Isolated tricuspid valve regurgitation

ISOLATED TRICUSPID VALVE REGURGITATION: ASSESSMENT, TIMING AND SURGICAL TREATMENT

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Printing: Digicopy

Lay-out: Alessandra Sala

ISBN: 979-12-210-3395-3

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DISSERTATION

to obtain the degree of Doctor at the Maastricht University,

on the authority of the Rector Magnificus,

Prof. dr. Pamela Habibovic

in accordance with the decision of the Board of Deans,

to be defended in public

on Tuesday 6th June 2023 at 16.00 hours

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Financial support by the **Dutch Heart Foundation** for the Publication of this thesis is gratefully acknowledged.

Additional support was provided by the **Alfieri Heart Foundation**.

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Tanzania 2010

Chapter 1

GENERAL INTRODUCTION

Tricuspid regurgitation (TR) is defined as the inability of the valvular leaflets to adequately coapt during ventricular systole, avoiding blood flow to return from the right ventricle (RV) to the right atrium during ventricular contraction. TR can be divided into “primary” and “secondary”[1]. Primary TR results from anatomic abnormalities intrinsically affecting the tricuspid valve (TV) or the subvalvular apparatus, such as congenital anomalies, or acquired diseases of the TV, like myxomatous disease, rheumatic disease, infective endocarditis, traumatic and iatrogenic causes. Primary TR accounts for a minority of cases, approximately 8-10% of patients[2]. A growing number of patients develop significant TR from iatrogenic causes; the development of relevant TR in patients undergoing de novo implantation of cardiac implantable electronic devices (CIEDs) is reported to be as high as 38%, and may progress over time[3,4]. Secondary TR is more common (>90% of cases) and arises as a result of annular dilation with a macroscopically intact tricuspid valve and subvalvular apparatus. Annular dilation may be caused either by right ventricular (RV) enlargement as a result of pressure and/or volume overload[1,5] induced by left-sided heart diseases, pulmonary hypertension or RV dysfunction, or by atrial fibrillation (AF) with normal RV pressures (atriogenic TR)[6]. In the currently aging society, the number of patients with severe TR concomitant with AF is increasing[7].

TR is a common echocardiographic finding in the general population[8]. Although minimal or trivial TR may be considered a normal variant in structurally normal valves with no clinical impact, moderate-to-severe TR is pathological and eventually leads to excess cardiac morbidity and mortality[9]. In fact, increasing degrees of TR negatively impact on survival, with a relevant difference between severe TR entity (63.9%) and no TR (91.7%)[10], regardless of pulmonary hypertension and left ventricular ejection fraction (LVEF). Furthermore, if left untreated, isolated severe TR results in a mortality rate at 5 years of approximately 50%[2,11,12]. The incidence of moderate or severe TR is higher in women and increases with advancing age, with the prevalence of moderate-severe TR that reaches 1.5% and 5.6% in men and women, respectively[2]. Severe TR has been reported in 23-37% of patients after mitral valve replacement, in most cases being diagnosed as late as 10 years following the procedure[13,14]. Furthermore, amongst patients with heart failure and reduced ejection fraction, the prevalence of moderate-severe TR is 26% and independently affects prognosis[15].

Despite the increasing prevalence and the well-established negative impact of TR on survival, more than 90% of patients with clinically relevant TR are not offered any treatment[12]. This mainly due to the long-standing misconception that TR improves following the treatment of left-sided heart diseases[16] and the relatively high mortality rates (8-10%) reported for isolated TV surgery[17–20]. Moreover, this unwillingness is related to the fact that, even if severe, TR is initially well tolerated, patients have a good quality of life and minor symptoms are easily and effectively controlled with medical treatment[21].

Patients' presentation can therefore range from asymptomatic to varying degrees of heart failure[11,22]. Early in the disease process, in response to TR and central venous congestion, compensatory mechanisms and remodeling of the RV contribute to maintenance of adequate hemodynamic compensation and cardiac output. Patients tend to be asymptomatic with no medical therapy. As the disease progresses, patients develop pulmonary and central venous congestion, with the occurrence of exertional dyspnea, orthopnea and peripheral edema. Long-lasting TR leads to a disproportionate RV dilation along the free wall and progressive RV dysfunction. This further aggravates TR and results in multi-organ involvement, with the development of hepato-splenomegaly, reduced renal function, pleural effusions, ascites and initial right heart failure (RHF) episodes. In late stages of the disease, overt chronic RHF develops, with end-organ damage due to chronic RV volume overload[23,24]. Patients experience frequent RHF hospitalizations, despite optimal medical management, and symptoms are related to low cardiac output[25]. Therefore, untreated TR leads to the development of a vicious cycle of increasing RV dilation and increasing degree of regurgitation. While initial RV remodeling can be accompanied by normal RV function, long-standing TR results in maladaptive RV remodeling, with changes in RV geometry that cause papillary muscle displacement, abnormal leaflet tethering, large coaptation gaps, which ultimately lead to torrential TR and severe RV dysfunction[26]. This cycle should be interrupted early on in order to positively impact on long-term prognosis of patients affected by TR.

This issue has caught the attention of both the cardiac surgery and the cardiological communities in recent years. Management of patients with isolated TV disease remains controversial and many uncertainties remain to date. Most recommendations of the current European[27] and American[28] guidelines for the management of valvular heart disease involve patients undergoing concomitant left-sided valve operations. TV surgery should be performed in patients with severe TR (Class I), or mild-to-moderate TR with annular dilation (≥40mm or >21mm/m^2 by bidimensional transthoracic echocardiography), or prior evidence of right heart failure in patients undergoing left-sided valve surgery (Class IIa). On the other hand, recommendations for isolated tricuspid surgery tend to be slightly different. American College of Cardiology (ACC)/American Heart Association (AHA)[28] guidelines tend to be more conservative and suggest waiting for the development of signs or symptoms of RHF before recommending TV surgery, in the absence of pulmonary hypertension and in patients poorly responsive to medical therapy (Class IIa). Only a Class IIb indication is given in asymptomatic patients with primary severe isolated TR and progressive RV dilation/dysfunction, and in patients with signs and symptoms of RHF and severe TR who have undergone previous left-sided valve surgery, in the absence of severe pulmonary hypertension or severe RV dysfunction. However, development of persisting symptoms usually occurs only in advanced stages of the disease. On the contrary, European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS)[27] guidelines strongly support an earlier surgical referral to achieve low in-hospital mortality and better postoperative outcomes. Surgery is indicated in patients with severe symptomatic primary TR without severe RV dysfunction (Class I) and should be considered in asymptomatic or mildly symptomatic patients with severe primary or secondary TR with RV dilation, in the absence of severe left ventricular or RV dysfunction and pulmonary hypertension (Class IIa).

Therefore, correct timing, together with adequate patient selection, is a crucial aspect in the treatment of isolated TV disease. Surgery should be carried out sufficiently early to avoid irreversible RV dysfunction[29]. The presence of RV dysfunction has been shown to be a risk factor associated with adverse outcome in patients with TR and in tricuspid valve surgery[26]. Therefore, RV size and systolic function are relevant parameters in the evaluation and management of patients with significant TR and may aid in the stratification of patients to better define the surgical risk. The right ventricle, initially considered a passive conduit with minimal pumping capability[30], is now in the spotlight. An integrated evaluation of multiple parameters is crucial in order to adequately assess RV function[27]. The most utilized clinical imaging modality is echocardiography, despite the numerous challenges, limitations and great complexity of non-invasive assessment. Both tricuspid annular plane systolic excursion (TAPSE) and 3D RV ejection fraction (3D-RVEF) have been found to predict outcome. More specifically, patients with mid-range RV function (TAPSE 13-17mm)[31] and patients with 3D-RVEF >45%[32] experienced survival benefit and greatest clinical improvement. However, findings in the literature have been discordant, probably related to the fact that TAPSE and 3D-RVEF might fail to capture the actual relationship between RV contractility and afterload[33]. RV-pulmonary artery (PA) coupling has been proposed to determine whether RV function is adequately compensated for specific loading conditions. Non-invasively derived RV-PA coupling is gained is gained through TAPSE/systolic pulmonary artery pressure (sPAP) ratios, and higher ratios have been shown to be associated to lower all-cause mortality and fewer hospitalizations for RHF[34]. However, recent data have shown that the diagnostic sensitivity of echocardiography in accurately detecting pulmonary hypertension (PH) is 55%, since the determination of sPAP might be limited in severe TR[35]. Therefore, echocardiography alone might not be sufficient in detecting PH and in accurately assessing RV function. Invasive assessment of the right heart through right heart catheterization (RHC) provides information regarding severity and mechanism of PH, pulmonary vascular resistance, preload conditions and RV function. Mean PAP, diastolic PAP, transpulmonary gradient, pulmonary vascular resistance and RV stroke work have all been identified as hemodynamic predictors of worse outcomes (1-year mortality, heart failure hospitalizations and re-intervention) in patients undergoing transcatheter tricuspid valve repair for severe TR[36]. RHC should thus be considered as part of the diagnostic workup and preoperative assessment of patients with severe isolated TR in order to better define their prognosis.

Right heart assessment is of paramount importance; however, a number of other parameters have also been identified that may help in guiding patients' stratification. A clinical and functional classification was proposed[37,38], based not only on TR grade and RV remodeling/function, but also on RHF episodes, symptoms, end-organ involvement and medical therapy. Patients are divided in 5 stages according to disease progression, ranging from asymptomatic with moderate TR (Stage 1) to overt RHF patients, regardless optimal medical therapy, with torrential TR (Stage 5). These indications were, however, lacking in specific cut-off values capable of guiding the decision-making process of optimal patient management and timing. In this regard, a dedicated risk score has been recently made available that aims at predicting the in-hospital outcomes of patients following isolated TV surgery[39]. The TRI-SCORE is based on eight easy to ascertain parameters: age (≥70 years), New York Heart Association (NYHA) functional class (≥III), RHF signs (ascites, peripheral edema, severe jugular venous distension), daily dose of furosemide (≥125mg), renal insufficiency (glomerular filtration rate <30ml/min), elevated total bilirubin, left ventricular ejection fraction (<60%) and moderate/severe RV dysfunction (TAPSE <17mm and tissue doppler imaging (s'TDI) <9.5cm/sec). Despite lacking external validation, this risk score is a first attempt at stratifying patients according to baseline characteristics, aiming at predicting favourable responders.

Surgery remains to date the only definitive treatment for severe TR, but it is rarely performed. Of the 4000-8000 TV operations performed annually in the USA, more than 80% occur concomitantly to left-sided valve procedures and only a minority are performed in isolation[17,18,40]. This occurs mainly in response to the historically reported high in-hospital mortality rates following TV surgery and the poor long-term outcomes. Older studies have in fact reported an in-hospital mortality ranging from 8.8 to 37%, associated to 55% mortality at 5 years[17,41–43]. However, the baseline clinical presentation of such patients and the stage of the disease may have negatively impacted on the outcome. More recent studies have shown that factors associated with disease duration and late clinical presentation are independent predictors associated to in-hospital mortality, such as NYHA functional class III/IV, moderate and severe RV dysfunction, decompensated heart failure and advanced end-organ liver disease[19,44]. Therefore, patients referred to TV correction late in the disease course experience high morbidity and mortality after surgery, further supporting the idea that TV surgery is a high-risk procedure, and further delaying or even rejecting the referral for surgery. Studies are needed in order to assess outcomes following tricuspid surgery in early stages of the disease and help set aside this belief, since tricuspid surgery can be safe and effective when performed in experienced centres[45].

In a rapidly expanding era of percutaneous procedures, transcatheter treatment of TR is becoming readily available and a constantly growing field. Current transcatheter treatment options mimic surgical techniques and are an attractive alternative to surgery, whenever indicated, feasible and in patients deemed inoperable or at high-risk for surgical treatment. Retrospective studies have reported a reduction in TR grade, symptomatic improvement (reduced hospitalizations for RHF) and lower mortality at 1 year in patients treated with various devices compared to medical treatment alone[46–48]. Moreover, reverse remodeling of the right ventricle, improved cardiac output and reduction of liver enzymes were also reported following transcatheter edge-to-edge repair[49–51]. Despite these encouraging results, indication and timing of transcatheter tricuspid valve interventions (TTVI) have also emerged as important factors: patients' clinical characteristics, disease stage, end-organ function and anatomical factors are of paramount importance. In fact, patients treated in late stages of the disease, with pronounced RV dysfunction, may not benefit from the reduction in venous congestion and reverse remodeling, impacting on clinical events[31,32,52]. Furthermore, NYHA class IV; pulmonary hypertension, renal dysfunction and significant hepatic congestion are all independent predictors of all-cause mortality, with an estimated one-year mortality approaching 50%[34,35,53]. Therefore, the widespread conception that all patients with severe isolated TR not offered surgical treatment could be instead approached with transcatheter procedures is being slowly adjusted. Even more importantly, as in most cases their efficacy in reducing TR severity remains limited and not comparable to results obtained with surgical correction. In this regard, a heart valve centre with expertise in TV disease and treatment is of utmost importance[54,55].

Surgery is the most effective treatment. The choice between the different surgical options should be driven by the underlying mechanism of regurgitation and etiology of the disease. Tricuspid valve repair (TVr) remains the preferred technique and should be performed whenever possible in patients requiring surgery[27,28]. TV repair mainly focuses on tricuspid annuloplasty, which aims at reducing annulus diameter and valve cross-sectional area, as well as restoring normal three-dimensional valve anatomy. Annuloplasty can be performed with suturing techniques or with the implantation of rings. The current gold standard for surgical repair is ring annuloplasty with an incomplete semi-rigid prosthetic ring. Ring annuloplasty, as compared to suture techniques (such as Kay bicuspidalization or De Vega suture annuloplasties[56]), is generally associated with improved long-term survival and event-free survival, and correlates with a trend towards fewer TV re-operations[42,57,58]. However, simply correcting annular dilation has been associated with failure in case of leaflet tethering and RV dysfunction or remodeling[59]. Surgical techniques that address leaflet pathology are available, such as the clover technique or anterior leaflet augmentation, with reported promising results, especially in complex lesions and marked leaflet tethering scenarios[60–62]. Even though TVr is preferred to replacement, whenever indicated and feasible, tricuspid valve replacement (TVR) represents another surgical option. Overall, TVR is performed in a minority of patients, approximately 10-15% of cases. Hesitance is mainly related to the very high immediate perioperative morbidity and mortality rates, reported as high as 10.9%, that have not changed significantly during the last decade[17,63]. Furthermore, studies have indicated that TVr is more beneficial in comparison to TVR regarding all-cause mortality[64,65]. These results seem to be related to the late referral and more severe TV disease at the time of surgery[66]. However, TVR may be beneficial and associated with improved outcomes in patients with primary/organic TR because of the extent and severity of the underlying pathology (such as infective endocarditis, rheumatic disease or iatrogenic causes) or in secondary TR when the TV leaflets are excessively tethered or the annulus is severely dilated[67]. In fact, a tethering height > 0.5cm and a tethering area > 0.8cm^2 are predictive of moderate-to-severe TR at 1 year following annuloplasty[68], and a tricuspid annular diameter >44mm is associated to improved survival following TVR as compared to valve repair[69]. Furthermore, due to the high-risk of reinterventions, a definitive solution is often preferred. A major concern of TVR is that approximately one third of patients receive a permanent pacemaker prior to discharge[70].

The optimal prosthesis for TVR is still controversial. On one hand, mechanical heart valves are durable and have low re-operation rates (97% 15-years freedom from TV re-operations); however, non-structural valve dysfunction (such as pannus formation), bleeding, thrombosis, thromboembolic events, and the impossibility of transvenous pacing are major concerns. Observed rates of mechanical valve thrombosis range from 3 to 18%[71–73]. On the other hand, bioprosthetic valves have the advantage of not requiring long-term anticoagulation therapy, but are associated to the limited durability of tissue valves, even if their degeneration is expected to be slower than prostheses implanted in the left heart positions[72,74]. A recent meta-analysis suggested an equal risk of in-hospital and late mortality, re-operation rate and 5-year valve failure in patients undergoing TVR with a mechanical versus biological prosthesis[75]. As there appears to be no superiority of one valve over the other, the final choice should be a shared decision between the patient and the physician. Also, the possibility of performing new percutaneous procedures of tricuspid valve-in-valve implantation following bioprosthetic failure may contribute to tipping the scale in favour of tissue valves.

New transcatheter solutions for the treatment of TR are now emerging[76]. Patients undergo leaflet-to-leaflet repair, incomplete ring annuloplasty, coaptation devices, heterotopic caval valve implantation as well as transcatheter TV replacement (TTVR) with orthotopic valve implantation. At present, the most widely applied technique is transcatheter edge-to-edge repair (T-TEER) of the tricuspid valve using the TriClip device (Abbott Vascular, Santa Clara, CA, USA)[77]. Results from retrospective studies assessing leaflet approximation devices have shown a durable reduction to moderate or less TR in approximately 70% of patients, together with symptomatic improvement (40% reduction in re-hospitalization rates) and lower mortality at 1 year[46,78–80]. Anatomical limitation, such as large coaptation gaps (<7-10mm) and non-anteroseptal location of the TR jet, have been identified as predictors of procedural failure[48,81]. Therefore, various other transcatheter techniques have been developed, however these new approaches are still in development and long-term data are lacking[82,83]. Moreover, there are many patients who do not qualify for a repair strategy. Valve performance and absence of residual TR seem superior in patients undergoing orthotopic

TTVR, however in spite of worse procedural safety, higher rates of major adverse events and higher reported in-hospital mortality (up to 10% in some series)[84–86].

