INFECTIVE ENDOCARDITIS

Long term outcome and EuroSCORE II validation in native valve surgery for active infective endocarditis in a South African cohort

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INTRODUCTION

Infective endocarditis was initially described in the early 16th century and only methodically reviewed after the 19th century when Osler made his contribution to the Royal College of Physicians in 1885.[1]

There has been little change in the mortality from infective endocarditis, despite the diagnostic and therapeutic advances made in the last 25 years. The current in-hospital mortality rate for patients with IE is 15% - 20%, with 1-year mortality approaching 40%. The morbidity associated with infective endocarditis includes: valvular incompetence, embolisation, cerebrovascular accidents and congestive heart failure which have influenced the surgical approaches to a great extent.[2]

Infective endocarditis is a significant problem in sub-Saharan Africa and is related to a high prevalence of rheumatic heart disease among the young indigent population. Africa has the highest burden of rheumatic heart disease contributing 17% - 43% of all heart disease.[3] The incidence of infective endocarditis in patients with rheumatic heart disease has not been clearly documented in literature.

The microbiological profile of infective endocarditis is dependent on patient risk factors and exposure. Coagulase Negative Staphylococci and Staphylococcus Aureus endocarditis have

ABSTRACT

Objectives: To evaluate the major risk factors for adverse short and long term outcomes in patients with active native valve infective endocarditis needing cardiac surgery and to validate the EuroSCORE II in our cohort of patients.

Methods: We retrospectively studied 149 patients who underwent native valve surgery for infective endocarditis in June 2000 - May 2011 at our referral centre. Ninety-six patients met the inclusion criteria for the study: 29 aortic valve replacements (AVR), 27 mitral valve replacements (MVR), 28 aortic/mitral (double) valve replacements (DVR) and 12 mitral valve repairs (MV Repair).

Results: Mechanical valves were implanted in 68 patients (70.8%), bioprosthetic valves in 16 (16.7%) and mitral annuloplasty rings in 12 (12.5%). The Cox proportional hazard model showed that the most important risk factors for early 30-day mortality were: critical pre-operative state, emergency surgery, EuroSCORE II >12%, low cardiac output state (LCOS), HIV positive status, preoperative embolic episodes, vegetation size >1cm and postoperative ventilation >24 hours. The EuroSCORE II underestimated early mortality for the entire cohort. The discriminatory ability was evaluated with the receiver operating characteristic (ROC) curve with an area under the curve of 0.796. The discriminatory ability in the subgroup analysis showed that the AUROC curve was poorer for MVR (0.696), 0.837 for DVR and better for AVR group (0.92).

Conclusions: The EuroSCORE II underestimated mortality in the highest risk groups and overestimated mortality in the lowest risk groups. The discriminatory ability and model fit were evaluated to be good and a EuroSCORE II >12% predicted a significantly higher early and medium term mortality.

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been shown to be associated with hospital acquired infections and streptococcal endocarditis with community acquired infections.[4] Early mortality has been associated with staphylococcal infections, vegetation size, embolic load and, most importantly, the immediate preoperative pathophysiologic state.[5] Studies have shown that there is little difference in the recurrence of infective endocarditis when comparing mechanical and bioprosthetic implants.[6] However, few studies have been done to show the role of mitral valve repair in patients with active

native valve endocarditis. The few studies show that the bene-fit of repair over replacement for non-infective mitral valve disease also holds true for active native mitral valve endo-carditis. In one study, mitral valve repair in active endocarditis has been shown to have a good overall survival and low reoperation rate, but few studies compare this with outcomes for mitral repair in fully treated endocarditis or mitral replace-ment in active endocarditis.[7]

In a cohort of 92 patients with active endocarditis from Tygerberg hospital, a fellow tertiary referral hospital in the Western Cape of South Africa, the majority of patients were young males with underlying rheumatic heart disease (76%). Intravenous drug use, HIV infection and degenerative heart disease were rare and 77% of patients were culture negative.[8] In a review of infective endocarditis with negative blood cultures, prevalence rates of culture negativity ranged from 10% - 30% and even higher in some poorly developed countries due to prior antibiotic use, fastidious organisms and fungal infections. This poses a problem in the choice of antibiotic regimens for these patients. Negative blood cultures were shown to be associated with a higher rate of major adverse cardiac events postoperatively.[9]

HIV infection in Africa, unlike that in the developed world, has been a major health problem in the last 20 years. HIV infection has widely affected the general population, unlike in most industrialised nations where HIV has been commonly asso-ciated with intravenous drug use and social instability. Studies have shown that the risk of infective endocarditis does not increase with HIV infection and marantic endocarditis has not been described in Africa.[10]

The therapeutic strategy for managing infective endocarditis lies in the identification of micro organisms and their antibiotic sensitivities with directed antibiotic treatment, echocardio-graphic assessment and early surgical intervention. Despite this approach, infective endocarditis has a high mortality and risk of major adverse cardiac events.[11] In all patients with infective endocarditis, approximately 50% require surgical interven-tion[12] and the predicted mortality can be assessed with a number of scoring systems. The European system for cardiac operative risk evaluation (EuroSCORE) was introduced in 1999, and in 2011 the updated EuroSCORE II was introduced with better prediction of operative risk.[13] The applicability and validity of this scoring model in the South African setting has not been evaluated.

The aim of our study is to determine the role of various risk factors in early and late mortality and in major adverse cardiac and cerebrovascular events (MACCE), as well as to validate the EuroSCORE II in predicting mortality in our cohort of patients undergoing surgical treatment for active native valve endocarditis.

MATERIALS AND METHODS

Study population and data collection
We retrospectively studied all patients (n=149) who had undergone cardiac surgery for infective endocarditis in June 2000 - May 2011 at our tertiary referral centre. The indications for surgery were elective in 73 (48.3%), urgent in 51 (34.2%) and emergent in 25 patients (16.8%). Native valve endocarditis was present in 123 patients (82.6%) and prosthetic valve endo-carditis in 26 patients (17.3%). The patients' clinical charac-teristics, i.e. demographics, microbiology, predisposing cardiac conditions, symptoms, previous cardiac surgery, echocardio-graphic parameters and operative techniques were recorded and postoperative morbidity and mortality were followed-up, analysed as per Table I. Active native valve endocarditis was seen in 100 patients (67.1%) and 29 had AVR, 27 had MVR, 28 had DVR, 12 had MV repair, 3 had isolated tricuspid valve surgery and one had aortic valve repair. Ninety-six patients met the inclusion criteria for the study and were thus included in the analysis. Exclusion factors were: fully treated endocarditis (n=23), prosthetic endocarditis (n=26), isolated tricuspid valve surgery (n=3) and primary aortic valve repair (n=1).

