SURGICAL OUTCOME OF INFECTIVE ENDOCARDITIS AT TYGERBERG HOSPITAL FROM 2010-2019: A RETROSPECTIVE REVIEW

by
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Thesis presented in fulfilment of the requirements for the degree of Master of Medicine – Cardiothoracic Surgery (MMED Thor Surg) in the Faculty of Medicine and Health Sciences, at University of Stellenbosch, Cape Town, South Africa

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1. Declaration

By submitting this thesis, "**Surgical Outcome of Infective Endocarditis at Tygerberg Hospital from 2010-2019: a Retrospective Review"** electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: December 2023

2. Abstract

2.1. ENGLISH

Background: There is a paucity of data on the outcome of left sided cardiac valve surgery for infective endocarditis in South Africa. It is hypothesised that outcomes may be poorer compared to international standards due to differences in disease burden, timing to surgery, organism prevalence, and co-morbidities.

Method: This is a retrospective study of 160 patients with left heart valve endocarditis who underwent cardiac surgery from January 2010 until December 2019. Demographic, operative, and admission-related parameters were assessed to determine their association with all-cause mortality during the early postoperative (<30 days) and late postoperative (>30 days) periods. The study aimed to measure early and long-term mortality as well as identify risk factors for morbidity and mortality.

Results: Early post operative mortality (<30 days) was 8.8% and late post-operative mortality (>30 days) was 13.1%. Late survival showed 77.5% of the patients were alive with a mean follow up period of 41 months. Increased age (p=0.04), critical illness (p<0.001), and higher urgency of intervention (p<0.001) were associated with higher early post-operative mortality. EuroScore II was a predictor of early mortality (p<0.001), but less accurate after 30 days. Peri-operative organ failure, including cardiac (p=0.025), renal (p=0.016), and respiratory failure (p<0.001), contributed significantly to both early and late mortality. Pre-operative antibiotics for fewer days (p=0.024), ongoing sepsis (p=0.022), and para-valvular extension (p=0.046) were associated with higher early mortality. Culture negative endocarditis was high at 52.5%. Both left and right ventricular function were significantly impaired early post-operatively but recovered well with long-term follow-up.

Conclusion: Infective endocarditis is a common indication for cardiac valve surgery in South Africa, with a high rate of culture-negative cases making antibiotic stewardship challenging. Goal-directed medical management and clinical optimization prior to surgery were crucial to achieving better outcomes. Salvage procedures and critical illness with organ failure prior to surgery were associated with poorer outcomes. Despite unique challenges, cardiac surgery for infective endocarditis at Tygerberg Hospital compares favourably to international standards.

2.2. AFRIKAANS

Agtergrond: Daar is 'n gebrek aan data oor die uitkoms van linker hartklep chirurgie vir infektiewe endokarditis in Suid-Afrika. Daar word vermoed dat die uitkomste swakker kan wees in vergelyking met internasionale standaarde as gevolg van verskille in siekte las, tydsberekening vir chirurgie, organisme voorkoms en mediese toestande.

Metode: Dit is 'n retrospektiewe studie van 160 pasiënte met linker hartklep endokarditis wat vanaf Januarie 2010 tot Desember 2019 hartchirurgie ondergaan het. Demografiese, operatiewe en opname verwante parameters is geëvalueer om hul assosiasie met alle-oorsaak mortaliteit tydens die vroeë postoperatiewe (<30 dae) en laat postoperatiewe (>30 dae) periodes te bepaal. Die studie het ten doel om vroeë en langtermyn mortaliteit te meet en risikofaktore vir morbiditeit en mortaliteit te identifiseer.

Resultate: Vroeë postoperatiewe mortaliteit (<30 dae) was 8.8% en laat postoperatiewe mortaliteit (>30 dae) was 13.1%. Laat oorlewing toon dat 77.5% van die pasiënte nog lewendig was met 'n gemiddelde opvolgperiode van 41 maande. Verhoogde ouderdom (p=0.04), kritieke siekte (p<0.001) en hoër dringendheid van ingryping (p<0.001) was geassosieer met hoër vroeë postoperatiewe mortaliteit. EuroScore II was 'n voorspeller van vroeë mortaliteit (p<0.001), maar minder akkuraat na 30 dae. Peri-operatiewe orgaan versaking, insluitend hartversaking (p=0.025), nierversaking (p=0.016) en respiratoriese versaking (p<0.001), het beduidend bygedra tot beide vroeë en laat mortaliteit. Pre-operatiewe antibiotika vir minder dae (p=0.024), aanhoudende sepsis (p=0.022) en abses formasie

(p=0.046) was geassosieer met hoër vroeë mortaliteit. Die voorkoms van kultuur-negatiewe endokarditis was hoog met 52.5%. Beide linker- en regter ventrikulêre funksie was aansienlik verswak vroeg postoperatief, maar het goed herstel met langtermyn opvolg.

Gevolgtrekking: Infektiewe endokarditis is 'n algemene aanduiding vir hartklep chirurgie in Suid-Afrika, met 'n hoë persentasie kultuur-negatiewe gevalle wat antibiotika-bestuur moeilik maak. Doelgerigte mediese behandeling en kliniese optimalisering voor chirurgie was noodsaaklik om beter uitkomste te behaal. Reddings prosedures en kritieke siekte met orgaan versaking voor die operasie is geassosieer met swakker uitkomste. Ondanks unieke uitdagings, vergelyk hartklep chirurgie vir infektiewe endokarditis by Tygerberg Hospitaal gunstig met internasionale standaarde.

3. Acknowledgements

The author wishes to express sincere appreciation to Professor Jacques T Janson (supervisor) for his assistance in the preparation of this manuscript. In addition, special thanks to Professor Willie (Wilhelm Bouwer) du Preez (assistant editor), for his general guidance in postgraduate research and publication. To Dr Clinton van der Westhuizen (microbiology), Prof Tonya Esterhuizen (biostatistics), Ms Filestea McGear (administration) and Ms Allizane Gertse (administration) for their assistance in capturing clinical data, record acquisition and statistical analysis of the results. Appreciation is also extended to the consultants and registrars of the division of Cardiothoracic Surgery, for their valuable input and support during this project.

The support from my wife Tillie was vital in completing the tremendous task of compiling this manuscript. Not only for keeping our daily lives afloat during the hours of my absence, but also for the numerous proofreads, advise, being my soundboard for ideas and helping in any way that you could think of. Your input and love were valued above all else. To my two daughters, Elana, and Leandri, thank you for understanding that daddy had to work so often, and that even though I might have been busy at the time, I would make up every hour of playtime missed.

To our heavenly father, without whom none of this would even be possible in the first place.

Table of Contents

4. Introduction

4.1. PROBLEM STATEMENT

Cardiac valve surgery is commonly required in patients with infective endocarditis. Several factors contribute to the morbidity and mortality associated with surgery in this patient population, including patient co-morbid conditions, organisms involved, type of corrective procedure performed, pre-operative antibiotic therapy and the optimal timing of intervention. The relative importance of these factors is not known within the setting of Tygerberg Hospital. A significant uncertainty remains whether internationally published developed world data is applicable to cardiac surgery within the constraints of the South African public healthcare sector.

4.2. HYPOTHESIS

It is hypothesised that the surgical outcomes in left-sided infective endocarditis surgery at Tygerberg Hospital, may be poorer compared to international standards due to differences in disease burden, timing to surgery, organism prevalence, and co-morbidities.

4.3. AIM AND OBJECTIVES OF THE RESEARCH

In the setting of the Western Cape, as representative of a developing country, several factors influence the outcome of infective endocarditis surgery.

The aim of this research is to review the surgical outcome of patients undergoing cardiac valve surgery for infective endocarditis at Tygerberg Hospital during January 2010 to December 2019.

The primary outcome is to measure the early (<30 day) mortality, mortality after 30 days, and the long-term survival of these patients.

The secondary outcome is to evaluate pre-operative, peri-operative and post-operative patient parameters to identify risk factors for morbidity and mortality.

Objectives:

- Protocol development and ethical approval from the University of Stellenbosch, Health Research Ethics Committee (HREC)
- Authorization from Tygerberg Hospital management and the National Health Research Database to conduct research and access clinical records, within a public hospital
- Identify all patients undergoing left-sided cardiac valve surgery for confirmed or suspected infective endocarditis at Tygerberg Hospital, during the period from 1 January 2010 until 31 December 2019
- Collecting of data parameters from various clinical records and capture it on a REDcap database
- Statistical analysis with the assistance from the Stellenbosch University Biostatistics department
- Compilation and editing of the research report (thesis)
- Adaptation and submission for publication in a peer-reviewed cardiac surgery journal

Submission of final thesis for evaluation, as required for the MMED Cardiothoracic Surgery degree

5. List of tables and figures:

6. Glossary

Infective Endocarditis:	An infection of the heart valve, endocardial surface, or indwelling intra-cardiac device
Native:	Involving the patient's own autologous tissue
Prosthetic:	A device or structure previously implanted during a procedure. Also described as a foreign object in relation to a patient's body
Outcomes:	A broad term used to describe various endpoints, including clinical condition, echocardiography parameters and measurable surgical numeric values.
Mortality:	A patient demised.
Morbidity:	Major adverse cardiovascular and cerebrovascular events, organ dysfunction, re-intervention required or post-operative complications. Including, but not limited to: Stroke, re-operation, renal failure requiring dialysis, pneumonia, arrhythmias, and surgical wound complications.
Pre-operative:	Period during surgical admission, before valve surgery is performed
Early Post-operative:	Period during the surgical admission, up to and including 30 days after completion of the valve surgery
Late Post- operative:	At least 30 days after surgery, up to and including the complete follow-up period. The last echo recorded on Echo PACS was used to collect the data set.
ECM:	Electronic Content Management – Digital patient records, including all clinical information and hospital notes relating to a patient's admission. All hospital records from 2013 onwards are captured and stored using this method.
PACS:	Picture Archiving and Content Services. A database used by Tygerberg Hospital to capture and store all Radiological examinations.
CardioWorkflow / EchoPACS:	A database used by Tygerberg Hospital to specifically capture Cardiology related information including Echo and Angiography data.
ECHO:	Echocardiography
TrackCare:	The official database used by the National Health Laboratory Services (NHLS) to capture all pathology and histology results from 2015 onwards.
wwDisa:	A provincial database like the TrackCare pathology database, but only used up until 2015.

