Profile, Presentation and Outcomes of Prosthetic Valve Endocarditis in a South African Tertiary Hospital: Insights From the Groote Schuur Hospital Infective Endocarditis Registry.

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Acknowledgements:

This work is dedicated to my friends and colleagues all-over the world, some of them no longer with us, for the monumental effort and dedication to serve fellow men. The past two or more years have been hard, marked by sacrifice and loss but we fight on.

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Declaration

This thesis/dissertation has been submitted to the Turnitin module and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor.

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Signed by candidate

11 January 2022

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1) Abstract

Profile, Presentation and Outcomes of Prosthetic Valve Endocarditis in a South African Tertiary Hospital: Insights From the Groote Schuur Hospital Infective Endocarditis Registry.

Background

Prosthetic valve infective endocarditis (PVE) is associated with high morbidity and mortality. The prevalence of PVE in local retrospective studies ranges between 13% and 16%. However, the clinical patient profile and outcomes remains unknown.

Methods

We performed a prospective observational study of patients presenting or referred to Groote Schuur Hospital with definitive or probably infective endocarditis based on the 2015 European Society of Cardiology (ESC) infective endocarditis diagnostic criteria. Consenting adult patients who met inclusion criteria were enrolled into the Groote Schuur Hospital Infective Endocarditis Registry which was approved by the University of Cape Town Human Research Ethics. The current study is an analysis of the cohort of patients who were enrolled between 01/01/2017 to 31/12/2019. The primary objective of this study was to define the clinical profile and outcomes of patients with PVE. The secondary objective aimed to compare the clinical profile and outcomes of PVE patients with those of native valve endocarditis patients (NVE).

Results

During the study period a total of 135 patients received a diagnosis of possible and definitive infective endocarditis (IE). Of these, 18 patients had PVE and 117 patients NVE. Therefore, PVE accounted for 13.3% of the overall IE cohort. PVE patients had mean (Standard Deviation) age of 39.1 (14.6) years, 56.6% were male. PVE occurred within one year of valve surgery in 50% and the Duke's modified diagnostic criteria for definitive IE was met in 94.4% of the PVE cohort. Prosthetic valves in the aortic position were affected in isolation or in combination with prostheses in the mitral area in 66.7%. Further, tissue prosthetic valves were affected in 61.1% of the PVE cases. 55.6% of the PVE cases were health care associated. On transthoracic echocardiography, vegetations (61.1%), prosthetic valve regurgitation (44.4%) and abscess (22.2%) were discovered. Staphylococcus species and streptococcus species

accounted for 38.8% and 22.2% of PVE cases, respectively. 27.8% cases were blood culture negative. Valve surgery was performed in 38.7% of the PVE patients. 55.6% of the PVE patients demised during the index hospitalisation. The secondary analysis indicated that the PVE patients were sicker, with a higher frequency of septic shock and heart block than the NVE patients, 22.2% vs 7% p= 0.02 and 27.8% vs 12% p =0.04 respectively. In addition, in-hospital mortality was higher in PVE patients than NVE patients, 55.6% vs 31.6% p=0.04.

Conclusion

PVE is relatively uncommon in resource-limited settings and is associated with a high in-hospital mortality. Staphylococcus and streptococcus species are the leading microbiological causes of PVE. The selected PVE patients that receive surgical treatment for endocarditis demonstrate better in-hospital survival than those who do not receive surgical treatment. This finding not only reaffirms the importance of surgery as treatment option for IE but further demonstrate the importance of the Heart team in selecting appropriate surgical candidates.

2) Publication Ready Manuscript: Edited for South African Medical Journal (SAMJ)

Profile, Presentation and Outcomes of Prosthetic Valve Endocarditis in a South African Tertiary Hospital: Insights From the Groote Schuur Hospital Infective Endocarditis Registry.

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2.1 Background

Infective Endocarditis (IE) is relatively infrequent but is associated with a high mortality and morbidity[1]. Infective Endocarditis related in-hospital mortality rate is reportedly as high as 22% and the 5 year mortality is up 45%[2-4]. The mortality rate has remained stable despite advances in health care. For example, the infective endocarditis associated global age standardised mortality rate in 2015 was 1.3 per 100 000 versus 1.4 per 100 000 in 2005[5]. In low- and middle-income countries (LMIC), IE tends to affect young patients with a high background prevalence of rheumatic valvular heart disease[6, 7] and the observed IE related age standardised mortality rate of 1.7 per 100 000 is higher than global figures [8].

Prosthetic Valve Infective Endocarditis (PVE) is the most lethal form of IE, with an in hospital mortality ranging between 20% and 40%[9-13]. One of the reasons may be related to the difficulty in making a definitive diagnoses of PVE, a challenging exercise, particularly in the setting of mechanical prosthetic valves[14, 15]. Indeed, the Dukes Criteria has a sensitivity of only 62% for PVE and the use of positron emission tomography with computed tomography (PET/CT) or Duke's Criteria plus PET/CT increase the sensitivity to 84% and 91% respectively[16]. This is important because at least 1% to 6% of patients with prosthetic valves will suffer from PVE[17]. In contemporary studies from the Europe and the United States, PVE accounts for up 30% of IE cases and the incidence is increasing [18, 19].

There is limited prospective data on the approximate proportion of PVE relative to the burden of infective endocarditis admissions in South African Hospitals. There is also scant information on the patient profile and PVE-related outcomes. Two retrospective hospital reviews from South Africa suggested that between 13.3%to 17%[6, 7] of IE admissions had PVE. However, none of these studies provided details on patient treatment and PVE-related morbidity and mortality which remain unknown. The primary objective of this study was to define the clinical profile and outcomes of patients with PVE. The secondary objective aimed to compare the clinical profile and outcomes of PVE patients with those of native valve endocarditis patients (NVE).

