicted poor results with PMBV. [8] In one large analysis, ~60% of patients with Wilkins scores 9–11 achieved a successful result with PMBV. [48] Wilkins score ≥ 12 achieved significant improvement of MVA, although fully success was uncommon (30%). PBMV relies on the mechanism of commissural splitting. [14,15] The ideal valve anatomy would have commissural fusion, pliable leaflets, and limited subvalvular apparatus calcification. [23] If there is minimal commissural fusion a successful result is unlikely. [8] In patients with RHD, commissural fusion is the hallmark. On the contrary, in the Western world, most patients with significant MS are older with degenerative, calcified, less pliable leaflets making PBMV unsuitable. [14,23]

4.2.1. A need for PBMV intervention in LMICs

Our study showed that PBMV has good short-term outcomes in selected patients. In countries where RHD is endemic, PBMV is an alternative to mitral valve surgery offering a similar survival rate despite a lower event-free duration, its main advantage over surgery is the lower cost. Ambari and his colleagues [48] have recently presented survival data of patients with rheumatic MS after PMBV in a LMIC showing that PBMV was non-inferior to mitral valve surgery in terms of survival. On the contrary, in high come countries PBMV is still performed occasionally, not only because of the lower incidence of RHD but also because they are strict with the scoring system in selecting appropriate

patients predicting safety and success. [49] Furthermore, in high-income countries there is a higher level of skills and techniques among cardiothoracic surgeons such as using minimally invasive techniques which have been shown to provide quick recovery and long-term survival. [50] PBMV is important in an LMICs where hemodynamically severe MS presents earlier in life, and young patients have thickened valve leaflets presenting with or without concurrent regurgitation. [51] It is also a bridging therapy to open heart surgery for MS patients during pregnancy, postponement of valvular replacement for females to finish their childbearing time (in avoidance of anticoagulation) or in patients who cannot withstand open heart surgery like those with significant comorbidities, frail elderly, irreversible pulmonary hypertension and severe LV systolic dysfunction. [8,11] Apart from the risk imposed by warfarin on pregnancy, managing a patient with a mechanical heart valve in resource-constrained countries is challenging in terms of anticoagulants and monitoring of the INR. [52,53] Other advantages are those related to its lower cost, lower morbidity, and lower procedure-related mortality. [6,19,21,22,54]

4.2.2. Challenges and solutions in performing PBMV

In the current study, among the twelve patients who underwent PBMV, 5 (41.7%) had a Wilkins score ≤ 8 and 7 (58.3%) had a Wilkins score of 9- 11. There was a procedural technical failure in two patients both of which had Wilkins a score of 8. This implies that the success of PBMV is not solely dependent on the score. In one patient there was a failure to cross a severe stenosed valve and the failure of septal puncture in the second. Similarly, previous studies have reported the failure rate ranging from 1% to 17%. [55] The often reported causes of failure are the inability of atrial septal puncture or to correctly position the balloon across the valve. [55] Unfavourable anatomy such as predominant subvalvular stenosis or severe valve stenosis can also result in failures. [55] Usually, the commonest reason for failure to cross the valve is when the septal puncture is either too posterior or too anterior. In our cohort, these procedures were done under the supervision of experienced operators and TEE guidance and therefore the techniques were correct. In a patient to whom we failed to puncture the septum despite a correct positioning of a sharp Brockenbrough needle at the fossa ovalis, we speculate that could be due to the extended rheumatic/inflammatory process involving the septum. In the second patient in whom we failed to cross the mitral valve orifice despite attempting several maneuvres, we think that the huge left atrium could be the reason. Intracardiac echocardiography (ICE) is nowadays considered the imaging modality of choice to guide puncture of the septum, however, the device is expensive hence limiting its application in most settings. [55] Recent studies suggest improved visualization of the septum and assessing of tenting during puncture of the septum by use of the real-time 3-dimensional TEE. [55] One of the failed PBMV in our cohort was converted to mitral valve surgery and the other one was on the waiting list for the same. Ten patients who underwent a successful PBMV were on a regular clinical follow-up.

4.3. THE ROLE OF TRAINING/SKILL TRANSFER IN PBMV INTERVENTIONS

Our findings are important to Africa as a whole because Tanzania being the host of the East African Centre of Excellence for Cardiovascular Sciences (EACoECVS), identified RHD as a priority disease due to its high morbidity and mortality in Africa. [2,56,57] Therefore, the lessons learnt will be useful to the East African community and the rest of Africa. The strategies of involving the heart team in selecting patients and eventual steps resulted in good short outcomes among patients who underwent PBMV. Our collaboration with the United States of America had been previously implemented in Uganda a few years ago, albeit a different approach, proved to be effective. [58] Similarly, several approaches to enhance PBMV skills in Africa have been suggested, for instance, using 3D and 4D echocardiography. [47] This is because 3D echocardiography has been shown to assess the mitral valve anatomy with accuracy, and guide atria septal puncture giving a clinician a better view to provide good PBMV outcomes. [55,59,60] However, the high cost of balloons in resource-limited countries and the setting where many patients do not own health insurance needs consideration. In this study, half of the patients had a monthly income of < 42$. Activity such as a recent PBMV workshop alongside the Tokyo International Conference on African Development (TICAD 8) in Tunisia, whereby one young cardiologist per African country was supported to attend, is an example of a forum to discuss challenges related to PBMV in Africa. [61]

4.4. FEMALE PREDOMINANCE WITH THE EARLY PRESENTATION IN LIFE

In this study, there was a female predominance (74.4%). Similarly, other previous rheumatic heart disease studies [62–70] have shown that the disease is more common in females than males. The reasons for these differences are not known. [65,71,72] Intrinsic factors such as genetically – mediated immunological factors that predispose women to autoimmune disease have been associated. [73] Extrinsic factors (such as child-rearing which might result in repeated exposure to group A streptococcus and limited access to health care whereby males are given more priority than females when they fall sick) also have been implicated. [71,72] Recently, Prothymosin alpha has been associated with a potential mediator of sex predisposition in RHD. [74] In the current study, two female patients aged 11 and 13 years presented with symptomatic rheumatic MS at 6 and 8 years respectively. Similarly, other studies report that MS in Africa shows a female predominance with the early presentation in life. [3,4] These findings underscore a need for screening (as a cost-effective measure) for sub-clinical RHD (e.g. among the risky population), as recommended by the World Heart Organization, as an effective way to detect the disease in the early stage when secondary prophylaxis can be administered. [75] In a recent publication of a clinical trial from Uganda confirmed the prevention of progression of sub-clinical RHD disease among children given secondary prophylaxis. [76] In the current study, 4 (9.3%) patients were firstly diagnosed with RHD during pregnancy. They all had uneventful spontaneous vertex deliveries before intervention. Similarly,

other African studies have shown that it is not uncommon to discover patients with RHD during pregnancy and delivery, most presenting with heart failure symptoms. [42,77] In Africa, RHD in pregnancy is becoming detected increasingly accounting for up to 30% of heart diseases in pregnancy and is associated with poor outcomes for the mother and the baby. [42,78,79] The 2018 European Society of Cardiology (ESC) guidelines on the management of cardiovascular diseases during pregnancy recommend performing risk assessment in all women of childbearing age with cardiac diseases using the modified World Health Organization (WHO) classification (class I- IV) of maternal risk. [80] Pregnancy is contraindicated in patients who fall in class IV. Another important observation from this study is that, most of the patients recruited in the Tanzania Mitral Stenosis study came from the Northern zone of the country. Similarly, anecdotal data shows that RHD is prevalent in the Northern part of Tanzania. However, this observation needs proper investigation in disease mapping as it could be a potential source of information for use in preventive measures.

5. STRENGTHS AND LIMITATIONS

The study has several advantages. Firstly, being a prospective study, there was a potential for follow-up of these patients. Secondly, it provides baseline data for future comparisons. Third, lessons learnt could benefit the East Africa region and beyond. The small sample size could not allow detailed analysis. However, we have described several parameters known to influence PBMV outcomes. Owing to a possible effect of small number of patients who undergone PBMV on skill transfer to the local team, our team is having several strategies. First, to continue collaborating with the visiting team, the latest mission was conducted from 23rd – 26th October 2022 in which five PBMV were performed. Second, two cardiologists will be going to Cleveland, USA, for a six months attachment in order to strengthen their skills. This approach had been done in Uganda and proved to be successful. [58] Third, our Cath lab is equipped with a system that is supporting remote proctoring of interventional procedures. This will allow ongoing supervision of a local team from our collaborators. Lastly, our team was involved in the Africa PBMV workshop held in Tunisia from 24th – 25th August 2022. [61] The workshop aimed at building sustainable PBMV programs across African countries.

6. CONCLUSION AND RECOMMENDATIONS

TEE should be done on all patients before PBMV to rule out LA thrombus. Despite a higher Wilkins score, PBMV can be done successfully among patients with rheumatic MS carefully screened by the heart team. Patients in Atrial fibrillation and with LA >

55mm should be anticoagulated. The ESC and AHA/ACC guidelines (Wilkin score ≤ 8) for a good outcome of PBMV need reconsideration. PBMV services should be available in catheterization laboratories in Africa. Enhancing and consolidating PBMV skills among the local team should be undertaken.

ABBREVIATIONS

AF -Atrial Fibrillation
ACC -American College of Cardiology
AHA -American Heart Association
ESC -European Society of Cardiology
INR -International Normalized Ratio
JKCI -Jakaya Kikwete Cardiac Institute
LA -Left Atrium
LASEC -Left Atrial Spontaneous Echo Contrast
LMICs -Low- and Middle-Income Countries
MS -Mitral Stenosis
MVA -Mitral Valve Area
MVR -Mitral Valve Replacement
PBMV -Percutaneous Balloon Mitral Valvuloplasty
TEE -Trans Esophageal Echocardiography
TTE -Trans Thoracic Echocardiography
RHD -Rheumatic Heart Disease

DECLARATION

Ethical approval and consent to participate

The study was approved by the Directorate of Research and Publications of Muhimbili University of Health and Allied Sciences (P. MUHAS – REC-9-2019-059). Participants gave the consent to participate.

Consent for publication

We obtained permission for the photographs used.

Availability of data and material

The data will be available to the readers upon reasonable request.

Competing interests

The authors declare no competing interests associated with this work.

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Authors' contributions

RKM: conceptualization, methodology, investigation, formal analysis, and writing original manuscript; **MJC, PC, GK, AK, SC:** supervision, formal analysis, visualization, manuscript review and editing; **JG:** investigation, supervision, formal analysis, manuscript writing and editing; **EK, AL, ABJ, DN, SM, SM, HM, CEN, PK, MJ, NBV, AB, MA**: investigation, manuscript review and editing. All authors have read and approved the manuscript.

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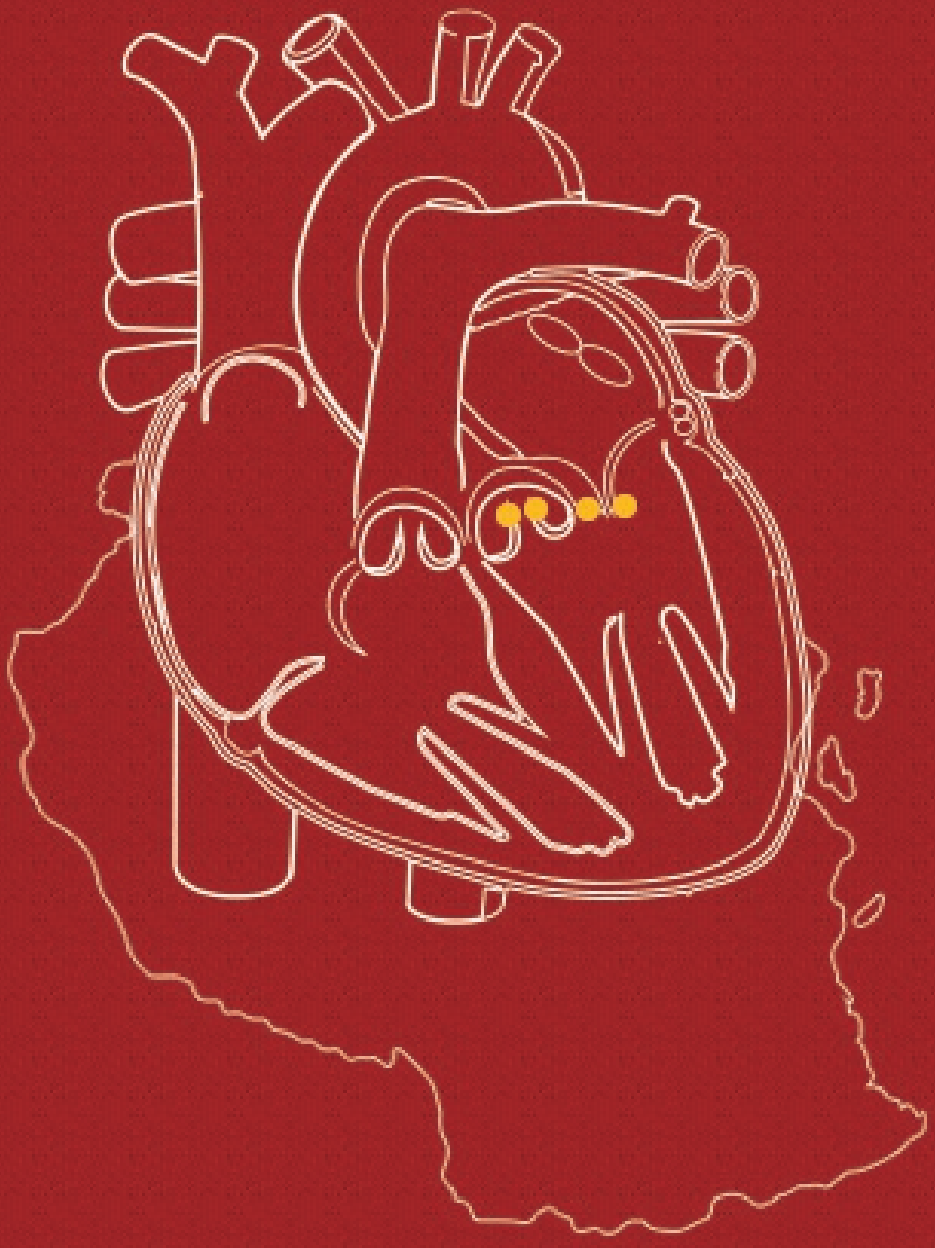
PART III

Progress in the management of rheumatic heart disease



CHAPTER 8

Predictors of early operative mortality for rheumatic heart disease at Muhimbili National Hospital

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ABSTRACT

BACKGROUND

Rheumatic heart disease (RHD) is endemic in Tanzania. It is ranked third among the most common causes of heart failure after hypertensive heart diseases and cardiomyopathies. This study aimed to determine the predictors of early operative mortality for RHD at Muhimbili National Hospital, Tanzania.

METHODS

This retrospective cross-sectional study of 212 patients operated due to RHD from May 2008 to December 2012. Patients' demographic and clinical data at admission and within 30 days of the index elective cardiac surgery were recorded in a predefined clinical record form. Data were entered and analysed using Statistical Package for Social Sciences version 24 and STATA version 13. The Chi-square and Fisher's exact tests were utilized to compare categorical variables. Variables with a p-value <0.2 at bivariable analysis were included in a multivariable modified Poisson regression model.

RESULTS

Out of 212 patients, 140 (66%) were females. The median age was 21 years (interquartile range 15 – 32 years). One hundred and forty-five (68.4%) patients underwent valve replacement, out of which 113 (77.9%) were single (mitral), 17 (11.7%) aortic, and 15 (10.4%) double (aortic and mitral) valve replacement. Valve repair was done in 42 (19.8%) patients, of which 41 were mitral and one aortic. Surgical mitral commissurotomy was performed in 25 (11.8%) patients. Thirty (14.1%) patients died in-hospital. In multivariable analysis, mortality was more than five times higher among patients who underwent double than single valve replacement {adjusted prevalence ratio (95% CI) = 5.65 (2.46-12.99), p < 0.001}. The patient's age, disease duration, ejection fraction, surgical modality, pulmonary hypertension, intensive care unit stay were not predictors of mortality.

CONCLUSION

The in-hospital mortality observed in this study was higher than those reported in previous studies. In patients with RHD, double valve replacement is associated with increased early mortality, which may require greater technical expertise and careful postoperative management. Our findings need to be confirmed in prospective studies.

KEYWORDS

Predictors; early mortality; rheumatic heart disease; cardiac surgery; intensive care unit.

INTRODUCTION

Rheumatic heart disease (RHD) is an important cause of cardiac morbidity and mortality among children and young adults, affecting an estimated 15.6 million people yearly and responsible for up to 300,000 deaths each year worldwide.[1] The disease is prevalent in developing countries, including sub-Saharan Africa, where the prevalence is as high as 1 – 3 for every 100 school children.[2,3] The most common clinical presentations are heart failure, pulmonary hypertension (PHT), atrial fibrillation, stroke, and infective endocarditis, all of which are factors signifying late presentation of patients to health facilities and/or delayed appropriate management.[4,5] Some of them are too late to be candidates of valvular interventions.[6–8] In studies done in Uganda, about 50% of newly diagnosed RHD patients presented with complications.[9,10]

Guidelines on the management of valvular heart diseases recommend valve surgery for clinically significant valve lesions.[11,12] However, most of these patients are likely to be managed conservatively in developing countries. Okello et al[13] found that out of 551 patients evaluated from the Uganda RHD Registry, 398 (72.3%) required invasive intervention, with 332 (60.3%) patients requiring surgery. Only 153 (27.7%) required medical management. Instead, 498 (90.4%) of the patients were on medical treatment. Of the 60.3% requiring surgery, only 44 (8.0%) patients underwent valvular surgery. Since the treatment of advanced forms of RHD is cardiac surgery, policymakers should improve access to cardiac surgery with simultaneous availability, affordability, and accessibility of medications for treating RHD complications such as heart failure.[14–18]

Several factors are known to affect the outcome of cardiac surgery for RHD.[8,19–24] Preoperative cardiac status of the patient such as advanced age, New York Heart Association (NYHA) class III-IV, PHT, left ventricular ejection fraction (LVEF) < 50%, and a large left atrium were found to be predictors of mortality.[22,25,26] Intraoperative predictors of early mortality include the duration of aortic cross-clamp, total surgical time, and cardiopulmonary bypass.[19,22–24,26] Double valve replacement (DVR), although technically difficult, offers excellent symptomatic relief and better late survival similar to that of single valve replacement (SVR).[22,23] It is important to recognize this because, in regions with a high prevalence of RHD, about 50% of patients have multivalvular involvement.[27,28] Post-operatively, low cardiac output syndrome, bleeding, thromboembolism, sepsis, and prosthesis-related complications are among the predictors of mortality.[19,21,24,29] Although the decision to repair or replace rheumatic mitral valve disease is controversial,[30] recent[31,32] and previous[8,33,34] publications have demonstrated that repair is superior to replacement for mortality and valve-associated complications. A recent review has reported that mitral valve repair may only outperform replacement in carefully selected patients as progressive valve deterioration and calcification may result

in valves that cannot be optimally repaired.[35]

This study aimed at reporting the predictors of early mortality in a relatively large sample of 212 RHD patients who underwent cardiac surgery at Muhimbili National Hospital (MNH) over a period of four years.