Bacteriologic characteristics
The microbiological etiology of endocarditis in our patients is shown in Table I. The most frequent organisms isolated were Staphylococci in 28 patients, comprising approximately equal numbers of Staphylococcus Aureus and Coagulase-negative Staphylococci. Streptococci were isolated from 29 patients. Various gram-negative organisms, including some from the HACEK group, occurred in 15% and no organisms were seen, cultured or identified from blood, valve tissue, serology or PCR in 26% of patients. Preoperative blood cultures were negative in 47% of patients.

Predisposing conditions
The predisposing cardiac conditions associated with infective endocarditis are reported in Table I. The most common under-lying cardiac condition was rheumatic heart disease in 84% of patients, which was either known on history preoperatively, identified intra-operatively or detected histologically. Rarer predispositions included: degenerative disease in 2%, calcific degeneration in 2%, congenital heart disease in 2%, previous infective endocarditis on normal valves in 1%, mitral prolapse in 1%, and pacemaker device infection in 1%. There was no known underlying heart disease in 7% of patients. It has also been noted that the prevalence of HIV infection in the entire surgical cohort of patients was 8%. The mean age of our cohort was 35.2 ± 14 years and 69% were males. The prevalence of

TABLE I: Demographic and clinical characteristics of patients with active left sided native valve infective endocarditis for the entire cohort and treatment sub-groups.

	Combined n=96	AVR n=29	MVR n=27	DVR n=28	MVRep n=12
Demographics					
Age (years)	35.2 ± 14.0	42.8 ± 13.6	29.7 ± 11.0	33.5 ± 11.8	33.7 ± 18.6
Male	66 (69%)	24 (83%)	14 (52%)	21 (75%)	7 (58%)
BMI	20.9 ± 4.5	22.1±4.5	20.9 ± 5.6	20.2 ± 3.9	20.1 ± 2.9
LVEF (%)	61.5 ± 11.9	57.1 ± 11.5	64.6 ± 13.1	62.5 ± 11.4	62.8 ± 9.5
LVEDD (mm)	6.0 ± 1.0	6.4 ± 0.8	5.9 ± 0.9	6.1 ± 1.1	5.3 ± 0.8
NYHA III-IV	55 (57%)	19 (66%)	17 (57%)	16 (57%)	3 (25%)
Comorbidities					
HIV positive	8 (8%)	2 (7%)	4 (15%)	2 (7%)	0
Dialysis	6 (6%)	3 (10%)	0	3 (11%)	0
Stroke	14 (15%)	1 (3%)	7 (26%)	3 (11%)	3 (25%)
Atrial fibrillation	10 (10%)	1 (3%)	4 (15%)	5 (18%)	0
Indications for surgery					
Vegetation size >1cm	43 (45%)	11 (38%)	14 (52%)	13 (46%)	5 (42%)
CCF	79 (82%)	27 (93%)	23 (85%)	19 (68%)	10 (83%)
Failed medical therapy	83 (87%)	24 (83%)	23 (85%)	27 (96%)	9 (75%)
Embolic phenomena	38 (40%)	8 (28%)	15 (56%)	12 (43%)	3 (25%)
Preoperative state					
Critical pre-op state	26 (27%)	8 (28%)	8 (30%)	9 (32%)	1 (8%)
Emergency	20 (21%)	6 (21%)	7 (26%)	6 (21%)	1 (8%)
Urgent	35 (36%)	14 (48%)	10 (37%)	10 (36%)	2 (17%)
Elective	39 (41%)	8 (28%)	10 (37%)	12 (43%)	9 (75%)
EuroSCORE II >12%	20 (21%)	4 (14%)	5 (19%)	10 (36%)	1 (8%)
Concomitant procedures					
Tricuspid Annuloplasty	13 (14%)	1 (3%)	3 (11%)	7 (25%)	2 (17%)
CABG	1 (1%)	0	0	1 (4%)	0
Prosthesis material					
Mechanical	68 (71%)	21 (72%)	23 (85%)	24 (86%)	0
Bioprosthesis	16 (17%)	8 (28%)	4 (15%)	4 (14%)	0
Pericardial patch	6 (6%)	3 (10%)	0	3 (11%)	0
Annuloplasty ring	12 (13%)	0	0	0	12 (100%)
Microbiologic profile					
Unidentified	26 (27%)	8 (28%)	5 (19%)	12 (43%)	1 (8%)
Staphylococci	26 (27%)	7 (24%)	11 (41%)	5 (18%)	3 (25%)
Streptococci	27 (28%)	4 (14%)	10 (38%)	8 (29%)	5 (42%)
Gram negative	17 (18%)	10 (34%)	1 (4%)	3 (11%)	3 (25%)

AVR = Aortic valve replacement, MVR = Mitral valve replacement, DVR = Double valve replacement, MV = Mitral valve, BMI = Body mass index,
LVEF = Left ventricular ejection fraction, LVEDD = Left ventricular end diastolic dimension, NYHA = New York Heart Association, HIV = Human immunodeficiency virus,
CCF = Congestive cardiac failure, EuroSCORE = European system for cardiac operative risk evaluation.

HIV infection in females was 20% and 3% in males but the rate was higher in those with a poorer socioeconomic status (33% vs. 11% respectively).

Preoperative characteristics and the EuroSCORE II

The preoperative characteristics are recorded in Table I. Operative risk was evaluated by the EuroSCORE II using the online calculator provided by the EuroSCORE study group.[13]

The patients were also assessed as being critically ill if they had the following: pulmonary oedema, mechanical ventilation, cardiogenic or septic shock or renal failure requiring dialysis. Emergency surgery was defined as occurring within 24 hours of presentation, urgent surgery defined between 24 - 48 hours of presentation and elective surgery thereafter. The variables included patient-related, cardiac-related and operation-related factors.