2.2 Methods

The Groote Schuur Hospital Infective Endocarditis registry is a prospective observational study of patients presenting or referred to Groote Schuur Hospital with definitive or probably infective endocarditis based on the 2015 European Society of Cardiology (ESC) infective endocarditis diagnostic criteria[14]. Consenting adult patients who met inclusion criteria were enrolled into the Groote Schuur Hospital Infective Endocarditis Registry which was approved by the University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee (HREC REF NO: R037/2017). The current study is an analysis of the cohort of patients who were enrolled between 01/01/2017 to 31/12/2019 (HREC REF NO: 406/2020).

2.2.1 Patient selection and data collection

Adult (>18 years of age) patients with possible or definitive infective endocarditis were included in the study. After informed consent, demographic data, clinical presentation, past medical history and past surgical history, data on recent hospitalisation, dental procedures, endoscopies (upper gastrointestinal tract and lower gastrointestinal tract) were collected. Further, data on clinical findings, electrocardiograms, microbiological findings, echocardiographic findings, use of other imaging techniques (Computed Tomography scan, and Magnetic Resonance Imaging), medical therapy, complications (embolic event, infectious, and haemodynamic complications), indications for surgery, and in-hospital mortality was collected. Data was extracted from source documents and captured onto

standardised electronic case report forms on Research Electronic Data Capture (REDCap), a secure online database hosted by the University of Cape Town.

2.2.2 Definitions

Early prosthetic infective endocarditis was defined as infective endocarditis occurring within one year of cardiac valve surgery and late prosthetic infective endocarditis is defined as infective endocarditis occurring after one year on cardiac valve surgery[14].

Health care associated PVE was defined as the development of Infective Endocarditis symptoms or the presence of a positive blood culture at the time of hospital admission or within 48 hours in a patient who fulfilled any of the following criteria: (1) Use Intravenous antibiotics at home, received specialised nursing care within 30 days of the onset of symptoms or positive blood culture; (2) Attended hospital or haemodialysis clinic or received intravenous chemotherapy within 30 days of the onset of symptoms or positive blood culture; (3) Hospitalisation for two days or more within three months of the onset of symptoms or positive blood culture; or (4) Nursing home or long-term care facility resident[11, 20].

2.2.3 Statistical analysis

Categorical variables are presented as number and percentages and continuous variables are presented as mean (± standard deviation) when normally distributed and mean (interquartile range) when skewed. Pearson's chi-square or Fisher's exact tests were used compare categorical variables and the independent sample T test was used to compare continuous variables between patients with prosthetic valve infective endocarditis and patients with native valve infective endocarditis. Kaplan Meier and the Log Rank tests were used to assess the cumulative survival difference, p value of less than 0.05 represent a statistically significant difference. Statistical analyses were performed using SPSS Statistics for Macintosh version 24.0 (IBM, USA).

2.3 Results

After the exclusion of 19 patients with Cardiac Implantable Electronic Device (CIED) related infection, 135 patients with possible and definitive IE were included in the study (figure 1). Eighteen patients had PVE (13.3%) and 117 patients had NVE (86.7%). The baseline

characteristics and demographics details of the overall patient population are presented in table 1. The patients with PVE had a mean (SD) age of 39.1(14.6) years, and 56.6% were male. Duke's definitive PVE diagnostic criteria was met in 94.4% and Duke's possible PVE criteria in 5.6%. PVE occurred within one year of valve replacement surgery (early PVE) in 50%. Isolated aortic valve PVE was present in 33.3%, a combination of aortic and mitral valve PVE was present in another 33.3%, isolated pulmonary valve PVE was present in 16.7% and isolated mitral valve PVE was present in 11.1% (Figure 2). Therefore, the aortic valve was involved in 66.7% cases of PVE. Tissue PVE account for 61.1% of cases and mechanical PVE accounted for 38.9%. A history of previous IE was present in 27.8% of PVE cases and health care associated IE in 55.6%. Eight (44.4%) of the PVE patients had a background history of rheumatic heart disease. A transthoracic echocardiogram (TTE) was performed in 94.1% of the PVE cases. Vegetations were documented in 61.1%, prosthetic valve regurgitation in 44.4% and abscesses in 22.2%. A transoesophageal echo (TOE) was performed in only 2 (11.1%)PVE cases, vegetations and prosthetic regurgitation were documented in both cases and an abscess in one.

Staphylococcus species were responsible for a 38.9% of PVE cases and *streptococcus* species for 22.2% (Table 2). Five (27.8%) of the PVE cases were culture negative, all them received antibiotics prior to blood culture sampling, none of these patients had serum serological tests done and one patient had positive tissue polymerase chain reaction for *Aggregatibacter aphrophilus*. The leading complications in PVE were heart failure (50%) , acute kidney injury (50%), atrioventricular block (28.7%), aortic root abscesses (27.8%), and septic shock (22.2%), (Table 3). After a "heart team" decision , redo valve surgery was performed in 38.7%. The indications for offering surgery and withholding surgery of PVE are depicted in figure 3. The mean (SD) duration of hospital stay was 28.6 (24.4) days and the in-hospital mortality for patient with PVE was 55.6%.