METHODS AND PARTICIPANTS

STUDY DESIGN, SUBJECTS, AND SETTING

This was a retrospective cross-sectional study of 212 patients who were admitted at MNH for cardiac surgery due to RHD, from May 2008 to June 2012. MNH is a tertiary referral and teaching hospital located in Dar es Salaam city. Dar es Salaam, the largest commercial city in Tanzania, had a population of nearly 5 million in 2012.[36] MNH cardiac unit used to receive referred cardiac patients from all regions of Tanzania. Open-heart surgery started at MNH in May 2008. Referred patients for assessment and listing for open-heart surgery were initially admitted in medical wards and perioperatively were cared for in the hospital intensive care unit (ICU) and cardiac wards. From the year 2012, cardiac surgeries have been performed at Jakaya Kikwete Cardiac Institute.

DATA COLLECTION PROCEDURES

Data were collected from medical ward admission books, operation books, and patients' files from hospital medical records. Information obtained was filled on a predefined clinical record form comprising of social demographics (age, sex, level of education, marital status, residential area, and employment); history and physical findings (symptoms and signs, duration of symptoms, co-morbidities, and a diagnosis made); investigations [chest X-ray, echocardiogram, electrocardiogram, and laboratory tests].

In all of the recruited patients, certified cardiologists performed echocardiograms. Before surgery, the valve team holds a clinical meeting to discuss each patient to reach a consensus for the operation. The hospital operates on RHD patients as per guidelines for the management of valvular heart disease.[11,12] Patients who had RHD but who underwent cardiac surgery for other cardiac conditions were omitted. We also excluded patients who were missing pulmonary arterial pressure records.

Operative technique

Local cardiac surgeons performed all surgeries on an elective basis. The general approach for surgery was median sternotomy with aortocaval (mitral/double valve surgeries) or aortic and two-stage cavoatrial cannulation (isolated aortic valve surgery) for cardiopulmonary bypass; cooling to 30-32^{0}C; antegrade (mitral valve surgeries); and

coronary ostial (multiple/aortic valve surgeries) St. Thomas' Hospital solution cardioplegia administration every 20-25 minutes. Sondergaard groove was used for approaching the mitral valve and J incision into the non-coronary cusp for the aortic valve surgeries. For securing the prosthetic valves, an interrupted suture technique was used. For patients who underwent valve replacement, mechanical heart valves were used.

Bilateral commissurotomy with chord-papillary preservation was a manoeuvre for open mitral valvotomy. Mitral valve repair was accomplished by the application of an annuloplasty ring, posterior mitral leaflet augmentation, and chordal splitting. For closed mitral valvotomy, the left atrial appendage was approached through the left anterolateral thoracotomy and the 4th intercostal space. The appendage was opened and the index finger was introduced through the opening and onto the stenotic mitral valve for dilatation.

FOLLOW-UP

We recorded the type and number of valve surgeries performed, the duration of stay in ICU, post-operative echocardiography, post-operative complications (surgical site infection, thromboembolism, endocarditis, anticoagulant-related bleeding), duration of in-hospital stay, and mortality at 30 days.

DEFINITION OF TERMS

This study defined PHT from echocardiography measurements as Right Ventricular Systolic Pressure > 35mmHg as determined by the peak systolic gradient across the tricuspid valve regurgitation.[37]PHT was classified as mild (35 – 50mmHg), moderate (50 – 70 mmHg), and severe (>70 mmHg). Early (operative) mortality was defined as death (in-hospital) within 30 days after index elective cardiac surgery, as recommended from the guidelines for reporting morbidity and mortality after cardiac valvular operations of the American Heart Association for thoracic and cardiovascular surgery.[38]SVR was defined as the replacement of the mitral valve alone, while DVR was a combined replacement of the mitral and aortic valve.

DATA MANAGEMENT AND ANALYSIS

The collected data were checked for quality and coding was done before entry. Two different people entered the data twice and checking was done to ensure no double entry or wrong entry. The analysis was done using Statistical Package for Social Sciences version 24.0 and STATA version 13. The factors analysed as predictors of mortality include duration of disease, age, sex, employment, LVEF, type of valvular lesion, PHT, the modality of surgery, number of the replaced valve(s), and the duration of ICU stay. Continuous data were presented as mean with standard deviation when distributed normally and as median with range when skewed. Discrete data were given as counts

and percentages. Chi-square and Fisher's exact tests were utilized to compare categorical variables. Variables with a p-value <0.2 at univariable modified Poisson regression were included in the multivariable modified Poisson regression model. The factors which were analysed in the multivariable regression model were duration of disease,age of the patient, LVEF, PHT, the modality of surgery, number of the replaced valve(s), and the duration of ICU stay. With each of the analyses, a p-value <0.05 was considered statistically significant.

ETHICAL CONSIDERATION

Ethical clearance to conduct the study was obtained from the research and publications committee of MUHAS (Ref. No. MU/PGS/SAEC/Vol.VI). MNH provided permission to conduct this study.

RESULTS

During the period of 4 years from May 2008 to June 2012, a total of 285 RHD patients were admitted and assessed for eligibility for cardiac surgery at MNH. Out of these, 240 (84.2%) had their pulmonary pressures recorded, with 212 (74.4%) of them being operated on.Twenty-eight patients were not operated on because they were not fulfilling the criteria for surgery which are adhered to by the hospital.[11] Data on pulmonary arterial pressure was missing in 45 (15.8%) patients, as shown in Fig 1.

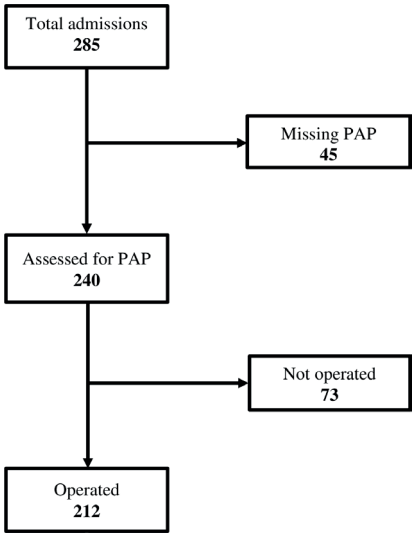

Fig 1. Consort diagram of RHD patients admitted at MNH cardiac unit from 2008 to 2012.
PAP = Pulmonary arterial pressure

The median age of the patients at the time of operation was 21 years (interquartile range: 15-32). About half of the patients were under the age of 20 years. There were 140 females and 72 males, giving a female/male ratio of 2:1. A majority, 176 (83%) of patients were not employed and 157 (74.1%) attained primary education. About two-thirds of the patients were residing outside of Dar es Salaam. The socio-demographic characteristics of the study population are presented in Table 1.

Table 1. Socio-demographic characteristics of patients operated for RHD at MNH cardiac unit from May 2008 to June 2012.

Variable	Median (IQR)/Frequency (%)
Age (years)	21 (15 – 32)
Age groups (years)	
< 20	105 (49.5)
21 – 40	83 (39.2)
41+	24 (11.3)
Sex	
Female	140 (66.0)
Male	72 (34.0)
Education level	
None/informal	23 (10.8)
Primary	157 (74.1)
Secondary	32 (15.1)
Employment status	
Employed	36 (17.0)
Not employed	176 (83.0)
Residence	
Dar es Salaam	76 (35.8)
Outside Dar es Salaam	136 (64.2)

IQR = Interquartile range

As per valvular lesions, 79 (37.3%) and 45 (21.2%) patients had pure mitral regurgitation and mitral stenosis (MS), respectively. Twenty-five (11.8%) had combined mitral regurgitation and MS, while 27 (12.7%) patients had combined mitral and aortic valve regurgitation as expressed in Fig 2.

The median (interquartile range) duration of symptoms was 36 (12 - 72) months. More than 95% of the patients had normal white blood cell counts and haemoglobin levels. PHT was detected in 178 (84%) patients. A majority, 182 (85.8%) of the patients, had normal LVEF. Valve replacement was done in 145 (68.4%) patients, out of which 113 (77.9%) were mitral, 17 (11.7%) aortic, and 15 (10.4%) double (aortic and mitral) valve replacement. Valve repair was done in 42 (19.8%) patients, of which 41 were mitral and one aortic. Surgical mitral commissurotomy was performed in 25 (11.8%) patients, out of which 5 and 20 were open and closed commissurotomies, respectively. De Vega tricuspid valve annuloplasty was done in 56 (26.4%) patients and tricuspid ring annuloplasty in 26

(12.3%) patients. Nearly a third, 62 (29.2%), of the patients stayed in ICU for more than five days. Clinical characteristics of the patients are depicted in Table 2.

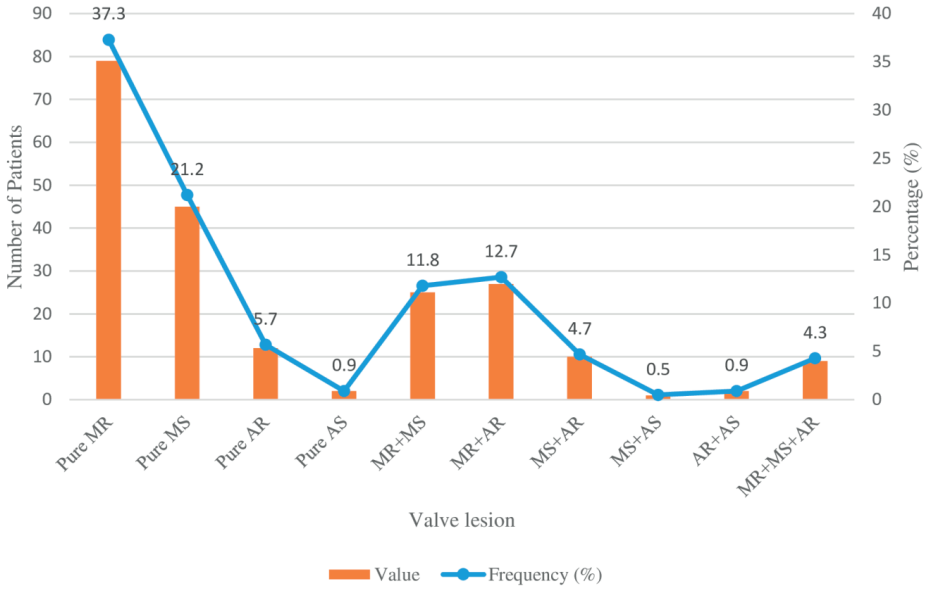

Fig 2. Categories of primary pathologies of the valve
MR = mitral regurgitation, MS = mitral stenosis, AR = aortic regurgitation, AS = aortic stenosis

Table 2. Clinical characteristics of patients operated for RHD at MNH cardiac unit from May 2008 to June 2012

Variable	Mean (±SD)/Frequency (%)
Median (IQR) duration of symptoms (months)	36(12- 72)
Duration of symptoms categories (months)	
< 24	96 (45.3)
24 – 60	46 (21.7)
60+	70 (33.0)
Mean White blood cell count (x10^9/L)	7.02 (±2.60)
Proportion with Abnormal WBC count	11 (5.2)
Mean Hemoglobin level (g/dl)	12.67 (±2.16)
Proportion with anemia	10 (4.7)
Mean Pulmonary Pressure (mmHg)	50.04 (±16.59)
Proportion with Pulmonary hypertension	178 (84)
Grades of Pulmonary arterial pressure	
Normal	34 (16)
Mild	62 (29.2)
Moderate	73 (34.4)
Severe	43 (20.3)
Mean Left Ventricular EF (%)	54.93 (±6.84)

Table 2. Continued.

Variable	Mean (±SD)/Frequency (%)
Proportion with reduced EF	30 (14.2)
Valve surgery modality	
Mitral valvotomy	25 (11.8)
Mitral/aortic valve replacement	145 (68.4)
Mitral/aortic valve repair	42 (19.8)
Number of replaced valve (s)*	
Single	128 (88.3)
Double	17 (11.7)
Mean duration of ICU stay (days)	5.2 (±3.1)
Proportion with ICU stay of ≥5 days	62 (29.2)

IQR: Interquartile range; WBC = White Blood Cell Count; EF = Ejection Fraction; ICU = Intensive Care Unit
**Valve replacement were single (mitral) or double (mitral and aortic) among 145 patients*

The in-hospital mortality occurred in 30 (14.1%) patients, out of which 22 (73.3%) deaths occurred in ICU. Of the demographic characteristics (Table 3), there was comparable mortality among males and females, {prevalence ratio (PR)=1.30, 95% CI (0.66–2.54)}; individuals with longer duration (≥24 months) of symptoms 19 (16.4%) and those with a shorter duration 11 (11.5%), p=0.241; younger patients of <20 years of age 10 (9.3%) compared to those with ≥20 years 20 (19.0%), p=0.65; and among unemployed compared to employed patients {PR= 1.33 (0.49–3.59)}.

Patients with mitral regurgitation had comparable mortality to patients without mitral regurgitation, {PR= 1.13 (0.46–2.76)} and patients with mitral stenosis compared to those without mitral stenosis, {PR= 0.84 (0.43–1.64)}. The mortality was comparable among patients with PHT and without PHT {PR= 2.67 (0.67–10.74)}. In terms of the severity of PHT, the mortalities were 14 (22.6%) in the mild, 8 (11%) in the moderate, and 6 (14%) in the severe group, p=0.122. Mortality was comparable among individuals with LVEF < 50% and with LVEF < 50% {PR= 0.21 (0.03 – 1.49)}. Patients who underwent valve repair had high mortality 10 (23.8%) when compared to patients who underwent valve replacement 19 (13.1%) or valvotomy 1 (4%), p=0.080. Mortality was higher among patients who underwent DVR than SVR {PR= 4.39 (2.00 – 9.64)} and among patients who had a longer ICU stay than a shorter ICU stay {PR= 2.42 (1.26 – 4.65), p=0.007}. There was no significant difference in mortality among patients with 7 (15.6%) and without 10 (16.9%) atrial fibrillation as well those with dilated 23 (14.0%) and without 2 (10.5%) dilated left atrium. The only independent predictor of early mortality was to be undergoing double (compared to single) valve replacement, adjusted prevalence ratio (APR) [95% CI] = 5.65 (2.46-12.99), p < 0.001}. The clinical characteristics predicting early mortality are shown in Table 3.

Table 3. Predictors of early operative mortality for rheumatic heart disease at MNH

Variable	Total, N = 212	Mortality, n (%)	Bivariate analysis		Multivariable analysis	
			PR (95% CI)	p-value	Adjusted PR (95% CI)	p-value
Sex						
Female	140	18 (12.9)	1			
Male	72	12 (16.7)	1.30 (0.66–2.54)	0.451		
Symptoms (months)						
<24	96	11 (11.5)	1		1	
24- 60	46	10 (21.7)	1.89 (0.87–4.15)	0.109	1.03 (0.33-3.27)	0.956
61+	70	9 (12.9)	1.12 (0.49–2.57)	0.785	2.04 (0.65-6.39)	0.220
Age (years)						
<20	105	20 (19.0)	1		1	
21- 40	83	6 (7.2)	0.38 (0.16–0.90)	0.029	0.44 (0.15-1.29)	0.135
41+	24	4 (16.7)	0.88 (0.33–2.33)	0.789	0.94 (0.28-3.15)	0.926
Employment						
Employed	36	4 (11.1)	1			
Not employed	176	26 (14.8)	1.33 (0.49–3.59)	0.574		
Mitral regurgitation						
No	72	7 (9.7)	1			
Yes	140	23 (16.4)	1.13 (0.46–2.76)	0.794		
Mitral stenosis						
No	122	20 (16.4)	1			
Yes	90	10 (11.1)	0.84 (0.43–1.64)	0.614		
Presence of PHT						
No	34	2 (5.9)	1			
Yes	178	28 (15.7)	2.67 (0.67–10.74)	0.165		
LVEF (<50%)						
No	182	29 (15.9)	1		1	
Yes	30	1 (3.3)	0.21 (0.03–1.49)	0.118	0.20 (0.03-1.17)	0.075
Valve surgery modality						
Mitral valvotomy	25	1 (4.0)	1			
MV/AV replacement	145	19 (13.1)	3.28(0.46-23.49)	0.238		
MV/AV repair	42	10 (23.8)	5.95(0.81-43.98)	0.080		
Replaced valve (s)*						
SVR	128	12 (9.4)	1		1	
DVR	17	7 (41.2)	4.39(2.00– 9.64)	<0.001	5.65 (2.46 12.99)	<0.001
Prolonged ICU stay (5 days)						
No	150	15	1		1	
Yes	62	15	2.42 (1.26–4.65)	0.007	1.36(0.55 – 3.38)	0.510

PR: prevalence ratio; APR: adjusted prevalence ratio; CI: confidence interval; PHT: pulmonary hypertension; LVEF: left ventricular ejection fraction; MV: mitral valve; AV: aortic valve; SVR: single valve replacement; DVR: double valve replacement; ICU: intensive care unit

**Valve replacement were single (mitral) or double (mitral and aortic) among 145 patients*

DISCUSSION

This study reports an in-hospital mortality rate of 14.1% (30/212). Our findings are slightly similar to that reported by Prashant et al[24] and lower to that reported by Nyawawa et al[19] in which mortality rates were 11.3% and 24% respectively. However, other studies reported lower mortalities of 2.5% by Pillai et al,[39] 3.8% by Akhtar et al,[23] 4% by Panda et al,[22] and Sharma et al,[40] 4.4% by Debel et al,[21] 8% by Gupta,[26] and 9.2% by John et al.[29] The observed differences in mortality from these studies could be explained by the difference in the type of the study population: DVR alone;[22,24–26,29,39] DVR, aortic valve replacement and SVR;[19,21,23,40] and valve repair.[8,19,21] The experience of the operating surgeon[19,21,26] and technical issues can also explain the differences in mortality.[21,26,29] The mortality rate of 24% reported in a 1-year experience of RHD surgeries after the inauguration of cardiac surgery at MNH had dropped over a period of four years.[19]

Our study showed that in RHD patients, DVR imposes a significantly higher early mortality than SVR. Similarly, Akhtar et al[23]observed higher in-hospital mortality in the DVR group (4.2%) than the SVR group (3.5%), while Panda et al[22] reported a mortality rate of 4%. On contrary, Sharma et al[40] did not report any 30 days mortality from the DVR group while Pillai reported it at a lower rate of 2.5%. The hospital mortality rate of DVR ranges from 5 – 15%.[22,23] The strikingly higher mortality of 42% observed in our DVR group could be explained by several reasons. Firstly, our patients had a longer duration of symptoms, it could be possible that these patients had a more advanced disease as it was previously reported in a study done at the same institution in which at presentation 80% of the patients were in NYHA class III and IV.[19] Secondly, cardiac surgeries were newly established at the hospital and skills and expertise among the operating team was likely inadequate. Thirdly, our sample size was smaller compared to those of the cited studies. Lastly, there were differences among studies population such that while some studies included DVR alone;[22,24–26,29,39] others involved DVR, aortic valve replacement and SVR;[19,21,23,40] and valve repair.[8,19,21] DVR, although technically challenging, has been advocated as a standard surgical option in patients requiring surgery for combined rheumatic mitral and aortic valve disease.[22,23] It is essential to recognize this because, in regions with a high prevalence of RHD, about 50% of patients have multivalvular involvement.[27,28] Moreover, these patients are young and present with severe disease at the time of presentation; hence a DVR is a preferred surgical modality.

