A cross-sectional study of the spectrum, aetiology and clinical characteristics of adult mitral valve disease at Chris Hani Baragwanath Academic Hospital

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Name of Primary Supervisor Dr Ruchika Meel

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Article 1 (Submissible Format): Title: A cross-sectional study of the spectrum, aetiology and clinical characteristics of adult mitral valve disease at Chris Hani Baragwanath Academic Hospital

The above article has been submitted to SA Heart for publication (outcome pending)

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Comments by primary supervisor:

I hereby declare that this is Students unaided work. The article has been submitted to South African heart association Journal.

Presentations/Publications

1. WITS annual research day 2019:

A poster abstract of the research report was displayed at the event. It won joint second best registrar research award for 2019.

2. South African Heart Congress/PASCAR 2019:

A poster abstract of this research report was selected by SA Heart for the congress. I was awarded a sponsorship to attend and display my research findings for the duration of the congress.

3. Publication (outcome pending)

The research article has been submitted to SAHeart journal for publication in January 2021 and is currently under a peer review process.

Abstract

Background

There is a scarcity of data regarding the current demographic and clinical characteristics of patients with mitral valve disease (MVD) at Chris Hani Baragwanath Academic Hospital (CHBAH). In this research report we aimed to systematically document the demographic, clinical and echocardiographic characteristics of current patients with adult MVD at CHBAH.

Methods

This was a cross-sectional descriptive study of adult MVD, conducted at CHBAH outpatient's valve clinic (December 2018- March 2019).

Results

The study included 134 patients (mean age 50 ± 13.3 years, 77% females). Majority were of African ethnicity (96%) in the New York Heart Association (NYHA) class II (54%). Dominant lesion was mitral regurgitation (39%) followed by mixed MVD (38%) and mitral stenosis (23%). The main aetiology of MVD was rheumatic heart disease (80%), mitral valve prolapse was noted in 11 % and myxomatous degenerative disease was present in 6%. Infective endocarditis was noted in 3%. Thirty per cent of the patients had concomitant involvement of other valves. Hypertension (30%) and human immunodeficiency virus (12%) were main co-morbidities. Heart failure was present in 78% at index hospitalisation. Fourteen patients were on rheumatic fever prophylaxis. MVD was complicated with pulmonary hypertension (28%) and atrial fibrillation in 14% of patients.

Conclusion

The current patients with MVD tended to be older females with co-morbidities. The predominant aetiology was chronic rheumatic heart disease and acute rheumatic fever was rare.

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LIST OF ABBREVIATIONS:

MS= Mitral stenosis

MR=Mitral regurgitation

MMVD= Mixed mitral valve disease

MVD= Mitral valve disease

AS= Aortic Stenosis

AR= Aortic regurgitation

RHD= Rheumatic Heart Disease

VHD= Valvular heart disease

IHD= Ischemic heart disease

CAD= Coronary artery disease

IE= Infective Endocarditis

HF= Heart failure

NYHA= New York Heart Association

CKD= Chronic Kidney Disease

HIV= Human Immune Virus

ARF= Acute rheumatic fever

AF= Atrial fibrillation

EF= Ejection fraction

LV= Left ventricle

LVEF= Left ventricular ejection fraction

RVD= Retro viral disease

CHBAH= Chris Hani Baragwananth Academic Hospital

HB= Haemoglobin

BPM= Beats per minute

SQM= Square metre

BSA= Body surface area

BMI= Body mass index

INR= International normalized ratio

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Approved protocol with extended literature review

A Cross Sectional study of the spectrum, aetiology and clinical characteristics of adult mitral valve disease at Chris Hani Baragwanath Academic Hospital (CHBAH)

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1. Summary

From the available literature, which will follow below, it is evident that in both the developing and developed countries little is known about patients suffering as a result of valvular heart disease (VHD). This is owing to the lack of data in this important field of cardiology. A previous study was done by Karen Sliwa et al [1] in 2006-2007 at Chris Hani Baragwanath Academic Hospital (CHBAH), however it was limited to newly diagnosed rheumatic VHD patients.

At CHBAH, we suspect that the clinical presentation, co-morbidities and aetiology of adult mitral valve disease (MVD) patients would differ from that of the past in developing countries. Additionally, no recent studies have documented the change in demographic and clinical profile of these patients. The level of education and age of our population at large have increased.[2, 3] There is better access for children to the relevant immunization/ prophylactic programmes. I therefore suspect to find less acute rheumatic fever (ARF) related MVD and more cases of chronic rheumatic and degenerative valve disease compared to prior studies done in developing countries. Coronary artery disease (CAD) is on the rise. It is postulated that this would lead to more ischemic related MVD. The impact of Human Immune Virus (HIV) related cardiac diseases is substantial. Intravenous and oral drug abuse and traumatic injuries is rife in our population. Taking the above into consideration, I suspect that the spectrum of MVD has changed significantly.

Thus the aim of the study is to provide an insight to the spectrum, aetiology and clinical characteristics of patients with MVD at CHBAH. By doing so, the findings of this study could be used as a future reference for the South African database.

2. Introduction

VHD remains a frequent aetiology of heart failure (HF). [1] It constitutes a considerable amount of cardiovascular morbidity and mortality worldwide. [4] In developed countries, degenerative valve disease is the most common aetiology of VHD. [5] Rheumatic heart disease (RHD) accounts for majority of VHD in developing countries. [5]

Mitral stenosis (MS) is characterized as an obstruction to left ventricular inflow due to the mitral valve being structurally abnormal. [6] An abnormal reversal of blood flow from the left ventricle (LV) to the left atrium (LA) is defined as mitral regurgitation (MR). [7] The normal mitral valve (MV) area is approximately 4-6 cm^2. Severe MS occurs with a valve area of less than 1.5cm^2. [6] As the valve progressively narrows, the resting diastolic MV gradient and left atrial pressure increases. This leads to transudation of fluid into the lung interstitium and dyspnoea at rest or with minimal exertion. Haemoptysis may occur if the bronchial veins rupture and left atrial dilatation increases the risk for atrial fibrillation (AF) and subsequent thromboembolism. [6]

In acute MR, [7] an increase in the preload and a decrease in the afterload causes an increase in left ventricular end diastolic volume and a decrease in left ventricular end systolic volume. This results to an increase in total stroke volume and subsequently to an increase in left atrial pressure. Pulmonary oedema is often the initial manifestation of acute MR. These acute MR patients typically present with dyspnoea, orthopnoea and fatigue. In chronic compensated MR, [7] the left atrial pressure is frequently normal or minimally increased because of the LA and LV having enough time to dilate and accommodate the regurgitant volume. The mitral annulus may stretch and prevent the leaflets from closing properly during systole as the left ventricle enlarges progressively. This worsens the MR and left ventricular dilatation. Patients may remain asymptomatic for years and have normal exercise tolerance until systolic LV dysfunction develops in chronic MR. Chronic atrial dilatation may give rise to AF and patients will experience chest palpitations.

Common causes of MVD include: RHD, infective endocarditis (IE), degenerative valve disease, mitral valve prolapse (MVP) and ischaemic events causing acute MR.

Less common aetiologies include systemic lupus erythematous, rheumatoid arthritis, carcinoid syndrome and others. MVD can cause complications such as AF, pulmonary artery hypertension, dilation of the heart chambers and subsequent HF. Treatment options for patients with MVD include that of medical management, percutaneous intervention (if the diseased mitral valve is suitable for this treatment method) and surgical management (mitral valve repair or replacement depending on the surgical team's skillset).

To date, there are very few studies looking at the clinical and echocardiography characteristics of VHD patients especially in the developing countries. There is a lack of data regarding demographic information such as age and gender; symptoms/functional class; aetiology of MV lesions; co-morbidities; severity and complications of these valve lesions. This study was conducted at CHBAH, which is a periurban tertiary Hospital and serves predominantly the community of Soweto.

2.1 DEVELOPING COUNTRIES

2.1.1 Aetiology and type of valve lesions

A total of 960 VHD cases were identified in a study conducted in Soweto by Sliwa et al. [1] Thirty six per cent (344) were related to RHD. [1] MR was found to be the most frequent heart valve lesion. This was followed by a combination of MR and aortic regurgitation (AR) lesions. [1] Ninety cases required admission for suspected bacterial endocarditis however only 20 patients met the Dukes criteria. Munyandu [8] reported on 308 echocardiograms of patients with VHD in Zimbabwe. RHD was diagnosed in 16% of the study group and MR was the most common lesion.

A definitive aetiology of a patient's VHD was found in only 13549 (69.7%) patients in a study conducted by Fang-Zhou Liu et al. [9] RHD was the most common aetiology (37%) in these VHD patients. This was followed by congenital (13.9%), degenerative (11.5%), ischaemic (12.7%), infective (3.1%) and auto immune disease (0.7%).[9] It was noted though that RHD was on the decline from the year 2009 to 2013 (42.8% to 32.8%). Potential reasons for this finding included improved socio economic status and favourable standard of living in the Guangdong region of China. Similarly there was a decline in IE from 3.5% to 2.2 %.[9] Conversely, congenital, degenerative and ischaemic causes increased during this period. [9]

One hundred and thirty RHD participants in Uganda were recruited in a research conducted by Zhang W et al. [10] Pure MR was the most prevailing VHD (40.2%), followed by combined MR and AR (29%). Mixed mitral valve disease (MMVD) and AR were reported in 11% of patients. One case involving the tricuspid valve was reported.

