**The profile of Rheumatic Heart Disease at a Tertiary hospital, Kwa-Zulu Natal, South Africa**

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**Preface and Declaration**

I, Shange Kwenzakwenkosi Siyabonga, declare that:

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II. This dissertation has not been submitted for any degree or examination at any other university.

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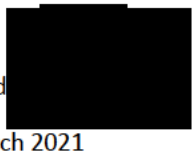
Signed 

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**Dedication**

## Gloria in excelsis Deo

**Executive Summary**

**Introduction**: Rheumatic heart disease (RHD) is a disease of poverty, and a significant public health concern globally. It is the leading cause of heart failure (HF) in children and young adults in endemic areas, and therefore contributes significantly to the non-communicable disease (NCD) burden of diseases in developing countries.

Although there has been a substantial decrease in the incidence of RHD in developed countries it remains endemic in developing countries. There is however limited data from African countries. In SouthAfrica (SA) there are no studies on the profile of RHD, especially in the post-apartheid era.

Therefore, the purpose of this retrospective descriptive study is to describe the pattern of RHD in the era of improved socioeconomic conditions and improved health care access in Kwa-Zulu Natal (KZN); and describe the demographic profile, clinical presentation, and outcomes of RHD at Inkosi Albert Luthuli hospital.

**Methods:** This is a retrospective five-year (2012-2016) study of the demographic, clinical, echocardiographic and outcomes data in 981 patients aged >12 years with RHD in KZN.

**Results:** Most patients were Black (87.9%); the median age was 24 years (IQR 15-36) and the female to male ratio 2.3:1. Dyspnoea (92.2%) was the commonest presenting symptom and mitral regurgitation (56.4%) was the commonest valve lesion. Atrial fibrillation (AF) (44.9%) was the commonest complication at presentation, followed by heart failure (HF) (28.6%). Atrial fibrillation mostly affected the 41 – 60 years age group (OR 2.075, CI 1.22 - 3.52, p=0.007). Compared to the adolescent group (<20 years), heart failure was less common in the age groups 21-40 and 41-60 years (OR 0.455, CI 0.286 - 0.723, p = 001 and OR 0.495, CI 0.288 - 0.852, p = 0.011, respectively). Valve replacement was performed in 723 (88.4%) (mitral 62.2%; aortic 4.8; mitral + aortic 29%, multiple valve surgeries 4%) of the 818 patients who had interventional procedures. The mortality was high (20.1%). Predictors of death were age between 41 - 60 years at the time of diagnosis (OR 1.916, CI 1.254 - 2.926, p = 0.003) and double valve replacement (OR1.521, CI 1.009 - 2.229, p=0.045). Less deaths occurred in those who underwent single valve surgery (Pearson Chi Square = 18.95, p = 0.000).

**Conclusion:** RHD remains a significant cause of cardiovascular morbidity especially in young Black Africans of disadvantaged communities in KwaZulu- Natal. Most patients presented at an advanced stage of the disease requiring immediate intervention. Valve replacement surgery remains the commonest intervention due to severe RHD at presentation. Older age at diagnosis and double valve replacement emerged as significant predictors of mortality.

**List of Abbreviations**

| | |
|---|---|
| AF | Atrial fibrillation |
| AIDS | Acquired Immunodeficiency Syndrome |
| AR | Aortic regurgitation |
| ARF | Acute rheumatic fever |
| AS | Aortic stenosis |
| CCF | Congestive cardiac failure |
| EC | Eastern Cape |
| GAS | Group A Streptococcus |
| GBD | Global burden disease |
| HIV | Human immunodeficiency virus |
| IALCH | Inkosi Albert Luthuli Central Hospital |
| ICD 10 | International Statistical Classification of Diseases |
| IE | Infective endocarditis |
| IgA | Immunoglobulin A |
| IgM | Immunoglobulin M |
| IgG | Immunoglobulin G |
| KZN | KwaZulu-Natal |
| LDL | Low density lipoproteins |
| MR | Mitral regurgitation |
| MS | Mitral stenosis |
| NCD | Non-communicable diseases |
| NP | Northern Province |
| NYHA | New York Heart Association |
| PC | Phosphorylcholine |
| RHD | Rheumatic heart disease |
| SA | South Africa |
| SADC | Southern African Development Community |
| SLE | Systemic lupus erythematous |
| TR | Tricuspid regurgitation |
| VCAM | Vascular cell adhesion molecule |
| WHO | World Health Organization |

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## Chapter 1: Literature review

### 1.1 Introduction

Rheumatic heart disease (RHD) is an acquired heart disease secondary to valvular damage following recurrent episodes of acute rheumatic fever (ARF) which occur during childhood (1). The pathogenesis of ARF is caused by the interaction of a rheumatogenic strain of group A streptococci (GAS) and a susceptible host living in poor socioeconomic conditions (2). ARF and RHD are a significant public health concern globally (3), however they remain diseases of poverty and a scourge in low socioeconomic circumstances (4). RHD is the leading cause of heart failure in children and young adults below the age of 25 years in RHD endemic areas (5, 6), and contributes significantly to the non-communicable disease (NCD) burden of diseases in developing countries (7).

Despite the disease being prevalent in developing countries, there is paucity of data from African countries (8). In South Africa (SA) the prevalence of RHD has primarily been reported amongst asymptomatic children of school going age, below the age of 14 years (7) and in symptomatic pregnant women (9). This has therefore created a scarcity of data of RHD in the greater adult population above age 14 years old (10).

This study highlights the burden of RHD in the adult population of KwaZulu-Natal, by assessing the prevalence of RHD in adult patients referred to the tertiary institution serving the greater part of the province. The secondary aims were to describe the common clinical characteristics of RHD in this population cohort and how these inform the management of disease. This will hopefully contribute toward achieving some of the core values of the Drakensberg declaration adopted in 2005 with the aim of combating RHD (11).

### 1.2 Pathogenesis and course of rheumatic heart disease

The pathogenesis of RHD is characterized by three stages namely, the group A streptococcal (GAS) infection, the development of ARF in 0.3 - 3% of the affected individuals with repeated infection (12), and subsequently the development of RHD (13).

Molecular mimicry between GAS and human proteins is the triggering factor leading to autoimmunity in rheumatic fever and RHD, in genetically susceptible individuals (14). This results in carditis secondary to structural damage of host tissues by B and T lymphocytic cell response (15) (16-18).

The cross-reactive antibodies bind to endothelial cells on the heart valve, leading to activation of the adhesion molecule, the vascular cell adhesion molecule- 1 (VCAM-1), with resultant recruitment of activated lymphocytes and lysis of the endothelial cells in the presence of complements. The ensuing tissue damage leads to the release of peptides such as laminin, keratin and tropomyosin, which activate cross reactive T-cells that invade the heart, amplifying the damage and causing epitope spreading (19).

Acute rheumatic fever may affect the endocardium (40 - 50%), pericardium (5 - 10%), or myocardium (rarely) may be affected, but endocardial involvement with valvular damage is the hallmark of rheumatic carditis (20,21). All four valves can be implicated in RHD, and the mitral valve is almost always affected, alone (50– 60% of cases) or in combination with the aortic valve (20% of cases) (22). In contrast, isolated aortic valve disease is uncommon. Damage to the pulmonary and tricuspid valves is usually secondary to increased pulmonary pressures resulting from left sided valvular disease (23). Mitral regurgitation is commonly the early valvular lesion following valve damage from ARF, then over the years a stenotic lesion may develop - usually because of recurrent episodes of rheumatic fever leading to leaflet thickening, scarring and calcification (23). Mitral stenosis is usually a late complication that develops at least after over a decade from the initial attack (24, 25). However, early development of mitral stenosis in adolescents living in areas with poor socioeconomic standing has been described at an incidence 7-15 times higher than that of adolescents in developed areas (19, 25, 26), due to persistent or recurrent valvulitis causing bicommissural fusion (27).

### 1.3 Epidemiology of Acute Rheumatic Fever and Rheumatic Heart Disease

Acute rheumatic fever usually occurs in children aged 5 - 15 years old (28), at an incidence of over 50 per 100 000 children in some developing countries (29). The frequency decreases in older adolescents and young adults (28). Approximately 3-6% of any population group are susceptible to ARF (20). Recurrent episodes of ARF, however; remain relatively common in adolescents and young adults in developing countries and therefore the prevalence of RHD peaks between the ages of 25 and 40 years (20), with a mean age of 28 years (30). The incidence of recurrent ARF is greatest in the first year after the first ARF episode (31) and the risk of progression to RHD following ARF, is very high in the first year after the first episode of ARF, with the risk decreasing thereafter (31). Approximately 60% of patients will progress to develop RHD, following cumulative episodes of ARF; with an estimated 300 000 of the 0.5 million individuals who acquire ARF every year developing RHD (32).

A substantial decrease in the incidence of RHD has been observed in developed countries, including SA in the last two decades (33), predominantly due to improved living conditions and better access to health care. Despite the declining incidence in developing countries, 33.4 million cases were reported

globally in 2015 resulting to 10.5 million disability – adjusted life years and 319 400 deaths (34). An incidence of 282 000 new cases is reported each year (35).

### 1.3.1 The global burden of Rheumatic Heart Disease

Approximately 62 - 78 million individuals worldwide may have RHD, which could potentially result in 1.4 million deaths per year owing to the disease and its complications (36). The majority of RHD patients (79%) reside in developing countries (3). A systematic review of 57 RHD studies using echocardiography criteria in children aged between 5 and 14 years found that the prevalence of RHD was highest in lower socioeconomic regions. Sub-Saharan Africa (SSA) has the highest calculated regional prevalence, followed by the Pacific, indigenous Australia and New Zealand and South-Central Asia (30), as shown in Table 1. The reason for the high incidence of ARF and RHD, in these countries is probably due to poverty, overcrowding, and increased frequency of sore throats and skin infections and lack of access to medical care (37).

Table 1. Global prevalence and estimation of number of rheumatic heart disease cases in children aged 5-14 years old

| Region | Number of RHD cases found | Calculated regional RHD prevalence (case per1000) | Population4 -14 years | Estimated RHD cases aged 5 -14 years |
|---|---|---|---|---|
| **Sub-Saharan Africa** | 528 | 5.7 | 177 244 000 | 1 008 000 |
| **South central Asia** | 279 | 2.2 | 340 530 000 | 735 000 |
| **Asia other*** | 199 | 0.8 | 124 677 000 | 102 000 |
| **Latin America** | 58 | 1.3 | 108 278 000 | 137 000 |
| **Middle East and North Africa** | 52 | 1.8 | 83 956 000 | 154 000 |
| **Eastern Europe** | 225 | 1.0 | 41 076 000 | 40 000 |
| **Pacific and indigenous Australia/ New Zealand** | 116 | 3.5 | 2 1185 798 | 7800 |
| **Established market economies*** | 116 | 0.3 | 110 621 202 | 33 000 |
| **China** | 25 | 0.8 | 220 226 000 | 176 500 |
| **TOTAL** | **1598** | **1.3** | **1 208 794 000** | **2 393 500** |

Adapted from: the estimated number of rheumatic heart disease cases in children 5 – 14 years. The global burden of group A streptococcal diseases (30).

*Asia other: Eastern Asia, South Eastern Asia, excluding China and Japan.

*Established market economies: Japan, non-indigenous Australia and New Zealand, northern Europe, southern Europe, western Europe, northern America.