7. Abbreviations

IE	Infective Endocarditis
LVEF	Left Ventricular Ejection Fraction
RVEF	Right Ventricular Ejection Fraction
LVED	Left Ventricular End Diastolic measurement
COPD	Chronic Obstructive Pulmonary Disease
HIV	Human Immunodeficiency Virus
TTE	Trans Thoracic Echocardiogram
TOE	Trans Esophageal Echocardiogram
ESC	European Society of Cardiology
EACTS	European Association of Cardiothoracic Surgeons
MRI	Magnetic Resonance Imaging
PET CT	Positron Emission Computer Tomography
ICU	Intensive Care Unit
NHLS	National Health Laboratory Service
ECM	Electronic Content Management
DOHA	Department of Home Affairs, South Africa
CPB	Cardiopulmonary Bypass
KDIGO	Kidney Disease Improving Global Outcomes
eGFR	Estimated Glomerular Filtration Rate
RBC	Red Blood Cell Count
WCC	White Cell Count
CRP	C-Reactive Protein
HB	Haemoglobin
BMI	Body Mass Index
BSA	Body Surface Area
PCR	Polymerase Chain Reaction
CI	Confidence Interval
NYHA	New York Heart Association
BCNIE	Blood Culture Negative Infective Endocarditis
LMIC	Low-Middle Income Country
RV	Right Ventricle
PHT	Pulmonary Hypertension
PVE	Prosthetic Valve Endocarditis

8. Publishable article:

SURGICAL OUTCOME OF INFECTIVE ENDOCARDITIS AT TYGERBERG HOSPITAL FROM 2010-2019: A RETROSPECTIVE REVIEW

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ABSTRACT

Background: There is a paucity of data on the outcome of left sided cardiac valve surgery for infective endocarditis in South Africa. It is hypothesised that outcomes may be poorer compared to international standards due to differences in disease burden, timing to surgery, organism prevalence, and co-morbidities. **Method:** This is a retrospective study of 160 patients with left heart valve endocarditis who underwent cardiac surgery from January 2010 until December 2019. Demographic, operative, and admission-related parameters were assessed to determine their association with all-cause mortality during the early postoperative (<30 days) and late postoperative (>30 days) periods. The study aimed to measure early and long-term mortality as well as identify risk factors for morbidity and mortality. **Results:** Early post operative mortality (<30 days) was 8.8% and late post-operative mortality (>30 days) was 13.1%. Late survival showed 77.5% of the patients were alive with a mean follow up period of 41 months. Increased age (p=0.04), critical illness (p<0.001), and higher urgency of intervention (p<0.001) were associated with higher early post-operative mortality. EuroScore II was a predictor of early mortality (p<0.001), but less accurate after 30 days. Peri-operative organ failure, including cardiac (p=0.025), renal (p=0.016), and respiratory failure (p<0.001), contributed significantly to both early and late mortality. Pre-operative antibiotics for fewer days (p=0.024), ongoing sepsis (p=0.022), and para-valvular extension (p=0.046) were associated with higher early mortality. Culture negative endocarditis was high at 52.5%. Both left and right ventricular function were significantly impaired early post-operatively but recovered well with long-term follow-up. **Conclusion:** Infective endocarditis is a common indication for cardiac valve surgery in South Africa, with a high rate of culture-negative cases making antibiotic stewardship challenging. Goal-directed medical management and clinical optimization prior to surgery were crucial to achieving better outcomes. Salvage procedures and critical illness with organ failure prior to surgery were associated with poorer outcomes. Despite unique challenges, cardiac surgery for infective endocarditis at Tygerberg Hospital compares favourably to international standards.

INTRODUCTION

Infective Endocarditis (IE) is an infection of the heart valve, endocardial surface, or indwelling intra-cardiac device.[1] The global burden of IE continued to increase from 1990 to 2019, with the incidence in Southern Africa estimated to be approximately 7-9 per 100 000 people. There is substantial heterogeneity in different genders, ages, regions, and organism prevalence making policy development challenging.[2–4] The 1-year mortality rate from IE remains at around 30%.[1] Nearly half of patients with infective endocarditis require cardiac valve surgery.[5] Rheumatic Heart disease affects approximately 15 million people on the African continent and is the most common cardiac valve disease at Tygerberg Hospital, with a lower number of patients requiring surgery for infective endocarditis.[6] Cohorts have reported up to 75% of patients with IE have underlying Rheumatic heart valve changes in South Africa.[7,8] In Cape Town, IE contributes significantly to cardiac surgery disease burden and 44.7% of confirmed cases require cardiac valve surgery.[7] Poor socio-economic conditions and poor dental healthcare may be contributing factors.[7] Staphylococci have overtaken Streptococci as the most common cause of the disease.[1,7,9] Blood culture negative endocarditis (BCNIE) is a typical finding in all cohorts of IE in South Africa, with recent data suggesting that Bartonella species is a common cause of BCNIE in South Africa. [10,11]

Surgical intervention in native valve endocarditis is complex, with surgery often withheld due to medical treatment being considered the best option or the risk of the operation being too high.[12] Surgery for IE is

associated with a high mortality, but the prognosis of IE surgery seems to be highly variable.[13] The EuroScore II is a valuable tool to identify high-risk IE patients which may not benefit from surgery, but cardiac surgery should only be withheld after thorough consideration.[12] Healthcare in South Africa, including Cardiothoracic Surgery, faces challenges due to resource limitations and patients presenting at an advanced disease stage. Microbial prevalence and patient characteristics creates unique challenges in managing patients within the South African setting, in comparison to trends seen in developed countries.[14] Guidelines recommend a multidisciplinary team approach to determine the optimal timing of surgery in patients with IE based on disease severity and patient factors.[15,16,17]

Surgical treatment options include valve replacement and repair, with repair showing a better early and late survival advantage in mitral valve endocarditis.[18,19,20] Mitral valve repairs are often challenging, and various factors has been shown to affect the durability of the repair and subsequent outcomes; including poor ventricular function, the presence of pulmonary hypertension, atrial fibrillation and the pathophysiology of the mitral incompetence.[21]

Pre-operative predictors of mortality in IE surgery include the EuroScore, age, gender, left ventricular ejection fraction (LVEF), shock, chronic obstructive pulmonary disease (COPD), creatinine levels, abscess presence, and the isolation of specific organisms. However, cardiac surgery, when indicated, is associated with a good prognosis.[12,13,22] Indications for surgery are shown in **Table 1**. However, the outcome of patients is often associated with the severity of IE, rather than the timing of intervention, and septic shock during initial admission is a notable predictor of poorer outcome.[23,24]

HIV's effect on surgical outcomes associated with infective endocarditis and cardiac valve surgery in South Africa is unclear and needs further research. Surgery for IE has shown excellent results with regard to re-infection and the need for re-operation, with relapse being uncommon.[25,26] IV drug users have a higher incidence of recurrent IE.[27]

The aim of this research is to review the surgical outcome of patients undergoing left sided cardiac valve surgery for infective endocarditis at Tygerberg Hospital, during January 2010 to December 2019. The primary outcome is to evaluate the factors influencing mortality at <30 days, >30 days, and the long-term survival of these patients. The secondary outcome is to evaluate pre-operative, peri-operative and post-operative patient parameters to identify risk factors for morbidity and mortality.

METHODS

The method used in this study was a retrospective data collection, with a final cohort of 160 patients. Ethical approval was obtained from the Stellenbosch University Research Ethics committee and data was collected from various databases and hospital records. All patients who underwent left sided cardiac valve surgery between 1 January 2010 and 31 December 2019 were identified using a Cardiothoracic Surgery departmental database search (n=1158). Inclusion criteria were all confirmed or suspected infective endocarditis patients, undergoing mitral, aortic or both mitral and aortic valve surgery during this time period. The clinical and operative notes were reviewed, and patients with isolated rheumatic degenerative valve changes were excluded, unless they also had infective endocarditis.

Patients undergoing concomitant surgery were included, but patients undergoing isolated right heart valve surgery were excluded. Prior to 2015, the diagnosis of IE was assessed according to the modified Dukes criteria.[28,29] From 2015 onwards, the Modified Duke's criteria in conjunction with the updated 2015 European Society of Cardiologist (ESC) Infective Endocarditis clinical guidelines, were used to confirm eligibility.[30] These guidelines are also endorsed by the European Association of Cardiothoracic Surgeons (EACTS) as well as the South African Heart Association.[31]

Patients with suspected infective endocarditis undergo initial workup and investigation at a peripheral referral hospital. If further surgical intervention is likely required, the patient is transferred to Tygerberg Academic Hospital to receive a confirmation of diagnosis, a formal assessment by the Division of Cardiology, and a transthoracic echocardiogram (TTE), according to the ESC guidelines.[32] Should further detail be required, a transoesophageal echocardiogram (TOE), cardiac MRI or PET CT may also be included in the work-up, but are not considered routine investigations. A multi-

disciplinary heart meeting is held weekly to discuss surgical consideration, and a treatment plan is decided upon.[16] This team includes Cardiologists, Cardiothoracic surgeons, Microbiologists, and Infective Disease specialists. Intra-operatively, a final decision regarding valve repair or replacement is made by the consultant Cardiothoracic surgeon, after thorough debridement of infected tissue has been completed, and the mechanism of incompetence evaluated.

Tygerberg hospital's Electronic Content Management (ECM) system and physical hospital files were used to capture clinical and Intensive Care Unit (ICU) data. Echocardiography (Echo) data was reviewed using the dedicated Echo-PACS system, and laboratory data was obtained and verified using the National Health Laboratory Service (NHLS) TrackCare and wwDisa pathology interfaces. The outcome of patients was reviewed using several methods, including reviewing clinical data on ECM, reviewing recent blood and INR results on TrackCare, reviewing Echo PACS for follow-up visits and imaging, and reviewing the hospital administration system (Clinicom) for admission dates, discharge dates, and records of mortalities.

Statistical analysis was done with the help of the Stellenbosch University Department of Biomedical Statistics, using various quantitative and comparative techniques. Data was imported into IBM SPSS software from REDcap®. Continuous variable data was expressed as median with percentiles, and categorical values were reported as frequency counts and percentages. Chi-Square and Kruskal-Wallis tests were used for comparative analysis, with a p-value of less than 0.05 being considered significant. Kaplan Meier graphs were used for survival analysis. Multivariate testing and ordinal logistic regression were used to assess changes over time.

See "**APPENDIX**" for further detail in relation to the conduction of this study.

RESULTS

In the patient cohort, the mean age was 37.3 years with a male prevalence of 70% (n=112). The average EuroScore II was 4.8%, body mass index (BMI) 23.0kg/m^2 and body surface area (BSA) 1.75m^2. The most common co-morbidities were smoking (46.4%, n=70), hypertension (27.2%, n=41), and chronic lung disease (16.6%, n=25). Acute infective endocarditis was confirmed in 75% (n=120) of patients at surgery, with isolated mitral and aortic valve interventions required in 46.3% (n=74) and 37.5% (n=60) of cases, respectively. In 16.3% (n=26) both the mitral and aortic valve were involved and addressed. Of all the mitral valves intervened on, 33.0% (n=33) were repaired and 67% (n=67) required replacement. For aortic valve interventions, 96.5% (n=83) were replaced and only 3 cases were deemed suitable for repair techniques.

The median days from admission to surgery was 18.5 days (CI 6.0 – 42.0) and median hospital stay after surgery was 29.0 days (CI 16.0 – 43.0), totalling 54.0 days (CI 37.3 – 75.0). Most surgeries were first time valve surgeries (89.4%, n=143), with native valve endocarditis being the most prevalent (89.3%, n=143). 56.3% (n=90) required urgent surgery, and 68.1% (n=109) had cardiac failure at the time of surgery. 42.1% (n=67) of patients developed acute kidney injury peri-operatively. Inotropic and respiratory support were required in 25.0% (n=40) and 17.5% (n=28), respectively. Important demographic and basic surgical admission parameters, and the effect on mortality are set out in **Table 2**.

After valve surgery, the median intubation time was 18 hours (CI 14-19h) and the average ICU blood-loss within the first 24 hours was 350 ml (CI 200-600ml). The common early surgical complications included significant blood-loss in 32.7% (n=52) patients, hospital-acquired pneumonia in 16.4% (n=26) patients, and cerebrovascular events in 8.2% (n=13) patients. The follow-up period of 41.0months (CI 23.0 - 70.0months) showed an infective endocarditis recurrence rate of 6.9% (n=11) and repeat valve surgery required in 8.1% (n=13) patients. Blood cultures were positive in 47.5% (n=76) patients, with Staphylococci being the most prevalent organism identified in 20.6% (n = 33) of patients. All cultures (including both blood and valve cultures) were negative in 41.9% (n=67) of patients operated. Specialized organism directed Polymerase Chain Reaction (PCR) testing was not routinely done on all samples.

In **Table 3**, sub-group analysis of mean age showed statistical significance with a higher late mortality rate in older patients (p=0.04). Functional classification according to the New York Heart Association (NYHA) grading, showed a direct correlation with an increase

in mortality in both the early and late periods (p<0.001) in patients with worse clinical status at the time of surgery. Comorbidities, gender, and the type of valve IE did not yield different outcomes.

The effect of important pre-operative factors on early and late mortality are tabulated in **Table 4**. The most notable factors influencing early, and late mortality was organ dysfunction, and critically ill patients. This can be demonstrated by an increased mortality in critically ill patients (p<0.001) and patients undergoing more urgent intervention (p<0.001). Cardiac function and pre-operative laboratory parameters were not found to be statistically significant.

Surgical factors, indications for surgery and concomitant procedures, as noted in **Table 5**, showed no significant influence on the mortality in this patient cohort.

