Long-term follow-up of triple valve surgery: a single center analysis

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Abstract

Objectives: The aims of this study were to analyze early and late outcomes of TVS and identify predictors of poor prognosis . Methods: Single centre retrospective study with 108 patients who underwent TVS between 2007 and 2016. Most of the patients were female (74.1%), mean age of 65 years; 61,1% were in New York Heart Association class III/IV, with a EuroSCORE II of 7.5%. Univariable and Multivariable analyses were developed to identify predictors of perioperative mortality and morbidity and long-term mortality. Results: In-hospital mortality was 12%. Creatinine clearance was an independent predictor of decreased perioperative mortality. This group had 28.7% rate of major perioperative complications. Systolic pulmonary pressure and obesity were predictors of early morbidity. The 10-year mortality was 29.6%. The survival at 1, 5 and 10 years was 80%, 76% and 45%, respectively. Diabetes Mellitus was a risk factor for long-term mortality and creatinine clearance was a predictor of long-term survival. Need for re-operation was identified in 3.5% of the patients. Conclusions: Patients undergoing TVS have high surgical risk making TVS an operation associated with high mortality and morbidity. This research identifies Diabetes Mellitus, renal function, pulmonary hypertension and obesity as the future challenges in TVS.

ORIGINAL ARTICLE

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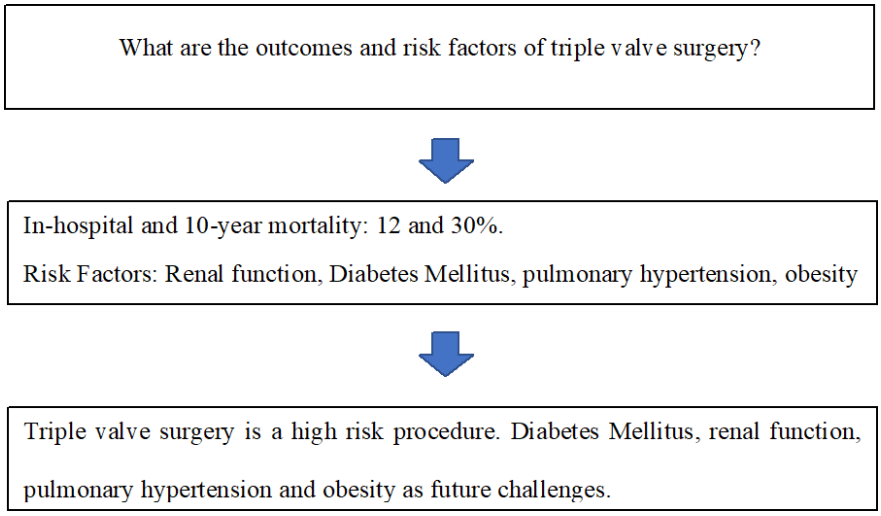
The 10-year mortality was 29.6%. The survival at 1, 5 and 10 years was 80%, 76% and 45%, respectively. Diabetes Mellitus was a risk factor for long-term mortality and creatinine clearance was a predictor of long-term survival. Need for re-operation was identified in 3.5% of the patients.

Conclusions: Patients undergoing TVS have high surgical risk making TVS an operation associated with high mortality and morbidity. This research identifies Diabetes Mellitus, renal function, pulmonary hypertension and obesity as the future challenges in TVS.

Graphical Abstract



KEYWORDS

Triple valve surgery; risk factors; early outcomes; long-term survival

Key points

- In-hospital mortality of 12%. Creatinine clearance was an independent predictor of decreased perioperative mortality.
- In-hospital morbidity of 28.7%. Systolic pulmonary pressure and obesity were risk factors of early morbidity.
- Mortality at ten years was 29.6%. Diabetes Mellitus and creatinine clearance were relevant for long-term survival.

Abbreviations: CPB, Cardiopulmonary bypass; CreatCl, Creatinine clearance; DM, Diabetes Mellitus; IQR, Interquartile range; LVEF, Left ventricle ejection fraction; NYHA, New York Heart Association; RF, Risk Factor; SD, Standard Deviation**;** sPAP, systolic pulmonary artery pressure; TVS, Triple valve surgery.

1 | INTRODUTION

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 center, with the aim to analyze early and late outcomes of this procedure and identify predictors of poor prognosis.

2 | METHODS

A retrospective research was conducted to identify all consecutive patients submitted to TVS at the Hospital Santa Cruz, between January 2007 and December 2016. The initial population included 142 patients. Patients with congenital heart diseases (3), active endocarditis (5), emergency surgery (2) or concomitant coronary artery disease (24) were excluded. These exclusion criteria were selected *a priori* . Therefore, the study population consisted of **108** patients operated during a 10 year interval.