### 1.3.2 Sub-Saharan Africa burden of rheumatic heart disease

Rheumatic heart disease continues to be a major cause of premature death and morbidity in low and middle-income countries, despite the decreasing prevalence in developed countries (23, 38).

In Africa, the highest prevalence is seen in sub-Saharan region at 5.7 per 1000 in children aged 5 - 14 years (30). The pickup rate and prevalence of RHD increases when using echocardiography as a

screening tool (39). The prevalence of RHD among children aged 6 to 17 years rose from 2.3 per 1000 to 30 per 1000 in a study from Mozambique (39), and from 4.9 cases per 1000 to 14.8 cases per 1000, in asymptomatic Ugandan schoolchildren with the use of echocardiography as a screening tool (40).

In SA, a prevalence of 6.9 per 1000 persons was reported from two auscultation-based screening studies based in low-income peri urban areas, in 1972 and 1986, in Soweto, Johannesburg and Hout bay, Cape Town respectively (41, 42). However, a lower prevalence of 1 per 1000 was reported from a 1987 auscultation-based study from Inanda, Durban among black school children aged between 4 and 18 years (43). This low detection rate was understood to be due to poor school attendance caused by political turmoil and severe disease (43). In contrast an echocardiogram-based screening study from Soweto (2006 and 2007) reported a higher incidence of new RHD cases at 23.5 per 100 000, in the 14-year-old age group (10). The exact reasons for the increased number of new cases is not known because a noticeable decline of both ARF and RHD had been shown, amongst children under the age of 14 years in SA (33) owing to improved socioeconomic conditions, better living conditions, decreased overcrowding and improved access to health care post-apartheid (33).

## 1.4 Rheumatic heart disease

### 1.4.1 Clinical presentation of acute rheumatic fever

Acute rheumatic fever presents as a combination of fever, polyarthritis (in 60 – 75%), carditis (in 50 - 60%), chorea, erythema marginatum and subcutaneous nodules three weeks after the initial streptococcal infection (25). Chorea and carditis however may occur up to six months later after the initial insult (25). Carditis manifests as a new or changing heart murmur, development of cardiac enlargement or cardiac failure, pericardial effusion and conduction abnormalities and arrhythmias (1).

### 1.4.2 Clinical presentation and complications of Rheumatic Heart Disease

Rheumatic heart disease is usually subclinical and asymptomatic for at least 10 years before progression to cardiac failure (40). The delayed presentation of the cardiac failure is a result of compensatory dilatation of the left atrium and the left ventricle before the onset of left ventricular systolic dysfunction (44). In a systemic review, 51 of the 330 (15.4%) patients newly diagnosed with RHD, presented with impaired systolic function and 34 of the 330 (10%) presented with atrial fibrillation (AF) (45). Rheumatic heart disease may present with symptoms of dyspnoea, (New York Heart Association class III/IV), fatigue and peripheral oedema usually at the ages of 20 – 50 years (46), due to complications of left ventricular systolic dysfunction, atrial arrhythmias, embolic events, infective endocarditis (IE), and angina pectoris (47).

The pattern of valve disease depends on the valve involved, and presentation also differs in different age groups. Patients between 10 – 29 years most commonly present with pure mitral regurgitation, while patients aged 20 - 39 years predominantly have mitral stenosis and older patients present with mixed mitral valvular heart disease (10).

### 1.4.3. Outcomes of rheumatic heart disease

Rheumatic heart disease results in 200 000 – 250 000 premature deaths every year and is one of the major causes of cardiovascular deaths and morbidity in children and young adults in developing countries (1, 23). The mortality burden is possibly underestimated, because of unavailable or incomplete data from developing countries (48). In 1990, ARF and RHD resulted in approximately 6.1 million years of potential lives lost before the age of 70 years, of which 5.5 million occurred in developingcountries (20). Rheumatic heart disease accounted for 5.9 million disability – adjusted life years lost during 2002 (49), which doubled to 10.5 million in 2015 (34).

#### 1.4.3.1 Complications of rheumatic heart disease

Commonly seen complications of RHD include heart failure (HF) (33%), pulmonary hypertension (29%), AF (22%), stroke (7%), IE (4%) and major bleeding (3%) (24). The complications of RHD are associated with a reduced quality of life and productivity in a workplace and/or school in adults and children of school going age (50), respectively.

Rheumatic heart disease also adversely affects pregnancy (51), increasing the risk of complications during pregnancy. One of the major contributing causes of non-obstetric maternal deaths in Africa is RHD which accounts for 50% of the deaths seen in the 10.4 % of women who die during pregnancy due to pre-existing medical conditions (51).

### 1.4.4. Management of rheumatic heart disease

The recommended strategy to the management of RHD is prevention, namely primary and secondary prevention (52). Primary prevention is defined as the administration of adequate antibiotic treatment in individuals diagnosed with GAS to prevent ARF (52). Secondary prevention refers to prolonged and uninterrupted administration of antibiotic therapy following the diagnosis of ARF, to prevent recurrence of ARF and progression to RHD (52). Secondary preventive therapy has been proven to reduce recurrence of episodes of ARF (53), preventing the risk of developing carditis if not present; or worsening existing valvular damage (45). Compared to primary prevention, secondary prevention is more cost effective at a community/population level and has been prioritized in the control of GAS disease (54).

Chronic medical, surgical, and interventional therapy in the management of RHD increase health care

costs (55) substantially, in already limited resource settings. Interventional treatment (surgery and cardiac catheterization) is warranted when patients are symptomatic with severe valvular lesion(s) (56).

#### 1.4.4.1. Surgical intervention of rheumatic heart disease

Management of advanced RHD involves one or a combination of medical management and/or surgical and non-surgical interventions (57). The surgical management includes valve repair and open valvuloplasty and/ or open valve replacement (57). The management of RHD patients is becoming increasingly complex, due to the use of more sophisticated non-invasive imaging modalities and technological advances in therapies (58).The choice of the type of surgical management for RHD-related valve disease is influenced by patient, socioeconomic and health care related factors namely age, gender and potential future pregnancies, adherence to other medications, co-existence of AF, the number of valves involved, pre-operative left ventricular size and co-existence of pulmonary hypertension, availability of local primary and specialist follow up and the skill of the operator (23, 59-61).

Rheumatic heart disease related mitral valve repair is associated with a reduced risk of complications from infection and anticoagulation therapy compared to valve replacement, and it is also associated with superior overall short – and intermediate – term outcomes (37, 62) (63). Ultimately the long- term outcome such as preservation of left ventricular function and survival; is dependent on the stage of the disease at presentation and the time of referral (52).

In rheumatic mitral regurgitation, mitral valve repair is recommended where possible, over valve replacement due to its favourable outcomes (64, 65). Whereas, in mitral stenosis, percutaneous mitral balloon commissurotomy (PMC) is preferred over surgical commissurotomy as it results in excellent early outcomes, with a 50 – 60% event free outcome at 10-year follow up (66). Despite the good evidence for the least invasive intervention there exists significant variation in the ascertainment and prevalence of cardiovascular complications and the use of percutaneous and surgical intervention between low, lower-middle, and upper-middle income countries. The use of percutaneous and surgical interventions is extremely low in low-income countries compared with upper-middle income countries, due to lack of surgical expertise and resources in developing countries (45).

While valve repair procedures offer an advantage to averting the long-term complications of anticoagulation therapy and achieve better outcomes, valve replacement is usually performed more than valve repair in cases of RHD, in developing countries (63). In a large retrospective study from Brazil (2017), more than two thirds of procedures performed in 78 808 patients who had undergone valve procedures between 2001 and 2007; for RHD - related valve disease were valve replacements (67). The

likelihood success of valve repair is associated with timing of surgical referral, the morphology of the damaged valve and the expertise of the operator, which are usually not favourable in low-income countries (68, 69).

The demand for surgical management for RHD supersedes the available resources in RHD endemic countries, leading to delayed in access to surgery and less non-invasive procedures due to advanced disease (67). In SA, 22 % of the 344 new cases of RHD documented in the Heart of Soweto study required valve replacement or repair within a year of diagnosis (56).

### 1.5 Rheumatic heart disease and the human immunodeficiency virus

There is a geographic overlap of RHD and human immunodeficiency virus (HIV) infection in endemic areas (31) (70). Sub Saharan African (SSA) accounts for at least 71% of the global burden of HIV, with most of the sub-Saharan countries still having a higher than acceptable incidence rates for HIV (70).

The interaction of HIV and RHD is not clearly known (31), however the immune deficiency and dysfunction caused by HIV and acquired immunodeficiency disease syndrome (AIDS) has been shown to impact susceptibility to and progression of other autoimmune disease (70, 71). A Ugandan study found decreasing prevalence of RHD in children living with HIV compared to the general paediatric population (31). This was in part due to the reduced levels of autoantibodies which play a pivotal role in immune regulation, in the HIV infected population (31). However, there were potential confounders in the study which could have contributed to the reduced prevalence of RHD in this cohort of patients, these include regular health care facility visits and the use of prophylactic antibiotics in the HIV infected group (31).

#### 1.5.1 The role of natural autoantibodies

Autoantibodies can mediate both protective and pathologic functions (72). They are formed spontaneously without any immunization and are the first line of defense of the new-born organism (73). The protective autoantibodies are produced by the innate B1 cells of the innate immune response, which have a restricted antibody repertoire, in contrast the pathogenic autoantibodies maybe produced by any B cell subset (72). The immunoglobulin (Ig) M is the most prominent autoantibody; however, IgG and IgA are also described (74). They are postulated to play a role in the homeostasis and immune regulation (72, 75). Altered serum levels of these autoantibodies correlate with certain disease state (75).

Some IgM natural autoantibodies cross react with phosphorylcholine (PC) – an immunogenic component found on some bacteria, oxidized low density lipoproteins and apoptotic cells (76), forming IgM anti-PC antibodies (77). These enhance the clearance of damaged and apoptotic cells and suppress Toll - like receptor mediated inflammatory response (78-80); hence protecting against atherosclerosis (81) and suppressing over exuberant inflammatory response (77).

Low disease activity in some autoimmune diseases such as systemic lupus erythematous (SLE), have been reported at high serum levels of IgM anti PC antibodies (75, 82). Therefore, it is presumed that high serum levels of the anti PC IgM antibodies have a similar role in resolution of cellular injury in damaged valvular tissue in RHD (77).

However, a recent study showed that HIV infection was associated with lower protective IgM natural autoantibodies and higher levels of IgG natural autoantibodies against oxidized forms of lower density lipoprotein (LDL) (83). This contributes to accelerated strokes and cardiovascular events in HIV infected patients. (77). Similar results of low IgM were found in individuals with RHD, even though at a smaller scale (77). It seems that both HIV infection and RHD alter the natural autoantibody levels in ways that increase the risk of atherosclerosis, thus contributing to the increased burden of the cardiovascular diseases presumably driven by autoimmunity in SSA (77).

### 1.6 Purpose and objectives of the study

There has been increasing research on the prevalence of ARF and RHD primarily in the paediatric age group (below 14 years), emerging from developing countries where RHD still remains a health burden competing with other infectious disease such as HIV/AIDS. Current literature shows considerable evidence that the recommended standard of care for these patients based on the developed countries' health model is effective.

However very few studies exist that speak to the prevalence of RHD and the related complications and the management of RHD - valve disease, in the adult population of developing countries.

