ORIGINAL ARTICLE

TRIPLE VALVE SURGERY: LONG-TERM FOLLOW-UP FROM A SINGLE CENTRE

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Abstract

Aims: *The aims of this study were to analyze early and late outcomes of TVS and identify predictors of short and long-term poor prognosis.*

Methods: *Single centre retrospective study with 130 patients who underwent TVS between 2007 and 2020. Most of the patients were female (72.3%), mean age of 64.4 years; 61.1% were in New York Heart Association class III/IV, with a EuroSCORE II of 7.5%. Univariable and Multivariable analyses were undertaken to identify predictors of perioperative mortality and morbidity and long-term mortality.*

Results: *In-hospital mortality was 10.8%, of which 7.6% were due to a cardiac cause. Diabetes Mellitus was an independent predictor of increased perioperative mortality. This group had 27.7% rate of major perioperative complications. Elevated systolic pulmonary pressure and obesity were predictors of early morbidity.*

All-cause mortality was 43.1% for 14 years. The survival at 1, 5 and 10 years was 83%, 60% and 43%, respectively. Diabetes Mellitus was a risk factor for long-term mortality.

Conclusions: *Patients undergoing TVS have a high surgical risk making TVS an operation associated with high mortality and morbidity. This research suggests Diabetes Mellitus, pulmonary hypertension and obesity as risk factors for mortality in TVS.*

Keywords: *triple valve surgery; risk factors; trivalvular*

INTRODUCTION

Despite all the improvements in cardiac surgery, triple valve surgery (TVS) remains a challenging procedure, with long cardiopulmonary bypass and myocardial ischemic times. In the literature, this surgery carries a perioperative complication rate around 50%, with a perioperative mortality rate of 5-17%.[1-10]

Furthermore, multiple valve surgery exposes the patients to added long-term prosthetic valve-related morbidities compared with single valve replacement, and it has been associated with reduced long-term survival, with reported survival at 10 years of 35-65%.[1-4,6]

There are limited data evaluating the risk after TVS in modern ages, with previous studies showing no consistency in the preoperative variables that predict adverse outcomes.[1-7]

This study reviews the experience with triple valve surgery at a single centre, with the aim to analyze early and late outcomes of this procedure and identify predictors of poor prognosis.

METHODS

A retrospective research was conducted to identify all consecutive patients submitted to TVS at the Hospital Santa Cruz, between January 2007 and December 2020. The initial population included 169 patients. Patients with

congenital heart diseases (3), active endocarditis (8), emergency surgery (4) or concomitant coronary artery disease (24) were excluded. These exclusion criteria were selected a priori. Therefore, the study population consisted of 130 patients.

Patient's characteristics

27,7% (n=36) of patients were male and 72,3% (n=94) female, with a mean age of 64,4 +/- 15,4 years. Patient demographics and comorbidities are shown in Table 1. Most of the patients were in NYHA functional class III/IV (61,1%). Thirty-eight patients (29,2%) had undergone previous cardiac surgery. Mean Systolic Pulmonary Artery Pressure (sPAP) was 54,35 +/- 20,3 mmHg. Patients had a medium-high surgical risk, with an average EuroSCORE II of 7,5 +/- 8,9 %. Most patients presented with a degenerative disease (61,5%).

The most common type of presentation was mixed aortic disease (40%), mitral (36.2%) and tricuspid regurgitation (94.6%). The complete list of valve disease presentation is shown in Table 2.

Operative technique

All procedures were done through a median sternotomy. The tricuspid valve was almost universally repaired, and mitral or aortic repair was preferred over replacement in the few cases it was possible. Standard valve repair or replacement techniques were used. The majority of TVS consisted of aortic (98,5%) and mitral (93,8%) valve replacement, along with tricuspid repair (96,9%). The surgeries were performed with the usual methods of cardiopulmonary bypass (CPB) with a single aortic cross-clamp technique. Myocardial protection strategies included antegrade and retrograde blood cardioplegia, and moderate hypothermia. Mean CPB time was 166,26 +/- 44,45 minutes and aortic cross-clamp time was 127,35 +/- 33.16 minutes. The operative data is listed in Table 3.