Therefore, the management of patients with severe symptomatic isolated TR remains extremely challenging. Little awareness remains to date within the clinical and scientific communities of “who”, “when” and “how” to treat severe isolated TR. The misconception that surgical treatment is always associated with an excessive morbidity and mortality has led to long-term medical management of such patients. However, medical treatment remains purely symptomatic, and in late stages of the disease surgery is associated with a prohibitive risk and transcatheter procedures may result futile.

Aim and outline of the thesis

The purpose of this thesis is to analyse isolated tricuspid valve regurgitation and patients that underwent TV surgery, either repair or replacement, in order to try and identify possible predictors of a favourable outcome. These findings may help in determining the ideal preoperative assessment and optimal timing for intervention, as well as provide further proof that early tricuspid valve surgery is feasible, with a low associated risk and good outcomes.

This was achieved through original research and review articles.

Outcomes of isolated TV surgery were analysed in a cohort of patients undergoing both TV repair and replacement. Initially in-hospital outcomes were assessed, more specifically in-hospital mortality, postoperative complication and length-of-stay. Then, mid-term outcomes were assessed, concerning both survival and freedom from re-hospitalization for right heart failure at follow-up.

The specific issue of isolated tricuspid regurgitation in patients with cardiac implantable electronic devices was then addressed in a surgical cohort of patients, assessing both short and long-term outcomes.

Finally, a single-centre validation study of a novel surgical risk score was performed, analysing whether the TRI-SCORE is a reliable tool for predicting in-hospital and long-term mortality in a cohort of patients undergoing isolated TV surgery.

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Chapter 2

ISOLATED TRICUSPID VALVE SURGERY: FIRST OUTCOMES REPORT ACCORDING TO A NOVEL CLINICAL AND FUNCTIONAL STAGING OF TRICUSPID REGURGITATION

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Eur J CardioThorac Surg 2021;60(5):1124-1130.

Abstract

Objectives: This study aims at assessing the applicability of a novel classification of patients with tricuspid regurgitation based on 5 stages and evaluate outcomes following isolated surgical treatment.

Methods: All patients treated with isolated tricuspid valve repair (TVr) or replacement (TVR) from March 1997-January 2020 at a single institution were retrospectively reviewed. Patients were divided according to a novel clinical-functional classification, based on the degree of regurgitation together with symptomatology, right ventricular size and function and medical therapy. 195 patients were treated, however 23/195 had to be excluded due to lack of sufficient preoperative data.

Results: 172 patients have been considered, among whom 129 (75%) underwent TVR and 43 (25%) TVr. The distribution of patients showed that 46.5% of patients who underwent TVr were in Stage-2, while 51.9% who underwent TVR were in Stage-3. TVR patients were in more advanced stages of the disease, with dilated right ventricles, more pronounced symptomatology and development of organ damage. Hospital mortality was 5.8%, in particular 0% in Stages 2-3 and 15.3% in Stages 4-5 ($p<0.001$). Both intensive care unit and hospital stay were significantly longer in more advanced Stages ($p<0.001$). Patients in Stages 4-5 developed more postoperative complications, such as acute kidney injury (3.7-10% in Stages 2-3 vs 44-100% in Stages 4-5,

$p<0.001$) and low cardiac output syndrome (15-50% in Stages 2-3 vs 71-100% in Stages 4-5, $p<0.001$).

Conclusions: Patients in more advanced Stages had higher hospital mortality and longer hospitalizations. Timely referral is associated with lower mortality, short postoperative course and mostly valve repair.

Introduction

Tricuspid valve (TV) pathology has been disregarded for a very long time due to firm belief that treatment of left-sided heart disease would lead to resolution of tricuspid insufficiency [1]. Therefore, conservative treatment has always been the gold-standard. However, with the advent of new transcatheter interventions, more attention has been paid to the tricuspid valve [2]. In fact, due to increasing interest in tricuspid valve disease, surgical and percutaneous treatments have recently been under the spotlight.

A growing number of studies have been published in the literature reporting high morbidity and mortality for the surgical treatment of isolated tricuspid regurgitation (TR) [3,4,5]. Poor outcome of tricuspid valve repair or replacement is mainly related to delayed surgical approach usually associated with dilation and/or dysfunction of the right ventricle (RV) [6]. Patients are often managed pharmacologically, mainly with diuretics, for a long period of time, and referred to surgery only after development of hepato-renal dysfunction and refractoriness to medical therapy. At this point, patients have prominent RV dilation and dysfunction, resulting in complicated and poor postoperative response, further strengthening the belief of a high-risk procedure, with a high early and late mortality [4,7,8]. This vicious circle should be interrupted early on in the TV disease progression [9].

A novel clinical and functional staging of TV regurgitation has been recently proposed [10,11]. The progression of morphological changes to the TV, annulus, and right ventricle has been described and associated to onset of symptoms. The classification proposed by Latib et al [10] and mentioned by Taramasso et al [11], identifies a number of parameters and factors that may be useful in better stratifying surgical risk, such as TR grade, symptoms, RV remodelling and function and medical therapy.
The aim of our study was to understand the distribution of patients submitted to isolated TV surgery into the 5 stages of this classification and assess their in-hospital outcomes accordingly.

Methods
A retrospective, single-centre study, including 195 patients affected by TV regurgitation and treated with isolated TV surgery from March 1997 to January 2020 at San Raffaele University Hospital, Milan, Italy, was conducted. All consecutive patients were individually reviewed. The Ethical Committee of our Institution approved the Study and waived individual informed consent for this retrospective analysis. The most relevant baseline factors for classification were specifically analysed. All patients had undergone both preoperative transthoracic (TTE) and transesophageal echocardiography (TEE) upon hospitalization. Transesophageal echocardiography was routinely used to better define the mechanism of TR. Within

the study period, and as a common practice within our Institution, patients were admitted to the hospital 48-72 hours before surgery, and within this time-frame adequately studied. Echocardiographic parameters together with all preoperative characteristics and data were inserted within a dedicated database. Symptomatology grading, ranging from none to overt right ventricular failure (RVF) and organ damage, was defined based on New York Heart Association Class, together with the presence upon presentation of peripheral edema, ascites, repeated previous episodes of hospitalization for RVF, and altered laboratory values specific for hepato-renal function. TR was graded on a four-grade scale as 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe), and 4+ (severe). In the more recent period of the study time frame, this grading was based on a multiparametric approach, according to the current European Association of Echocardiography recommendations [12–14]. Overall, 55/195 (28.2%) patients were evaluated with newer and more extensive echocardiographic approaches. RV remodelling and function was defined based on preoperative TTE and TEE values, such as RV end-diastolic diameter (RV-EDD), tricuspid annular plane systolic excursion (TAPSE), tissue doppler imaging (S' TDI) and systolic pulmonary artery pressure (sPAP). Medical therapy was assessed based on daily diuretic use, dosage and combination therapies, and retrospectively judged as low-dose, moderate-to-high dose and frequent need for intravenous diuretic use [15,16]. Based on combination of all factors, patients were divided according to the 5 Stages of the Classification (**Figure 1**).

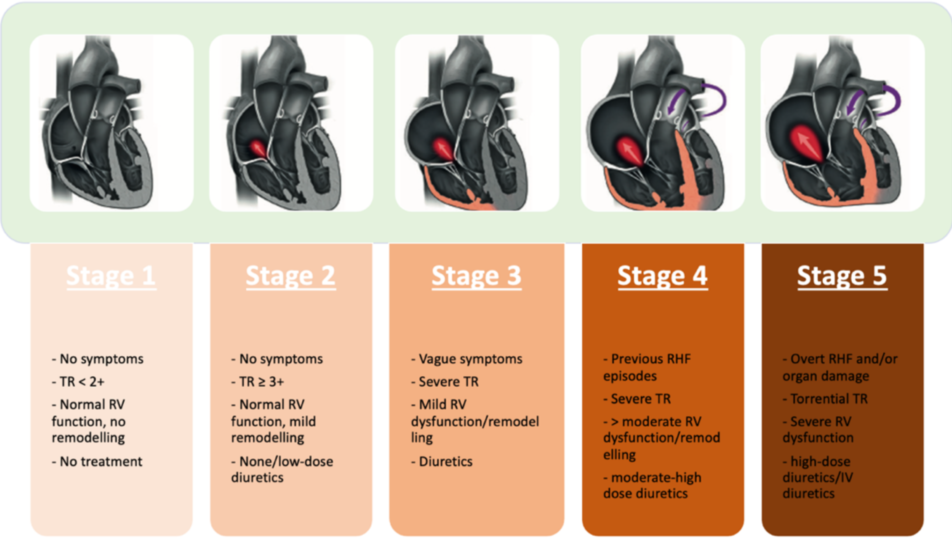


Figure 1. 5 Stages Classification and determinants/characteristics for distribution of patients.

Surgery was performed using standard techniques including bicaval cannulation or peripheral venous cannulation based on surgeon's preference. TV surgery was performed either on beating-heart (BH) or arrested-heart (AH), using standard median sternotomy approach or right anterior thoracotomy [17,18].

All patients underwent TEE in the operating room after weaning from cardiopulmonary bypass and transthoracic echocardiography before discharge, in order to assess biventricular function, and outcomes of either tricuspid valve repair or replacement. Primary end-points of the study were in-hospital mortality, intensive care unit (ICU) postoperative length-of-stay (LOS), and hospital LOS. Secondary end-points of the study were development of postoperative in-hospital complications as well as general assessment of the distribution of our patient population according to the 5 stages.

Statistical analyses

Statistical analysis was conducted using SPSS (IBM, Amonk, New York, USA) and Stata Software (Statacorp, LLC, TX, USA; version 15). Categorical variables were expressed as absolute number and percentages. Normal distribution of continuous variables was assessed with the Shapiro-Wilk test. Continuous variables normally distributed were expressed as mean ± standard deviation (SD). Continuous variables not normally distributed were reported as median and interquartile range [IQR]. Differences between stages for categorical variables was tested with χ^2 test or Fisher's exact test, as appropriate. Differences between stages for continuous variables was tested with ANOVA or Kruskal-Wallis tests, as appropriate.

Logistic regression model was employed to assess differences between stages for in-hospital mortality. Poisson regression model or negative binomial regression model, whenever there was overdispersion, were utilized to assess differences between stages in terms of ICU length-of-stay (LOS) and hospital LOS.

Dunnet test with Bonferroni correction was run to perform multiple comparisons between stages. Univariate and multi-variate analyses were performed to assess predictive factors for hospital mortality. A p-value of less than 0.05 was employed to define statistical significance.

Results

A total of 195 patients, who underwent isolated tricuspid valve surgery at our Institution, were reviewed and, based on preoperative characteristics, divided according to the 5 Stages. 23/195 (12%) patients were excluded from the study due to lack of sufficient preoperative data and, therefore, inability of adequately allocating them in the correct Stage (**Figure 2**). None of our patients fulfilled criteria for Stage 1, since by definition TR grade is to be considered less than moderate, and therefore patients undergoing isolated surgical treatment had at least moderate-to-severe TR. Furthermore, an extremely limited number of patients treated were part of the end-stage disease group (Stage 5).

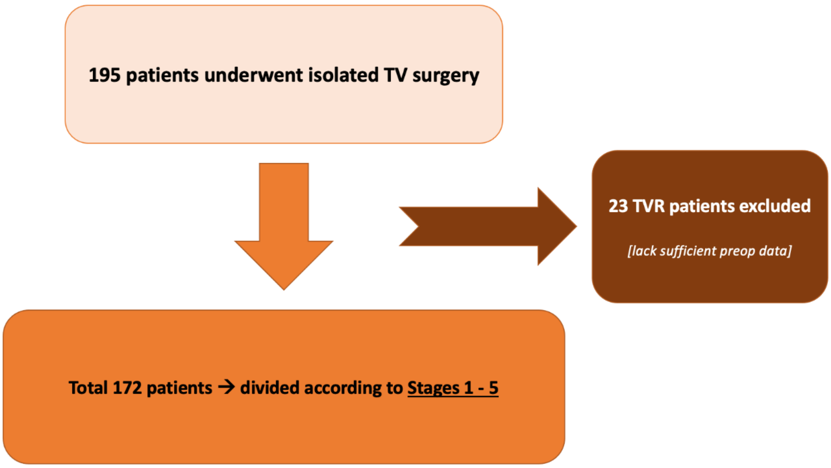


Figure 2. Flow Chart of the Study Population.

The distribution of patients in Stages is reported in **Table 1**. A total of 172 patients have been considered for the purpose of this study, among which 129 (75%) underwent isolated TV replacement (TVR) and 43 (25%) underwent TV repair (TVr). The main etiologies were: functional TR in 75 patients (43.6%), primary TR in 40 patients (23.3%, among whom 2 had carcinoid disease, 4 patients had congenital anomalies, 14 rheumatic disease and 20 degenerative involvement), endocarditis in 15 patients (8.7%), failure of previous TV repairs was present in 14 cases (8.1%) and bioprosthesis degeneration in 4 patients (2.3%), a mix etiology was seen in 11 patients (6.4%), and traumatic TR in 10 patients (5.8%).

A beating-heart operation was carried out in 110 patients (64%). A beating heart rather than arrested-heart approach was chosen based on surgeon's preference. In general, a BH operation was preferred in patients with more advanced right ventricular dysfunction to avoid any further myocardial damage potentially due to cardioplegic arrest, and in patients undergoing tricuspid valve replacement. On the other hand, patients with patent foramen ovale or inter-atrial septal defects were preferably treated with an AH approach. No difference between surgical technique and in-hospital outcomes was noted within our patients population.

Table 1. Distribution in Stages of Patients

	Stage 1 *N=0 (0%)*	Stage 2 *N=27 (15.7%)*	Stage 3 *N=80 (46.5%)*	Stage 4 *N=62 (36%)*	Stage 5 *N=3 (1.7%)*	*p-value*
Surgery						
• TVR	-	7 (5.4%)	67 (51.9%)	52 (40.3%)	3 (2.3%)	
• TVr	-	20 (46.5%)	13 (30.2%)	10 (23.3%)	0 (0%)	
Preop characteristics						
• Age (Years)	-	48 [28-64]	68 [58-75]	70 [63-76]	75 [68-79]	*<0.001*
• Sex (Female)	-	13 (48%)	51 (64%)	46 (74%)	2 (67%)	*0.107*
• NYHA III-IV	-	5 (19%)	44 (55.5%)	55 (89%)	3 (100%)	*<0.001*
• A Fib	-	7 (26%)	53 (66%)	54 (87%)	2 (67%)	*<0.001*
• CKD	-	0 (0%)	15 (19%)	21 (34%)	3 (100%)	*<0.001*
• eGFR (ml/min)	-	94 [77-138]	66 [49-90]	52 [37-69]	28 [27.6-28]	*<0.001*
• Bilirubin (mg/dL)	-	0.8 [0.5-1.3]	0.9 [0.6-1.5]	1.1 [0.8-1.4]	0.7 [0.3-1]	*0.083*
• Albumin	-	62 [59-63]	58 [54-61]	57 [52-59]	54 [45-58]	*<0.001*
• AST (U/L)	-	22 [18-29]	27 [22-38]	30 [24-39]	19 [15-26]	*0.004*
• ALT (U/L)	-	26 [17-29]	22 [18-29]	22 [14-27]	12 [9-14]	*0.060*
• Ascites	-	0 (0%)	3 (3.8%)	31 (50%)	3 (100%)	*<0.001*
• Diuretics Dose (mg)	-	0 [0-16.25]	25 [0-50]	100 [50-175]	375 [125-500]	*<0.001*
• RHF hospitalization	-	0 (0%)	8 (10%)	48 (77%)	3 (100%)	*<0.001*
• REDO	-	7 (26%)	42 (53%)	47 (76%)	3 (100%)	*<0.001*
Preop TEE parameters						
• LVEDD (mm)	-	45.3±6.18	46.6±5.17	48.5±7.57	59±10.54	*<0.001*
• LVEF (%)	-	60 [60-63]	60 [57-62]	55 [51-60]	60 [50-60]	*0.003*
• sPAP (mmHg)	-	35 [30-40]	40 [35-50]	40 [35-50]	43 [38-50]	*<0.001*
• TAPSE (mm)	-	26.2±3.71	21.4±5.56	18±4.54	17	*0.001*
• TDI (m/s)	-	12 [10-16]	11 [10-13]	9.4 [8-10]	N.A.	*0.001*

A Fib: atrial fibrillation; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RHF: right heart failure; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue doppler imaging; TEE: transesophageal echocardiography; TVr: tricuspid valve repair; TVR: tricuspid valve replacement

In case of TVR, a bioprosthesis was used in 123 patients (95.4%) and a mechanical prosthesis was preferred in the remaining 6 (4.6%). Among these, four patients occurred early within our experience. The remaining two patients were both young women with history of extremely rapid bioprosthesis degeneration. Among the 43 patients submitted to repair for the different etiologies reported, a ring annuloplasty was performed in 37 of them (86%), with or without concomitant leaflet repair (including edge-to-edge or clover technique), whereas in the remaining 6 no ring was used and the repair consisted in suture annuloplasty and/or leaflet repair. Considering the overall population, the great majority of patients were classified either in Stage 3 (46.5%) or Stage 4 (36%). However, when analysing separately patients who underwent either repair or replacement, 46.5% of patients who underwent TVr were in Stage 2, while more than half of TVR patients were in Stage 3 (51.9%).