Therefore, the purpose of this study is to highlight the burden of RHD, and RHD related complications and the management of RHD in the adult population of a resource limited province: KwaZulu Natal, in SA. This information will be used to improve the prevention and control of this preventable health burden, in line with the Drakensberg declaration of 2005.

**Study Objectives**

1. To document the demographic profile of patients aged 12 years and above, with an established diagnosis of RHD referred to IACLH, between 2012 and 2016.
2. To describe the clinical features and echocardiographic findings of RHD in the patient aged12 years and older.
3. To document the interventions (surgical vs medical interventions) of RHD patients in IALCH during this period (2012 – 2016).

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# The profile of rheumatic heart disease in a tertiary hospital, Kwa-Zulu Natal, South Africa

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**Abstract**

**Background.** Rheumatic Heart Disease (RHD) is a disease of poverty and a significant public health concern in developing countries. There is little data on the profile of RHD in KwaZulu Natal (KZN), South Africa.

**Objectives.** To describe the profile of RHD in patients referred to a tertiary cardiology facility, in KwaZulu Natal.

**Methods.** This is a five-year (2012-2016) retrospective analysis of all patients with RHD referred to the cardiology department at Inkosi Albert Central Luthuli Hospital (IALCH). A structured format was used to extract demographic, clinical, echocardiographic and outcome data of 981 eligible patients aged >12 years. Descriptive analysis was used to report on quantitative data and logistic regression was used to identify significant associations and independent variables.

**Results:** Most patients were Black (87.9%); the median age was 24 years (IQR 15-36) and the female to male ratio 2.3:1. Dyspnoea (92.2%) was the commonest presenting symptom and mitral regurgitation (56.4%) was the commonest valve lesion. Atrial fibrillation (AF) (44.9%) was the commonest complication at presentation, followed by heart failure (HF) (28.6%). Atrial fibrillation mostly affected the 41 – 60 years age group (OR 2.075, CI 1.22 - 3.52, p=0.007). Compared to the adolescent group (<20 years), heart failure was less common in the age groups 21-40 and 41-60 years (OR 0.455, CI 0.286 - 0.723, p = 001 and OR 0.495, CI 0.288 - 0.852, p = 0.011, respectively). Valve replacement was performed in 723 (88.4%) (mitral 62.2%; aortic 4.8; mitral + aortic 29%, multiple valve surgeries 4%) of the 818 patients who had interventional procedures. The mortality was high (20.1%). Predictors of death were age between 41 - 60 years at the time of diagnosis (OR 1.916, CI 1.254 - 2.926, p = 0.003) and double valve replacement (OR1.521, CI 1.009 - 2.229, p=0.045). Less deaths occurred in those who underwent single valve surgery (Pearson Chi Square = 18.95, p = 0.000).

**Conclusion**: RHD is a disease of young patients and remains a significant cause of morbidity and mortality in KZN. Heart failure during the teenage years probably reflects ongoing carditis with haemodynamic failure. Valve replacement surgery was protective in patients with severe RHD.

**Key words:** Rheumatic heart disease, rheumatic fever, cardiac failure, mitral valve, South Africa.

**Introduction**

Rheumatic heart disease (RHD) remains a public health problem in low to middle income countries [1, 2]. It is estimated to affect 30 - 40 million people globally; [3, 4] at least 319400 deaths were recorded in 2015 [1, 3], with 60% of the deaths classified as premature (below 70 years of age) [1, 3, 5].

In Africa a high prevalence of RHD has been reported in Uganda (15/1000 persons) [6], and an even higher prevalence in Mozambique (30.4/1000 cases) [7] in a study based on echocardiographic screening. In the 1980s the prevalence of RHD in South African schoolchildren was reported to be 6.9 per 1000 persons in both Cape Town and Soweto [8]. Later studies (1993 - 1995) have shown a decline in acute rheumatic fever (ARF) and RHD in children under <14 years in both Soweto [9] and in Limpopo province [10].

There is limited data on the burden and the outcomes of RHD in KwaZulu-Natal [11]. In 1987 a much lower prevalence of 1/1000 of RHD was reported in a school survey in the Inanda district of Durban [12] This low prevalence was attributed to poor school attendance as a result of political turmoil at that time [12]. About 30 years later Cilliers suggested that there has been little change in the numbers of children presenting to tertiary hospitals in KwaZulu Natal and rural parts of the Eastern Cape [10]. In this study we describe the clinical profile and outcomes in patients with RHD patients referred for tertiary care in the province of KZN.

**Objectives**

The aim of the study was to describe the demographic profile, clinical presentation, complications, management, and treatment outcomes of patients with RHD referred to the cardiology unit at Inkosi Albert Luthuli Central hospital (IALCH) during 2012 to 2016.

**Methods**

A retrospective chart review was performed using the hospital SpeedMiner software program (Speedminer, Malaysia) to extract the relevant patient records. The patients' records were identified using the ICD 10 codes for RHD (I05-I09.8): ARF, mitral stenosis (MS), mitral regurgitation (MR), aortic stenosis (AS), aortic regurgitation (AR), and mixed valve disease (MVD) were used for data abstraction. All patients aged 12 years and over, with a diagnosis of RHD confirmed on echocardiography were included in the study. The diagnosis of RHD on echocardiography was based on World Heart Federation (WHF) criteria [13]. A structured data collection tool captured demographic characteristics, New York Heart Association (NYHA) functional class, valve involved, clinical findings, complications, comorbidities, echocardiographic findings, and the outcomes of intervention**.**

Data was analysed using Statistical Package for Social Sciences (SPSS) version 24 [International Business Machine]. Simple descriptive analysis was used to document clinical characteristics, and results are presented as frequencies, means, and percentages. Continuous variables are expressed as medians ± interquartile ranges (IQR). The Student's

t-tests and the chi-square tests were used to compare continuous variables and categorical variables, respectively. A p value of < 0.05 indicated significant findings for the variables being measured. Logistic regression analysis was used to estimate the association between study variables and the disease severity and outcomes.

**Ethical approval**

Ethical approval for this study was obtained from the Biomedical Research Ethics Committee (BREC) of the University of the KwaZulu-Natal (BE 598/17), the provincial Department of Health and from Inkosi Albert Luthuli Central Hospital (IALCH). All patients provided written consent for intervention at the time of admission to IALCH.

## 2.3 Results

**Demographic characteristics**

A total of 984 eligible patients were identified; of these three records were excluded due to insufficient data. The demographic characteristics of the remaining 981 patients are shown in Table 1. The median age was 24 years (IQR 15-36), and the majority of subjects were female (70%) and Black African (87.9%). Over half (52.6%) of the Black African patients were residing in peri-urban areas. Human immunodeficiency virus (HIV) tests were performed in 880 (89%) patients and of these 159 (18.1%) were positive *(Table 1).*

**Clinical presentation**

A history of ARF was obtained in 14% of patients. Half of the patients (n = 486, 49.5%) presented within six months of symptom onset *(Table 2)*. Dyspnoea was the commonest presenting symptom (92.2%), especially in the 41 – 60-year age group (OR 3.335, CI 1.39 – 7.98, p = 0.007) *(Table3b)*. Almost one third of patients (n = 307, 31.3%) presented with advanced symptomatology of heart failure (NYHA class III/IV).

**Pattern of valve involvement**

A total of 1337 valve lesions (divided between mitral and aortic) were identified from the study population. The mitral valve was the commonest valve involved (n=961, 71.9%): mitral regurgitation (MR) (n=554, 57.6%), mitral stenosis (MS) (n=139, 14.5%) and mixed mitral valve disease (MMVD) (n=268, 27.9%) *(Table 2)*. Aortic valve lesions occurred in 376 (28.1%) cases: aortic regurgitation (AR) (n=273,72.6%), aortic stenosis (AS) (n=62, 16.5%) and mixed aortic valve disease (MAVD) (n=41, 10.9%). Most aortic valve lesions (n=356, 94.7%) coexisted with mitral valve disease, with only 20 (5.3%) patients having isolated aortic valve (AR, n=2), (AS, n=3) and (MAVD, n=15) *(Table 2)*. Aortic regurgitation was the commonest lesion to coexist with mitral valve disease (n = 273, 72.6%) *(Table 2).*

Tricuspid regurgitation (TR) was present in 51.5% of patients, mostly secondary to elevated pulmonaryarterial systolic pressure (PAS)[14]. Almost a third of these patients (31.8%) had moderate to severe elevated PAS. *(Table 2).*

The severity of the valve lesions stratified by ethnic and age groups and by gender, is shown in Figure 1. Severe valve lesions were more common in the Black African patients (Fig 1A). Severe MR was the commonest valve lesion in both men (n=168, 31%) and women (n=376, 69%), with no statistical significance between the two genders. (p= 0.125) (Fig 1B). In contrast, severe AR was commoner among women (n=98, 77.8%) than men (n=28, 22.2%), (p = 0.003) (Figure 1B). Severe valve lesions were more common in the <20 years and 21 -40 years age groups, (MS p= 0.019, MR p= 0.043, AS p=0.002, AR p= 0.132) (Fig 1C).

**Complications**

Over half of the patients (n=563, 57.4%) presented with complications of RHD *(Table 2).* The commonest complication was atrial fibrillation (AF) (n = 253, 44.9%), followed by heart failure (HF) (n = 161, 28.6%), stroke (n = 81, 14.4%) and infective endocarditis (IE) (n= 68, 12.1%). Atrial fibrillation was significantly less common in the elderly (>60 years) (p = 0.040) on univariate analysis (Table 3a). On multivariate analysis the risk of AF was two times higher in the 41 – 60 year age group compared to the younger population < 20 years (OR 2.075, CI 1.22 – 3.52, p = 0.007) *(Table 3b)*.

The median ejection fraction (EF) was 53% (IQR 45-58). Only 12.4% (n=20) had an EF less than 40%, indicating that in the majority of cases heart failure was due to advanced regurgitant valve disease. In the multivariate analysis HF was less common in the 21 – 40 years (OR 0.455, CI 0.28 – 0.72, p 0.001) and 41 – 60 years age groups (OR 0.495, CI 0.28 – 0.85, p = 0.011), compared to the reference age group (< 20 years) *(Table 3b)*. No differences were observed in the prevalence of AF (OR1.181, CI 0.76 – 1.82, p 0.442) or HF (OR 1.06, CI 0.67 – 1.67, p=0.793) between women and men.

Infective endocarditis (IE) was less common in men (12.1%) than in women (22.9%), (OR 0.47, CI 0.27 – 0.80, p=0.006*).*

**Management of rheumatic heart disease**

A total of 818 patients (83.4%) underwent intervention [surgery, (88.4%) and percutaneous mitral balloon commissurotomy (PMC) (11.6%)]; the remaining 16.6% had less severe lesions and were managed with medical therapy *(Table 2)*. Mitral valve replacement (MVR) was the most common surgery performed (62.2%) *(Table 2)*; it was the most frequently performed procedure in the <20-year age group compared to the other age groups (p=0.033) *(Table3a).*

On multivariate analysis aortic valve replacement was more frequently undertaken in patients aged 60 years and over *(OR 5.17, CI 1.01- 26.4, p = 0.048)* and in the 41 – 61 years age group (*OR 3.49, CI 1.45* – 8.38, p = *0.005)* compared to the reference group (<20 years) *(Table 3b)*. After controlling for gender, double valve replacement was commonly performed in the 21 – 40 years age group *(OR 1.57, CI 1.09 – 2.25, p = 0.013)* compared to the other age groups *(Table 3b)*. Women were more likely than men to have undergone MVR (OR 1.585, CI 0.92 – 2.72, p = 0.004) and less likely to have had DVR (OR 0.626, CI 0.44 – 0.8, p = 0.007) or AVR (OR 0.389, CI 0.19 – 0.78, p = 0.009).