The results of the secondary analysis indicated that patients with PVE were more likely to have a past history of infective endocarditis, and more likely to have health care associated infective endocarditis than NVE patients. Further, in patients with PVE a transthoracic echocardiogram was less likely to pick up vegetation, valve regurgitation or abscesses (Table 1). Although there was no statistically significant difference in the frequency of *Staphylococcus aureus* as the cause of IE between PVE and NVE, coagulase negative staphylococcus (CoNS) was significantly more frequent in PVE than NVE (Table 2). Septic shock and AV block were

more common in PVE cases than NVE cases, 22.2% vs 7%, p = 0.02 and 27.8% vs 12% ,p = 0.04 respectively. The decision to perform cardiac surgery for infective endocarditis or to continue with only medical therapy was a "heart team" decision. In figure 3A and 3B, the indication for cardiac surgery in patients who underwent surgery and the indications to withhold surgery are presented. For the overall Infective Endocarditis patient population patients who underwent cardiac surgery had a better cumulative survival than those who did not(Log Rank p= 0.002) (figure 4B). For PVE patient population there was a trend towards better cumulative survival for those who underwent cardiac surgery but this was not statistically significant (Log Rank p=0.08) (Figure 5). The in-hospital mortality rate for PVE patients was significantly higher than for NVE patients, 55.6% vs 31.6%; p= 0.04 (log rank 0.022) (Figure 4A).

2.4 Discussion

In this prospective observational study we investigated the patient profile , presentation and outcomes of PVE in a resource-limited setting with a high background valvular Rheumatic Heart Disease (RHD). The major findings of this study are: 1) The PVE patients are young, 2) have a high background history of RHD, congenital heart disease and previous IE, 3) a majority of PVE cases are health care associated, 4) staphylococcus species are responsible for a majority of PVE cases, however large number of case are culture negative, 5) septic shock are and AV block are common complications for PVE, 6) PVE associated in-hospital mortality is very high, and 7) in comparison with NVE, PVE patients were sicker, with more complications and higher in-hospital mortality.

Considering previous regional reports, the prevalence of PVE in the Western Cape province is stable over time. For example, in a prospective observational study from 1997 to 2000 Koegelenberg and colleagues reported a PVE prevalence of 16.6%[7] and in a retrospective study from 2009 to 2016 de Villiers et al[6]. reported a PVE prevalence of 13.3%. This prevalence is lower than reported in the latest European Society of Cardiology-EURObservational Research Programme (ESC-EORP) European Endocarditis registry, were PVE accounted for 30.1% of IE cases[18]. For the first time in our context, we report that 25.9% of all IE cases and 55.6% of PVE cases are health care associated. The prevalence rate for health care associated PVE of 55.6% in this study is markedly higher than previously

reported for PVE[11]. For example, in a prospective multiple center observational study from 2000 to 2005 , Wang et al. reported a prevalence of health care associated PVE of 36.5%[11]. Infective endocarditis, both PVE and NVE in this study affected a young patient population, this finding is in corroboration with previous reports from this region(6)(7). This cohort is at least 20 years younger than the ESC-EORP European Endocarditis registry cohort with a mean (SD) age of 59.2(18.0)years[18], and the Olmos et al. cohort with a mean age of 63.8 (17.5) years[19]. This is mainly due to a high prevalence of RHD which frequently require surgical treatment at a younger age[21], an important cause of valvular heart disease in our population.

Similarly to the ESC-EORP European Endocarditis registry, where staphylococcus were the leading microorganism detected on blood culture (41%) in PVE [18], in the current study Staphylococcus species remained the leading causative microorganism for PVE accounting for 38.9%. . However, in the current study Coagulase negative staphylococcus (33.3%) was cultured more frequently than *staphylococcus aureus* (5.6%). There was no specific mention of Coagulase negative staphylococcus in the ESC-EORP European Endocarditis registry[18]. This result must be interpreted with caution as the current study has a high rate of culture negative endocarditis, a small sample of PVE and non-adherence to the European Society of Cardiology (ESC) algorithm for culture negative infective endocarditis[14]. The ESC-EORP European Endocarditis registry had lower rate of culture negative PVE[18]. In addition, our finding are in contrast to the findings by Wang et al. were *staphylococcus aureus* was responsible for 23.0% and Coagulase negative staphylococcus for 16.9% of PVE cases, and only 11.2% culture negative endocarditis[11]. All the blood culture negative PVE cases in our study had documented receipt of antibiotics prior to the collection of blood cultures.

PVE is a challenging diagnoses to make, there are important technical challenges with the use of the readily available transthoracic echocardiography (TTE) in the context of prosthetic valves[15]. As noted in the current study, there is a significant difference in the recognition of characteristic endocarditis abnormalities like vegetations, regurgitation and abscesses with TTE between patients with PVE and NVE. Contemporary imaging modalities like 18F-Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET) with Computed Tomography (CT) have been shown to improve the diagnostic accuracy of the modified Duke's Criteria. For example, in a prospective study of 92 patients with suspected PVE, the incorporation of PET/CT finding to the Duke's criteria improved the sensitivity, specificity, positive predictive value and negative predictive value from 52%, 94.7%, 92.9% and 59.7%

for Duke's Criteria to 92.1%, 89.5%, 92% and 87.9% for the combination of the Duke's criteria and PET/CT respectively[16]. PET/CT was used in 25% of PVE patients in the ESC-EORP European Endocarditis registry(10). There were important variation in the utilisation of the form imaging in the ESC-EORP European Endocarditis registry, more frequently used in Western Europe (33.9%) but less so in South America (2.1%), North America (0%) and Asia (8.5%)[18]. Our institution currently does not have access to ^{18}F-FDG PET/CT. Therefore, there may have been cases in which the PVE diagnoses was missed due to the absence of this diagnostic modality.