Outcomes and follow-up

Early post-operative outcomes were in-hospital mortality (from all causes) and major perioperative complications, and late post-operative outcome was all-cause

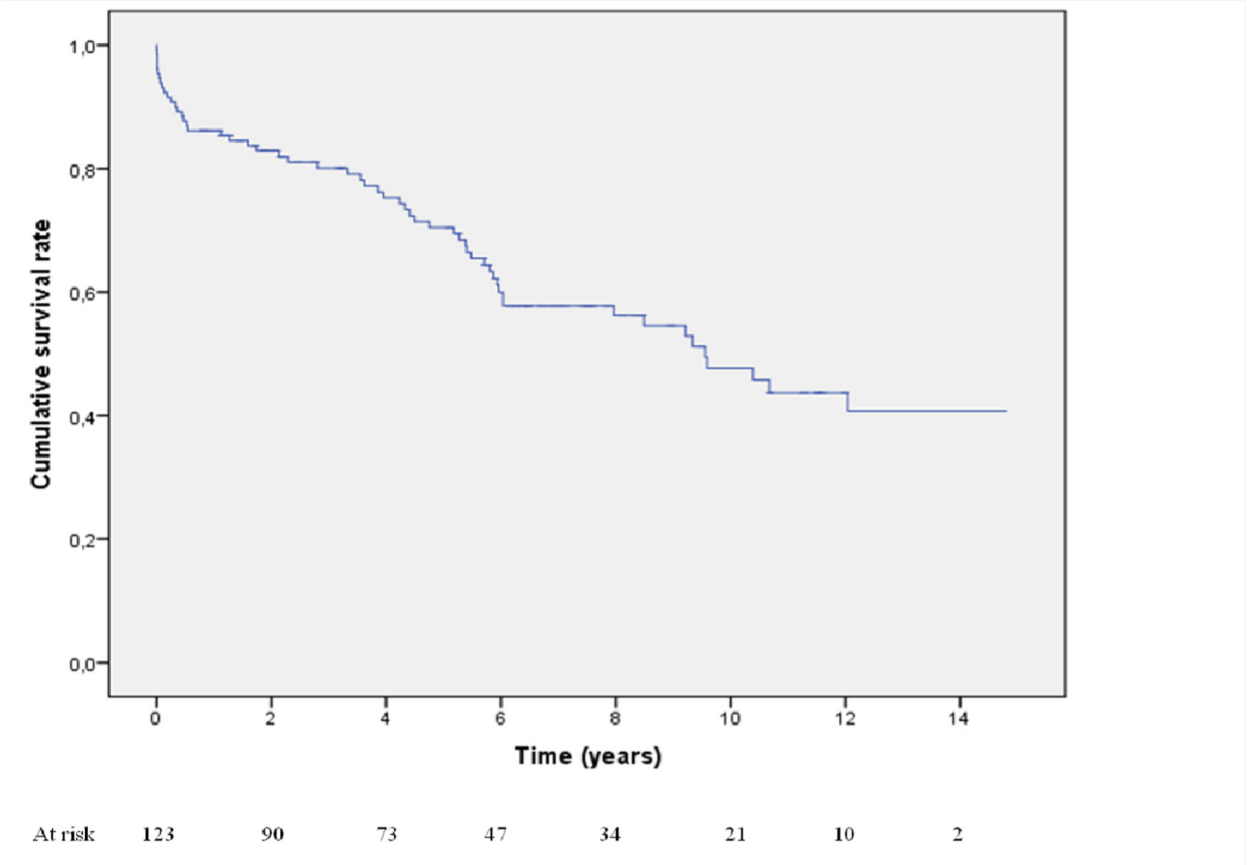

Figure 1 Kaplan-Meier curve of long-term survival.

mortality.