When considering the overall distribution, patients in Stages 2-3 were younger and in less advanced stages of the disease (**Table 1**). In fact, patients presented with fewer signs and symptoms of RVF, with ascites being almost absent and atrial fibrillation not being the main presenting rhythm; lesser organ involvement and development of hepato-renal syndrome was seen, as underlined by higher albumin levels and lower frequency of chronic kidney disease (CKD). Furthermore, patients in Stages 4-5 were more frequently patients who had previously undergone cardiac surgeries (REDO operations). Regarding echocardiographic parameters, patients in Stages 2-3 had less dilated and dysfunctional left ventricles (LV), better right ventricular function and lower systolic pulmonary artery pressure (sPAP).

Moreover, TV repair could be performed in most patients in Stage 2.

Postoperative outcomes were significantly different between Stages, more specifically, the advancement in Stage was correlated with higher mortality and development of postoperative complications. Indeed, mortality in the overall population was 5.8% (10/172 patients), but it was 0% in Stage 2 and 3 and 15.3% in Stages 4-5 (p<0.001), and it was uniquely seen in patients who underwent TVR and who were in Stage 4.

Table 2. Univariate and multivariate analyses

	Univariate			Multivariate		
variables	OR	*p-value*	95% CI	OR	*p-value*	95% CI
Age	1.04	0.182	0.98-1.11			
Sex	0.45	0.320	0.09-2.18			
NYHA III-IV	**5.88**	**0.097**	**0.73-47.51**	4.50	0.175	0.51-39.56
EF	**0.89**	**0.001**	**0.84-0.96**	**0.92**	**0.015**	**0.85-0.98**
sPAP	1.01	0.871	0.94-1.08			
AFib	1.99	0.391	0.41-9.79			
PM	**3.33**	**0.076**	**0.88-12.62**	2.65	0.185	0.63-11.24
COPD	2.46	0.213	0.60-10.20			
CKD	**3.76**	**0.045**	**1.03-13.76**	2.24	0.259	0.55-9.07

Afib: atrial fibrillation; CI: confidence interval; CKD: chornic kidney disease; COPD: chronic obstructive pulmonary disease; EF: ejection fraction; NYHA: New York Heart Association; OR: odds ratio; PM: pacemaker; sPAP: systolic pulmonary artery pressure

At univariate analysis CKD and LVEF emerged as predictors of hospital mortality but at multivariate analysis, only LVEF was identified as an independent predictor of this event (OR 0.92, p=0.015, CI 0.85-0.98) (**Table 2**). Patients in more advanced stages experienced more postoperative complications, such as acute kidney injury (AKI) (3.7-10% in Stages 2-3 vs 44-100% in Stages 4-5, p<0.001) and low cardiac output syndrome (LCOS) with the need of high dose of inotropic support (15-50% in Stages 2-3 vs 71-100% in Stages 4-5, p<0.001). The incidence of new postoperative permanent pacemaker overall was 10.4% (18/172) and all cases occurred after TVR (18/129, 13.9%) (**Table 3**). All implanted prostheses functioned adequately postoperatively (mean gradient among Stages 3.6±1.3mmHg) and all TV repairs had good outcome, with the exception of two patients who were discharged with residual moderate (2+/4+) tricuspid regurgitation. No difference among Stages was reported.

Table 3. Postoperative complications

	Stage 1 N=0 (0%)	Stage 2 N=27 (15.7%)	Stage 3 N=80 (46.5%)	Stage 4 N=62 (36%)	Stage 5 N=3 (1.7%)	*p-value*
AKI	-	1 (3.7%)	8 (10%)	27 (44%)	3 (100%)	*<0.001*
Shock - LCOS	-	4 (15%)	40 (50%)	44 (71%)	3 (100%)	*<0.001*
New PM	-	2 (7.4%)	8 (10%)	8 (13%)	0 (0%)	*0.853*
Death	-	0 (0%)	0 (0%)	10 (16.1)	0 (0%)	*p<0.001*

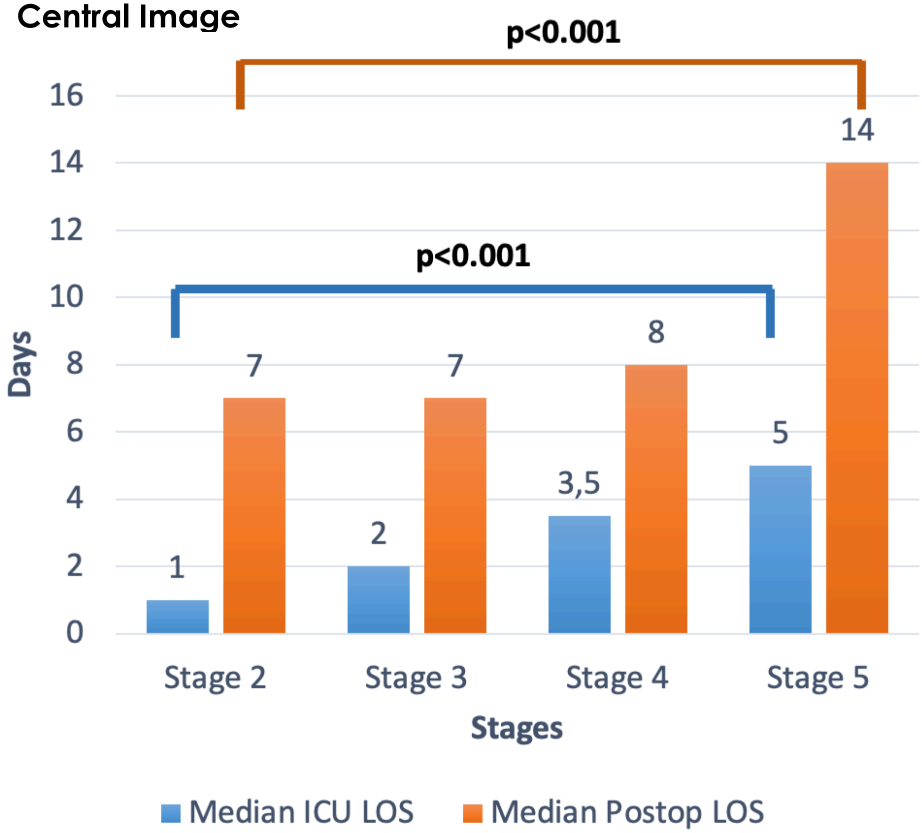
AKI: acute kidney injury; LCOS: low cardiac output syndrome; PM: pacemaker

As shown in **the Central Image**, both ICU and hospital length-of-stay were significantly longer in the more advanced Stages.

Discussion

This retrospective, single-centre study evaluated the applicability of a novel clinical and functional classification of patients with TR proposed by Latib and colleagues [10,11] to our isolated tricuspid valve surgery series. To the best of our knowledge this is the first study assessing the outcomes of isolated TVr or TVR according to this 5 Stage preoperative classification. Overall, this classification does reflect the population of patients affected by isolated TR we have been surgically treating. In fact, in our series around 40% of patients

Central Image



belonged to the advanced Stages 4 and 5, showing more pronounced
RV dilation and dysfunction, presenting with important symptomatology and organ involvement/damage. This resulted in higher in-hospital mortality, higher rate of postoperative complications, longer ICU and hospital length-of-stay. Furthermore, these patients were more frequently REDO cases and were more likely to undergo valve replacement because of the important geometric deformation of the tricuspid valve with severe tethering besides annular dilation secondary to advanced right ventricular remodelling. Our findings are in-line with a great number of retrospective studies that have underlined a very poor clinical outcome in patients submitted to surgical treatment for severe TR late after left-sided heart surgery [19,20]. High in-hospital mortality and poor follow-up results seem to be related to the high-risk profile of the treated patients, who are frequently elderly, with advanced functional class and concomitant pathologies, rather than being related to tricuspid valve surgery per se [21].
In the current era, a great number of technologies and new devices have been investigated and proposed, in order to address such patients that are considered too high-risk for surgery [22]. However, few data are to-date available, and none of the currently developed technologies effectively solve this growing problem [23]. On the other hand, a very timely surgical referral could dramatically change the surgical risk as

well as the late outcome of this challenging population. The lack of data reporting positive outcomes following early TV surgery for isolated TR have contributed to the uncertainty as to when and how to treat this pathology. Timing remains controversial. Our data further support current ESC/EACTS guidelines recommending early referral for surgery in patients with isolated TV regurgitation, even asymptomatic, in case of progressive RV dilation or initial dysfunction, well before advanced RV remodelling/failure and organ damage [24,25]. In our opinion the 2014 AHA/ACC guidelines [23] are not able to change the poor outcomes associated with Stages 4-5 surgical referral. Indeed, they suggest, for instance, that reoperation for isolated TV disease may be considered (IIb) for persistent symptoms due to severe TR in patients who had previously undergone left-sided heart surgery. Such symptoms typically occur in the very advanced stages of the disease. Our data support the concept that the timing of surgical referral should be chosen looking not mainly at the symptoms but essentially at the stage, which include the degree of TR, RV size and function, geometry of the tricuspid valve, dose of diuretics. This is confirmed by the fact that Stages 2-3 were associated to better outcomes as compared to Stages 4-5, but basically no individual predictors of mortality were identified at multivariate analysis, with the exception of LVEF. We speculate that the Stage is expression of a number of parameters which are more important for risk stratification than the single clinical or echocardiographic variables.

In our experience, particularly patients belonging to Stage 2 had no hospital mortality, a smooth and short postoperative course following tricuspid valve repair, which could be performed in the majority of cases. These findings are in-line with studies that have identified as determinants of good outcome both left and right ventricular function and pulmonary pressures, emphasizing the importance of timely referral before the development of end-stage cardiac impairment [26]. Therefore, early referral and intervention in patients with isolated tricuspid regurgitation is of utmost importance, as demonstrated by our surgical experience. Both TV repair and replacement, when performed in early stages of the disease are feasible, safe, with a low rate of postoperative complications and low reported mortality. Repair should be pursued whenever possible, being associated with lower mortality, smoother postoperative course and no/low need of pace-maker and, according to our series, its likelihood is higher in the early Stages of the disease.

Whenever early interventions are not performed and patients in advanced stages are treated, due to the high-risk of further exacerbating RV dysfunction and LCOS, a more protective perioperative management should be considered. Preoperative and/or postoperative support, with either inotropes or mechanical support devices, has been shown to rapidly result in hemodynamic improvement and contribute to a favourable survival [27,28]

Study limitations

Our study has limitations, mainly related to the fact that it is a retrospective single-centre study. Thorough assessment of preoperative baseline characteristics and echocardiographic parameters was completed to try and perform the most accurate division into Stages possible. However retrospective adjudication has its limitations, which need to be kept in mind. The sample size is relatively small due to the few isolated TV surgical procedures performed, and partly due to the lack of sufficiently complete data, especially systematic echocardiographic parameters. Furthermore, the fact that most patients were evaluated using older echo techniques to grade TR, may have affected the division in Stages. Another limitation is that we focused on the hospital outcome of the patients and further studies should address the late results at follow-up.

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New York - 2016

Chapter 3

COMPLICATED POSTOPERATIVE COURSE IN ISOLATED TRICUSPID VALVE SURGERY: LOOKING FOR PREDICTORS

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J Card Surg 2021;36(9):3092-3099.

Abstract

Background: This study aims at better defining the profile of patients with a complicated versus non-complicated postoperative course following isolated tricuspid valve (TV) surgery to identify predictors of a favourable/unfavourable hospital outcome.

Methods: All patients treated with isolated tricuspid surgery from March 1997-January 2020 at our institution were retrospectively reviewed. Considering the complexity of most of these patients, a regular postoperative course was arbitrarily defined as a length-of-stay in intensive care unit <4 days and/or postoperative length-of-stay <10days. Patients were therefore divided accordingly in two groups.

Results: 172 patients were considered, among whom 97 (56.3%) had a regular (REG) and 75 (43.6%) a non-regular (NEG) postoperative course. The latter had worse baseline clinical and echocardiographic characteristics, with higher rate of renal insufficiency, previous heart failure hospitalizations, cardiac operations, and right ventricular dysfunction. NEG patients more frequently needed tricuspid replacement and experienced a greater number of complications (p<0.001) and higher in-hospital mortality (13% vs 0%, p<0.001). The majority of these complications were related to more advanced stage of the tricuspid disease. Among most important predictors of a negative outcome univariate analysis identified chronic kidney disease, ascites, previous right heart failure hospitalizations, right

ventricular dysfunction, previous cardiac surgeries, TV replacement and higher MELD scores. At multivariate analysis, liver enzymes and diuretics' dose were predictors of complicated postoperative course.

Conclusions: In isolated TV surgery a complicated postoperative course is observed in patients with more advanced right heart failure and organ damage. Earlier surgical referral is associated to excellent outcomes and should be recommended.

Introduction

Interest in tricuspid valve (TV) pathology has recently grown, due to reported poor clinical outcome of patients affected by tricuspid regurgitation (TR) and the impact on long-term survival of such pathology[1–3]. In particular, isolated TR has been traditionally managed with medical therapy for a long time before referring patients to surgery. Indeed earlier referral has been discouraged by the poor results of tricuspid repair or replacement whose hospital mortality has remained stable around 10%[4–7] over the years. The current European[8] and American[9] Guidelines for the management of valvular disease provide somehow different recommendations for isolated tricuspid surgery. The American guidelines tend to be more conservative and suggest waiting for signs or symptoms of "right heart failure" before recommending tricuspid repair (TVr) or replacement (TVR) (class IIa or IIb depending on the etiology). In asymptomatic patients with primary severe isolated TR and progressive RV dilation/dysfunction only a class IIb recommendation is given. Unfortunately, in severe isolated TR, "persisting symptoms" usually develop only in advanced stages of the disease being mainly the clinical manifestation of right ventricular failure, with organ damage and hepato-renal syndrome[10]. These patients face high morbidity and mortality after surgery, further fuelling the belief of TV surgery being a high-risk procedure. On the other hand, European Guidelines strongly support an earlier surgical referral, even in asymptomatic patients, with initial RV dilation/dysfunction to achieve low hospital mortality and better postoperative outcome[8]. Indeed, the surgical act of tricuspid repair or replacement is not technically demanding in itself and the outcome is therefore almost exclusively depending on the baseline patient's profile. The absence of a validated risk score for such surgical procedures, poses further uncertainty regarding the best management of these patients and the correct timing of intervention[11–14]. A better understanding of the baseline characteristics of patients who experience a regular versus a non-regular postoperative course can help the decision-making regarding the surgical timing of those challenging cases.

The aim of this study was to better define the profile of patients who had a smooth versus a complicated postoperative course following isolated tricuspid valve surgery, in order to try to identify predictors of a favourable or unfavourable in-hospital outcome.

Materials and Methods

A retrospective, single-centre study including patients affected by tricuspid regurgitation and treated with isolated tricuspid valve surgery from March 1997 to January 2020 at San Raffaele University Hospital, Milan, Italy, was conducted. All consecutive patients were individually reviewed and preoperative, intraoperative and postoperative data was collected in a dedicated database. The Ethical Committee of our Institution approved the Study and waived individual informed consent for this retrospective analysis. Patients were divided into regular (REG) and non-regular (NEG) postoperative course. Patients were arbitrarily defined as regular when length-of-stay (LOS) in intensive care unit (ICU) was less than 4 days and/or postoperative overall LOS was less than 10 days, without major complications. All patients had undergone transthoracic (TTE) and transesophageal echocardiography (TEE) before surgery and transthoracic echocardiogram before discharge. Transesophageal echocardiography was routinely used to better define the mechanism of TR. TR grade was graded on a four-grade scale as 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe), and 4+ (severe). In the most recent years a multiparametric approach according to the current European Association of Echocardiography recommendations was adopted to confirm TR grading[15–17].

Surgery was performed using standard techniques including bicaval cannulation or peripheral venous cannulation based on surgeon's preference. TV surgery was performed either on beating-heart (BH) or arrested-heart (AH), using standard median sternotomy approach or right anterior thoracotomy[18,19]. Whenever feasible, tricuspid valve repair was performed. However, valve replacement was preferred in presence of major geometric deformations of the tricuspid valve with significant leaflet tethering.

The primary endpoint of the study was the definition of the profile of patients who had a complicated versus non-complicated postoperative course. Secondary endpoints were assessment of in-hospital mortality, number of postoperative complications and identification of predictors of a favourable or unfavourable hospital outcome.

Statistical analysis

Statistical analysis was conducted using SPSS (IBM, Amonk, New York, USA) and Stata Software (Statacorp, LLC, TX, USA; version 15). Categorical variables were expressed as absolute number and percentages. Normal distribution of continuous variables was assessed with the Shapiro-Wilk test. Continuous variables normally distributed were reported as mean ± standard deviation (SD). Continuous variables not normally distributed were reported as median and interquartile range [IQR]. Poisson regression model was used to assess differences between groups in terms of number of complications (a negative binomial regression model was not employed due to no overdispersion). Univariate and multivariate logistic analysis was performed to identify predictors of a negative/non-regular postoperative course.

Results

A total of 195 patients who underwent isolated tricuspid valve surgery at our institution were reviewed and, based on the postoperative course, divided in regular and non-regular categories. 23/195 patients (12%) were excluded from the study due to lack of sufficient data and therefore inability of correctly assigning them to either category (**Figure 1**). A total of 172 patients were finally considered for the purpose of this study, among whom 97 (56.3%) had a regular postoperative course and 75 patients (43.7%) a complicated one. In the overall population, 43 patients underwent TVr (25%) and 129 (75%) underwent TVR. Among the 43 patients submitted to repair, a ring annuloplasty was performed in 37 of them (86%), with or without concomitant leaflet repair (including edge-to-edge or clover technique), whereas the remaining 6 patients received suture annuloplasty and/or leaflet repair. 7/43 (16.3%) patients with TVr experienced a complicated postoperative course. In case of TVR a bioprosthesis was used in 123 patients (95.4%) and a mechanical prosthesis was used in the remaining 6 patients (4.6%). Among patients submitted to replacement, 68 (55.3%) had a non-regular postoperative course.

