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Peri-operative outcomes of mitral valve surgery at Charlotte Maxeke Johannesburg Academic Hospital

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Peri-operative outcomes of mitral valve surgery at Charlotte Maxeke Johannesburg Academic Hospital

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

Johannesburg, 2021

Declaration

I, Tebogo Mokotong-Mosekama Tabane declare that this research project is my own unaided work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand. It has not been submitted before for any degree or examination at this or any other University.



_____

5 July 2021

Abstract

Background

The distribution and determinants of heart disease vary greatly between developed countries and Sub-Saharan Africa, where rheumatic heart disease (RHD) remains a major public health issue. Studies from across Africa show that RHD, specifically of the mitral valve, is the main cause of morbidity and mortality from valvular heart surgery. Data on mitral valve surgery outcomes in South Africa are however limited. The aim of this study was to describe the peri-operative outcomes of patients that have undergone mitral valve surgery at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Methods

All patients above the age of 18 years who underwent mitral valve surgery at CMJAH between 1 January 2015 and 31 December 2018 were retrospectively included in the study. Cardiac Intensive Care Unit files including anaesthesia charts were assessed to describe pre-operative, intra-operative and post-operative data of each patient. Pre-operative data included patient demographic information and comorbidities. Intra-operative data included aortic clamp and bypass times. Post-operative variables included outcomes such as sepsis, bleeding, re-operation and the development of acute kidney injury (AKI). The pre-operative, intra-operative and post-operative outcomes were then compared to determine the effect each variable had on post-operative mortality.

Results

Two hundred and seventeen patients underwent mitral valve surgery at CMJAH between 1 January 2015 and 31 December 2018. Four of the patients had incomplete files. RHD was the predominant primary aetiology for mitral valve surgery. The mortality rate in this study was 6,10%. Pre-operative findings that contributed to mortality were: EuroSCORE II > 2%, pre-operative ventilation, dialysis dependence, pre-operative inotropic support, chronic obstructive pulmonary disease, congestive cardiac failure, renal insufficiency, low ejection fraction % and New York Heart Association ≥III. Post-operative findings that contributed to increased mortality were prolonged mechanical ventilation,

pneumonia, re-operation, AKI, sepsis, bleeding and transfusion. Increased aortic clamping and cardio-pulmonary bypass times increased the risk of prolonged mechanical ventilation, re-operations, use of pacemakers, AKI and bleeding.

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List of Abbreviations

RHD:	Rheumatic heart disease
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
AKI:	Acute kidney injury
EuroSCORE II:	European System for Cardiac Operative Risk Evaluation Score II
COPD:	Chronic obstructive pulmonary disease
CCF:	Congestive cardiac failure
EF:	Ejection fraction
NYHA:	New York Heart Association
CPB:	Cardio-pulmonary bypass
CPBT:	Cardio-pulmonary bypass time
RF:	Rheumatic fever
WHO:	World Health Organisation
AF:	Atrial fibrillation
PAP:	Pulmonary artery pressure
CKD:	Chronic kidney disease
CVA:	Cerebrovascular accident

Statement

The Research Report consists of a literature review, draft article, study proposal and appendices. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the author guidelines of the South African Heart Journal, the journal to which it is intended to be submitted, in order to comply with the university's style guide.

SECTION 1: LITERATURE REVIEW

In this section the literature regarding mitral valve disease, mitral valve surgery, rheumatic heart disease, acute kidney injury (AKI), cardiopulmonary bypass (CPB), bleeding and re-operation will be reviewed.

1.1 Introduction

The distribution and determinants of heart disease vary greatly between developed countries and Sub-Saharan Africa; where RHD remains a major public health issue[1]. RHD is the predominant cause of valve disease in Africa[2] resulting in Africa having the highest prevalence of cardiac disease in children and young adults[1]. Mitral valve disease, in the form of mitral stenosis and mitral regurgitation, is the commonest form of valve disease associated with RHD[3] and its treatment usually involves surgical repair or replacement. These surgical procedures are highly invasive and not without risk of complications[3]. In South Africa, data on the management and outcomes of mitral valve surgery are limited[4].

1.2 Rheumatic Heart Disease

A World Health Organisation (WHO) update[2] estimates that 2.4 million children aged 5-14 years are affected by RHD worldwide, with 42% of these children located in Sub-Saharan Africa[2]. It is estimated that the annual mortality rate worldwide for patients with RHD is 1,5% and the estimated number of deaths due to RHD ranges from 233 000 to 294 000 per year[2].

The condition is a sequela from repeated acute rheumatic fever (RF) attacks following exposure to Group A streptococci infections of the throat[1, 5, 6]. RF affects many organs and the diagnosis is determined by the revised Jones Criteria. The presence of 2 major criteria; or 1 major and 2 minor criteria, alongside evidence of an active Group A beta haemolytic streptococcal infection confirms the diagnosis[7].

Table 1 with the Revised Jones Criteria[7] is given below.

Table 1: The Revised Jones Criteria[7]

Major Criteria	
Low risk population	**High risk population**
Carditis (clinical or subclinical)	Carditis (clinical or subclinical)
Arthritis (polyarthritis)	Arthritis (mono-arthritis or polyarthritis)
Polyarthritis	Polyarthralgia
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
Minor Criteria	
Low risk population	**High risk population**
Polyarthralgia	Monoarthralgia
Fever > 38.5	Fever > 38.0
ESR > 60mm/h and or CRP > 3.0mg/dl	ESR > 30mm/h and or CRP > 3.0mg/dl
Prolonged PR interval (if there is no carditis as a major criterion and after considering differences according to age)	Prolonged PR interval (if there is no carditis as a major criterion and after considering differences according to age)

Reprinted and adapted from Alqanatish et al[7] as per the South African Copywrite Act no 98 of 1978, as amended sect 12.

The majority of patients who present with carditis during an episode of RF will develop inflammation and subsequent scarring of the left heart valves (aortic and mitral valves), resulting in regurgitation or stenosis requiring repair[6].

Prevention of RHD includes[1]:

1. Improvement of socio-economic conditions
2. Primary prevention with antibiotic treatment for Group A Streptococcus pharyngitis
3. Secondary prevention of acute RF recurrence with penicillin prophylaxis against acute attacks

1.3 Mitral Valve Disease

The majority of mitral valve surgery is indicated for mitral regurgitation[8]. Mitral regurgitation can be classified as either primary or secondary. Rheumatic heart disease myxomatous degeneration of the mitral valve, endocarditis and mitral valve prolapse are common causes of primary mitral valve disease. Secondary mitral

valve disease is commonly due to ischaemic mitral regurgitation or dilated cardiomyopathy[8].

The incompetent mitral valve seen in mitral regurgitation is either due to abnormalities in the valve itself, the sub-valvular components or functional abnormalities as a result of annular or left ventricular dilation[9]. Trans-oesophageal echocardiography is the gold standard in assessing severity of disease. The regurgitant orifice area, regurgitant volume and fraction are measured to determine the extent of disease. A regurgitant orifice area of ≥ 0.40cm^2, volume of ≥ 60ml/beat and a fraction of ≥ 50% constitute severe mitral regurgitation[10]. Patients often present with fatigability, palpitations and signs of congestive heart failure[9]. Mitral valve repair surgery is preferred over replacement and is indicated in patients presenting with left ventricular ejection fractions below 30% and/or left ventricular end systolic diameter of above 55mm in otherwise healthy patients free of comorbidities[10].

In Africa, mitral stenosis that requires surgical intervention is usually caused by RHD[10]. The inflammation caused by the progression of the disease results in thickening of the valves and fusing at the leaflet areas. Mitral stenosis is normally well tolerated due to compensatory mechanisms of the heart. The left atrium dilates to keep pulmonary pressures stable but as the disease advances the compensation gradually fails and pulmonary artery pressures rise. Eventually, pulmonary oedema and dyspnoea develop with chest infections becoming more common[10].

The classification of mitral stenosis is determined with the use of echocardiography by calculating the valve area and pressure gradients across the valve. A normal mitral valve area is between 4-6cm^2 with symptoms often only developing when the valve area is below 2cm^2 [10].

Surgery for mitral stenosis is indicated in the presence of an atrial thrombus, calcification of the valve or if an additional open cardiac surgery is required. Mitral valve replacement is the preferred surgery[10].

1.4 Mitral Valve Surgery

Currently, mitral valve replacement surgery is the preferred treatment for mitral stenosis due to improved long-term clinical outcomes and reduced need for further

intervention as compared to repair[10]. Biological valves for replacement are derived from glutaraldehyde-fixed porcine aortic leaflet or bovine pericardial tissue. Mechanical valves are made from pyrolytic carbon and have the disadvantage of the long-term need for anticoagulation to prevent thromboembolism. There is a high incidence of re-operation in patients with biological valves and a higher risk of bleeding noted with mechanical valves[11].

Operative mortality specifically in mitral valve replacement surgery is 5-6% and 1-2% in mitral valve repair[11]. The presence of atrial fibrillation (AF) and pulmonary hypertension contribute to this relatively high mortality rate[10].

AF is an abnormal, fast heart rate, characterised by irregular ventricular contractions and stroke volume in the presence of trembling atria. Approximately 50% of patients presenting with mitral valve disease will have AF[12]. Peri-operative AF is an independent risk factor for poor peri-operative outcomes in mitral valve surgery[12].