A total amount of 2005 patients suffering with RHD in India were entered into a study by Negi et al [11] over a period of six years. Multiple valve lesion involvement was frequent (43.2%) and lesions of the MV were the most predominant (83.3%). *A* study by Manjunath et al [12] was performed at a tertiary centre in Bangalore over a period of 2 years. The results showed that MVD was the dominant lesion. RHD was the aetiology in 60.2% of these MV lesions. In patients with rheumatic MVD, MS was the dominant lesion (37.1%) versus MMVD (35.7%). MS was almost exclusively rheumatic in nature (97.4%). MR was the most frequent isolated valve lesion with a predominance being rheumatic (41.1%) followed by MVP and myxomatous disease (40.8%). [12]

Essien et al [13] conducted research on 55 patients from Nigeria with RHD. MVD was reported in 54 (98.2%) and isolated aortic valve disease in 1 (1.8%) case. MR occurred in 64.8%, MMVD in 25.9% and pure MS in 9.3% of patients. Zühlke L et al [14] registered 3343 RHD patients at 25 different hospitals across twelve African countries. RHD participants from India and Yemen were included as well. MMVD was found in 63.9% of patients.

2.1.2 Demographic and clinical characteristics of patients with MVD

The average age of patients with RHD was 40.3 ± 14.3 years reported by Negi et al. [11] RHD of the MV primarily affected females (72.3%) and patients from less advantageous backgrounds (92%). Manjunath et al [12] found that MS was the predominant lesion in females compared to males with a ratio of 1.94. MS patients were typically between 20-59 years of age with a peak of 30-39 years, whereas MR patients were younger with majority aged less than 20 years. [12]

Zhang W et al [10] concluded that 71% of RHD patients were female with a median age of 33 years. The peak age of the study population was 20 to 39 years. The commonest presenting symptoms were palpitations, fatigue, chest pain and

dyspnoea. The higher prevalence of disease in females, compared to the males, correlated with their levels of literacy and unemployment status. [10] However, factors such as varying hormonal responses, genetic predisposition and a lack of health-seeking behaviour could all have contributed to a higher amount of females with RHD. [10] Below (Table 1) are the differences in age groups with the various valve lesions found in this study. [10]

TABLE 2. DISTRIBUTION OF VALVE LESION BY AGE GROUP

	All	*<12 years*	*12–19 years*	*20–39 years*	*40–65 years*
Valve lesion(s)	130 (100%)	7	20	72	31
MR	55 (42.31)	4 (57.14)	12 (60)	26 (36.11)	12 (38.71)
MS	9 (6.92)	0	0	7 (9.72)	2 (6.45)
MR + MS	9 (6.92)	0	1 (5)	6 (8.33)	2 (6.45)
MR + AR	36 (27.69)	3 (42.86)	5 (25)	20 (27.78)	8 (25.81)
MS + AR	7 (5.38)	0	0	4 (5.56)	3(9.68)
MR + MS + AR	11 (8.46)	0	1 (5)	6 (8.33)	4 (12.90)
MS + AS + AR	1 (0.78)	0	0	1 (1.39)	0
MR + MS + AR + AS	2 (1.54)	0	0	2 (2.78)	0

MR = mitral regurgitation; MS = mitral stenosis; AR = aortic regurgitation; AS = aortic stenosis.

Table 1: The differences in age groups with various valve lesions by Zhang W et al. [10]

In a study by Sliwa et al, [1] Black African females (68%) predominated the 344 new cases of RHD being diagnosed. There was an early peak of RHD in the third decade of life. There were no statistical differences in symptoms of dyspnoea, peripheral oedema, resting heart rates, blood pressure or education in the different gender groups. Anaemia and AF were found concurrently in 8% and 10% of newly diagnosed RHD. Sixty four patients consented to a HIV test and 36% were found to be positive. Table 2 below illustrates the demographic and clinical characteristics of the study participants reported by Sliwa et al [1] of patients from Soweto:

Table 2 Socioeconomic data and clinical presentation of newly diagnosed rheumatic heart disease (*n* = 344)

	ALL (*n* = 344)	Women (*n* = 234)	Men (*n* = 110)
Socio-demographic profile			
Female	234 (68%)	234 (100%)	–
Median (IQR) age in years	43 (32 to 56)	41 (30 to 55)	42 (31 to 55)
Black African	314 (91%)	220 (94%)	94 (85%)
0–10 years standard education	314 (91%)	213 (91%)	101 (92%)
Median (IQR) years in Soweto	36 (20–50)	35 (20–49)	37 (20–50)
Clinical presentation			
Dyspnoea	226 (66%)	159 (68%)	67 (61%)
Palpitations/chest pain	227 (66%)	156 (67%)	71 (65%)
Raised jugular venous pressure	19 (5.5%)	12 (5.1%)	7 (6.4%)
NYHA Functional Class III/IV	61 (18%)	38 (16%)	23 (21%)
Peripheral oedema	94 (27%)	69 (29%)	25 (23%)
Mean heart rate (b.p.m.)	84 ± 17	86 ± 18	81 ± 16
Systolic blood pressure (mm Hg)	122 ± 24	122 ± 24	121 ± 24
Diastolic blood pressure (mm Hg)	69 ± 20	69 ± 21	67 ± 18
Clinical profile			
Renal dysfunction	57 (22%)	28 (17%)	29 (32%)
Anaemia	27 (8.2%)	23 (10%)	4 (4%)
Atrial fibrillation	34 (10%)	20 (9%)	14 (13%)

NYHA, New York Heart Association. Renal dysfunction defined = an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (moderate to severe renal impairment): calculated in 254 cases using the modification of diet in renal disease abbreviated formula (estimated GFR mL/min/1.73 m^2) =186.3 × (serum creatinine mg/dL) $^{-1.154}$ × (age) $^{-1.154}$ × (0.742 female sex) × (1.21 if black African) using serum creatinine concentrations (μmol/L) converted to mg/dL. Anaemia defined as haemoglobin level <11 d/L in men and <10 d/L in women from 330 cases.

Table 2: The socio-demographic profile and clinical characteristics of newly diagnosed rheumatic heart disease by Sliwa et al. [1]

It was established that 9.8% of patients had an echocardiographic diagnosis of RHD in a report by Sani MU et al. [15] Forty seven males and 82 females (ratio 1:1.7) had RHD and their ages ranged from 5 to 60 (mean 24.02 +/- 12.75) years. [15] In RHD patients reported by Zühlke L et al, [14] 66.2% were of the female gender. They had a median age of 28 years and majority were unemployed (75.3%). Patients from the lower income countries tend to experience more New York heart association (NYHA) class III/IV symptoms. HF was a common presentation in all participants irrespective

of the country they resided in. Pulmonary hypertension and AF were common complications throughout the various income classes. See table 3 below for other clinical characteristics. [14] Unemployment which leads to poor socio economic status, overcrowding and poor living conditions is considered to be an increased risk of developing ARF and subsequently RHD. [16]

Table 2 **Clinical characteristics of 3343 children and adults with rheumatic heart disease**

	Low-income countries (*N* 1110) *N* (%)	Lower-middle-income countries (*N* 1370) *N* (%)	Upper-middle-income countries (*N* 863) *N* (%)	*P*
New York Heart Association Functional Class III & IV	306 (27.6)	384 (29.1)	119 (13.9)	0.24
Medical history				
Acute rheumatic fever	247 (22.3)	593 (44.3)	500 (59.0)	0.06
Congestive heart failure	476 (43.0)	285 (21.0)	349 (40.6)	0.06
Pulmonary hypertension	329 (29.9)	465 (34.2)	163 (19)	0.5
Stroke	58 (5.2)	52 (3.8)	125 (14.5)	<0.01
Infective endocarditis	25 (2.3)	59 (4.36)	49 (5.7)	0.1
Major Bleeding	21 (1.9)	38 (2.8)	30 (3.5)	0.61
Peripheral embolism	3 (0.3)	3 (0.2)	19 (2.2)	<0.001
Cardiovascular complications[a]	96 (8.7)	137 (10.1)	191 (22.2)	0.02
Atrial fibrillation	163 (17.9)	241 (22.0)	182 (22.7)	0.49

Table 3: Clinical characteristics of 3343 participants with RHD by Zühlke L et al. [14]

We have observed a decline in ARF at CHBAH. In a study by A M Cilliers, [17] the patient records of children suffering with ARF and RHD were recalled from a database at CHBAH paediatric cardiology department. A total of 467 cases were identified. A declined from 64 in 1993 to three cases of ARF in 2010 was documented in children suffering with RHD. The reduction in the number of children with ARF and RHD presenting to CHBAH was attributed to an enhancement in socioeconomic conditions and greater access to medical care for the population in the past twenty years. [17]

Tibazarwa et al [18] did a summary of all population-based studies of the incidence of ARF in the world. A systematic literature search identified 10 eligible studies from 10 countries on all continents, except Africa. The overall mean incidence rate of first attack of ARF was 5–51/100 000 population. A lower incidence rate of 10/100 000 per year was found in America and Western Europe, while a higher incidence (>10/100 000) was documented in Eastern Europe, Middle East (highest), Asia and Australasia.

2.1.3 Mitral valve disease related complications

Sliwa et al [1] found that 14% of MR and 9% of MS patients suffered with LV systolic dysfunction. Twenty four per cent of MR and 7% of MS patients were found to have a left ventricular end diastolic diameter (LVEDD) > 55mm. [1] Negi PC et al [11] found that most of the patients had moderate to severe valve dysfunction (69.3%). Major adverse cardiovascular events were recorded in 23.4% of patients which comprised mainly of advanced HF (15.6%), peripheral venous thrombotic disease (4.1%), and cerebrovascular accidents (3.9%). Munyandu NT [8] reported that the most frequent complications were pulmonary hypertension and left atrial enlargement.