2.1 | Patient's characteristics

There were 28 men and 80 women (N=108) with mean age of 65 ±14.1 years. Patient demographics and comorbidities are delineated in Table 1. Most of the patients were in NYHA functional class III/IV (61.1%). Thirty-five patients (32.4%) had undergone previous cardiac surgery. Median Systolic Pulmonary Artery Pressure (sPAP) was 55 (interquartile range (IQR): 40-70) mmHg. Patients had high surgical risk as evidenced by the overall EuroSCORE II of 7.5% (SD: 8.9).

The most common type of presentation was aortic mixed disease (40.7%), mitral (34.3%) and tricuspid regurgitation (93.5%). The complete list of valve disease presentation is presented in Table 2.

2.2 | Operative technique

All procedures were done through a median sternotomy. Valve repair, if possible, was preferred over replacement. Standard valve repair or replacement techniques were used. The majority of TVS consisted of aortic (98.1%) and mitral (92.6%) valve replacement, along with tricuspid repair (97.2%).

TABLE 1 Patient demographics and comorbidities

Demographics	n (%)
Female sex	80 (74.1)
Mean age (years)	64.7
Obesity	12 (11.1)
NYHA III/IV	66 (61.1)
LVEF <40%	16 (14.8)
Mean EuroSCORE II (%)	7.5
Median sPAP	55
Mean CreatCl (mL/min)	60.5
Comorbidities	
Arterial Hypertension 86 (79.6)	Arterial Hypertension 86 (79.6)
DM	16 (14.8)
Dyslipidemia	39 (36.1)
Smoker	15 (13.9)
Hemodialysis	3 (2.8)
Previous Valvular Surgery	35 (32.4)
Peripheral vascular disease	8 (7.4)
Respiratory disease	6 (5.6)
Gastrointestinal disease	10 (9.3)
Liver failure	0 (0)
Atrial fibrillation	54 (50)

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

TABLE 2 Preoperative valve disease

Disease	Aortic Valve (%)	Mitral Valve (%)	Tricuspid Valve (%)
Stenosis	33.3	19.4	0
Regurgitation	19.4	34.3	93.5
Mixed	40.7	31.5	4.6
Malfunction	6.5	14.8	1.9

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 166,69 minutes (SD: 42.57) and aortic cross-clamp time was 126.19 minutes (SD: 33.28). The operative data are listed in Table 3.

TABLE 3 Operative data

Surgery	Aortic Valve (%)	Mitral Valve (%)	Tricuspid Valve (%)
Mechanical valve	61.1	60.2	0.9
Bioprosthetic valve	37	32.4	1.9
Repair	1.9	7.4	97.2

2.3 | Outcomes and follow-up

Early post-operative outcomes were in-hospital mortality (from all causes) and major perioperative complications.

Late post-operative outcomes were all-cause mortality and need for reoperation.

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 3.8 years (IQR: 1.8-7.4) for 98% of patients and freedom from reoperation was 1.8 years (IQR:0.25-5.4) for 94.5%.

2.4 | Statistical Analysis

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

The pre-operative variables were selected *a priori* (not a stepwise method): age, gender, obesity, hypertension, Diabetes Mellitus (DM), smoking (included ex-smokers), New York Heart Association (NYHA) III/IV, Left ventricular ejection fraction (LVEF) <40%, peripheral vascular disease, creatinine clearance (CreatCl),

respiratory disease, gastrointestinal disease, previous valvular surgery, sPAP and atrial fibrillation. Categorical variables were compared using $\chi 2$ test. Normal distributed continuous variables were compared with Student's T-test and Levene's test for variance equality assessment. Mann–Whitney U-test was used for independent samples not normally distributed.

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)

3 | RESULTS

3.1 | Early post-operative outcomes

A total of 13 patients (12%) died within hospital stay. Causes of death were: myocardial failure and continuous low cardiac output syndrome (3), sudden cardiac arrest (2), severe arrhythmia (4), septic shock (2) and stroke (2). On univariable analysis, DM (p=0.024) was a significant predictor of in-hospital mortality and CreatCl (p=0.005) was associated with reduced risk of in-hospital mortality. On multivariable analysis, CreatCl was an independent predictor of increased perioperative survival (OR 0.95 CI95: 0.924-0.994; p=0.021) (Table 4).