Operative characteristics and surgical techniques

All surgical procedures were performed via a median sternotomy on cardiopulmonary bypass with systemic cooling to 28 and 32 degrees Celsius in all cases. Myocardial protection was by antegrade cardioplegia with, or without, additional retrograde cold blood cardioplegia. Aortic valve exposure was through an oblique aortotomy and mitral valve exposure was either through the Waterstons groove or via a biatrial transseptal approach.

Gross pathological findings were leaflet destruction, vegetations, intracardiac abscesses and fistulae. The affected valves and surrounding structures were debrided off all macroscopically infected material after which repair or replacement was performed.

The types of prosthetic material implanted were: mechanical valves, bioprosthetic valves, annuloplasty rings and bovine pericardial patches for reconstruction of the aortic root. Concomitant procedures were: atrial fibrillation ablation (1%), coronary artery bypass surgery (1%) and tricuspid annuloplasty (13%).

Follow-up

The patients were traced through telephonic contact, email contact, friends and relatives, through their local clinic, prison system, local police and the South African National Health Laboratory Service (NHLS). Long term follow-up was completed in 98.6% of patients. Cause of death was determined through the records of forensic pathology examination, death certificates and clinical notes prior to death in those patients who had been in hospital. Out-of-hospital deaths were determined from feedback of patients' relatives, death certificates in the patients' folders and the South African Home Affairs death registry. In-hospital mortality and less than 90-day mortality was classified as early and >90-day mortality as late. For the purpose of evaluating the EuroSCORE II which predicts 30-day mortality, the early mortality category was further subdivided into ≤30-day mortality (Table III). In the reporting of death and MACCE, the guidelines for the reporting of mortality and morbidity after cardiac valve intervention were followed.[14]

The results of long term follow up were evaluated using: NYHA functional status, hospital readmissions, thromboembolic events, bleeding episodes, prosthetic endocarditis, arrhythmias and heart block, paravalvular leaks, reoperations and mortality. The dates of these events were determined and the time to events calculated from the time of operation. Categorical, or continuous, variables that were missing due to incomplete medical records were left blank in the data sheets and this was accounted for during analysis.

Statistical methods

In the analysis of the data, variables were systematically expressed with standard definitions. The continuous variables were presented as median (range) and mean ± standard deviation in the manuscript, where appropriate. Categorical variables were expressed as percentages. The Kaplan-Meier analysis was used to present actuarial survival estimates and freedom from major adverse valve related or cardiac events. The Cox proportional hazard regression model was used to evaluate hazard ratios, for both short and long term outcomes, after adjusting for confounding factors. The primary endpoints included in the study were: early 30-day mortality, early 90-day mortality and late mortality (>90 days). The secondary endpoints were: early MACCE and late MACCE. Significant hazard ratios at 95% confidence interval were identified and tabulated. A p-value of <0.05 was considered to be statistically significant.

The validity of the EuroSCORE II was evaluated by its goodness of fit and discriminatory capacity. The Hosmer-Lemeshow test assessed the goodness of fit by estimating a statistic from the difference between observed and expected values for mortality in 10 different risk groups. A p-value of >0.05 indicates that the EuroSCORE II fits the data well and thus accurately predicts mortality. The EuroSCORE II's ability to discriminate was assessed by its capacity to distinguish between patients who had died within 30 days from those who had not. The area under the receiver operating characteristic (AUROC) curve was used to evaluate the discriminatory power of the EuroSCORE II in our cohort of patients and the treatment sub-groups. The area under the curve ranges from 0.5 (no power) to 1.0 (absolute discriminatory ability). A cut point of predicted operative mortality, at which the highest specificity and sensitivity coincided, was determined for the entire cohort and confirmed by a maximal Youden's index. The entire cohort was divided into 2 groups, one above and the other equal to or below this cut point. The 2 groups were then compared with Kaplan Meier survival estimation and freedom from MACCE.

The entire cohort was also divided into DVR and non-DVR groups (single valve replacement and mitral valve repair) and their long term survival and freedom from MACCE were compared with Kaplan Meier curves.

RESULTS

Surgical procedure and study population

The preoperative demographic and clinical characteristics of the 96 included patients are summarised in Table I. Gross pathological findings were: vegetations in 76 patients (79%),

intra-cardiac abscess in 30 (31%), ventricular septal defect in 3 (3%) whilst all had various degrees of leaflet damage. Mechanical valves were most commonly implanted (70.8%) and pericardial patch reconstruction of the aortic root was only needed in 6 patients.

The cut point of the EuroSCORE II model was evaluated to be 12% at which the sensitivity and specificity were maximal (Youden's index), and 21% of the entire cohort of patients had a score >12%. At the 12% cut point, the sensitivity of the EuroSCORE II to predict 30-day operative mortality was 73%, specificity of 88% and the positive predictive value was 44%.

Aortic Valve Replacement (Table I)

Of those patients who had an AVR (n=29): the mean age was higher than the other sub-groups (42.8 ± 13.6 years) and the majority were males (86%). More than half the patients had a poor functional status (NYHA ≥III) and only 7% were HIV positive. Thirty eight percent of patients had vegetation >1cm and only 3% had a preoperative stroke. A pericardial patch repair of the debrided aortic root was undertaken in 10% of patients. The majority of patients (72%) had a mechanical valve implanted and 14% had a concomitant mitral annuloplasty ring. The mean EuroSCORE II was 5.8 ± 6.1% and 14% of patients had a EuroSCORE II >12%. Among the 8 patients who were in a critical preoperative state, 7 required an emergency operation. The commonest organisms isolated were staphylococci in 7 (24%) patients and streptococci in 4 (14%).

Mitral Valve Replacement (Table I)

In those patients who had MVR (n=27), the male to female ratio was not significantly different and more than half were in a poor functional status (NYHA ≥III) This group had the highest HIV positive rate (15%) and 52% had vegetations >1cm with a preoperative stroke rate of 26%. The majority of patients (85%) had a mechanical valve implanted. The mean EuroSCORE II was 5.39 ± 6.16 and 19% of patients had a score >12%. Among the 8 who were in a critical preoperative state, 7 required emergency surgery. The commonest organisms were again staphylococci (41%) and streptococci (38%).