This study revealed a higher mortality rate among patients with < 20years than those with more than 20 years of age. On the contrary, advanced age has been reported in several studies to predict mortality following cardiac surgery.[22,25,26] The high mortality observed in young individuals in our study could be explained by the fact that RHD in developing countries presents at an early age with already advanced disease.[4,5]

Our patients had a longer duration of symptoms with a median of 36 (12 - 72) months. The mortality was higher among patients with a longer duration of symptoms. It could be possible that these patients had a more advanced disease as it was previously reported in a study done at MNH in which at presentation 80% of the patients were in NYHA class III and IV.[19] It can be postulated that the longer the disease duration the higher the chance of myocardial tissue remodelling.

Our study has shown a comparable mortality rate between patients with PHT and those without PHT (15.7% vs 5.9%, p=0.176). Debel et al[21] reported that three out of five deaths that occurred in their cohort had severe PHT. Also, in the current study, mortality was comparable between patients with mild PHT to those with moderate and severe PHT. Other studies have reported a significant association between PHT and mortality post-cardiac surgery for RHD.[22,25,26] However, most of these studies analysed the association of PHT with long-term mortality.

In our study, LVEF was not a predictor of early mortality. This finding is similar to what was observed by Nyawawa et al,[19] who concluded that the mere presence of suboptimal ventricular dysfunction should not contraindicate cardiac surgery. However, our findings should be cautiously interpreted because of a few patients with a low LVEF. In contrast to other studies,[22,25,26] LVEF <50% has been found to predict mortality post-cardiac surgery for RHD.

This study showed a mortality of 23.8% among patients who underwent valve repair compared to valve replacement (13.1%) and valvotomy (4%). Similarly, Nyawawa et al reported that mitral valve repair accounted for 64.3% of all deaths and concluded that it requires special consideration.[19] In a situation like this, where cardiac surgeries had just begun, skills and expertise must be acquired to reach acceptable outcomes post mitral valve repair. In contrast, Debel et al[21] found no death among patients who underwent mitral valve repair. The authors argued that they were too sceptical about mitral valve repair because the valves were calcified, and the durability of repaired valves in a setting with resource constraints is an issue.[21] The benefits of mitral valve repair have been established,[33,41] it offers better early and late survival and it is important to patients who do not require oral anticoagulants. In sub-Saharan Africa, managing a patient with a mechanical valve is challenging in terms of anticoagulants and monitoring of the International Normalized Ratio.[8,42] However, owing to the less durability of valve repair, advocating it in resource-constrained countries in which redo surgery is challenging remains debatable. The recommendations from a recent review is that in low- and middle-income countries mitral valve repair for RHD patients should be considered.[35] The authors suggested several approaches aiming at increased exposure and training in rheumatic valve surgery by initiating international bilateral collaboration in endemic

areas, visiting cardiovascular surgeons from endemic areas, simulation methods of teaching, and courses by professional organizations.[35]

In this study, mortality was higher among patients with a longer duration of ICU stay. This is similar to what was observed in the previous study in which mortality was higher among patients who stayed longer in ICU.[19] The authors argued that longer ICU stay was influenced by the total surgical time and the aortic cross-clamp duration. Similarly, other studies have reported a significant association between mortality with surgical time, aortic cross-clamp duration, and cardiopulmonary bypass.[22–24,26]There was no difference among patients who stayed shorter or longer in ICU in terms of the mean age, mean duration of symptoms, female sex, lower LVEF, pulmonary hypertension, and the modality of surgery. Therefore, it could be possible that the duration of ICU stay was driven by the intraoperative factors as previously elucidated.[19]

Despite the fact that cardiovascular disease remains the leading cause of morbidity and mortality globally, six million people have no access to timely, safe, and affordable cardiac surgery services when required.[43] As reported in several recent publications, there is a need of improving access to cardiac care services for RHD in sub-Saharan Africa.[16–18] With the increase in the coverage of interventions targeting RHD/acute rheumatic fever spectrum i.e primary, secondary, and tertiary prevention could prevent about 74,000 deaths from RHD and acute rheumatic fever from 2021 to 2030 in the African Union (AU).[16] From an economic perspective, if secondary and tertiary care interventions for RHD were scaled up, there would be a net benefit of US $ 2.8 billion for the AU through 2030.[16] Emmy Okello et al[17] stated in their comment on Coates et al study[16] that “scaling up tertiary intervention measures in the AU is achievable, but will need multisectoral involvement”. By strengthening local health systems through investing in domestic services for heart surgery rather than referring patients abroad for treatment, governments of low and middle income countries can save millions of dollars every year. [44] However, that will only happen if there is a good political will and commitment, better understanding and availability of funds.[18]

In developing countries, patients’ selection and the choice of valvular surgery are among the important issues to take into consideration because patients come late with a severe presentation of the disease. There are no local guidelines in our setting that could probably fit our patients’ presentation with treatment outcomes. In Tanzania, from the year 2018 cardiac surgeries are solely performed at Jakaya Kikwete Cardiac Institute. Anecdotal data shows that the annual mortality following cardiac surgery for RHD at Jakaya Kikwete Cardiac Institute is < 4%. Our study findings show a milestone from the establishment of a cardiac centre towards success in offering a state-of-the-art cardiac service.

STUDY LIMITATIONS AND STRENGTHS

This study has all the inherent limitations of a retrospective study. Firstly, missing/incomplete information like co-morbidity variables. For heart failure and NYHA functional class, LVEF was taken as a surrogate measure. Patients with missing/incomplete data could have predictive factors for early mortality. Other comorbidities were reported in small numbers and could not allow for detailed analysis. Secondly, we could not analyse intraoperative variables (such as total operation time, cardiopulmonary bypass time, and aortic cross-clamp time) and postoperative complications (congestive cardiac failure, arrhythmias, wound infection, and acute respiratory distress syndrome). However, the influence of those variables on patients' outcomes was previously analysed at the same institution,[19] albeit a small sample size of that study. Thirdly, our multivariable model is over-adjusted because we included ICU stay (an outcome) as a predictor. The strengths of our study are the relatively bigger sample size and the ability to contribute to the findings of the study which was previously done at the same institution. Although most of the variables that are known to influence early mortality post-cardiac surgery were not statistically significant, we believe that they are clinically significant to be considered upon the selection of candidates for valvular interventions.

CONCLUSION AND RECOMMENDATION

The in-hospital mortality observed in this study is higher compared to those reported in previous studies. In patients with RHD, double valve replacement is associated with increased early mortality, which may require greater technical expertise and careful postoperative management. Prospective studies with larger samples are needed to confirm these findings and explore the determinants of early and late mortality among such patients. There is a need for local guidelines for the management of these patients.

CONFLICT OF INTEREST

None declared

AUTHORS' CONTRIBUTION

RKM: was involved in designing the study, data collection and analysis, and manuscript writing; BAK and AM: statistical analysis; MC, SC, EN and PC: manuscript writing; BT: was involved in data management, statistical analysis and manuscript writing; JL: study design and manuscript writing.

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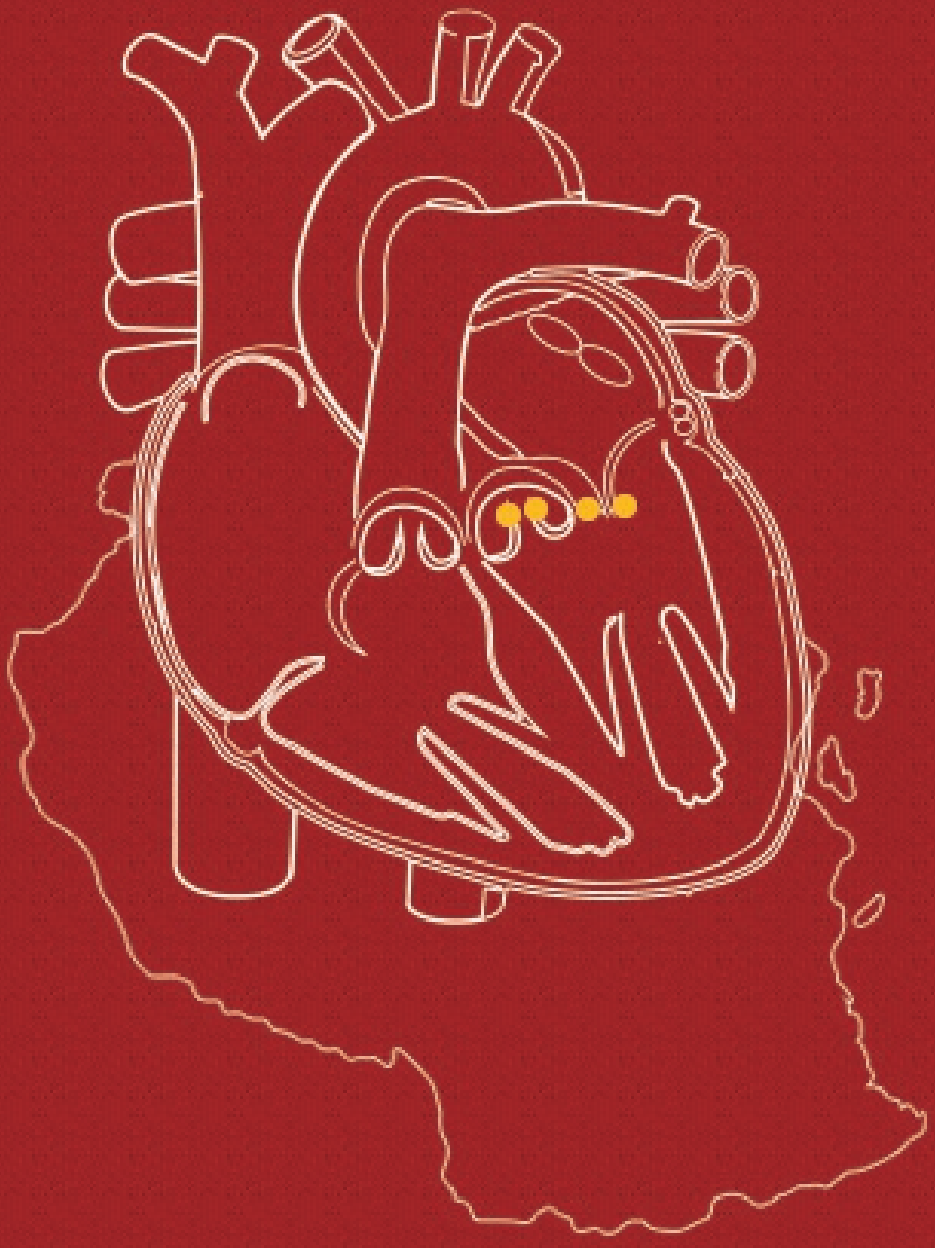

CHAPTER 9

Health related quality of life of patients following mechanical valve replacement surgery for rheumatic mitral stenosis in Tanzania

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ABSTRACT

BACKGROUND

The assessment of outcomes of interventions based on the patient's perspective using patient-reported outcome measures (PROMs) has been increasingly highlighted in clinical practice. However, health related quality of life (HRQoL), one of the common constructs measured by PROMs remain unknown among patients after heart valve replacement (HVR) in Tanzania.

OBJECTIVES

To assess the HRQoL amongst patients operated on for rheumatic mitral stenosis at Jakaya Kikwete Cardiac Institute (JKCI).

METHODS

A prospective study of patients operated on due to rheumatic mitral stenosis at JKCI from January 2020 to April 2021 was undertaken. The HRQoL was assessed by using the MacNew questionnaire, addressing three domains (physical, emotional, and social function); the score ranges from 0 - 7. We categorized HRQoL as low (mean score ≤ 4.9), moderate (5 - 6) and high (>6). We analysed several sociodemographic and clinical variables for HRQoL.

RESULTS

Out of 54 patients, there were 34 females and 20 males. Their mean (±SD) age was 37.98 (±12.58) years. The reliability of translated Kiswahili version of MacNew was good. The mean (±SD) global scores were 3.47 ± 0.59, 4.88 ± 0.71 and 6.14 ± 0.50 preoperatively, at 3 months and 6 months respectively (p-values <0.001 preoperatively vs 3 months, preoperatively vs 6 months and at 3 months vs. 6 months). The median of individual mean difference HRQoL score pre-operatively and at 6 months was 2.67. The preoperative and 6 months mean difference HRQoL scores were higher among patients with vs without atrial fibrillation (2.95 ± 0.59 vs 2.45 ± 0.53, p=0.003) and those on anticoagulants (preoperatively) vs not on anticoagulants (3.14 ± 0.58 vs 2.57 ± 0.57, 0.009). The mean difference HRQoL scores were similar for sociodemographic and other clinical parameters, including those with stroke vs without stroke.

CONCLUSION

Six months after HVR the overall MacNew HRQoL scores improved markedly. This improvement in HRQoL was regardless of the presence of comorbidities (e.g. stroke and atrial fibrillation) which underscores the importance of considering valvular surgery if they fit the criteria. Clinicians and researchers in low-resource settings should collaborate to promote the utilization of PROMs in the routine care of patients.

KEYWORDS
Rheumatic heart disease; patient-reported outcome measures; health related quality of life; interventions

1. INTRODUCTION

Rheumatic heart disease (RHD) continues to be among the causes of cardiac morbidity and death among school children and young adults in Africa and the third most common cause of heart failure after hypertension and cardiomyopathy. (1) The prevalence of RHD in this region is as high as 1 – 3 for every 100 school children. (2,3) Although it has been reportedly eradicated in developed countries; globalization, refugee crises and migration have led to its evolution resulting in a global health problem. (4–6)

In sub-Saharan Africa, patients present late in hospital with advanced stage of RHD requiring interventions such as heart valve replacement (HVR). (7–9) Effectiveness of surgical interventions such as HVR has been traditionally assessed based on morbidity and mortality outcomes. (10,11) However, the impact of these interventions on the patient's perspective assessed by patient-reported outcome measures (PROMs) is as well an important component of effectiveness as the symptomatic and functional status improvement. (12,13) To recognize this, the American Heart Association (AHA) included health related quality of life (HRQoL) assessment as part of the treatment-impact objective for cardiac health. (12) HRQoL, one of the common constructs measured by PROMs is defined by AHA as the discrepancy between actual and desired functional status and an overall impact of health on well-being. (14) In the past two decades, PROMs have been increasingly implemented in clinical practice in countries outside of Africa. (13,15)

PROMs can be broadly divided into generic or disease-specific. (16) Generic PROMs are widely applicable and can be utilized for comparison with the general population or with patients with different characteristics or diseases. An example of generic PROMs is Short Form-36 (SF-36). (17) Disease-specific PROMs include questions on specific health problems hence making them more sensitive to small and probably important changes in the quality of life for the patient. (18) With this advantage, disease-specific PROMs are popular among healthcare providers. (16) Example of disease-specific PROMs is the MacNew questionnaire. (19,20) The MacNew questionnaire has been used for patients with different kinds of cardiac diseases, such as heart valve diseases, (19,21) angina pectoris, (22) myocardial infarction, (23) heart failure, (24) and cardiomyopathy. (25) It is also used in different interventions such as heart valve surgery, (19,21) percutaneous coronary interventions/coronary artery bypass graft,(26,27) pacemaker implantation,

(28) and cardiac rehabilitation. (19,21,26)

With PROMs, patients are involved in the decision-making process (13,29) and clinicians may understand how diseases and their treatment affects outcomes that are important to patients. (15) There is a scarcity of published data evaluating HRQoL outcomes for patients before and/or after HVR in developing nations. (30,31) This study was undertaken to evaluate the HRQoL of patients in Tanzania who underwent HVR for rheumatic mitral stenosis at Jakaya Kikwete Cardiac Institute (JKCI).