Pulmonary hypertension presents in 78% of patients awaiting mitral valve surgery[12]. It has been postulated that for every 10mmHg increase in systolic pulmonary artery pressures there is a 50% increase in peri-operative mortality[12].

The peri-operative mortality in mitral valve surgeries is 3%[4, 13]. The common complications of mitral valve surgery and their associated mortality risks[10] are listed in table 2.

Table 2: The common complications of mitral valve surgery and their associated mortality risks[10]

Complication	Percentage mortality risk approximation
Re-operation for bleeding	1%
Sternal wound infection	1%
Respiratory failure	5%
Renal failure	1%
Stroke	2%
Sepsis	1%

Complications associated with mitral valve surgery are commonly related to cardio-pulmonary bypass (CPB)[14]. Cardiopulmonary bypass is used to redirect blood from the heart and lung to facilitate cardiac surgery[15]. Platelets are activated and

subsequently bind to the exposed sub-endothelium, the CPB circuit or to the circulating monocytes and neutrophils, resulting in a decrease in platelet numbers[15]. The decrease in platelet numbers and altered platelet function is the primary cause of the major blood loss encountered during cardiac surgery[15].

In addition to the major blood loss attributed to CPB, there is a significant association between increased CPB time and the development of acute kidney injury (AKI)[14]. AKI develops in 2,8% of patients following valvular heart surgery[14, 16].

The low stroke volume seen in patients undergoing mitral valve surgery increases the risk of injury to the kidneys. AKI presents as a sudden impairment of kidney functioning with retention of nitrogenous waste products. An increase in plasma creatinine and/or increase in blood urea nitrogen, often accompanied by a decrease in urine output, confirms the diagnosis[16].

CPB, bleeding and AKI are independent risk factors of morbidity and mortality in mitral valve surgery[15, 17-20].

1.5 Mitral Valve Surgery in Africa

Epidemiological distribution of heart disease differs greatly between developed countries and Sub-Saharan Africa, where RHD is a major public health problem. The cumulative effect of poverty, social instability, lack of infrastructure, resources and awareness contribute to the underestimated impact of RHD[1, 2]. Studies from across Africa agree that RHD is the main cause of cardiac morbidity and mortality from valvular heart surgery, specifically of the mitral valve[1, 2, 9, 21]. Heart failure, native valve infective endocarditis, systemic embolization, pulmonary hypertension, atrial arrhythmias and complications related to surgery are contributing factors[2]. Patient demographics and the peri-operative risk of patients undergoing surgery have also been found to influence mortality[4].

1.6 Peri-Operative Risk Assessment

It is crucial to identify patients who are at high risk of peri-operative morbidity and mortality. Knowledge of the predictors of poor peri-operative outcomes can assist anaesthesiologists and surgeons in risk stratifying patients prior to mitral valve surgery[22].

1.6.1 EuroSCORE II

Despite advances in surgical techniques, anaesthesia and critical care; cardiac surgery is associated with high risks of morbidity and mortality. Risk stratification scores in cardiac surgery are sophisticated and are used worldwide to determine peri-operative risk[23].

The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) has been validated in the United Kingdom, Europe and North America[23]. This score has been shown to be predictive of peri-operative outcomes in cardiac surgery[24]. Variables used to determine the degree of risk prior to surgery are listed in table 3.

Table 3: EuroSCORE II risk predictors of mortality[23]

1. Age
2. Gender
3. Chronic obstructive pulmonary disease (COPD)
4. Extra cardiac arteriopathy
5. Neurological dysfunction
6. Previous cardiac surgery
7. Serum creatinine
8. Active endocarditis
9. Critical pre-operative states, such as intubation or use of inotropes prior to surgery
10. Unstable angina
11. Left ventricular dysfunction
12. Recent myocardial infarct
13. Pulmonary hypertension
14. Emergency operations
15. Surgery on the thoracic aorta
16. Post infarct septal rupture

A study by Kurlansky et al[25,26] found that well-established cardiac risk scoring systems in one population are of limited value in another major population group having racial and ethnic differences[25,26]. The study concluded that there should be wariness in applying the same risk stratification scores to all populations that may have constitutionally different populations and risk factors[25,26].

Pre-operative risk assessment is imperative to provide patients, anaesthesiologist's and surgeons with clinical information to modify surgical techniques and peri-

operative strategies[27]. Nevertheless, the EuroSCORE II has proven to have poor post-operative predictive rates in patients with optimal pre-operative states[28, 29].

Literature from large population subgroups such as Africa, describing the ability of risk scoring systems to predict peri-operative outcomes in African patients undergoing cardiac surgery have not been validated[23, 26].

1.6.2 New York Heart Association

Adequate physiological reserve is necessary to tolerate the stress of cardiac surgery. To quantify this, anaesthesiologists need to assess their patient's symptom severity and effort tolerance pre-operatively. Hellgren et al[30] showed that advanced New York Heart Association (NYHA) class was a risk factor for early post-operative mortality and that patients with NYHA class I and II demonstrated greater survival[30]. In a study done in Brazil, Fernandes et al[31] also demonstrated that a NYHA class III and IV was significantly associated with mortality in patients undergoing mitral valve surgery.

Table 4 describes the objective assessment of the NYHA functional capacity.

Table 4: An objective assessment of the NYHA functional capacity[23]

Class	Description	Objective Assessment	
I	Patients with cardiac disease but without resulting limitation of physical activity	A	No objective evidence of cardiovascular disease
II	Patients with cardiac disease resulting in slight limitation of physical activity	B	Objective evidence of minimal cardiovascular disease
III	Patients with cardiac disease resulting in marked limitation of physical activity	C	Objective evidence of moderately severe cardiovascular disease
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort	D	Objective evidence of severe cardiovascular disease

1.7 Acute Kidney Injury

Thirty percent of patients undergoing cardiac surgery develop post-operative AKI[16]. AKI prolongs hospital stay and increases the risk of infectious complications and mortality[16, 32]

According to a study done in Taiwan, 38.7% of patients who underwent mitral valve surgery developed post-operative AKI[32]. These patients presented with pre-operative NYHA III and IV, dilated cardiomyopathy and low ejection fraction, all of which lead to hypoperfusion of the kidneys and increased baseline creatinine[32].

Pre-operative serum creatinine above 132.63umol/L significantly increases the risk of post-operative death in patients undergoing cardiac surgery, rendering it an independent risk factor for morbidity and mortality in the peri-operative period of cardiac surgery[14].

CPB in valvular heart surgery contributes 2,8% to the development of AKI[16, 33]. Risk factors associated with AKI after CPB include:

1. Female gender
2. Diabetes mellitus
3. Peripheral vascular disease
4. COPD
5. Decreased left ventricular function
6. Congestive cardiac failure (CCF)
7. Emergency surgery
8. Elevated pre-operative serum creatine[16, 34]

Cardio-pulmonary bypass time (CPBT) plays a pivotal role in post-operative renal dysfunction and is an independent risk factor for post-operative AKI. However, a study done in Japan demonstrated that operative time may be a better predictor than CPBT for the development of AKI as it accounts for the cumulative effects of prolonged CPBT and the time to achieve haemostasis[35]. A study done in Cleveland, North America, demonstrated that pre-operative renal dysfunction independently increased the risk of serious infection, acute renal failure and mortality following cardiac surgery. The same study also demonstrated that CPB also impaired cellular and humoral immune responses, contributing to post-operative infection risk[36].

Older age and pre-existing chronic kidney disease (CKD) are predictors for AKI[37-39]. According to Mao et al[37], pre-existing CKD, prior myocardial infarction, pre-operative low haemoglobin, prolonged operative time and blood transfusion were strong predictors of AKI in octogenarians[37].

1.8 Cardio-Pulmonary Bypass and Aortic Clamping

Multiple studies report that CPB has negative effects on haemostasis and the inflammatory response[15, 40]. The blood cell activation and plasma protein alteration that occurs during CPB, increases bleeding time, post-operative blood loss and increases the risk for massive blood transfusion[15] .

A study conducted in Bangladesh between 2014-2016 concluded that prolonged CPBT was associated with haemostatic abnormalities[15]. This study demonstrated that CPBT of above 90 minutes resulted in higher mean blood losses

peri-operatively[15]. According to a study done by David[41], re-operation in mitral valve surgery was closely linked to prolonged CPBT[41]. Another study on African patients in Accra, Ghana, identified that a CPBT of above 120 minutes was associated with a reduction in platelet counts in comparison with CPBT of less than 60 minutes[42].

Prolonged CPBT increases post-operative infection risk[41, 43]. Nadeem et al[44] confirmed that prolonged CPBT resulted in an increased incidence of prolonged mechanical ventilation, further increasing the post-operative risk of pneumonia and peri-operative infection. Surgical site infection due to prolonged CPBT ranges from 0,3-8%[18, 45]. According to a recent study done in Iraq, patients who developed post-operative infection had prolonged CPB and operative times. The study further demonstrated that shorter operative times, higher haemoglobin level and higher haematocrit significantly decreased the post-operative risk of infection. The incidence of post-operative infection was 4,5%[18].

Prolonged CPBT and aortic clamping time have significant associations with morbidity and mortality in the peri-operative period of cardiac surgery.