PVE is associated with a high in-hospital mortality that ranges between 20% and 40%[11, 14, 18]. Older age (>65 years), Health care associated infections, PVE due to *staphylococcus aureus*, persistent bacteraemia, and the presence of complications like heart failure, intracranial abscesses, stroke and renal impairment have been identified as poor prognostic markers[11, 14]. The combination of surgery and medical therapy in appropriately selected patients is the treatment strategy of choice for PVE[14, 22]. In the recent the ESC-EORP European Endocarditis registry only 46% of PVE patients received surgical management[18]. In the current study surgery was performed in 38.7% of PVE cases. In our cohort, after a heart team discussion surgery was withheld due to the presence of poor prognostic markers, high surgical risk or good response to medical therapy. For the overall patient population, the cumulative survival was significantly worse in patients who did not get surgery for IE and there was a trend towards a lower cumulative survival but not statistically significant for PVE patients who did not get surgery. The heart team discussion is particularly important in resource limited-settings where there is a high demand and competition for cardiothoracic surgical intervention to facilitate allocation of this resource to candidates who are more likely to benefit.

The single center nature of this study is an important limitation, these results are not necessarily generalisable. Further, there was a small number of PVE cases. However, we believe that this is a true reflection of the prevalence of PVE in the Western Cape Province of South Africa for two reasons: Firstly, at least two studies, two decades apart report a PVE prevalence of less than 17%[6, 7]. Secondly, our centre is the referral center for all secondary and regional hospitals in the Coastal and Western regions of the Cape serving approximately 50% by geography and population. Furthermore provincial referral pathways stipulate that all patients with Prosthetic valves who are unwell are referred to tertiary centres where the investigative and complete treatment capacity for PVE reside. In this study we only report an overall PVE

associated in-hospital mortality of 55.6%. Long-term follow up has been severely compromised by the coronavirus disease 2019 (COVID 19) pandemic. We therefore do not have long-term follow up outcomes.

2.5 Conclusion

PVE is relatively uncommon in resource-limited settings and is associated with a high in-hospital mortality. Staphylococcus and streptococcus species are the leading microbiological causes of PVE. However a large proportion of cases remain culture negative. Making the PVE diagnoses is difficult, the advent of newer diagnostic modality that improve the diagnostic yield are not yet available in resource constraint centres like ours. The selected PVE patients that receive surgical treatment for endocarditis demonstrate better in-hospital survival than those who do not receive surgical treatment. This finding not only reaffirms the importance of surgery as treatment option for IE but further demonstrate the importance of the Heart team in selecting appropriate surgical candidates.

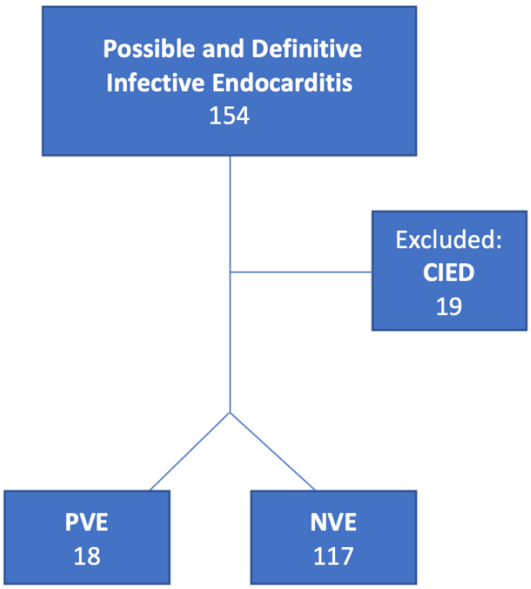

Figure 1: Study inclusion flow chart.

Abbreviation: CIED = Cardiac Implantable Electronic Device, NVE= Native Valve Endocarditis, PVE= Prosthetic Valve Endocarditis

Table 1: Patient Demographic and baseline characteristics.