Zhang W et al [10] reported that many of the patients presented with moderate to severe systolic dysfunction (seven per cent in MS patients and 18% in MR patients). Fifty three per cent of the MS and 50% of the MR patients had pulmonary hypertension. [10] AF was a reported complication in 10% of MR patients and 23% of MS patients. Dilated atria were found in 70% of MR and 83% of MS patients. [10] The finding that ± 40% of MVD patients presented with NYHA class III and IV indicates poor quality of life, delayed diagnosis and a lack of knowledge and awareness of the disease by both patients and health care workers in that population group.

Chockalingam A et al [19] found that pulmonary hypertension was present in 81% in patients older than 18 years and functional tricuspid regurgitation in 77%. In summary, 6% of patients suffered with AF, 1% had left atrial thrombus (seen on transthoracic echocardiography) and less than one per cent had embolic cerebrovascular events. [19] IE was diagnosed at presentation in 0.6% of the cases [17]. In RHD patients reported by Zühlke L et al [14], 28.8% had pulmonary hypertension and 21.8% had AF. Congestive HF was found in 33.4% which implies that these patients were diagnosed at an advanced stage of their VHD.

Left atrial enlargement and AF are the most common electrocardiographic (ECG) findings in patients with MR. [4] LV enlargement is noted in approximately one-third of patients, and RV hypertrophy is observed in 15%.[4] The most common ECG finding in patients with MS is left atrial enlargement (P-wave duration in lead II ≥0.12 s and/or a P-wave axis between +45° and −30°). [4] Atrial fibrillation is also a common finding. ECG evidence of RV hypertrophy occurs in individuals with pulmonary hypertension. [4] Left atrial enlargement produces a negative P wave in lead V1,

and/or a wide notched P wave in leads II, III, or aVF. LV dilatation and hypertrophy are observed with increased QRS voltage and ST-T wave changes in the lateral precordial leads

2.1.4 Conclusions and limitations of the literature review in developing countries

In terms of aetiology, it is clear that RHD is still the leading cause of VHD in developing countries. However the focus in majority of these articles were mainly on RHD and the other aetiologies were not well described. Complications of VHD, such as pulmonary hypertension and AF, are well reported in the literature. ECG findings and abnormalities were not well documented in previous studies. There is a lack of data with regards to specific demographic, clinical characteristics and echocardiographic parameters related to adult MVD in isolation in previous literature.

There is a paucity of data on current spectrum of adult MVD at CHBAH. I suspect that the spectrum of MVD has changed at CHBAH. Due to an ageing population and the adoption of the western sedentary lifestyle and diets, I expect to find an increase in degenerative and ischaemic related valve disease compared to previous literature. I expect to find a much larger number of drug and iatrogenic related IE, HIV related and trauma related VHD cases involving the MV. Furthermore, chronic RHD is likely more prevalent than ARF due to better living conditions.

2.2 DEVELOPED COUNTRIES

A prospective study by Demirbag et al [20] in Turkey evaluated patients with VHD. A total of 1300 patients were recruited in this study. [20] There were 1090 native VHD patients, 201 patients where previous intervention was done and nine IE patients. Mean age was reported to be around 57±18 years with a female to male ratio of 1.5:1.[20]

The most common native valve disease was MR at 43%. The main aetiologies were degenerative and ischaemic heart disease (IHD). [20] Thirty two per cent had multiple valve lesions. Pure MS was seen in 15% of the study population. The main aetiology of MS was RHD (98%) and aortic stenosis (AS) was of degenerative aetiology in 86% of the cases. [20]

The most common symptom across all native valvular lesions was dyspnoea with a functional class between NYHA II and III for 75% of patients. [20] An interesting finding was that of VHD being more prevalent in patients with only primary school education. [20] The types of valve lesions were similar to that of previous European studies [20], where AS and MR were the dominant valve lesions. Figure 4 illustrates the clinical and laboratory characteristics of the study participants reported by Demirbag et al: [20]

Table 3. The clinical and laboratory characteristics of the patients

	All cases (n=1300)	AS (n=66)	AR (n=45)	MS (n=164)	MR (n=466)	MVD (n=349)
Female (%)	60	54	71	70	61	60
Age (years)	57±18	70±16*	53±22	48±13	62±16	60±18
Application symptoms (%)						
Dyspnea	73	71	66	91	80	77
Angina	20	24	27	18	25	18
Palpitation	48	32	47	65†	48	47
Syncope	4	15	6	4	3	5
Etiologies (%)						
Degenerative	29	86‡	40	2	30	33
Rheumatic	46	8	24	98§	24	55
Congenital	1.9	6	11	0	3	2
Endocarditis	1.2	0	3	0	1	1
Ischaemic	11	0	5	0	30¶	6
Other	11	0	18	0	11	3
Functional capacity (%)						
NHYA Class I	21	28	24	11	19	23
NHYA Class II	43	38	55	42	45	42
NHYA Class III	32	34	21	43	31	28
NHYA Class IV	4	0	0	4	5	6
Comorbide risk factors (%)						
Hypertension	49	60**	44	35	46	50
ARF	28	2	3	24	22	25††
Hyperlipidemia	21	2	10	11	23	23
DM	10	16	5	4	11	13
Smoking	7	1	3	3	9	6
CAD	8	2	5	1	11‡‡	8
TR (%)	26	2	6	15	32	40
AF (%)	28	15	8	38	30	31
LVEF (%)	54±12	56±8	56±9	62±5	49±14¶¶	53±11
LVEDD (mm)	52±8	49±5	54±10***	47±4	54±8	52±7
LVESD (mm)	36±9	32±6†††	38±8	30±4	39±10	36±8

Table 4: The clinical and laboratory characteristics of study participants by Demirbag et al. [20]

Iung et al [21] oversaw a prospective study of patients with VHD in Europe from April to July 2001 in 92 cardiology centres from different European countries. A total of 5001 patients were included in the study. AS was the most frequent isolated lesion (43.1%) followed by MR (31.5%), AR (13.3%) and MS (12.1%). Degenerative valve disease was the commonest aetiology in developed countries with the aortic valve most frequently affected. Much lower rates of RHD and IE was reported in developed countries most notably due to better living conditions and a superior socioeconomic status amongst these patients. The aetiology of native left sided valve disease is shown in table 5.

Table 3 Etiology of single native left-sided valve disease

	Aortic stenosis *n*=1197	Aortic regurgitation *n*=369	Mitral stenosis *n*=336	Mitral regurgitation *n*=877
Degenerative (%)	81.9	50.3	12.5	61.3
Rheumatic (%)	11.2	15.2	85.4	14.2
Endocarditis (%)	0.8	7.5	0.6	3.5
Inflammatory (%)	0.1	4.1	0	0.8
Congenital (%)	5.4	15.2	0.6	4.8
Ischaemic (%)	0	0	0	7.3
Other (%)	0.6	7.7	0.9	8.1

Table 5: The aetiology of native left sided valve disease by Iung et al [21]

As regards to the main clinical characteristics, [20] mean age was 65 +- 14 years. At inclusion, 30.2% of patients were in the NYHA class I. The main comorbidities were previous myocardial infarction (13%) and chronic obstructive lung disease (14.8%).

In summary, a comparison from the above literature, from both the developed and developing worlds, of the clinical characteristics, type of valve lesion most encountered and aetiology thereof will be depicted in the table below:

A comparison of adult MVD between developed and developing countries		
	Developed World	Developing World
Age of onset	➢ 55-65 years	➢ 20-40 years
Gender	Male predominance	Female predominance
Type of valve lesion	AS and MR	MR and MMVD
Aetiology of the VHD	Degenerative and ischaemic	RHD

Table 6: A comparison of adult MVD between developed and developing countries

Thus the aim of the study is to provide a current insight to the spectrum, aetiology and clinical characteristics of patients with MV disease at CHBAH. By doing so, the findings of this study could be used as a future reference for the South African database.

3. Study Objectives / Aims

Aim of the study: To describe the spectrum, aetiology and clinical characteristics of adult mitral valve disease patients at Chris Hani Baragwanath Academic Hospital.

Objectives:

- Describe the demographic information of all participants – Age, sex, race, level of education
- Describe the symptomatology of all participants including their functional class and any pre-existing co-morbid states
- Describe the aetiology and complications of adult MVD patients.

4. Methods

Study setting/design/selection

This will be a cross sectional review of adult MVD patients that meet the inclusion and exclusion criteria below. It will be conducted weekly on a Tuesday at the valve clinic of CHBAH. The valve clinic sees approximately 30 patients every Tuesday of which 10 are usually MVD related. Patients will be enrolled into the study over a period of 4 months**.** The reason for this is that most valve patients are seen at least once in this period. This would therefore reflect more accurately the findings of the current review. Consideration for public holidays that fall on a Tuesday and the closing of the cardiology valve clinic during the festive period in December 2018/ January 2019 will be given. Collection of data will be extended to compensate for these events. The cardiology valve clinic at CHBAH is staffed with cardiology fellows, a full time consultant and a few cardiac technologists that are trained to do echocardiograms.

The aim of the study design is to recruit and complete all data collection required on that particular Tuesday as this would incur no additional cost to the researcher. Based on the desired sample size of 150-160 patients, as set out below, this would require ±10 patient's data to be collected every Tuesday. The aim is to collect and transfer all data required onto the relevant data sheets as seen below in the appendices section. However if this is not possible, photocopies (paper or electronic photocopying) of the patient files will be made to capture all relevant information required for the completion of the data sheets.