Aortic and Mitral Valve Replacement-DVR (Table I)

In patients with active native endocarditis who had DVR (n=28): the majority were males (71%) and more than half had an NYHA class ≥III. Most of the patients (86%) had mechanical valves implanted and 11% required a pericardial patch to reconstruct the aortic root. The mean EuroSCORE II was 10.6 ± 9.4 and 11 patients (39%) had a EuroSCORE II >12%. There were 9 patients (32%) who were in a critical pre-operative

state, 6 of whom required emergency surgery (21%), and a further 10 (36%) patients needed urgent surgery.

Mitral Valve Repair (Table I)

A total of 12 patients had isolated mitral valve repair for active native mitral valve endocarditis. The male to female ratio was not significantly different and only 25% were in NYHA class ≥III. None of the patients were HIV positive. The preoperative stroke rate was 25% and 42% had vegetations >1cm. The pathology found at surgery included: leaflet perforation in 67%, chordal rupture and prolapse in 83%, and all were assessed to have annular dilation intraoperatively and required annuloplasty to reduce the annular diameter. All the patients received Colvin-Galloway future band annuloplasty prosthesis, chordi were replaced with Goretex in 83% and 1 patient required a pericardial patch augmentation of the posterior leaflet. The mean EuroSCORE II was 3.0 ± 3.9% and only 1 patient had a EuroSCORE II >12%. Only 1 patient required emergency surgery and was in a critical condition preoperatively. The commonest organism isolated was Streptococci in 42% of patients.

Postoperative morbidity and early mortality

Table II shows the early and late postoperative outcomes of the 96 patients with active native valve endocarditis. Two patients (2%) died immediate postoperatively and a total of 14 patients (15%) died early (90-day mortality). Postoperative inotropic support was needed in 73% of patients and 5% of patients developed low cardiac output state of which 1 patient required IABP support. Postoperatively, 6% of patients underwent re-exploration for tamponade or bleeding.

Table III shows that the commonest causes of in-hospital 30-day mortality were septic shock (4 patients) and stroke (4 patients), and the other 3 were due to cardiogenic shock (2 patients) and tamponade (1 patient). Two more patients died of septic shock within 60 days and 1 of cancer within 90 days. The patient with cardiogenic shock developed a low cardiac output state after AVR: transesophageal echocardiography showed possible valve dehiscence, after emergent relook and repair on bypass the patient died 2 hours postoperatively in ICU due to cardiogenic shock.

The intensive care duration of stay was more than 24 hours in all of patients who had valve replacement and survived in ICU, and the ventilation period was greater than 24 hours in more than two thirds in each subgroup. DVR had the highest early mortality with 7 patients (24%) dying within 90 days.

Of the 6 patients who had reoperations: 3 were early (1 for cardiogenic shock due to suspected prosthetic endocarditis but no paravalvular leak noted at surgery, 1 for definite prosthetic

TABLE II: The early and late postoperative characteristics of the entire cohort and the treatment sub-groups.

	Combined n=96	AVR n=29	MVR n=27	DVR n=28	MVRep n=12
Early postoperative course					
Inotropic support	70 (73%)	26 (90%)	21 (78%)	19 (68%)	4 (33%)
LCOS	5 (5%)	0	2 (7%)	3 (11%)	0
Dialysis	6 (6%)	3 (10%)	0	3 (11%)	0
Tamponade/Relook	6 (6%)	3 (10%)	0	3 (11%)	0
30-day mortality	11 (11%)	1 (3%)	4 (15%)	6 (21%)	0
90-day mortality	14 (15%)	2 (7%)	4 (15%)	7 (24%)	1 (8%)
ICU stay >24hrs	91 (95%)	29 (100%)	26 (96%)	26 (93%)	10 (83%)
Ventilation >24hrs	78 (81%)	26 (90%)	22 (81%)	20 (71%)	10 (83%)
Early MACE					
Bleeding	3 (3%)	1 (3%)	0	1 (4%)	1 (8%)
Clotted valve	1 (1%)	0	0	1 (4%)	0
Embolic stroke	4 (4%)	1 (3%)	3 (11%)	0	0
Heart block	3 (3%)	2 (7%)	1 (4%)	0	0
Haemorrhagic stroke	2 (2%)	0	0	2 (7%)	0
Paravalvular leak	1 (1%)	0	0	1 (4%)	0
Repaired valve failure	1 (1%)	0	0	0	1 (8%)
Reoperation					
Other valve failure	1 (1%)	0	1 (4%)	0	0
Paravalvular leak	2 (2%)	2 (7%)	0	0	0
Late MACE					
Clotted valve	3 (3%)	1 (3%)	0	2 (7%)	0
Embolic stroke/endocarditis	1 (1%)	0	0	1 (4%)	0
Embolic stroke	1 (1%)	0	0	1 (4%)	0
Haemorrhagic stroke	2 (2%)	1 (3%)	1 (4%)	0	0
Paravalvular leak	1 (1%)	1 (3%)	0	0	0
Repaired valve failure	1 (1%)	0	0	0	1 (8%)
Reoperation					
Embolic stroke/ endocarditis	2 (2%)	0	1 (4%)	1 (4%)	0
Embolic stroke/ bioprosthesis failed	1 (1%)	0	0	1 (4%)	0
>90-day all mortality	12 (13%)	3 (10%)	3 (11%)	6 (21%)	0
>90-day valve mortality	10 (10%)	2 (7%)	2 (7%)	6 (21%)	0
All-cause mortality	26 (27%)	5 (17%)	7 (26%)	13 (46%)	1 (8%)
Valve related mortality	23 (24%)	4 (14%)	6 (22%)	13 (46%)	0

AVR = Aortic valve replacement, MVR = Mitral valve replacement, DVR = Double valve replacement, MV = Mitral valve, LCOS = Low cardiac output state, ICU = Intensive care unit, MACE = Major adverse cardiac event.

endocarditis and the other iatrogenic native aortic regurgitation after MVR). The most common early MACCE after aortic valve replacement was heart block in 2 patients and reoperation in 2 other patients. Relook for tamponade/bleeding occurred in 3 patients post DVR (11%) and 3 patients post AVR (11%).