The most notable early in-hospital complications associated with mortality was pneumonia (p=0.012) and prolonged intubation (p<0.001). In the late post-operative period patients that presented with recurrence of IE had a significantly worse outcome (p=0.002). A more detailed breakdown of complications and analysis of early and late mortality is tabulated in **Table 6** and **Figure 4**.

Figure 1 shows a Kaplan Meier analysis of the overall survival over time in the cohort. The non-events (alive), but where someone didn't make it to the end of the study (dropouts) are censored, thus the proportion alive at each point is calculated with a denominator excluding the censored. During the mean follow-up period of 41.0months, 77.5% of patients were still confirmed to be alive. The effect that the urgency of intervention and clinical status of the patient at surgery has on mortality and late survival can be visualized in the Kaplan Meier graphs (**Figure 2** &**Figure 3**)

Even though routine late follow-up echoes are not routinely done on all patients, creating the risk for selection bias, **Figure 5** shows the effect on various echocardiography parameters during three time periods (Pre-operative, early post operative, and late postoperative). It is interesting to note that the patients show notable decrease in early post operative Left- and Right Ventricular function (LVEF/RVEF), but that recovers almost fully by the late post-operative assessment in the patients that did in fact get a late echo.

DISCUSSION

The most significant factors, in this cohort of 160patients, leading to increased mortality were the urgency of intervention, critical pre-operative state, and presence of single- and multi-organ failure. Other factors included older age, higher pre-operative EuroScore assessment, ongoing pre-operative sepsis, paravalvular extension of the infection, pneumonia, prolonged ventilation, recurrence of infective endocarditis, and need for repeat valve surgery in the late post-operative period. These findings emphasise the complexity of clinical management of often seriously ill patients, and the multitude of clinical factors that need to be considered in the medical and surgical management of patient with IE requiring surgical intervention. A high number of patients required "Urgent" surgery (56%), but the median time before surgery is 18.5days. Further discussion and explanation of this findings is noted in the "APPENDIX" section.

The outcomes observed in this cohort, as a representation of a low-to-middle income country (LMIC), compares very well to data from international studies representing high income countries. An article published in 2013 by Chirillo et al., from Treviso, Italy reported an in-hospital mortality of 13% and a 3-year mortality of 16%, in a cohort of 190 patients, undergoing left sided heart valve surgery for IE.[17] This compares very well with the 8.8% early (<30 day) mortality and 13.1% late (>30 day) mortality observed in this cohort.

In the cohort, with confirmed or suspected infective endocarditis, most patients were previously healthy individuals with a low prevalence of co-morbidities. HIV was present in 15.7% of patients, which is in contrast to data from a recent similar study (2021) by Gwila et al. (2021) at the University of the Free-State, that reported an HIV positive incidence of 31% in patients with IE requiring cardiac valve surgery.[33] The prevalence observed in our cohort, however, correlates well with data from the Western-Cape Government statistics (2022), stating the incidence of HIV in the local population at 7.3% and 13.4% for males and females respectively.[34] No significant difference in surgical outcome in these patients was

observed. Older patients and those with higher urgency of intervention had an increased risk for both early and late mortality. Gender did not show a significant difference in outcome. The salvage group had a 100% mortality rate, prompting a debate regarding ethical and resource considerations for operative and ICU care of these patients. Bearing in mind that patients with a surgical indication that did not undergo surgery, or were declined for surgery on clinical grounds, also showed a similar dismal outcome in a recent prospective cohort study at Tygerberg hospital by Pecoraro et al. (2022).[16] An inherent selection bias should also be considered in this patient subgroup, as salvage patients are usually critically ill and the patients declined for surgery are assessed, on pre operative risk stratification, to be too ill to survive surgical intervention. New York Heart Association (NYHA) functional status showed a significant relation to early and late mortality, with the NYHA IV group having the highest risk. A critical pre-operative state, even with single organ dysfunction, significantly increased the risk of mortality in both early and late operative periods. Co-morbidities did not significantly affect mortality, except for chronic lung disease, which showed a marginal increase in risk but with small numbers, making the clinical significance debatable.

The study found no statistically significant difference in outcomes between mitral and aortic valve intervention, or if concomitant procedures were performed. This finding is interesting and warrants further investigation as previous research by Østergaard et al. (2020) found a higher mortality risk with mitral valve surgery, in comparison to aortic valve surgery in patients with IE.[35] The small sample size may have affected the results, and ongoing sepsis contributes greatly to mortality regardless of the affected valve.

EuroScore II was highly associated with early post-operative mortality but not with long-term mortality. The median Euroscore II of 4.8%, was significantly lower than the early mortality (<30 day) of 8.8% that was observed. This is in keeping with findings from several other studies, including articles by Patrat-Delon et al. (2016) and Koshy et al (2018), that found that EuroSCORE II calculations underestimate post-cardiac surgery mortality in certain patient subgroups of patients with IE.[36,37]

Blood culture negative endocarditis (BCNIE) was still a frequent observation in this cohort of patients. Since the data collection period has ended, a new article was published by Pecoraro et al. (2021) highlighting the prevalence of Bartonella species and Mycoplasma species as the most common organisms as cause for previously documented BCNIE within the Tygerberg hospital setting. Previously routine blood culture investigations did not specifically investigate for these organisms.[11] A new protocol was adopted in November 2019, whereby all patients with preliminary BCNIE, undergo further PCR testing for Bartonella, Mycoplasma, Legionella, Brucella and Coxiella species to help in identification of a causative organism for IE. Serological samples are collected pre-operatively and valve tissue samples are sent at the time of surgery for a full PCR array assessment for all patients. This has significantly reduced the incidence of BCNIE in Tygerberg Hospital and has since shown great benefit in aiding goal directed antibiotic management in surgical IE patients. The incidence of BCNIE in a prospective cohort was shown to be significantly lower compared to a retrospective cohort since the adaptation of the protocol change in Tygerberg Hospital (62.7% vs 42.1% (p=0.039)). In up to 86.2% of patients a cause could be established in the prospective group, using non-culture techniques. This benefit is substantiated by the observation of a downward trend observed in the in-hospital mortality of the prospective cohort (14.2%) compared to a retrospective cohort in-hospital mortality (23.4%) (p=0.35). [38]

The study found no statistically significant association between aortic cross-clamp time and post-operative mortality, but there was a noticeable trend towards longer cross-clamp time in the early mortality group. Longer cross-clamp time is typically associated with more complex surgical repairs. A longer cardiopulmonary bypass time was significantly associated with increased mortality risk and is often also associated with worse coagulopathic tendencies, cardiac stunning, systemic inflammatory response, and acute kidney injury, that may also independently contribute to worse outcomes.[39–41] Indications for surgery as a risk for mortality were difficult to interpret, as patients often had multiple indications, but ongoing sepsis and paravalvular extension of infection to the aortic root or para-aortic region were associated with increased mortality.

Pre-operative laboratory parameters, including White Cell Count (WCC), Haemoglobin (HB), and C-Reactive Protein (CRP), were assessed and higher CRP values were observed in patients at higher risk for early mortality, potentially indicating ongoing sepsis. No specific association between organism prevalence and mortality outcomes was observed in this cohort.

Early in-hospital complications are common after major cardiac surgery, but were observed to be generally low in the Tygerberg Cardiothoracic unit, and may be indicative of good post-operative care. Pneumonia and prolonged ventilation were independent risk factors for increased mortality, while other parameters investigated did not show statistical significance. Late complications showed that IE relapse and the need for recurrent valve surgery were statistically significant risk factors for increased mortality, highlighting the importance of prophylaxis and prevention of re-infections.[30,31]

Kaplan Meier analysis observed a mean overall survival probability period of 100.1 ±4.7months (8.3 years). Kaplan-Meier analysis further indicated that the urgency of intervention was highly significant, with a higher risk of early mortality in the salvage group. The mean survival of the other three groups declined progressively, correlating with the higher risk expected with more urgent surgery. This is consistent with a previous study by Rankin et al. that also showed a higher odds ratio (2.11) for mortality in patients with acute IE compared to elective IE valve surgery.[42]

In this study, survival rates were significantly affected by clinical functional assessment, especially in patients with NYHA IV functional class. Patients in this group were critically ill and had high mortality rates compared to other groups, highlighting the importance of optimizing patients' medical status prior to surgery.

Mitral and aortic repair techniques were found to have similar outcomes, with a trend towards better survival with mitral valve repair. A systematic review by Feringa et al. (2007) underlined that mitral valve repair was possible in patients presenting with mitral valve endocarditis, with repair being associated with lower in-hospital and long-term mortality. Since this review, those findings have been supported by various published results: Rostagno et al. from Italy (2017) and El-Gabry et al. from Germany (2019).[19,43,44]

LVEF decreased in the early post-operative period but recovered to near pre-operative values on late post-operative assessment, an effect likely due to cardiac stunning associated with cardiopulmonary bypass in the early post-operative period. The study found that left ventricular end diastolic (LVED) measurement showed progressive improvement from pre- to early post- and late post-operative period, indicating cardiac remodelling and improved volume load on the myocardium during diastole. Pulmonary hypertension also showed a trend of improvement over time. Right ventricular (RV) failure was observed in the early post-operative period but recovered remarkably over time, also likely due to the effect of peri-operative cardiac stunning and subsequent remodelling during the recovery period.

Limitations and challenges:

A significant limitation of this study is the inherent bias related to the retrospective and observational nature of the study. Exceptional completeness of data could be achieved, but occasional missing information or absence of clinical recordkeeping impaired data collection and integrity. Despite using a multidisciplinary team approach, the indications and timing of surgery is based on clinical judgement, and adds to the heterogenicity of patient management. A further major limitation is that the information in relation to IE patients with surgical indications, that were not deemed to be operative candidates and thus declined surgical intervention, is not known or well documented, and makes assessment of this specific patient subgroup impossible.

CONCLUSION

In South Africa, infective endocarditis is still a common indication for heart valve surgery despite medical advancements. The study aimed to identify factors affecting patient outcomes at TBH hospital. The limited sample showed good overall outcomes for both valve repair and replacement. Antibiotic therapy and pre-operative optimization were crucial for better surgical outcomes. Early mortality correlated with EuroScore II pre-operative mortality risk assessment, and several factors associated with increased early mortality were identified. The study provided insight into long-term expected survival in the Western Cape.

The study found that salvage procedures or critical illness with multi-organ failure prior to surgery were associated with poorer outcomes and require ethical considerations. There is a high rate of culture negative IE, which makes antibiotic stewardship difficult, but newer protocols and additional testing will likely yield improved goal directed management in surgical IE patients.

The operative outcome of infective endocarditis at Tygerberg Hospital compares well with international standards, despite unique challenges faced by South Africa.

APPENDIX

In addition, the study team attempted to contact the outstanding patients on all available telephone numbers on record to confirm their alive status. The patients for whom no clinical data could be traced or verified were coded as lost-to-follow-up (n=9). The patients that were deemed lost to follow-up, were excluded for the analysis looking at the parameters affecting early and late mortality as their follow-up information was incomplete. The South African National Department of Home Affairs (DOHA) was consulted to verify the alive status of these 9 patients, of whom 8 could be confirmed to still be alive. However, for the Kaplan Meier mortality over time assessment, they were included in the analysis and captured as still being alive. These 8 patients were also included in the pre- and peri-operative data analysis regarding their hospital admission and surgery, as this data could be obtained from the operative notes and hospital administration system. If a mortality or early complication occurred during the admission period, it was documented and included in the analysis. The data were censored from the time of last healthcare contact, and late complications that might have occurred after this censor date, were thus also excluded from analysis.

Unique study identifiers were assigned to the initial list of possible participants for anonymous data collection, which could be cross-referenced through a password-protected MS Excel file. After applying exclusion and inclusion criteria, a new REDcap record number was assigned to the final list of 160 participants. A 172-parameter database was created using REDcap, divided into 10 sections including demographics, pre-operative history, intervention, surgery details, complications, and three sections for echocardiographic data. A paper-based template was used to capture data initially, which was later entered into the REDcap electronic database for easy data extraction and statistical analysis. Despite being challenging, the study achieved excellent completeness through various sources and systems.