Sample size and recruitment

Population Size	10 mitral valve disease patients x 16 weeks	N = 160 patients	160 prior to inclusion/ exclusion criteria

An estimated 480 patients would attend the Tuesday valve clinic over a 4 month period. These include all types of VHD patients. MVD patients are generally one third of each clinic day. For the goal of this study, the aim is to recruit ± 150-160 patients with MVD during this 4 month period.

Recruitment of these patients, after obtaining informed consent, is needed as currently the division of cardiology does not have a filing system conducive for a complete retrospective study to be carried out. All patient records are kept with the patients themselves thus consent to access patient files would be required.

Recruitment of these 150-160 patients will be done with the assistance of the research assistant in the department of cardiology at CHBAH.

Recruitment of patients will be subject to following inclusion and exclusion criterion.

Inclusion criteria:

- ✓ Age ≥ 18 years of age
- ✓ All native mitral valve participants
- ✓ Patients with previous mitral valve intervention (mitral valve repair or percutaneous balloon mitral vulvuloplasty)
- ✓ Informed consent given

Exclusion Criteria:

- ✓ Refusal to participate in the study
- ✓ Prosthetic mitral valve patients
- ✓ Congenital valvular heart disease and functional lesions secondary to underlying dilated cardiomyopathy.
- ✓ All other valve lesions apart from mitral valve disease

Clinical Evaluation

Demographic information, comorbidities and relevant past cardiovascular symptoms and systemic enquiries for all enrolled patients will be retrieved from the patient file records by the researcher with the aid of a questionnaire attached below. Relevant clinical findings focusing mainly on the cardiovascular system, previously documented in the patient records, will be documented. Relevant ECG findings like AF or pulmonary hypertension will be retrieved from patient files. In cases where information is insufficient, patients were interviewed prospectively. Examination not done routinely in the clinic such as weight and height will be done prospectively.

Echocardiographic Evaluation

Transthoracic echocardiography would have been performed on all patients in the left lateral position by trained technicians using a S5-1 transducer on a Philips iE33 system (Amsterdam, The Netherlands). The transducer transmits a frequency of 1.7MHz and receives a frequency of 3.4 MHz. The images are usually obtained from the standard parasternal long axis, short axis, apical 3 chamber, apical 4 chamber and apical 2 chamber views. The data would have been transferred by the cardiac technician or fellow onto a cardiac echocardiogram template, as attached below in the appendices section. I will access this template directly from the patient records and transfer it to my echocardiography data collection sheet.

<u>Assessment of mitral valve morphology</u>

The MV was considered of rheumatic aetiology when there was evidence of chordal thickening, thickened anterior mitral leaflet, calcification and excessive leaflet motion in systole as per the WHF criteria. [22]

<u>Assessment of mitral valve severity</u>

Severity of MVD was assessed by echocardiographic measurements as per the European and American guidelines set out below [23, 24] in tables 7 and 8:

Table 11. Stages of MS

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of MS	• Mild valve doming during diastole	• Normal transmitral flow velocity	• None	• None
B	Progressive MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA >1.5 cm^2	• Increased transmitral flow velocities • MVA >1.5 cm^2 • Diastolic pressure half-time <150 ms	• Mild-to-moderate LA enlargement • Normal pulmonary pressure at rest	• None
C	Asymptomatic severe MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS)	• MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)	• Severe LA enlargement • Elevated PASP >30 mm Hg	• None
D	Symptomatic severe MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm^2	• MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)	• Severe LA enlargement • Elevated PASP >30 mm Hg	• Decreased exercise tolerance • Exertional dyspnea

The transmitral mean pressure gradient should be obtained to further determine the hemodynamic effect of the MS and is usually >5 mm Hg to 10 mm Hg in severe MS; however, due to the variability of the mean pressure gradient with heart rate and forward flow, it has not been included in the criteria for severity.

LA indicates left atrial; LV, left ventricular; MS, mitral stenosis; MVA, mitral valve area; and PASP, pulmonary artery systolic pressure.

Table 7: Stages and severity of MS as per ACC/AHA guidelines [23]

MS is classified on the basis of valve area and pressure gradients across the valve. Pressure gradients are assessed using echocardiography, with a mean pressure >5 mmHg indicating moderate stenosis, and >10 mm Hg indicating severe stenosis. Mild stenosis has a valve area between 2.0-1.6cm^2, moderate MS with a valve area 1.5-1.0cm^2 and severe MS with a valve area < 1.0cm^2. [23]

MR severity is determined by a combination of structural echocardiography parameters and qualitative/quantitative Doppler measurements. [24] Mild MR has a normal LA/LV size. It has a small central jet, usually less than 4cm^2 or less than 20% of the LA area. The vena contracta width is less than 0.3cm. Severe MR has a dilated LA/LV. The MV leaflet is flail. Severe MR has a large central jet (> 50% of LA area) and the vena contracta width is ≥ 0.7cm. See figure 7 for complete MR severity parameters.

Table 8 Grading the severity of chronic MR by echocardiography

	MR severity*			
	Mild	Moderate		Severe
Structural				
MV morphology	**None or mild leaflet abnormality** (e.g., mild thickening, calcifications or prolapse, mild tenting)	Moderate leaflet abnormality or moderate tenting		**Severe valve lesions** (primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation; secondary: severe tenting, poor leaflet coaptation)
LV and LA size†	Usually normal	Normal or mild dilated		Dilated‡
Qualitative Doppler				
Color flow jet area§	**Small, central, narrow, often brief**	Variable		Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size
Flow convergence‖	**Not visible, transient or small**	Intermediate in size and duration		**Large throughout systole**
CWD jet	Faint/partial/parabolic	Dense but partial or parabolic		Holosystolic/dense/**triangular**
Semiquantitative				
VCW (cm)	<0.3	Intermediate		≥0.7 (>0.8 for biplane)¶
Pulmonary vein flow#	**Systolic dominance** (may be blunted in LV dysfunction or AF)	Normal or systolic blunting#		Minimal to no systolic flow/ **systolic flow reversal**
Mitral inflow**	**A-wave dominant**	Variable		E-wave dominant (>1.2 m/sec)
Quantitative††,‡‡				
EROA, 2D PISA (cm^2)	<0.20	0.20-0.29	0.30-0.39	≥0.40 (may be lower in secondary MR with elliptical ROA)
RVol (mL)	<30	30-44	45-59††	≥ 60 (may be lower in low flow conditions)
RF (%)	< 30	30-39	40-49	≥50

Table 8: Grading the severity of chronic MR by the American Society of Echocardiography [24]

Echocardiography definitions and cut-offs

All images and echocardiographic measurements were interpreted and reported as per standardised guidelines on chamber quantification and VHD assessment and quantification of severity. [25] As per the current HF guidelines, preserved left ventricular ejection fraction (LVEF) was reported as an ejection fraction (EF) above 50%. Severe left ventricular systolic dysfunction was reported as an EF below 40%. An EF between 40%-49% was defined as mid- range. [26] For MR an LVEF of ≤60% was considered significant as per VHD guidelines. [27] Pulmonary artery systolic pressure (PASP) was estimated from the peak velocity of the tricuspid regurgitation jet plus the estimated right atrial pressure. Patients with a high PASP were classified

into mild (30-50mmHg), moderate (50–79mmHg) and severe (≥ 80 mmHg) pulmonary hypertension. [28] Functional MR has traditionally been defined as a disorder of regional or global left ventricular remodelling in which anatomically normal leaflets fail to coapt adequately. The abnormal closure pattern, seen with echocardiography, is one of apical tethering of one or both leaflets. [29] This is in contrast to patients with organic disease of the mitral valve.

In mixed MVD, MR was considered to be the dominant lesion when the LV was dilated. MS was the dominant lesion when:

- The left ventricle was normal in size
- Echocardiographic measurement of the mitral valve area suggested severe MS as per above criteria [23]
- Doppler mitral gradient was suggestive of MS severity

The most widely used linear dimension is the LA anteroposterior measurement in the parasternal long-axis view using M-mode, or preferably 2D, echocardiography. [25] LA size should be measured at the end of LV systole when the LA chamber is at its greatest dimension. Normal reference ranges are 27-38mm for women and 30-40mm for men. Severely dilated LA is ≥ 47mm for a woman and ≥ 52mm for a man. [25] Quantification of right atrial (RA) size is most commonly performed from the apical four-chamber view, although it can be assessed from different views. [25] A dilated minor-axis RA for both men and women is ≥ 55mm. [25]

Left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) must be measured when the end-diastolic and end-systolic valves (MV and aortic valves) are closed in the parasternal long axis view. The measurement is performed in the basal portion of the LV by the chordae [30] Normal LVEDD reference ranges are between 39-53mm for women and 42-59mm for men. Severely abnormal ranges are ≥ 62mm for women and ≥ 69mm for men. [30] In chronic MR patients, a LVESD ≥ 45mm and LVEF ≤ 60% would be an indication for definitive surgical management as per ESC guidelines. [27] Right ventricular (RV) focused apical four-chamber and modified apical four-chamber views provide the images required for a comprehensive assessment of the RV size, systolic and diastolic function, and RV systolic pressures. [25] Tricuspid annular plane systolic

excursion (TAPSE) represents a measure of RV longitudinal function. A TAPSE of < 17 mm is highly suggestive of RV systolic dysfunction. RV myocardial performance index (RIMP) is an index of global RV performance. RIMP > 0.43 by pulse wave Doppler and > 0.54 by tissue Doppler indicate RV dysfunction. [25]

5. Data Analysis

Statistical analyses will be performed with Statistica version 13 series 0414 for windows.