2. MATERIAL AND METHODS

2.1. STUDY DESIGN AND SETTING

This was a prospective, hospital-based cross-sectional study of Tanzanian patients who underwent mechanical HVR for moderate to severe rheumatic mitral stenosis at the cardiac surgery department at JKCI which is the only institute offering heart valve surgeries in the country. This study consecutively enrolled patients (January 2020 to April 2021) who were accepted for mechanical HVR due to moderate to severe rheumatic mitral stenosis. We chose to recruit patients who underwent mechanical HVR because we wanted consistent results for comparison purposes. Moreover, it the one that is most commonly done at our institute. When mitral stenosis was associated with other valve lesions such as mitral regurgitation, aortic valve disease, and secondary tricuspid regurgitation the patients were also included. Patients with mild mitral stenosis, other forms of non-rheumatic valvular heart disease or other cardiac diseases (such as triple vessel disease necessitating coronary artery bypass graft) were excluded from this study. All patients were operated on by the same local surgeons on an elective basis and all surgeries were done with the same approach. One of our study objectives was to determine factors associated with HRQoL improvement. Based on available literature, New York Heart Association (NYHA) functional class is among those factors. From the article by Shan et al, (32) the mean (SD) HRQoL score among patients in NYHA class II and class III – IV were 5.2 ± 0.9 and 4.6 ± 0.8 respectively, $p < 0.001$. Using OpenEpi Software for statistical calculations (33) we determined the minimum sample size to be 64.

2.2. DATA COLLECTION

The sociodemographic, medical and comorbidity history was obtained from all patients. New York Heart Association (NYHA) functional class score, intraoperative variables (number of valves replaced, cardiopulmonary bypass time, and aortic cross-clamp time), postoperative ICU stay, postoperative complications (congestive cardiac failure, arrhythmias, wound infection, acute respiratory distress syndrome), and mortality

information was also obtained. All patients were evaluated for evidence of moderate to severe mitral stenosis according to the recommended clinical and echocardiographic parameters. (34) Several echocardiographic (e.g. pulmonary hypertension defined Right Ventricular Systolic Pressure > 35mmHg as determined by the peak systolic gradient across the tricuspid valve regurgitation (35)), electrocardiographic (e.g. atrial fibrillation) and laboratory parameters (e.g. C-reactive protein) were documented.

2.3. ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE

This study aimed to detect small changes in the quality of life for the patient who underwent HVR and hence the authors preferred to use the MacNew questionnaire which is an internationally accepted and valid questionnaire to assess HRQoL. It has 27 questions focusing on three important HRQoL domains namely; the physical, emotional, and social functions. (19–22,36) The scale used is a Likert type (never = 7, very often = 6, often = 5, sometimes = 4, few times = 3, rarely = 2, always = 1). The timeframe for the MacNew is the previous two weeks. In this study, HRQOL was categorized as low (mean score $\leq$ 4.9), moderate (mean score between 5 and 6) and high (mean score >6) to compare results with previous studies. (37) All the scores were transformed according to meaning. The maximum possible score in any domain is 7 (high HRQoL) and the minimum is 1 (poor HRQoL). Domain scores were calculated as the averages of the respective responses of the item. The global score was assessed as the average of all items (Figure 1).

The questionnaire was translated into Kiswahili at the University of Dar es Salaam, Department of Kiswahili studies. A pilot study was conducted in a sample of 10 patients to ascertain the applicability of this questionnaire in the Kiswahili language and the responses were satisfactory. The internal consistency (reliability) of the Kiswahili version of the scale was good, with Cronbach's α coefficient ranging from 0.853 to 0.911 for the subscales of Emotional, Physical, and Social domains, and 0.923 for the Global score.

We employed a pre and post-test design with completion of the questionnaires before HVR, at 3- and 6- months post-HVR. The questionnaires were interviewer-administered in which preoperatively they were administered in-person the day before HVR and postoperatively at 3 and 6 months they were either administered in-person during clinic visits or by phone for patients who could not come for follow-up visits at JKCI. To limit interview bias, the same researcher (RM) undertook all of the interviews.

macnew.org
HEALTH-RELATED QUALITY OF LIFE INSTRUMENT

Recommended Scoring System

Item		Emotional	Physical	Social
1.	Frustrated	✓		
2.	Worthless	✓		✓
3.	Confident	✓		
4.	Down in the dumps	✓		
5.	Relaxed	✓		
6.	Worn Out	✓	✓	
7.	Happy with Personal Life	✓		
8.	Restless	✓		
9.	Short of Breath		✓	
10.	Tearful	✓		
11.	More Dependent			✓
12.	Social Activities	✓	✓	✓
13.	Others/less Confidence in you	✓		✓
14.	Chest Pain		✓	
15.	Lack Self-Confidence	✓		✓
16.	Aching Legs		✓	
17.	Sports/Exercise Limited		✓	✓
18.	Frightened	✓		
19.	Dizzy/Lightheaded		✓	
20.	Restricted or Limited		✓	✓
21.	Unsure about Exercise		✓	✓
22.	Overprotective Family			✓
23.	Burden on Others	✓		✓
24.	Excluded		✓	✓
25.	Unable to Socialise		✓	✓
26.	Physically Restricted		✓	✓
27.	Sexual Intercourse		✓	

1. Ticks show domains to which the items contribute.
2. The maximum possible score in any domain is 7 and the minimum is 1.
3. The Emotional Score is calculated as the average of the 14 item responses which contribute to the Emotional domain shown in the above table, the Physical Score is the average of 13 responses and the Social Score is the average of 13 responses.
4. Missing responses do not contribute to the Score. For example, if only 10 of the 14 Emotional items are answered, the Emotional Score is the average of 10 responses. At least 50% of items must have a score for a domain score to be calculated.
5. If desired, a Global Score can be calculated as the average over all items.
6. Item 27, 'Sexual intercourse', may be excluded in the Physical domain.

Figure 1. Scoring System of MacNew questionnaire

2.4. STATISTICAL ANALYSIS

Data analysis was done using Statistical Package for Social Sciences (IBM SPSS Statistics) version 28.0 and STATA (StataCorp) version 13. Continuous data were presented as mean or median and categorical data as counts or percentages. Repeated measure ANOVA and one-way ANOVA or independent sample T-Test were used to compare different means of continuous variables. Variables which were analysed for HRQoL included patients' age, sex, residence, education level, marital status, insurance, disease duration, NYHA class, preoperative LVEF, preoperative pulmonary arterial pressure (PAP), Tricuspid Annular Plane Systolic Excursion (TAPSE), income, preoperative atrial fibrillation (AF), left atrial size, mitral valve area (MVA), mitral valve mean pressure gradient, level of CRP, Wilkins' grade, anticoagulants use, diuretics use, history of hypertension, history of stroke, and intraoperative variables (number of valves replaced, cardiopulmonary bypass time, and aortic cross-clamp time), and post-operative ICU stay. With each of the analyses, a p-value <0.05 was considered statistically significant.

2.5. ETHICAL CONSIDERATION

We obtained written informed consent from all participants. The study was approved by the Directorate of Research and Publications of Muhimbili University of Health and Allied Sciences (P. MUHAS – REC-9-2019-059). Permission to conduct this study was obtained from JKCI (AB.157/334/01'A) ethical committee. Written permission (license: D3FCH-17E5A-2B7BB-B73EF-C1BB4-8HD5H) to utilize the MacNew questionnaire was obtained from its developers at the College of Health Sciences at the University of Wisconsin-Milwaukee.

3. RESULTS

3.1. PATIENTS CHARACTERISTICS

All patients underwent surgical intervention for RHD. The mean (± SD) age of the patients at the time of surgery was 37.98 (± 12.78) years. There were 34 females and 20 males, thus there was a female predominance (F: M = 1.7:1). The mean duration of symptoms was 6.83 ± 5.51 years. The majority, 45 (83.3%) of the patients were residing outside of Dar es Salaam. More than two-thirds of the patients were married, had primary school education and had low income while about a third had no health insurance. Twenty-four (44.4%) patients had AF, 10 (18.5%) were on anticoagulants (preoperatively), and 9 (16.7%) had previous strokes (all of them in AF and not on oral anticoagulants). The majority, 45 (83.3%) of the patients had pulmonary hypertension. About a quarter was in NYHA class III-IV and 9 (16.7%) had reduced LVEF. Nineteen (35.2%) patients had pure MS. Other lesions were 5 (9.3%) mixed mitral valve disease (MMVD), 6 (11.1%) MMVD with tricuspid regurgitation (TR), and 24 (44.4%) MMVD with aortic valve disease (AVD) and TR. The mean mitral valve area was 1.14 ± 0.39 cm^2 and the mean trans-mitral

pressure gradient was 12.54 ± 3.57 mmHg. Single (mitral) valve replacement was done in more than two-thirds of the patients (Table 1). Tricuspid valve repair was done in 16 (53.3%) patients. The type of mechanical prostheses used were Sorin Bicarbon bileaflet valves (43), Medtronic ATS mechanical heart valve (10), Bicarbon St. Jude mitral valve (1).

Table 1. Sociodemographic and clinical characteristics of patients on operated for rheumatic mitral stenosis at JKCI from January 2020 to April 2021 (N=54).

Variable	Mean (±SD)/Frequency (%)
Gender (female)	34 (63)
Age of patients (years)	37.98 ± 12.78
Duration of symptoms, mean (years)	6.83 ± 5.51
Proportion residing outside of Dar Es Salaam	45 (83.3)
Proportion married	36 (66.7)
Proportion without health insurance	17 (31.5)
The proportion of low income	42 (77.8)
The proportion of primary education	35 (64.8)
Hypertensives	6 (11.1)
Patients with stroke	9 (16.7)
Patients with atrial fibrillation	24 (44.4)
Patients in heart failure NYHA class III-IV	15 (27.8)
Proportion on anticoagulants (preoperatively)	10 (18.5)
The proportion with pure MS	19 (35.2)
The proportion of pulmonary hypertension	45 (83.3)
The proportion with moderate-severe dilated LA	43 (79.6)
Mitral valve area, mean (cm^2)	1.14 ± 0.39
Trans mitral pressure gradient, mean (mmHg)	12.54 ± 3.57
Proportion with elevated C-reactive protein	33 (61.1)
Proportion who underwent SVR	37 (68.5)

Legend: *NYHA = New York Heart Association, MS = Mitral stenosis, LVEF = Left ventricular ejection fraction, TAPSE = Tricuspid Annular Plane Systolic Excursion, LA = left atrium, SVR = Single (mitral) valve replacement.*

3.2. DURATION OF ICU STAY, CARDIOPULMONARY BYPASS, AND AORTIC CROSS-CLAMP

The median duration of intensive care unit (ICU) stay was 2 (25th and 75th percentiles, 2- 3) days. The median cardiopulmonary bypass time and aortic cross-clamp time were 138 (25th and 75th percentiles, 108.50 – 188.25) minutes and 104 (25th and 75th percentiles, 76.50 – 144.75) minutes respectively.

3.3. CLINICAL COMPLICATIONS

Two (3.7%) patients died in-hospital (death within 30 days following surgery). About half of the patients experienced no complications. Non-fatal arrhythmias occurred in 8 (14.8%),

two of which being AF, two bradycardias, and four sinus tachycardia. Low cardiac output syndrome and electrolyte imbalance occurred in 4 (7.4%) patients each. The frequency of occurrence of re-exploration for bleeding, acute respiratory failure, neurological dysfunction, and bleeding due to warfarin was in 2 (3.7%) patients each (Table 2).

Table 2. Clinical complications of patients operated on from January 2020 to April 2021 for rheumatic mitral stenosis at JKCI during the 6 months follow-up period (N=54).

Complications	Frequency (%)
Without complications	26 (48.1)
Arrhythmias	8 (14.8)
Re-exploration for bleeding	2 (3.7)
Low cardiac output syndrome	4 (7.4)
Acute respiratory failure	2 (3.7)
Electrolyte imbalance	4 (7.4)
Sternal wound gaping	1 (1.9)
Neurological dysfunction	2 (3.7)
Bleeding due to warfarin toxicity	2 (3.7)
Warfarin resistance	1 (1.9)
Prolonged intensive care unit stay (> 5 days)	2 (3.7)

3.4. HEALTH-RELATED QUALITY OF LIFE

3.4.1. HRQoL of individual patients operated on from *January 2020 to April 2021* for rheumatic mitral stenosis at JKCI (N=50).

As shown in figure 2, the HRQoL scores per patient over time was varying from one patient to another.

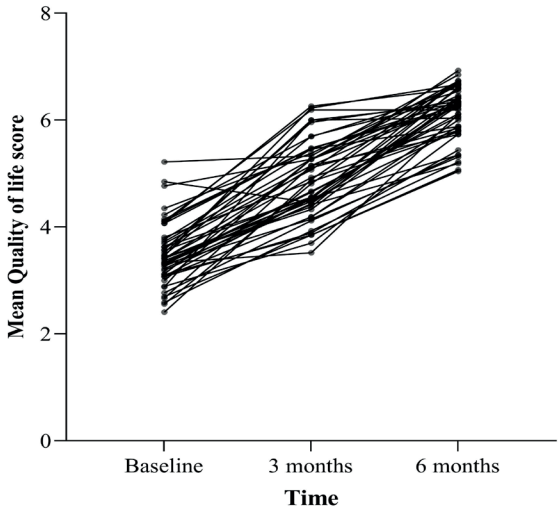

Figure 2. A graph showing individual HRQoL scores of patients over time

3.4.2. Health-related quality of life preoperatively and over time

The preoperative MacNew questionnaire was completed by all (54) patients the day before HVR, and by 50 patients at three and six months. Preoperatively and at three months, patients had a low HRQoL (mean score ± 4.9). Six months after HVR the overall MacNew scores improved significantly. The mean (±SD) McNew global scores were 3.47 ± 0.59, 4.88 ± 0.71 and 6.14 ± 0.50 preoperatively, at 3 months and 6 months respectively (p-values <0.001). Similarly, there was a significant improvement in HRQoL for the other domains (Table 3).

Table 3. MacNew HRQoL mean domain scores of patients operated on from January 2020 to April 2021 for rheumatic mitral stenosis at JKCI, preoperatively and over time (n=50).

Domains	HRQoL Score			p-Value
	Preoperative Mean (±SD)	3 Months Mean (±SD)	6Months Mean (±SD)	
Global	3.47 ± 0.59	4.88 ± 0.71	6.14 ± 0.50	<0.001[a,b,c]
Emotional domain	3.49 ± 0.59	4.92 ± 0.77	6.16 ± 0.50	<0.001[a,b,c]
Physical domain	3.43 ± 0.64	4.86 ± 0.75	6.13 ± 0.58	<0.001[a,b,c]
Social domain	3.44 ± 0.69	4.86 ± 0.81	6.09 ± 0.58	<0.001[a,b,c]

Legend: *[a]Preoperative vs. 3 months; [b]Preoperative vs. 6 months; [c]3 months vs. 6 months*. P-value for overall trend is < 0.001

3.4.3. Global HRQoL scores by patients' sociodemographic characteristics

As shown in Table 4, the preoperative and 6 months mean difference HRQoL scores were similar among patients aged > 30 years and those with ≤ 30 years (2.72 ± 0.11 vs 2.57 ± 0.60, p=0.301) and among males and females (2.72 ± 0.66 vs 2.64 ± 0.58, p= 0.648). Similarly, the mean difference HRQoL scores among patients with secondary vs primary education, who are married vs not married, having national vs other insurance, duration of disease ≥ 10 years vs <10 years, and with low vs fair income were not different. There was an improvement in the overall global mean scores, from low (mean score ± 4.9) preoperatively to high (mean score > 6) at 6 months in all of the analysed variables.

Table 4. Association of global HRQoL scores with sociodemographic characteristics of patients operated on from January 2020 to April 2021 for rheumatic mitral stenosis at JKCI, preoperatively and over time (N=54).

Variable		Mean (± SD) Global scores		Mean difference (± SD)	*P Value
		Preoperative	6 months		
Age (yrs):	≤ 30	3.57 ± 0.65	6.14 ± 0.45	2.57 ± 0.60	0.391
	>30	3.39 ± 0.57	6.14 ± 0.53	2.72 ± 0.11	
Sex:	Female	3.49 ± 0.60	6.16 ± 0.46	2.64 ± 0.58	0.648
	Male	3.36 ± 0.59	6.11 ± 0.57	2.72 ± 0.66	
Education:	Sec- college	3.52 ± 0.55	6.11 ± 0.46	2.70 ± 0.17	0.994
	Primary	3.40 ± 0.62	6.11 ± 0.53	2.68 ± 0.69	

Table 4. Continued.

Variable	Mean (± SD) Global scores		Mean difference (± SD)	*P Value
	Preoperative	6 months		
Marital: Married	3.42 ± 0.60	6.22 ± 0.50	2.78 ± 0.59	0.152
Not married	3.50 ± 0.60	6.01 ± 0.48	2.51 ± 0.61	
Insurance: National insurance	3.44 ± 0.57	6.13 ± 0.56	2.70 ± 0.67	0.838
Public & others	3.44 ± 0.64	6.16 ± 0.41	2.54 ± 0.40	
Disease duration <10 yrs	3.50 ± 0.57	6.14 ± 0.48	2.63 ± 0.61	0.472
≥ 10 yrs	3.32 ± 0.64	6.14 ± 0.56	2.76 ± 0.62	
Income: Low	3.40 ± 0.58	6.10 ± 0.50	2.68 ± 0.65	0.944
Fair	3.60 ± 0.65	6.26 ± 0.49	2.66 ± 0.48	

**P value for the mean difference*

3.4.4. Global HRQoL scores by patients' clinical characteristics

Table 5 shows that the preoperative and 6 months mean difference HRQoL scores were similar among patients who were in NYHA class I-II vs III-IV, with normal vs low preoperative LVEF, with vs without stroke, hypertensives vs non-hypertensives, with vs without pulmonary hypertension, with severe vs moderate mitral stenosis, with elevated vs normal CRP, and those who underwent mitral valve replacement vs double valve. The preoperative and 6 months mean difference HRQoL scores were statistically significantly higher among patients with vs without AF (2.95 ± 0.59 vs 2.45 ± 0.53, p=0.003) and those on anticoagulants (preoperatively) vs not on anticoagulants (3.14 ± 0.58 vs 2.57 ± 0.57, 0.009). The overall global mean scores improved from low (mean score ± 4.9) preoperatively to high (mean score > 6) at 6 months in all of the analysed variables.