Major perioperative complications were defined as a composite endpoint including at least one of the following in-hospital variables: low cardiac output syndrome (persistent cardiac index below 2,0L/min/m2 with use of high dose catecholamines and/or mechanical circulation support), myocardial infarction (Troponin values > 10 times the 99th percentile of upper reference limit in association with new Q waves), severe arrhythmia (arrhythmia with hemodynamic instability and need for urgent/emergent treatment), stroke, reoperation for bleeding, acute renal failure with need for haemodialysis, pulmonary complications (including pneumonia, respiratory failure with need for long-time invasive ventilation, non-invasive ventilation or reintubation) and sepsis (systemic inflammatory response syndrome in response to an infectious process).

Clinical records and National Data Base were used for long term follow-up. Median follow-up for survival was 5,52 years (interquartile range IQR: 1,8-9,0) for 98% of patients.

Statistical Analysis

Categorical variables were expressed as absolute numbers and percentages and continuous variables were expressed as mean (SD) or median (IQR) depending on the distribution. Kolmogorov-Smirnov test was used to assess the normal distribution.

The pre-operative variables were selected a priori (not a stepwise method): age, gender, degenerative disease, obesity, high blood pressure (HBP), dyslipidemia, Diabetes Mellitus (DM), smoking (included ex-smokers), New York Heart Association (NYHA) III/IV, Left ventricular ejection fraction (LVEF) <50%, peripheral vascular disease, creatinine clearance (CreatCl), respiratory disease, gastrointestinal disease, previous valvular surgery, sPAP and atrial fibrillation. Categorical variables were compared using □2 test. Normal distributed continuous variables were compared with Student's T-test and Levene's test for variance equality assessment.

Variables with a univariate p<0,05 were included in the Multivariable Cox Proportional Hazards Regression and Logistic Regression models to identify risk factors for in-hospital mortality, in-hospital morbidity and follow-up mortality. Long-term survival was estimated using the Kaplan-Meier method. A probability value of p<0,05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp. Armonk, NY)

Table 1 **Patient demographics and comorbidities**

Demographics	n(%)
Female sex	94 (72,3)
Mean age (years)	64,4
Obesity	16 (12,3)
NYHA III/IV	80 (61,5)
LVEF <50%	20 (15,4)
Mean EuroSCORE II (%)	7,5
Mean sPAP (mmHg)	54,4
Mean CreatCl (mL/min)	62,2
Pathology	
Degenerative	61,5
Rheumatic	38,5
Comorbidities	
HBP	99 (76,2)
DM	22 (16,9)
Dyslipidemia	49 (37,7)
Smoker	19 (14,6)
Hemodialysis	4 (3,1)
Previous Valvular Surgery	38 (29,2)
Peripheral vascular disease	8 (6,2)
Respiratory disease	10 (7,7)
Gastrointestinal disease	10 (7,7)
Liver failure	0 (0)
Atrial fibrillation	57 (43,8)

Abbreviations: CreatCl, creatinine clearance; DM, Diabetes Mellitus; HBP, high blood pressure; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure.

RESULTS

Early post-operative outcomes

A total of 14 patients (10,8%) died during the index hospital stay. Causes of death were: myocardial failure and continuous low cardiac output syndrome (4), sudden cardiac arrest (2), severe arrhythmia (4), septic shock (2) and stroke (2). On univariable analysis, DM (p=0,014) and lower CreatCl (p=0,038) were significant predictors of in-hospital mortality. On multivariable analysis, DM was associated to increased in-hospital mortality (OR 3,6 CI95: 1,059-12,551; p=0,040) (Table 4).

The median length of stay was 12 (IQR:8-21) days. The frequency of major perioperative complications was 27,7%. Fifteen patients (11,5%) required re-exploration

of the mediastinum for bleeding; 2 patients (1,5%) had a perioperative myocardial infarction. Acute kidney injury requiring renal replacement therapy occurred in 9 patients (6,9%) and stroke in 5 (3,8%). The list of major perioperative complications is presented in Table 5.

On univariable analysis, DM (p=0,013), sPAP (p=0,020) and obesity (p=0,010) were significant predictors of in-hospital complications. On multivariable analysis, sPAP (OR 1,02 CI95: 1,01-1,04; p=0,028) and obesity (OR 3,84 CI95: 1,24-11,92; p=0,020) increased the risk of early morbidity in 1,02 and 3,84 folds, respectively (Table 6).