The Cox proportional hazards model (Table IV) shows that the most significant hazard ratios for early 30-day mortality were: critical preoperative state, emergent surgery, EuroSCORE II >12%, HIV positive, LCOS, preoperative embolic episodes, vegetations >1cm, NYHA ≥III, and ventilation >24 hours. After adjusting for age, sex, DVR, HIV positive status and NYHA class; LCOS, preoperative embolic episodes and ventilation >24 hours were the most significant hazard ratios. When we evaluated early 90-day mortality, the most significant hazard ratios after adjusting for these risk factors were: critical preoperative state, EuroSCORE II >12%, LCOS, preoperative embolic episodes, and ventilation >24 hours. The most

TABLE III: The causes of early and late mortality in the entire cohort of patients (n=96).

Mortality cause	≤30 day mortality n=11	≤90 day mortality n=14	>90 day mortality n=12
Valve related			
Cardiac tamponade	1	1	0
Cardiogenic shock	2	2	0
Clotted valve	0	0	3
Prosthetic valve endocarditis	0	0	1
Septic Shock	4	6	0
Embolic CVA	2	2	4
Haemorrhagic CVA	2	2	2
Non valve related			
Bowel Obstruction	0	0	1
Cancer	0	1	0
HIV related	0	0	1

CVA = Cerebrovascular accident, HIV = Human immunodeficiency virus.

significant adjusted hazard ratios for early MACCE (Table IV) were: critical preoperative state, EuroSCORE II >12%, LCOS, pre-op embolic episodes, pre-op dialysis and NYHA ≥III.

The EuroSCORE II had a Hosmer-Lemeshow statistic of 12.4 (p-value=0.13) and an AUROC of 0.796. When the discriminatory ability was evaluated within the subgroups, the AUROC curve was poorer for MVR (0.696), 0.837 for DVR, better for AVR (0.92) and not assessed for MV repair, as there were no early deaths (Table V). The EuroSCORE II underestimated mortality in the entire cohort as well as the subgroups, except in the AVR and MV repair groups, where the observed mortality was lower, or absent, respectively (Table V).

Long term outcome, reoperation and major adverse cardiac events

A total of 98% of the patients were followed-up completely and 2 patients were lost to follow-up at 62 and 64 months after

TABLE IV: Cox proportional hazard analysis: The statistically significant risk factors for early mortality (30 day), early MACCE, late mortality and late MACCE (>90 day) in the entire cohort of patients, adjusted for age, sex, NYHA, DVR and HIV status.

		N	Person-time	N events	Event Rate/1 000	Adj. HR (95% CI)
Variable for Early mortality 30 Day						
HIV positive	No	88	128 900	8	0.06	1.0 (ref)
	Yes	8	4 571	3	0.66	5.4 (1.4 - 20.7)
LCOS	No	91	133,400	6	0.05	1.0 (ref)
	Yes	5	42	5	119.00	36.4 (6.5 - 203.7)
Pre-op emboli	No	58	82,440	2	0.02	1.0 (ref)
	Yes	38	50,989	9	0.18	10.2 (1.8 - 58.0)
Ventilation >24 hours	No	76	115,900	4	0.03	1.0 (ref)
	Yes	17	16,577	5	0.30	6.9 (1.4 - 33.4)
Variable for Early MACCE°						
Critical Pre-op State	No	70	92,484	6	0.06	1.0 (ref)
	Yes	26	23,956	12	0.50	3.5 (1.2 - 10.1)
EuroSCORE II >12	No	70	94,238	6	0.06	1.0 (ref)
	Yes	26	22,202	12	0.54	4.4 (1.5 - 12.9)
LCOS	No	91	116,400	15	0.13	1.0 (ref)
	Yes	5	42	3	71.43	6.1 (1.5 - 24.6)
Pre-op emboli	No	58	77,493	7	0.09	1.0 (ref)
	Yes	38	38,947	11	0.28	3.1 (1.1 - 8.5)
Pre-op dialysis	No	90	115,900	13	0.11	1.0 (ref)
	Yes	6	531	5	9.42	5.0 (1.5 - 17.1)
NYHA ≥III	No	41	55,681	1	0.02	1.0 (ref)
	Yes	55	60,759	17	0.28	16.8 (2.2 - 128.3)
Variable for Late Mortality						
HIV	No	88	128,900	10	0.04	1.0 (ref)
	Yes	8	4571	2	0.11	6.6 (1.0 - 42.9)
DVR	No	68	106,300	6	0.06	1.0 (ref)
	Yes	28	27,147	6	0.22	8.1 (1.9 - 34.0)
Variable for Late MACCE						
DVR	No	68	104,900	6	0.06	1.0 (ref)
	Yes	28	27,147	6	0.22	6.0 (1.6 - 22.2)

MACCE = Major adverse cardiac and cerebrovascular events, NYHA = New York Heart Association, EuroSCORE = European system for cardiac operative risk evaluation, LCOS = Low cardiac output state, Pre-op = Preoperative, AF = Strial fibrillation, DVR = Double valve replacement.

TABLE V: Observed and predicted 30-day mortality of the combined and treatment sub-groups with the AUROC curve.

	Average Predicted 30-day mortality EuroSCORE II (%)	Observed 30-day mortality %	p-value	AUROC
AVR (n=29)	5.8	3.4	0.54	0.92
MVR (n=27)	5.4	14.8	0.03	0.696
DVR (n=28)	10.6	21.4	0.06	0.837
MV repair (n=12)	3	0	0.54	-
Combined (n=96)	6.6	11.5	0.06	0.796

AUROC = Area under receiver operating characteristic, AVR = Aortic valve replacement, MVR = Mitral valve replacement, DVR = Double valve replacement, MV repair = Mitral valve repair.

surgery. After excluding 90-day early mortality (14 patients), the median follow-up was 51 months and ranged from 7 - 140 months during which period 12 patients died. Kaplan-Meier survival analysis was used to estimate the actuarial survival at 5 years (77.6% ± 4.6%) and 10 years (52.6% ± 15.9%) for the entire cohort of 96 patients. All-cause mortality after 90 days was 13% and valve related mortality was 10%. The most common causes of >90 day valve related mortality were stroke (6%) and clotted valve (3%) and 1 patient died of prosthetic endocarditis (Table III). The 2 patients who died of non-valve related causes were due to HIV related infection in 1 (11 months) and bowel obstruction in the other (63 months).