Descriptive statistics will be used in data analysis. Continuous variables will be shown as mean plus or minus the standard deviation for data that is normally distributed. The median analyses will be used for non-parametric distributions. Categorical variables will be demonstrated as frequencies and percentages. Confidence intervals calculated at 95%.

6. Ethics

The protocol will be submitted for ethics committee approval at the University of the Witwatersrand. The study is performed in accordance with guidelines set out in the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. (http://www.wma.net/en/30publications/10policies/b3/index.html.pdf Accessed 08/02/2014) (Revised October 2013).

Patients will be allowed to withdraw consent at any time. The information sheet and informed consent form is included in the appendices 1 and 2. The consent form will be discussed with the individual patients in their own language using an interpreter. After allowing time for due consideration and questions from the patient, the person obtaining consent and the investigator will sign the consent form. Permission will also be obtained from the medical superintendent of the hospital for permission to access medical records. All patient information will be kept confidential by a case number being assigned to each patient. The number allocated to each patient will only be known by the investigators.

7. Timing

2018 to 2019	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug
Literature Review																
Preparing Protocol																
Ethics Application																
Protocol Submission																
Procure Funds and Collection of Data																
Data Analysis, Write up and Submission																

8. Funding

- ✓ The main costs for this study would include sundry costs
- ✓ Sundry costs would be very minimal as I am using my own laptop and the department has a personal computer (PC) available too.

- ✓ The division of cardiology already has the necessary ECG and Echocardiography machines in place so no further costs would be incurred.
- ✓ The study design is a retrospective one. Thus all special investigations required for the purpose of my study would have been done previously.

I intend applying to the South African Heart Association and other companies like Discovery Health for the financial assistance required to complete this study successfully. However the cost is rather minimal and I would be happy to fund it myself. Below is a table depicting a summary of the costs expected for this study:

Item	**Number**	**Total Cost**	**Funding source**
Stationery		R2500	South African Heart Association; Discovery Life, Momentum, Medical Research Council, Pharmaceutical companies
Other Sundry Expenses		R1500	
Total Cost		**R 4 000**	

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CHAPTER TWO: SUBMISSIBLE ARTICLE

1. Introduction

Valvular heart disease (VHD) remains a frequent aetiology of heart failure (HF). [1] It constitutes a considerable cause of cardiovascular morbidity and mortality worldwide. [2] In developed countries, degenerative valve disease is the most common aetiology of VHD. [3] Rheumatic heart disease (RHD) is responsible for majority of VHD in developing countries, with mitral valve disease (MVD) being a common lesion. [3]

There is a scarcity of data in developing countries with respect to the demographic information such as age and gender; symptoms and functional class; co-morbidities; aetiology of the valve lesion (s); severity and complications of adult MVD. A study done by K Sliwa et al at Chris Hani Baragwanath Academic Hospital (CHBAH) in a similar setting focused on newly diagnosed RHD patients.[1]

From the available developing countries literature review, the mean/median age for patients with adult MVD was between 20-39 years. [4, 5] Females were found to have greater prevalence of adult MVD than males. [6] The most common symptoms included that of dyspnoea, decline is effort tolerance, palpitations and chest pains. Hypertension, diabetes mellitus, strokes and thyroid disease were common co-morbidities. Patients with adult MVD were reported to have New York heart association (NYHA) class III/IV symptoms. [1]

Mitral Regurgitation (MR) was documented as the most common isolated adult valve lesion. [4, 7] Mitral stenosis (MS) predominance in female patients was almost exclusively related to RHD in all previous literature.[7] RHD was the commonest aetiology in developing countries as opposed to degenerative calcific disease in developed countries. This was followed by mitral valve prolapse (MVP), myxomatous MVD, ischaemic, infective and auto immune disease. Most of the patients had moderate to severe valve dysfunction. The general complications of adult MVD patients included atrial fibrillation (AF) and pulmonary hypertension. [5, 7]

No recent study has explored the clinical and socio-demographic profile of patients with MVD at CHBAH. We suspect that there has been a change in the clinical and

demographic characteristics of these patients compared to the past due to an aging population with better health care access [8] and a decline in acute rheumatic fever (ARF). [9] Thus, the objective of the study is to describe the demographics, spectrum, aetiology, clinical and echocardiographic characteristics and management of current adult MVD patients at CHBAH.

2. Methods

Study population

This was a cross sectional descriptive analysis and review of 134 patients with MVD conducted between December 2018 and March 2019. All patients above 18 years of age with native MVD formed part of the study. Patients with previous mitral valve (MV) repair were included. Patients with prosthetic mitral valves, congenital VHD, non-dominant MVD and functional lesions were excluded. Demographic information, co-morbidities and relevant past cardiovascular symptoms and systemic enquiries for all enrolled patients were retrieved from the patient file records on the day of their routine clinic visit, as the files are kept with the patients and not at the cardiac clinic. Echocardiographic and electrocardiographic (ECG) data were also collected from patient files. In cases where information was insufficient, patients were interviewed prospectively. Examination not done routinely in the clinic such as weight and height were done prospectively after obtaining patient's consent.

Echocardiography

Transthoracic echocardiography was performed on all patients in the left lateral position by trained technicians using a S5-1 transducer on a Philips iE33 system (Amsterdam, The Netherlands) during routine clinic visit. All images and echocardiographic measurements were interpreted and reported by attending cardiologist as per standardised guidelines on chamber quantification and VHD assessment and quantification of severity. [10-12] As per the current HF guidelines, preserved left ventricular (LV) ejection fraction (LVEF) was described as an ejection fraction (EF) above 50%. Severe left ventricular systolic dysfunction was stipulated as an EF below 40%. An EF between 40%-49% was defined as mid- range. [13] For MR an LVEF of ≤60% was considered significant as per VHD guidelines. [14] Pulmonary artery systolic pressure was estimated from the peak velocity of the

tricuspid regurgitation jet plus the estimated right atrial pressure. Patients with PASP ≥ 30 mmHg were classified into mild (< 50 mmHg), moderate (50–79mmHg) and severe (≥ 80 mmHg) pulmonary hypertension. [15]

Case Definition

The MV was considered of rheumatic aetiology when there was a previous history of ARF and echocardiographic evidence of chordal thickening, thickened anterior mitral leaflet, calcification and excessive leaflet motion in systole as per the WHF criteria. [10]

ARF was diagnosed on the basis of clinical manifestations (carditis, arthritis, chorea, erythema marginatum, subcutaneous nodules) supported by laboratory tests (for a preceding group A streptococcal infection) and echocardiography as per revised Duckett Jones 2015 recommendations for a moderate to high risk population. [16]

A standard 12-lead ECG recording or a single-lead ECG tracing of ≥ 30s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF. ECG documentation is required to establish the diagnosis of AF. [17]

Surgical intervention included previous percutaneous mitral balloon valvotomy patients (where the Wilkins score was favourable). Patients with previous MV repair were also included. Prosthetic mitral valve patients were excluded from this study.

Statistical Analyses

Statistical analyses were performed with Statistica version 13 series 0414 for windows. Descriptive statistics was used in the data analysis. Continuous variables were shown as mean plus minus the standard deviation for data that was normally distributed. The median analyses were used for non-parametric distributions. Categorical variables were demonstrated as frequencies and percentages.

Ethics

The study was performed in accordance with guidelines set out in the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.

(http://www.wma.net/en/30publications/10policies/b3/index.html.pdf Accessed 08/02/2014) (Revised October 2013). Ethics approval and clearance was obtained from the University of the Witwatersrand human research ethics committee, Clearance certificate number: M180811.

3. Results

Clinical and demographic characteristics of study patients

Ninety six per cent of the patients were of African ancestry. The current group of patients with MVD were older and had numerous co-morbidities. Majority of the patients were overweight and 36% of patients were obese with a Body Mass Index (BMI) >30 kg/m^2. All retroviral disease (RVD) positive patients were on appropriate antiretroviral treatment regimens. Only 11% of patients were on penicillin prophylaxis for rheumatic fever. Most patients were on medical therapy for HF and heart rate control. Thirty one per cent of patients were on anticoagulation for AF.

Table I Demographic and Clinical characteristics of patients with mitral valve disease

Variable	Study patients (n=134)
Age (years), mean ± SD	50 ± 13.3
Gender, n (%)	
Females	103 (77%)
Males	31 (23%)
Body mass index (kg/m2), mean ± SD	29 ± 3
Heart rate (bpm), mean ± SD	75 ± 17
Systolic blood pressure (mmHg), mean ± SD	127 ± 21
Diastolic blood pressure (mmHg), mean ± SD	77 ± 12
Race, n (%)	
African	128 (96%)

Mixed ancestry	3 (2%)
Indian	3 (2%)
Clinical indices	
NYHA functional class	n (%)
I	58 (43%)
II	71 (54%)
III	5 (3%)
IV	0 (0%)
Heart failure hospitalization	n (%)
1 Admission	104 (78%)
2 Admissions	17 (12%)
3 or more Admissions	13 (10%)
Co-morbidities	n (%)
Hypertension	40 (30%)
Diabetes mellitus type 2	6 (4%)
Graves/Hyper/Hypothyroidism	6 (4%)
Human Immunodeficiency virus	16 (12%)
Cerebrovascular accident/Transient ischemic event	10 (7%)
Arrhythmias	3(2%)
Medication	n (%)
HAART	16 (12%)
Penicillin prophylaxis	14 (11%)
Furosemide	126 (94%)
Aldosterone receptor antagonist	64 (47%)

Angiotensin converting enzyme inhibitor	85 (63%)
Carvedilol or Atenolol	75 (55%)
Amlodipine	51 (38%)
Warfarin	41 (31%)
Digoxin	55 (41%)

Echocardiographic characteristics of the study patients are summarised in Table II

RHD was the commonest aetiology (80%) of adult MVD in this study group. Infective endocarditis (IE) was diagnosed in 4 study participants. The dominant lesion in the study group was MR (39%) closely followed by mixed mitral valve disease (MMVD) (38%) and MS (23%) (Figure 1). Rheumatic MS was seen more frequently in younger females with 64% being less than fifty years of age. Rheumatic MR was more prevalent in older females with 60% being greater than 50 years of age. Myxomatous MVD was noted in 8 patients with an average age of 52 years (Figure 2). Eighty two per cent of patients in this research group suffered with moderate to severe MVD. Fifty one per cent of the study population was found to have severe MVD with severe MR being the predominant pathology (20%) (Figure 3).