Table 5. Association of global HRQoL scores with clinical characteristics of patients operated on from January 2020 to April 2021 for rheumatic mitral stenosis at JKCI, preoperatively and over time (N=54).

Variable	Mean (± SD) Global scores		Mean difference (± SD)	*P value
	Preoperative	6 months		
NYHA class: I-II	3.43 ± 0.59	6.15 ± 0.51	2.72 ± 0.63	0.420
III-IV	3.48 ± 0.63	6.12 ± 0.50	2.56 ± 0.56	
Preop LVEF: Low	3.58 ± 0.77	6.58 ± 0.24	2.65 ± 0.72	0.930
Normal	3.42 ± 0.59	6.08 ± 0.50	2.67 ± 0.60	
Stroke: No	3.52 ± 0.56	6.12 ± 0.44	2.59 ± 0.50	0.135
Yes	3.07 ± 0.63	6.28 ± 0.49	3.20 ± 0.93	
Hypertension: No	3.49 ± 0.60	6.16 ± 0.48	2.65 ± 0.58	0.423
Yes	3.10 ± 0.30	5.89 ± 0.76	2.91 ± 0.96	
Preop PAP: Normal	3.53 ± 0.38	5.98 ± 0.38	2.47 ± 0.49	0.315
Elevated	3.42 ± 0.63	6.17 ± 0.52	2.71 ± 0.63	
Preop Atrial fibrillation: No	3.66 ± 0.61	6.14 ± 0.45	2.45 ± 0.53	0.003
Yes	3.17 ± 0.45	6.14 ± 0.56	2.95 ± 0.59	
Mitral Valve Area: Moderately reduced	3.52 ± 0.67	6.25 ± 0.47	2.66 ± 0.64	0.883
Severely reduced	3.38 ± 0.52	6.06 ± 0.54	2.68 ± 0.59	

Table 5. Continued.

Variable	Mean (± SD) Global scores		Mean difference (± SD)	*P value
	Preoperative	6 months		
Anticoagulants (preoperatively): No	3.53 ± 0.58	6.11 ± 0.50	2.57 ± 0.57	0.009
Yes	3.05 ± 0.51	6.27 ± 0.64	3.14 ± 0.58	
C-Reactive Protein: Normal	3.46 ± 0.63	6.06 ± 0.53	2.61 ± 0.60	0.546
Abnormal	3.42 ± 0.54	6.29 ± 0.42	2.72 ± 0.62	
Type of surgery: DVR	3.36 ± 0.60	6.05 ± 0.61	2.58 ± 0.40	0.542
SVR	3.47 ± 0.60	6.17 ± 0.46	2.70 ± 0.66	

Legend: *NYHA = New York Heart Association, LVEF = Left ventricular ejection fraction, PAP = pulmonary arterial pressure, TAPSE = Tricuspid Annular Plane Systolic Excursion, DVR = Double (aortic and mitral) valve replacement, SVR = Single (mitral) valve replacement. *P value for the mean difference*

4. DISCUSSION

4.1. THE MAIN FINDINGS

This single-centre prospective study represents the investigation of HRQoL for patients after valve replacement for RHD in Africa and shows that preoperative HRQoL is considerably low before surgery but substantially improves post-surgery. Moreover, the improvement in HRQoL experienced post-surgery is sustained over time in all of the MacNew HRQoL domains. The preoperative and 6 months mean difference HRQoL scores were statistically significantly higher among patients with vs without atrial fibrillation and those on anticoagulants (preoperatively) vs not on anticoagulants. The mean difference HRQoL scores were similar for sociodemographic parameters and other clinical parameters. Patients with other comorbidities (e.g. stroke and hypertension) had a lower HRQoL at baseline but all improved after surgery to similar levels of the patients with no comorbidity. The internal consistency (reliability) of the Kiswahili version of MacNew tool was good (with Cronbach's α coefficient ranging from 0.853 to 0.911) similar to the 0.75 to 0.89 observed in a study done by Merkouris et al. (37)

4.2. PRE-OPERATIVE HRQoL

In our study, all patients perceived that their HRQoL was impaired pre-operatively with a mean (±SD) score of 3.47 ± 0.59 on a global scale, and 3.49 ± 0.59, 3.43 ± 0.64, 3.44 ±0.69 in the emotional, physical and social domains respectively. Our findings are similar to that reported in a study done by Mangnall et al (10) which showed that preoperatively all mean HRQoL eight domains scores were much lower than the reference population with severe impairment in the general health and physical function domains. Similarly, Joshi et al (38) reported that the HRQoL was impaired in all eight domains with the lowest scores in the general health and physical function domain before surgery (15.61 ± 1.30), which improved after surgery (22.95 ± 0.45). In RHD, as valve damage progresses, the consequences for the affected patients are devastating in terms of morbidity and

mortality as well as poor quality of life (11,39). In developing countries, including sub-Saharan Africa, patients usually present in New York Heart Association (NYHA) functional class II-III, atrial fibrillation (28%), thromboembolic events (3.2%) pulmonary hypertension, and infective endocarditis. (1,7,11,40,41) These factors are signifying late presentation of patients to health facilities and/or delayed appropriate management. (7,42) Medical treatment may retard the rate of deterioration in function, however physiological and hemodynamic changes and/or heart failure progression eventually necessitate interventions such as heart valve replacement (HVR). (7–9,11) Some of the patients are too late to be candidates for valvular interventions. (43–45)

4.3. OVERALL HRQoL

This study showed that patients who receive HVR for RHD in Tanzania experience a positive and sustained improvement in all of the MacNew HRQoL domains. There was a statistically significant improvement in the mean (±SD) MacNew global scores from 3.47 ± 0.59, 4.88 ± 0.71 and 6.14 ± 0.50 preoperatively, at 3 months and 6 months respectively. Our findings are in keeping with those reported in a study done in Nepal, South Asia which showed improvement in all domains of quality of life after valve replacement for RHD. (38) Similarly, in another study done in Fiji, an improvement was observed in all HRQoL domains except for mental health. A previous review reported a lack of published studies on HRQoL outcomes for patients with RHD pre-and/or post-heart valve surgery in developing countries. (30) Our study, together with the two cited (Fiji and Nepal) studies is addressing this scarcity. All three studies assessed HRQoL pre-operatively and post-operatively in the RHD population from resource-limited countries. However, while our study used the MacNew HRQoL questionnaire, the Nepal study assessed it by using Ferrans and Power HRQoL index, cardiac version IV and the Fiji study used the SF-36v2 questionnaire implying that the interpretation of the findings might slightly differ. Moreover, while the Nepal study translated and validated the questionnaire in the Nepalese language, our study and the Fiji study only translated the questionnaire into Kiswahili and Fijian languages respectively highlighting a need for further evaluation of the tools in future research.

4.4. ASSOCIATION OF GLOBAL HRQOL SCORES WITH SOCIODEMOGRAPHIC CHARACTERISTICS

4.4.1. Age

Our study showed a comparable mean difference HRQoL scores among patients aged > 30 years to those with ≤ 30 years. This could probably partly be explained by the observation that regardless of age, most of our patients had no comorbidities such as hypertension, diabetes, and infectious diseases which presumably could affect HRQoL. Our findings are similar to those reported in other studies, showing that age does not effect HRQoL after cardiac surgery. (38,46) A study in Nepal concluded that the amount

of HRQoL improvement gained by the elderly after heart valve surgery is similar to that of the young. (38) Similarly, Sedrakyan et al (46) found that among patients who have undergone heart valve surgery, age does not limit the HRQoL advantages of surgery. Another study done among octogenarians concluded that despite a poor health status pre-operatively, an improvement in symptoms, general well-being and physical health of similar magnitude with the young counterparts was seen. (47) These observations underscore the recommendations that valve replacement should be performed even for the elderly if fits the criteria. (11,47) However, other studies reported that younger age is associated with less HRQoL improvement. (48–50) In cardiac patients, studies reported young age as a predictor of poor HRQoL improvement. (51–53). The authors mentioned why HRQoL is better in older than younger patients: valve noise perception is likely to be exaggerated in young patients, (48) older patients have a concept that surgery has made them get better otherwise "it could be worse", (52) and they have better psychosocial status, less anxiety and depressive behaviors. (52) Interestingly, in African culture, ageing goes along with reduced life expectancy and HRQoL and therefore elderlies probably perceive that surgery makes them feel better. Another study (10) found that older age was an independent predictor of poor HRQoL over time. Noteworthy, the observed differences between these studies could be attributed to the differences in sample size, the studied populations and the difference in the PROMs used to assess HRQoL. For example, while our study and another (38) recruited patients with RHD, other studies (46,47) recruited patients with degenerative valve diseases.

4.4.2. Sex

In the current study, the mean difference HRQoL scores among female and male patients were similar. Our findings are in keeping with those reported in previous studies (54,55) which have shown that post-operative HRQoL is similar among females and males. Indeed, studies have shown that sex is neither a risk factor for morbidity and mortality perioperatively nor for a prolonged intensive care unit stay. (56) Similarly, Mangnall et al (10) have reported that male gender was a predictor of less HRQoL improvement in only one of the eight domains (the role-emotional domain) implying that there is no sex difference. Another study by Taillefer et al (57) has shown that females had some advantage over males in terms of HRQoL improvement but the observed results on that aspect were weak. However, other studies (14,37,58) have demonstrated that females with cardiovascular diseases have worse HRQoL scores than males by both disease-specific and generic PROMs. These studies report that this affection is more marked preoperatively than postoperatively (55,59) and in the physical and social domains. (54–56,59,60) Among other reasons, lower social supports and psychological stress among women are important determinants of poor health. (61) Given contradicting results, authors have recommended that gender perceptions and roles are important areas for research in the future. (62)

4.5. ASSOCIATION OF GLOBAL HRQOL SCORES WITH CLINICAL CHARACTERISTICS

4.5.1. Atrial fibrillation/patients on anticoagulation

In this study, the proportion of patients with AF was 44.4% which is slightly higher than the approximated 30% in some studies (7,40,63) but lower than the 60% that was reported in another study. (64) Patients with preoperative AF had statistically significant improvement in HRQoL at 6 months when compared to those without AF. It is recognized that, even if asymptomatic, AF has a negative effect on HRQoL. (65) At presentation, patients with mitral stenosis (unlike mitral regurgitation) have advanced RHD with consequences of worse physical and emotional states. (35,66,67) HVR is considered to improve the well-being of these patients. Similarly, patients on anticoagulants (preoperatively) had significant improvement in HRQoL compared to those not on anti-coagulants. However, in our cohort being on anti-coagulants could be explained as a proxy for having AF. As per the institute protocol, all patients with mechanical valve prosthesis are put on oral anticoagulants with warfarin with follow up of International Normalized Ratio (INR) targeting therapeutic range. For single mitral valve replacement, target INR is 2 – 2.5 and for double valve replacement the target INR is 2 – 3.

4.5.2. Other clinical characteristics

Our study showed comparable HRQoL among patients who underwent double (mitral and aortic) valve replacement (DVR) with those who underwent single (mitral) valve replacement (SVR). On the contrary, Mangnall et al (10) have reported that isolated MVR was a predictor of less improvement in HRQoL postoperatively. The authors argued that the less improvement could be due to the advanced RHD which commonly occurs with mitral stenosis (versus mitral regurgitation) at the initial presentation. However, the authors recommended further research to better understand their scenario. In our previous publication (35) we found a significantly higher mortality among patients who underwent DVR (five times) than SVR while the other study (68) reported that there was no differences between the two groups. The reported difference in mortality data could be extrapolated to HRQoL showing that the results are inconclusive and hence calling for further studies.

4.6. OTHER FINDINGS

In the current study, the in-hospital mortality was 3.7% which is comparable to the 3.8% reported by Akhtar et al (69), the 4% by Panda et al (70) and Sharma et al (68), 2.5% by Pillai et al (71), and 4.4% by Debel et al. (72) This mortality rate is significantly lower than the 11% reported by Nyawawa et al (67) and the 14% reported by Mutagaywa et al (35), at the same centre indicating significant improvement which could probably be explained by the improved surgical techniques and perioperative care, among other reasons. Similarly, the number of complications observed in the current study is comparable with those reported by Debel et al (72). Moreover, in the current study,

the median cardiopulmonary bypass and aortic cross-clamp time were 138 (108.50 – 188.25) and 104 (76.50 – 144.75) minutes respectively. This figure is similar (and ideal) to the mean cardiopulmonary bypass time of 137 minutes and aortic cross-clamp time of 102 minutes reported in a study done by Aditya et al. (73) Furthermore, in this study we have found comparable HRQoL with respect to LVEF and NYHA functional class. To our knowledge, this finding has not been reported in literatures, but in our previous publications (35,67) we found that NYHA and LVEF are not contributory to mortality. These mortality data could in a way be extrapolated to HRQoL showing that the results are not conclusive and hence highlighting a need for future research.

5. STRENGTH AND LIMITATIONS

This study report on HRQoL among patients undergoing cardiac surgery. The study has several advantages: being a prospective design, using the disease specific questionnaire and comparing HRQoL before and after HVR. Although HRQoL is arguably correctly assessed using a qualitative approach, in the evaluation of clinical practice like in the current study, quantitative methods are the best. The small sample size of this study could not allow for the detection of the possible presence of statistical significance of association between HRQoL domains with most of the parameters. However, we analysed several parameters which revealed the association with HRQoL knowing that a lack of statistical significance does not mean that there is no clinical significance and relevance. Lastly, although we could not validate the MacNew tool, the translation into Kiswahili which is very well-spoken by most Tanzanians made the tool to be easily administered and accepted as is also reflected by the good internal consistency observed during a pilot study. Also, since the relationships observed in our study are comparable to that of previous studies could indicate validity.

6. CONCLUSION AND RECOMMENDATIONS

Despite having different comorbidities, patients who receive valve surgery for RHD experience improvement in HRQoL. This study will build a body of knowledge regarding HRQoL after valve surgery for RHD in developing countries. Clinicians and researchers in low-resource settings should collaborate to promote the utilization of PROMs in the routine care of patients.

DECLARATION

Ethical approval and consent to participate

The study was approved by the Directorate of Research and Publications of Muhimbili

University of Health and Allied Sciences (P. MUHAS – REC-9-2019-059). Participants gave their consent to participate.

Consent for publication

We obtained permission for the photographs used. We obtained permission to utilize the MacNew questionnaire from its developers at the College of Health Sciences at the University of Wisconsin-Milwaukee (license: D3FCH-17E5A-2B7BB-B73EF-C1BB4-8HD5H).

Availability of data and material

The data will be available to the readers upon reasonable request.

Competing interests

The authors declare no competing interests associated with this work.

FUNDING

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AUTHORS' CONTRIBUTIONS

RKM: conceptualization, methodology, investigation, formal analysis, and writing the original manuscript; **MJC, PC, GK, AK, SC, RHK:** supervision, formal analysis, visualization, manuscript review and editing; **RB, AM, MB, BN, PK**: investigation, manuscript review and editing. All authors have read and approved the manuscript.

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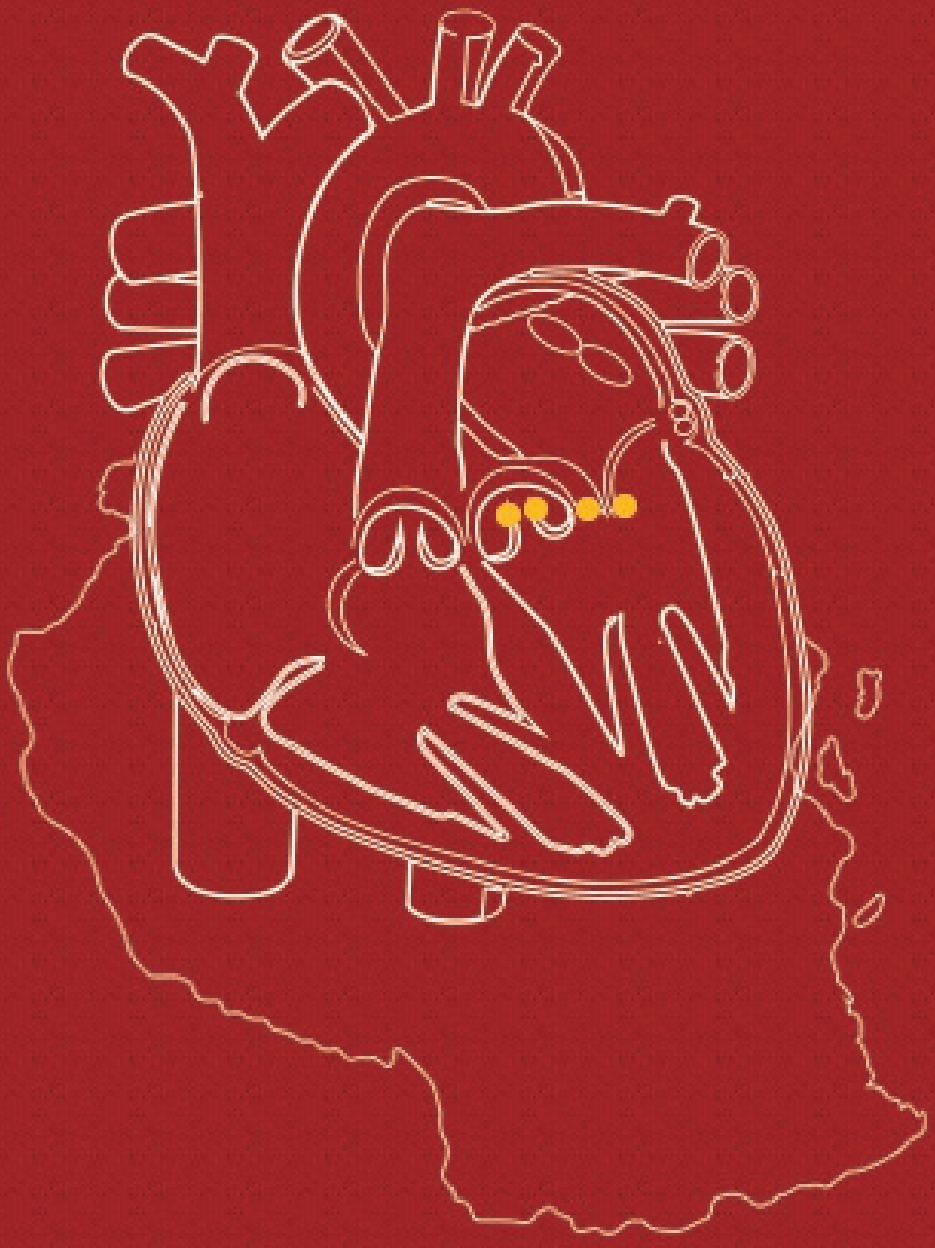

CHAPTER 10

Discussion, including summary and future perspective

Globally, the prevalence of rheumatic heart disease (RHD) increased by 70.49% from 1990–2019 and reached 40.50 million in 2019. [1] The prevalence of subclinical RHD in sub-Saharan Africa (SSA) is up to 30 per 1,000 school children, [2] with Tanzania reporting a prevalence of 21 – 34 per 1,000 population. [3,4] Due to late presentation of patients in hospital, the management is complex amongst these patients owing to advanced disease. Studies have investigated the underlying mechanisms for the pathogenesis of RHD but none is conclusive. As a consequence, the management is challenging and accompanies several unsolved and ongoing problems for today's researchers, community, clinicians and policymakers. RHD is still the leading cause of morbidity and mortality among young adults in low-middle income countries (LMICs), including Tanzania. Deliberate pragmatic strategies need to be implemented to overcome this potentially preventable disease. In this thesis, we aimed at exploring the clinical aspects and outcome of RHD in Tanzania with the focus on 3 parts: RHD in special populations, clinical aspects of rheumatic mitral stenosis (MS), and progress in the management of RHD.