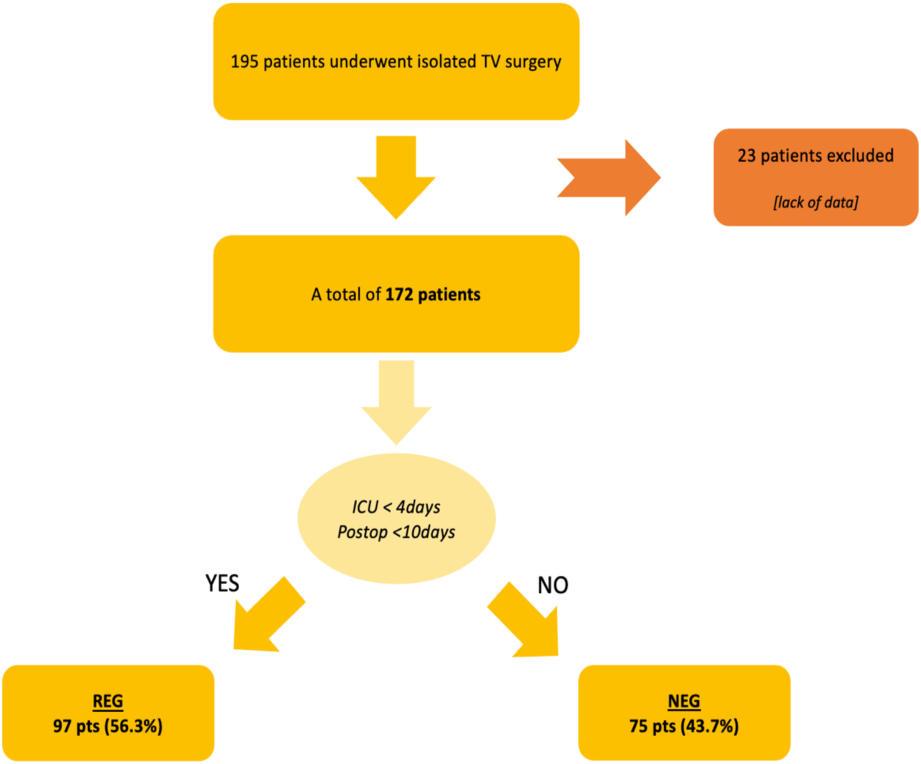

Figure 1. Flow-chart showing patients

Analysing the preoperative characteristics, patients in the NEG group had worse baseline clinical and echocardiographic parameters, as shown in **Table 1**. Indeed, patients with an unfavourable postoperative course were more frequently presenting with higher New York Heart Association (NYHA) functional class, previous episodes of right heart failure, ascites and higher diuretics dose. In addition, NEG patients presented with organ damage, such as chronic kidney disease (CKD), low albumin levels, and higher liver enzymes. Interestingly enough, the MELD score[20] (Model for End-stage Liver Disease) was calculated for all patients and was found to be significantly higher in patients with a negative postoperative course. Furthermore, both right ventricular size and function, together with left ventricular dilation and pulmonary hypertension were more marked in patients with a complicated postoperative course (**Table 1**).

Table 1. Baseline clinical, echocardiographic and intraoperative characteristics

	NEG N=75	REG N=97	*p-value*
Preop characteristics			
• Age (years)	67 [57-75]	68 [54-75]	*0.655*
• Logistic EuroSCORE	8.5 [4.3-15.3]	4 [1.3-7.2]	*<0.001*
• Afib	53 (70.7%)	63 (64.9%)	*0.427*
• CKD	23 (30.7%)	16 (16.5%)	*0.028*
• Diabetes	15 (20%)	9 (9.3%)	*0.044*
• NYHA III-IV	55 (73.3%)	52 (53.6%)	*0.023*
• Bilirubin (mg/dL)	0.9 [0.6-1.5]	1 [0.6-1.4]	*0.333*
• Albumin	55.7 [51.3-58.7]	59 [56.2-61.4]	*0.013*
• AST (U/L)	29.5 [23-43]	25 [20.5-33.5]	*0.031*
• ALT (U/L)	22 [16-30]	22 [17-27]	*0.591*
• Ascites	22 (29.3%)	15 (15.5%)	*0.028*
• Diuretics dose (mg)	50 [25-150]	25 [25-50]	*0.002*
• RHF hospitalization	33 (44%)	26 (26.8%)	*0.014*
• REDO	58 (77.3%)	41 (42.3%)	*<0.001*
• >1 REDO	22 (29.3%)	7 (7.2%)	*<0.001*
• MELD Score	15 [10-18]	13 [7.5-16]	*0.010*
Echo parameters			
• LVEDD (mm)	48.8±7.33	46.4±5.98	*0.028*
• LVEF (%)	58.5 [55-60]	60 [55-62]	*0.089*
• ≥ moderate RV dysfunction	15 (20%)	9 (9.3%)	*0.040*
• TAPSE (mm)	18.9±4.91	21±5.96	*0.085*
• TDI (cm/s)	10 [8-11]	11 [10-13]	*0.033*
• sPAP (mmHg)	45 [40-50]	40 [33-45]	*0.001*
Intraop characteristics			
• CPB (min)	55 [49-77]	56.5 [46-71]	*0.771*
• XCT (min)	39 [29-46]	36 [28-46]	*0.205*
• Beating Heart	52 (69.3%)	58 (59.8%)	*0.196*
• Urgent	2 (2.7%)	0 (0%)	*0.189*

Afib: atrial fibrillation; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD: chronic kidney disease; CPB: cardiopulmonary bypass; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; MELD score: Model for End-stage Liver Disease; NEG: non regular course; NYHA: New York Heart Association; REG: regular course; RHF: right heart failure; RV: right ventricle; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue doppler imaging; XCT: cross-clamp time

Comparing the operative findings of the two groups, both cardiopulmonary bypass times (CPB) (55min [49-77] in NEG group vs. 56.5min [46-71], p=0.771) and cross-clamp times (XCT) (39min [29-46] vs. 36min [28-46] in REG, p=0.205) were similar. The number of beating heart operations were also similar between the two groups. As expected, in-hospital mortality was significantly higher in the complicated group, resulting in 13% vs 0% in REG patients (p<0.001). Moreover, as shown in **Figure 2**, patients within the NEG group developed a higher number of postoperative complications, such as acute kidney injury (AKI), surgical revision for bleeding, low cardiac output syndrome (LCOS), need for high dose inotropic support and infection/sepsis (**Table 2**). There was a higher chance of requiring new pacemaker implantation in patients with an unfavourable course (OR=28.1, 95% CI [3.65-217.04], p=0.001).

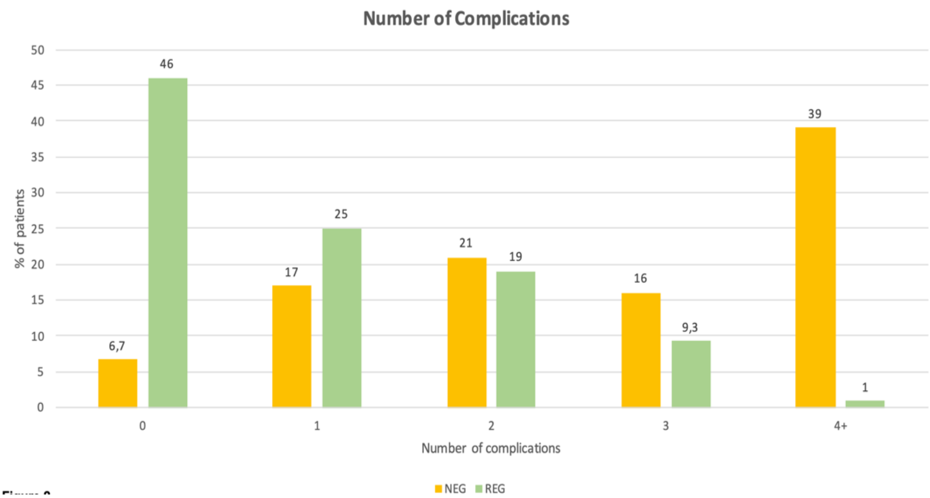

Figure 2. Chart showing increasing number of complications in patients with non-regular (NEG) postoperative course.

Table 2. Postoperative complications

Postoperative Complications	NEG N=75	REG N=97	*p-value*
Revision for bleeding	17 (22.7%)	2 (2.1%)	*<0.001*
AKI	29 (38.7%)	10 (10.3%)	*<0.001*
LCOS	20 (26.7%)	2 (2.1%)	*<0.001*
• Norepinephrine	21 (28%)	2 (2.1%)	*<0.001*
• Epinephrine	39 (52%)	30 (30.9%)	*<0.001*
• Dopamine	57 (76%)	34 (35.1%)	*<0.001*
Infection	34 (45.3%)	8 (8.2%)	*<0.001*
Permanent Neurologic damage	3 (4%)	0 (0%)	*<0.001*
New PM	17 (22.7%)	1 (1%)	*<0.001*
Death	10 (13.3%)	0 (0%)	*<0.001*

AKI: acute kidney injury; LCOS: low cardiac output syndrome; NEG: non regular course; PM: pacemaker; REG: regular course

This can be explained by the fact that patients with a complicated postoperative course needed TVR more frequently than patients with a smooth course, which were mainly subjected to TVr (**Figure 3**). Furthermore, a higher MELD score was associated with a higher risk of developing a greater number of postoperative complications, longer ICU and postoperative length-of-stay and was associated with a higher in-hospital mortality (**Table 3**).

Table 3. MELD Score analyses associated to postoperative complications, length-of-stay and in-hospital mortality.

	Univariate Analysis											
	Postop Complications			***ICU LOS***			***Postop LOS***			***In-hospital mortality***		
	Coeff.	*p-value*	95% CI	Coeff	*p-value*	95% CI	Coeff.	*p-value*	95% CI	OR	*p-value*	95% CI
MELD Score	0.07	*<0.001*	0.05-0.09	0.05	*0.002*	0.02-0.08	0.04	*<0.001*	0.02-0.06	1.15	*0.037*	1.01-1.32

CI: confidence interval; Coeff: coefficient; ICU: intensive care unit; LOS: length-of-stay; MELD: Model for End-stage Liver Disease

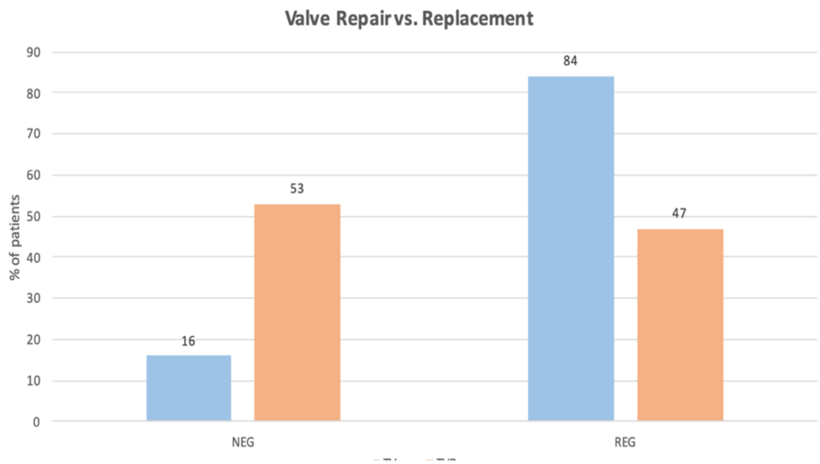

Figure 3. Chart showing difference between valve repair (TVr) and replacement (TVR) in patients undergoing a regular (REG) vs. non-regular

The most important predictors of an unfavourable postoperative course (NEG group) at univariate analysis were chronic kidney disease, ascites, previous hospitalizations for right heart failure, RV dysfunction, previous heart surgeries, need of TVR and an elevated MELD score. The other (less powerful) predictors of this event identified at univariate analysis are detailed in **Table 4**. At multivariate analysis, liver enzyme values and preoperative dose of diuretics were identified as the only independent predictors of a negative outcome (**Table 4**).

Table 4. Univariate and Multivariate analyses for predictors of negative outcome

	Univariate analysis			Multivariate analysis		
Variables	**OR**	***p-value***	**95% CI**	**OR**	***p-value***	**95% CI**
Logistic EuroSCORE	1.14	*<0.001*	1.08-1.21			
CKD	**2.24**	***0.030***	**1.08-4.63**			
AST	1.02	*0.020*	1.00-1.04	**1.02**	***0.048***	**1.00-1.07**
Albumin	0.92	*0.003*	0.87-0.97			
Ascites	**2.27**	***0.030***	**1.08-4.76**			
Diuretics dose	1.00	*0.011*	1.00-1.01	**1.03**	***0.002***	**1.01-1.03**
RHF hospitalizations	**2.22**	***0.015***	**1.17-4.23**			
≥moderate RV dysfunction	2.49	*0.045*	1.02-6.05			
sPAP (mmHg)	1.04	*0.016*	1.01-1.08			
TAPSE (mm)	0.93	*0.089*	0.85-1.01			
TDI (cm/s)	0.87	*0.049*	0.76-1.00			
REDO	**4.66**	***<0.001***	**2.37-9.14**			
>1 REDO	**5.34**	***<0.001***	**2.14-13.33**			
TVR vs. TVr	**5.73**	***<0.001***	**2.37-13.83**			
MELD Score	**1.11**	***0.003***	**1.04-1.19**			

AST: aspartate aminotransferase; CI: confidence interval; CKD: chronic kidney disease; MELD Score: Model for End-stage Liver Disease; OR: odds ratio; RHF: right heart failure; RV: right ventricle; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue doppler imaging; TVr: tricuspid valve repair; TVR: tricuspid valve replacement

Comments

This retrospective, single-centre study evaluated the profile of patients undergoing isolated TV surgery based on our surgical experience. The overall postoperative course of patients undergoing isolated TV surgery was complicated in approximately 43.6% of patients, as arbitrarily defined by an ICU LOS ≥ 4days and/or total hospital LOS ≥ 10days. We are aware that those cut-offs are not evidence based but, as a matter of fact, clinical experience has demonstrated that these are challenging patients in the vast majority of cases and that their postoperative course usually needs an ICU stay longer than 24 hours, even when no major complications occur. In our series, patients with a longer postoperative stay developed complications usually related to their more advanced disease at baseline, such as AKI, LCOS with the need of inotropic support and infections. This also translated in a higher in-hospital mortality, accounting for 13% within this subgroup. Only 3 patients, among those with a NEG postoperative course, experienced a permanent neurological damage, which is unlikely to be explained by the preoperative conditions. Although these events prolonged the ICU and hospital stays of those 3 patients, we believe that such a small percentage does not represent a relevant source of bias for our study. As in other series[21], our study confirmed that NEG patients did have more advanced TV disease, with right ventricular failure (RVF), high dose diuretic therapy, ascites, organ damage, RV dysfunction and pulmonary hypertension. Despite being affected by more advanced disease, when analysing the intraoperative characteristics of the REG and NEG groups, both CPB and cross-clamp times were similar, further supporting the fact that the outcome of these patients is not related to TV surgery by itself, but mainly to the baseline profile of the patients[14]. Even the adoption of a beating heart approach was similarly distributed between the two groups and therefore not related to the postoperative outcome.

In-line with previously published studies reporting the development of late TR after left-sided heart surgery in 23-37% of patients[22,23], NEG patients had undergone more frequently previous cardiac surgery and referred late for re-operation. Consequently, due to the advanced stages of their disease, TVR rather than TVr was unavoidable in the majority of them due to advanced RV remodelling and tethering of the tricuspid leaflets, which might also explain the higher percentage of new pacemaker implants in this group.

When analysing clinical predictors of poor outcome in patients in the NEG group, chronic kidney disease doubles the risk of an unfavourable course, together with ascites, previous right heart failure (RHF) hospitalizations, more-than-moderate RV dysfunction, REDO interventions, TV replacement and MELD score. These findings further underline the need of early referral and early intervention for patients affected by isolated TV disease[3]. Matter of factly, the MELD score[24] calculated for each patient, showed how long-standing disease and multi-organ involvement, resulting in liver dysfunction, was associated with overall worse outcomes. These findings also underline how patients affected by chronic RVF might require a more aggressive preoperative management, with either inotropic support or mechanical support devices, in order to improve postoperative outcomes and survival[25,26].

Patients currently referred for tricuspid valve surgery are high-risk individuals, frequently elderly, with a high percentage of re-operations, high pulmonary artery pressure, end-stage functional class and concomitant pathologies. Such patients and such scenarios support the belief of the high-mortality rate associated to tricuspid surgery, as also seen in our experience. In this context new percutaneous technologies have been proposed but their effectiveness and durability is still suboptimal[27,28]. To-date, the most effective and durable treatment, when feasible with a reasonable risk, remains surgery[29]. However, out data emphasize that timely referral and early surgery are crucial to treat isolated TR with a very low operative risk. As a matter of fact, patients who were treated earlier, before organ damage, less pronounced RV dilation/dysfunction and lower dose diuretics, could receive a repair rather than a replacement procedure, with 1% postoperative permanent pacemaker, acceptable rate of low-cardiac output syndrome and no hospital mortality. Timing is of paramount importance in isolated tricuspid valve surgery[11] and should lead to a thoughtful consideration of how misleading can be the assumption that tricuspid valve surgery is by definition a high risk procedure. Isolated tricuspid valve surgery, particularly repair, is indeed a very simple operation which can be accomplished with a very low risk if carried out for severe TR before development of symptoms (which are usually expression of RV failure) and when only initial dilatation of the right ventricular chamber is detected. Unfortunately, despite current ESC/EACTS guidelines, this is almost never the case. Physicians and patients are reluctant to propose and accept surgery in the absence of symptoms and prefer waiting for their development and refractoriness to high-dose of diuretics. At that stage patients present the features of the NEG group of our study with the inevitable unfavourable outcome. Our analysis identified several predictors of poor postoperative outcome in a rather heterogeneous population of patients with isolated TR. Among them diuretic dose and live enzymes emerged as independent risk factors for this event. In our opinion this is a first step towards the development of dedicated risk scores useful to predict the surgical candidacy and the postoperative course of such challenging patients. Nevertheless, our study further confirms that early referral is key to really impact on outcome and prognosis of this population.