At Tygerberg hospital, registrar training is a routine part of daily activities. A senior consultant performs valve repair surgeries, while replacement surgeries are performed by registrars under consultant supervision or by consultants themselves. Surgeon experience is not expected to impact the data. Post-operative care is provided in a 14-bed Cardiothoracic ICU by consultants and registrars. Mild hypothermia is used during surgery as per the standard protocol, with a core temperature of 32°C during bypass and rewarming to 36°C prior to decannulation from cardiopulmonary bypass (CPB). An underbody warming air blanket is used until a consistent body temperature is maintained in the unit.

In this study, the transfusion trigger for donor packed red blood cells (RBC) are typically set at a Haemoglobin (HB) value of 8.0g/dL or a haematocrit of less than 29% after the patient has been weaned from CPB and the auto transfusion of Cellsaver® blood has been completed. Excessive bleeding over 500ml within the first 24 hours after surgery warrants medical correction of coagulation with blood products or surgical re-exploration. Acute kidney injury is defined according to KDIGO (Kidney Disease Improving Global Outcomes) guidelines and classified by serum creatinine levels, urine volume, and severity.[45] Chronic kidney disease is defined as kidney damage or eGFR less than 60 ml/min/1.73m^2 for 3 months or more, and further classified by glomerular filtration and albuminuria levels.[46,47] A standard serum creatinine cut-off of 150 umol/L was used for all patients, and discharge with residual serum creatinine above this value was considered a degree of chronic renal impairment.

Critical pre-operative state and timing of surgery classification were determined by using the EUROSCORE II scoring system definitions.[48] Patients who require surgery on the current admission for medical reasons and cannot be discharged without a definitive procedure is regarded as an urgent procedure. An operation is deemed emergency if it is

done before the beginning of the next working day after the decision to operate was made. [48]

In Tygerberg Hospital the protocol regarding timing of surgery is based on a holistic assessment of the patients' clinical condition, by the combined heart team.[16] If the patient is clinically stable, the aim is to complete the full 42days of IV antibiotics, prior to doing the valve surgery. The cardiac tissue is often very friable and inflamed during the acute phase of IE, requiring careful suture placement. Longer antibiotic therapy aid in improving tissue quality, by reducing the bacterial load and inflammation. Clinical deterioration prior to the completion of the 42days antibiotics, peri-valvular extension or persistently large high embolic risk vegetations, often require urgent surgical intervention prior to the completion of this period and are guided by ESC and EACTS guidelines.[30] In these cases, the patient will have to complete the remainder of the 42days of IV antibiotics post-surgery, and explains the longer than expected post-surgery to discharge hospital admission stay (29.0 days) duration.

Post-operative antibiotic therapy is further guided by intra-operative tissue assessment and evidence of ongoing active infection. If significant residual vegetations is visualized, source control is deemed to only be established at the time of surgery, and a full 42day course will be restarted. Active infection on histology or a positive valve tissue culture, or an organism not susceptible to the pre-operative blood culture identified sensitivities, will also prompt the re-initiation of a full 42 days of postoperative organism sensitivity guided antibiotic therapy. If a susceptible organism, with definitive sensitivities is confirmed on microbiological culture or PCR investigation, the antibiotic regime would be de-escalated according to the recommendation from the infectious disease and microbiology consultant on the IE team.

Despite advances in modern medicine, and better laboratory testing the prevalence of culture negative infective endocarditis is still very high within the WC setting. In some countries, the identification of causative organisms is as high as 90%, using various advanced PCR assays and laboratory testing.[49] Within the Tygerberg hospital setting, resource limitations preclude the performance of all the expensive investigations routinely, and they are limited to funded research or complex cases. Cultures and antimicrobial susceptibility testing will guide the choice of antibiotics once they become available. The standard protocol dictates that 3x blood cultures, using the Standard BacT/ALERT® FA Plus (Fastidious Antimicrobial Neutralization Plus Media) blood-culture bottle, should be taken at least 30 min apart. This should be done, from 3 different sites using a sterile technique, and completed prior to initiation of antibiotic therapy. Due to Tygerberg hospital being a tertiary level care referral centre, these cultures are often performed at primary or secondary care hospitals, prior to the transfer of the patient. The accuracy and quality of these samples can thus often not be verified accurately, and often do not meet the criteria required. Due to initiatives world-wide that advocate early antibiotic therapy to decrease mortality in septic patients, as seen in the "Surviving Sepsis campaigns", junior doctors would often start treating sepsis empirically, prior to sufficiently completing the necessary blood cultures.[50] Unfortunately, this results in a large number of patients with confirmed IE, but without a specific organism identified pre-operatively, representing the large incidence of BCNIE.

Empirical therapy will usually be similar to what is given to culture-negative cases. For native valve endocarditis intravenous Penicillin G (5-6 million Units q6hrly IV for 6 weeks), Cephazolin (2g q6hrly IV for 6 weeks) and Gentamicin (1 mg/kg q8h IV for 2 weeks). If a Staphylococcus is confirmed, the Cephazolin will be replaced with Cloxacillin (2 g q6hg IV for 6 weeks). The antibiotic strategy is guided by the European Society of Cardiology (ESC) and European Association of Cardiothoracic Surgeons (EACTS) guidelines, that are reviewed periodically.[30]

Prosthetic valve endocarditis is treated with a combination of intravenous Vancomycin and oral Rifampicin for 6 weeks in combination with 8 hourly intravenous Gentamicin for the first 2 weeks of the therapy.[7] Patients will not receive out-patient parenteral, antibiotic therapy (OPAT), unless they have completed at least 28 days IV antibiotics, and have a proven organism, e.g. Mycoplasma or Coxiella Brunetti, that is sensitive to oral Doxycycline. However, this has only recently become practice within the TBH setting, and most of the patients in the study have still received the full 6 weeks (42 days) of in-patient IV antibiotics, either at TBH or a secondary referral hospital.

Early mobilization is one of the most important parameters in decreasing morbidity and mortality in the ERAS (enhanced recovery after surgery) guidelines. It is important that each patient has a good functional status assessment prior to surgery. Infective endocarditis patients often present with embolic phenomenon resulting in cerebral vascular accident (CVA) with complications of a hemiplegia, aphasia, or mycotic aneurysms. This greatly impacts the post operative rehabilitation process and adds additional strain on nursing staff, as well as supporting disciplines like physiotherapists. Silent embolic phenomenon, especially to the brain and spleen, have been reported in up to 20-50% of IE patients on CT and MRI, with 15-30% of patients having symptomatic neurological complication.[51,52] Unfortunately due to resource constraints, routine pre-operative radiological investigation on all IE patients is not feasible, but are guided by clinical findings if any neurological compromise is suspected. TTE has been accepted as a valuable adjunct to visualization of vegetations and vital in the assessment of high embolization risk vegetations. It is routinely used as an assessment tool and vegetations with a linear length longer than 10mm has been associated with a higher in-hospital mortality incidence.[32]

Patients with confirmed neurological compromise, will all undergo CT Brain assessment and the further management is based on the ESC/EACTS 2015 guidelines on IE.[30] If a haemorrhagic CVA has been confirmed on imaging, surgery will be delayed for at least 1 month. If haemorrhage has been excluded, the timing of surgery would be individualized according to the patient's extent of neurological compromise, expected recovery and risk for further embolization. A heart team discussion will guide management, with the aim of optimizing rehabilitation pre-operatively, while limiting the risk for further embolization and maximise the benefit from early surgery.[16,32] Clinical features of cardiac failure and ongoing sepsis would also be taken into consideration. If a mycotic aneurysm is identified, the treatment of the extra-cardiac disease will be guided by Neurosurgery or Vascular surgery – depending on the severity and location involved. If a patient is completely stable, and is deemed a low risk for further embolization, a more conservative intense outpatient rehabilitation program, with elective surgery after 6 months, may be considered in select cases.

TTE assessment is routinely used preoperatively and postoperatively to evaluate cardiac and valvular function in patients undergoing cardiac surgery. All patients receive an early post-operative echo, prior to discharge, after the pericardial drains has been removed. This is to ensure good valve function and to exclude the presence of any paravalvular leaks or significant pericardial effusions. Follow-up is arranged with all patients, receiving a cardiothoracic surgery outpatient clinic booking approximately 6-8 weeks after discharge. Once the patient has fully recovered from his surgery, he will be referred back to the division of Cardiology at Tygerberg hospital, for annual long-term follow-up and surveillance. Routine late follow-up echoes are not done, and are guided by clinical judgement if indicated. Patients are provided with extensive counselling on Warfarin compliance, wound care, and general health, and are offered an open-door policy for any concerns during the early operative period. INR monitoring is done at the local community healthcare clinic, and medication therapy is optimised based on the type of valve replacement or repair. Patients with valve replacements are usually prescribed angiotensin converting enzyme (ACE) inhibitors, beta blockers, and Warfarin anticoagulation, while those with valve repairs typically only receive single anti-platelet therapy (Aspirin). Patients who develop complications requiring further surgical intervention, are represented at a weekly multi-disciplinary team meeting for discussion of possible re-intervention.

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INDICATIONS FOR SURGERY	*Class*	*CONSIDERATION FOR EARLY SURGERY*
HEART FAILURE		
Severe aortic or mitral valve incompetence Heart failure (HF) caused by severe aortic or mitral regurgitation, intracardiac fistulae or valve obstruction caused by vegetations. In the absence of clinical HF but with echocardiographic signs of elevated left ventricular end-diastolic pressure (e.g. premature closure of the mitral valve), high left atrial pressure or moderate to severe pulmonary hypertension.	**I**	Cardiogenic Shock, pulmonary oedema, refractory cardiac failure not responding to medical therapy or echo signs of poor haemodynamic tolerance.
UNCONTROLLED INFECTION		
Locally uncontrolled infection Perivalvular extension of infection, including abscess, false aneurysms, fistula or enlarging vegetations or new onset heart block	**I**	Persistent positive blood-cultures despite appropriate antibiotic therapy (7-10 days [ESC], 5-7days [AATS]) and adequate control of septic embolic foci.
Infection caused by Fungi or multi-resistant organisms	**I**	
PVE caused by Staphylococci or non-Hacek gram-negative bacteria	**I**	
PVE with relapse infection after completing a full course of antibiotics and being culture negative	**IIa**	
PREVENTION OF EMBOLISM		
Persistent vegetations (>10mm) after one or more embolic episode despite appropriate antibiotic therapy	**I**	In order to prevent vegetation emboli, consider the presence of previous embolic events, other complications of IE, the size and mobility of the vegetation, the likelihood of conservative surgery and the duration of antibiotic therapy.
Isolated large vegetation (>15mm)	**IIb**	

Table 1: Indications for surgery and early surgery in IE [27,46]

BASIC FINDINGS	n = 160
Confirmed acute IE	75.0% (120)
Suspected acute IE	12.5% (20)
Sub-acute (fully treated, elective surgery)	12.5% (20)
Number of primary surgeons	11
Intra-aortic balloon pump required	3.8% (6)
Admission to surgery	18.5 days (0-115)
Admission to discharge	54.0 days (7-157)
Surgery to discharge	29.0 days (0-98)
Hours intubated post operatively	18 hours (6-1464)
Blood loss within first 24 hours	350 ml (50-2250)
FOLLOW-UP	
Post-operative follow-up period	41.0 months (1-131)
Recurrence of infective endocarditis during follow-up	6.9% (11)
Repeat valve surgery required during follow-up	8.1% (13)
MORTALITY	
Alive	72.5% (116)
Demised – Early (within 30 days)	8.8% (14)
Demised – Late (after 30 days)	13.1% (21)
Lost to follow-up, but still alive according to home affairs	5.0 % (8)
Lost to follow-up, unknown if alive	0,6% (1)
CULTURES	
Pre op blood culture positive for organism	47.5 % (76)
Valve culture positive for organism	21.3 % (34)
HISTOLOGY	
Acute infection	39.4% (63)
Chronic inflammation	30.0% (48)
Myxoid degeneration	24.4% (39)
No active or chronic infection/inflammation	38.8% (62)
Other findings	5.6% (9)
ECHO FEATURES PRE-OPERATIVELY	
Rheumatic valves	41.8% (66)
Vegetations visualized	75.9% (120)
Paravalvular extension	15.9% (25)