Percutaneous mitral balloon commissurotomy for tight mitral stenosis was performed in 95 patients and was more frequently undertaken in the younger age groups (<20 years n= 35, 41.2% and 21– 40 years n = 40, 47% compared to the older age groups 40 – 60 years n=9, 10.6% and > 60-yrs n=1, 1.2%) (Table 3a) but this difference was not statistically significant (p=0.110) *(Table 3a)*. Fifty three percent (53%) of the 95 patients who underwent PMC went on to have surgery for mitral valve replacement due to restenosis of the mitral valve, two or more years after the initial procedure.

**Rheumatic heart disease mortality**

A minority of patients (n = 58, 5.9%) were lost to follow up. One hundred and forty-seven (15%) were referred to continue follow up at their base hospitals *(Table 2).* Of these patients 7 had declined surgery and 15 were deemed unfit for surgery due to comorbid illnesses (advanced HIV (CD4<200cells/$mm^3$) (n=6), anaemia (n=2), hypothyroidism (n=1), untreated syphilis (n=1), and cardiomyopathy (n=5).

A fifth of patients died during the 5-year period of the study and the median age at the time of death was 27 years (IQR 18-44). In total there were 197 deaths (20.1%): (n = 53 while awaiting surgery, n = 97 peri-operative and n=47 reported by their families, upon telephonic follow up).Deaths were due to HF and cardiogenic shock (n=80, 40.6%), AF (n = 96, 48.7%), IE (n = 4, 3.0%) and septic shock (n=9, 4.6%); and massive stroke (n= 8, 4.1%).

Age was shown to have a significant association with mortality (p = 0.016**).** Most deaths occurred in the 21 - 40 years age group (n=78, 39.6%), followed by <20 years age group (n=67, 34%), and the 41 - 60 years age group (n=48, 24.2%), and the least in the > 60 years (n=4, 2%). On univariate analysis the age group 41 - 60 years emerged as a significant predictor for death (OR 1.916, CI 1.254 - 2.926, p = 0.003). *(Table 4a).* Surgical intervention was found to be protective against death in those with severe valve disease (OR 0.471, CI 0.339- 0.665, p = 0.000), with fewer deaths occurring in the patients who underwent surgery (n = 122, 16.7%) compared to those who did not have surgery (n = 75, 29.3%) *(Table 4b)*.Amongst patients who underwent surgical intervention, DVR carried the highest risk of death after surgery (OR 1.521, CI 1.009 - 2.229, p = 0.045).

On multivariate analysis age 21 - 40 years (OR 1.916, CI 1.248 - 2.939, p = 0.003) and DVR (OR 1.655, CI 1.109-2.472 p = 0.014), emerged as independent predictors of death. *(Table 5)*.

**Discussion**

In this study we have shown that RHD patients in KZN present with a full spectrum of advanced chronic RHD manifestations occurring at a much younger age, similar to the earlier study from Inanda, Durban in 1987 [12]. Also RHD affected predominantly Black African females, which is in keeping with the most recent Heart of Soweto prospective study[15]. However, in contrast to the Heart of Soweto study findings, the peak presenting age in ourstudy was in adolescence and young adults, instead of the third decade [15]. A striking finding was that most of these

younger subjects were referred with severe symptoms of NYHA III/IVdyspnoea, often in decompensated heart failure with RHD complications. This is similar to the findings by Maharaj et al. in patients with severe MR from KZN in 2019 [16], as well as a study by Okello et al in Uganda [17].

Similar to previous studies we have observed that RHD is more common in Black women [18-20]. The70% female predominance in our study is the same as that found in the heart of Soweto study [15] but slightly higher than the 1.7:1 reported in a Nigerian study in 2007 [21]. A striking finding was that 42.2% of our patients were below 20 years of age at the time of diagnosis and 57.6% of those below 20 years had severe rheumatic valve disease. Severe disease in early age was also observed in an Australian study [22] which showed a rapid progression of RHD and a high incidence of RHD within a year after the first episodeof ARF, suggesting that many of these patients may have had ongoing smouldering active carditis. The poor recall history of rheumatic fever (14%) and ongoing ARF in young adults observed in this study suggests delayed medical attention seeking behaviour when infection occurred in childhood. Untreated ARF episodes are often followed by recurrent infections and recrudescence of carditis resulting in ongoing valvular damage [3] and missed opportunities for secondary prophylaxis measures [2, 17, 23]. The majority (90%) of patients were Black Africans with over half (52.6%) residing in peri-urban areas. Peri-urban areas are not only densely populated but also characterized by a rapid rise in informal settlements where overcrowding, low socioeconomic standing and poor access to basic services such as water and sanitation, and lack of health care facilities together contribute to the development of ARF and consequently RHD [24, 25]. There is evidence that susceptibility to and severity of RF and RHD differs amongst different ethnic groups, but the other ethnic group numbers were too few for us to assess this [26].

This study confirms a high incidence of valve related complications (AF and HF) at presentation similarto other African studies [15, 17, 21]. Complications usually occurred in the first year after diagnosis of RHD, similar to the Australian study [22]. Like Maharaj et al we have also shown that patients with severe MR frequently presented late, in advanced heart failure [16, 27], resulting in late clinical assessment and delayed surgical intervention. Other possible reasons for late presentation include delayed diagnosis at the referral hospitals [28], lack of awareness of RHD at primary level andunavailability of point of care echocardiographic services which would have facilitated earlier referral of patients [29].

Similar to previous studies [28, 30, 31], we found that a majority of younger adult patients had severeMR followed by MMVD and less frequently MS. This is likely related to a more prolonged period of time required for fibrosis to develop with organization of valvular tissue resulting in narrowing of thevalve orifice and the development of valve stenosis [32]. The coexistence of mitral valve disease in the majority of patients with aortic valve disease in our study is also not unusual since this is typical ofthe natural history of RHD [23], in which the mitral valve is affected first followed by

the aortic and less frequently tricuspid valve involvement [33]. Although the majority of patients with TR were secondary to pulmonary hypertension, TR was also detected at normal PAS pressures in 3.6% patients. Albeit small this implies that these patients had organic tricuspid valve disease secondary to RHD. This has been described in a cross-sectional study from Nepal [34] and a WHO review by Sultan et al whofound tricuspid valve disease (TVD) in 7.7% of cases, with 99.3% of these patients having co-existing mitral valve disease (MVD) [35].

The majority (88.4%) of our study population underwent valve replacement surgery and only 11.6% had PMC. The choice of the intervention modality was informed by the suitability of the valve morphology, the severity of valve damage [36] and operator skills [37]. Surgery in our cohort was favoured because patients presented with severe regurgitant lesions and multiple valve disease. Isolated mitral stenosis (MS) was common in the 21 - 40 years group, particularly in women of childbearing age. Percutaneous mitral balloon commissurotomy was performed almost exclusively in patients with isolated tight mitral stenosis. Although PMC has been reported to have a favourable short - and long-term outcome in suitable candidates [38, 39], there is however a high rate of restenosis [40]. In our study, 53% of those who had PMC went on to have MVR within a two-year period after the intervention, due to restenosis of MV.

Despite KZN having the highest number of persons with HIV on treatment [41, 42] and a geographic overlap of RHD and HIV [43], only 18.1% of patients were HIV positive. A Ugandan study found a lower prevalence of RHD in schoolchildren living with HIV compared to HIV uninfected children (1.5% vs 3%).The authors postulated that HIV infection has a protective effect on the development of RHD in regions where RHD is endemic due to the alteration of the pathogenetic basis of RHD by the HIV infection [43]. We did not have the opportunity to interrogate this phenomenon since advanced HIV infection with a low CD4cell count (<200 cells/$mm^3$) influenced the surgeon's decision to defer surgery, until patients had received antiretroviral therapy (ART) and their viral loads were suppressed. Also, the temporal relationship of the HIV infection to RHD could not be interrogated and therefore no inferences could be drawn on the effects of HIV infection on RHD.

The mortality related to RHD remains a serious burden affecting young patients from low to middle incomecountries (44), with a two-year case fatality rate of 500 deaths (16.9%) in Africa [44]. Our study founda mortality rate of 20.1% which is higher than the case fatality rate of 16.9% described in the REMEDYstudy [44]. However, the median age at the time of death is very similar: 27 (IQR 18 - 44.7) years to 28,7 years [44]. Similar to other reports [3] most of the deaths in our study were due to complications of HF and AF, resulting from advanced disease with very large atria and clot formation as well as valve destruction with haemodynamic failure [44]. Similar to the REMEDY study, we found that the age group 41-60 years was an independent predictor of death. There was no significant association between demographic characteristics, comorbidities, severe symptoms of NYHA III/IV, complications such AF, HF, IE,

and mortality. We also found that valve surgery was protective against mortality, with less deaths reflected among those with severe disease who underwent surgery. However multiple valve surgeries, particularly DVR carried the highest risk of dying.

**Study Limitations**

There are several limitations to this study, largely relating to its retrospective design. These include missing or incomplete data for analysis, thereby limiting our ability to interrogate data relating to outcomes of complications and mortality. The results may not accurately represent the total burden of RHD in the community, as it does not include patients managed at peripheral hospitals and clinics with milder forms of the disease. Although the centralization of referrals of severe disease to a single state tertiary centre has created an inherent referral bias, this study does reflect the profile of the patients at highest risk of severe RHD. The study sample is therefore limited with regards to ethnicity and grades of disease severity. A strength of our study, however, is that echocardiography was used to document the clinical profile of RHD at a tertiary referral hospital in KZN, enabling us to provide a detailed morphology of the underlying rheumatic pathology and its associated complications. Lastly, long term outcome was not evaluated in this study.

**Conclusion**

This study shows that RHD remains a significant cause of cardiovascular morbidity especially among young Black Africans from disadvantaged communities in KwaZulu-Natal. Most patients presented at an advanced stage of the disease requiring urgent valve replacement intervention which was lifesaving. Increasing age and double valve replacement emerged as significant predictors of mortality. HIV infection did not appear to influence the disease outcome.

The study highlights the need for early diagnosis and management of RHD, through continued rheumatic fever surveillance at community level as well as effective primary and secondary prophylaxis to prevent the devastating consequences of this disease. Establishment of a RHD registry will reflect the true burden of RHD at the community level and inform policies and programs to increase awareness of RHD in the communities and ensure effective screening and therapeutic measures.

**Declaration.** This study was required for KSS's MMed (Internal Medicine), although publication was not a requirement.

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**Author contributions.** KSS developed the protocol, collected the data, and wrote the manuscript. FP and DPN assisted with developing the research question, supervised the writing of the protocol, and the writing of the manuscript.