TABLE 4 Predictors of in-hospital mortality

Variable	Univariable analysis	Multivariable analysis	Multivariable analysis	Multivariable analysis
	p value	OR	CI 95%	p value
Female sex	0.291			
Mean age (years)	0.138			
NYHA III/IV	0.612			
LVEF <40%	0.345			
Mean sPAP (mmHg)	0.139			
Mean CreatCl (mL/min)	0.005	0.95	0.924-0.994	0.021
DM	0.024			0.178
Obesity	0.560			
Gastrointestinal disease	0.655			
Arterial Hypertension	0.206			
Dyslipidemia	0.461			
Smoker	0.126			
Previous Valvular Surgery	0.077			
Peripheral vascular disease	0.345			
Respiratory disease	0.454			
AF	0.500			

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

The median length of stay was 12 (IQR:9-22) days. The incidence rate of in-hospital complications was 28.7%. Eleven patients (10,2%) required re-exploration of the mediastinum for bleeding; 2 patients (1.9%) had a perioperative myocardial infarction. Acute kidney injury requiring renal replacement therapy occurred in 9 patients (8.3%) and stroke in 4 (3.7%). The list of major complications are listed in Table 5.

On univariable analysis, DM (p=0.012), sPAP (p=0.019) and obesity (p=0.013) were significant predictors of in-hospital complications and CreatCl (p=0.015) was associated with reduced risk of in-hospital complications. On multivariable analysis, sPAP (OR 1.023 CI95: 1.0-1.05; p=0.047) and obesity (OR 6.28 CI95:

1.48-25.69; p=0.013) increased the risk of early morbidity in 1.02 and 6.28 folds, respectively (Table 6).

TABLE 5: In-hospital morbidity

Morbidity	n (%)
Low cardiac output syndrome	3 (2.8)
Myocardial infarction	2 (1.9)
Severe arrhythmia	10 (9.3)
Stroke	4 (3.7)
Bleeding requiring reoperation	11 (10.2)
Hemodyalisis	9 (8.3)
Acute respiratory failure	9 (8.3)
Sepsis	2 (1.9)
Total (%)	28.7
Median ventilation time (hours)	11.5
Median hospital stay (days)	12

TABLE 6 Predictors of in-hospital morbidity

Variable	Univariable analysis	Multivariable analysis	Multivariable analysis	Multivariable analysis
	p value	**OR**	**CI 95%**	**p value**
Female sex	0.230			
Mean age (years)	0.589			
NYHA III/IV	0.059			
LVEF <40%	0.585			
Mean sPAP (mmHg)	0.019	1.023	1.0-1.05	0.047
Mean CreatCl (mL/min)	0.015			0.08
DM	0.012			0.104
Obesity	0.013	6.28	1.48-25.69	0.013
Gastrointestinal disease	0.311			
Arterial Hypertension	0.341			
Dyslipidemia	0.228			
Smoker	0.320			
Previous Valvular Surgery	0.253			
Peripheral vascular disease	0.272			
Respiratory disease	0.227			
AF	0.198			

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

3.2 | Late outcomes

During the follow-up period, thirty-two patients died (29.6%). Five-year and 10-year survival was 66% and 45%, respectively, as illustrated in Figure 1.