Table 2: Basic findings

		Alive (n=116)	<30 Day Mortality (n=14)	>30 Day Mortality (n=21)	p Value
DEMOGRAPHICS					
Mean age (years)		36.2	44.1	40.3	0.04
Median EUROSCORE		4.4% (116)	28.3% (14)	5.1% (21)	< 0.001
BMI – Body Mass Index (kg/m2)		23.4879	23.6857	23.9571	0.090
BSA – Body surface area (m2)		1.7560	1.7143	1.7333	0.735
GENDER:					0.340
Male		80.0% (84)	8.6% (9)	11.4% (12)	
Female		69.6% (32)	10.9% (5)	19.6% (9)	
TYPE OF VALVE					0.625
Native		76.6% (105)	8.8% (12)	14.6% (20)	
Prosthetic valve in-situ		78.6% (11)	14.3% (2)	7.1% (1)	
FUNCTIONAL STATUS					<0.001
NYHA I		83.3% (5)	0	16.7% (1)	
NYHA II		91.8% (45)	0	8.2% (4)	
NYHA III		82.7% (43)	7.7% (4)	9.6% (5)	
NYHA IV		53.5% (23)	23.3% (10)	23.3% (10)	
COMORBIDITIES					
Hypertension	n=41	78.0% (32)	7.3% (3)	14.6% (6)	0.901
Diabetes Mellitus	n=7				0.791
Insulin		75% (3)	0	25% (1)	
Oral only		100% (3)	0	0	
Smoking	n=70				0.376
Current smoker		73.8% (45)	14.8% (9)	11.5% (7)	
Ex-smoker (> 6 months)		88.9% (8)	0	11.1% (1)	
Alcohol abuse	n=19	57.9% (11)	21.1% (4)	21.1% (4)	0.061
Illicit substance abuse	n=20	85.0% (17)	0	15.0% (3)	0.332
HIV Positive	n=23	65.2% (15)	13.0% (3)	21.7% (5)	0.194
Chronic lung disease	n=25	60.0% (15)	20.0% (5)	20.0% (5)	0.051
Poor mobility	n=6	83.3% (5)	16.7% (1)	0	0.632

Table 3: Demographics

		Alive (n=116)	<30 Day Mortality (n=14)	>30 Day Mortality (n=21)	p Value
TIME RELATED FACTORS					
Days from admission to surgery		20.50 [6.0 – 42.0]	9.00 [1.0 – 18.0]	18.00 [7.0 – 46.0]	0.112
Days antibiotics before surgery		28.00 [6.5 – 42.0]	8.00 [1.0 – 18.0]	24.00 [9.0 – 42.0]	0.024
Aortic cross-clamp time in minutes		90.00 [70.0 – 115.0]	110.50 [73.0 – 190.0]	77.00 [62.0 – 112.0]	0.190
Cardiopulmonary bypass (CPB) time in minutes		121.50 [102.5 – 146.5]	155.50 [119.0 – 241.0]	111.00 [85.0 – 134.0]	0.017
URGENCY OF INTERVENTION	n=151				< 0.001
Stable		88.9% (16)	-	11.1% (2)	
Urgent		84.7% (72)	3.5% (3)	11.8% (10)	
Emergency		66.7% (28)	14.3% (6)	19.0% (8)	
Salvage		-	83.3% (5)	16.7% (1)	
CARDIAC FUNCTION	n=149				0.549
LVEF < 50%		76.5% (26)	5.9% (2)	17.6% (6)	
LVEF ≥50%		77.4% (89)	10.4% (12)	12.2% (14)	
ORGAN DYSFUNCTION	n=151				
Peri-operative cardiac failure		70.6% (72)	12.7% (13)	16.7% (17)	0.025
Inotropes required pre-induction		61.5% (24)	17.9% (7)	20.5% (8)	0.023
Intubated / CPAP required pre-induction		55.6% (15)	37.0% (10)	7.4% (2)	< 0.001
Acute renal failure during admission		70.3% (45)	17.2% (11)	12.5% (8)	0.016
Chronic renal impairment/ residual with discharge		43.5% (10)	39.1% (9)	17.4% (4)	0.001
CRITICAL PRE-OPERATIVE STATE	n=150				< 0.001
No		81.3% (100)	4.1% (5)	14.6% (18)	
Yes		55.6% (15)	33.3% (9)	11.1% (3)	
LABORATORY PARAMETERS AND MORTALITY					
White cell count (WCC) (X109 /L)	n=150	7.61 [5.95 – 9.69]	9.87 [7.80 – 12.0]	8.46 [6.50 – 9.80]	0.078
C-reactive protein (CRP) (mg/L)	n=116	43.0 [17.0 – 88.0]	99.5 [70.0 – 197.5]	39.0 [12.3 – 118.0]	0.064
Haemoglobin (HB) (g/dL)	n=151	11.15 [9.65 – 12.5]	10.80 [8.8 – 11.8]	10.90 [9.8 – 11.6]	0.680

Table 4: Pre-operative factors

		Alive (n=116)	<30 Day Mortality (n=14)	>30 Day Mortality (n=21)	p Value
INDICATION FOR SURGERY	n=151				
Acute severe MR/AR, with signs of CCF		75.4% (89)	9.3% (11)	15.3% (18)	0.659
Large vegetation (>10mm)		76.2% (32)	11.9% (5)	11.9% (5)	0.737
Embolic event during first 2 weeks of AB therapy		81.6% (31)	7.9% (3)	10.5% (4)	0.761
Ongoing sepsis, despite adequate AB therapy		61.1% (11)	27.8% (5)	11.1% (2)	0.022
Sub-acute IE with CCF unresponsive to medical therapy		86.7% (13)	0	13.3% (2)	0.506
Paravalvular extension of infection (abscess)		62.5% (20)	18.8% (6)	18.8% (6)	0.046
TYPE OF INTERVENTION					0.929
First time valve surgery	n=135	76.3% (103)	8.9% (12)	14.8% (20)	
First redo	n=13	76.9% (10)	15.4% (2)	7.7% (1)	
Second redo	n=2	100% (2)	-	-	
Third + fourth redo	n=1	100% (1)	-	-	
PRIMARY VALVE INTERVENTION					0.409
Mitral valve	n=74	82.9% (58)	5.7% (4)	11.4% (8)	
Aortic valve	n=60	71.9% (41)	10.5% (6)	17.5% (10)	
Both mitral AND aortic valves	n=26	70.8% (17)	16.7% (4)	12.5% (3)	
CONCOMITANT PROCEDURES					
CABG		75.0% (3)	25.0% (1)	-	0.434
Tricuspid valve annuloplasty/replacement		33.3% (1)	33.3% (1)	33.3% (1)	0.174
Vein patch leaflet repair		100% (7)	-	-	0.330
Other procedures		65.0% (13)	15.0% (3)	20.0% (4)	0.396

Table 5: Surgical factors

		Alive (n=116)	<30 Day Mortality (n=14)	>30 Day Mortality (n=21)	p Value
EARLY IN-HOSPITAL POST-OPERATIVE COMPLICATIONS					
Excessive bleeding (> 500 ml in 24 h)	n=48	68.8% (33)	14.6% (7)	16.7% (8)	0.197
Re-operated for bleeding	n=13	61.5% (8)	15.4% (2)	23.1% (3)	0.531
Re-operated for pericardial effusion	n=7	100% (7)	0	0	0.234
Pneumonia	n=24	54.2% (13)	16.7% (4)	29.2% (7)	0.012
Wound sepsis	n=12	83.3% (10)	0	16.7% (2)	0.606
Prolonged intubation (> 24 h)	n=26	50.0% (13)	30.8% (8)	19.2% (5)	< 0.001
Neurological Event (CVA/TIA)					0.771
(Pre-Op)	n=36	83.3% (30)	5.6% (2)	11.1% (4)	
(Post/Peri-Op)	n=13	76.9% (10)	15.4% (2)	7.7% (1)	
Peripheral Emboli					0.795
(Pre-Op)	n=10	80.0% (8)	10.0% (1)	10.0% (1)	
(Post/Peri-Op)	n=2	100.0% (2)	0	0	
Atrial Fibrillation					0.338
(Pre-Op/ Chronic)	n=9	100.0% (9)	0	0	
(Post/Peri-Op)	n=12	58.3% (7)	33.3% (4)	8.3% (1)	
Permanent Pacemaker					0.121
(Pre-Op / Chronic)	n=1	0	0	100% (1)	
(Post/Peri-Op)	n=4	75.0% (3)	25.0% (1)	0	
LATE POST SURGERY DISCHARGE COMPLICATIONS					
Re-admitted with surgery related complication	n=15	66.7% (10)	0	33.3% (5)	0.123
Re-infection diagnosed as infective endocarditis	n=11	45.5% (5)	0	54.5% (6)	0.002
Repeat valve surgery required	n=13	61.5% (8)	0	38.5% (5)	0.038
Re-operation for paravalvular leak	n=1	100% (1)	0	0	1.0

Table 6: Post-operative factors

PREDICTORS OF MORTALITY IRRESPECTIVE OF TIME-PERIOD		Alive	Dead	p Value
ORGANISM				
Streptococci Viridans	n=14	100% (14)	0% (0)	0.041
Group D Streptococci	n=7	57.1% (4)	42.9% (3)	0.349
Streptococcus other	n=12	83.3% (10)	16.7% (2)	0.740
Staphylococcus	n=33	81.8% (27)	18.2% (6)	0.644
Hacek organisms	n=6	50% (3)	50% (3)	0.119
Fungi	n=3	66.7% (2)	33.3% (1)	1.000
Other gram positives	n=11	63.6% (7)	36.4% (4)	0.258
Other gram negatives	n=23	82.6% (19)	17.4% (4)	0.608
All cultures negative	n=67	76.1% (51)	23.9% (16)	0.699
REPAIR VS REPLACEMENT				
MITRAL VALVE				0,076
Repair	n=33	90.9% (30)	9.1% (3)	
Replacement	n=67	76.1% (51)	23.9% (16)	
AORTIC VALVE				0,793
Repair	n=3	66.6% (2)	33.3% (1)	
Replacement	n=83	73.5% (61)	26.5% (22)	