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*Table 1: Demographic data of 981 rheumatic heart disease patients seen at IALCH*

| *Characteristics* | *Total cohortn* (%) | *Black* *n* (%) | *White* *n* (%) | *Indiann* (%) | *Coloured* n (%) |
|---|---|---|---|---|---|
| *Ethnicity* | 981 | 862 (87.9) | 11 (1.1) | 101 (10.3) | 7 (0.7) |
| **Age (years) | 24 (37 -15) | 23 (37 -14) | 27 (49 -20) | 24 (36 -15) | 16 (24 -14) |
| Age at Diagnosis (years) | | | | | |
| <20 | 402 (422) | 390 (97) | 0 | 11 (2.7) | 1 (0.3) |
| 20-40 | 355 (37.2) | 316 (89) | 1 (0.3) | 33 (9.3) | 5 (1.4) |
| 41-60 | 174 (18.2) | 120 (69) | 8 (4.6) | 45 (25.9) | 1 (0.6) |
| >60 | 22 (2.3) | 14 (63.6) | 2 (9.1) | 6 (27.3) | 0 |
| Gender | | | | | |
| Female | 687 (70 | 603 (87.7) | 7 (1) | 71 (10.3) | 6 (0.9) |
| Male | 294 (30) | 259 (88.1) | 4 (1.4) | 30 (10.2) | 1 (0.3) |
| Area of Residence | | | | | |
| Rural | 340 (35.3) | 340 (100) | 0 | 0 | 0 |
| Peri-urban | 506 (52.6) | 457 (90.3) | 0 | 46 (9.1) | 3 (0.6) |
| Urban | 116 (12.1) | 47 (40.5) | 11 (9.5) | 54 (46.6) | 4 (3.5) |
| Type of housing | | | | | |
| Formal Informal | 634 (66.3)<br>323 (33.7) | 345 (36.1)<br>494 (51.6) | 11 (1.1) | 100 (10.4) | 7 (0.7) |
| Referral Hospital | | | | | |
| District Regional | 202 (20.7) | 197 (97.5) | 0 | 5 (2.5) | 0 |
| Tertiary | 656 (67.1) | 545 (83.1) | 11 (1.7) | 95 (14.5) | 5 (0.8) |
| No records | 110 (11.2) | 108 (98. | 0 | 0 | 2 (2) |
| | 11 (1) | 10 (91) | 0 | 1 (9) | 0 |
| Province | | | | | |
| KZN | 864 (88.3) | 748 (86.7) | 10 (1.2) | 101 (11.7) | 5 (0.6) |
| EC | 115 (11.8) | 112 (97.4) | 1 (0.9) | 0 | 2 (1.7) |
| HIV | | | | | |
| Positive | 159 (18.1) | 154 (96.9) | 0 | 4 (2.5) | 1 (0.6) |

* IALCH: Inkosi Albert Luthuli Central Hospital.

** Median (IQR interquartile range), KZN KwaZulu Natal, EC Eastern Cape, HIV human immunodeficiency virus.

*Table 2: Clinical characteristics, valve lesions, and outcomes of 981 rheumatic heart disease patients at IALCH*

| ***Clinical feature*** | ***n (%)*** |
|---|---|
| History of rheumatic fever | 138 (14) |
| *Onset of symptoms < 6 months | 486 (49.5) |
| Dyspnoea (NYHA I-IV) | 905 (92.2) |
| Dyspnoea (NYHA) III-IV | 307 (31.3) |
| Cough | 183 (18.6) |
| Lower limb oedema | 308 (31.3) |
| Fatigue | 357 (36.4) |
| ***Valve disease*** | ***n (%)*** |
| Mitral valve lesions | 961 (71.9) |
| Aortic valve lesions | 376 (28.1) |
| ***Valve lesion distribution*** | |

| | ***Aortic only*** | ***MR*** | ***MS*** | ***MMVD*** | ***Total*** |
|---|---|---|---|---|---|
| | ***N*** | ***n*** | ***N*** | ***n*** | |
| ***Mitral only*** | | 362 | 85 | 158 | 605 |
| ***AR*** | 2 | 183 | 21 | 67 | 273 |
| ***AS*** | 3 | 0 | 23 | 36 | 62 |
| ***MAVD*** | 15 | 9 | 10 | 7 | 41 |
| ***Total*** | 20 | 554 | 139 | 268 | 981 |

| | ***n (%)*** |
|---|---|
| ***Tricuspid Valve regurgitation [a]*** | 506 (51.5) |
| ***Echo estimation of PASP+*** | |
| Median PASP (mmHg) (IQR) | 38 (28-45) |
| Normal <35mmHg | 18 (3.6) |
| Mild 36-45mmHg | 327 (64.6) |
| Moderate 46-60mmHg | 132 (26.1) |
| Severe >60mmHg | 29 (5.7) |
| ***Complications*** | |
| Atrial fibrillation | 253 (44.9) |
| Infective endocarditis | 68 (12.1) |
| Stroke | 81 (14.4) |
| Heart failure | 161 (28.6) |
| ***Ejection Fraction*** | |
| Median (IQR) | 53 (58-45) |
| No data | 27 (16.8) |
| <40 | 20 (12.4) |
| 41-49 | 30 (18.6) |
| >50 | 84 (52.2) |
| ***Treatment modality*** | |
| Medical treatment only | 163 (16.6) |
| Interventions | |
| PMC | 95 (11.6)) |
| Surgery | 723 (88.4) |
| *MVR* | *450 (62.2)* |
| *AVR DVR* | *35 (4.8)* |
| *More than one intervention* | *210 (29.0)* |
| | *27 (4)* |
| ***Mortality*** | |
| Died | 197 (20.1) |
| Awaiting surgery | 53 (26.9) |
| Peri-operative (within 24hours of surgery) | 61 (30.9) |
| Post-operative | 36 (18.3) |
| Cause not established | 47 (23.9) |

PMC: Percutaneous mitral commissurotomy, MVR mitral valve regurgitation, AVR aortic valve regurgitation, DVR double valve replacement, IQR interquartile range, LTFU lost to follow up. [a] detected-on echocardiogram [b] Details of more than 1 surgical procedure: PMC followed by MVR 38 (69.1), PMC followed by DVR 12 (21.8), MVR followed by DVR 4 (7.3), MVR followed by AVR 1 (1.8), +PASP pulmonary arterial systolic pressure.

*Table 3a: Complications, interventions, and outcomes of RHD stratified by age group and gender.*

| | <20yr, n (%) | 21-40yr, n (%) | 41-60yr, n (%) | >60yr, n (%) | p-values |
|---|---|---|---|---|---|
| **Complications (overall)** | | | | | |
| AF | 71 (29.1) | 103 (42.2) | 64 (26.2) | 6 (2.5) | 0.040 |
| IE | 26 (38.8) | 26 (38.8) | 13 (19.4) | 2 (3) | 0.823 |
| HF | 68 (44.7) | 49 (32.2) | 29 (19.1) | 6 (4) | 0.003 |
| Stroke | 24 (30.8) | 33 (42.3) | 20 (25.6) | 1 (1.3) | 0.659 |
| **Complications in women** | | | | | |
| AF | 44 (24.3) | 82 (45.3) | 49 (27.1) | 6 (3.3) | 0.068 |
| IE | 14 (37.8) | 12 (32.4) | 9 (24.3) | 2 (5.5) | 0.519 |
| HF | 42 (38.5) | 38 (34.9) | 23 (21.1) | 6 (5.5) | 0.047 |
| Stroke | 10 (19.6) | 25 (49) | 15 (29.4) | 1 (2) | 0.279 |
| **Complications in men** | | | | | |
| AF | 27(42.2) | 21 (32.8) | 15 (23.4) | 1 (1.6) | 0.177 |
| IE | 12(40) | 14 (46.7) | 4 (13.3) | 0 | 0.569 |
| HF | 26(59.1) | 11 (25) | 6 (13.6) | 1 (2.3) | 0.056 |
| Stroke | 14(51.9) | 8 (29.6) | 5 (18.5) | 0 | 0.781 |
| **Interventions** | | | | | |
| PMC | 35(41.2) | 40 (47.0) | 9 (10.6) | 1 (1.2) | 0.110 |
| MVR | 203(46.8) | 140 (32.3) | 83 (19.1) | 8 (1.8) | 0.033 |
| AVR<br>DVR | 10 (29.4)<br>80 (39.0) | 10 (29.4)<br>90 (43.6) | 12 (35.3)<br>31 (15.0) | 2 (5.9)<br>5 (2.4) | 0.013<br>0.009 |
| **Outcomes** | | | | | |
| Compliant | 140(44.8) | 112 (35.9) | 56 (18.0) | 4 (1.3) | |
| LTFU | 154(39.2) | 148 (37.7) | 75 (19.1) | 16 (4.0) | 0.130 |
| Died | 41(38.0) | 46 (42.6) | 20 (18.5) | 1 (0.9) | |
| Discharged | 67(48.3) | 48 (34.5) | 23 (16.5) | 1 (0.7) | |

AF atrial fibrillation, IE infective endocarditis, HF heart failure, PMC percutaneous mitral commissurotomy, MVR mitral valve replacement, AVR aortic valve replacement, DVR double valve replacement., LTFU lost to follow up.

*Table 3b: Multivariate analysis of clinical symptoms, interventions, complications, and outcomes, stratified by age group at diagnosis*

| | **21-40** Years | | | **41-60** Years | | | **>60** years | | |
|---|---|---|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** |
| ***Symptoms*** | | | | | | | | | |
| *Dyspnoea* | 2.361 | 1.32-4.22 | 0.004 | 3.335 | 1.39-7.98 | 0.007 | 2.591 | 0.32-19.06 | 0.376 |
| *PND* | 1.379 | 1.00-1.89 | 0.048 | 2.478 | 1.70-3.60 | 0.000 | 2.483 | 1.04-5.92 | 0.004 |
| *Cough* | 1.534 | 1.04-2.25 | 0.029 | 1.955 | 1.24-3.06 | 0.003 | 2.271 | 0.84-6.07 | 0.102 |
| *LL Oedema* | 1.320 | 0.96-1.80 | 0.082 | 1.395 | 0.95-2.04 | 0.088 | 2.138 | 0.89-5.10 | 0.087 |
| ***Surgical procedures*** | | | | | | | | | |
| PMC | 1.320 | 0.81-2.15 | 0.264 | 0.568 | 0.26-1.21 | 0.147 | 0.565 | 0.72-4.42 | 0.587 |
| MVR | 0.592 | 0.42-0.81 | 0.001 | 0.924 | 0.61-1.38 | 0.701 | 0.656 | 0.23-1.80 | 0.414 |
| AVR | 1.368 | 0.55-3.37 | 0.496 | 3.494 | 1.45-8.38 | 0.005 | 5.172 | 1.01-26.4 | 0.048 |
| DVR | 1.575 | 1.09-2.25 | 0.013 | 0.969 | 0.60-1.55 | 0.896 | 1.537 | 0.51-4.58 | 0.441 |
| ***Complications of RHD*** | | | | | | | | | |
| *AF* | 1.552 | 0.99-2.41 | 0.051 | 2.075 | 1.22 - 3.52 | 0.007 | 1.070 | 0.32-3.47 | 0.910 |
| *HF* | 0.455 | 0.28-0.72 | 0.001 | 0.495 | 0.28 - 0.85 | 0.011 | 1.161 | 0.35-3.76 | 0.083 |

[c] Age <20 years is the reference group. OR odds ratio, PND paroxysmal nocturnal dyspnoea, LL lower limb, PMC percutaneous mitral valvulotomy, MVR mitral valve replacement, AVR aortic valve replacement, DVR double valve replacement, AF atrial fibrillation, HF heart failure.

Dyspnoea was the commonest presenting symptom in 41 -60yr and 21-40 yrs.