Characteristic	Overall Infective Endocarditis Population (no 135)	Prosthetic Valve Endocarditis (no 18)	Native Valve Infective Endocarditis (n=117)	P value
Age (years), , mean (SD)	41.0 (16.2)	39.1 (14.6)	41.2 (16.5)	0.57
Male, no (%)	87 (64.4)	10 (55.6)	77 (65.8)	0.40
Hypertension, no (%)	39 (28.9)	2 (11.1)	37 (31.6)	0.07
Diabetes Mellitus, no (%)	13 (9.6)	-	13 (11.2)	
Current Intravenous Drug Use, no (%)	29 (21.5)	1 (5.6)	28 (23.9)	0.17
Current Alcohol use history, no (%)	56 (41.5)	3 (16.7)	53 (45.3)	0.015
Current Smoker, no (%)	55 (40.7)	2 (11.1)	53 (45.3)	0.014
Degenerative Heart Disease, no (%)	8 (5.9)	2 (11.1)	6 (5.1)	0.32
Chronic Kidney Disease, no (%)	9 (6.7)	1 (5.6)	8 (6.8)	0.83
Haemodialysis/ peritoneal dialysis, no (%)	3 (2.2)	-	3 (2.6)	
Chronic Liver Disease , no (%)	4 (3.0)	-	4 (3.4)	0.43
HIV infection , no (%)	22 (16.3)	2 (11.1)	20 (17.1)	0.70
Rheumatic Heart Disease, no (%)	37 (34.8)	8 (44.4)	39 (33.3)	0.36
Congenital Heart Disease, no (%)	19 (14.1)	4 (22.2)	15 (12.8)	0.289
Previous Infective Endocarditis , no (%)	14 (10.4)	5 (27.8)	9 (7.7)	0.009
Health Care Associated IE, no (%)	35 (25.9)	8 (55.6)	27 (23.1)	0.05
Duke's Definitive Infective Endocarditis, no (%)	128 (94.8)	17 (94.4)	111 (94.9)	0.94
Duke's Possible Infective Endocarditis , no (%)	7 (5.2)	1 (5.6)	6 (5.1)	0.94
Transoesophageal Echo Performed , no (%)	17 (12.6)	2 (11.1)	15 (12.8)	0.84
TOE Findings				
Vegetation , no (%)	15(11.1)	2 (11.1)	13 (11.1)	1.00
New Regurgitation , no (%)	17 (12.6)	2 (11.1)	15 (12.8)	0.84
Abscess , no (%)	4 (3.0)	1 (5.6)	3 (2.6)	0.49
Transthoracic Echo Performed, no (%)	133 (98.5)	17 (94.1)	116 (99.1)	0.124
TTE Findings				
Vegetation , no (%)	121 (89.6)	11 (61.1)	110 (94.0)	<0.001
New Regurgitation, no (%)	116 (85.6)	8 (44.4)	108 (92.3)	<0.001
Abscess , no (%)	11 (8.1)	4 (22.2)	7 (6.0)	0.019
Number of days in hospital, mean (SD)	32.8 (25.0)	28.6 (24.4)	33.5 (25.1)	0.44
In hospital Death , no (%)	47 (34.8)	10 (55.6)	37 (31.6)	0.04

Abbreviations: HIV, Human Immunodeficiency Virus; TOE, Transoesophageal echocardiography; TTE, Transthoracic echocardiography.

Table 2: Microbiological Characteristics.

Microorganism	Overall Infective Endocarditis Population (no 135)	Prosthetic Valve Endocarditis (no 18)	Native Valve Infective Endocarditis (no 117)	P value
Staphylococcus , no (%)	**37 (27.4)**	**7 (38.9)**	**31 (26.3)**	0.241
Staphylococcus aureus, no (%)	28 (20.7)	1 (5.6)	27 (22.9)	0.09
MSSA, no (%)	27 (20.0)	1 (5.6)	26(22.0)	
MRSA, no (%)	1 (0.7)	0	1 (0.8)	
Coagulase Negative , no (%)	9 (6.7)	6 (33.3)	3 (2.6)	<0.001
Streptococcus , no (%)	**37 (27.4)**	**4 (22.2)**	**33 (28.0)**	0.596
Viridins , no (%)	32 (23.7)	4 (22.2)	28 (23.7)	
Agalactiae , no (%)	3 (2.2)	0	3 (2.5)	
Gallolyticus , no (%)	1 (0.7)	0	1 (0.8)	
Porcinus , no (%)	1 (0.7)	0	1 (0.8)	
Enterococcus , no (%)	**8 (5.9)**	**1 (5.6)**	**7 (5.9)**	0.94
Feacium , no (%)	1 (0.7)	0	1(0.8)	
Feaculis , no (%)	7 (5.2)	1 (5.6)	6 (5.1)	
HACEK species , no (%)	2 (1.5)	-	2 (1.7)	
Corynebacterium , no (%)	1 (0.7)	0	1 (0.8)	
Serratia marcescens , no (%)	1 (0.7)	0	1 (0.8)	
Gemella bergeri, no (%)	1 (0.7)	1 (5.6)	-	
Culture Negative , no (%)	**48 (35.6)**	**5 (27.8)**	**43 (36.4)**	0.46

Abbreviations: MSSA, Methicillin Sensitive *Staphylococcus Aureus*; MRSA, Methicillin Resistant *Staphylococcus Aureus*; HACEK, Haemophilus species, Aggregatibacter species, Cardiobacterium Homonis, Eikinella corrodens and Kengella species.

Table 3: Comparison of Infective Endocarditis related complications in patients PVE and NVE.

Complications	Prosthetic Valve Endocarditis (no 18)	Native Valve Infective Endocarditis (no 117)	P value
Surgery , no (%)	7 (38.7)	52 (44.4)	0.66
Heart Failure , no (%)	9 (50)	59 (50.4)	1.00
Atrioventricular (AV) Block, no (%)	5 (27.8)	12 (10.3)	0.04
Mycotic Aneurysm , no (%)	2 (11.1)	5 (4.3)	0.22
Limb Ischemia, no (%)	1 (5.6)	8 (6.8)	0.84
Septic Shock, no (%)	4 (22.2)	7 (6.0)	0.02
Disseminated Intravascular Coagulation (DIC) , no (%)	2 (11.1)	8 (6.8)	0.52
Acute Kidney Injury, no (%)	9 (50)	47 (40.2)	0.43
Ischemic Hepatitis, no (%)	3 (16.7)	8 (6.8)	0.16
Root Abscess , no (%)	5 (27.8)	16 (13.7)	0.12
Ischemic Stroke , no (%)	3 (16.7)	22 (18.8)	0.83