Late outcomes

During a follow-up period of 14 years, 46 patients died (43,1%). One-year, five-year and 10-year survival were 83%, 60%% and 43%, respectively, as illustrated in Figure 1.

As listed in Table 7, the predictors of long-term mortality were DM (p<0,001), lower CreatCl (p=0,006), degenerative disease (p=0,013), older age (p=0,009) and HBP (p=0,020), on univariable analysis. On multivariable analysis, DM (HR 3,60 CI95: 1,94-6,67; p<0,001) increased the risk of follow-up mortality.

Table 2 **Preoperative valve disease**

Disease	Aortic Valve (%)	Mitral Valve (%)	Tricuspid Valve (%)
Stenosis	34,6	18,5	0
Regurgitation	19,2	36,2	94,6
Mixed	40	32,3	3,8
Malfunction	6,2	13,1	1,6

Table 3 **Operative data**

Surgery	Aortic Valve (%)	Mitral Valve (%)	Tricuspid Valve (%)
Bioprosthetic valve	63,8	63,8	0,8
Mechanical valve	34,6	30	2,3
Repair	1,5	6,2	96,9

Table 4 **Predictors of in-hospital mortality**

Variable	Univariable analysis	Multivariable analysis		
	p value	OR	CI 95%	p value
Female sex	0,195			
Mean age (years)	0,139			
NYHA III/IV	0,612			
LVEF <50%	0,632			
Mean sPAP (mmHg)	0,162			
Lower mean CreatCl (mL/min)	**0,038**			
Rheumatic disease	0,196			
DM	**0,014**	3,6	1,059-12,551	0,040
Obesity	0,540			
Gastrointestinal disease	0,707			
HBP	0,105			
Dyslipidemia	0,559			
Smoker	0,096			
Previous Valvular Surgery	0,071			
Peripheral vascular disease	0,391			
Respiratory disease	0,306			
AF	0,218			

Abbreviations: CreatCl, creatinine clearance; DM, Diabetes Mellitus; HBP, high blood pressure; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure

Table 5 **In-hospital morbidity**

Morbidity	n(%)
Low cardiac output syndrome	6 (4,6)
Myocardial infarction	2 (1,5)
Severe arrhythmia	10 (7,7)
Stroke	5 (3,8)
Bleeding requiring reoperation	15 (11,5)
Hemodyalisis	9 (6,9)
Acute respiratory failure	11 (8,5)
Sepsis	4 (3,1)
Total (%)	27,7
Median ventilation time (hours)	11,5
Median hospital stay (days)	12

DISCUSSION

To the best of our acknowledgement, the literature of TVS is based on retrospective studies with multiple criteria inclusion - ischemic heart disease with or without concomitant coronary surgeries[1-4,6-7,9-10], infective endocarditis[8] or contemplating a selected group of patients[5], which narrows down the true effect of TVS. With this research, we tried to focus only on the outcomes of isolated triple valve disease.

As mentioned above, reported operative mortality in the modern era ranges between 5 and 17%[1-4,6-10]. Akay reported a very low operative mortality (2.5%), but it was from a young population with rheumatic valve disease and, consequently, lower surgical risk[5]. Our experience, including patients only with valvular disease, detected a similar mortality rate (10,8%). Of note, our series included almost 2/3 of patients in NYHA class III or IV, 1/4 with previous valve surgery, important pulmonary hypertension and with a substantial operative risk (mean EuroSCORE II 7,5%).

Age, NYHA class IV, depressed LVEF, prolonged CPB, HBP, previous cardiac surgery, peripheral vascular disease, preoperative shock, and preoperative renal dysfunction were already identified as independent risk factors for perioperative mortality after TVS[2-3,7,9,10]. Our study suggests an important role for normal renal function in patients submitted to TVS, identifying it as a marker of increased perioperative survival on univariable analysis (but not on multivariable analysis). DM was considered a major risk factor for in-hospital mortality, highlighting the importance of this systemic disease on perioperative period. Patients submitted to previous valve surgeries did not present with a higher risk of perioperative morbimortality in this research. This finding suggests surgical care should not be refused only because the patient had a previous surgery.