The 3 late reoperations were for prosthetic endocarditis (2 patients at 59 and 100 months) and bioprosthetic mitral valve stenosis (1 patient at 58 months after DVR); and all 3 patients who had late reoperation died. Recurrence of endocarditis on the prosthetic valve occurred in 3 patients (3%) with 100% mortality and all were on mechanical valves (NS).

The Cox proportional hazards model (Table IV) showed that the most significant adjusted hazard ratios for late mortality were: female sex, HIV positive status and patients who had DVR; and for late MACCE were: DVR and the use of pericardial patch reconstruction of the aortic root.

Figure 1A, shows the Kaplan Meier survival analysis of patients with a EuroSCORE II >12% vs. ≤12%. The higher risk group had a significantly lower early to midterm survival and similar late survival when compared to the lower risk group (55.0 ± 11.1% vs. 94.7 ± 2.5% at 90 days; 55.0 ± 11.1% vs. 83.3 ± 4.7% at 5 years; and 45.8 ± 12.5 vs. 39.1 ± 27.8 at 10 years with p=0.0001).
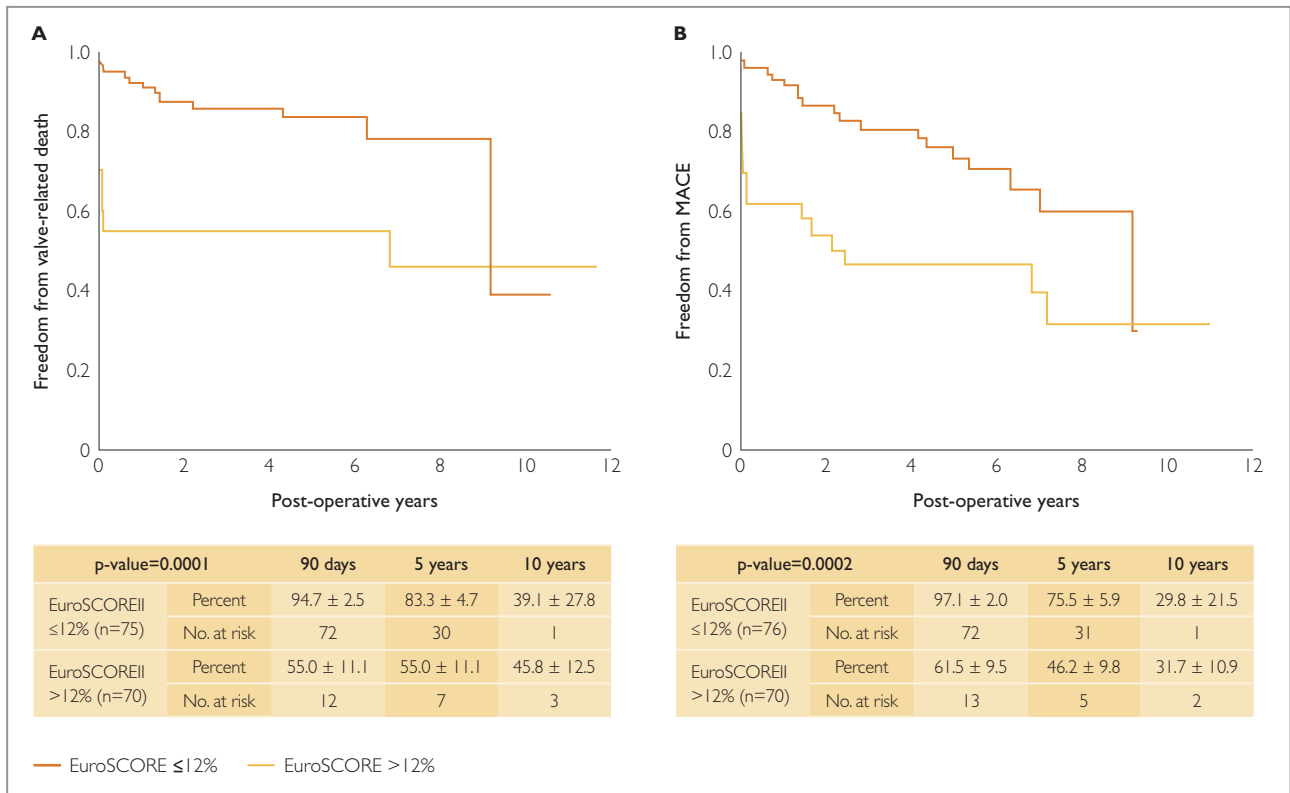
Actuarial survival estimates of freedom from valve related mortality determined for the 4 main treatment groups at 5 and 10 years (AVR was 84.9 ± 7.1% and 84.9 ± 7.1%; for MVR was 79.1 ± 8.6% and 39.6 ± 28.3%; for DVR was 59.3 ± 9.5%