1.9 Bleeding and Re-Operation

Bleeding occurs commonly in cardiac surgery and is a significant cause of morbidity and mortality[46]. Two to eight percent of cardiac re-operations are indicated for uncontrolled bleeding[20, 46, 47].

The PLASMACARD study[48] defined excessive bleeding as “abnormal, diffuse or microvascular bleeding that is unable to be controlled by compression and electrocoagulation, needs two or three units of transfused blood or >400 or 600ml of cell saved blood depending on the patients weight being above and below 60kg respectively, with a post-operative drain output of above 1.5ml/kg/h for at least three hours or a need for surgical re-exploration during the first 48 hours after surgery”[48].

The universal definition of peri-operative bleeding in cardiac surgery defines bleeding according to classes[49]:

(0) Insignificant
(1) Mild
(2) Moderate
(3) Severe

(4) Massive.

Bleeding is considered severe when:

1. Sternal closure is delayed
2. Five to ten units of blood or freshly frozen plasma are transfused after chest closure
3. Chest drains exceed 1000ml/12h
4. The use of recombinant activated factor VII was the final resort[49].

The literature defines multiple predictors of excessive bleeding and need for transfusion related to cardiac surgery and these are listed in table 5 below[50].

Table 5: Predictors of post-operative bleeding[50]

1. Extremes of age
2. Female gender
3. Renal dysfunction
4. Left ventricular ejection fraction (EF%)
5. EuroSCORE II > 2% (low/moderate risk)
6. Low pre-operative Hb
7. Prolonged CPBT
8. Emergency operation
9. NYHA > III
10. Lowest temperature during CPB
11. Large volume of intra-operative cell salvage
12. Prior cardiac surgery
13. CCF
14. Coagulation defect

The incidence of peri-operative blood transfusion in cardiac surgery is high, ranging between 40 and 90%. Common contributing factors are the difficulty of surgery, duration of surgery, age of the patient and pre-existing low haemoglobin level[51]. Complications of blood transfusions include transfusion related acute lung injury, circulatory overload, immune related reactions, haemolytic reactions, renal and neurological complications and prolonged hospital stay[51].

Due to the potential complications of blood transfusions, it is critical that transfusions be performed only when indicated[52]. The common practice of treating Jehovah's Witness patients has demonstrated that a haemoglobin level of between 7-8g/dl can be tolerated without any risk of death in patients who are free of underlying comorbidities[51].

The Society of Thoracic Surgeons and Society of Cardiovascular Anaesthesiologists 2011 guidelines[53] recommend red blood cell transfusion for a haemoglobin level < 6g/dL during CPB and < 7g/dL post-operatively, apart from patients who are at risk for decreased cerebral oxygen delivery, in whom lower thresholds for commencement of transfusion are needed[53].

Currently, haemoglobin and haematocrit threshold values are used as transfusion triggers as there is a lack of specificity in determining inadequate oxygen delivery to organs[51]. Haematocrit < 35% has been found to be an independent predictor of blood transfusion[42]. According to a study done in Accra, Ghana, pre-operative haemoglobin level was inversely correlated with the mean number of units of blood transfused in cardiac surgery. Interestingly, the same study found that good nutrition, and the use of erythropoietin, haematinics and anti-malarial drugs have been shown to increase the level of Hb pre-operatively[42].

Prophylactic manoeuvres to decrease the risk of post-operative bleeding in cardiac surgery are necessary. Early discontinuation of antiplatelet and anticoagulant medications pre-operatively, prophylactic usage of antifibrinolytic medications and effective surgical haemostasis are common techniques used to combat post-operative bleeding[46]. Patients who require re-operation due to bleeding have a higher risk of mortality, which is directly proportional to the time delay before re-operation[46].

There is an increased risk of morbidity and mortality due to re-operation because of bleeding regardless of the amount of blood transfused[42, 43]. Jeppsson et al[17] described a mean re-exploration rate of 5.5% for single valve surgery and 15% for emergency cardiac surgeries[17]. Re-operation results in an increased risk of mortality, peri-operative stroke, AKI and prolonged mechanical ventilation[54].

A study done between 2008 and 2017 in Brazil confirmed that a decrease in left ventricular EF% was the most consistent variable in mortality seen in re-operations in mitral valve surgery. Mortality in the above study was 13.8% with low cardiac output being the biggest contributing variable[47].

Peri-operative bleeding has a great economic impact due to the costs of agents needed to treat it[55]. A study done in Germany found that patients that bled severely needed twice the cost of treatment compared to those that did not bleed[56].

Bleeding, need for transfusions and re-operations all contribute to peri-operative morbidity and mortality and increase the overall cost of surgery[40].

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SECTION 3: DRAFT ARTICLE

Abstract

Background

The distribution and determinants of heart disease vary greatly between developed countries and Sub-Saharan Africa; where Rheumatic Heart Disease (RHD) remains a major public health issue. Studies from across Africa agree that RHD is the main cause of morbidity and mortality from valvular heart surgery, specifically of the mitral valve. Data on mitral valve surgery outcomes in South Africa are however limited. The aim of this study was to describe the peri-operative outcomes of patients that have undergone mitral valve surgery at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Methods

All patients above the age of 18 years who underwent mitral valve surgery at CMJAH between 1 January 2015 and 31 December 2018 were retrospectively included in the study. Cardiac Intensive Care Unit files including anaesthesia charts were assessed to describe pre-operative, intra-operative and post-operative data of each patient. Pre-operative data included patient demographics and comorbidities. Intra-operative data included aortic clamp and bypass times. Post-operative variables included outcomes such as sepsis, bleeding, re-operation and the development of acute kidney injury. The pre-operative, intra-operative and post-operative outcomes were then compared to determine the effect each variable had on post-operative mortality.

Results

Two hundred and seventeen patients underwent mitral valve surgery at CMJAH between 1 January 2015 and 31 December 2018. Four of the patients had incomplete files. Rheumatic heart disease was the predominant primary aetiology for mitral valve surgery. The mortality rate in this study was 6,10%. Pre-operative findings that contributed to mortality were: EuroSCORE >2%, pre-operative ventilation, dialysis dependence, pre-operative inotropic support, chronic obstructive pulmonary disease, congestive cardiac failure, renal insufficiency, low ejection fraction % and New York Heart Association ≥III. Post- operative findings that

contributed to increased mortality were: prolonged mechanical ventilation, pneumonia, re-operation, AKI, sepsis, bleeding and transfusion. Increased aortic clamping and cardio-pulmonary bypass times increased the risk of prolonged mechanical ventilation, re-operations, use of pacemakers, AKI and bleeding.

Introduction

The distribution and determinants of heart disease vary greatly between developed countries and Sub-Saharan Africa; where Rheumatic Heart Disease (RHD) remains a major public health issue.[1] RHD is the predominant cause of valve disease in Africa[2] resulting in Africa having the highest prevalence of cardiac disease in children and young adults.[1]

The cumulative effects of poverty, social instability and lack of infrastructure, resources and awareness contribute to the underestimated impact of RHD.[1, 2] Studies from across Africa agree that RHD is the main cause of cardiac morbidity and mortality from valvular heart surgery, specifically of the mitral valve.[1-3]

Mitral valve disease, in the form of mitral stenosis and mitral regurgitation, is the commonest form of valve disease and its treatment usually involves surgical repair or replacement. These surgical procedures are highly invasive and not without risk of complications.[3] In South Africa, data on the management and outcomes of mitral valve surgery are limited.[4]

Operative mortality specifically in mitral valve replacement surgery is 5-6% and 1-2% in mitral valve repair.[5] Complications associated with mitral valve surgery are commonly related to cardio-pulmonary bypass (CPB).[6] Platelets are activated and subsequently bind to the exposed sub-endothelium, the CPB circuit or to the circulating monocytes and neutrophils, resulting in a decrease in platelet numbers.[7] The decrease in platelet numbers and altered platelet function is the rationale behind the major blood loss encountered during cardiac surgery.[7, 8]

Multiple studies report that CPB has negative effects on haemostasis and the inflammatory response.[7, 9, 10] The blood cell activation and plasma protein alteration that occurs during CPB, increases bleeding time, post-operative blood loss and increases the risk for massive blood transfusion.[7] Bleeding occurs commonly in cardiac surgery and is a significant cause of morbidity and mortality.[11] Two to eight percent (2-8%) of cardiac re-operations are indicated for uncontrolled bleeding.[11-13]

A study conducted in Bangladesh between 2014 and 2016 concluded that prolonged cardiopulmonary bypass time (CPBT) was associated with haemostatic abnormalities.[7] This study demonstrated that CPBT of above 90 minutes resulted in

higher mean blood losses peri-operatively.[7] According to a study done by David[14], re-operation in mitral valve surgery was closely linked to prolonged CPBT.[14] Another study on African patients in Accra, Ghana, identified that a CPBT of above 120 minutes was associated with reduction in platelet counts in comparison with CPBT of less than 60 minutes.[15]