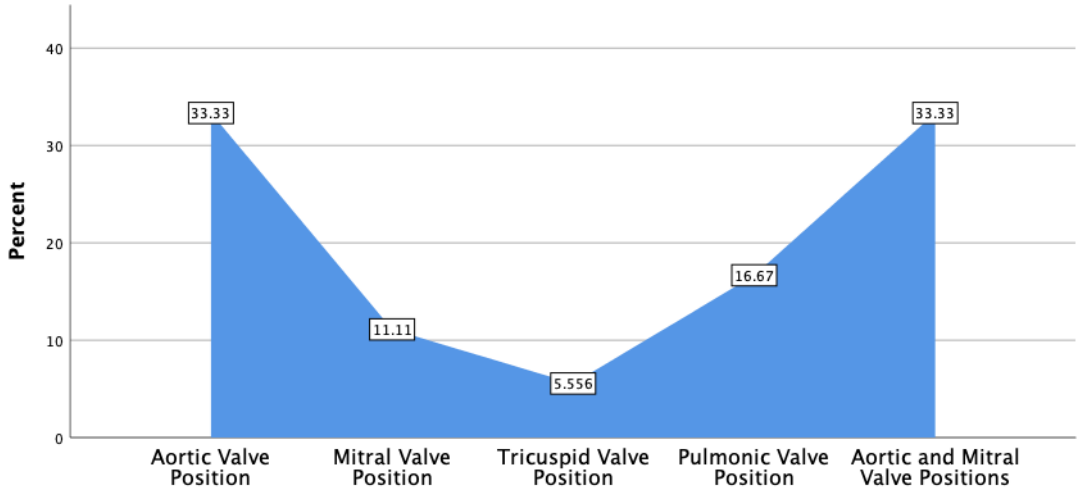

Figure 2: Area chart depicting the positions of the infected prosthetic valves.

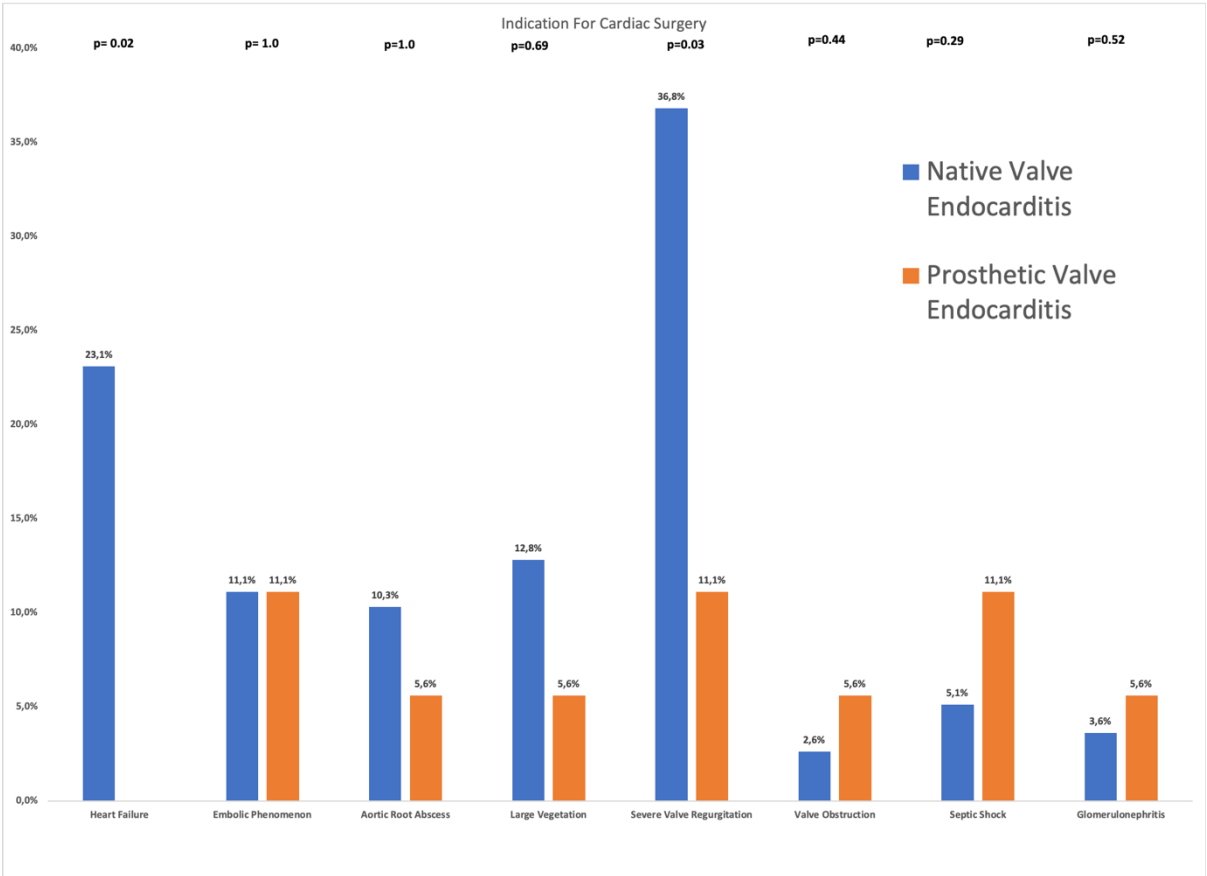

Figure 3A: Bar chart depicting the indication for surgery in patients who underwent surgery.