and 19.8 ± 16.5%; and no valve related mortalities in the MV repairs). A comparison of the long term survival of DVR vs. the rest of the patients (non-DVR group) shows that the former group had a significantly higher mortality and lower freedom from MACCE (Figure 1B: p=0.0002 and p=0.007, respectively).
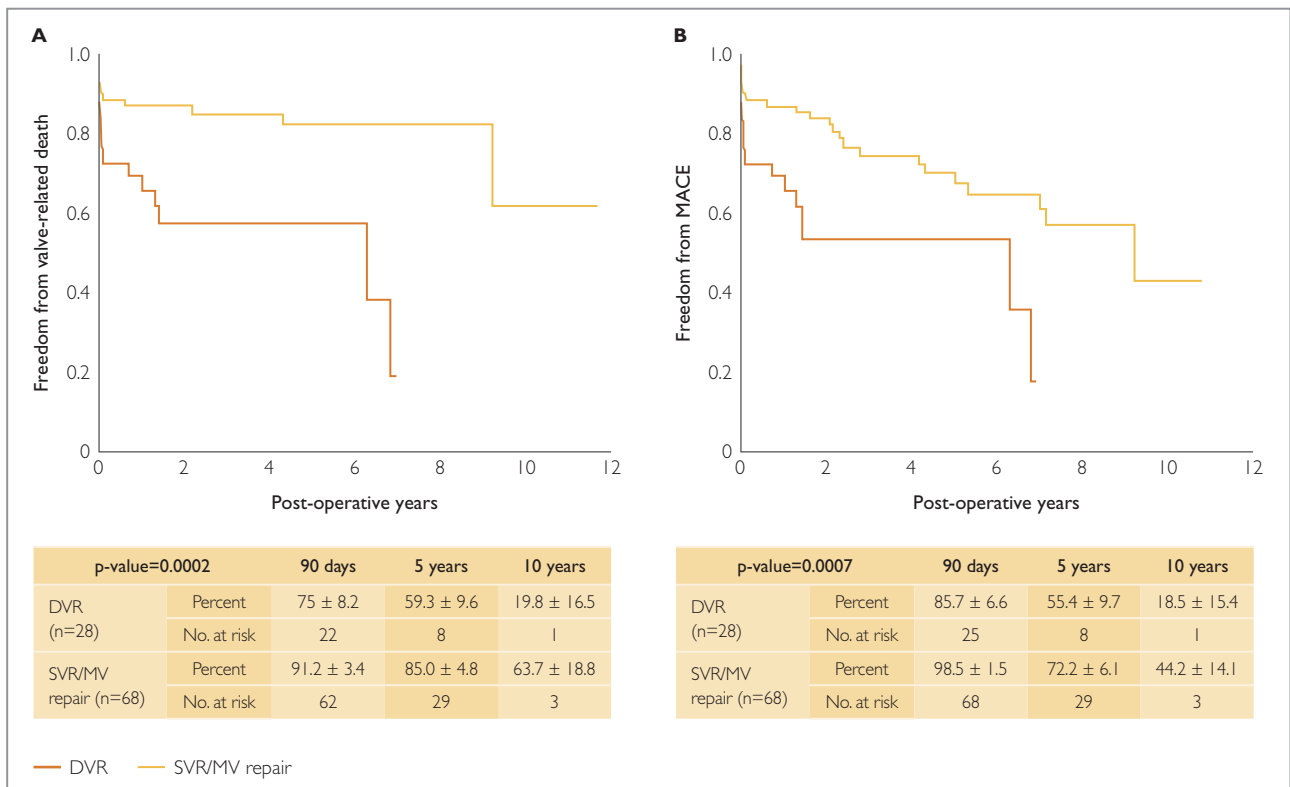
DISCUSSION

Our retrospective study describes the early and long term outcomes of 4 main surgical options for active native valve endocarditis and the validity of the EuroSCORE II in the cohort of patients at a single centre. We have shown that the overall early 30-day mortality was high (11%) and the most significant risk factors were: LCOS, preoperative embolic episodes and ventilation >24 hours after adjusting for age, sex, NYHA class ≥III, DVR and HIV status. The most significant risk factors for late mortality were: the female sex, HIV positive status and patients who had DVR (after adjusting for HIV status and female sex). In our cohort of patients, the prevalence of HIV infection in females (20%) was higher than the reported prevalence of HIV infection of 11% - 18% in this age group in the Western Cape population during our study period. There was a low prevalence of HIV infection of 3% in our male cohort compared to the reported prevalence of 6% - 8%.[15] The lower prevalence rate in males may be attributed to selection bias during the time of surgery, even though the clinical decision to operate a patient with infective endocarditis was not directly influenced by concomitant HIV infection. Other factors, beyond the scope of this study, may influence the prevalence rates seen. When we looked at the composite end point of MACCE, the most significant preoperative adjusted risk factors were: critical preoperative state, EuroSCORE II >12%, preoperative embolic episodes, preoperative dialysis and NYHA ≥III. The most important immediate postoperative risk factor for MACCE was low cardiac output state (LCOS). Within the AVR sub-group, preoperative stroke, critical physi-

A

p-value=0.0001		90 days	5 years	10 years
EuroSCOREII ≤12% (n=75)	Percent	94.7 ± 2.5	83.3 ± 4.7	39.1 ± 27.8
	No. at risk	72	30	1
EuroSCOREII >12% (n=70)	Percent	55.0 ± 11.1	55.0 ± 11.1	45.8 ± 12.5
	No. at risk	12	7	3

— EuroSCORE ≤12% — EuroSCORE >12%

B

p-value=0.0002		90 days	5 years	10 years
EuroSCOREII ≤12% (n=76)	Percent	97.1 ± 2.0	75.5 ± 5.9	29.8 ± 21.5
	No. at risk	72	31	1
EuroSCOREII >12% (n=70)	Percent	61.5 ± 9.5	46.2 ± 9.8	31.7 ± 10.9
	No. at risk	13	5	2

FIGURE 1A: Long term freedom from (A) Valve related mortality and (B) Major adverse cardiac events (MACCE) in patients with a EuroSCOREII of >12% and ≤12%. Difference in survival was statistically significant in the early half compared to the latter half in both graphs.

A

p-value=0.0002		90 days	5 years	10 years
DVR (n=28)	Percent	75 ± 8.2	59.3 ± 9.6	19.8 ± 16.5
	No. at risk	22	8	1
SVR/MV repair (n=68)	Percent	91.2 ± 3.4	85.0 ± 4.8	63.7 ± 18.8
	No. at risk	62	29	3

— DVR — SVR/MV repair

B

p-value=0.0007		90 days	5 years	10 years
DVR (n=28)	Percent	85.7 ± 6.6	55.4 ± 9.7	18.5 ± 15.4
	No. at risk	25	8	1
SVR/MV repair (n=68)	Percent	98.5 ± 1.5	72.2 ± 6.1	44.2 ± 14.1
	No. at risk	68	29	3

FIGURE 1B: Long term freedom from (A) Valve related death and (B) Major adverse cardiac events in patients who had double valve replacement (DVR) compared to those who had single valve replacements and mitral valve repair. DVR is shown to be a higher risk group with higher mortality and MACE.

ologic state and the use of pericardial patch (marker of extensive root pathology) were significant risk factors for valve related mortality. In the MVR group the significant risk factors for valve related mortality were LCOS. And finally, in the DVR group, the significant risk factors were LCOS and the use of the pericardial patch. Our patients with mitral valve repairs had no valve related mortality and the significant risk factor for adverse events was prolonged ventilation >24 hours. The DVR group had a significantly higher early and late mortality and lower freedom from major adverse cardiac events (p=0.0002) than the other treatment groups.