Study limitations

The main limitations of our study are related to the retrospective and single-centre nature of the study, which cannot therefore be compared to randomized trials. Furthermore, the numerosity of the population was partly limited due to lack of sufficient preoperative and postoperative data. A larger sample size might have been useful in identifying more preoperative predictors of unfavourable outcomes, making analyses and comparisons more effective. Larger multicentre studies on this topic are therefore warranted.

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Chapter 4

ISOLATED TRICUSPID REGURGITATION: A PLEA FOR EARLY CORRECTION

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Int J Cardiology 2022;353:80-85.

Abstract

Isolated tricuspid regurgitation (TR) is gaining increasing recognition. Left untreated, isolated TR significantly worsens survival. Management of patients with severe isolated TR remains controversial and stand-alone surgery is rarely performed due to reported high in-hospital mortality. However, recent data has underlined how early referral and surgical correction result in excellent both short-and long-term results, with no in-hospital mortality, 100% 5-year survival and no further hospitalizations for right heart failure. These results should prompt a drastic change in attitude in the treatment, management and referral of patients with severe isolated TR, especially since surgery remains the only effective therapy.

Introduction

In recent years, the cardiological community has focused its attention on the tricuspid valve (TV), long forgotten and disregarded, and has emphasized some key aspects of this pathology in its various clinical presentations. Furthermore, current guidelines [1,2] have given precise indications regarding treatment of tricuspid regurgitation (TR). However, in the real world, current clinical practice is strongly influenced by the nature of TR. While the recommendation of surgical correction of TR concomitantly to left-sided heart diseases has been strongly accepted and is liberally performed, reluctancy remains to date regarding surgical treatment of isolated TR. The main reason behind such pronounced unwillingness is related to the fact that, even if severe, isolated TR is initially well tolerated, patients are asymptomatic, with a good quality of life and minor symptoms are easily and effectively controlled with medical treatment [3]. Moreover, data from the literature are extremely discouraging, reporting an extremely high in-hospital mortality following surgery, associated with uncertainty regarding long-term outcomes [4–8].

In this manuscript, we would like to focus our attention on isolated TR:

a) better identifying and defining the various clinical scenarios;
b) underlining the poor natural history of this pathology due to the negative effects of TR on right ventricular (RV)

shape and function and, as a consequence, on end-organ function;

c) critically examining the available therapeutic options and results;

d) formulating a convincing therapeutic strategy capable of improving both short and long-term outcomes of patients affected by isolated TR.

Isolated TR: definition of the disease and clinical scenarios

Isolated TR is tricuspid valve dysfunction in the absence of other hemodynamically significant cardiac abnormalities. Different clinical scenarios have been identified in patients affected by isolated TR [9,10]:

- *Isolated TR due to organic disease involving the TV*, also known as *Primary TR*. This accounts for a minority of cases and includes congenital anomalies, rheumatic disease, endocarditis, degenerative disease such as leaflet prolapse, traumatic and iatrogenic causes. There is an increasing number of patients with isolated primary TR caused by endomyocardial biopsy or intracardiac leads. The development of more than moderate TR in patients undergoing de novo device implantation is reported to be as high as 38% [11].
- *TR following left-sided valve surgery or percutaneous interventions for correction of mitral regurgitation (MR).* This most frequently occurs whenever TR is not treated

while addressing mitral valve (MV) pathology. Some patients may present with baseline TR, while other may develop clinically significant TR even many years following left-sided valve surgery or transcatheter MV repair. Severe TR has been reported in 23-37% of patients following surgical MV replacement, and up to 50% of patients undergoing MV repair may experience TR progression of two grades [12,13]. Data following MR correction with the MitraClip device have shown a 10-16% progression in TR grade at 12 months [14,15].

- *TR in the presence of Congestive Heart Failure (CHF)* with dilated cardiomyopathy and both left and right ventricular dysfunction. TR frequently develops in patients with CHF and is associated with worse outcomes and increased mortality [16,17].
- *TR in chronic atrial fibrillation (AF)* occurs in patients that are frequently elderly and have a history of long-standing AF, which causes extreme annular dilation and ultimately results in TR. In the aging society, the number of patients with severe TR concomitant with AF is increasing [18].

Regardless the clinical scenario, quantification of TR is of paramount importance because severity of TR is a strong predictor of prognosis. Several investigations have underlined how increasing degree of TR negatively impacts on survival, with a relevant difference between severe TR entity (63.9%) and no

TR (91.7%) [19,20]. Furthermore, if left untreated, isolated severe TR results in lower overall survival, with a mortality rate at 5 years of approximately 50% [21–23]. TR severity should be graded using a multiparametric approach according to the current European Association of Echocardiography recommendations [24].

Natural History

Isolated TR can be well tolerated functionally for many years, even if severe [25]. Patients' presentation can therefore range from asymptomatic to varying degrees of heart failure [22]. A novel clinical and functional classification has been recently proposed, which divides patients in 5 Stages (**Figure 1**) according to TV disease progression [26].

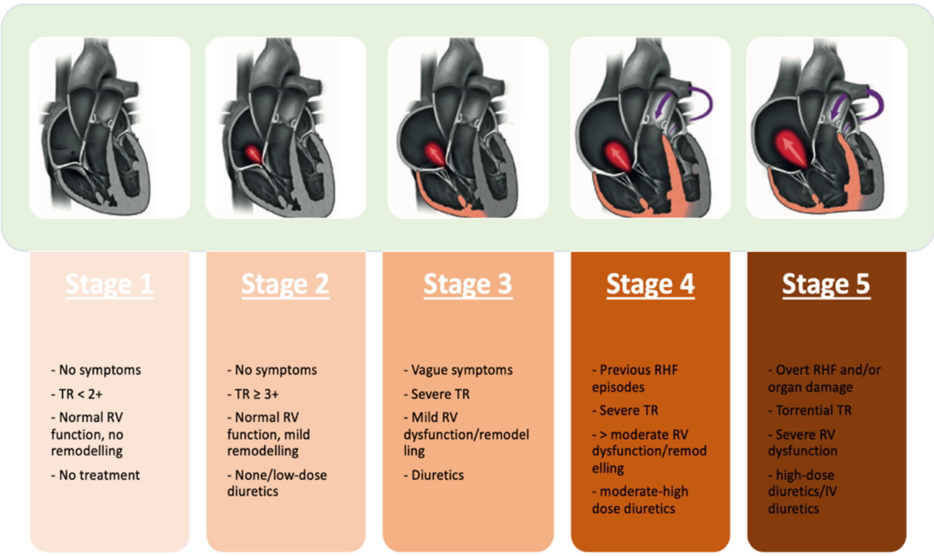

Figure 1. 5 Stages classification and determinants/characteristics for distribution of patients.

Early in the disease process, *Stages 1-2*, in response to TR and central venous congestion, compensatory mechanisms and remodelling of the RV contribute to maintenance of adequate hemodynamic compensation. Patients tend to be asymptomatic, with no medical therapy. However, compensatory mechanisms are less lasting in the RV compared to the left ventricle [3]. As the disease progresses, *Stage 3*, patients develop both pulmonary and central venous congestion, with the occurrence of symptoms, such as exertional dyspnea, orthopnea and peripheral edema. Long-lasting TR further leads to dilation and progressive dysfunction of both the right atrium (RA) and the RV, which results in multi-organ involvement, with occurrence of initial right heart failure (RHF) episodes *(Stage 4)* and later hepatosplenomegaly, ascites, and pleural effusions *(Stage 5)*. In late stages of disease, *Stage 5*, overt chronic RHF develops, with end-organ damage (hepatorenal dysfunction) due to chronic RV volume overload, with severe RV dysfunction and remodelling [27,28]. At this stage, patients have frequent RHF hospitalizations, and symptoms are related to low cardiac output, such as fatigue, asthenia and poor functional capacity.

Initial adaptive RV remodelling occurs to accommodate volume load and maintain cardiac output. Ventricular enlargement due to RV volume overload causes disproportionate dilatation along the RV free wall, resulting in a more spherical RV shape. This further aggravates TR, with the development of a self-perpetuating vicious cycle of increasing degree of regurgitation. While initial RV remodelling and dilatation can be accompanied by normal RV function, non-corrected TR results in maladaptive RV remodelling, with changes in RV geometry that cause papillary muscle displacement, abnormal leaflet tethering, large coaptation gap, which ultimately leads to torrential TR and severe RV dysfunction [29]. Therefore, even if initially quality of life of patients with isolated TR is good, outcome of untreated isolated TR is ultimately poor, with progressive decrease in functional capacity, refractoriness to medical therapy and increase in hospitalizations for heart failure episodes [29].

Therapeutic Options

Medical treatment

Conservative treatment of isolated TR has always been the gold standard, with a complex interplay of pharmacological therapies. This strong belief, profoundly rooted within the cardiological community, mainly arises from the initial good quality of life of patients affected by isolated TR. In fact, patients affected by isolated TR are initially asymptomatic, and minor symptoms can be easily controlled with medical therapy. Symptomatic treatment is mainly based on diuretics, with fluid and sodium restriction [3]; although such drugs improve peripheral edema and heart failure symptomatology, the decrease in cardiac output may further exacerbate fatigue and dyspnea. Furthermore, with progression of the disease, patients develop refractivity to medical therapy due to advanced stages of RV dilation and dysfunction.

Surgical treatment

Most recommendations of the current European [1] and American Guidelines [2] **(Table 1)** for the management of valvular heart disease are targeted at patients undergoing concomitant left-sided valve operations. Even though the only effective treatment for isolated TR is surgical correction, a paucity of recommendations for surgery in patients with isolated TR exist, and indications tend to be slightly different. American guidelines tend to be more conservative and suggest waiting for the development of signs or symptoms of RHF before recommending tricuspid repair (TVr) or replacement (TVR) (Class IIa). In asymptomatic patients with primary severe isolated TR and progressive RV dilation/dysfunction, only a class IIb recommendation is given. European guidelines strongly support an earlier surgical referral with RV dilation, even in asymptomatic patients, to achieve low hospital mortality and better postoperative outcome.

Table 1. Current European and American Guidelines for the treatment of tricuspid regurgitation	
2021 ESC/EACTS Guidelines	**2020 ACC/AHA Guidelines**
Class I 1. Severe TR (primary or secondary) undergoing left-sided valve surgery (B-C) 2. Severe symptomatic primary TR without severe RV dysfunction (C)	*Class I* 1. Severe TR undergoing left-sided valve surgery (B)
Class IIa 1. Moderate primary TR or mild or moderate secondary TR with dilated TA (>40mm) undergoing left-sided valve surgery (B-C) 2. Asymptomatic severe primary TR with RV dilation, appropriate for surgery (C) 3. Severe secondary TR (with or without previous left-sided surgery), with symptoms or RV dilation, in the absence of severe LV or RV dysfunction and PH (B)	*Class IIa* 1. Progressive TR undergoing left-sided valve surgery in case of either TA dilation (>40mm) or prior signs/symptoms of RHF (B) 2. Signs/symptoms of RHF and severe primary TR (B) 3. Signs/symptoms of RHF and severe isolated secondary TR due to TA dilation without PH, poorly responsive to medical therapy (B)
Class IIb 1. Transcatheter treatment of symptomatic secondary TR in inoperable patients at a Heart Valve Centre with expertise (C)	*Class IIb* 1. Asymptomatic with severe primary TR and progressive RV dilation or systolic dysfunction (C) 2. Signs/symptoms of RHF and severe TR following left-sided valve surgery, in the absence of PH or severe RV dysfunction (B)

ACC: American College of Cardiology; AHA: American Heart Association; EACTS: European Association for Cardio-Thoracic Surgery; ESC: European Society of Cardiology; LV: left ventricle; PH: pulmonary hypertension; RHF: right heart failure; RV: right ventricle; TA: tricuspid annulus; TR: tricuspid regurgitation

Even though surgery is the only definitive treatment for isolated TR, it is rarely performed. Of the 4000-8000 TV operations performed annually in the USA, approximately 80% occur concomitantly to left-sided valve procedures [30,31]. This occurs mainly in response to the historically reported high in-hospital mortality rates following TV surgery and poor long-term outcomes. Older studies have in fact reported an in-hospital mortality ranging from 8.8 to 37%, associated to 55% mortality at 5 years [5,32,33]. However, in the majority of these studies, the sample size analysed was small, and the population comprised a broad variety of patients, among which many underwent re-intervention, with frequent severe RV dysfunction and associated pulmonary hypertension. The baseline clinical presentation of such patients and the stage of disease may have negatively impacted on the perioperative outcome [26,34]. In fact, studies have shown how the surgical act of TV repair or replacement is not technically demanding in itself and the outcome is therefore almost exclusively depending on the baseline patient's profile and, particularly, on RV functional state.

The classification mentioned above identifies a number of parameters and factors that may aid in stratifying surgical risk, based not only on TR grade, but also symptoms, RV remodeling and function, RHF episodes and medical therapy. This may help in identifying the most adequate treatment strategy for each stage of TV disease.

In our experience, we have seen that patients operated upon in early stages of the disease (Stages 2 and 3), without prominent symptomatology, RV dilation or dysfunction, and without organ involvement, most frequently receive TVr with no in-hospital mortality, fewer postoperative complications and shorter postoperative length-of-stay [35,36] (**Table 2**). Furthermore, patients at early stages of the disease, following TV correction, experienced 100% survival at 5 years and no further hospitalizations for RHF. On the other hand, patients belonging to more advanced stages (Stages 4 and 5 according to the Classification) experienced higher in-hospital mortality, postoperative complications, longer both intensive care unit and hospital stay. Survival at 5 years for such patients was 60.5%, with 1 out of 5 patients experiencing at least one hospitalization for RHF following surgery [data submitted for publication].

Therefore, patients referred to TV correction late in the disease course experience high morbidity and mortality after surgery, further supporting the belief that TV surgery is a high-risk procedure, and further delaying or even rejecting the referral for surgery.

The above-mentioned vicious circle should be interrupted early on in disease progression, especially considering the low-risk of TVr and the not technically challenging surgical act of TV replacement [32] (**Figure 2**).

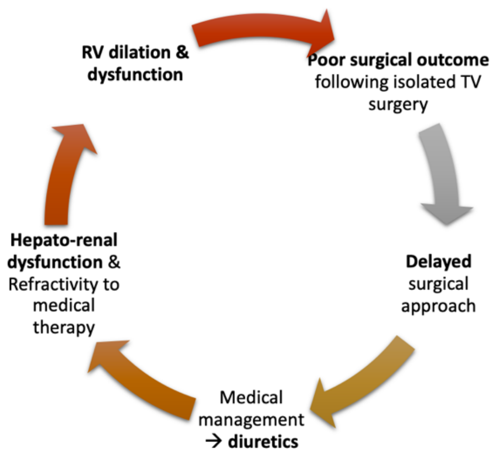

Table 2. Baseline characteristics and in-hospital outcomes according to different baseline clinical and functional classification in Stages

	Stage 1 N=0	Stage 2 N=27	Stage 3 N=80	Stage 4 N=62	Stage 5 N=3
Surgery					
• TVR	-	7 (5.4%)	67 (51.9%)	52 (40.3%)	3 (2.3%)
• TVr	-	20 (46.5%)	13 (30.2%)	10 (23.3%)	0 (0%)
Preop					
• Age	-	48 [28-64]	68 [58-75]	70 [63-76]	75 [68-79]
• NYHA III-IV	-	0 (0%)	44 (55.5%)	55 (89%)	3 (100%)
• CKD-eGFR	-	94 [77-138]	66 [49-90]	52 [37-69]	28 [27.6-28]
• Ascites	-	0 (0%)	3 (3.8%)	31 (50%)	3 (100%)
• REDO	-	7 (26%)	42 (53%)	47 (76%)	3 (100%)
• TAPSE	-	26.2±3.71	21.4±5.56	18±4.54	17
Postop complications					
• AKI	-	1 (3.7%)	8 (10%)	27 (44%)	3 (100%)
• LCOS	-	4 (15%)	40 (50%)	44 (71%)	3 (100%)
LOS (days)					
• ICU	-	1	2	3.5	5
• Postop	-	7	7	8	14
In-hospital death	-	0 (0%)	0 (0%)	10 (16.1%)	0 (0%)

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AKI: acute kidney injury; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ICU: intensive care unit; LCOS: low cardiac output syndrome; LOS: length-of-stay; NYHA: New York Heart Association; Postop: postoperative; REDO: re-intervention; TAPSE: tricuspid annular plane systolic excursion; TVr: tricuspid valve repair; TVR: tricuspid valve replacement

In this regard, a novel dedicated risk score has been recently made available that aims at predicting the outcome of patients following isolated TV surgery [37]. The parameters identified are not only strictly related to right and left ventricular function, but also reflect end-organ involvement (liver and kidney), medical therapy and clinical status. This dedicated score, that still requires validation, should help in guiding the clinical decision-making process of patients with severe isolated TR.