MVR was commonly performed in young patients (<20 and 21 -40 years old). AVR in older patients (> 60 and 41 – 60 years old). AF was the common complication in patients > 20 years old and CCF in patients < 20 years

[d] Patients > 60 years are more likely to die from RHD compared to younger patients – positive predictor of death on multivariate analysis for age groups.

*Table 4a: The association of age and mortality in all patients.*

| **Age categories** | **Aliven (%)** | **Died n (%)** | **Totaln** |
|---|---|---|---|
| **<20** | 337 (43) | 67 (34) | 404 |
| **21-40** | 277 (35.3) | 78 (39.6) | 355 |
| **41-60** | 126 (16.7) | 48 (24.4) | 174 |
| **>60** | 44 (5.6) | 4 (2) | 48 |
| **Total** | 784 (79.9) | 197 (20.1) | 981 |

**[R] Pearson Chi-square = 10.26, p = 0.016. The odds of dying increase with age: 41 -60 years and 21 -40 years.**

*Table 4b: The effect of valve surgery on mortality*

| Procedure | Aliven (%) | Died n (%) | Totaln |
|---|---|---|---|
| **No surgical procedure** | 106 (65) | 57 (35) | 163 |
| **Surgical procedure** | 678 (82.9) | 140 (17.1) | 818 |
| **Total** | 784 (79.1) | 197 (20.1) | 981 |

**[Q]Pearson Chi- square = 18.95, p = 0.000. Surgical procedures are protective against death.**

*Table 5: Logistic regression of variables associated with mortality.*

| Characteristics | ALL | | | PRE-OPERATED | | | OPERATED | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | P value | OR | 95% CI | P value | OR | 95% CI | P value |
| **Gender** | 0.705 | 0.492-1.008 | 0.705 | 0.624 | 0.329- 1.183 | 0.149 | 0.766 | 0.495- 1.188 | 0.234 |
| **Age** | 1.269 | 1.051- 1.531 | 0.013 | 1.565 | 1.126- 2.176 | 0.008 | 1.127 | 0.888- 1.430 | 0.324 |
| **Ethnicity** | 1.164 | 0.931- 1.452 | 0.183 | 1.123 | 0.763- 1.654 | 0.556 | 1.166 | 0.884- 1.539 | 0.277 |
| **HIV** | 1.361 | 0.907- 2.042 | 0.137 | 1.741 | 0.905- 3.351 | 0.097 | 1.065 | 0.618- 1.835 | 0.821 |
| **NYHA III/VI** | 0.827 | 0.605- 1.131 | 0.235 | 0.696 | 0.260- 1.858 | 0.469 | 0.786 | 0.334- 1.852 | 0.582 |
| **BMV/PMV** | 0.895 | 0.491- 1.633 | 0.718 | - | - | - | 0.847 | 0.463- 1.549 | 0.589 |
| **MVR** | 0.894 | 0.615- 1.300 | 0.557 | - | - | - | 0.782 | 0.528- 1.160 | 0.782 |
| **AVR** | 0.666 | 0.231- 1.921 | 0.452 | - | - | - | 0.633 | 0.219- 1.827 | 0.633 |
| **DVR** | 1.655 | 1.109- 2.472 | 0.014 | - | - | - | 1.521 | 1.009- 2.293 | 1.521 |
| **AF** | 1.094 | 0.693- 1.729 | 0.699 | 0.556 | 0.229- 1.348 | 0.194 | 1.442 | 0.831- 2.502 | 1.442 |
| **IE** | 0.753 | 0.385- 1.469 | 0.405 | 1.409 | 0.458- 4.333 | 1.409 | 0.515 | 0.210- 1.262 | 0.147 |
| **Heart failure** | 0.913 | 0.568- 1.466 | 0.705 | 0.800 | 0.329- 1.943 | 0.800 | 0.880 | 0.497- 1.558 | 0.662 |
| **Stroke** | 1.146 | 0.647-2.031 | 0.640 | 2.417 | 0.641-9.117 | 2.417 | 1.066 | 0.553- 2.055 | 0.849 |

**OR odds ratio. Age and DVR emerged as significant predictors of death.**

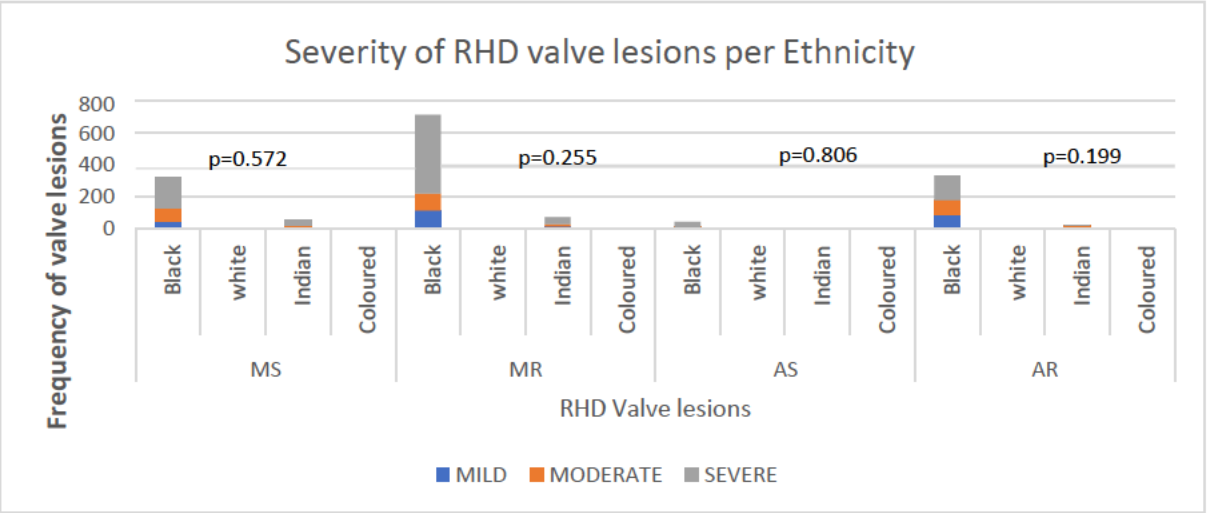


**Figure 1A RHD valvular lesion severity by ethnicity**

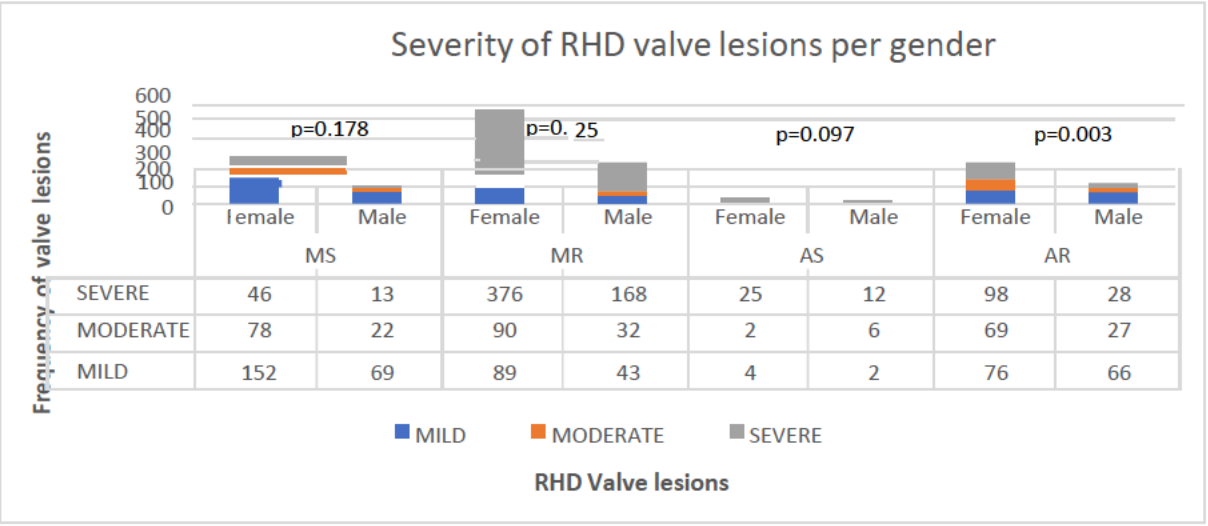


**Figure 1B RHD valvular lesion severity by gender**

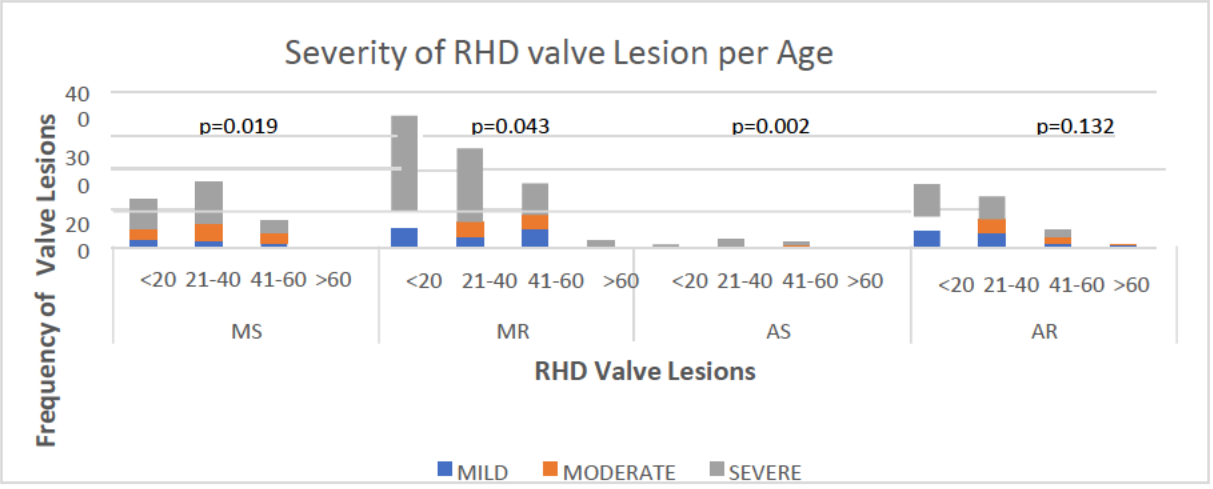


**Figure 1 C: RHD valvular lesion severity by age group**

Fig1a: Severe valve lesions were common in the Black group. Fig 1B/C: Severe MR was the commonest valve lesion in both genders. Both mitral and aortic valve lesions were commoner in females and occurred more frequently in the younger age groups (<20 and 20-40yr) compared to those over 40 years of age. Except for AS, which was the least common valve lesion, all other lesions (MS, MR and AR) were more severe and occurred more frequently and were more severe in the younger age groups (<20and 20-40yr).

## Appendix A: The guidelines for authorship for the journal selected for submission of the manuscript.

**Authorship**

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript

**Research**

*Guideline word limit: 4 000 words*

Research articles describe the background, methods, results, and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion, and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarize the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

*Structured abstract*

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

*Main article*

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

*Results*

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

*Discussion*

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

*Conclusions*

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the articles

## Appendix B: Research Protocol

**University of KwaZulu-Natal**

**College of Health Sciences**

**School of Clinical Medicine**

**Title:** The profile of rheumatic heart disease at a regional hospital in Kwa-Zulu Natal, South Africa

**Degree:** MMED

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**EXECUTIVE SUMMARY**

Acute rheumatic fever (AF) and its consequent complication of Rheumatic Heart Disease (RHD) is a significant public health concern globally. Rheumatic heart disease is the leading cause of heart failure in children and young adults in RHD endemic areas, and therefore contributes significantly to the non-communicable disease (NCD) burden of diseases in developing countries (7).