The EuroSCORE II underestimated 30-day mortality in the combined and sub-groups, except the AVR group and its discriminatory power was the least in the MVR group. We determined that at a cut-point of 12%, the EuroSCORE II had the highest sensitivity (73%) and specificity (88%) for the entire cohort with a positive predictive value of 44%.

In a review by Anguera, et al., severe aortic or mitral valve regurgitation causing congestive cardiac failure is the most important indication for surgery, the most frequent cause of mortality and a significant risk factor for early mortality and morbidity.[16] In a study evaluating the risk factors for embolism and 6-month mortality in 216 patients with infective endocarditis, Hill, et al. showed that mobile vegetations, size >10mm were associated with new embolic episodes and the latter predicted 6-month mortality[17] which was a consistent finding in our study. When surgical management is the option for managing infective endocarditis, a thorough debridement and bioprosthetic or mechanical valve replacement has a low endocarditis recurrence risk.[18] There was no significant difference in rate of recurrent endocarditis between mechanical and bioprostheses in our patient cohort, although no endocarditis was reported on bio-prostheses. The current literature shows that there is no significant difference between the incidence of mechanical and bioprosthetic endocarditis.[6]

In a study of 78 patients operated for mitral endocarditis at a single centre in France by Iung, et al., 80% were amenable for repair. Repair in active endocarditis was associated with a higher rate of major adverse cardiac events but had equivalent survival to those with fully treated endocarditis.[19] Only 30% of our patients with mitral endocarditis were amenable for repair and they had no valve related mortality but 33% had major adverse cardiac events.

A retrospective study by Chu, et al., on 267 patients with infective endocarditis, found that critical physiological state, staphylococcal infection, diabetes mellitus and embolic events were independent predictors of in-hospital mortality.[20] In

another study by Davids, et al., 383 patients having surgery for infective endocarditis had staphylococci as the most common organism. A critical preoperative state and staphylococcal infection were independent risk factors for operative mortality. In addition age, recurrent endocarditis and ventricular ejection fraction of less than 40% were independent predictors of all-cause mortality.[21] Our study showed that a critical preoperative state, but not staphylococcal infection, was associated with early mortality, and recurrent endocarditis was associated with reoperation and mortality in over 60%.

In a long term outcome study of 346 patients between 1986 - 2005, the 10- and 15-year survival after valve replacement surgery for patients with infective endocarditis without intravenous drug use was 56% and 42% respectively.[22] Our cohort had a similar 10-year survival at 52.6 ± 15.9. A review of 37 patients with active infective endocarditis had mitral valve repair surgery and a 10-year survival and freedom from reoperation of 80%.[7] This study showed that mitral valve repair could be achieved with good long term survival and low rate of reoperation that was comparable to patients with no endocarditis and consistent with our findings.

Most of the studies reviewing active native valve endocarditis had a heterogeneous cohort of patients with different treatment modalities, and assessed outcomes of the overall group. Our study shows that the cohort consists of a heterogeneous group and analysing them, based on different treatment modalities, reveals that patients who had DVR had a significantly higher valve related mortality compared to the non-DVR treatment groups (59.3 ± 9.5 vs. 78 ± 6.3 at 5 years p=0.009), probably related to the more extensive degree of infection.

In a study evaluating the EuroSCORE II in 3 479 Chinese patients, the model gave a more accurate prediction for single valve (AUROC of 0.792) than multiple valve surgery (AUROC of 0.605) with respect to discriminatory ability and calibration. This was attributed to the lack of the incorporation of certain valve related risk factors such as left ventricular dimensions into the EuroSCORE II model.[23] In another study comparing the EuroSCORE II in a Turkish cohort of 428 patients, the model was shown to underestimate mortality risk for the entire cohort.[24] Our study cohort, though small, showed a similar pattern with the predicted mortality being underestimated in the entire cohort but overestimated in the lower risk AVR and MV repair groups. In addition, the EuroSCORE II had a better discriminatory ability for early mortality in the AVR group than the other sub-groups in our study. In general, the EuroSCORE II had good discrimination and calibration for our entire cohort. Contrary to the results of our study, a recent

prospective validation of the EuroSCORE II in Argentina showed that it underestimated in-hospital mortality in the lowest risk cases but performed well in the higher risk patients. They attributed this to inadequate model behaviour and/or surgical care.[25] However, in our situation the EuroSCORE II overestimated operative mortality in the lower risk groups and underestimated mortality in the higher risk groups. This may be explained by good surgical performance in the lower risk groups and poor surgical performance in the higher risk groups.

Study limitations

The major limitation of this study is the inherent bias related to the retrospective and observational nature of the study. Patient selection, indication and timing of surgery may also affect the findings related to referral patterns and duration of antibiotic therapy. Another limitation is the heterogeneity of the procedures undertaken and micro-organisms involved in the disease process. The small sample size also affects the assessment of the validity of the EuroSCORE II in our cohort of patients. Our cohort of patients is a high-risk category due to the underlying nature of the disease and this can have an influence on the underestimation of the predicted mortality by the EuroSCORE II.

CONCLUSIONS

We concluded that the most important risk factor for early outcome was LCOS, and for long term outcome it was DVR. The EuroSCORE II had a good discriminatory ability and cali-bration, but generally underestimated mortality for the entire cohort of patients. Underestimation occurred particularly in the DVR and MVR groups, whereas, the EuroSCORE II over-estimated mortality in the AVR and MV repair groups. This may be due to poor surgical performance in the higher risk patients and good surgical performance in the lower risk patients, respectively. When evaluating the EuroSCORE II at a cut point of 12%, it was evident that the higher risk group (>12%) had a significantly higher early and medium term mortality than the lower risk group (≤12%).

We will, however, need to evaluate a larger cohort of patients with other underlying cardiac conditions in order to make a more robust validation of the EuroSCORE II model in the South African context.

Conflict of interest: none declared.

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