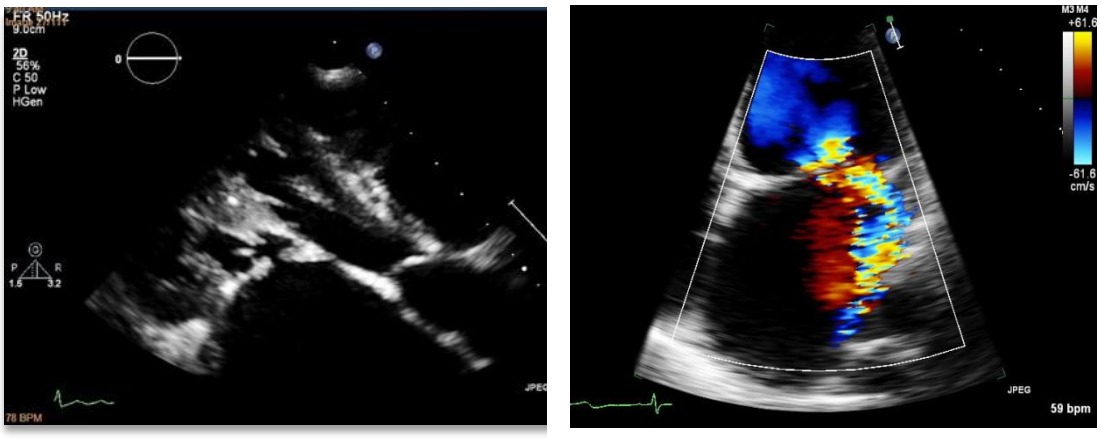

Figure 1: Two dimensional long axis view depicting chronic rheumatic heart disease of the mitral valve with thickening of the sub-valvar apparatus and the mitral valve leaflets (left) and severe rheumatic mitral regurgitation in a 50- year- old female (right).

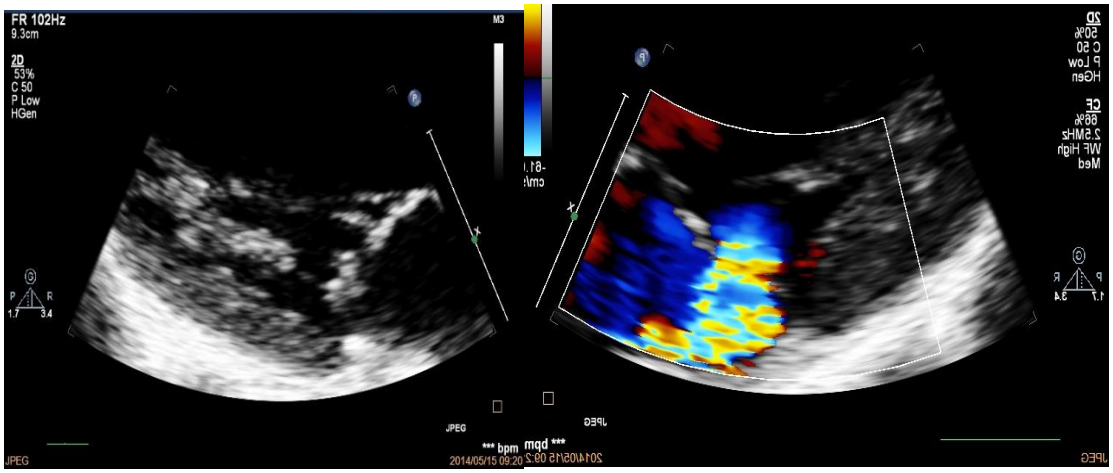

Figure 2: Two dimensional long axis view depicting myxomatous degenerative disease in a 52- year- old female with multiple scallop involvement and predominant prolapse of anterior mitral leaflet (left) with eccentric mitral regurgitation (right).

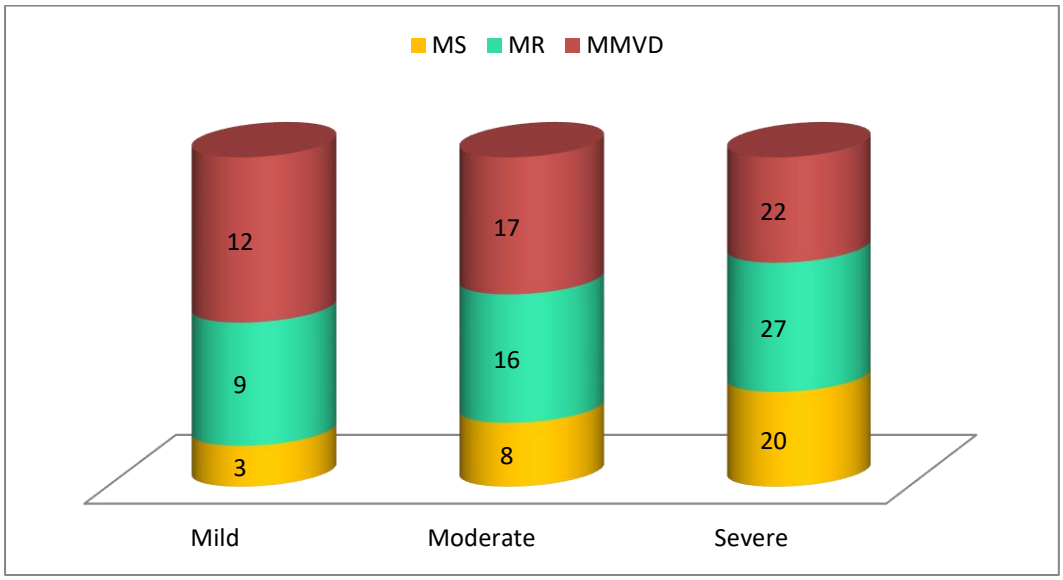

Figure 3: Severity of adult mitral valve disease presented in absolute numbers.

Concomitant valve lesions were frequently noted with MVD. Aortic regurgitation (AR) coexisted in 17% of patients with MVD. The overall mean LVEF was 57.5 ± 11.5%. Majority had preserved LV systolic function (80%). Out of the 9 patients with severe LV systolic dysfunction 5 had severe MR, 2 had severe MMVD and 2 had severe MS (Figure 4). Forty eight per cent of MR patients had a LVEF of less than 60%.

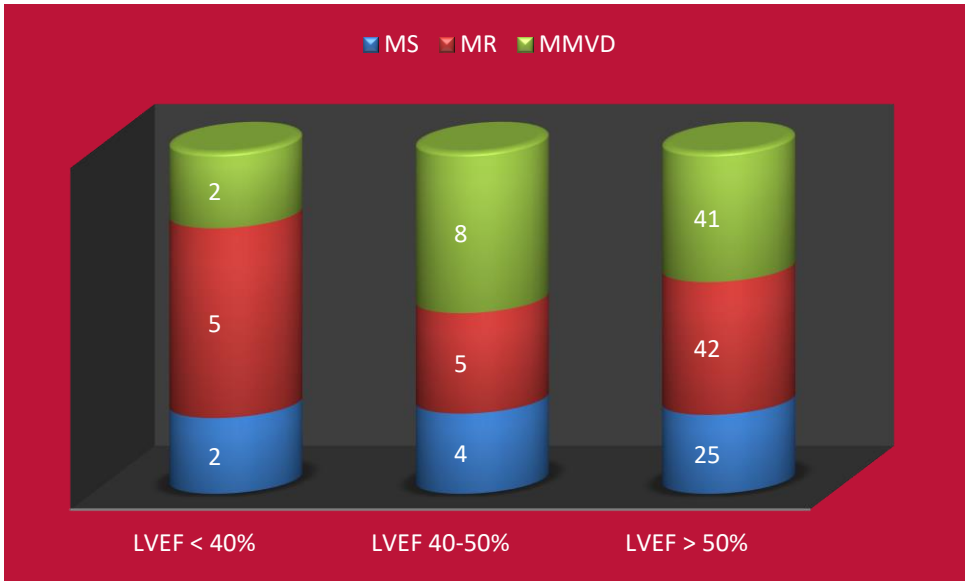

Figure 4: Left ventricular ejection fraction according to valve lesion in absolute numbers (n)