Although there has been a substantial decrease in the incidence of RHD in developed countries including South Africa (SA) in the last two decades(33), predominantly due to improved living conditions and better access to health care, RHD continues to be a major cause of premature death and morbidity in low and middle-income countries(23, 38, 109), accounting for 200 000 – 250 000 premature deaths every year in the young population group globally(10).

Therefore, the purpose of this retrospective descriptive study is to describe the pattern of RHD in the era of improved socioeconomic conditions and improved health care access in Kwa-Zulu Natal (KZN); and describe the demographic profile, clinical presentation and outcomes.

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# 1. Background and literature review

## 1.1. Introduction

Rheumatic heart disease (RHD) is an acquired heart disease secondary to valvular damage following repeated episodes of acute rheumatic fever (ARF), an inflammatory disease caused by an abnormal immune response to group A streptococcal infection usually during childhood (1). Acute rheumatic fever and its consequent complication of RHD is a significant public health concern globally. Rheumatic heart disease is the leading cause of heart failure in children and young adults in RHD endemic areas, and therefore contributes significantly to the non-communicable disease (NCD) burden of diseases in developing countries (7).

## 1.2. Epidemiology of acute rheumatic fever and rheumatic heart disease

Acute rheumatic fever usually occurs in children aged 5 - 14 years old and decreases in frequency in older adolescents and young adults. It is rarely seen in persons above the age of 30 years. Recurrent episodes of ARF, however; remain relatively common in adolescents and young adults. In view of this prevalence of ARF, intuitively the prevalence of RHD peaks between the ages of 25 and 40 years (109), with a mean age of 28 years (30). Although no clear gender association for ARF has been observed, RHD affects womenof childbearing age more commonly, with a ratio of 2:1 compared to men (33).

Approximately 3 – 6% of any population group may be susceptible to ARF(109). Further 60% of the affected population of patients will progress to develop RHD and it is therefore estimated that approximately 300 000 of about 0.5 million individuals who acquire ARF every year go on to develop RHD (110).

A substantial decrease in the incidence of RHD has been observed in developed countries, including South Africa (SA) in the last two decades (33), predominantly due to improved living conditions and better access to health care. The former has resulted to a reduction in Group A Streptococci transmission and consequently reduction in the cases of ARF and RHD (1). Despite this declining pattern, it is still estimated that RHD affect 15.6 million persons globally (110), with 282 000 new cases reported each year(35). Furthermore, RHD is estimated to cause 200 000 – 250 000 premature deaths every year in the young population group (10).

## 1.3. The global burden of rheumatic heart disease

Current estimates suggest that 62 - 78 million individuals worldwide may have RHD, which could potentially result in 1.4 million deaths per year owing to the disease and its complications(36). A majority of RHD patients (79%) are in developing countries(3). A systematic review of 57 RHD studies using echocardiography criteria in children aged between 5 and 14 years found that the prevalence of RHD was highest in lower economic regions. Sub-Saharan Africa has the highest calculated regional prevalence, followed by the Pacific, indigenous Australia and New Zealand and South-Central Asia *(Table 1)(3).* The

reason for the high incidence of ARF and RHD, in these countries is probably due to poverty, overcrowding, an increased frequency of sore throats and skin infections and lack of access to medical care(37).

### 1.4. The Sub-Saharan Africa burden of rheumatic heart disease

Although the prevalence of RHD has decreased significantly in developed countries, it continues to be a major cause of premature death and morbidity in low and middle-income countries.(23, 38).

In Africa, the highest prevalence is seen in sub-Saharan region at 5.7 per 1000 in children age 5 - 14 years(3). The prevalence of RHD increases when echocardiography is used as a screening tool, as seen in a study from Mozambique, where the prevalence of RHD among children aged 6 through to 17 years of age rose from 2.3 per 1000 to 30 per 1000 when echocardiography was used as a screening tool (39) and 14.8 cases per 1000 from 4.9 cases per1000, in asymptomatic school children of Uganda (40).

A study in Soweto in 1972 SA, found a prevalence of RHD of 6.9 per 1000 persons in schoolchildren. Acute rheumatic fever and RHD were listed among the top 10 causes of death in the 15 - 24-year age group in SA (46) in 1973, furthermore RHD accounted for 15% of the paediatric cardiac patients' admission to hospitals in 2006(111).

Simultaneously a high incidence of new RHD cases at 23.5 per 100 000, was seen in the 14-year-old age group at Chris Hani Baragwanath Academic Hospital, Soweto (2006 and 2007) (10). The exact reason for the increased number of new cases seen is not known as a noticeable decline of ARF and RHD, amongst children under the age of 14 years in SA, over the past two decades has been noted (33). As mentioned above, the decline in ARF is attributed to improved socioeconomic conditions, better living conditions, decreased overcrowding and improved access to health care post-apartheid (33).

### 1.5. Pathophysiology of acute rheumatic fever and the pathology of rheumatic heart disease

Acute rheumatic fever is an inflammatory disease, that results from an infection of the upper respiratory tract with group A streptococcus and usually occurs three weeks after group A streptococcal pharyngitis. It can affect the joints, skin, brain and heart (112). Susceptibility to ARF is due to a combination of factors; genetic predisposition, host factors and immunological factors, the latter being the most widely accepted theory (30). The abnormal immune response theory is based on the concept of molecular mimicry, whereby an immune response targeted at the streptococcal antigen also recognises human tissue (110). The cross-reactive antibodies bind to endothelial cells on the heart valve, leading to activation of the adhesion molecule, the vascular cell adhesion molecule – 1 (VCAM -1), with resultant recruitment of activated lymphocytes and lysis of the endothelial cells in the presence of complement. The ensuing tissue damage leads to the release of peptides such as laminin, keratin and tropomyosin, which activate cross reactive T - cells that invade the heart, amplifying the damage and causing epitope spreading (110).

The endocardium, pericardium, or myocardium may be affected, and valvular damage is the hallmark of rheumatic carditis (109). All four valves can be implicated in RHD and the mitral valve is almost always affected, alone or in combination with the aortic valve. In contrast, isolated aortic valve disease is uncommon. Damage to the pulmonary and tricuspid valves is usually secondary to increased pulmonary pressures resulting from left sided valvular disease (23). Early valvular damage leads to regurgitation, and then over ensuing years, usually because of recurrent episodes of rheumatic fever, the leaflet thickens, scars, calcify and valvular stenosis may develop (23). Mitral stenosis usually develops later (24), although it

has been described in adolescents (19, 25); as a result of persistent or recurrent valvulitis with bicommissural fusion (27).

The characteristic manifestation of carditis in previously unaffected individuals is mitral regurgitation, sometimes accompanied by aortic regurgitation (39). Myocardial inflammation on the other hand, may affect electrical conduction pathways, leading to PR interval prolongation and softening of the first heart sound (39).

### 1.6. Clinical presentation of acute rheumatic fever and rheumatic heart disease

Acute rheumatic fever presents as a combination of fever, polyarthritis (in 60 – 75%), carditis (in 50 – 60%), chorea, erythema marginatum and subcutaneous nodules three weeks after the streptococcal infection (109). Chorea and carditis however may occur six months later after the initial insult (109). Carditis manifests as a new or changed heart murmur, development of cardiac enlargement or cardiac failure, pericardial effusion and conduction abnormalities and arrhythmias (1).

A sequel of recurrent ARF episodes – RHD usually remains subclinical. People with RHD are often asymptomatic for at least 10 years before their valvular disease progresses to cause cardiac failure (24). This is as a result of compensatory dilatation of the left atrium and the left ventricle, before the onset of left ventricular systolic dysfunction (44). Rheumatic heart disease may also present after a complication such as atrial arrhythmias, an emboli event or infective endocarditis (44). Most patients present after the onset of left ventricular systolic dysfunction, usually at the ages of 20 – 50 years, with dyspnoea, (New York Heart Association class III/IV) (25). They may also present with chest pain or angina pectoris, fatigue and peripheral oedema (47). In a systemic review, 51 of the 330 (15.4%) patients newly diagnosed with RHD, presented with impaired systolic function and 34 of the 330 (10%) presented with atrial fibrillation (AF) (45).

The pattern of valve disease differs according to valve involved and presentation also differs in different age groups. Patients between 10 – 29 years most commonly present with pure mitral regurgitation, while patients 20 -39 years develop mitral stenosis and older patients develop mixed mitral valvular heart disease (10).

### 1.7. Outcomes of rheumatic heart disease

Rheumatic heart disease causes 200 000 – 250 000 premature deaths every year and is a major cause of cardiovascular deaths in children and young adults (1, 23). This mortality burden could however be an underestimation, because of either unavailable or incomplete data from developing countries.(48) Rheumatic heart disease also causes significant morbidity especially in developing countries. Acute rheumatic fever and RHD resulted in approximately 6.1 million years of potential lives lost before the age of 70 years during the 1990's, of which 5.5 million occurred in developing countries (37). Further RHD accounted for 5.9 million disability – adjusted life years lost during 2002(52).

Patients with RHD usually present with advanced disease; congestive heart failure (33%), pulmonary hypertension (29%), atrial fibrillation (22%), stroke (7%), infective endocarditis (4%) and major bleeding (3%) (30). Rheumatic heart disease also adversely affects pregnancy (51); it increases the risk of complications in pregnancy and is one of the major causes of non-obstetric maternal deaths in Africa.

Rheumatic heart disease accounts for 50% of the deaths seen in the 10.4 % of women who died during pregnancy due to pre-existing medical conditions (47).

Rheumatic heart disease and its complications reduce quality of life and productivity in a workplace and/ or school in adults and children of school going age (50). Further, it requires chronic medical, surgical and interventional therapy, which increase health costs (55). Secondary preventive therapy has been proven to reduce recurrence of episodes of ARF(53), therefore preventing the risk of developing carditis if not already present; or worsening existing valve damage(47). On the other hand, interventional treatment (surgery and cardiac catheterisation) is warranted when patients are symptomatic with severe valvular lesion (56).

In the Heart of Soweto study which documented 344 new cases of RHD at Chris Baragwanath hospital, 22% of the new patients required valve replacement or repair within a year of diagnosis (53). Mitral valve repair results in better outcome compared to valve replacement in rheumatic mitral regurgitation and is the recommended intervention if possible (64). In mitral stenosis, percutaneous mitral balloon commissurotomy is preferred over surgical commissurotomy as it results in excellent early outcomes, with a 50 – 60% event free outcome at 10-year follow up (66). Despite the good evidence for the least invasive intervention there exist significant variation in the ascertainment and prevalence of cardiovascular complications and the use of percutaneous and surgical intervention, between low, lower-middle and upper-middle income countries. The use of percutaneous and surgical interventions is extremely low in low income countries compared with upper-middle income countries, despite the greater prevalence of patients with RHD in low income countries, this is largely due to lack of surgical expertise and resources in developing countries (47).