Percutaneous Interventions

Percutaneous procedures are becoming nowadays readily available and growing evidence support transcatheter solutions in patients deemed high-risk for surgical treatment. At present, the most widely applied technique is edge-to-edge repair of the tricuspid valve [38]. Retrospective analyses have reported a reduction in TR grade, symptomatic improvement (reduced RHF hospitalization rates at 1 year) and lower mortality following edge-to-edge repair [39,40]. Therefore, various transcatheter-based techniques have been developed and applied, mainly addressing annuloplasty, such as the Cardioband system (Edwards Lifesciences, Irvine USA) [41]. Although initially promising, these new approaches are still in development and both short and long-term data are still lacking. Furthermore, selection and optimal timing are crucial also in these settings, as transcatheter procedures may still result futile in candidates with end-stage heart failure, untreated pulmonary hypertension and end-organ damage. Even more importantly, in most cases, their efficacy in reducing the severity of TR remains extremely limited and not comparable to results obtained with surgical correction [42–45].

A convincing strategy and new perspectives

Analysing the available therapeutic options for patients with isolated severe TR, it appears rather evident that surgery remains the only definitive treatment. This is especially true in light of recent analyses that show that early surgical correction, before the development of prominent symptomatology, RV dysfunction and end-organ involvement, results in excellent in-hospital outcomes, with an extremely high rate of TV repair vs. replacement, and good long-term outcomes, with low-to-none mortality at 5 years and significant improvement in symptomatology [35]. Patients in advanced stages of the disease may still present at our clinical attention. The new risk scores available, together with a careful evaluation of baseline conditions, should help in determining the surgical risk and therefore select the most appropriate treatment strategy for every patient. Whenever the surgical risk is acceptable, surgery should be considered; if the patient is considered at high-risk for surgery or inoperable, transcatheter options should be evaluated, even if only palliative in the majority of cases. Great fervour is present in identifying new devices for the percutaneous treatment of TR. Therefore, in the future, with further development and improvement of the currently available transcatheter options, percutaneous procedures might be proposed and performed also in earlier stages of the disease.

Conclusions

Isolated severe TR results in progressive right heart failure and adversely impacts survival. To date, there was little data to guide management of patients with isolated TR. However, recent knowledge, that shows that early surgical correction results in excellent short- and long-term outcomes, should prompt a drastic change in attitude in the referral and surgical indication in patients with severe isolated TR. Even more so, since TV surgery is the only definitive treatment, and available transcatheter options result in pure palliative strategies. European guidelines have recognized that surgery is reasonable in patients prior to development of RV dysfunction and end-organ damage and currently support an earlier surgical referral for isolated TV surgery. Further awareness within the clinical communities is necessary in order to interrupt the misconception that surgical treatment of isolated TR is always associated to excessive morbidity and mortality, and in order to obtain optimal timing for surgical referral and contribute to better short and long-term outcomes for these patients.

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Palau - 2017

Chapter 5

MID-TERM OUTCOMES OF ISOLATED TRICUSPID VALVE SURGERY ACCORDING TO PREOPERATIVE CLINICAL AND FUNCTIONAL STAGING

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Eur J CardioThorac Surg 2022;62(2):1-8.

Abstract

Objectives: This study aimed at assessing mid-term outcomes of patients undergoing isolated tricuspid valve surgery based on a preoperative baseline clinical and functional classification.

Methods: All patients treated with isolated tricuspid valve repair (TVr) or replacement (TVR) from March 1997 to May 2020 at a single institution were retrospectively reviewed and assessed for mid-term postoperative outcome according to a novel classification [Stage 1 to 5 related to absence or presence and extent of right heart failure (RHF)]. Kaplan-Meier survival curves were used to estimate mid-term survival. Competing risk analysis for time to cardiac death and hospitalizations for RHF were also carried out.

Results: Among the 172 patients included, 129 (75%) underwent TVR and 43 (25%) TVr. At follow-up (median 4.2 years [2.1-7.5]), there were 23 late deaths. At 5 years, overall survival was 100% in Stage-2, 88±4% in Stage 3 and 60±8% in Stages 4-5 (p=0.298 and p=0.001, respectively). Cumulative Incidence Function (CIF) of cardiac death at 5 years was 0%, 8.6±3.76% and 13.2±5% for Stages 2, 3 and 4-5, respectively. At follow-up, CIF of re-hospitalizations for RHF was 0% for Stage-2, 20±5% for Stage 3 and 20±6.7% for Stages 4-5 (p=0.118 and p=0.039, respectively).

Conclusions: Both short and mid-term outcomes support early referral for surgery in isolated tricuspid valve disease, with excellent survival at 5 years and no further hospitalizations for RHF.

Introduction

Tricuspid regurgitation (TR) has been identified as an independent prognostic factor associated with excess mortality and morbidity, regardless of left ventricular (LV) function and pulmonary hypertension [1–3]. Surgery is mostly performed at the time of left-sided valve surgery, while isolated surgical treatment of tricuspid valve (TV) disease has been avoided for many years due to reported poor short and long-term outcomes, or usually delayed until severe symptoms or signs of right heart failure (RHF) appear [4,5].

In the past, ideal timing for surgical treatment has been difficult to determine because patients either tend to be asymptomatic or symptoms can be well tolerated for many years. Medical treatment has always been the gold standard, employed in these patients for many years. Recently, it has been demonstrated that TV interventions result in increased survival and reduced RHF hospitalizations with respect to medical therapy alone [6]. However, despite being a disabling condition, an extremely low percentage of patients are currently being referred for surgical treatment.

In recent years, several studies have highlighted how the reported poor outcomes following isolated TV surgery seem to be related to the baseline characteristics of the patients and their late referral, rather than to the surgical act in itself [7–9]. To facilitate patient screening, a novel clinical and functional staging of TV regurgitation has been recently proposed [10]. This classification, that assesses progression of morphological changes to the TV and right ventricle (RV) in association to symptoms onset, identifies a number of parameters and factors that may be useful in better stratifying surgical risk. Rather than simply evaluating TR grade, this novel staging mechanism also focuses on symptoms, RV remodeling and function, medical therapy and RHF hospitalizations.

We had previously focused on the short-term (mainly in-hospital) outcomes of patients undergoing isolated TV surgery for severe TR, who were classified according to this preoperative baseline clinical and functional staging [11]. Results showed that a more comprehensive classification reflects the population and in-hospital outcomes of patients affected by isolated TR surgically treated.

The aim of this study was to eventually assess their mid-term outcomes and evaluated the impact of the baseline stage on long-term outcomes.

Materials and Methods

Ethics statement

The Ethical Committee of our Institution approved the Study and waived individual informed consent for this retrospective analysis.

Study population

A retrospective, single-centre study, including patients affected by TV regurgitation and treated with isolated TV surgery from March 1997 to May 2020 at San Raffaele University Hospital, Milan, Italy, was conducted. For a former study, all consecutive patients had previously been individually reviewed and all baseline characteristics were thoroughly analysed.

For completion, a brief description of the study material will be presented, even though it had been previously extensively described. All patients had undergone both preoperative transthoracic (TTE) and transesophageal echocardiography (TEE) upon hospitalization. TEE was routinely used to better define the mechanism of TR. Echocardiographic parameters together with all preoperative characteristics and data were inserted within a dedicated database. Symptomatology was defined based on New York Heart Association (NYHA) class, and degree of heart failure was defined based on presence of peripheral edema, ascites, repeated previous episodes of hospitalization for RHF and organ damage, defined as altered laboratory values specific for hepato-renal function. TR was graded on a four-grade scale as 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe), and 4+ (severe). A limited number of patients, in the more recent period of the study, were evaluated and TR grading was based on a multiparametric approach [12,13]. RV remodeling and function was based on preoperative values, such as RV end-diastolic diameter (RV-EDD), tricuspid annular plane systolic excursion (TAPSE), tissue doppler imaging (s' TDI) and systolic pulmonary artery pressure (sPAP). Medical therapy was assessed based on daily diuretic use, dosage and combination therapies [14]. Based on a combination of all these factors, patients had been previously divided according to the 5 Stages of the Classification (**Figure 1**).

All patients underwent TTE before discharge, in order to assess biventricular function and outcomes following either TV repair or replacement.

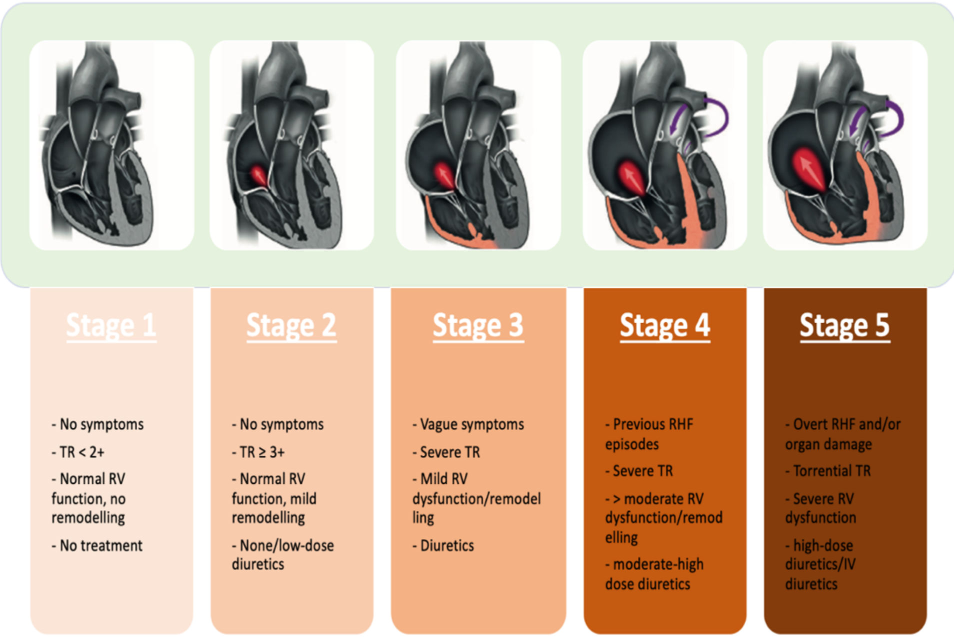

Figure 1. 5 Stages Classification and determinants/characteristics for distribution of patients

Follow-up

Survival and echocardiographic follow-up data were obtained either via regular out-patient clinic visits or querying the informatic hospital system. If follow-up information was not retrieved through the hospital system, patients, or their referring cardiologists, were reached with telephone calls and asked
to provide recent laboratory and echocardiographic data (< 6months).

Cause of death was determined by death certificates or information from family members or referring physician. Clinical and echocardiographic follow-up was 93% complete; the median follow-up time was 4.2 years [2.1-7.5], with the longest follow-up time of 16.5 years.

Primary end-points of the study were overall survival and cardiac mortality at follow-up. Secondary end-points were freedom from re-intervention, freedom from re-hospitalizations for right heart failure and symptomatology at long-term follow-up.

Statistical analyses

Statistical analyses were performed using SPSS (IBM, Amonk, New York, USA) and Stata Software (Statacorp, LLC, TX, USA; version 15). Analyses were exploratory in nature. Categorical variables were expressed as absolute number and percentages. Normal distribution of continuous variables was assessed with the Shapiro-Wilk test. Continuous variables normally distributed were expressed as mean ± standard deviation (SD). Continuous variables not normally distributed were reported as median and interquartile range [IQR].

Kaplan-Meier survival curves were used for estimating mid-term survival, and log-rank test was used to assess intergroup comparisons. For competing risk analysis, we calculated the cumulative incidence function (CIF) for cardiac death (with non-cardiac death as competing risk), for re-intervention (with death as a competing risk), and for re-hospitalizations for RHF (with death as a competing risk). The Fine and Gray model was used for intergroup comparisons. 95% confidence intervals and p-values were not adjusted for multiple comparisons. Due to the limited number of patients classified in Stage 5, for better statistical analyses and more straightforward interpretation of results, patients in Stages 4 and 5 were grouped.

Results

Patients' Characteristics and in-hospital results

A total of 172 patients who underwent isolated TV surgery at our Institution were reviewed and, based on preoperative characteristics, divided according to the 5 Stages. None of our patients fulfilled criteria for Stage 1, since by definition TR grade is to be considered less than moderate, and therefore patients undergoing isolated surgical treatment had at least moderate-to-severe TR. Furthermore, an extremely limited number of patients treated were part of the end-stage disease group

(Stage 5). We had previously focused on in-hospital outcomes of this study population, therefore such results will be briefly summarized for completion of data. Baseline characteristics and in-hospital outcomes are reported in **Table 1**. Among the total population, 129 (75%) patients underwent isolated TV replacement (TVR) (a bioprosthesis was used in 95.4% of cases) and 43 (25%) underwent TV repair (TVr). The main etiologies were: functional TR in 75 patients (43.6%), primary TR in 40 patients (23.3%, among whom 2 had carcinoid disease, 4 patients had congenital anomalies, 14 rheumatic disease and 20 degenerative involvement), endocarditis in 15 patients (8.7%), failure of previous TV repairs was present in 14 cases (8.1%) and bioprosthesis degeneration in 4 patients (2.3%), a mix etiology was seen in 11 patients (6.4%), and traumatic TR in 10 patients (5.8%).

Table 1. Baseline characteristics and in-hospital outcomes according to different baseline clinical and functional classification in Stages.

	Stage 1 N=0	Stage 2 N=27	Stage 3 N=80	Stage 4 N=62	Stage 5 N=3
Surgery					
• TVR	-	7 (5.4%)	67 (51.9%)	52 (40.3%)	3 (2.3%)
• TVr	-	20 (46.5%)	13 (30.2%)	10 (23.3%)	0 (0%)
Preop					
• Age	-	48 [28-64]	68 [58-75]	70 [63-76]	75 [68-79]
• NYHA III-IV	-	0 (0%)	44 (55.5%)	55 (89%)	3 (100%)
• CKD-eGFR	-	94 [77-138]	66 [49-90]	52 [37-69]	28 [27.6-28]
• Ascites	-	0 (0%)	3 (3.8%)	31 (50%)	3 (100%)
• REDO	-	7 (26%)	42 (53%)	47 (76%)	3 (100%)
• TAPSE	-	26.2±3.71	21.4±5.56	18±4.54	17
Postop complications					
• AKI	-	1 (3.7%)	8 (10%)	27 (44%)	3 (100%)
• LCOS	-	4 (15%)	40 (50%)	44 (71%)	3 (100%)
LOS (days)					
• ICU	-	1	2	3.5	5
• Postop	-	7	7	8	14
In-hospital death	-	0 (0%)	0 (0%)	10 (16.1%)	0 (0%)

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AKI: acute kidney injury; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ICU: intensive care unit; LCOS: low cardiac output syndrome; LOS: length-of-stay; NYHA: New York Heart Association; Postop: postoperative; REDO: re-intervention; TAPSE: tricuspid annular plane systolic excursion; TVr: tricuspid valve repair; TVR: tricuspid valve replacement

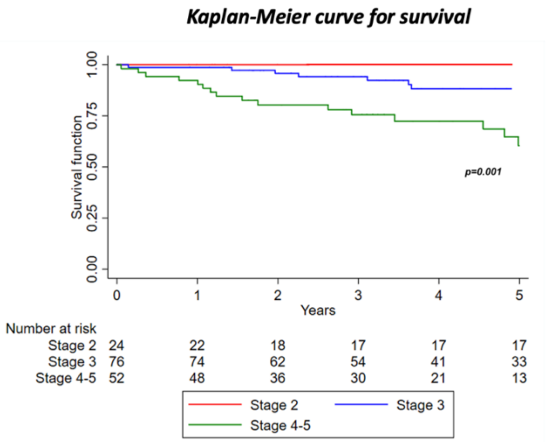
Considering the overall population, the great majority of patients were classified either in Stage 3 (46.5%) or Stage 4 (36%). However, when analysing separately patients who underwent either valve repair or replacement, 46.5% of patients who underwent TVr were in Stage 2, while more than half of TVR patients were in Stage 3 (51.9%). Patients in Stage 2 were younger and in less advanced stages of the disease with fewer signs and symptoms of RHF and organ involvement. In this stage, TV repair could be performed in most patients, with no in-hospital mortality and lower risk of developing postoperative complications. On the contrary, patients in more advanced stages experienced more postoperative complications, such as acute kidney injury (AKI) and low cardiac output syndrome (LCOS) with the need of high-dose inotropic support (**Table 1**).

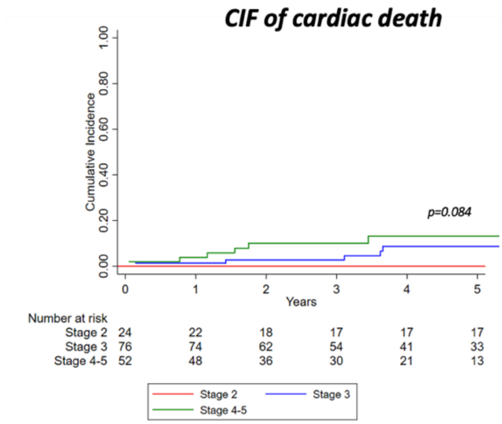
Mid-term survival

Clinical and echocardiographic follow-up was 93% complete. Median follow-up time was 4.2 years [2.1-7.5], with the longest follow-up time of 16.5 years.

In the first 5 years of follow-up, 23 deaths (15%) occurred. Among these, no patient was in Stage 2 (0%), 7 patients were in stage 3 (9.2%) and 16 in Stages 4-5 (31%). Therefore, at 5-year follow-up there was a statistically significant difference in survival according to the baseline preoperative classification. More specifically, mid-term survival for patients in Stage 2 is 100%, 88.2±4.26%, 95% CI [76.62-94.29] for patients in Stage 3, without significant difference with respect to Stage 2 ($p=0.298$) and 60.4±8.45%, 85% CI [42.00-74.65] for patients in Stages 4-5 ($p=0.001$, vs. Stage 2) (**Figure 2**).