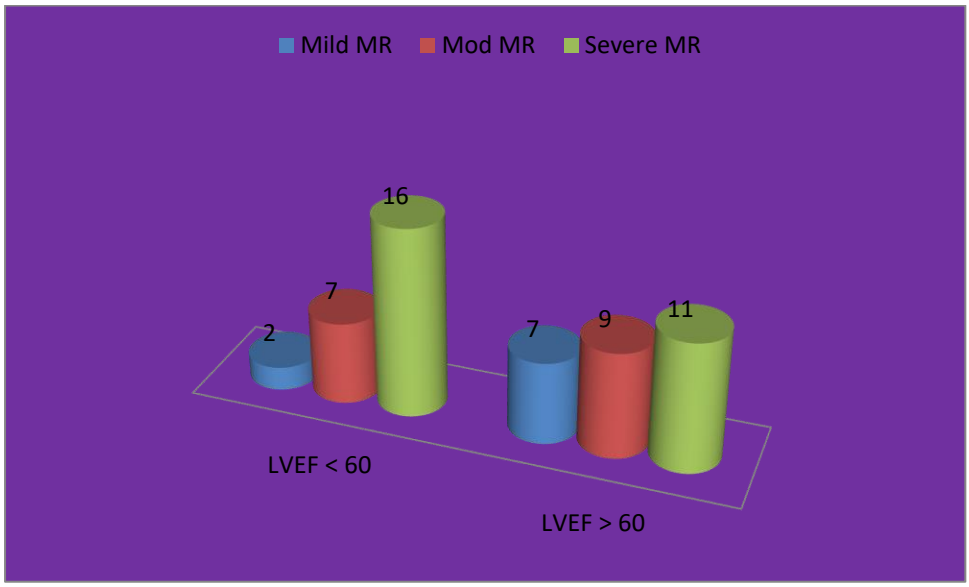

Figure 5: Left ventricular ejection fraction according to severity of mitral regurgitation in absolute numbers (n)

Table II- Echocardiographic findings of patients with mitral valve disease in absolute numbers and percentages

Variables	Study group (n=134)
Type of Valve lesion	n (%)
Isolated Mitral Stenosis	31 (23%)
Isolated Mitral Regurgitation	52 (39%)
Mixed mitral valve disease	51 (38%)
Mitral valve disease Severity	n (%)
Mild	24 (18%)
Moderate	41 (31%)
Severe	69 (51%)
Aetiology	n (%)
Rheumatic heart disease	107 (80%)
Mitral valve prolapse	15 (11%)
Myxomatous degenerative disease	8 (6%)
Infective Endocarditis	4 (3%)
Concomitant Valve Disease	n (%)
Aortic Regurgitation	23 (17%)
Aortic Stenosis	3 (2%)
Mixed aortic valve disease	8 (4%)
Tricuspid Regurgitation	9 (6%)
Left ventricle (LV) function	Mean ± SD
LV ejection fraction (%)	57.5 ±11.5
LV end- diastolic diameter (mm)	50.7± 7.2
LV end- systolic diameter (mm)	34.6± 7.3

LV systolic function according to valve lesion and ejection fraction	n (%)
LVEF <40%	9 (7%)
Mitral regurgitation	5 (4%)
Mitral stenosis	2 (1.5%)
Mixed mitral valve disease	2 (1.5%)
LVEF 40-50%	17 (13%)
Mitral regurgitation	5 (4%)
Mitral stenosis	4 (3%)
Mixed mitral valve disease	8 (6%)
LVEF > 50%	108 (80%)
Mitral regurgitation	42 (31%)
Mitral stenosis	25 (19%)
Mixed mitral valve disease	41 (30%)
Mitral valve disease related complications	n (%)
Pulmonary Hypertension	38 (28%)
Arrhythmia (Atrial Fibrillation & Flutter)	35 (26%)
Left ventricular systolic dysfunction	26 (19%)
Left Atrial clot	1 (0.7%)

RHD subgroup analysis

One hundred and seven patients had RHD with a mean age 51 ± 12.6 years and 78% were females. Majority were of African ethnicity (95%) and 55% of RHD participants were in the NYHA class II. The commonest lesion was MMVD (44%) followed by MS (29%) and MR (27%). Eighty three per cent of the RHD patients had moderate to severe MVD. Thirty five per cent of the patients had concomitant involvement of other valves. Hypertension (19%), retroviral disease (14%), and

cerebrovascular incidents (9%) were main co-morbidities. Heart failure was present in 75% of RHD patients at initial hospitalisation. MVD was complicated with pulmonary hypertension (34%) and AF in 30% of patients. Eight patients had a reduced LVEF of <40%. Fourteen patients were on rheumatic fever prophylaxis. All patients were on medication for HF or their co-morbidities.

Management of mitral valve disease

Majority of the patients were on medical therapy (94%). Fifty one per cent of these patients are awaiting surgery and suffer with severe isolated MVD or MMVD and require definitive surgical management. Twelve per cent of patients underwent previous MV surgery and 13% had previous percutaneous mitral valve procedures successfully performed. No reported cases of concomitant ischemic heart disease (IHD) were noted amongst patients that underwent previous surgical or percutaneous intervention.

4. Discussion

The major findings of this study are:

1. Adult MVD due to chronic RHD is common amongst a predominantly older African population with multiple co-morbidities.
2. Majority of the patients are female. MR was more prevalent in older females and MS in younger females
3. HF was the most common reason for hospitalisation. A significant proportion of patients were on medical therapy
4. There is a decline in ARF
5. Long waiting period for surgical intervention

The mean age in this study group was 50.82 +- 13.31years. This was older compared to previous studies reported above by Negi PC et al [6] and K Sliwa. [1] Better accessibility to healthcare, [8] less overcrowding and improved socioeconomic

status are likely reasons for this finding of an older study population suffering with MVD. Female gender pre-dominated in this study, comprising 77% of the sample. This concurs with findings from previous studies by K Sliwa [1] and Zhang W et al. [5] The possible reasons include health seeking behaviour amongst females [18] and its been shown that rheumatic MVD inherently has predilection for females. [1, 18] It is uncertain whether RHD prevalence is due to more vulnerability to developing an autoimmune response after Streptococcus Pyogenes infection or whether social factors, such as involvement in parenting, leads to an increased susceptibility. [9] RHD often becomes apparent during pregnancy especially with stenotic lesions, because of its associated higher cardiac output. [9] This may explain the younger age of patients with MS in the current study.

Risk factors for RHD include ones age, sex, and numerous different environmental factors as reported by Carapetis et al. [9] With regards to age, the peak prevalence of RHD occurs in the second and third decade of life. [19] This is in contrast to the findings of this study, where the peak prevalence ranged between 30 and 70 years of age. The aforementioned findings can be attributed to the decline in cases of acute rheumatic carditis which has a predilection for the younger patient, as opposed to the chronic rheumatic MR which is now commonly seen in an older RHD patient due to a decline in ARF. MR is generally well tolerated with fewer complications than MS patients and thus patients can live longer with MR and thus are likely to have delayed presentation. Further, better access to health care and advances in medical therapy for HF serves to stabilise the disease process thus prolonging the time to decompensated HF. [20] In this study, severe LV systolic dysfunction (LVEF < 40%) occurred in very few MR patients, however 48% of MR patients had LVEF of less than 60% which heralds the onset of LV systolic dysfunction in this subgroup. [21] Eighty two per cent of patients in this research group suffered with moderate to severe MVD. These findings were consistent with studies from developing countries. [5, 6]

In the current African population MVD is complicated by older age, being overweight, RVD reactive and hypertensive which makes it challenging to assess severity of MVD and aetiology of LV dysfunction in these patients. This is exemplified by cases where a high afterload from hypertensive heart disease results in overestimation of

MR severity. In patients with co-existing RVD and chronic severe MR it can be difficult to elucidate the predominant aetiology of LV systolic dysfunction. Therefore, a careful assessment is required that takes into account the confounding effects of these co-morbidities on LV function in patients with MVD.

The prevalence of myxomatous degenerative MVD was 6% in this study. This was greater than previously reported by Sliwa et al, [1] where myxomatous disease of the mitral valve was noted in 3 cases only. This is likely due to more accurate diagnosis of this condition as a result of evolution in echocardiographic imaging with better image resolution. Further, the older age of the current study patients may partly explain the increase in degenerative myxomatous disease. [22] In contrast to the study by Sliwa et al, [1] we did not observe any cases of calcific degenerative disease.

In the current study none of the patients that underwent a diagnostic coronary angiography, as part of surgical workup, had coronary artery disease (CAD). This is in line with the discoveries from a recent study by Meel et al. [23] In the aforementioned study a low prevalence of CAD was reported amongst patients undergoing valve replacement [23] and the value of routine coronary angiography prior to surgery in VHD patients was also questioned.

IE (3%) was rare in this study group. This is likely an underrepresentation as majority of these patients are sick and undergo emergency or urgent surgery soon after admission and therefore are not seen in an outpatient's clinic setting.

Most of the patients were in the NYHA II functional class (54%). Patients suffering with chronic HF and NYHA III and IV functional class have poorer outcomes. [24, 25] Eighty one per cent of patients in this research group had a preserved LVEF. All were on HF therapy. The vast majority of patients with MVD were on loop diuretics (95%), beta blockers (76%) and angiotensin converting enzyme (ACE) inhibitors (43%) compared to the findings of Sliwa et al. [1] Cardiac-specific treatment was better prescribed compared to the findings of the above mentioned study, [1] where loop diuretics, ACE inhibitors, beta-blockers, and aldosterone inhibitors were prescribed in 57, 26, 22, and 14% of cases.

In the current study despite being on medical therapy a large proportion of patients were symptomatic, this brings to the fore the advanced nature of disease in this population, likely a result of delayed medical attention, delayed diagnosis and limited resources. Twenty two per cent of the patients had more than one HF related admission. This translates into increased morbidity and mortality associated with HF secondary to VHD. [26] There is also an associated economic burden with repeated HF admissions to CHBAH. Facility fees for a patient at CHBAH, besides all other costs related to the HF admission, can range anywhere between ZAR135 to ZAR733 per night.[27] In a study by Ogah OS et al,[28] the total cost for one HF patient per year equated to US$ 1260.