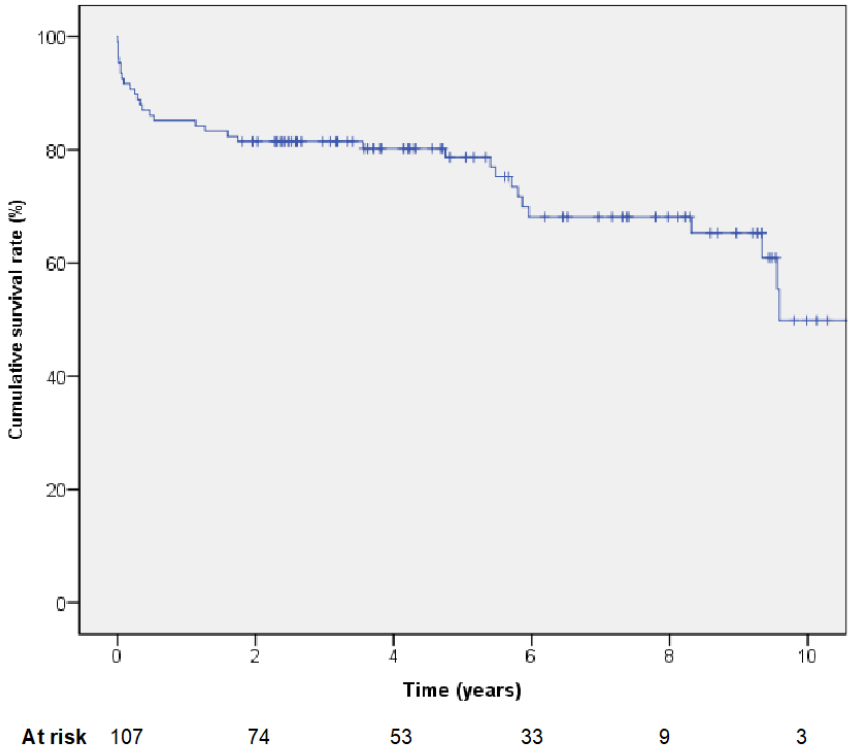


FIGURE 1 Kaplan-Meier curve of long-term survival

As listed in Table 7, the predictors of long-term mortality were DM (p=0.003), gastrointestinal disease (p=0.03) and CreatCl (p=0.001) as a predictor of long-term survival, on univariable analysis.

On multivariable analysis, DM (HR 2.78 CI95: 1.15-6.72; p=0.023) increased the risk of follow-up mortality and CreatCl (HR 0.98 CI95: 0.95-0.99; p=0.013) was associated with a lower risk of follow-up mortality.

Three patients (3.5%) required late reoperation. The causes for reoperation were prosthesis/repair malfunction (2.3%) or endocarditis (1.2%).

TABLE 7 Predictors of late mortality

Variable	Univariable analysis	Multivariable analysis	Multivariable analysis	Multivariable analysis
	p value	**HR**	**CI 95%**	**p value**
Female sex	0.356			
Mean age (years)	0.06			
NYHA III/IV	0.512			
LVEF <40%	0.179			
Mean sPAP (mmHg)	0.227			
Mean CreatCl (mL/min)	0.001	0.98	0.95-0.99	0.013
DM	0.003	2.78	1.15-6.72	0.023
Obesity	0.500			
Gastrointestinal disease	0.037			0.638

Variable	Univariable analysis	Multivariable analysis	Multivariable analysis	Multivariable analysis
Arterial Hypertension	0.145			
Dyslipidemia	0.196			
Smoker	0.526			
Previous Valvular Surgery	0.472			
Peripheral vascular disease	0.252			
Respiratory disease	0.062			
AF	0.264			

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

4 | 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], active 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 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 (12%). 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, arterial hypertension, previous cardiac surgery, peripheral vascular disease, preoperative shock, and preoperative renal disfunction were already identified as independent risk factors for perioperative mortality after TVS [2-3,7,9,10]. Our study underlines the important role of normal renal function in patients submitted to TVS, identifying it as a marker of increased perioperative survival. We also consider DM as a challenge on TVS in-hospital mortality.

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 (28.7%), possibly explained by the inclusion criteria in the different series. To our acknowledgement, there is no evidence of predictors of perioperative morbidity after TVS in literature [1-10]. However, our study identified the increase of sPAP and obesity as independent predictors of early morbidity. DM and normal renal function are also important clinical factors 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]. In the present research, late mortality rates were 66% at 5 years and 45% at 10 years, which fall 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 and the increase of creatinine clearance as predictor of long-term survival. Patients with gastrointestinal diseases seem to have also a higher risk of long-term mortality.

The rates of freedom from reoperation at 5-10 years have been reported from 84.3 to 97% [3,8-9]. At our institution, only 3,5% required late reoperation, which supports the late good results of this surgery.

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. The constrained access to other institutions' records limited us to accurately identify morbidity during follow-up.

5 | CONCLUSION

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

CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

HUMAN ETHICS APPROVAL DECLARATION

This study complies with the Declaration of Helsinki and the Informed Consent was waived by the Ethics' Committee of our institution (RNEC number 20170700050 at 18th December 2020)

AUTHOR CONTRIBUTIONS

Paulo Veiga Oliveira: Conceptualization; Data curation; Formal Analysis; Investigation; Methodology; Project administration; Software**;** Visualization; Writing – original draft.**Márcio Madeira:** Conceptualization; Data curation; Project administration; Resources; Supervision; Validation; Writing – review & editing. **Sara Ranchordás:** Resources; Supervision; Validation; Writing – review & editing. **Marta Marques:** Resources; Supervision; Validation; Writing – review & editing. **Manuel Almeida:** Supervision; Validation; Writing – review & editing.**Miguel Sousa-Uva:** Resources; Supervision; Validation; Writing – review & editing. **Miguel Abecasis:** Resources; Supervision; Validation; Writing – review & editing. **José Pedro Neves:**Resources; Supervision; Validation; Writing – review & editing.

DATA AVAILABILITY STATEMENT

In accordance with the "DFG Guidelnes on the Handling of Research Data", we will make all data available upon request. The data set will be archived for at least 10 years after publication.

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