Of the registered long-term deaths, only 11 were reported as being cardiac-related (7%). Once again, 0% were in Stage 2, 5 patients (6.6%) were in Stage 3 and 6 patients (12%) were in Stages 4-5. The CIF for cardiac death, with death for any cause as competing event, at 5 years was 0% in Stage 2, 8.6±3.76%, 95% CI [3.10-17.74] in Stage 3, and 13.2±5.14%, 95% CI [5.19-24.91] in Stages 4-5. Even though the difference wasn't statistically significant (Stage 3 vs Stage 2: p=0.391, and Stage 4-5 vs. Stage 2: p=0.084), as shown in **Figure 3**, there was a relevant trend towards an increase of cardiac deaths in more advanced stages of the disease.





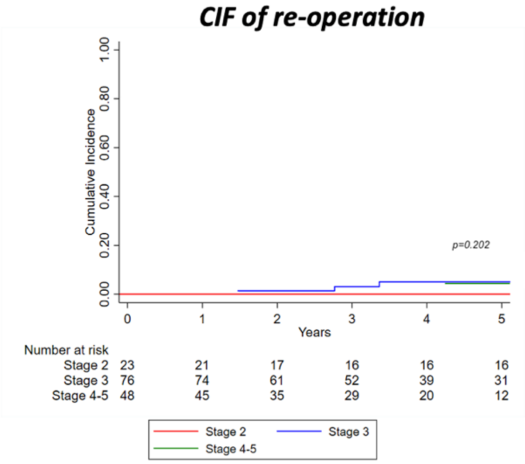
On the left – Figure 2: Kaplan-Meier curve for survival at follow-up according to different preoperative baseline classification in Stages. At 5 years survival was 100 % in Stage 2 (red line), 88.2±4.26% in Stage 3 (blue line) and 60.4±8.45% in Stages 4-5 (green line) [p=0.001].
On the right – Figure 3: Graph showing Cumulative Incidence Function of cardiac death according to each Stage. At 5 years CIF was 0% in Stage 2 (red line), 8.6±3.76% in Stage 3 (blue line) and 13.2±5.14% in Stages 4-5 (green line) [p=0.084].

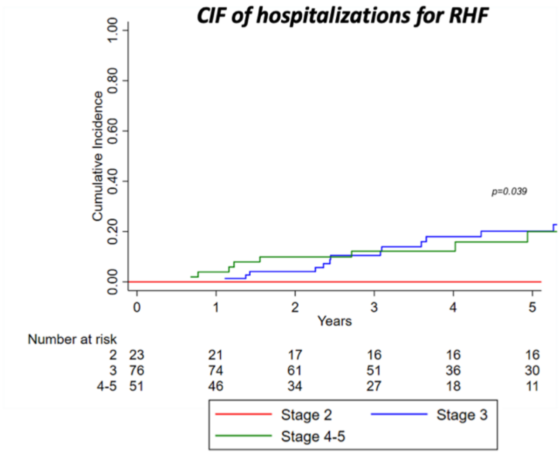
Re-hospitalizations for right heart failure

Analyses performed to evaluate re-operation or re-hospitalization for RHF aimed at assessing whether, regardless long-term survival, treatment in late stages of the disease would resolve TV disease but wouldn't provide full clinical benefit on the long run due to marked RV dysfunction. At 5-year follow-up, only 4 patients (2.7%) underwent re-operation; among these, three were in Stage 3 (3.9%) and only 1 in Stages 4-5 (2.1%). The CIF for re-operation, with death from any cause as competing event, at 5 years was 0% in Stage 2, 5.0±2.87%, 95% CI [1.31-12.79] in Stage 3 and 4.3±4.15%, 95% CI [0.31-17.85] in Stage 4-5, with no significant difference among groups ($p=0.392$ and $p=0.202$, respectively) (**Figure 4**).

On the other hand, when considering long-term rehospitalizations, 20 patients (13%) experienced RHF at 5 years. Interestingly enough, RHF occurred in no patient in Stage 2, however patients in Stages 3 and 4-5 experienced the same rate of rehospitalizations [12/76 (16%) vs. 8/51 (16%), respectively]. The CIF for rehospitalization for RHF, with death for any cause as competing event, at 5 years was 0% in Stage 2, 20.2±5.31%, 95% CI [10.96-31.34] in Stage 3, and 20.0±6.76%, 95% CI [8.81-34.43] in Stages 4-5 ($p=0.039$) (**Figure 5**).

Furthermore, at last follow-up, NYHA class I was reported in all patients in Stage 2, 20% in Stage 3, and in only 5% of patients in Stages 4-5 ($p<0.001$). At follow-up, no difference was reported among stages regarding recurrence of at least moderate TR. More specifically, recurrence of ≥ moderate TR occurred in 8 patients, among which two had residual moderate TR at discharge. Regarding TVR, all implanted prostheses functioned adequately at last follow-up, with the exception of 8 patients which experienced prostheses degeneration/malfunction (one patient experienced mechanical prosthesis' thrombosis). No difference among stages was reported.





On the left – Figure 4: Graph showing Cumulative Incidence Function of re-operation according to each Stage. At 5 years CIF was 0% in Stage 2 (red line), 5.0±2.87% in Stage 3 (blue line) and 4.3±4.15% in Stages 4-5 (green line) [p=0.202].
On the right – Figure 5: Graph showing Cumulative Incidence Function of re-hospitalizations for right heart failure according to the different baseline Stages. At 5 years CIF was 0% in Stage 2 (red line),

Discussion

This retrospective, single-centre study evaluated the mid-term results of patients undergoing isolated TV surgery based on a novel baseline clinical and functional classification of patients with TR [10]. To the best of our knowledge, this is the first study to assess long-term outcomes of isolated TV surgery according to this 5 Stage classification.

Management of isolated severe TR still remains strongly influenced by two misleading concepts: first, that TR is a benign condition to be treated with diuretics until symptoms occur, and second, that surgical treatment of isolated TR is high-risk surgery, with elevated short and long-term morbidity and mortality, particularly if performed with signs of RHF [15–17]. Many studies have now demonstrated that the presence of TR is a predictor of negative outcome and worse survival, independently of baseline characteristics or other conditions [18–20]. Poor outcomes following isolated TV surgery, ranging from 10-30% mortality [21,22], come from limited and old series of patients. It was hypothesized that the high rate of complications and postoperative mortality was related to the associated comorbidities or the very advanced clinical presentation of patients. This was further corroborated by a recent multicentric study that showed that in-hospital and mid-term outcomes were predicted by the preoperative presentation of patients [9]. Indeed, TV surgery is relatively simple and well reproducible.

Thus, the aim of our study was to specifically assess mid-term outcomes of patients undergoing isolated TV surgery stratified according to baseline characteristics.

In-hospital results of our experience had been previously reported [11] and showed, not surprisingly, that patients in more advanced stages of the disease experienced higher number of postoperative complications, a longer both intensive care unit and postoperative length of stay, and, therefore, higher in-hospital mortality. However, the other side of the coin of such findings, further supporting our beliefs, was that whenever patients were referred early to surgery and underwent surgical treatment before the development of important symptomatology and organ involvement/damage (Stage 2), a smooth and short postoperative course following TV repair, as well as no in-hospital mortality were observed in the majority of cases. However, those data were limited to in-hospital outcomes, not addressing late results at follow-up. In fact, the lack of data reporting positive outcomes following early TV surgery for isolated TR have contributed to the uncertainty as to when and how to treat this pathology. Timing for TV surgery has been controversial, and even though recent updated guidelines promote earlier intervention [23,24], early referral is not a common practice. Patients are managed with medical therapy for years. However, surgical treatment is, to date, the only curative treatment for severe TR, while medical therapy remains mostly palliative [25].

Our surgical experience underlines how early/timely surgical treatment of TV disease results in both good short and mid-term results. In fact, patients undergoing isolated TV surgery classified accordingly in Stage 2 experienced an excellent in-hospital postoperative course, with 100% survival at 5 years, no further hospitalization for RHF and remained asymptomatic. Therefore, before the development of overt RHF symptomatology, regardless of adequate medical therapy, and RV dysfunction, isolated TV surgery is feasible and safe, with no in-hospital mortality, a very low rate of postoperative complications, a very low reported long-term follow-up mortality and excellent clinical status. Thus, not only does early surgery resolve TV disease, which negatively impacts on survival, but it also provides clinical improvement and benefit to patients. These findings should help in changing the misconception that surgical treatment is associated with excessive morbidity and mortality in all patients. In this regard, a novel dedicated risk score has been made recently available that aims at predicting the outcome of patients following isolated TV surgery, based on echocardiographic parameters and baseline clinical status. This score should help in guiding the clinical decision-making process of patients with severe isolated TR [26].

Transcatheter therapies are becoming readily available, and growing evidence support such interventions in patients deemed high-risk for surgical treatment. However, selection and optimal timing are crucial also in these settings, as transcatheter procedures may still result futile in patients with end-stage heart failure, untreated pulmonary hypertension and organ damage. In addition, in most of the cases, their efficacy in decreasing the severity of TR is still limited and not comparable to the one provided by surgery [27].

Therefore, an increased awareness in the community, together with adequate patient monitoring, early referral and timely intervention, are of utmost importance, as demonstrated by our surgical experience. Both TV repair and replacement, when performed early on in disease progression (Stages 2 and 3), are safe, with excellent in-hospital results and good mid-term follow-up outcomes. Moreover, referral in high-volume centres, with patient evaluation by a multidisciplinary heart team, are fundamental aspects in order to provide a thorough workup, determine adequate classification and stratification of patients, supply perioperative advanced treatment strategies and whenever necessary circulatory support, and offer a broad-spectrum of treatment options.

Conclusions

Both short and mid-term outcomes support early referral for surgery in isolated tricuspid valve disease, with excellent in-hospital results, survival at 5 years and no further hospitalizations for RHF.

Study Limitations

Our study has limitations mainly related to a retrospective single-centre study, which may have led to selection bias. The sample size is relatively small due to the few isolated TV interventions performed, and also to some extent linked to the lack of sufficiently complete data. Furthermore, follow-up was not 100% complete, therefore we cannot exclude that patients lost to follow-up died of cardiac causes or experienced re-hospitalizations for RHF.

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New York - 2017

Chapter 6

SURGICAL TREATMENT OF TRICUSPID VALVE REGURGITATION IN PATIENTS WITH CARDIAC IMPLANTABLE ELECTRONIC DEVICES: LONG-TERM RESULTS

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Eur J CardioThorac Surg 2022;62(3):1-7.

Abstract

Background: With the expanding use of cardiac implantable electronic devices (CIEDs), lead interference with the tricuspid valve (TV) causing significant tricuspid regurgitation (TR) has gained increasing recognition. However, the current knowledge about the long-term results of the surgical treatment of TR in in this setting is scanty and represent the aim of this study.

Materials and methods: A retrospective review of our Institutional database was carried out to select all patients, with CIEDs previously implanted, who underwent tricuspid valve repair and replacement within the time frame 2000-2019. Kaplan–Meier methods were used to analyze long-term survival. To describe the time course of TR, we performed a longitudinal analysis using generalized estimating equations (GEE).

Results: 151 patients were identified. Mechanical interference with leaflet mobility and coaptation was detected in 103 pts (68%) (CIEDs induced group), in the remaining 48 pts (32%), the lead was associated with TR without being the cause of it (CIEDs associated group). 105 patients underwent TV repair, and in the remaining 46 a TV replacement was necessary. In patients who underwent TV repair no significant difference in moderate TR recurrence rate was highlighted between CIEDs induced and CIEDs associated TR.

Conclusion: In patients with CIEDs and tricuspid regurgitation surgically treated, TR is CIEDs-induced in about 2/3 of the cases

and CIEDs associated in 1/3 of them. In our experience TV repair was still possible in 63% of the cases, with good long- term results and no significant durability difference between CIEDs-induced and CIEDs associated TR.

Introduction

Old trials focusing on Implantable Cardioverter-Defibrillator (ICD) safety and efficacy demonstrated a significant decrease in the rate of sudden death [1, 2]. At that time, the chance that an endocardial lead could cause significant tricuspid regurgitation (TR), leading to worsening heart failure, was not widely considered. Nowadays, it is well established that in patients with cardiac implantable electronic devices (CIEDs), moderate or severe TR occurs frequently (up to 45 %) [3, 4] and it is associated with increased mortality and hospitalization for heart failure [5, 6].

Indeed, patients with TR and CIEDs can be divided in 2 categories: those with CIEDs-induced TR and those with CIEDs-associated TR. In patients with CIEDs induced TR, the valve dysfunction is directly caused by the lead with several mechanism such as mechanical interference with tricuspid valve (TV) leaflet mobility and coaptation (impingement), valve damage during lead placement or manipulation and sub-valvular entanglement. In patients with CIEDs associated TR the valve dysfunction is not directly caused by the lead.

In 2009 approximately 720 000 CIEDs were implanted worldwide [7] and since then a steady increase of CIEDs implantations was registered, with an estimation of 1.4 millions of CIEDs implantation in 2023. With this impressive number of CIEDs requirement, the need for surgical or trans-catheter treatment of severe CIEDs-induced or associated TR increased steadily in the past years [8] and it will likely continue to increase in the next years. However, limited data are available regarding the outcome of tricuspid valve surgery in patients with CIEDs, particularly at long-term. With this study we aim to report the long-term result of tricuspid valve repair and replacement in patients with CIEDs.

Materials and methods

Ethics statement

The Ethical Committee of the San Raffaele Hospital approved the study (CE: 194/INT/2021) and waived the individual informed consent for this retrospective anonymous analysis.

Study population and follow-up design

A retrospective review of our prospectively maintained Institutional database was carried out to select all patients, with previously implanted CIEDs, who underwent tricuspid valve repair or replacement within the time frame 2000-2019, with or without concomitant left side valve surgery. Patients with tricuspid valve endocarditis were excluded. Overall, 151 patients fulfilled the inclusion criteria and represent the study cohort. Patients' charts were then analyzed to obtain pre-operative characteristics, intra-operative variables and in-hospital outcomes. Out of these 151 patients, 46 patients (30%) underwent TV replacement, 105 patients (70%) underwent TV repair: 64 by means of ring annuloplasty, 25 with a Kay procedure and 16 using a De Vega technique.

The Ethical Committee approved the study and waived the individual informed consent for this retrospective analysis.
Survival and echocardiographic follow-up data were obtained by querying the informatic hospital system for out-patients visits and echocardiographic examinations. If follow-up information was not present in the hospital system, patients and the referring cardiologists were reached via telephone and asked to provide all the results of echocardiographic examinations performed. The cause of death was determined by death certificates or information from the physician who was caring for the patient at that time. Clinical and echocardiographic follow- up were 95% complete; the median follow-up time was 6.9 years (3.8-10.8). The majority of the patients had their echocardiographic examinations performed at our institution (72%; n = 109/151).

Surgical and echocardiographic details

All operations were performed through a median sternotomy with standard cardio-pulmonary by-pass (CPB). In case of isolated tricuspid valve surgery, the decision to perform the operation on a beating heart or under cardioplegic arrest was left to the operating surgeon. A beating heart technique was employed in 11 patients who underwent isolated tricuspid valve replacement. The role of the CIEDs lead in contributing to TR was mainly based on the intra-operative findings combined with pre-operative echocardiographic characteristics. Patients were divided into 2 groups: CIEDs-associated TR in which patients had significant TR which was not found to be caused by CIEDs leads; and CIEDS-induced TR, in which the pre-operative echocardiography showed a restricted motion of the leaflet and intraoperatively was confirmed that the leads directly contributed to the development of significant TR with one of the following mechanisms: restriction of the mobility of otherwise normal-appearing leaflets or leaflet adherence to the leads (impingement) or sub-valvular entanglement.

In case of CIEDs-induced TR, tricuspid repair was attempted, at the operating surgeon discretion, when the valve was not extensively damaged. Repair techniques included: detaching and moving away from the leaflet adherent leads, pericardial patch repair of perforated leaflets, and translocations of the leads in the postero-septal or anteroposterior commissures with suture fixation [9]. Annuloplasty was always used to complete the valve repair. Trans-esophageal echo was always used to assess the result of valve repair after weaning from CPB. In case of more than moderate residual TR a second CPB run was started and tricuspid valve replacement was carried on. This was necessary in 5 cases (3%).

Replacement was deemed unavoidable in case of excessive valve damage or when marked apical tethering with wide coaptation gap was present. In such cases, the prosthesis was implanted avoiding excising the leaflets to preserve the valvular apparatus. In all cases the CIEDs lead was left between the native annulus and the sewing ring of the prosthesis [10]. A biological valve was selected in all patients.

Preoperatively, all patients underwent trans-thoracic echocardiography, followed by trans-esophageal echo in selected cases. A non-linear 3 grade scale was adopted to define TR as mild, moderate, and severe. Whenever possible, particularly in patients who underwent trans-esophageal echo, the role of the CIEDs lead in the development of TR was investigated but the final distinction in CIEDs-induced and CIEDs-associated TR was always based on the intra-operative findings. In the first part of the study period a semi quantitative method, using doppler color flow imaging, was used to quantify the degree of TR. The TR was defined as mild if the percentage of the right atrial area subtended by the TR jet was 1% to 15%; moderate if it was 16% to 55%; and severe if greater than 55%. In addition, the vena contracta width at the narrowest portion of the regurgitant jet was measured [11]. Since 2010 this method was integrated with the current European guidelines for TR grading [12], particularly adding the PISA radius and the EROA whenever possible .