Table 7: Other factors

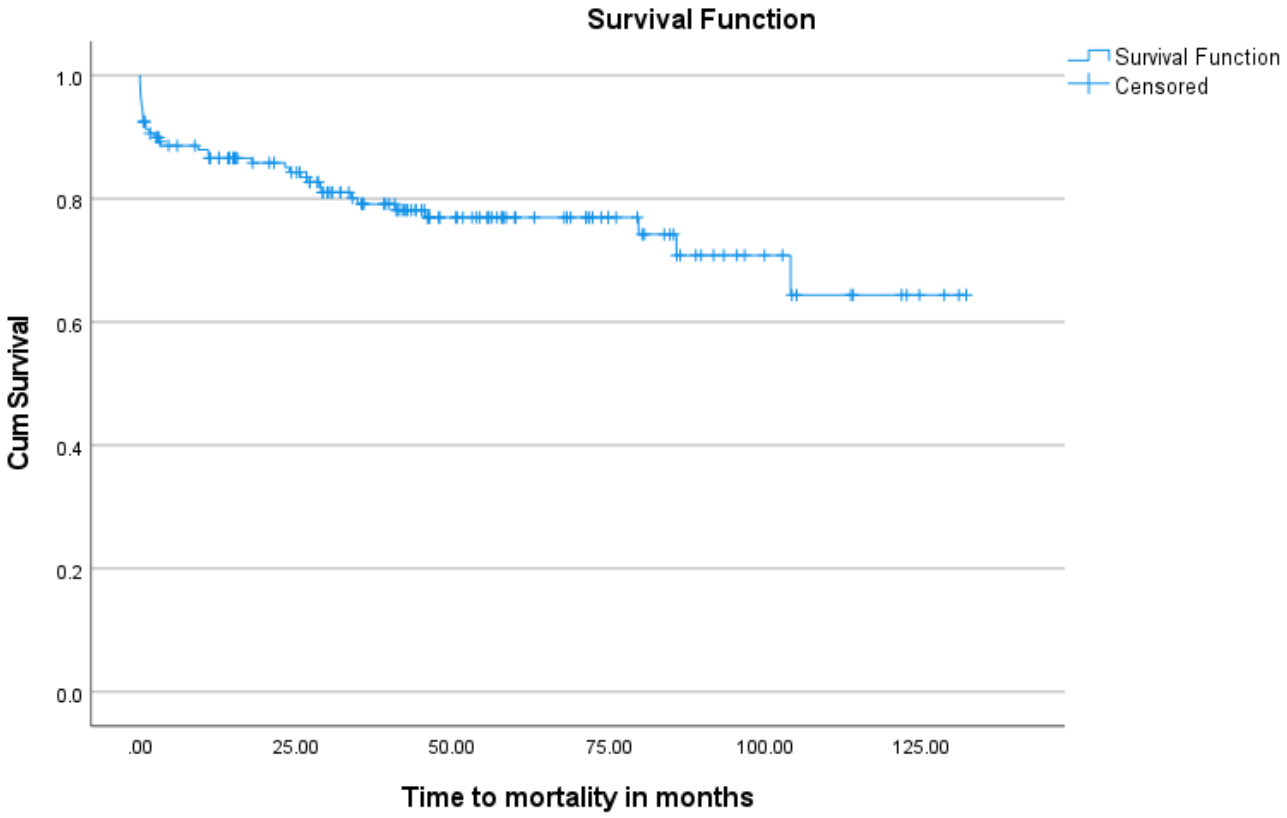

Figure 1: Kaplan Meier graph indicating probability of survival over time

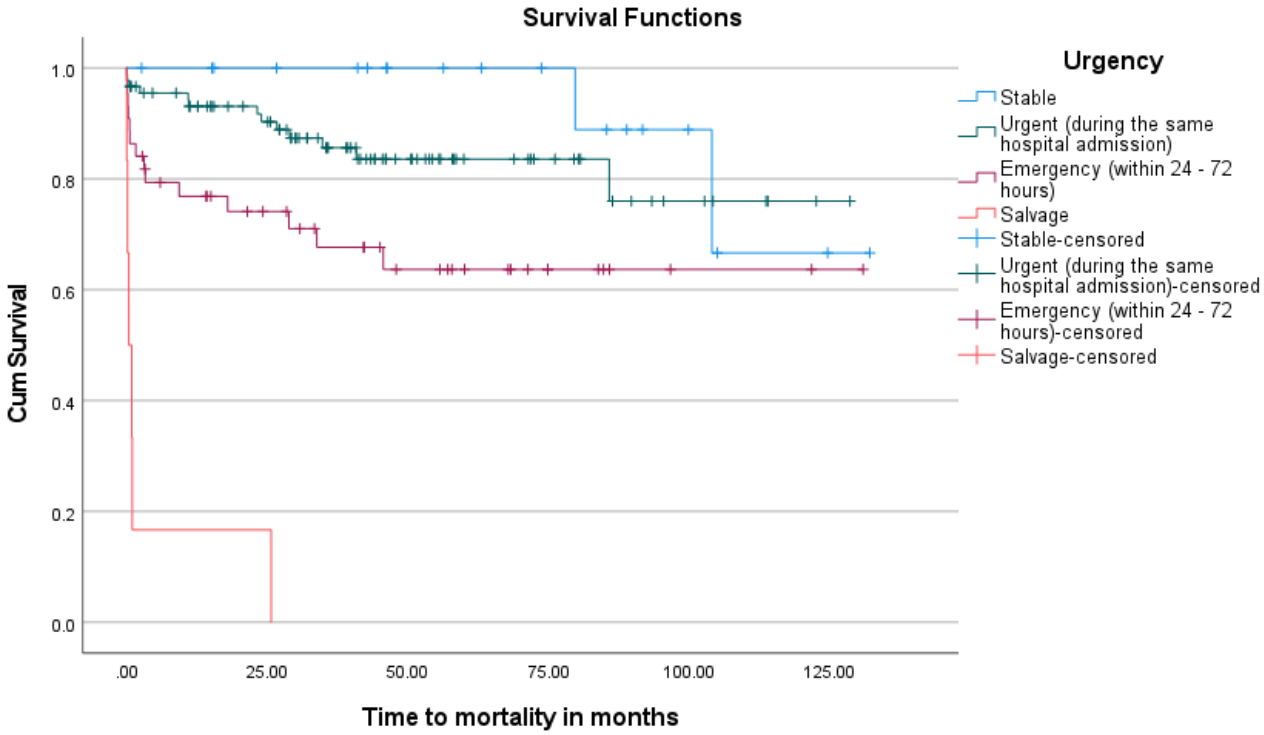

Figure 2: Kaplan Meier graph of survival over time according to urgency of surgical intervention

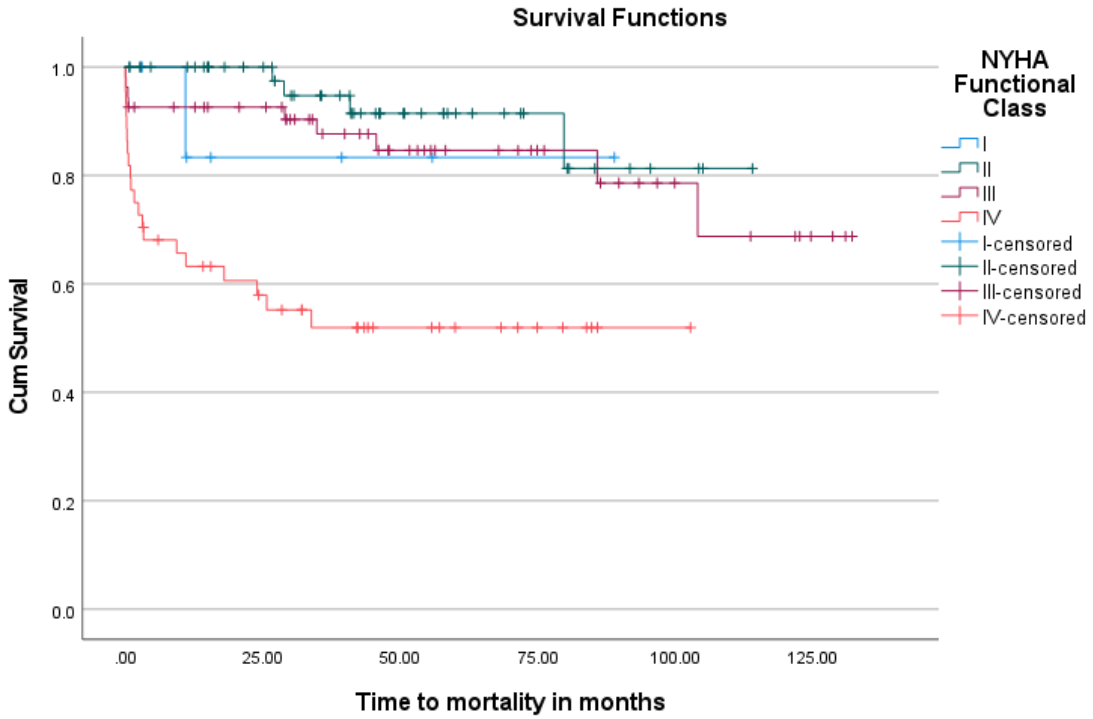

Figure 3: Kaplan Meier graph of survival over time according to pre-op clinical functioning