In addition to the major blood loss attributed to CPB, there is a significant association with increased CPBT and the development of acute kidney injury (AKI).[16] AKI develops in 2,8% of patients following valvular heart surgery.[6, 17] According to a study done in Taiwan, 38.7% of patients who underwent mitral valve surgery had post-operative AKI. These patients presented with pre-operative New York Heart Association (NYHA) class III and IV, dilated cardiomyopathy and low ejection fractions, all of which lead to hypoperfusion of the kidneys and increased baseline creatinine.[18] Cardiac surgery contributes 30% to the development of AKI.[17] AKI prolongs hospital stay and increases the risk of infectious complications and mortality.[17, 18]

The risk of infection significantly increases with prolonged CPBT.[10, 14] Nadeem et al[19] confirmed that prolonged CPBT resulted in an increased incidence of prolonged mechanical ventilation, further increasing the post-operative risk of pneumonia and peri-operative infection. Surgical site infection due to prolonged CPBT ranges from 0,3- 8%.[20, 21] According to a recent study done in Iraq, patients who developed post-operative infection had prolonged CPB and operative times.[20] The study further demonstrated that shorter operative times, higher haemoglobin (Hb) and higher haematocrit significantly decreased the post-operative risk of infection. The incidence of post-operative infection was 4,5%.[20]

Despite advances in surgical techniques, anaesthesia and critical care; cardiac surgery is associated with high peri-operative risk. Risk stratification scores in cardiac surgery are sophisticated and are used worldwide to determine peri-operative risk.[22]

The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) has been validated in the UK, Europe and North America.[22] This score has been shown to be predictive of peri-operative outcomes in cardiac surgery.[23] However, literature from large population subgroups such as Africa, describing the ability of risk scoring

systems to predict peri-operative outcomes in African patients undergoing cardiac surgery have not been validated.[22, 24]

A study by Kurlansky et al[24, 25], found that well-established cardiac risk scoring systems in one population are of limited value in another major population group having racial and ethnic differences.[24,25] The study concluded that there should be wariness in applying the same risk stratification scores to all populations that may have constitutionally different populations and risk factors.[24,25]

Anaesthesiologists need to assess their patient's symptom severity and effort tolerance pre-operatively to determine risk. Hellgren et al[26] confirmed that advanced NYHA class was a risk factor for early mortality. Patients with NYHA class I and II demonstrated greater survival.[26] In a study done in Brazil, Fernandes et al.[27] also confirmed that a NYHA class III and IV was significantly associated with mortality in patients with RHD undergoing mitral valve surgery.

Methods

This study was a retrospective, contextual, descriptive review of all patients who underwent mitral valve surgery at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 1 January 2015 and 31 December 2018. A maximum of 60 patients undergo mitral valve surgery per annum at CMJAH. The start and end date were realized by the sample size calculated. All patients above the age of 18 years old were included in the study.

Cardiac Intensive Care Unit files including anaesthesia charts were assessed to describe pre-operative, intra-operative and post-operative data of each patient included in the study. Pre-operative data included patient demographics and comorbidities. Intra-operative data included aortic clamp and bypass times. Post-operative variables assessed included outcomes such as sepsis, bleeding, re-operation and the development of AKI. The pre-operative, intra-operative and post-operative outcomes were then compared to determine the effect each variable had on post-operative mortality.

Statistical Analysis

STATA version 15, licensed to the Faculty of Health Sciences, University of the Witwatersrand, was used to analyse the data. Descriptive statistics were used for pre-operative, intra-operative and post-operative data. Categorical variables were described using frequencies and percentages. Inferential statistics were used to compare different variables. A p value <0.05 was deemed statistically significant. The effect of categorical variables (pre-operative demographics and post-operative outcomes) on mortality were analysed using the Fishers Exact test due to the limited sample size. The Shapiro Wilk test was used to test for the normality of distribution of the continuous variables (aortic clamping and bypass times). As the data was not normally distributed, means and inter-quartile ranges were used to describe the continuous variables. The two sample Wilcoxon Rank-Sum Mann-Whitney test was used to compare variables.

Ethical Aspects

Approval (M220343) from the Human Research and Ethics Committee (Medical) and all other relevant authorities was obtained. Data was managed according to the standards stipulated by the University of Witwatersrand. RedCap® was the data management tool used to obtain information. Information will be stored and secured for a period of six years. Each patient was assigned a study number and a separate list of patient details was available only to the researcher.

Results

Two hundred and seventeen patients underwent mitral valve surgery at CMJAH between 1 January 2015 and 31 December 2018. Four of the patients had incomplete files, therefore 213 were included in the study.

The preoperative demographic data of these patients is described in table 1.

Table I: Pre-operative demographic data of mitral valve surgery patients at CMJAH

Demographics	Variable	Frequency	Missing data	Percentage
EuroScore II (%)	<2 %	71	135	91.03
	2- 5 %	6		7.69
	>5 %	1		1.28
Age Group	<60	175	0	82.16
	>60	38		17.84
Sex	Male	78	0	36.62
	Female	135		63.38
Body Mass Index (BMI)	<20	1	7	0.49
	21-34	196		95.61
	>35	8		3.90

One hundred and thirty-five patients (63,38%) were female and 78 were male. 86,15% were <60 years of age. A large group of patients 135 (63%) did not have a documented EuroSCORE II. Of those with a documented EuroSCORE II, 71 (91,03%) had a score <2%, 6 (7,69%) had scores between 2-5% and 1 (1,28%) had a score >5%.

The patients' pre-operative comorbidities are described in Table 2.

Table II: Pre-operative comorbidities

Cardiac History	Variable	Frequency	Missing data	Percentage
Previous cardiac surgery	No	177	5	85.10
	Yes	31		14.9
Unstable angina	No	204	7	99.03
	Yes	2		0.97
LV dysfunction	No	186	6	89.86
	Yes	21		10.14
Recent myocardial infarct	No	205	7	99.51
	Yes	1		0.49
Hypercholesterolaemia	No	179	4	85.65
	Yes	30		14.35
IHD (Ischaemic heart disease)	No	197	7	95.63
	Yes	9		4.37
HPT (Hypertension)	No	147	9	70.33
	Yes	62		29.67
CCF (Congestive cardiac failure)	No	178	5	85.58
	Yes	30		14.42
EF% (Ejection fraction)	<35%	8	23	4.21
	>35%	182		95.79
Aetiology (primary)	RHD	119	9	58.33
	Myxomatous	13		6.37
	Endocarditis	19		9.31
	MV prolapse	28		13.37
	Other	25		12.25
Aetiology (Secondary)	IMR (Ischaemic mitral regurgitation)	181	9	88.73
	DCMO	4		1.96
	Other	19		9.31
NYHA	< Class 3	133	42	77.78
	> Class 3	38		22.22
Respiratory History				
Smoker	No	190	5	91.35
	Yes	18		8.65
COPD	No	194	4	92.82
	Yes	15		7.18
PAP (mmHg)	<30	44	17	22.45
	>30	152		77.55
Renal History				
Serum Creatinine	<110umol/l	180	9	88.24
	>110umol/l	24		11.76
Renal insufficiency	No	177	14	88.94
	Yes	22		11.06

One hundred and eighty-two patients (95,79%) had ejection fractions (EF) of >35%. 152 (77,55%) had pulmonary artery pressures (PAP) of >30mmHg. RHD 119 (58,33%) was the primary aetiology for patients undergoing mitral valve surgery and ischaemic mitral regurgitation (IMR) 81 (88,73%) was the predominant secondary aetiology. Sixty-two (29,67%) patients had hypertension (HPT), 38 (22,22%) had NYHA class >3, 31(14,95%) had previous cardiac surgery, 30 (14,35%) had hypercholesterolaemia and 30 (14,42%) had congestive cardiac failure (CCF). Serum creatinine >110umol/L was observed in 24 (11,76%) patients, 22 (11,06%) had renal insufficiency, 21 (10,14%) presented with left ventricular (LV) dysfunction, 18 (8,65%) were smokers and 15 (7,18%) presented with pre-operative chronic obstructive pulmonary disease (COPD). Diabetes was present in 21 (10,19%) patients and 9 (4,37%) patients had ischaemic heart disease (IHD).

Aortic clamping and bypass times are shown in table 3.

Table III: Mean and median for aortic clamping and bypass time

Variable	Frequency	Mean±SD (min)	Median [IQR] (min)
Aortic clamp time	200	97.01 ± 36.22	92[71.5; 113.5]
Bypass time	198	144.19 ± 43.33	141[118;170]

One hundred and five patients (75%) were started on inotropic support and 48 (35,92%) had intra-operative blood transfusions. The mean aortic clamping and bypass time was 97.01 minutes and 144.19 minutes, respectively.

Post-operative outcomes are shown in table 4.