## 2. Rationale for this study

Despite political transformation in SA, a significant burden of diseases of poverty has not been eradicated especially in certain provinces. In 1995 in SA, nine million children were living in poverty of which 69% were from KZN, the Eastern Cape (EC) and the Northern Province (NP) (113). The NP, KZN and Mpumalanga were amongst the provinces identified with higher than expected numbers of ARF/RHD in the period of 1993 - 1995 in the Soweto study (114). Furthermore, patients from these provinces and parts of southern and eastern parts of Gauteng were more likely to present with severe disease (114).

There are limited studies from KZN on the burden of disease due to RHD and the outcomes in adults. Therefore, this study aims to describe the demographic profiles of patients referred with RHD. The study also aims to describe the changes in the pattern of clinical presentation, outcomes and follow up of RHD patients in the recent 5 years at IALCH.

## 3. Aim

The aim of the study was to describe the disease profile and outcomes of RHD in patients referred to IALCH, in KZN.

### 3.1 Objectives

a) Document the demographic profile of patients aged 12 years and above, with RHD referred to Inkosi Albert Luthuli Central hospital (IALCH) cardiology unit during 2012 to 2016.
b) Describe the clinical features and echocardiographic findings of RHD in patients aged 12 years and over.
c) Document the interventions (surgical versus medical interventions) of the RHD patients referred to cardiology service

## 4. Methodology

Study design

This study was a retrospective descriptive chart review of patients with a diagnosis of RHD who were referred to the department of cardiology, IALCH; during the period of 2012 to 2016.

Study setting

Kwa-Zulu Natal has an estimated population of 11.1 million, which is 19.9% of the country's total population (55.91million) (115). Twenty three percent (3.86 million 0f 55.9 million) of the country's population younger than 15 years of age live in KZN [46], and this is the group most affected by ARF and subsequent RHD.

The study was conducted at IALCH, in KZN; a quaternary hospital serving the whole of KZN and the Eastern Cape. The catchment area of the hospital largely represents the rural parts of South Africa. Though there has been improvement in the quality of living and that of health care, the two provinces remain largely rural.

The study population and sampling

The study included all new patients seen at IALCH during a five-year period interval. The selected five-year period spans from 2012 to 2016.

All patients above the age of 12 years, who had a history of ARF and/or a diagnosis of RHD, clinically and/or on echocardiography were included in the study.

Sampling criteria

Records of all patients above the age of 12 years, who had a diagnosis of RF/RHD seen at IALCH were included. The electronic records were extracted from the database using the ICD 10 coding for rheumatic heart disease: acute rheumatic fever, mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation and mixed valve disease *(ICD codes I05.0 to I09.8)*. Codes for mixed valve disease were covered in the codes for the specific valves involved (Table 2).

Inclusion criteria

All patients with a primary diagnosis of RHD, clinically and/or on echocardiography, who are above the age of 12 years, seen during the five-year period of January 2012 to December 2016.

Exclusion criteria

All patients with primary valvular heart disease other than RHD were not included in the study.

Data collection

Each patient record was carefully scrutinised to ensure that the aetiology of valve disease is rheumatic before inclusion. Previous history of RF and echocardiographic features showing typical rheumatic valve morphology were used to confirm a rheumatic aetiology (Remenyi et al 2012)[39].

A structured questionnaire will be used to collect the data from the clinical records. The following information will be collected:

a) Demographic information: age, gender, ethnicity, area of and type of residence
b) Clinical data as recorded at the time of initial presentation.
    This will include the following details:
    i) Cardiovascular symptoms: dyspnoea (graded as per New York Heart classification)
    ii) Lower limb oedema
    iii) Advanced symptoms of clinical heart failure (as per Framingham's criteria)
c) The pattern of valvular involvement
d) Complications associated with the disease: heart failure, infective endocarditis, arrhythmias, and strokes
e) Co-existing comorbidities such as HIV
f) Investigation results: echocardiography – specifically looking at the valve lesion and valve area if stenotic, the pulmonary pressures and the ventricular function (ejection fraction)
g) Patient outcome in terms of management

Sample size

As this is a descriptive study, not testing a statistical hypothesis, all patients seen from January 2012 to December 2016 were included. All patient records of new patients seen within the 5-year period, who had an echocardiographic diagnosis of RHD were reviewed.

This was confirmed with Dr Nkwanyana who is a statistician in the University of KwaZulu Natal.

Data analysis

All de-identified data will be entered and analysed using IBM SPSS Statistics version 24. Descriptive statistics such as frequencies and percentages will be calculated to summarize categorical data. Measures of central tendency such as mean and median, and measures of dispersion such as standard deviation and interquartile range will be calculated for continuous variables. Categorical variables will be analysed by the Chi square and Fisher exact test when necessary. A p value<0.05 will be considered significant.

## Ethical considerations

Ethical clearance will be obtained from the Biomedical Research Ethics Committee (BREC), cardiology department and management of IALCH and the provincial department of Health prior to study commencing.

Each clinical record will be assigned a unique study number and only de-identified data will be entered. This will ensure that patients' confidentiality is upheld, as no name or any other identifying patient information will be used.

The results of this study will assist in the better planning of the of health care directed at patients with RHD, as prevalence and clinical pattern of the disease will be better understood.

## Methodological challenges and study limitations

The study is based in a public hospital and only focused on patients referred to IALCH and therefore may not represent all ethnic groups and all income groups.

Further due to lack of expertise some patients with RHD may not have been referred to IALCH for further management and therefore the study may potentially under-represent the burden of RHD. RHD. On the other hand, it may over represent patients with advanced disease or over-represent the burden as most patients seen come from middle- and lower-income groups

## Timeline

The study was initially expected to run for at least 1 year, however due to other academic commitments and a lengthy data collection progress that was only done by the principle investigator, it took at least 3 years to complete

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## Appendix C1: Biomedical Research Ethics Committee (BREC)

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

NHRD Ref: KZ_202001_019

Dear Dr KS Shange
UKZN

**Approval of research**

1. The research proposal titled **'The profile of rheumatic heart disease at a regional hospital in KwaZulu Natal, South Africa'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.
   c. Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za
   d. Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]
Dr E Lutge
Chairperson, Provincial Health Research Committee
Date: 17/03/2020

Fighting Disease, Fighting Poverty, Giving Hope

## Appendix C2: KwaZulu Natal Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

NHRD Ref: KZ_202001_019

Dear Dr KS Shange
UKZN

**Approval of research**

1. The research proposal titled **'The profile of rheumatic heart disease at a regional hospital in KwaZulu Natal, South Africa'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
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   b. Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.
   c. Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za
   d. Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]
Dr E Lutge
Chairperson, Provincial Health Research Committee
Date: 17/03/2020

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## Appendix C3: Inkosi Albert Luthuli Hospital Permission

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Office of The Medical Manager
IALCH

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401060 Email: ursulanun@ialch.co.za
www.kznhealth.gov.za

Reference: BE 598/17
Enquiries: Medical Management

28 January 2020

Dr K S Shange 216075218
School of Clinical Medicine
College of Health Sciences

Dear Dr Shange

**RE: PERMISSION TO CONDUCT RESEARCH AT IALCH**

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **The trend of Rheumatic Heart Disease at a regional hospital in KwaZulu-Natal, South Africa.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]

.....

**Dr L P Mtshali**
**Medical Manager**

## Appendix D: ICD 10 coding, table 2

| ICD 10 code | Description |
|---|---|
| I05.1 | Rheumatic mitral insufficiency |
| I05.0 | Mitral stenosis |
| I06.1 | Rheumatic aortic insufficiency |
| I07.1 | Tricuspid insufficiency |
| I05.2 | Mitral stenosis with insufficiency |
| I08.0 | Disorders of both mitral and aortic valves |
| I06.0 | Rheumatic aortic stenosis |
| I05.9 | Mitral valve disease, unspecified |
| I05.8 | Other mitral valve disease |
| I09.9 | Rheumatic heart disease, unspecified |
| I06.2 | Rheumatic aortic stenosis with insufficiency |
| I05 | Rheumatic mitral valve disease |
| I08.1 | Disorders of both mitral and tricuspid valves |
| I08.9 | Multiple valve disease, unspecified |
| I08.8 | Other multiple valve disease |
| I08.3 | Combined disorders of mitral, aortic and tricuspid valves |
| I09.8 | Other specified rheumatic heart disease |
| I06.9 | Rheumatic aortic valves disease, unspecified |
| I08 | Multiple valves diseases |
| I01.9 | Acute rheumatic heart disease, unspecified |
| I06.3 | Other rheumatic aortic valve disease |
| I07.8 | Other tricuspid valve diseases |
| I07.0 | Tricuspid stenosis |
| I02.9 | Rheumatic chorea without heart involvement |
| I07.2 | Tricuspid stenosis with insufficiency |
| I07.9 | Tricuspid valve disease, unspecified |

| ICD 10 code | Description |
|---|---|
| I09 | Other rheumatic heart disease |
| I01.1 | Acute rheumatic endocarditis |
| I06 | Rheumatic aortic valve diseases |
| I02.0 | Rheumatic chorea with heart involvement |
| I08.2 | Disorders of aortic and tricuspid valves |
| I01.3 | Other acute rheumatic heart disease |
| I07.0 | Tricuspid stenosis |
| I08.2 | Disorders of both aortic and tricuspid valves |
| I01.8 | Other acute rheumatic heart disease |
| I09.1 | Rheumatic disease of endocardium, valve unspecified |
| I01 | Rheumatic fever with heart involvement |
| I09.0 | Rheumatic myocarditis |
| I02 | Rheumatic chorea |

## Appendix E: Questionnaire

**Section A DemographicsAge**

| | | | |
|---|---|---|---|
| **<20** | **21 – 40** | **41 – 60** | **>60** |

Gender

| | |
|---|---|
| **Male** | **Female** |

**Ethnicity**

| | | | |
|---|---|---|---|
| **Black** | **White** | **Indian** | **Coloured** |

Area of residence

| | | |
|---|---|---|
| **Rural** | **Peri urban** | **Urban** |

**Type of housing**

| | |
|---|---|
| **Formal** | **Informal** |

Referring hospital

| | | |
|---|---|---|
| **Primary** | **District** | **Regional** |

**Province of origin**

| | | |
|---|---|---|
| **Kwa-Zulu Natal** | **Eastern Cape** | **Other** |

Section B

**Rheumatic heart disease History of Rheumatic fever**

| | |
|---|---|
| **Yes** | **No** |

Symptoms

| | | | | |
|---|---|---|---|---|
| **Dyspnoea** | **Paroxysmal nocturnal dyspnoea** | **Cough** | **Lower limb oedema** | **Fatigue** |

**Onset of symptoms**

| | |
|---|---|
| **Sudden** | **Gradual** |

Diseased valve

| | | | |
|---|---|---|---|
| **Mitral** | **Aortic** | **Tricuspid** | **Pulmonary** |

**Valve lesion**

| | |
|---|---|
| **Regurgitation** | **Stenosis** |

Valve area Mitral stenosis

| | | |
|---|---|---|
| **Mild (>1.5 $cm^2$)** | **Moderate (1.0 – 1.5 $cm^2$)** | **Severe ( < 1$cm^2$)** |

**Aortic stenosis**

| | | |
|---|---|---|
| **Mild (>1.5 $cm^2$)** | **Moderate (1.0 – 1.5 $cm^2$)** | **Severe (< 1$cm^2$)** |

Complications of RHD

| | | | |
|---|---|---|---|
| **Atrial fibrillation** | **Infective endocarditis** | **Congestive Heart failure** | **Stroke** |

**HIV status**

| | |
|---|---|
| **Positive** | **Negative** |