10.1. SUMMARY

Chapter 1 is the general introduction and an outline of this thesis. In this chapter, three issues are addressed: 1) the burden of RHD is high and increasing; 2) the management of patients with RHD in LMICs is complex; and 3) the pathogenesis of RHD is not quite well known. Here, also gaps related to RHD are highlighted that need to be addressed in research and clinical practice perspectives.

PART 1. OF THE THESIS ASSESSED RHD IN SPECIAL POPULATIONS.

In the first part of **chapter 2,** we reported on the influence of gender in the management of rheumatic MS. We found that females present late in hospital with postulated reasons such as: poor socioeconomic status, better cardiac functions in the majority, and vague symptomatology of heart failure. Diagnostic and management approaches do not differ between males and females. We obtained inconclusive results on the differences in mitral valve anatomy and the amount of leaflet calcium by sex, a subject that have been debatable in literature. The review showed a change in epidemiology of the disease, RHD patients are now reporting to hospitals in Europe in a significant number. Furthermore, a proportion of the migrant population and refugees has undiagnosed RHD. Therefore, there is a need of adapting health systems and health system delivery to changing needs of refugees and migrants such as screening for sub-clinical RHD.

In response to address the inadequacy of data on infective endocarditis (IE), **chapter 3** reviewed IE in LMICs. The review summarizes the current state of IE in developing countries and investigates whether there is a change over time in the presentation of

IE. It shows a scarcity of studies on IE in developing countries especially SSA. Of the compared two cohorts i.e studies published before 2015 (group 1) and studies ≥ 2015 (group 2), RHD was higher in group 1 than in group 2 (42.3% vs 30.3%, p<0.001) while for congenital heart disease (CHD) there was no change. Streptococci infections was lower in group 1 than group 2 (26.2% vs 37.7%, p<0.001). The proportion of *Staphylococcus aureus* was 15.3% in group 1 and 23.6% in group 2, p<0.001. Negative blood culture (NBC) was higher in group 1 than in group 2 (42.2% vs 34.1%, p=0.002). Patients in group 1 received more surgery than in group 2 (38.8% vs 28.8%, p<0.001). Mortality did not change over time. This data demonstrates that timely diagnosis and management of patients with RHD and CHD, and comprehensive management of IE such as involving the "endocarditis team" are required for good outcomes.

Chapter 4 determined the prevalence of sub-clinical RHD detected by hand-held echocardiogram in children participating in a school-based RHD prevention program in Tanzania. This is the largest and one of the few studies on RHD prevalence in East Africa. It is part of on-going program that is expected to provide longitudinal data on RHD. In total, 4436 children were screened and sub-clinical RHD was found in 95 children, which is a prevalence of 2.1%, [95% CI 1.7% – 2.6%]. Independent factors associated sub-clinical RHD were female sex (adjusted odds ratio{aOR} 1.83, 95% CI 1.18 – 2.85, p = 0.007), older age (aOR 1.73, 95% CI 1.10 – 2.72, p = 0.018 for age group 11-14 years) and (aOR 3.02 95% CI 1.01 – 9.05, p = 0.048 for age group 15-16 years), as well as presence of a cardiac murmur, aOR 5.63 95% CI 2.31 – 13.69, p < 0.0001. None of the studied socio- or economic factors were associated with the presence of sub-clinical RHD in our study. Our data supports the recommendation given by the World Health Organization (WHO) and the World Heart Federation (WHF) that screening for sub-clinical RHD is a critical initial step for a comprehensive RHD control program in order to obtain data on the community burden of the disease.

PART 2. OF THIS THESIS DISCUSSES THE CLINICAL PRESENTATION OF PATIENTS WITH RHEUMATIC MS, ITS DISEASE PATHOGENESIS, AND SUBSEQUENT INTERVENTIONS.

WHF has since 2013 prioritized RHD as an important public health problem and proposed strategies, including the availability of data on the disease burden, to reduce and eradicate RHD. In **chapter 5**, we provided contemporary data on the clinical profile, treatment and follow-up of patients with rheumatic mitral MS attended at Jakaya Kikwete Cardiac Institute (JKCI) in Tanzania. We prospectively enrolled 290 patients. We found that the disease affects young people, predominantly females, and with low income. Patients present late in the hospital and there is a low (27.7%) uptake of secondary antibiotic prophylaxis. Interventions were done in half of the patients (46.2% surgical and 3.8% percutaneous balloon mitral valvuloplasty {PBMV}). Thirty-nine

(14.4%) patients died, of which 11 (4 %) deaths occurred in the surgical and 28 (10.4%) in the medical treatment arm. The independent predictors of mortality were: being on medical vs surgical treatment (crude HR 3.12, 95% CI 1.50 – 6.49, p = 0.002) and having arrhythmias vs not having arrhythmias (crude HR 2.44, 95% CI 1.19 – 4.49, p = 0.015). These data serve as a basis for establishment of Tanzania RHD registry.

In **chapter 6** we studied the histopathological changes in surgically excised rheumatic MS valves using advanced techniques and corroborated them with clinical presentation, pathogenesis, and management. We confirmed that high mitral valve calcium is found in older patients, males, and in patients with severe MS. A low rate of secondary antibiotic prophylaxis was observed, and two patients with evidence of acute rheumatic fever. More than two-thirds of the excised valves showed evidence of on-going inflammation with fibrinoid degeneration (FD), polymorphonuclear leucocytes (PMNL) and fibrosis on haematoxylin-eosin. About a half of the specimens showed evidence of calcification of different severity and one-tenth had Aschoff nodules. A majority of the specimens were positive for markers of inflammatory cells namely CD3 (85.2%), CD20 (64.8%), CD68 (72.2%), and CD8 (14.8%). The degree of inflammatory cellular infiltration was associated with valvular calcification, FD with ARF, PMNL with disease duration < 10 years, and fibrosis with the absence of atrial fibrillation. C-reactive protein and anti-streptolysin titres were high in CD20 and CD8 staining cells. The association between clinical parameters with histopathological-immunohistochemical studies observed in our study partly explains the pathogenesis of RHD.

With increased availability of Catheterization Laboratory in Africa, PBMV interventions are feasible options for selected patients with rheumatic MS. Therefore, enhancing PBMV training/skill transfer across most of African countries is possible. **Chapter 7** examined the clinical practice of patients with rheumatic MS that were evaluated for PBMV and defined the role of imaging, heart team, training/skill transfer in PBMV interventions in a Tanzania teaching hospital. We demonstrated that left atrium thrombi were present in five patients, four of which could not be detected with a transthoracic echocardiogram but only with a transoesophageal echocardiogram (TEE) highlighting the importance of pre-PBMV TEE. We showed in our cohort that patients with Wilkins score of up to 11 underwent successful PBMV urging for reconsideration of European and American guidelines' recommended cut-off score ≤ 8 for a good outcome. We observed that PBMV has good short-term outcomes in selected patients that underscores the importance of appropriate patients' selection. Finally, we established a well-planned multidisciplinary valvular heart team, which if sustained, can be impactful in the management of patients with rheumatic MS in LMICs.

PART 3. FOCUSES ON PROGRESS IN THE MANAGEMENT OF RHD

In **chapter 8,** we retrospectively investigated 212 RHD patients who underwent cardiac surgery in Tanzania between the year 2008 – 2012. The mortality rate dropped in 4 years to 14.1% compared to the 24% reported after 1-year of establishing RHD cardiac surgery at Muhimbili National Hospital (MNH). In patients with RHD, double valve replacement is associated with increased early mortality, which may require greater technical expertise and careful postoperative management. We also highlighted the need for local guidelines for the management of RHD patients. **Chapter 9** prospectively assessed the Health-Related Quality of Life (HRQoL) of 54 patients operated on due to rheumatic MS. The mean (±SD) MacNew global scores were 3.47 ± 0.59, 4.88 ± 0.71 and 6.14 ± 0.50 preoperatively, at 3 months and 6 months respectively (p-values for trend <0.001). The preoperative and 6 months mean difference HRQoL scores were higher among patients with vs without atrial fibrillation (2.95 ± 0.59 vs 2.45 ± 0.53, p=0.003) and those on anticoagulants (preoperatively) vs not on anticoagulants (3.14 ± 0.58 vs 2.57 ± 0.57, 0.009). The mean difference HRQoL scores were similar for sociodemographic and other clinical parameters. This data shows that six months after surgery the overall MacNew HRQoL scores improved markedly. This improvement was regardless of the presence of comorbidities which underscores the importance of considering valvular surgery for indicated patients. The mortality in this cohort was 4% showing significant improvement in surgery compared to the previously reported 14.1%.

10.2. GENERAL DISCUSSION

In the past decade, several concerted global efforts have been initiated towards prevention, management and eradication of acute rheumatic fever (ARF)/RHD. These efforts probably resulted (as a rebound phenomenon) from a global dramatic fall of activities targeting a reduction of ARF/RHD partly due to eradication of the disease in developed countries. [5] In most areas endemic for the disease, there is renewed interest on advocacy of researches concerning it. We are witnessing a new surge of research and advocacy. New initiatives at regional and international levels to address the problem have emerged. The World Heart Federation (WHF) in the year 2013 endorsed the goal of achieving a 25% reduction in premature deaths from ARF/RHD among individuals aged <25 years by 2025. [6] To achieve the target, the WHF defined five goals including ARF/RHD-related research hubs in each WHO-defined geographic region by 2025. In the year 2015, members of African Union (AU) adopted seven key action plans (including research/training activities) toward elimination and eradication ARF/RHD in Africa. [7] Moreover, for the first time in the year 2018 during the 71st World Health Assembly (WHA), ARF/RHD was recognized as a global health priorities on the world stage. [8] It was recommended that countries in endemic areas should invest in activities related to

ARF/RHD such as training, research, and treatment.

The proposed strategies need an understanding of the contemporary characteristics of disease presentation and the use of evidence-based interventions. In Tanzania, there is dearth of data with respect to insight in clinical aspects and outcomes of RHD. The Tanzania Rheumatic Mitral Stenosis (TAMS) study was conducted to fill this gap. In this thesis, we addressed the following questions: 1) What is the current status of RHD in special populations?, 2) What is the clinical profile, treatment patterns, and outcomes of patients with rheumatic MS in Tanzania?**,** 3) What are the valvular pathology and histological changes of surgically excised rheumatic mitral valves in patients undergoing valvular replacement surgery?**,** 4) What is the valvular suitability or non-suitability for catheter-based interventions in this cohort?, and 5) What is a progress made over time in the management of RHD in Tanzania?

10.2.1. CURRENT STATUS OF RHD IN SPECIAL POPULATIONS

To introduce the starting point of this thesis, we conducted two systematic reviews and one original research on RHD in special populations. The first review concerned the influence of gender and migration on the epidemiology and in the management of RHD. The second review examined the epidemiology of infective endocarditis in LMICs. The original research investigated the prevalence of sub-clinical RHD among school – aged children in Tanzania.

Influence of gender and migration on the epidemiology and in the management of RHD

Gender has been reported to influence the epidemiology and management of cardiovascular diseases. [9] This could be much so with RHD that commonly affects females and people from the world's poor communities. [10] Our review showed a female predominance in all of the retrieved RHD studies. Similarly, previous studies have shown that RHD affects more females than males. [11,12] Intrinsic, [13] and extrinsic factors, [10,14] as well as Prothymosin alpha [15] have been implicated for this. Furthermore, it has been inconclusively reported that, females presents in hospital with severe form of disease and that diagnostic approach and management does not differs with sex. [16] Similarly, the review showed that females present with advanced disease probably due to late referral because they have higher prevalence of preserved left ventricular function, [17,18] less clear symptoms, [19] and have poor socioeconomic status. It is not uncommon to diagnose RHD for the first time when a woman become pregnant. The risk imposed by RHD to a pregnant women, to the pregnancy itself and in management is immense. [20] We found no gender difference in diagnostic and management approaches except during pregnacy where echocardiography and cardiovascular magnetic resonance appear to be safe. [21] Moreover, it has been debatable to whether mitral valve anatomy and the

amount of leaflet calcium, important determinants of outcome post-PBMV, differs with gender. [22] The review revieled few studies on gender influence on RHD and the available studies shows inconclusive findings, hence the need for more research in this area.

The effects of migration on epidemiology of cardiovascular diseases other than RHD has been previously reported. [23] It is important to understand the effects of migration on RHD because about half of refugees are females and children, the population at a high risk of ARF/RHD. [24] Also, being a migrant can be regarded a risk factor and a proxy for other risk factors, such as low education level and lower socioeconomic status that are prevalent amongst RHD patients. We observed an evolving trend in the global epidemiology of RHD. We found that, 2.1% of refugees recently screened for RHD in Italy were reported to have sub-clinical RHD. [25] This prevalence is similar to those reported in India (2.0%), Cambodia (2.2%), and Tanzania (2.1%). [3,26] This is a wake-up call for developed nations to revive their medical education programs to include RHD because clinicians and health systems have become unfamiliar with the condition. We further observed that, the effects imposed by migration on migrants' health is huge. For example, if not registered, female migrants are likely not to have access or be informed about the presence of reproductive health services including antenatal care resulting in late diagnoses and eventually obstetric complications. [27] Therefore, migration requires new strategies for implementation to address health issues of migrants including RHD. However, owing to the complexity of migration, well designed researches are needed to address issues relating migration with diseases.

Updates on the epidemiology of infective endocarditis in LMICs

IE is a cardiovascular complication that impose significant morbidity and mortality. Until recently there has been a lack of data on IE from developing countries. The few published review articles had limitations: comprised few studies, did not address the disease trend and had mixed study populations. [28,29] We reviewed the current information on IE in the LMICs where the commonest predisposing condition (RHD) is prevalent. [30] We found that RHD, CHDs and prosthetic heart valves are the common predisposing conditions. Our findings are similar to what has been reported in previous studies. [28,29] We observed that, while the proportion of *Streptococci* and *Staphylococcus aureus* has increased, the number of negative blood cultures and patients undergoing surgery has decreased; which is similar to what has been reported by other researchers. [28,31] On the contrary, Noubiap et al [29] has reported that *Staphylococcus* is the leading cause of IE in Africa, same as it is in high-income countries (HIC). [32,33] The difference between these studies could be due to the difference in the studied populations. Lastly, we highlighted that the mortality imposed by IE has remained unchanged over time, similar to what has been reported from studies in LMICs [28,29] and HICs. [32–34] This is interesting because one could expect a higher mortality in LMICs than HICs. Possible reason for the similarities is that

the most common pathogen in LMICs is *Streptococcus spp* rather than *Staphylococcus spp* which is fatal. Other reasons could be due to the use of cardiac surgery on patients with guideline-recommended indications, and majority of individuals being young and with few comorbidities in LMICs compared in HICs. [29,32] We recommended that RHD control programs should be instituted in areas with high endemicity of the disease. Moreover, appropriate diagnostic and treatment modalities comprising of endocarditis team should be established. Unlike in Europe [35] and North America [36] where there are clear guidelines on the management of IE, it is not so in most of the LMICs. Whether guidelines from HICs can be applied to LMICs is an area for further studies.

Sub-clinical RHD among school – aged children in Tanzania

The WHO and the WHF recommends screening as an effective way for early detection of RHD when secondary antibiotic prophylaxis can be offered. [6,37] Results from a recent clinical trial from Uganda confirmed that the prophylaxis prevents disease progression [38] We found that the prevalence of subclinical RHD among primary school children in Tanzania is similar to the previously reported in other studies from SSA, [4,11,12] signifying a regional population similarities. In this study, RHD was most likely to be diagnosed at older age similar to what have been reported in previous studies. [4,11] Therefore, there is a likelihood of missing potential cases in screening primary school children only. We propose that screening programs should be extended to secondary schools and to communities. In our study, the prevalence of RHD was higher among girls than boys similar to what have been reported in other studies. [4,11,12] Owing to this, strategies to screen women for sub-clinical/established RHD could be cost-effective taking the advantage that they can be screened during pregnancy at antenatal clinics. Our recent recent study have shown that, the majority of women of reproductive age with RHD in a hospital cohort are at the highest pregnancy risk and few of them are on contraception. [39] We recommend that, efforts to prevent and control RHD in our communities are needed. However, to coordinate these efforts, a registry needs to be established. Registry-based control strategies have been reported to be the best framework for delivering secondary prophylaxis and for the establishment of a countrywide RHD control program. [6] For unknown reasons Tanzania was not involved in the two largest RHD registries, i.e. the VALVAFRIC [40] and REMEDY, [26] hence this study could be a base for the country registry.