Table IV: Post-operative outcomes

Variable	Class	Frequency	Missing Data	Percentage
Arrythmias	No	96	4	45.93
	Yes	113		54.07
Prolonged Mechanical Ventilation	No	185	1	87.26
	Yes	27		12.74
Pneumonia	No	202	2	95.73
	Yes	9		4.27
CVA	No	199	1	93.87
	Yes	13		6.13
Re-operation	No	187	0	87.79
	Yes	26		12.21
Pacemaker insertion	No	184	3	87.62
	Yes	26		12.38
PAP (pulmonary artery pressure)	No	5	201	41.67
	Yes	7		58.33
HPT	No	210	2	99.53
	Yes	1		0.47
AKI	No	176	1	83.02
	Yes	36		16.98
Sepsis	No	186	3	88.57
	Yes	24		11.53
Death	No	200	0	93.90
	Yes	13		6.10
Bleeding	No	185	0	86.85
	Yes	28		18.15
Transfusion	No	171	1	80.66
	Yes	41		19.34

Arrythmias were documented in 113 (54,07%) patients, 41 (19,34%) were transfused post-operatively, AKI was present in 36 (16,98%), 28 (18,15%) had significant bleeding and 27 (12,74%) had prolonged mechanical ventilation. Re-operations were done in 26 (12,21%) patients, 26 (12,38%) needed pace making post-operatively, 24 (11,53%) had sepsis, cerebro-vascular accident (CVA) was noted in 13 (6,13%) patients, 13 (6,10%) died, 9 (4,27%) had pneumonia and one patient (0,47%) had HPT post-operatively.

The association between pre-operative factors and mortality are shown in table 5.

Table V: Association between pre-operative factors and mortality

Variable	Class	Death n (%)	Alive n (%)	Fisher's Exact Test Statistic (p-value)
EuroSCORE	< 2 %	1 (1.41)	70 (98.59)	0.020
	2- 5 %	2 (3.33)	4 (66.7)	
	>5 %	0 (0.00)	1 (100.00)	
Pre-operative Ventilation	No	8 (3.96)	194 (196.04)	0.028
	Yes	2 (33.33)	4 (66.67)	
Dialysis Dependent	No	9 (4.35)	198 (95.65)	0.048
	Yes	1 (100.00)	0 (0.00)	
Pre-operative inotropic support	No	7 (3.45)	196 (96.55)	0.01
	Yes	2 (50.00)	2 (50.00)	
PAP (mmHg)	<30	4 (9.09)	40 (90.91)	0.27
	>30	7 (4.61)	145 (95.39)	
LV dysfunction	No	8 (4.30)	178 (95.70)	0.27
	Yes	2(9.52)	19 (90.48)	
Smoker	No	9 (4.74)	181 (95.26)	0.60
	Yes	1 (5.56)	17 (94.44)	
COPD	No	8 (4.12)	186 (95.88)	0.035
	Yes	3 (20.00)	12 (80.00)	
CCF	No	4 (2.25)	174 (97.75)	0.004
	Yes	5 (16.67)	25 (83.33)	
Renal insufficiency	No	5 (2.82)	172 (97.18)	0.046
	Yes	3 (18.64)	19 (86.36)	
EF%	<35%	2 (25.00)	6 (75.00)	0.03
	>35%	5 (2.75)	177 (97.25)	
Aetiology (primary)	RHD	4 (3.36)	115 (96.64)	0.043
	Myxomatous	0 (0.00)	18 (100.00)	
	Endocarditis	4 (21.05)	15 (78.95)	
	MV prolapse	2 (7.14)	26 (92.86)	
	Other	2 (8.00)	23 (92.00)	
Aetiology (Secondary)	IMR	10 (5.52)	171 (94.48)	0.29
	DCMO	1 (25.00)	3 (75.00)	
	Other	1 (5.26)	18 (94.74)	
NYHA	< Class 3	2 (1.50)	131 (98.50)	0.006
	≥Class 3	5 (18.16)	33 (86.84)	

Pre-operative data that was associated with mortality: dialysis dependent 1 (100%), pre-operative inotropic support 2 (50%), pre-operative ventilation 2 (33.33%), EF <35% 2 (25%), COPD 3 (20%), NYHA ≥3 5 (18.16%), renal insufficiency 3 (18.64%), CCF 5 (16.67%) and EuroSCORE >2-5% 2 (3.33%). The association between post-operative outcomes and mortality are shown in table 6.

Table VI: Association between post-operative outcomes and mortality

Variable	Class	Death n (%) 13 (6.10%)	Alive n (%) 200 (93.10%)	Fisher's Exact Test Statistic (p-value)
Arrythmias	Yes	7 (6.19)	106 (93.81)	1.00
	No	5 (5.21)	91 (94.79)	
Prolonged mechanical ventilation	Yes	10 (37.04)	17 (62.96)	<0.01
	No	2 (1.08)	183 (98.92)	
Pneumonia	Yes	3 (3.33)	6 (66.67)	<0.01
	No	8 (3.96)	194(96.04)	
CVA	Yes	2 (15.38)	11 (84.62)	0.16
	No	10 (5.03)	189 (94.97)	
Re-operation	Yes	9 (34.62)	17 (65.38)	<0.01
	No	4 (2.14)	183(97.86)	
Pacemaker insertion	Yes	1 (3.85)	25 (96.15)	1.00
	No	10 (5.43)	174 (94.57)	
AKI	Yes	7 (19.44)	29 (80.56)	<0.01
	No	5 (2.84)	171 (97.16)	
Sepsis	Yes	7 (29.17)	17 (70.83)	<0.01
	No	3 (1.61)	183 (98.39)	
Bleeding	Yes	8 (28.57)	20 (71.43)	<0.01
	No	5 (2.70)	180 (97.30)	
Transfusion	Yes	8 (19.51)	33 (80.49)	<0.01
	No	4 (2.34)	167 (97.66)	

Post-operative data that appeared to be independent risk factors for mortality were: prolonged mechanical ventilation 10 (37.04%), re-operation 9 (34.62%), bleeding 8 (19.51%), transfusion 8 (19.51%), AKI 7 (19.44%), sepsis 7 (29.17%) and pneumonia 3 (3.33%).

The associations between aortic clamping times and post-operative outcomes as well as bypass times and post-operative outcomes are shown in table 7.

Table VII: Association between post-operative outcomes and the intra-operative times

Variable	Class	Aortic Clamp Time Median [IQR]	Aortic Clamp Time P value	Bypass Time Median [IQR]	Bypass Time P value
Arrythmias	No	91(40.5)	0.37	133(43.5)	0.12
	Yes	98(43)		147(55)	
Prolonged Mechanical Ventilation	No	91(41)	0.55	137(50.5)	0.029
	Yes	107(51)		156(55)	
Pneumonia	No	92(42)	0.54	140(52)	0.76
	Yes	96.5(53)		141.5(20)	
CVA	No	92(43)	0.92	139(52)	0.28
	Yes	94(37)		151.5(43)	
Re-operation	No	91(41)	0.40	137(53)	0.03
	Yes	106(46)		146.5(66.5)	
Pacemaker insertion	No	91(40)	0.20	136(51)	0.01
	Yes	108(59)		157(57)	
AKI	No	91(42)	0.40	137(52)	0.01
	Yes	105.5(46.5)		157.5(45)	
Sepsis	No	91.5(42.5)	0.98	138(52)	0.36
	Yes	100(33)		147(71)	
Death	No	92(41)	0.66	141(52)	0.30
	Yes	86(63)		150.5(83)	
Bleeding	No	91(42)	0.15	137(51)	0.02
	Yes	106(51)		154(61)	
Transfusion	No	92(40)	0.93	140(52.5)	0.33
	Yes	98(44)		145(53)	

The results obtained from univariate analysis showed no significant association between aortic clamping time and post-operative outcomes as all the p values were greater than 0.05 ($p > 0.05$). However, cardio-pulmonary bypass times had a significant effect on post-operative outcomes. Post-operative variables that proved to be associated with increased cardio-pulmonary bypass times were prolonged mechanical ventilation, re-operation, pacemaker usage, AKI and bleeding.

Discussion

Internationally published data approximate the peri-operative mortality rate of mitral valve surgery to be 3%, dependent on the population and the peri-operative risk of the patient prior to surgery.[3, 28] In contrast to internationally published data our peri-operative mortality rate was 6,1%. RHD secondary to rheumatic fever continues to be the main form of valve heart disease in Africa. Multiple studies across Africa confirm that RHD is the primary cause of morbidity and mortality seen in younger populations undergoing cardiac surgery.[2] This study is consistent with African data, confirming RHD as the primary indication for mitral valve surgery, commonly performed in patients below the age of 60.

Advanced age and NYHA class ≥ III have been shown in multiple studies to increase peri-operative mortality of valve surgery.[26, 27, 29] This study did not show age having a direct effect on peri-operative mortality but confirmed that NYHA class ≥ III is an independent risk factor for mortality. This may be due to more patients in this study being below the age of sixty years and a relatively small sample size. This study also found that ejection fraction of < 35% was a strong predictor of mortality. This demonstrates the importance of pre-operative echocardiography and functional assessment of the patient. An increase in mortality was noted in patients presenting pre-operatively with COPD, CCF and the need for inotropic support. A possible explanation for this finding is the misdiagnosis of CCF for COPD or visa-versa in the peri-operative period. A suggestion would be to include pulmonary function tests as part of the pre-operative assessment in combination with echocardiography. A limitation of this study is the lack of documentation of the rationale for pre-operative inotropic support. It is difficult to determine whether inotropic support was an independent risk factor for mortality or the pre-operative state requiring inotropic support was a greater contributor to the increase noted.

Left ventricular dysfunction, atrial fibrillation and pulmonary hypertension are definite risk factors for peri-operative morbidity and mortality.[30] In this study arrythmias and increased PAP > 30mmHg were commonly documented, proving to be signs and sequelae of advanced disease requiring surgery. A limitation of our results is that pulmonary artery pressures were only documented prior to surgery in the majority of

patients, making it difficult to assess whether increasing pressures had a direct correlation with the risk of mortality.