Another fact that emphasizes TVS as a serious procedure is the high operative major complication rate, reported in the recent registries as 43-53%[1-2,5]. This study reports a lower complication rate (27,7%), possibly explained by the inclusion criteria in the different series. To our knowledge, there is no evidence of predictors of perioperative morbidity after TVS in literature[1-10]. Our study identified a higher sPAP and obesity as independent predictors of early morbidity. DM is also an important clinical factor respecting post-operative complications. This study highlights the importance of the comorbidities not only for mortality issues, but also for early morbidity. This might have important implications as some of these risk factors are potentially modifiable before surgery. Whereas pulmonary hypertension depends on the correction of the underlying valve disease, obesity is clearly modifiable and a potential target for preoperative intervention strategies to improve outcomes.

Former reports had shown that TVS is associated with 5- and 10-year survival rates of 55-87% and 35-65%, respectively[1-4,6]. The present research falls within the range of previously reported results. Noack identified older age, NYHA class IV, preoperative liver failure, preoperative HD and depressed LVEF as risk factors of late mortality[4]. We identified DM as a risk factor for long-term mortality. This fact probably reflects the major involvement of multiple organ systems in DM, increasing all-cause mortality. Lower CreatCl, degenerative disease, older age and HBP were also relevant clinical factors. Reduced LVEF did not contribute to an increased mortality, suggesting LV dysfunction is not a total contra-indication for surgery in these patients

This study has multiple limitations. It is based on the retrospective analysis of a population submitted to several combinations of procedures and operated by different surgeons. It is also limited by the small sample size of our study population, with low number of events, turning the statistical analysis into a difficult procedure with associated inherent uncertainty.

CONCLUSION

In summary, this research shows that TVS is a complex procedure associated with high mortality and perioperative complications, with DM as a crucial clinical condition for TVS. We also describe for the first time the importance of pulmonary hypertension and obesity in perioperative morbidity after TVS.

Table 6 **Predictors of in-hospital mortality**

Variable	Univariable analysis	Multivariable analysis		
	p value	OR	CI 95%	p value
Female sex	0,263			
Mean age (years)	0,399			
NYHA III/IV	0,059			
LVEF <50%	0,144			
Degenerative disease	0,088			
Lower mean CreatCl (mL/min)	0,065			
Mean sPAP (mmHg)	**0,020**	**1,02**	**1,01-1,04**	**0,028**
Obesity	**0,010**	**3,84**	**1,24-11,92**	**0,020**
DM	**0,013**			0,082
Gastrointestinal disease	0,285			
HBP	0,169			
Dyslipidemia	0,202			
Smoker	0,165			
Previous Valvular Surgery	0,333			
Peripheral vascular disease	0,295			
Respiratory disease	0,559			
AF	0,249			

Abbreviations: CreatCl, creatinine clearance; DM, Diabetes Mellitus; HBP, high blood pressure; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure.

Table 7 **Predictors of late mortality**

Variable	Univariable analysis	Multivariable analysis		
	p value	OR	CI 95%	p value
Female sex	0,346			
Mean age (years)	**0,009**			0,777
NYHA III/IV	0,512			
LVEF <50%	0,519			
Mean sPAP (mmHg)	0,051			
Degenerative disease	**0,013**			0,777
Lower mean CreatCl (mL/min)	**0,006**			0,130
DM	**<0,001**	**3,6**	**1,94-6,67**	**<0,001**
Obesity	0,080			
Gastrointestinal disease	0,213			
HBP	**0,020**			0,286
Dyslipidemia	0,413			
Smoker	0,369			
Previous Valvular Surgery	0,329			
Peripheral vascular disease	0,478			
Respiratory disease	0,213			
AF	0,368			

Abbreviations: CreatCl, creatinine clearance; DM, Diabetes Mellitus; HBP, high blood pressure; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure.

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