No cases of ARF were reported in this study. Only 11% of patients took penicillin prophylaxis. This is likely due to the older age and patients are therefore past the window period for ARF prophylaxis. [14] The decline in ARF is largely related to the general epidemiological transition to more degenerative diseases in our society and improved socioeconomic status with better access to health care. [29] The other possible explanation of this perceived decline in rates of rheumatic fever may be due to under-reporting of rheumatic fever in South Africa. [30]

In this study group there was a significant time delay prior to surgical intervention. Currently, all state patients are being operated at a single tertiary hospital in Gauteng with limited resources and this result in delayed definitive surgical management of these patients with resultant increase in morbidity and mortality, and further burdening of an under-resourced health care system. This highlights the dire need for an onsite cardiothoracic surgery service at CHBAH, largest healthcare facility in the Southern hemisphere. [1]

5. Study limitations

The main limitation of this study was its short duration and in part reliance on collection of data from patient files. Few patients had systematically documented coronary angiography findings. The level of education was poorly documented in

patient records. IE patients were underrepresented in this study as majority of these patients do not present to an outpatient clinic. The echocardiographic technicians had varying levels of expertise and experience. Due to a lack of existing database we did not have access to information on mortality and hence were unable to report on this finding.

6. Conclusions

Isolated rheumatic MR was the most common lesion found in this study. Patients with MVD were found to be older when compared to prior literature. They had more co-morbidities and majority were on HF treatment. We found no cases of ARF. Penicillin prophylaxis was under-prescribed and only a few patients underwent surgery.

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CHAPTER THREE: LIST OF APPENDICES

Ethics clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Ebrahim Banderker

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180811

NAME: (Principal Investigator)	Dr Ebrahim Banderker
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	A prospective audit of patients with valvular heart disease at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	31/08/2018
DECISION:	Approved Unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Ruchika Meel
APPROVED BY:	Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	31/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore be due in the month of August each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

27/06/2019

Dr E Banderker
School of Clinical Medicine
Department of Medicine
Division of Internal Medicine
Chris Hani Baragwanath Academic Hospital

Sent by e-mail to: heib15@yahoo.com

Dear Dr Banderker

Re: **Protocol Ref No: M180811**
Protocol Title: *A cross-sectional study of spectrum, aetiology and clinical characteristics of adult mitral valve disease at Chris Hani Baragwanath Academic Hospital*
Principal Investigator: Dr E Banderker

Thank you for your letter of 16/04/2019, received here on 13/06/2019

I confirm that the proposed amendment has been noted and approved.

For the record the scope of the study has been narrowed on the recommendation of the Postgraduate Degrees Committee; you will now confine your enquiry to patients with mitral valve problems seen during a 4 month period ending on 31/03/2019.

Fortunately it does not matter in this context, but this is not what the HREC (Med) would regard as a sub-study - just for noting.

Thank you for keeping us informed.

Yours Sincerely

.....

Mr I Burns
For the Human Research Ethics Committee (Medical)

cc Dr R Meel

Participant Information Sheet

Dear Sir/Madam,

My name is Ebrahim Banderker and I am a student at Wits University in Johannesburg. As part of my studies I have to do a research project. I plan to look at patients with abnormal valves of the heart (the structures that allow blood to flow between the four chambers of the heart).

I would need about ten minutes of your time on a Tuesday morning when you visit the valve clinic at Chris Hani Baragwanath Hospital to access your patient records. I will check your patient records for important demographic (age, gender, race and level of education) and clinical findings previously found on you. Your vital signs (your blood pressure, heart rate, rate of breathing) and your height and weight will be accessed from your patient records. An electrocardiogram (ECG) was previously performed on you. I would need some information from this ECG for my study. Lastly, an echocardiogram (scan of your heart / pictures of your heart) was previously done for you. I would like to access this information. If you agree, I will use your previous blood results and other relevant medical records from your patient file.

You will not receive any benefits (like money, food or gifts) for participating in this study and there is no disadvantage or punishment for not participating. I will ensure that you do not lose your number in the normal queue for when you are supposed to be seeing the doctor at the valve clinic.

All information retrieved from your file will be kept completely confidential and anonymous (no one else will know). Your name will not be used at all. I will be using a number system to represent your participation in my final research report.

Should you wish to participate, please fill in your details on the consent form. You may contact me, my supervisor or Dr Penny (for any ethical concerns) at any point in time if you need any further clarification. Your participation would be greatly appreciated

Kind Regards,

Dr E Banderker

WITS UNIVERSITY

PARTICIPANT CONSENT SHEET

Project title: ***A Cross Sectional study of the spectrum, aetiology and clinical characteristics of adult mitral valve disease at Chris Hani Baragwanath Academic Hospital (CHBAH).***

1. I have been given all the relevant information
2. I was given time to read it or had it read to me
3. I was given time to ask questions and the answers given to me was satisfactory
4. I fully understand why the study is being conducted
5. I am aware that my medical records in my patient file (previous blood results, scans and other relevant information) will be viewed and used by the investigator
6. I understand that there will be no immediate benefit to me should I agree to participate, nor will it cost me anything to participate
7. I understand that even if I initially consent to take part in the study, I may withdraw at any time afterwards and would not be required to give any reasons
8. I have been given contact details listed below. If I require further information or become concerned about any aspect of this study I am free to speak to any of these contacts.

Contact details:

Dr E Banderker, Principal Investigator, telephone no: 0735162786

Dr R Meel, Supervisor

Dr C Penny, Chairperson of HREC (Medical), telephone no: 011 717-2031, email: Clement.Penny@wits.ac.za

Name of Participant: _____
Date: _____
Place: _____
Signature or mark _____

Witnessed by:

Name of Witness: _____
Signature: _____
Date: _____

PARTICIPANT INFORMATION DETAILS (confidential)

Participant unique number assigned: "……"

Name _____

Address _____

Contact phone numbers _____

Birth date _____

DEMOGRAPHIC AND MEDICAL HISTORY QUESTIONNAIRE

Participant unique number: "……"

General Information

Age:

Race:

□ Black □ Mixed Race □ Caucasian □ Indian

Sex:

□ Male □ Female

Education:

□ Primary School □ High School □ Diploma □ Graduate

Past medical history/ comorbidities retrieved from patient files

Were there any heart failure symptoms previously at time of diagnosis?

Any Arrhythmia or angina symptoms documented previously?

Functional class documented at time of presentation

Prior rheumatic fever prophylaxis – Yes/ No?

Previous cardiac failure admissions

High Blood Pressure

Diabetes or abnormal blood-sugar tests

Chronic kidney disease (kidney failure)

Human Immune Virus (HIV) →Yes/No? If Yes, ARVS? CD4/VL?

Any previous cardiac related surgery? Yes/No?

Other Heart Disease Risk Factors

Smoking

Have you ever smoked cigarettes, cigars or drugs?

□ Yes □ No

Alcohol

□ Yes □ No

List of current medications retrieved from patient files:

CLINICAL EXAMINATION, BEDSIDE TESTS AND SPECIAL INVESTIGATIONS

Vitals: Blood Pressure ( ), Heart Rate ( ), Saturation ( ), Respiratory Rate ( ), Temperature -Infective Endocarditis patients only ( )

Height, Weight (BMI calculation):

Cardiovascular examination:

See template

Electrocardiography Findings:

Collect data of complications such as Atrial Fibrillation, pulmonary hypertension and others

Echocardiography Findings: Transthoracic Echocardiography (TTE)

Coronary Angiography Findings: (if applicable)

Relevant Blood Results (HIV where applicable, Hb, Urea, Creatinine, INR, Lipogram, and Liver function tests):

CARDIOVASCULAR TEMPLATE

Date of cardiology examination previously:

Patient ID:

Vital signs

Pulse:

BP: Both arms (if indicated)

Height:

Weight:

BMI: (kg/m^2)

BSA: (sqm)

Cardiac

Inspection: neck- JVP & Bruits, chest wall deformities if noted, cyanosis, clubbing

Palpation:

Palpation of Pulses:

Apex Beat:

Auscultation findings previously documented:

CARDIAC CLINIC

Chris Hani Baragwanath Hospital

ECHOCARDIOGRAM REPORT

Name: Date:

Sex: Age: Hosp Number:

Operator:

CLINICAL DIAGNOSIS:

BP = Heart Rate = beats/min Rhythm:

HT(cm) Weight(kg) BSA

DIMENSIONS:

LVEDD: IVSD: LVPWD: AORTIC ROOT:

LVESD: LVOT: LA: LA Vol:

LV SYSTOLIC FUNCTION:

FS: EF: LV MPI MITRAL S' =

LV DIASTOLIC FUNCTION:

Mitral Inflow: E = A = **Pulmonary Vein Doppler:**

Tissue Doppler: E' = A' = E/E' =

MV E/A =

REGIONAL WALL MOTION ABNORMALITIES:

VALVES:

MITRAL VALVE :

AORTIC VALVE :

TRICUSPID VALVE :

PULMONARY VALVE :

RIGHT VENTRICLE:

TAPSE = Tricuspid S' = RV MPI =

RA: IVC = mm & aspiratory collapse Main pulmonary artery:

HEPATIC VEIN DOPPLER:

PERICARDIUM:

OTHER:

ASSESSMENT:

RECOMMENDATION (S):