Risk scoring systems for predicting peri-operative morbidity and mortality are mandatory.[31] There are no risk scoring systems in large population groups like Sub-Saharan Africa that have been validated.[22, 24] In our study, the EuroSCORE II was used as a pre-operative assessment to predict the risk of mortality. Unfortunately, very few patient records included EuroSCORE II scores and the findings can therefore not reflect outcomes for the general population. It is suggested that a risk scoring system be validated in Africa to assist in predicting mortality in our population that has proven in literature to have significantly different aetiologies for mitral valve surgery due to the increased burden of RHD.

AKI and its detrimental peri-operative effects during mitral valve surgery have been extensively reviewed.[6, 16, 17] Patients undergoing mitral valve surgery commonly display a decrease in the volume of blood ejected from the mitral valve due to regurgitation, resulting in poor perfusion to the kidneys. A study done in Taiwan found that 38,7% of patients who underwent mitral valve surgery developed AKI.[18] The same study also revealed that patients presenting with AKI had increased rates of hypertension and diabetes. Although our study did not typically have a high prevalence of HPT and diabetes, AKI proved to be a major independent predictor of mortality. Another finding in our study was that increased CPBT of ≥ 157.5min and aortic clamping times of ≥ 105.5min directly increased the risk of AKI, which is in keeping with multiple studies worldwide.[6, 18, 32]

Increased CPBT is an independent risk factor for bleeding and subsequent blood transfusions following cardiac surgery.[7, 15] In addition to the above findings, this study confirmed that increased cardio-pulmonary bypass and aortic clamping times increased the risk of prolonged mechanical ventilation and subsequent pneumonia.[19] A novel finding in this series is the increased use of pacemakers associated with increased bypass and aortic clamping times. Contrary to previous studies, we did not find that sepsis was directly linked to increased CPBT and aortic clamping times. Sepsis, however, was a strong predictor of peri-operative mortality seen in our study. This may be related to inadequate dosing of antibiotics peri-operatively, sub-optimal peri-operative sterility and wound cleaning or even abnormal temperatures

documented in theatre during cardiac surgery. A suggestion for the future would be to identify risks associated with peri-operative sepsis in cardiac surgery.

The cost of transfusing blood products on the economy as well as on patient's well-being is high.[33] The limitation in this study is that data on the number of blood products transfused was not collected nor were the negative outcomes of transfusion documented. A suggestion would be to collect further data to quantify blood transfusion in cardiac surgery, its risks and negative outcomes to improve blood salvage techniques and pre-operative transfusion protocols.

The peri-operative outcomes of mitral valve surgery found in this study can be avoided, anticipated and effectively managed. A multidisciplinary team of anaesthesiologists, cardiac surgeons, physicians, nurses and allied health professionals are needed to decrease morbidity and assess each patient pre-operatively for the risk of peri-operative mortality.

Conclusion

RHD was the predominant primary aetiology for mitral valve surgery. The mortality rate in this study was 6,10%. Pre-operative findings that contributed to increased mortality were: EuroSCORE II ≥2%, pre-operative ventilation, dialysis dependence, pre-operative inotropic support, COPD, CCF, renal insufficiency, low EF% and NYHA ≥III. Post- operative findings that contributed to increased mortality were: prolonged mechanical ventilation, pneumonia, re-operation, AKI, sepsis, bleeding and transfusion. Increased aortic clamping and cardio-pulmonary bypass times significantly increased the risk of prolonged mechanical ventilation, re-operations, use of pacemakers, AKI and bleeding.

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SECTION 4: PROPOSAL

Peri-operative outcomes of mitral valve surgery at Charlotte Maxeke Johannesburg Academic Hospital

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4.1 Introduction

Africa has one of the highest prevalence rates of heart disease in children and young adults (1, 2). Cardiovascular disease remains the number one cause of death worldwide (1, 3). Data on the management and outcomes, particularly of mitral valve surgery in South Africa is limited (4).

A study conducted in the Western Cape, included 106 patients over a period of four and a half years who had undergone mitral valve surgery (4). The identified comorbidities in this study were hypertension (HPT), diabetes mellitus type 2 (DM2), hypercholesterolemia, smoking, cerebrovascular accident (CVA), ischaemic heart disease (IHD) and atrial fibrillation (AF). A majority (56%) of the patients had pre-operative New York Heart Association (NYHA) functional class III. All patients in the study had pre-operative echocardiograms, which described pulmonary artery pressures (PAP), functional state of the mitral valve, aetiology of the mitral valve disease and left ventricular function. The mortality rate at 30 days was 5% and at six months 7%. The immediate post-operative survival rate was 95% and decreasing at six months to 93% (4).

In the United Kingdom (UK), the majority of mitral valve surgery is indicated for mitral regurgitation (5, 6). Mitral regurgitation can be classified as either primary or secondary. Rheumatic heart disease (RHD), myxomatous degeneration of the mitral valve, endocarditis and mitral valve prolapse are common causes of primary mitral valve disease. Secondary mitral valve disease is commonly due to ischaemic mitral regurgitation or dilated cardiomyopathy (5, 6).

The detection of a pansystolic murmur radiating to the axilla may be the sole indicator of mitral valve disease. In some patients, the onset of AF or congestive cardiac failure (CCF) may be the only presenting sign. Approximately 2% of patients presenting with asymptomatic mitral valve disease are at risk of sudden death, annually. A decrease in ejection fraction (EF) and the presence of AF were strong predictors of sudden death (5, 6).

Without these risk factors, the rate of sudden death was less than 1% per year. An ejection fraction below 60% and end systolic diameter of above 45mm demonstrated overt left ventricular dysfunction (5).

Intermittent echocardiography to assist in early recognition of deteriorating left ventricular dysfunction is crucial. Intra-operative transoesophageal echocardiography (TOE) provides the anaesthetist with improved haemodynamic management. It is beneficial for the anaesthetist to have a systematic approach in assessing the mitral valve intra-operatively using a TOE (5, 7, 8).

The primary role of the anaesthetist prior to repair or replacement of the mitral valve is to reduce the regurgitant fraction. To achieve this; systemic vascular resistance should be low, maintaining moderate tachycardia and ensuring optimal pre-load to maintain forward flow across the valve. The threshold to commence inotropic support should be low (5).

A retrospective study done in North Carolina, North America, identified six independent predictors of inotropic support during separation from cardiopulmonary bypass (CPB) in mitral valve surgery. These included:

Table 1: Predictors of inotropic support during separation from CPB (5).

Ventricular motion wall abnormalities
Combined mitral valve and coronary artery bypass surgery (CABG)
Left ventricular EF of below 35%
Re-operation
Moderate to severe mitral regurgitation
Aortic clamp time

Table below outlines the post-operative cardiac surgery complications as:

Table 2: Post-operative complications after cardiac surgery (9).

Arrhythmias
Prolonged mechanical ventilation
Pneumonia
CVA
Re-operation
Pacemaker insertion due to permanent atrioventricular block

Morbidity in this study was calculated to be 75% after mitral valve surgery. Out of the twelve mitral valve cases investigated, three (25%) of the patients died in hospital within 30 days, the identified causes of death were all cardiac in origin. The results reported in this study depict a very small group of the elderly who had mitral valve repair or replacement, but the operative mortality was significantly high (9).

The risk factors associated with increased mortality in the peri-operative period of cardiac surgery are presented in table 3 below.

Table 3: Risk factors for mortality after cardiac surgery (11, 12).

Age above 60 years
Arterial and pulmonary hypertension
Body mass index (BMI) of above 35 or below 20
CCF
Peripheral vascular disease (PVD)
Aortic atheroma
Diabetes mellitus
Renal insufficiency
Acute coronary syndromes (ACS)
Chronic obstructive pulmonary disease (COPD)
Neurological disease
Previous cardiac surgery

Despite advances in surgical techniques, anaesthesia and critical care; cardiac surgery is associated with high risk of morbidity and mortality. Risk stratification scores in cardiac surgery are sophisticated and are used worldwide in order to determine peri-operative risk (11, 13, 14).

The European System for Cardiac Operative Risk Evaluation (EUROSCORE II) has been validated in the UK, Europe and North America (11). This score has been shown to be predictive of peri-operative outcomes in cardiac surgery (10, 15). Variables used to determine the degree of risk prior to surgery are described in table 4 below.

Table 4: EUROSCORE II risk factors (11)

Age
Gender
COPD
Extra cardiac arterioplasty
Neurological dysfunction
Previous cardiac surgery
Serum creatinine
Active endocarditis
Critical pre-operative states, such as intubation or use of inotropes prior to surgery
Unstable angina
Left ventricular dysfunction
Recent myocardial infarct
Pulmonary hypertension
Emergency operations
Surgery on the thoracic aorta
Post infarct septal rupture

Literature from large population subgroups such as Africa, describing the ability of risk scoring systems to predict peri-operative outcomes in African patients undergoing cardiac surgery have not been validated (11).

A study conducted in North America, found that well- established scoring systems in one population are of limited value in another major population group having racial and ethnic differences (13). The study concluded that there should be wariness in applying the same risk stratification scores to all populations that may have constitutionally different populations and risk factors (13).