10.2.2. CLINICAL ASPECTS OF PATIENTS WITH RHEUMATIC MITRAL STENOSIS

Clinical profile, treatment and follow-up of patients with rheumatic MS in Tanzania

Evidence-based medicine is important for the improvement of medical practice. In this context, we have for the first time in Tanzania provided systematically collected data on clinical profile, treatment and outcomes of patients with rheumatic MS. In our study, the majority of patients were young, females, had low monthly income, presented late in hospital with advanced disease, and were not on regular secondary antibiotic

prophylaxis. Except for the extremely low uptake of secondary prophylaxis, other findings are similar to those reported in previous African RHD registries. [26,40] In our cohort, five patients were diagnosed with RHD for the first time during pregnancy. Unlike in western countries where congenital and non-rheumatic valvular heart diseases are the common forms of heart disease in pregnancy, [41] RHD is the common cause in Africa. Recognising this, antenatal services with support from obstetric and cardiology clinics should be implemented. [42] The low (27.7%) uptake of secondary prophylaxis in our study compared to the 60% in Ugandan [43] and 67% in REMEDY [26] registries is a concern. Reasons for low uptake are lack of BPG prescription, believing not in need of BPG, forgetting, painful injection and lack of knowledge about the disease and prevention. These should be addressed through health education.

In our study, surgery and PBMV were provided in half of the patients. Although not meeting guideline-recommended targets in which most of symptomatic patients would require these interventions, [44,45] the proportion of patients who underwent surgery and PBMV is encouraging. In LMICs the uptake of these interventional procedures is low due several reasons including lack of services in most of the countries. [26,40,43,46] In this study, medical treatment carries a higher mortality compared to surgery and PBMV. Smilarly, studies have shown that if left untreated the prognosis of RHD is poor with average age of death of 26 years. [47] We recommend that all patients who require surgery or PBMV as per guidelines should timely receive them if available. We have also shown that arrhyhthmias (predominantly AF) are an independent predictor of mortality in patients with rheumatic MS. Similarly, other studies reported higher mortality in patients with AF than in patients without AF. [26] This indicates the need for early detection and control of arrhythmias including AF.

Histopathological evaluation of chronic rheumatic mitral stenosis

Despite advances in research technology, the pathogenesis of ARF/RHD remains complex and poorly understood. The famous molecular mimicry and failure of the human immune system theories and a recent neo-antigen theory could only explain part of the pathogenesis. [48] Basic science research must continue to unravel this disease which continues to affect many people in LMICs. For the first time in SSA three decades after the last publication on the pathogenesis of RHD, [49,50] in this PhD thesis we have provided a recent RHD pathogenetic mechanism with insights from histopathology. We demonstrated that there is an ongoing inflammatory process in the explanted mitral valves and that the extent of inflammation is associated with the degree of MV leaflet calcification. These calcification, inflammation and neo-anagenesis have been implicated in the formation of fibrosis which is the end result of RHD pathology. [51] Similarly, accumulating research findings had shown that there is resemblance of this scenario with that of atherosclerotic diseases. [13,52] In this study, we confirmed that

there is no significant difference in MV leaflet calcium in relation to sex, age or severity of MS; this has been debatable in literature. [22,53] In this study, the extent of cells of acute inflammation (a proxy of calcification) was significantly higher amongst patients with ARF and short disease duration signifying a rapid progression of the disease in the studied population. Previous studies have reported similar findings that the clinical presentation of MS in Africa is of severe form than for patients from developed countries. [54,55] This underscores a need of early disease detection and eventual secondary prophylaxis for prevention of recurrent attacks of ARF. [38] We propose that the use of anti-inflammatory and anti-remodeling medications in rheumatic valvulitis may reduce the fibrosis and scarring which occur in the valves. These could probably significantly reduce the morbidity and mortality from the disease. Further studies are needed to explore the mechanisms underlying pathogenesis of ARF/RHD.

Characteristics and immediate outcomes of patients who are undergoing PBMV

Cardiac catheterization laboratory plays a central role in the diagnosis and management of RHD. For rheumatic MS, PBMV provide better results comparable to surgery. [44,45] With the high burden of RHD, the increasing availability of access to cardiac interventional services in Africa and the guidelines recommendation for the management of clinically significant MS; [44,45] it is important that PBMV skills should be expanded in disease endemic areas. In HICs, PBMV is occasionally done because of strict selection criteria, advanced surgical services and low incidence of RHD. [56] In this thesis, we have highlighted the role of a heart team in patient selection including proper imaging with transoesophageal echocardiography (TEE) to rule out left atrium (LA) thrombus pre-PMBV interventions. LA thrombus is common among patients with rheumatic MS and it is an absolute contraindication for PBMV. [44,45] The sensitivity of transthoracic echocardiography (TTE) in detecting LA thrombus is about 50% while that of TEE is about 99%. [57] In our cohort, four out of five patients with LA thrombus were missed on TTE that were performed by an experienced operator. The cut-off Wilkins' score that predict better outcomes has been debatable. In this thesis, we have demonstrated that Wilkins scores 9 – 11 achieved a successful result with PBMV, similar to what has been reported in few previous studies. [58–60] We postulate that the young age of our patients and presence of few/no co-morbidities could contribute to this finding. We suggest that, the European and American guidelines [44,45] for a good outcome of PBMV (cut-off Wilkins score ≤ 8) needs to be re-visited. Furthermore, we have shown the importance of skills transfer camps by experts from centres that had established cardiac catheterization. For the first time in Tanzania, we have demonstrated that a well-planned program, which if sustained, could make significant differences in the diagnosis, treatment, and outcomes of patients with rheumatic MS.

10.2.3. PROGRESS IN THE MANAGEMENT OF RHD

A significant number of patients with RHD from LMICs have no access to cardiac surgery when required. [61–63] Therefore, deliberate efforts towards establishing and maintaining interventional services such as cardiac surgery should be embraced and scaled-up in disease-endemic nations. Scaling up of cardiac surgical services, one of tertiary interventions of RHD, in the AU is a possibility but needs multisectoral approach. [64] In this PhD thesis, we compared the progress made in surgical management of RHD in Tanzania between the two-time period, the year 2018 – 2012 (first phase) and the year 2020 – 2021 (second phase).

Predictors of early operative mortality for RHD

In the first phase, we reported the outcomes of RHD cardiac surgery at a Tanzania cardiac centre in a span of four years after its inauguration. We observed a drop in mortality rate from 24% that was reported after 1-year of starting the services [65] to 14%. The only predictor of early mortality was mainly due to double valve replacement surgery in patients. Explanations for the observed improvement were: better selection of patients suitable for surgery, proper choice of the type of valvular surgery, development in skills and expertise among the surgical team, and improved post-operative care. With a good political will and commitment, better communication between policymakers and clinicians/researchers and availability of funds, governments from LMICs can strengthens the local systems including delivery of cardiac surgical services. [66] This is important for early provision of patients care, improving surgical skills of local teams and in helping these countries to save millions of dollars by not referring patients abroad.

HRQoL of patients following mechanical valve replacement surgery for rheumatic MS

In the second phase, we investigated four main issues that are related to the achievement attained one decade after establishment of cardiac surgical services for RHD in Tanzania. First, we observed a drop-in mortality rate from the previously reported 14% [67] to 3.7%. This mortality rate is similar to those reported in other studies. [68,69] Reasons for such improvement are probably same as those reported in the first phase, among others. Second, to the best of our knowledge, for the first time in Africa we have reported the investigation of HRQoL of patients after valve replacement for RHD. With Patients Reported Outcome Measures (PROMs), patients are involved in the decision-making process [70,71] and clinicians may understand how diseases and their treatment affects outcomes that are important to patients. [72] We demonstrated that despite having different comorbidities, patients who receive valve surgery for RHD experience sustained improvement in HRQoL. Our findings are in keeping with other studies which showed improvement in all domains of quality of life after valve replacement for RHD. [73] Third, as part of addressing the gap that could not be answered in the first phase (a retrospective study), we prospectively assessed the role of intraoperative factors

in predicting outcomes post valve replacement. We found that none of those factors (aortic cross-clamp time, cardiopulmonary bypass time and total surgery time) were predictors of HRQoL improvement. To the best our knowledge, this is the first study to investigate the association between intraoperative factors and HRQoL.

10.3. FUTURE PERSPECTIVES

10.3.1. GENERAL OUTLOOK

In studies presented in this thesis, we have consistently observed that RHD continues to be among the leading cause of morbidity and mortality in children and young adults and that the disease has became a public health problem. We further noticed that, the management of RHD is complex and is associated with several unanswered and ongoing challenges among researchers, community, clinicians and policymakers. Keeping that in mind, we advocate the adoption (in disease-endemic countries) of a conceptual framework comprising of baseline data on disease burden, human resources, and treatment protocols as well as requirements for implementing preventive measures for RHD control. Research agenda should be an integral part of the program.

10.3.2. SOCIETAL IMPACT OF THE THESIS

Due to the known problem of ARF underdiagnosis, especially where clinicians and the community are not familiar with the condition, nationwide clinicians/community education should be introduced to improve awareness and clinical diagnostic capability. There is an urgent need for RHD endemic countries to invest in prevention and early detection of the disease to avoid complications. In this sub-section we are discussing the importance of improving diagnostic capability, investing in preventive measures and the role of policymakers. In Tanzania, ARF/RHD was not part of the national health (research) agendas or strategies despite its intersection with priorities like child and adolescent health, maternal health, and noncommunicable diseases (NCDs). However, several activities/researches dealing with ARF/RHD are currently underway in well-coordinated programs/projects at the country level. For instance, the Ministry of Health in collaboration with the World Diabetic Federation and Tanzania Diabetic Association has been conducting a series of trainings on early detection and management of NCDs including ARF/RHD since June 2022. The trainees are health care workers (HCWs) at primary health care facilities throughout the country (***Figure 1***). [74] Importantly, under this program, the ministry has been able to establish several NCDs registries including RHD registry.

Figure 1. On the left is Dr Reuben Mutagaywa giving a lecture during a series of lectures on NCDs including RHD to HCWs in the Lake zone regions, November 2022 in Mwanza. On the far left is the regional medical officer, Dr Thomas Rutachunzibwa. On the right is part of HCWs in training. A total of 600 HCWs were trained.

From October 2022, Tanzania began to implement the PEN-Plus (the Package of Essential Non-communicable Disease Interventions – Plus) project. PEN-Plus is a strategy to increase access to services and save lives by decentralizing care for severe NCDs (ARF/RHD, sickle cell disease, and type 1 diabetes) in highly constrained health systems. [75] The project is focusing on training, research and provision of care (treatment). HCWs at district level hospitals are equipped with diagnostic point-of-care technologies (such as electrocardiogram, echocardiogram, and rapid streptococcal antigen test kits) and medications to early detect and manage these severe NCDs (***Figure 2***). As part of its research arm, the project is conducting a screening for sub-clinical RHD among secondary school students and in general communities in Kondoa district, Dodoma region. Results from this screening program are expected to be available by September 2023. This will help to address the un-answered question of the prevalence of sub-clinical RHD in those populations. To strengthen the strategy, the WHO Regional Office of Africa met to approve regional PEN-Plus draft as part of the agenda for its seventy-second Regional Committee Meeting in August 2022. [76]

Figure 2. On the left is Dr Reuben Mutagaywa lecturing during a series of lectures on RHD for HCWs involved in PEN Plus project in Kondoa on 7th March 2023. On the right are HCWs being trained to do echocardiography. A total of 60 HCWs were trained.

Tanzania is among the six countries (Brazil, India, Uganda, United States of America, and Israel) that are involved in a project aiming at developing a diagnostic test for early detection of ARF. The research is being pursued through the Leducq PRIMA (Preventing Rheumatic Injury Biomarker Alliance) study (*Chillo P et al, personal communication, March 2023*). The PRIMA project will also increase awareness on ARF/RHD in schools, in the community, and among HCWs at the primary healthcare facilities by utilizing the available training materials of ARF/RHD for school-based RHD control program (***Figure 3***). [3,77] Establishment of sustainable secondary antibiotic prophylaxis in Tanzania is among the goals of our school-based RHD control program.

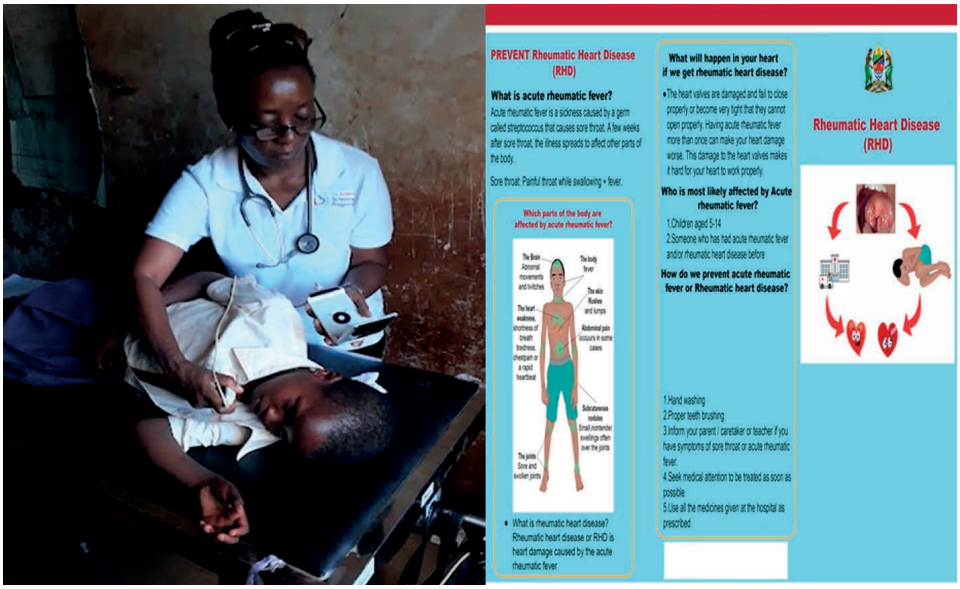

Figure 3. On the left is Prof Pilly Chillo screening subclinical RHD with hand-held echocardiogram in a school- based RHD prevention program in Tanzania. [3] On the right is one of the training materials used in the program.

With two years toward WHF target of 25% reduction in death due to RHD, we hope that the outcomes of these initiatives will be game changer for success in combating ARF/ RHD.

CONCLUDING REMARKS

- Globally, the prevalence of RHD is high and increasing. With globalization and migration, the epidemiology of RHD is evolving. Patients with RHD are now reporting to hospitals in Europe in a significant number.
- Females are more affected and receives late referral to hospital with already advanced disease. Screening of these women for RHD in communities or when they attend antenatal clinics, especially those residing in endemic areas is warranted.
- Despite of few studies on infective endocarditis in LMICs, RHD remains the commonest predisposing condition.
- Surgically excised rheumatic valves reveal evidence of active inflammation underscoring the importance of prophylactic antibiotics even after valve surgery. However, the overall uptake of prophylaxis is low calling for a need of addressing the associated barriers. There is no difference in mitral leaflet calcium in relation to sex, age or severity of MS.

- Patients with Wilkins score of up to 11 can still undergo successful PBMV. With a well-planned program, PBMV skills transfer and expansion is possible in most of LMICs.
- Strengthening of local systems for RHD patients care including delivery of cardiac surgical services in LMICs is possible.

Summary of main findings and recommendations from this thesis are as depicted in ***Figure 4***.

Figure 4. Central illustration showing our study findings and recommendations on RHD interventions in Tanzania

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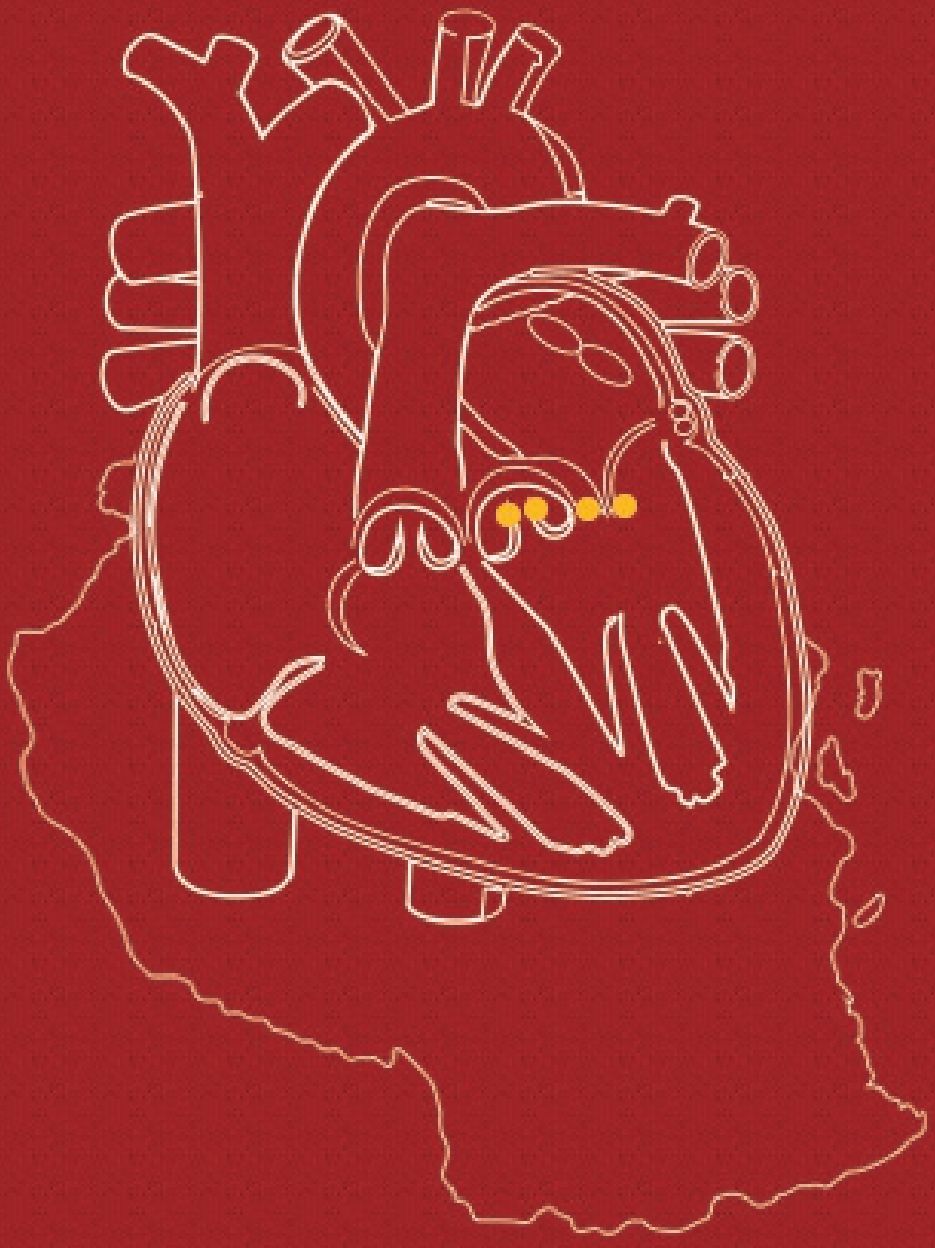

APPENDICES

SAMENVATTING

Hoofdstuk 1 is de algemene introductie en overzicht van dit proefschrift. In dit hoofdstuk komen drie zaken aan de orde: 1) de ziektelast van reumatische hartziekten (RHD) is hoog en neemt toe; 2) de zorg voor patiënten met RHD in (lage en midden- inkomenslanden (LMIC's) is complex; en 3) de pathogenese van RHD is nog niet volledig ontraffeld. In dit proefschrift worden ook kennishiaten met betrekking tot RHD geidentificeerd die moeten worden opgepakt in de onderzoeksagenda in de klinische paraktijk van alledag.