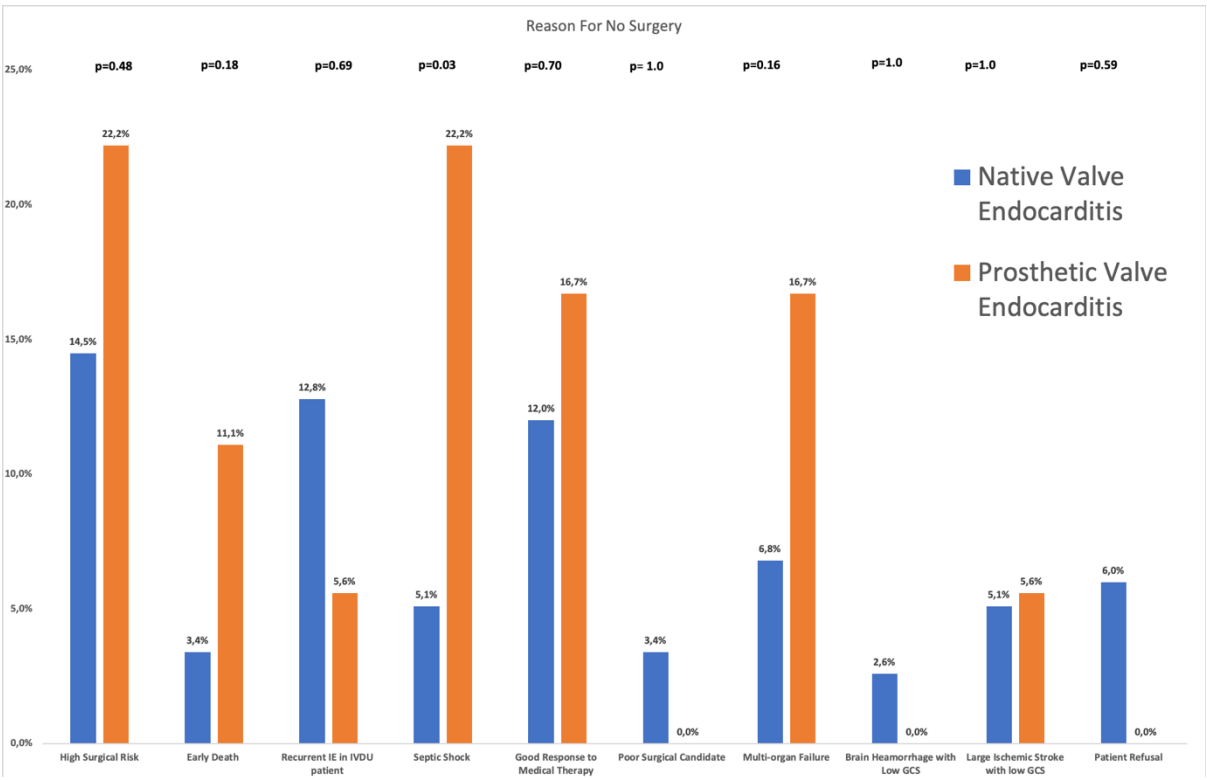

Figure 4 B: Bar chart depicting the indications for withholding surgery.

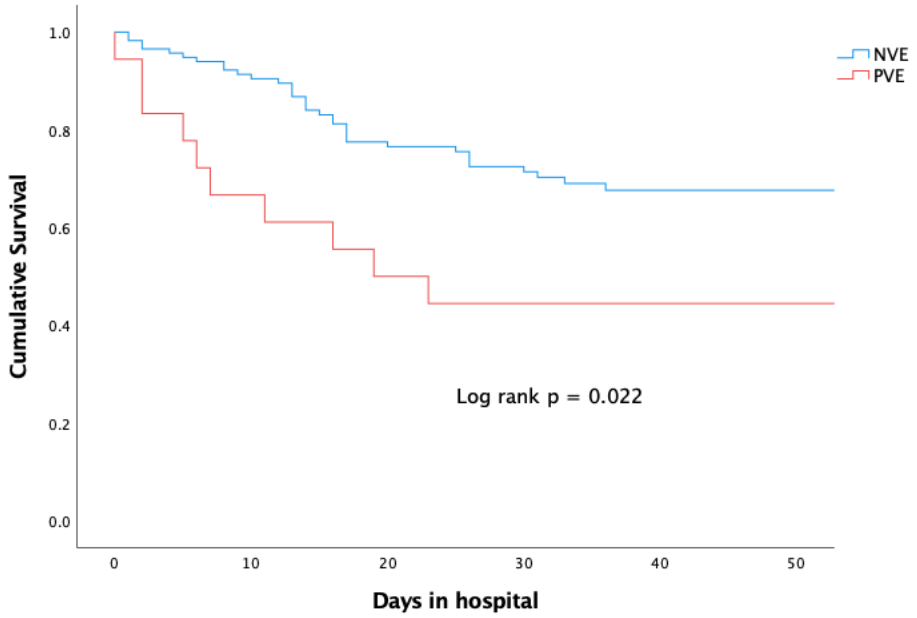

Figure 4A: Kaplan Meier curves depicting cumulative in-hospital survival for patients with Prosthetic Valve Endocarditis and Native Valve Endocarditis.