RHD as a result of Rheumatic fever (RF) is the predominant form of valve disease in Africa (16). It is the principal cause of acquired heart disease of the mitral valve, affecting people living largely in poverty and deprived conditions (16). Studies across Africa emphasize that RHD is a major contributing factor of morbidity and mortality in children and young adults. Heart failure, native valve infective endocarditis, systemic embolization, pulmonary hypertension, atrial arrhythmias and complications related to surgery are contributing factors to the increased morbidity and mortality noted (16).

In an update by the World Health Organisation (WHO), it was estimated that 2.4 million children aged 5-14 years are affected by RHD worldwide, with 42% of these children being located in Sub-Saharan Africa (16).

Difficulties associated with valve surgery outcomes in Africa are evident (16). Lack of availability of surgical resources and expertise are contributing factors (16). Patient demographics and the peri-operative risk of patients undergoing surgery were found to influence the mortality rate (4).

Another study comparing operative outcomes in mitral valve surgery, between different surgeons and between units with different patient volumes, found that the surgeon's volume of patients affected mortality rates, irrespective of hospital patient volumes. This emphasizes that surgeon exposure and expertise has a direct correlation with peri-operative outcomes in mitral valve surgery (17).

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is a large training hospital in Johannesburg, South Africa and receives large patient volumes. CMJAH employs well- trained specialists in cardiac surgery and anaesthesiology. There is an estimated 50 mitral valve surgeries done annually (18).

It is therefore imperative that the morbidity and mortality rates of patients undergoing mitral valve surgery at CMJAH be described and the contributing factors to the peri-operative outcomes be determined.

This study will aim to identify contributing factors to the peri-operative morbidity and mortality seen in mitral valve surgery at CMJAH.

4.2 Problem Statement

Patients undergoing cardiac surgery are the most highly evaluated patients an anaesthetist will confront in their careers. However, advances in surgical techniques, anaesthesia and critical care do not eliminate the high risks involved in cardiac surgery. Cardiac valve disease is a key public health problem in Africa (11, 16). Data on mitral valve surgery outcomes in South Africa is limited (4). Risk-scoring systems to predict peri-operative morbidity and mortality have been developed but there is

lack of evaluation of the applicability of these risk-scoring systems for population groups in Africa (13).

4.3 Aims

The aim of this study is to describe the peri-operative outcomes of patients that have undergone mitral valve surgery at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

4.4 Objectives

Primary objectives

- To determine the peri-operative morbidity and mortality rates of patients that have undergone mitral valve surgery at CMJAH.
- Compare the pre-operative EUROSCORE with post-operative mortality
- To determine factors associated with poor outcomes following mitral valve surgery

4.5 Research Assumptions

Peri-operative: Occurring or performed at or around the time of surgery

Outcomes: Defined by morbidity and mortality:

Morbidity: Consequences and complications resulting from disease

Mortality: Number of deaths

Mitral valve: The valve between the left atrium and left ventricle of the heart

Surgery: The treatment of injuries or disorders of the body by incision or manipulation, especially with instruments

Adult: Any person over the age of 18 years

4.6 Demarcation of Study Field

The study will be conducted at CMJAH, which is a major teaching hospital in Parktown, Johannesburg, South Africa. Patient records will be assessed, including anaesthetic charts, cardiac Intensive Care Unit (ICU) charts and pre-operative assessment cardiology notes.

4.7 Ethical Considerations

4.7.1 Ethics Approval

Approval from the Human Research and Ethics Committee (Medical) and Graduate studies committee at Wits University will be sought. Permission to conduct the research will be requested from the CMJAH Chief Executive Officer (CEO) (Appendix 1) and the Head of Department of cardiothoracic surgery at CMJAH (Appendix 2).

4.7.2 Data Management

In this research, data will be managed according to the standards stipulated by the University of Witwatersrand. RedCap® will be the data management tool used to secure information. Information will be stored and secured for a period of six years. Each patient will be assigned a study number and a separate list of patient details will be available only to the researcher.

4.8 Data Collection

4.8.1 Research Design

The research design in this study is that of a retrospective, contextual, descriptive study. A retrospective study measures variable that have occurred in the past. A contextual study focuses on a particular group and a descriptive study aims to describe variables without manipulating them (19, 20).

In this study the researcher will retrospectively assess cardiac ICU records and the respective anaesthetic charts of patients who have undergone mitral valve surgery at CMJAH. Through this, the researcher will be able to describe morbidity and mortality seen post-operatively and compare it to the risk stratified preoperatively.

4.8.2 Study Population

Patients over the age of 18 years who have undergone elective mitral valve surgery at CMJAH will be included in the study.

4.8.3 Study Sample

The study sample is patients who have undergone elective mitral valve surgery at CMJAH.

Study Sample Method

Consecutive, convenience sampling will be used in this study. Consecutive sampling is the attempt by the researcher to include all accessible subjects into the sample. Convenience sampling includes the most easily available subjects non-randomly (20).

All patients above the age of 18 years, who have undergone mitral valve surgery, during the study period, will be included in the study.

4.8.4 Inclusion and Exclusion Criteria

Inclusion

1) Elective patients undergoing rheumatic mitral valve surgery at CMJAH
2) Patients over the age of 18 years old

Exclusion

1) There will be no exclusion criteria

Sample Size

The calculated minimum required sample size n=217 as calculated by an estimated mortality of 25% with precision of +9% to the power of 80%. Sample sizes were calculated using STATA v 14. The study period will be realized by the sample size. Records will be assessed retrospectively until the sample size is reached. It is estimated that 5 years of records will be assessed.

Collection of Data

A data collection instrument has been developed (Appendix 3) based on literature available and the current EUROscore variables used to predict peri-operative morbidity and mortality. The data collection tool will be sub-divided into pre-operative, intra-operative and post-operative variables.

4.9 Data Analysis

Statistical analyses will be performed using STATA software, version 15 (STATA Corporation, College Station, Texas). The researcher will do a descriptive and inferential analysis to compare categorical variables collected pre-operative, intra-operative and post-operative. A p value of <0.05 will be considered as statistically significant. Categorical variables will be described using frequency tables and percentages. Continuous data (urine output, aortic clamp time and bypass time) will be checked for normality of distribution and will be described using means and standard deviations if found to be plausibly normally distributed or with medians and interquartile ranges if skewed.

Cross tabulation tables will be used to compare pre-operative EuroSCORE II with post-operative mortality. Pearson Chi-squared test will be used to determine the significance. A p value of <0.05 will be considered significant.

Factors associated with poor outcomes will be determined using the Chi squared test for categorical variables and ANOVA test for continuous variables (urine output, bypass time and aortic clap time). The F- test will be used to determine significance. A p value of <0.05 will be considered significant.

4.10 Significance of The Study

There are no specific risk scoring systems available to predict the peri-operative outcomes in mitral valve surgery in African cardiac patients. Data on mitral valve surgery outcomes in South Africa is limited (4). Literature from large population subgroups such as Africa, describing the ability of risk scoring systems to predict peri-operative outcomes in African patients, undergoing cardiac surgery have not been validated (11).

The EuroSCORE II has been used and developed in first world countries where surgical resources, surgical expertise, patient volumes, patient comorbidities and access to health care favour optimal outcomes (4, 16).

This study will describe the morbidity and mortality rates of patients undergoing mitral valve surgery and describe the correlation between the peri-operative outcomes and the internationally recognised Euro-scoring system used to stratify risk pre-operatively in cardiac surgery patients at CMJAH. The findings of this study will assist anaesthesiologists to identify, optimise and adequately manage patients peri-operatively who are undergoing mitral valve surgery; resulting in a decrease in morbidity and mortality rates.

Cardiac surgeons will be able to identify common complications occurring in the peri-operative period resulting in improved surgical techniques and reduced peri-operative surgical complications. The Cardiac ICU staff and specialists will be more informed and vigilant about the post- operative complications and their management in the unit.

The data collected on the peri-operative outcomes of mitral valve surgery will optimise education, through training, workshops, seminars, conferences and publications.

The consideration of an African risk stratification score can be developed if the outcomes of this study implicate that the EUROscore II used in predicting morbidity and mortality rates in cardiac surgery patients at CMJAH is poor.

4.11 Validity and Reliability

Reliability

Reliability is defined as whether the results from the study will be consistent if the study were to be repeated (20).

In this research, reliability will be confirmed by ensuring that definitions of all variables assessed are well understood by all interested in mitral valve surgery and its outcomes.

Validity

In this research, validity will be ensured by confirming that the measurement of variables is accurate (20).

External validity

External validity determines whether the result of a study can be generalised beyond the specific research context in which it was conducted (20).

This study is contextual and therefore the findings will only be true to the population studied, which in this case is the population of patients who have undergone elective mitral valve surgery at CMJAH between 1st January 2015- 31st December 2018.

4.12 Potential Limitations of the Study

Data regarding peri-operative outcomes might not be accurately captured and therefore may not be reliable. The quality of the available records may be a major limitation as patient records may be incorrectly completed. The study is also limited to CMJAH and may not be generalisable to other population

4.13 Project Outline

	Oct 19	Nov 19	Dec 19	Jan 20	Feb 20	Mar 20	Apr 20	May 20	Jun 20	Jul 20	Aug 20	Sep 20	Oct 20
Synopsis													
Research Methodology													
Protocol													
Protocol assessment													
Ethical Clearance													
Data collection													
Data analysis													
Write up													
Submission of research report													

4.14 Financial plan

The University of the Witwatersrand will fund the following research budget.