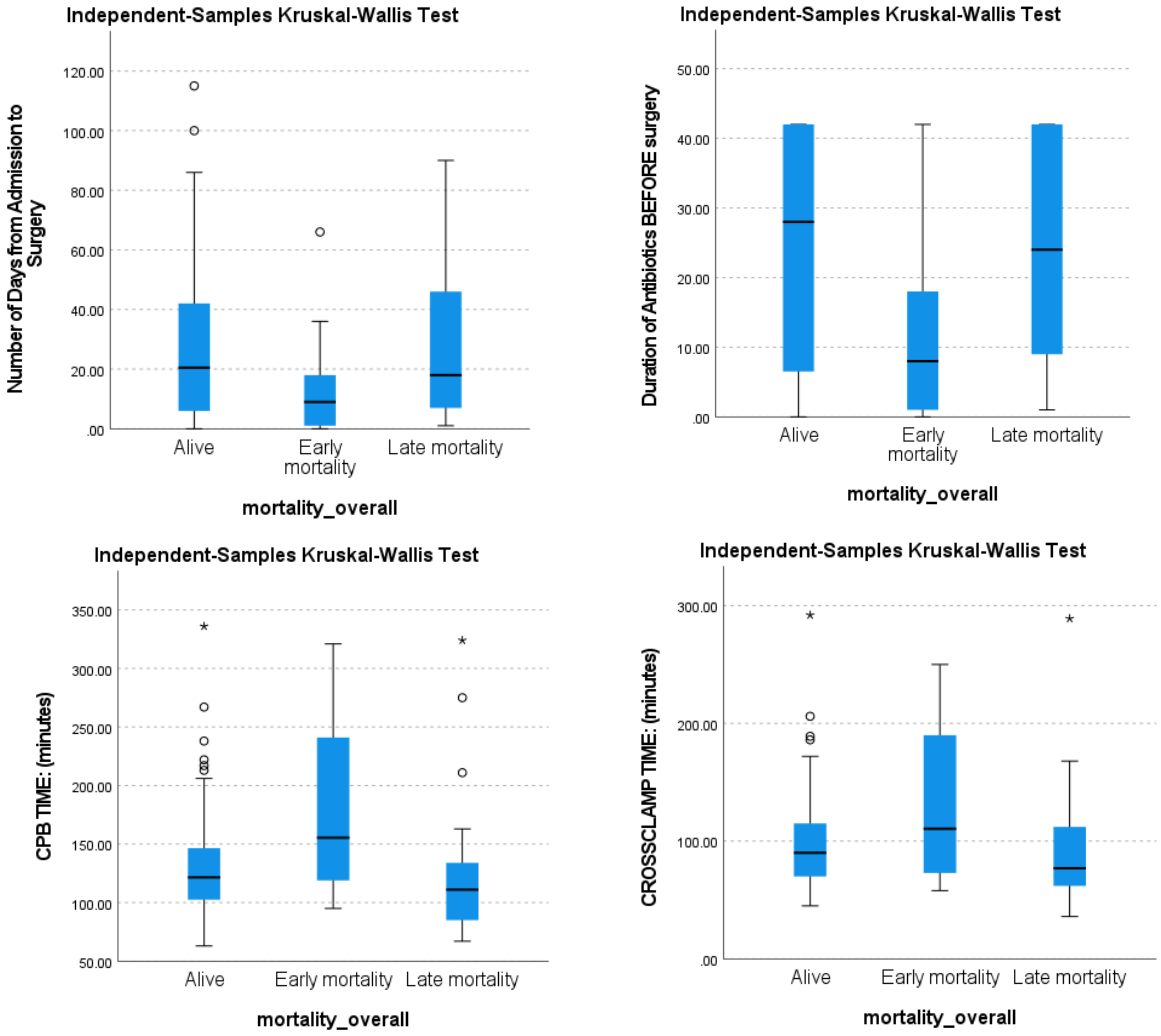

Figure 4: Effect of various parameters on early and late mortality

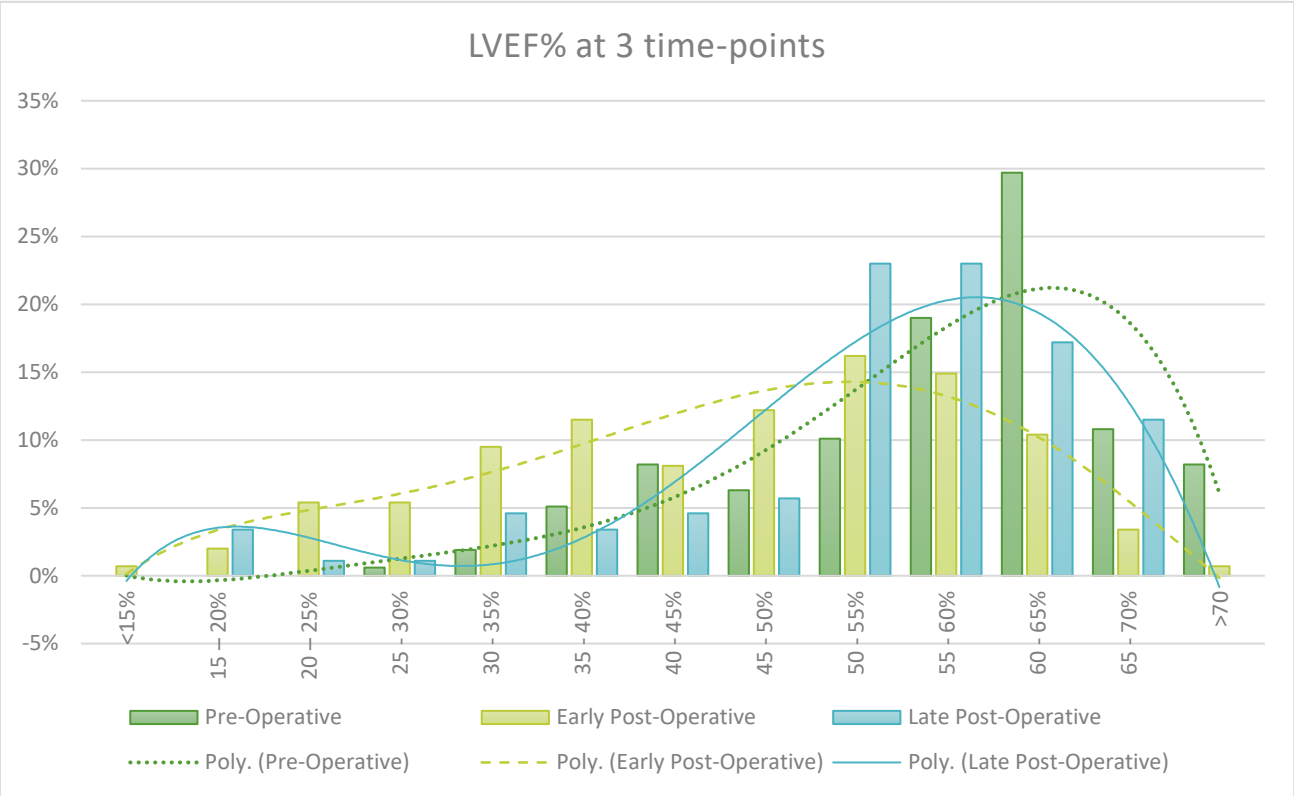

Figure 5: Changes in echo measured left ventricular function (LVEF) at 3 time points

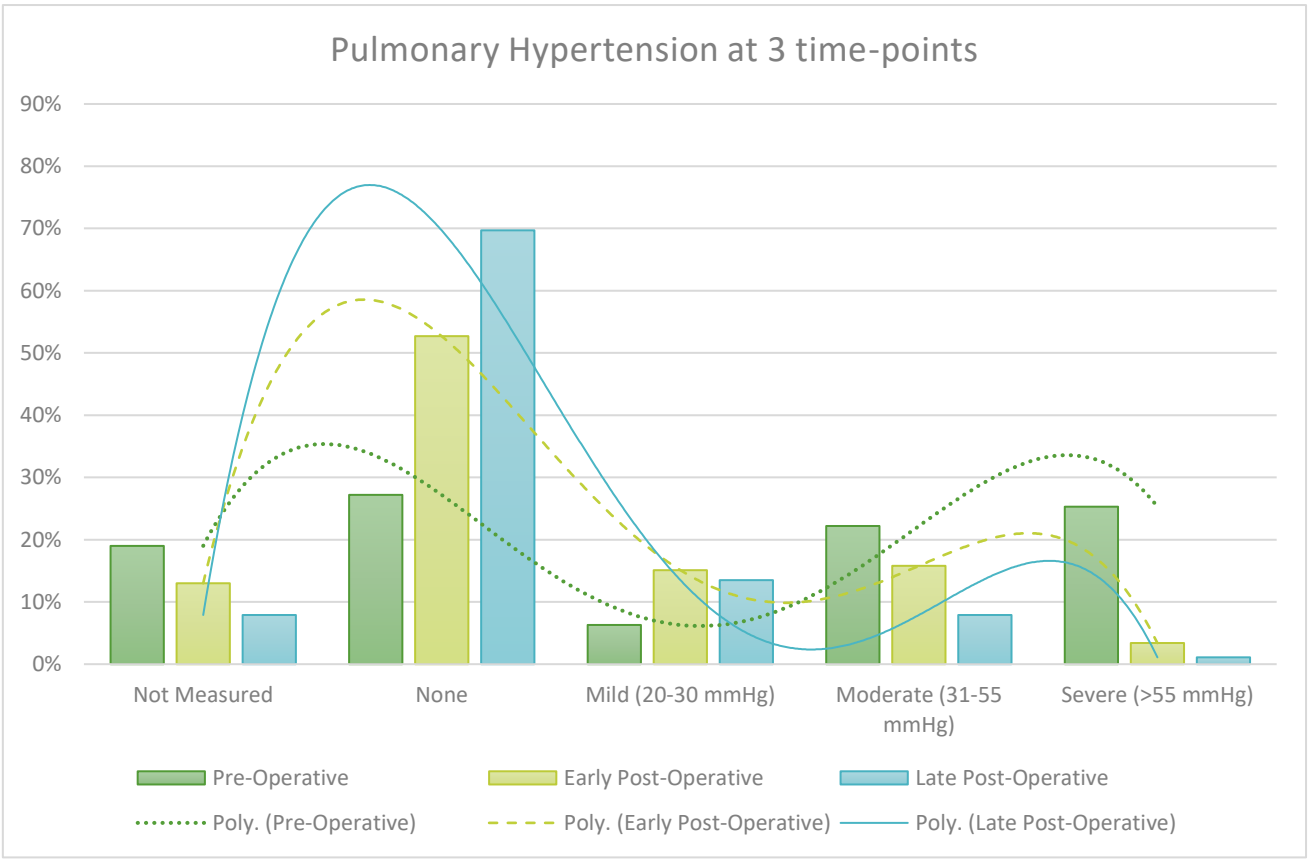

Figure 6: Changes in echo measured pulmonary hypertension (PHT) at 3 time points

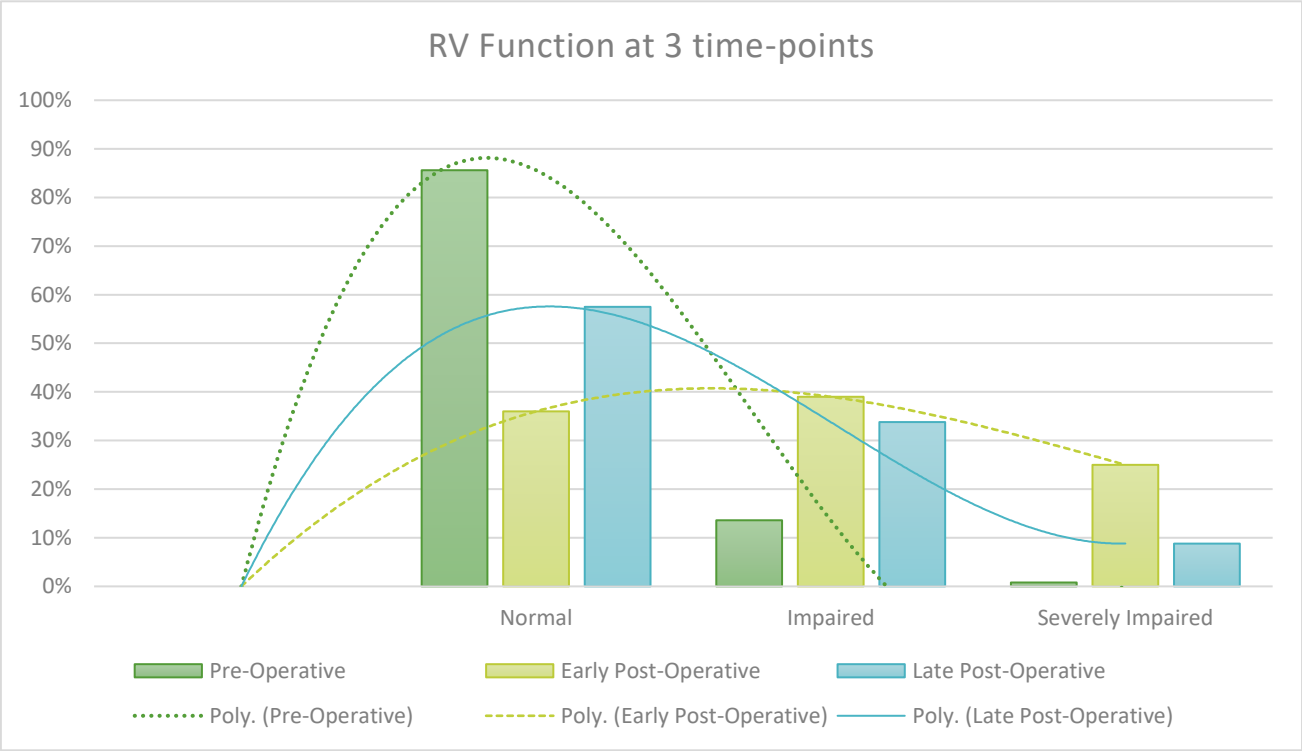

Figure 7:Changes in echo measured right ventricular function (RVEF) at 3 time points

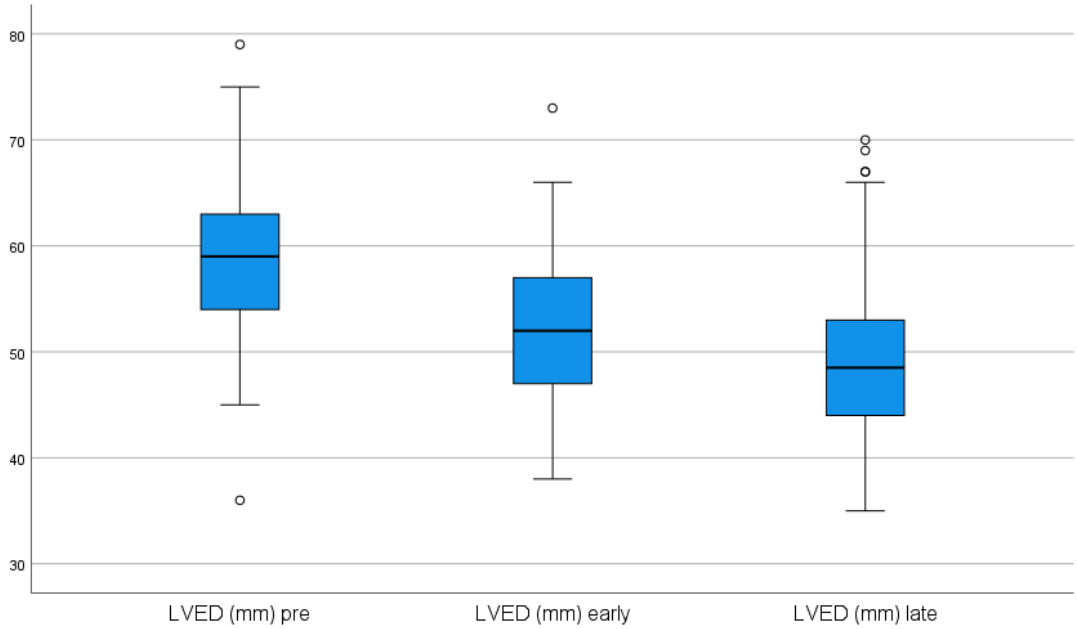

Figure 8: Changes in echo measured left ventricular end diastolic volume (LVEd) at 3 time points

9. Annexures

9.1. ETHICAL APPROVAL & PROGRESS REPORTS

9.2. DATA COLLECTION SHEET

9.3. AUTHORIZATION TO ACCESS CLINICAL HOSPITAL RECORDS

Approved with Stipulations

New Application

18/09/2018

Project ID: 6387

HREC Reference #: S18/06/123

Title: Review of Surgical Outcomes in Infective Endocarditis

Dear Dr Riaan Nel

The **New Application** received on 31/07/2018 13:24 was reviewed by members of the **Health Research Ethics Committee** via Minimal Risk Review procedures on 18/09/2018 and was approved with stipulations.