DEEL 1. VAN HET PROEFSCHRIFT GAAT OVER RHD IN SPECIALE POPULATIES.

In het eerste deel van **hoofdstuk 2** rapporteerden we over de invloed van gender op de behandeling van reumatische mitralisstenose (MS). We ontdekten dat vrouwen pas in een ver voortgeschreden ziekteproces naar het ziekenhuis kwamendoor: slechte sociaaleconomische status, beter intact gebleven hartfuncties dan bij de mannen en vage klachten. Diagnostische en behandeling verschilde niet tussen mannen en vrouwen. We hebben inconclusieve resultaten verkregen over de verschillen in anatomie van de mitralisklep en de hoeveelheid calcium tussen mannen en vrouwen, een onderwerp waarover in de literatuur ook nog steeds discussie bestaat. Verder wordt een verandering gezien in de epidemiologie van de ziekte, RHD wordt in toenemende mate gediagnosticeerd in iekenhuizen in Europa. Bovendien blijkt een deel van de migrantenen vluchtelingen niet-gediagnosticeerde RHD te hebben. Derhalve zal ook het gezondheidsysteem in Westerse landen aangepast moeten worden aan de veranderende behoeften van migranten en vluchtelingen zoals screening op subklinische RHD.

Er is weinig bekend over infectieuze endocarditis (IE) in LMIC's. **Hoofdstuk 3** geeft de de huidige stituatie van IE in ontwikkelingslanden weer en onderzoekt of er in de loop van de tijd een verandering is opgetreden in de presentatie van IE. Van de vergeleken twee cohorten, d.w.z. studies gepubliceerd vóór 2015 (groep 1) en studies na2015 (groep 2), kwam RHD meer voor in groep 1 dan in groep 2 (42,3% vs 30,3%, p<0,001), mbt congenitale hartziekten (CHD) was er geen verschil. Streptokokkeninfecties waren minder aanwezig in groep 1 dan in groep 2 (26,2% versus 37,7%, p<0,001). Het aandeel Staphylococcus aureus was 15,3% in groep 1 en 23,6% in groep 2, p<0,001. Een negatieve bloedkweek (NBC) kwam vaker voor in groep 1 dan in groep 2 (42,2% vs 34,1%, p=0,002). Patiënten in groep 1 ondergingen meer operaties dan in groep 2 (38,8% vs 28,8%, p<0,001). De mortaliteit veranderde niet in de loop van de tijd. Ons onderzoek toont aan dat een tijdige diagnose en behandeling van patiënten met RHD en CHD, en uitgebreide behandeling van IE, zoals het inschakelen van het "endocarditisteam", van groot bel;ang zijn voor goede behandelingsuitkomsten.

.

In **hoofdstuk 4** werd de prevalentie bepaald van subklinische RHD gedetecteerd door

middel van een handheld-echocardiogram bij kinderen die deelnamen aan een RHD-preventieprogramma op scholen in Tanzania. Dit is het grootste en een van de weinige studies naar de prevalentie van RHD in Oost-Afrika. Het maakt deel uit van een lopend onderzoeksprogramma naar longitudinale gegevens over RHD. In totaal werden 4436 kinderen gescreend en bij 95 kinderen werd subklinische RHD gevonden, wat een prevalentie geeftvan 2,1% [95% BI 1,7% – 2,6%]. Onafhankelijke factoren geassocieerd met subklinische RHD waren vrouwelijk geslacht (gecorrigeerde odds ratio{aOR} 1,83, 95% BI 1,18 – 2,85, p = 0,007), hogere leeftijd (aOR 1,73, 95% BI 1,10 – 2,72, p = 0,018 voor leeftijdsgroep 11-14 jaar) en (aOR 3,02 95% BI 1,01 – 9,05, p = 0,048 voor leeftijdsgroep 15-16 jaar), evenals aanwezigheid van een hartruis, aOR 5,63 95% BI 2,31 – 13,69, p < 0,0001. Geen van de bestudeerde socio- economische factoren was in ons onderzoek geassocieerd met de aanwezigheid van subklinische RHD. Onze gegevens ondersteunen de aanbeveling van de Wereldgezondheidsorganisatie (WHO) en de Wereldhartfederatie (WHF) dat screening op subklinische RHD een cruciale eerste stap is voor een alomvattend RHD-controleprogramma om gegevens te verkrijgen over de ziekte last van RHD in de maatschappij in verschillende delen van de wereld.

DEEL 2. VAN DIT PROEFSCHRIFT BESPREEKT DE KLINISCHE PRESENTATIE VAN PATIËNTEN MET REUMATISCHE MS, DE PATHOGENESE VAN DE ZIEKTE EN DE DAAROPVOLGENDE INTERVENTIES.

De WHF heeft RHD sinds 2013 geprioriteerd als een belangrijk probleem voor de volksgezondheid en heeft strategieën voorgesteld, waaronder de beschikbaarheid van gegevens over de ziektelast, om RHD te verminderen en uit te roeien. In **hoofdstuk 5** hebben we hedendaagse gegevens beschreven over het klinische profiel, de behandeling en de follow-up van patiënten met reumatische mitralisklepstenose (MS) die werden opgenomen in het Jakaya Kikwete Cardiac Institute (JKCI) in Tanzania. Prospectief werden 290 patiënten bestudeerd We ontdekten dat de ziekte vooral jonge mensen treft, voornamelijk vrouwen, en met een laag inkomen. Patiënten komen laat in het ziekenhuis en er is een lage (27,7%) graad van secundaire antibioticaprofylaxe. Interventies werden uitgevoerd bij de helft van de patiënten (46,2% chirurgische en 3,8% percutane mitralisklepplastiek {PBMV}). Negenendertig (14,4%) patiënten stierven, waarvan 11 (4%) sterfgevallen in de chirurgische en 28 (10,4%) in de medische behandelarm. De onafhankelijke voorspellers van mortaliteit waren: medische versus chirurgische behandeling (crude HR 3,12, 95% BI 1,50 – 6,49, p = 0,002) en de aanwezigheid van aritmieën vs geen aritmieën (crude HR 2,44, 95% BI 1,19 – 4,49, p = 0,015). Deze gegevens dienen als basis voor het opzetten van het RHD-register in Tanzania.

In **hoofdstuk 6** bestudeerden we de histopathologische veranderingen in chirurgisch verwijderde reumatische MS-kleppen met behulp van geavanceerde techniekenvergeleken de histopathologie met klinische presentatie, pathogenese

en behandeling. We hebben waargenomen dat veel mitralisklepcalcium wordt aangetroffen bij oudere patiënten, mannen en bij patiënten met ernstige MS. Er werd een laag percentage secundaire antibiotische profylaxe vastgesteld en twee patiënten vertoonden acute reumatische koorts. Meer dan tweederde van de uitgesneden kleppen vertoonde tekenen van aanhoudende ontsteking met fibrinoïde degeneratie (FD), polymorfonucleaire leukocyten (PMNL) en fibrose op hematoxyline-eosine kleuring. Ongeveer de helft van de specimens vertoonde tekenen van verkalking van verschillende ernst en een tiende had Aschoff-noduli. Een meerderheid van de specimens was positief voor markers van ontstekingscellen, namelijk CD3 (85,2%), CD20 (64,8%), CD68 (72,2%) en CD8 (14,8%). De mate van inflammatoire cellulaire infiltratie was geassocieerd met klepverkalking, FD met ARF, PMNL met ziekteduur < 10 jaar en fibrose met de afwezigheid van atriumfibrilleren. C-reactief proteïne en anti-streptolysinetiters waren hoog in CD20- en CD8-kleurende cellen. De associatie tussen klinische parameters met histopathologische-immunohistochemische studies waargenomen in onze studie verklaart een deel van de pathogenese van RHD.

Met de toegenomen beschikbaarheid van katheterisatielaboratoriain Afrika, zijn PBMV-interventies haalbare opties voor geselecteerde patiënten met reumatische MS. Daarom is het belangrijk om PBMV-training/overdracht van vaardigheden in Afrikaanse landen te verbeteren. **Hoofdstuk 7** onderzocht de klinische praktijk van patiënten met reumatische MS die werden geëvalueerd voor PBMV en definieerde de rol van beeldvorming, hartteam, training/vaardigheidsoverdracht bij PBMV-interventies in een academisch ziekenhuis in Tanzania. We toonden aan dat bij vijf patiënten trombi in het linker atrium aanwezig waren, waarvan er vier niet konden worden gedetecteerd met een transthoracaal echocardiogram, maar alleen met een transoesofageaal echocardiogram (TEE), wat het belang van pre-PBMV TEE benadrukte. We toonden in ons cohort aan dat patiënten met een Wilkins-score tot 11 een succesvolle PBMV ondergingen, derhalve adviseren wij aan te drinegn op heroverweging van de door Europese en Amerikaanse richtlijnen aanbevolen cut-off score ≤ 8. We hebben vastgesteld dat PBMV goede kortetermijnresultaten heeft bij geselecteerde patiënten, wat het belang van de juiste patiëntenselectie onderstreept. Voorts hebben we een multidisciplinair ” hartkleppen team” opgezet, dat een grote impact kan hebben bij de behandeling van patiënten met reumatische MS in LMICs.

DEEL 3. RICHT ZICH OP DE VOORTUITGANG IN HET MANAGEMENT VAN RHD.

In **hoofdstuk 8** hebben we retrospectief 212 RHD-patiënten onderzocht die hartchirurgie ondergingen in Tanzania tussen het jaar 2008 – 2012. Het sterftecijfer daalde in 4 jaar tot 14,1% vergeleken met de 24% die werd gerapporteerd na 1 jaar na het instellen van RHD-hartchirurgie bij Muhimbili National Hospital (MNH). Bij patiënten met RHD gaat een dubbele klepvervanging gepaard met een verhoogde vroege mortaliteit, waarvoor

meer technische expertise en zorgvuldige postoperatieve behandeling een oplossing zijn. We hebben ook duidelijk gemaakt dat er een grote behpoefte is aan lokale richtlijnen voor de behandeling van RHD-patiënten. **Hoofdstuk 9** onderzocht prospectief de gezondheidsgerelateerde kwaliteit van leven (HRQoL) van 54 patiënten die werden geopereerd vanwege reumatische MS. De gemiddelde (±SD) globale MacNew-scores waren preoperatief 3,47 ± 0,59, 4,88 ± 0,71 en 6,14 ± 0,50, respectievelijk na 3 maanden en 6 maanden (p-waarden voor trend <0,001). De preoperatieve en 6 maanden gemiddelde verschil HRQoL scores waren hoger bij patiënten met vs. zonder boezemfibrilleren (2,95 ± 0,59 vs 2,45 ± 0,53, p=0,003) en degenen die anticoagulantia (preoperatief) hebben vs niet op anticoagulantia staan(3,14 ± 0,58 vs 2,57 ± 0,57 , 0,009). Het gemiddelde verschil in HRQoL-scores was vergelijkbaar voor de sociodemografische en andere klinische parameters. Deze gegevens laten zien dat zes maanden na de operatie de algehele MacNew HRQoL-scores aanzienlijk verbeterden. Deze verbetering was onafhankelijk van de aanwezigheid van comorbiditeit, wat het belang onderstreept van het overwegen van klepchirurgie ook bij patiënten met comorbiditeiten. De mortaliteit in dit cohort was 4%, wat een significante verbetering in de chirurgische behandeling laat zien in vergelijking met de eerder gerapporteerde 14,1%.

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DEDICATION

I would like to dedicate this thesis to my father **Ta Paulo Samwel Mutagaywa Mutabuzi** who is no longer with us. He was my teacher in many ways- taught me to work hard, love and help people, and love God. He was confident in me and always assured me that success in life is possible if one has determination, I wish he could be here to witness this success.

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ABOUT THE AUTHOR

Reuben K. Mutagaywa was born on 14th August 1977 in Bukoba, Tanzania. He attended Ilboru Secondary Special School for Advanced studies. He then proceeded to the University of Dar es Salaam in Tanzania where he carried out his clinical studies and graduated with a Doctor of Medicine (MD) degree. He undertook compulsory internship in Bugando Medical Center in Mwanza, Tanzania where he undergone rotations in Internal Medicine, Paediatics and Child Health, Obstetrics and Gynecology, and Surgery.

Reuben joined Muhimbili Orthopaedic and Neurosurgical Institute (MOI) where he worked as a Registar. He proceeded to pursue Masters of Medicine (MMed) in Internal Medicine at Muhimbili University of Health and Allied Sciences (MUHAS) in Dar es Salaam, Tanzania and graduated as the best final year MMed student in Internal Medicine.

Reuben cultivated much interest in Cardiovascular science and joined MUHAS and Apollo Hospital Bangalore in India to pursue Masters of Science (MSc) in Cardiology. To further his skills, Reuben was selected by the Pan African Society of Cardiology (PASCAR) for a Fellowship in Cardiac Pacing at the University of Cape Town – Groote Schur Hospital Iin South Africa under the supervision of Prof Ashley Chin. When he came back to Tanzania, Reuben maintained a strong presence in clinical work at the Jakaya Kikwete Cardiac Institute (JKCI), MUHAS and MOI.

Due to his interest in Cardiovascular research, Reuben developed a proposal with Prof. Steven Chamuleau and Prof. Pilly Chillo which later became the focus of his PhD thesis. During the course of the PhD thesis, Reuben supervised dissertations for Undergraduate students (9), Masters students (22), and Cardiology fellows (10) from MUHAS, University Medical Centre Utrecht, the Netherlands, and the University of Dodoma in Tanzania. He has been an Internal examiner of ten Postgraduate dissertations. Reuben continued with his clinical and teaching role at MUHAS, MOI, and JKCI. At MUHAS, Reuben is a Course Coordinator of Masters of Science in Cardiology while at MOI he is the Head of Internal Medicine Unit and Manager of Physician and Pharmacy Section. He is also a Chairman of MOI Medical Tourism Committee.

During the course of the PhD he worked, and still works, with several research projects in Tanzania: I. Parkinson's disease and its social and economic impact in Tanzania - University of Dar Es Salaam winners of competitive research proposal and public grants (year 2019; $ 10,900). II. A Study on Pregnancy-related Cardiovascular Diseases in Tanzania (PRECARDT): The Gsk grant on fighting NCD in Africa (2019 - 2020; $ 100,000); III. COVID-19 & NCDI Poverty: Rapid Responses for Innovative Care Redesign and Social Protection (2020 – 2021; $25,000); IV. The PEN Plus project: interventions

for severe NCDs such rheumatic heart disease at district hospitals in Tanzania (2021 – to date; $ 375,573); and V. Leducq Foundation Acute Rheumatic Fever Biomarker Project Preventing Rheumatic Injury Biomarker Alliance (2022 – to date; $ 8,000,000). He is Ad hoc reviewer for medical journals: BMV Cardiovascular disorders, BMJ Open, Cardiovascular Journal of Africa, Tanzania Medical Journal, Global Heart, Reproductive Health, Health Promotion International, International Archives of Nursing and Health Care, Journal of Saudi Heart Association, Journal of Public Health, and Annals of Public Health Reports.

He is currently registered by Tanganyika Medical Council to practice as Super Specialist in Tanzania in good standing. He is a member of: The Medical Association of Tanganyika (MAT), Association of Physicians of Tanzania (APHYTA), Tanzania Cardiac Society (TCS), East, Central and Southern Africa College of Physicians (ECSACOP), Pan African Society of Cardiology (PASCAR), African Heart Rhythm Association (AFHRA), Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), and Fellow, European Society of Cardiology (FESC). Reuben was recently selected by the HRS to participate in the 2023-2024, Growth and Leadership Opportunity for Black Electrophysiologists (GLOBE). He is the Committee member of the Africa Regional Advisory Group (RAG) of the International Society of Hypertension for 2022-2024. Reuben is the Director and owner of Muhumuliza Healthcare Polyclinic that is situated in Dar es Salaam.

Reuben's hobbies include reading, travelling, jogging and involvement in community services.

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