Printing	**Rands/Page**	**Total**
Synopsis x 6 copies	R1,50 x 4 pages	R36.00
Protocol x6 copies	R1,50 x 20 pages	R180.00
Data collection sheet	R1,50 x (+/-) 400 copies	R600.00
Final research report	R1,50 x 100 pages	R150.00
Total		R966.00 (estimation)

4.15 References

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Appendix A: Request for Data Collection

Request to collect data from patients' records at Charlotte Maxeke Johannesburg Academic Hospital

Re: Request to CEO to collect data from patients' records at Charlotte Maxeke Johannesburg Academic Hospital

My name is Tebogo Tabane and I am currently registered for a Master of Medicine Degree in the Department of Anaesthesiology at the University of the Witwatersrand.

I am at present working at Charlotte Maxeke Johannesburg Academic Hospital in the Department of Anaesthesiology. As part of my studies, I am required to conduct research and write a research report. My research seeks to describe the peri-operative morbidity and mortality rates in patients undergoing mitral valve surgery at Charlotte Maxeke Johannesburg Academic Hospital.

The research will only be conducted after ethical clearance from the University of the Witwatersrand Human Research Ethics Committee has been granted.

I request permission to conduct this research at Charlotte Maxeke Johannesburg Academic Hospital.

If you have any further enquiries, please contact either my supervisors or myself

Dr T. Leonard (tristanleonard@hotmail.com)

Dr T. Kleyenstuber (kleyenstuber@hotmail.com)

Your assistance will be greatly appreciated.

Kind regards

……

Dr Tebogo Tabane

Registrar: Department of Anaesthesia

Mobile: 0798575660

Email: tebogo.tabane@gmail.com

Appendix B: Data Collection Instrument

Pre-operative data					
EUROscore	<2%	2-5%	>5%		
Age	<60	>60			
Gender	F	M			
previous cardiac surgery	Yes	No			
serum creatinine	>110umol/L	<110umol/L			
Active endocarditis (patient still on antibiotics at time of surgery)	Yes	No			
Critical pre-operative state:					
Ventricular tachcardia/ventricular fibrillation	Yes	No			
aborted sudden death	Yes	No			
pre-operative cardiac massage	Yes	No			
pre- operative ventilation	Yes	No			
Pre-operative acute renal failure	Yes	No			
Dialysis dependent	Yes	No			
pre-operative inotropic support	Yes	No			
PAP	<30	>30			
Unstable angina requiring IV nitrates prior to surgery	Yes	No			
LV dyfunction	Yes	No			
Recent MI	Yes	No			
Emergency operation	Yes	No			
Surgery on thoracic aorta	Yes	No			
Post infarct septal rupture	Yes	No			
neurological dysfunction	Yes	No			
BMI	>35	<20	21-34		
HPT	Yes	No			
DM2	Yes	No			
Hypercholesterolaemia	Yes	No			
IHD	Yes	No			
CVA	Yes	No			
Smoker	Yes	No			
COPD	Yes	No			
PVD	Yes	No			
CCF	Yes	No			
Renal insufficiency	Yes	No			
EF%	<35%	>35%			
Aetiology (Primary)	RHD	Myxomatous Degeneration	Endocarditis	MV prolapse	Other
Aetiiology (Secondary)	Ischemic Mitral Regurgitation		Dilated Cardiomyopathy		Other
NYHA	> Class III	< Class III			
Intra-operative data					
`					
Aortic clamp time					
Inotropic support	Yes	No			
Bypass time (hours)					
Urine output (total ml)					
Blood transfusion	Yes	No			
Post-operative data					
Arrythmias	Yes	No			
Prolonged mechanical ventilation >48hours	Yes	No			
Pneumonia	Yes	No			
CVA	Yes	No			
Reoperation	Yes	No			
Pacemaker insertion	Yes	No			
PAP	>30	<30			
Hypertension	Yes	No			
Acute kidney injury	Yes	No			
Sepsis	Yes	No			
Death	Yes	No			
Bleeding	Yes	No			
Transfusion	Yes	No			

Section 5: Annexures

5.1 Ethical Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Tebogo Tabane

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200343

NAME: (Principal Investigator)	Dr Tebogo Tabane
DEPARTMENT:	Anaesthesiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Peri-operative outcomes of mitral valve surgery at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	27/03/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Tristan Leonard and Dr Thomas Kleyenstuber
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/06/2020

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 **March** and will therefore be due in the month of **March** 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

5.2 Graduate Studies Committee Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

14 April 2020
Person No: 0603236J
PAG

Dr TM Tabane
P O Box 714
Irene
Irene
0062
South Africa

Dear Dr Tebogo Tabane

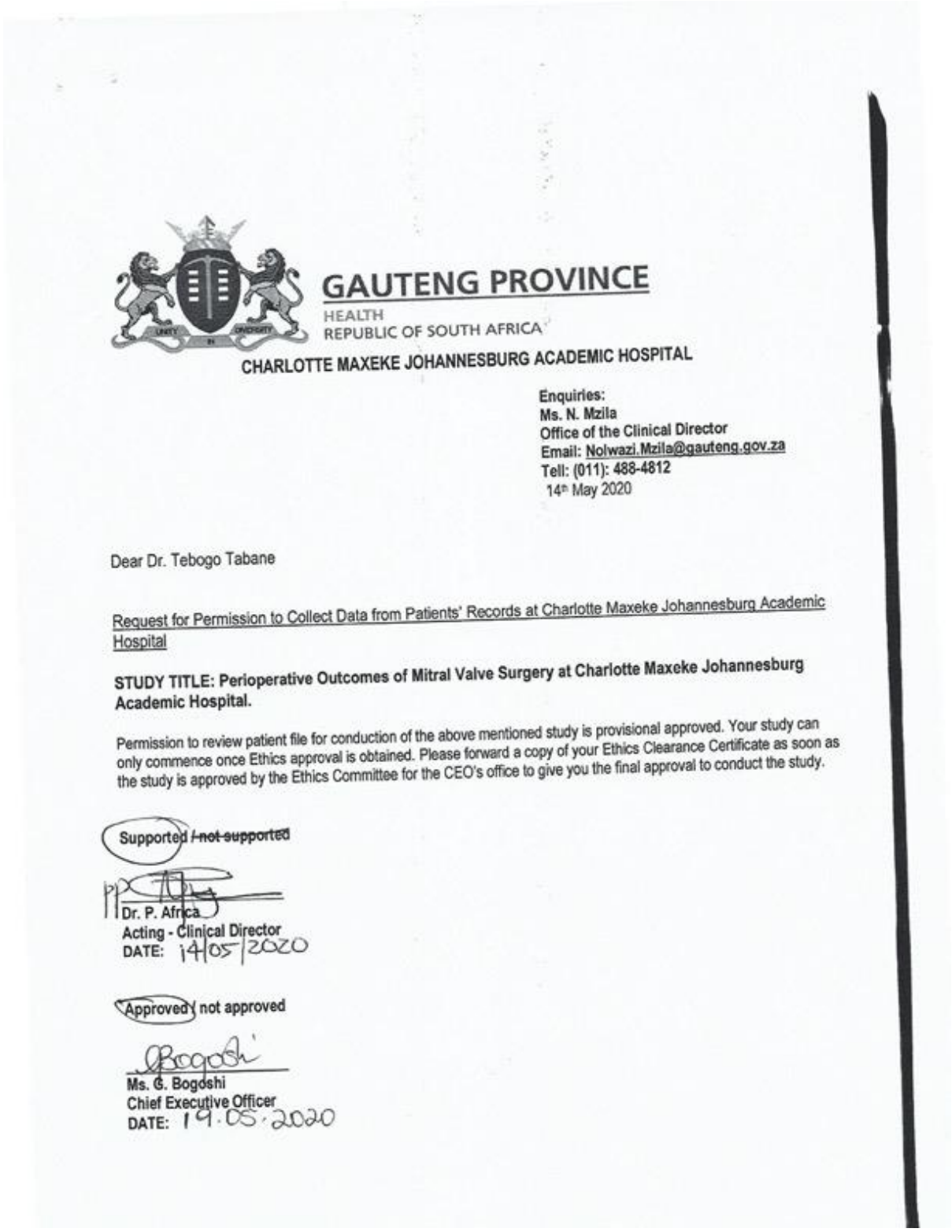
Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Peri-operative outcomes of mitral valve surgery at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.3 Approval from CMJAH Chief Executive Officer



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email: Nolwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
14th May 2020

Dear Dr. Tebogo Tabane

Request for Permission to Collect Data from Patients' Records at Charlotte Maxeke Johannesburg Academic Hospital

STUDY TITLE: Perioperative Outcomes of Mitral Valve Surgery at Charlotte Maxeke Johannesburg Academic Hospital.

Permission to review patient file for conduction of the above mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported ~~/ not supported~~

Dr. P. Africa
Acting - Clinical Director
DATE: 14/05/2020

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 19.05.2020

5.4 Turnitin Report

Medical Protocol Tebogo Mokotong-Mosekama Tabane 0603236J

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