Please note the following information about your approved research protocol**:**

Protocol Approval Period: **18 September 2018 - 17 September 2019**.

The stipulations of your ethics approval are as follows:

1. Ensure that correct terminology WRT Divisions and Departments at Stellenbosch University FMHS is used eg. Cardiology is a Division and not a Department. Please also be consistent with this terminology in the protocol
2. There are minor spelling errors in the document that must be corrected

Please remember to use your project ID 6387 and ethics reference number S18/06/123 on any documents or correspondence with the HREC concerning your research protocol.

Translation of the consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note that this decision will be ratified at the next HREC full committee meeting. HREC reserves the right to suspend approval and to request changes or clarifications from applicants. The coordinator will notify the applicant (and if applicable, the supervisor) of the changes or suspension within 1 day of receiving the notice of suspension from HREC. HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note you can submit your progress report through the online ethics application process, available at: https://apply.ethics.sun.ac.za and the application should be submitted to the Committee before the year has expired. Please see Forms and Instructions on our HREC website for guidance on how to submit a progress report.

The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website (www.sun.ac.za/healthresearchethics)

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mrs. Ashleen Fortuin

Health Research Ethics Committee 1 (HREC1)

National Health Research Ethics Council (NHREC) Registration Number:

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)•IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects;the South African Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

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Approval Letter
Progress Report

21/10/2019

Project ID: 6387

Ethics Reference No: S18/06/123

Project Title: Review of Surgical Outcomes in Infective Endocarditis

Dear Dr Riaan Nel

We refer to your request for an extension/annual renewal of ethics approval received 19/09/2019 14:11 .

The Health Research Ethics Committee reviewed and approved the annual progress report through an expedited review process.

The approval of this project is extended for a further year.

Approval date: 21 October 2019

Expiry date: 20 October 2020

Kindly be reminded to submit progress reports two (2) months before expiry date.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your Project Id 6387 and ethics reference number S18/06/123 on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mrs. Melody Shana

Coordinator

Health Research Ethics Committee 1

National Health Research Ethics Council (NHREC) Registration Number:
REC-130408-012 (HREC1)•REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)•IRB0005239 (HREC2)

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Approval Letter
Progress Report

23/06/2021

Project ID: 6387

Ethics Reference No: S18/06/123

Project Title: Review of Surgical Outcomes in Infective Endocarditis

Dear Dr RF Nel

We refer to your request for an extension/annual renewal of ethics approval received 24/05/2021.

The Health Research Ethics Committee reviewed and approved the annual progress report through an expedited review process.

The approval of this project is extended for a further year.

Approval date: 23 June 2021

Expiry date: 22 June 2022

Kindly be reminded to submit progress reports two (2) months before expiry date.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your Project Id 6387 and ethics reference number S18/06/123 on any documents or correspondence with the HREC concerning your research protocol.

Please note that for studies involving the use of questionnaires, the final copy should be uploaded on Infonetica.

Yours sincerely,

Melody E Shana
Coordinator: Health Research Ethics Committee 1

National Health Research Ethics Council (NHREC) Registration Number:
REC-130408-012 (HREC1)•REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)•IRB0005239 (HREC2)

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Surgical outcome of infective endocarditis at Tygerberg Hospital from 2010-2019: A retrospective review

DATA CAPTURING SHEET

Unique Study Identifier

Demographics

	Folder Number		
*	Age (years)		
*	Gender		M / F

Co-Morbidities

	Hypertension		Y / N / Unknown
*	Diabetes Mellitus		Oral Meds Only / + Insulin / N /Unknown
	HIV		Y / N / Unknown
	CD4	=	
	VL	=	
	ARV's		*Y/N/Newly initiated*
	Smoking		Y / N / Stopped >6m / Unknown
	IV Drug use		Y / N / Stopped >6m / Unknown
*	Previous Cardiac Event >90 days		>90 Days / <90 Days / N / Unknown
*	Previous Cardiac Surgery		Y / N
	Previous Proven Infective Endocarditis		Y / N
	Prosthetic valve in-situ		Y / N
	if Yes		*Mechanical / Bioprothetic*
*	Extra-Cardiac Arteriopathy		Y / N
*	Poor Mobility		Y / N
*	Chronic Lung Disease		Y / N
*	NYHA Class		I / II / III / IV
*	Class IV Angina		Y / N

Time Frames

Date of Admission (to primary hospital) YYYY/MM/DD		
Date of Diagnosis		
Date of Surgery		
Date of Discharge		
Total number of days from Diagnosis to Surgery		
Total number of days from Admission to D/C		

Medical Intervention

Antibiotic Therapy Regime	1	Cephazoline (Kefzol)
(More than one to be selected)	2	Cloxacillin
	3	Gentamycin
	4	Ampicillin
	5	Clindamycin
	6	Co-Amoxiclav
	7	Ertapenem
	8	Meropenem
	9	Vancomycin
	10	Azoles
	11	Other (Specify)
Duration of Ab treatment prior to surgery (Days)		
Duration of Ab treatment after surgery (Days)		

Special Investigations

Blood culture Organism		
Blood Culture Sensitivities		
Valve Culture/PCR Organism		
Valve Culture/PCR Sensitivities		
LAB parametres (Prior to Surgery) WCC= CRP= HB=		

Echo : Pre-operative

*	LVEF (%)	
	LVED (cm)	
	LVES (cm)	
	MS (0-4) None / Trace / Mild / Mod / Severe	
	MR (0-4) None / Trace / Mild / Mod / Severe	
	AS (0-4) None / Trace / Mild / Mod / Severe	
	AR (0-4) None / Trace / Mild / Mod / Severe	
	TR (0-4) None / Trace / Mild / Mod / Severe	
	Mitral Valve Gradient (Max & Mean) mmHg	/
	Aortic Valve Gradient (Max & Mean) mmHg	/
	RV Function Normal / Impaired / Severely impaired	
	Pulmonary Hypertension No / Mild (20-30) / Mod (31-55) / Severe (>55)	
	Rheumatic	Y / N
	Myxomatous	Y / N
	Vegetations visualized	Y / N

Echo: Early post operative (Prior to D/C)

Paravalvular Leak	Y / N
Re-operation for Paravalvular Leak	Y / N
Pericardial effusion	Y / N
LVEF (%)	
LVED (cm)	
LVES (cm)	
MR (0-4) None / Trace / Mild / Mod / Severe	
AR (0-4) None / Trace / Mild / Mod / Severe	
TR (0-4) None / Trace / Mild / Mod / Severe	
Mitral Valve Gradient (Max & Mean) mmHg	/
Aortic Valve Gradient (Max & Mean) mmHg	/
RV Function Normal / Impaired / Severely impaired	
Pulmonary Hypertension No / Mild (20-30) / Mod (31-55) / Severe (>55)	

Echo: Late post operative (As outpatient))

Paravalvular Leak	Y / N
Re-operation for Paravalvular Leak	Y / N
Pericardial effusion	Y / N
LVEF (%)	
LVED (cm)	
LVES (cm)	
MR (0-4) None / Trace / Mild / Mod / Severe	
AR (0-4) None / Trace / Mild / Mod / Severe	
TR (0-4) None / Trace / Mild / Mod / Severe	
Mitral Valve Gradient (Max & Mean) mmHg	
Aortic Valve Gradient (Max & Mean) mmHg	
RV Function Normal / Impaired / Severely impaired	
Pulmonary Hypertension No / Mild (20-30) / Mod (31-55) / Severe (>55)	

	Surgical Intervention		
	INDICATION FOR SURGERY	1	Acute Severe AR / MR with signs of cardiac failure
		2	Large Vegetations (> 10mm)
		3	Embolic event during first 2/52 of Antibiotic Therapy
		4	Ongoing Sepsis
		5	HF unresponsive to medical management
		6	Paravalvular Extension
		7	Other
*	Operation performed (Primary)	1	Mitral valve repair only
	(Tricuspid & Pulmonary valve procedures ignored)	2	Mitral valve replacement only
		3	Aortic valve repair only
		4	Aortic valve replacement only
		5	Mitral & Aortic valve repair
		6	Mitral valve repair and Aortic valve replacement
		7	Mitral valve replacement and Aotic valve repair
		8	Mitral & Aortic valve replacement
*	Other (secondary) procedures performed	1	CABG
		2	Tricuspid valve annuloplasty
		3	Pericardial Patch for aortic root repair
		4	Vein Patch for valve leaflet repair
		5	Aortic Root replacement (Bental/Supra-coronary Graft)
		6	Other (Specify)
*	Thoracic Aorta Surgery		Y / N
	MITRAL PROSTHESIS Size (mm)		
	Prosthesis type	1	Mechanical Valve
		2	Bioprosthetic Valve
		3	Annuloplasty Ring
	AORTIC PROSTHESIS Size (mm)		
	Prosthesis type	1	Mechanical Valve
		2	Bioprosthetic Valve
		3	Mechanical Valve + Aortic Graft
		4	Bioprosthetic Valve + Aortic Graft
		5	Bioroot (Freestyle)
	Cardiopulmonary Bypass Time (minutes)		
	Aortic Crossclamp Time (minutes)		
	Intra-Aortic Balloon Pump placed		Y / N
	Primary Surgeon (unique anonomous identifier)		
	Notable Intra-operative Complications		Y / N
	Specify	=	

	Clinical Operative Status		
*	Urgency	1	Stable
		2	Urgent
		3	Emergency
		4	Salvage
*	Critical Pre-operative State		Y/N
	Infective Endocarditis Diagnosis		Confirmed / Supected

	Major Organ Dysfunction Peri-operatively		
	Cardiac Failure		Y / N
	Inotropic Support Required Pre-operatively		Y / N
	Respiratory Failure requiring Pre-operative intubation		Y / N
	Renal Creatinine >150		Y / N
	Creatinine Pre-Operative		
*	Creat Clearance (ml/h)		
	*EUROSCORE II (Calculated Parametres required = *)*		

	Early Outcomes		
	Significant post op Bleeding (>500ml/24h)		Y / N
	Units Transfused (Number)		
	Re-operation for bleeding		Y / N
	Re-operation for Pericardial Effusion		Y / N
	30 day Mortality		Y / N
	Evidence of peripheral embolic phenomenon		Y / N
	Evidence of CVA / TIA		Y / N
	Pneumonia		Y / N
	New onset AF post surgery		Y / N
	Pacemaker required post-operatively		Y / N
	Wound complications		Y / N
	Renal Impairment (Acute - fully resolved prior to DC)		Y / N
	Renal Impairment (Chronic)		Y / N

	Late Outcomes		
	Recurrence of Infective Endocarditis		Y / N
	Repeat valve surgery required		Y / N
	Functional status: NYHA		I / II / III / IV
	Last Follow-up Date (DD/MM/YYYY)		
	Period of follow-up post operatively (MM/YY)		
	Late mortality		Y/N/Unknown
	Repeat Hospital Admission for related problem in 6 months		Y / N

	Final outcome		
	DC from CTS OPD / Lost to FU / Referral Cardiology		

Western Cape Government
Health

TYGERBERG HOSPITAL
REFERENCE:
Research Projects
ENQUIRIES: **Dr GG Marinus**
TELEPHONE:**021 938 5752**

Project ID: 6387

Ethics Reference: S18/06/123

TITLE: **Review of Surgical Outcomes in Infective Endocarditis**

Dear Dr Riaan Nel

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL.

1. In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

2. Researchers, in accessing Provincial health facilities, are expressing consent to provide the Department with an electronic copy of the final feedback within six months of completion of research. This can be submitted to the Provincial Research Co-Ordinator (Health.Research@westerncape.gov.za).

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Manager: Medical Services

DR GG MARINUS
MANAGER: MEDICAL SERVICES

Date: 8/06/2020