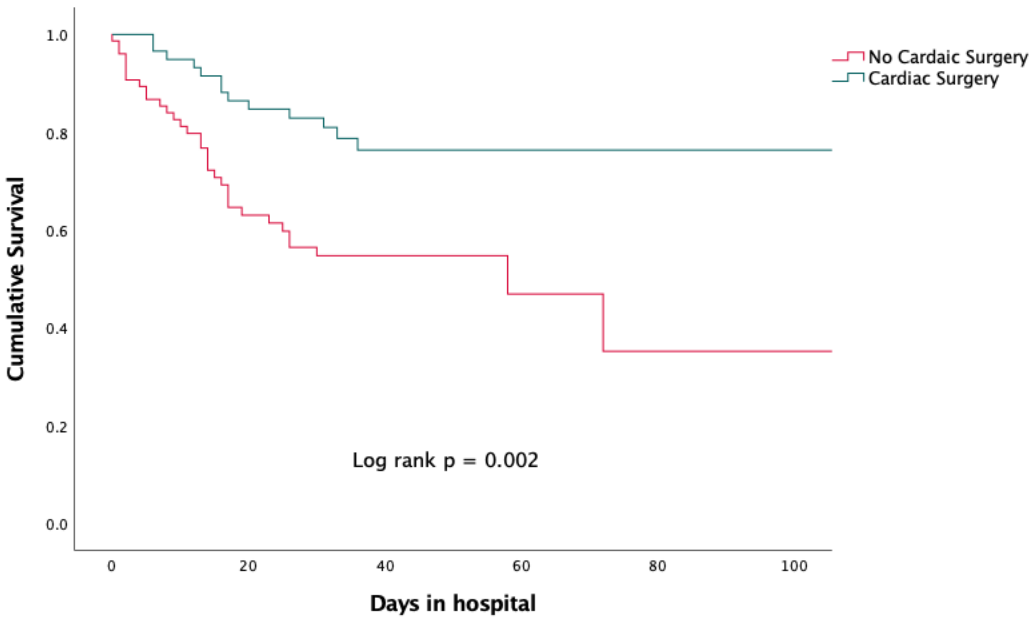

Figure 5B: Kaplan Meier for the overall patient population depicting cumulative survival for patients who underwent or did not undergo cardiac surgery for Infective Endocarditis.

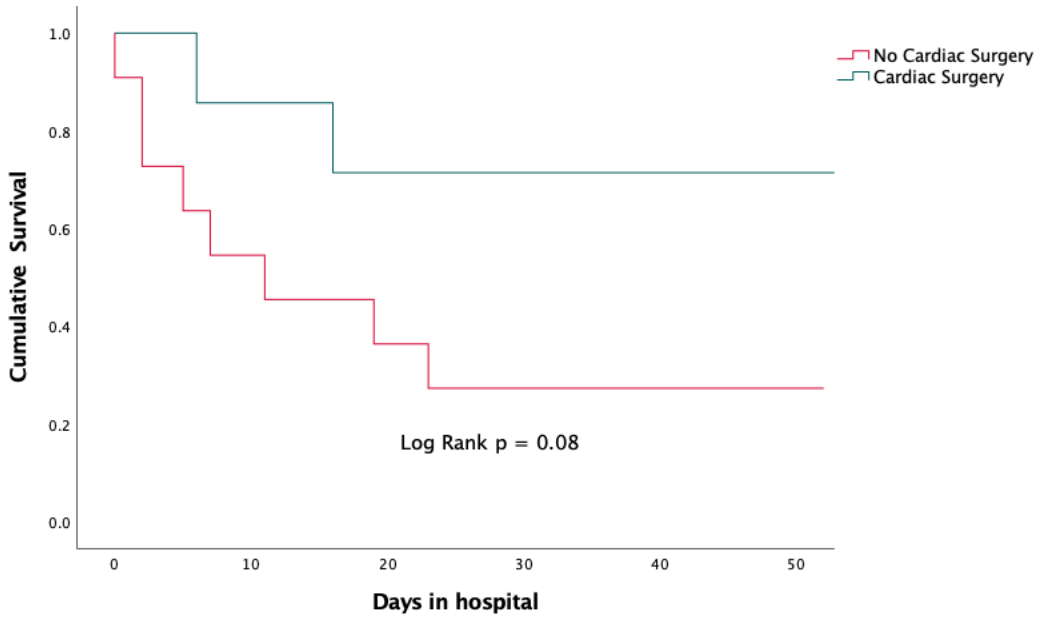

Figure 6: Kaplan Meier for PVE patient population depicting cumulative survival for with PVE who underwent or did not undergo surgery for Infective Endocarditis.

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2.7 Appendices

2.7.1 Groote Schuur Infective Endocarditis Registry ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

16 August 2017

HREC REF NO: R037/2017

Prof M Ntsekhe
Cardiology
Medicine

Dear Prof Ntsekhe

Project Title: GROOTE SCHUUR HOSPITAL INFECTIVE ENDOCARDITIS REGISTRY

Thank you for your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC has **approved** the registration of your registry

Please Note: All research, including that undertaken for a master's or doctoral degree, using registered databases, registries and repositories, requires submission as a new study. It requires an application form (FHS013) and a protocol which has undergone departmental review. The study will receive its own HREC REF number which will be linked to the main database or repository.

The registration of this registry is valid until **30 August 2020.**

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

2.7.2 Ethics approval for access to the Groote Schuur Infective Endocarditis Registry for the current study.

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

21 July 2020

HREC REF: 406/2020

Prof M Ntsekhe
Division of Cardiology
E-16 NGSH
Email: mpiko.ntsekhe@uct.ac.za
Student: Mkoko25@yahoo.com

Dear Prof Ntsekhe

PROJECT TITLE: PREVALENCE AND OUTCOMES OF PROSTHETIC VALVE ENDOCARDITIS IN A SOUTH AFRICAN TERTIARY HOSPITAL: INSIGHTS FROM THE GROOTE SCHUUR HOSPITAL INFECTIVE ENDOCARDITIS REGISTRY-MPHIL CANDIDATE-PHILASANDE MKOKO

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 July 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Philasande Mkoko will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.