Statistical analysis

Categorical data were described as absolute and percentage (%) values. Continuous normal distributed variables were expressed as mean ± standard deviation (SD), while continuous not-normal variables were reported as median and [25th percentile; 75th percentile]. The Shapiro–Wilk test was employed to assess normal distribution. Missing values were handled by single imputation of mean value.

The endpoints analyzed were TR recurrence and mortality (both overall and cardiac related). It must be emphasized that 95% confidence intervals were not adjusted for multiple comparisons and inferences drawn from them may not be reproducible.

Kaplan-Meier method was employed to estimate survival during the follow-up and log-rank test was used to make intergroup comparison. To identify risk factors for mortality during the follow-up a univariate and multivariate Cox regressions were employed and the Schoenfeld residuals was used to assess the proportional hazards assumption.

For competing risk analysis, Cumulative Incidence Function (CIF) using death as competing risk was used to estimate cardiac death. The non-parametric Pepe-Mori test was used to make intergroup comparison. The Fine and Gray model for competing risk analysis was employed to evaluate the predictors of cardiac death with death for other reasons as competing risk. Covariates with a *P*-value of <0.1 at univariate analysis were included into the multivariate model.

Finally, to describe the time course of TR recurrence during the follow-up, we performed a longitudinal analysis using generalized estimating equations (GEE) with random intercept for correlated data (binomial and logit with the patient as a random intercept and the time interval as fixed effect)

All the analyses were performed with Stata software (College Station, TX, USA) version 15.

This retrospective study was conducted according to the STROBE checklist [13].

Results

Patients' characteristics and in hospital results

Median age was 71 years and 40% were male (N= 61). The vast majority of the patients [N=140 (93%)] had a Pace Maker (PM), while an Implantable Cardioverter Defibrillator (ICD) was present only in 11 (13%) cases. Median LVEF was 55% (IQR 50-60). Almost one half of the patients were REDO cases (N=73; 48%), and 15 patients (10%) presented chronic renal failure. The baseline preoperative characteristics are summarized in **Table 1**.

CIEDs induced TR was intraoperatively highlighted in 103 (68%) while in the remaining 48 patients (32%), the lead was associated to TR without being the direct cause of it (CIEDs associated TR).

Table 1: Baseline characteristics

Number of patients	151
Female sex, n (%)	90 (60%)
Age (IQR)	71 (64-76)
Hypertension n (%)	112 (74%)
Diabetes n (%)	14 (9%)
NYHA functional class, n (%)	
I	10 (6%)
II	75 (50%)
III	63 (42 %)
IV	3 (2%)
LVEDD, mm (IQR)	55 (49-60)
PAPs, mmHg (IQR)	45 (40-50)
PAPs $\geq$ 50 mmHg; n (%)	37 (24%)
TAPSE, mm (± SD)	17,2 ± 4,5
RVEDD, mm (IQR)	38 (35-45)
RVEDD > 41 mm n (%)	54 (36%)
Peak systolic velocity(s′) TDI; cm/sec (±SD)	11 ± 2,9
Tricuspid annulus diameter, mm (IQR)	45 (39-50)
Tricuspid regurgitation grade, n (%)	
2+	10 (7%)
3+	47 (31%)
4+	94 (62%)
Chronic renal failure n (%)	15 (10%)
Redo n (%)	73 (48%)
MELD score; (± SD)	13.8 ± 4.6
EuroSCORE II ;(±SD)	3.20 ± 1.5
Pacemaker n (%)	140 (93%)
Implantable cardioverter defibrillator n (%)	11 (7%)

IQR: interquartile range; LVEDD: left ventricular end-diastolic diameter; MELD: Model for End-Stage Liver Disease; NYHA: New York Heart Association; PAPs: pulmonary artery pressure score; RVEDD: right ventricular end-diastolic diameter; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue Doppler imaging.

In 46 patients (30%) a tricuspid valve replacement was unavoidable; in the remaining 105 patients (70%) tricuspid valve repair was performed. Patients who underwent TV replacement had a significantly more dilated right ventricle (median RVEDD 46 mm [IQR 42-49] as compared to those who received a repair (median RVEDD 38 mm [IQR 30-42], *p<0.001*) and a subsequent much more severe apical tethering was observed at the preoperative echocardiogram, although the related coaptation depth was not systematically measured.

Within the valve replacement group, the great majority was represented by CIEDs induced TR (N=38/46; 83%). In the valve repair group, TR was CIEDs induced in 63% of the cases (N= 65/105). Within these 65 patients with CIEDs induced TR who underwent tricuspid valve repair, a ring annuloplasty was employed in 40 patients. In all of these cases the leaflet was detached from the adherent lead which was subsequently fixed in the recess of the antero-posterior commissure in 5 patients, in the recess of the postero-septal commissure in other 5 patients and left in the center of the tricuspid valve in 29 patients after careful evaluation of the absence of interference with the valve closure. Finally in 1 patient the lead was secured at the annulus level after posterior leaflet division and reconstruction [14]. In the remaining 25 patients with CIEDs induced TR who underwent tricuspid valve repair, a suture annuloplasty technique was employed. In all of these, the lead was detached from the leaflets and left in the center of the valve.

In the majority of the patients the indication for surgery was driven by other reason besides TV surgery (N=122, 80%), with mitral valve surgery (both repair and replacement) being the most common (N=112/122; 92 %). Intra-operative variables are summarized in **table 2**.

In-hospital mortality occurred in 10 (6,6%) patients. In 3 patients the cause of death was multi-organ failure syndrome, 3 patients died for septic shock and the remaining 4 patients died for heart failure. The last 4 cases were all patients at very high risk with severely dilated left ventricle and impaired bi-ventricular function. Six out of the 10 in-hospital deaths were REDO cases. The majority of patients did not present any residual TR at hospital discharge (92% of the whole cohort) and only 7% of the whole cohort left the hospital with more than mild TR.

Table 2: Intraoperative variables

Total number of patients	***151***
CPB time, min (IQR)	91 (70-120)
Cross-clamp time, min (IQR)	70 (52-89)
Associated procedure, N (%)	122 (80%)
Mitral valve repair	39 (32%)
Mitral valve replacement	73 (60%)
Aortic valve replacement	10 (8%)
CIED-induced TR	103 (68%)
TV replacement in CIED-induced TR	38 (25%)
TV repair in CIED-induced TR	65 (43%)
Lead detachment + ring annuloplasty	30 (20%)
Lead detachment and fixation in the commissure + ring annuloplasty	10 (6%)
Lead detachment + suture annuloplasty	25 (16%)
CIED-associated TR	48 (32%)
TV replacement in CIED-associated TR	8 (5%)
TV repair in CIED-associated TR	40 (26%)
Ring annuloplasty	24 (16%)
Suture annuloplasty	16 (10%)

CIED: implantable cardioverter defibrillator; CPB: cardiopulmonary bypass; IQR: interquartile range; TR: tricuspid regurgitation; TV: tricuspid valve.

Long-term survival

Follow-up was 95% complete, and median follow-up time was 6.9 years [IQR 3.8-10.8].

No significant difference was evident in the 8-years estimated survival between patients who underwent tricuspid valve repair and tricuspid valve replacement *(p=0.156)*. In particular, in the tricuspid valve replacement group, the 8-years estimated survival was 63.8±9.30%, 95% CI [42.82-78.84], while it was 69.3±5.42%, 95% CI [57.24-78.51] in the TV repair group (**Figure 1**). Being the patients in the replacement group in a more advanced stages of the disease, with severely dilated right ventricle and marked apical tethering, a significantly higher rate of cardiac death during the follow-up was observed *(p=0.024)*.

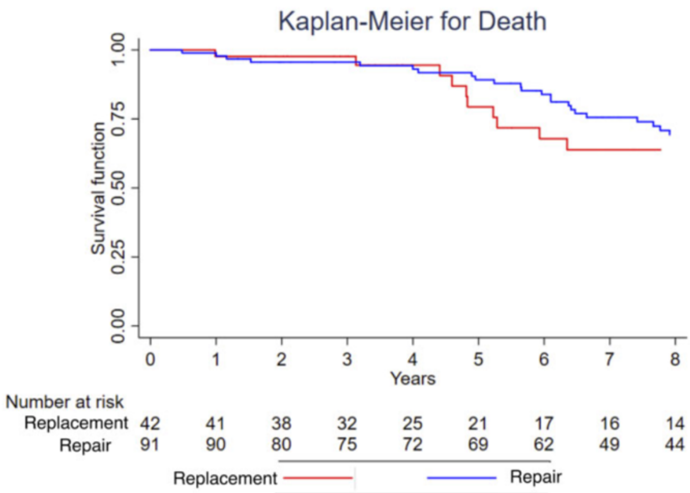

Figure 1: Estimated survival using the Kaplan-Meier method. At 8 years, the estimated survival was 63.8 ± 9.30%, 95% confidence interval [42.82–78.84] in tricuspid valve replacement group (red line) and 69.3 ± 5.42%, 95% confidence interval [57.24–78.51] in the tricuspid valve repair group (blue line) without a statistically significant difference (*P = 0.156*).

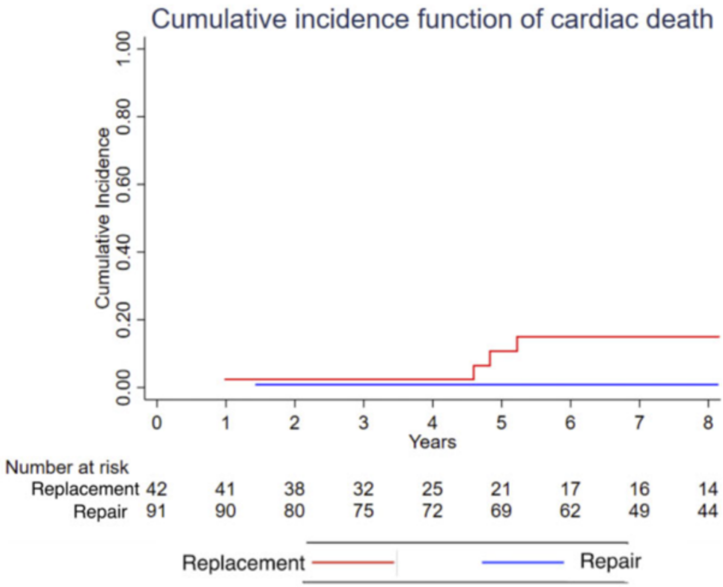

Figure 2: Cumulative incidence function for cardiac death using death for any other reason as the competing event. At 8 years, the cumulative incidence function was 15.0 ± 7.08, 95% confidence interval [4.52–31.17] in the tricuspid valve replacement group (red line); and it was 1.2 ± 1.14, 95% confidence interval [0.10–5.57] in the tricuspid valve repair group (blue line). A statistically significant difference was highlighted between the 2 groups (*P* = 0.024).

The CIF for cardiac death with death for any other reason as competing event at 8 years was 15.0 ±7.08, 95% CI [4.52-31.17] in the tricuspid valve replacement group whereas it was only 1.2 ±1.14, 95% CI [0.10-5.57] in the tricuspid valve repair group (**Figure 2**). Again, as expected, TV repair appeared to be a significant protective factor for cardiac death at the multivariate analysis by means of the Fine and Gray model: HR:0.07, 95% CI [0.01-0.65], p=0.020. Once again, this data must be interpreted cautiously, reflecting a significant selection bias because great part of the patients who underwent TV replacement were in a significantly more advanced disease status.

Within the TV repair group, dividing the patients in CIEDs induced TR and CIEDs associated TR no significant difference in the estimated 8-year survival was showed *(p=0.445)* (**Figure 3**).

Regarding the clinical condition of the patients at the last contact the great majority were in NYHA class I (76%) with no statistically significant difference between patients who underwent TV replacement and repair (respectively 66% vs 80% p= 0.091)

<u>*TR recurrence*</u>

No patient submitted to tricuspid valve replacement had TR greater than mild at follow-up. In addition, no need for lead

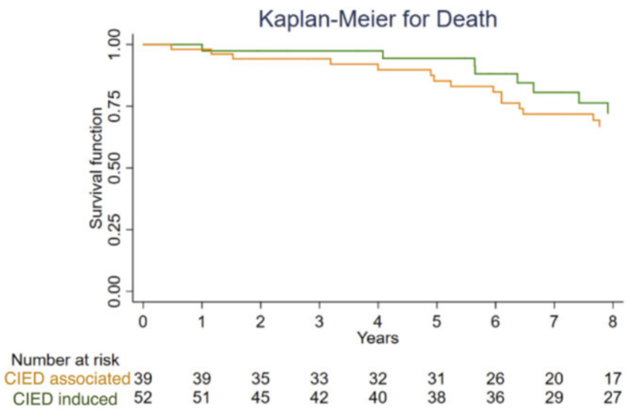

Figure 3: Estimated survival using the Kaplan–Meier method for the tricuspid valve repair group. At 8 years, the estimated survival was 72.1 ± 8.60%, 95% confidence interval [51.25–85.22] in the cardiac implantable electronic device-associated (green line) group, and it was 66.8 ± 7.07%, 95% confidence interval [50.98–78.60] in the cardiac implantable electronic device-induced group (orange line), without a statistically significant difference between the 2 groups (*P* = 0.445).

extraction for endocarditis occurred in those patients.

Within the TV repair group, a significant increase of moderate TR recurrence during the follow-up was noted (*p=0.018*). When dividing the patients in CIEDs associated and CIEDs induced TR, no significant difference of moderate TR recurrence was observed with the longitudinal analysis performed with the GEE (*p=0.359)*. However, a trend to an increase of TR recurrence in the CIEDs induced group was evident and we cannot exclude that the lack of statistical significance might be due to the relatively small size of the cohort. Indeed, at 8 years the predicted rate of moderate TR recurrence was 5.48 % in the CIEDs associated TR group and 8.98% in the CIEDs induced TR one (**Figure 4**). At the multivariate analysis no significant

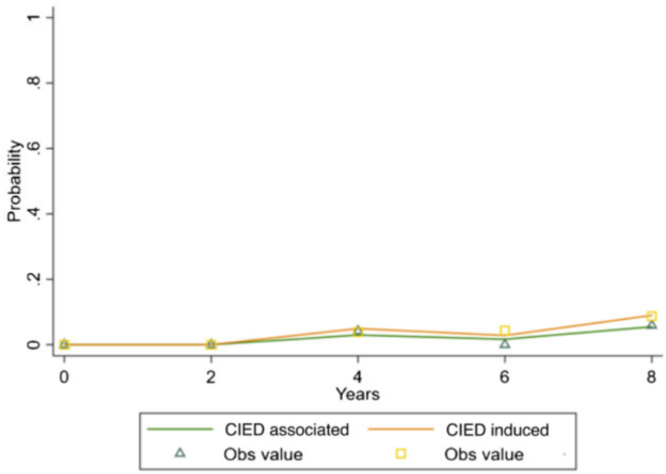

Figure 4: Longitudinal analysis for moderate tricuspid regurgitation recurrence in patients who underwent tricuspid valve repair using the generalized estimating equations with a random intercept for correlated data. At 8 years, the predicted rate of recurrence of moderate TR was 5.49% in the cardiac implantable electronic device-associated (green line) group whereas it was 8.98% in the cardiac implantable electronic device-induced group (orange line). No significant difference in the recurrence rate was noted (*P* = 0.359).

predictors of moderate TR recurrence were identified in the TV repair group.

Information about the echocardiographic data at the last follow-up are summarized in **table 3**.

Table 3: Postoperative echocardiographic anatomical and functional parameters at the last follow-up

Patients with CIED-associated TR who underwent tricuspid valve repair	
LVEF % (IQR)	50 (45-55)
LVEDD mm (IQR)	53 (47-58)
PAPs; mmHg (IQR)	33 (25-45)
TAPSE, mm (± SD)	18.2 ± 4.2
RVEDD mm (IQR)	38 (32-44)
Tricuspid annulus diameter mm (IQR)	30 (28-36)
Patients with CIED-induced TR who underwent tricuspid valve repair	
LVEF % (IQR)	48 (45-55)
LVEDD mm (IQR)	50 (46-57)
PAPs; mmHg (IQR)	30 (25-45)
TAPSE, mm (± SD)	19.2 ± 5.1
RVEDD mm (IQR)	37 (31-41)
Tricuspid annulus diameter mm (IQR)	32 (28-38)
Patients who underwent tricuspid valve replacement	
LVEF % (IQR)	40 (30-45)
LVEDD mm (IQR)	58 (50-65)
RVEDD mm (IQR)	48 (42-50)

CIED: implantable cardioverter defibrillator; IQR: interquartile range; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; PAPs: pulmonary artery pressure score; RVEDD: right ventricular end-diastolic diameter; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

Discussion

With the expanding use of CIEDs device in an ever-aging population the interference of the leads with the tricuspid valve, causing significant TR, has gained increasing recognition. The reported frequency of developing significant TR following CIED implantation varies, ranging from 7% to 45% [5, 15–18] (**Fig. 5**). With the impressive number of CIEDs implantation worldwide (it has been estimated that in 2023 there will be 1.4 million of CIEDs implantation worldwide) and the increased awareness to TV disease, it is likely that the need for surgical and trans-catheter treatment of significant TR in presence of CIEDs will increase in the future. However, scanty data are available in the literature about the surgical results of both CIEDs induced and CIEDs associated TR, particularly as far as long-term results is concerned. Thus, we undertook this study to report our experience with TV surgery in this peculiar setting. Our study has several key findings.

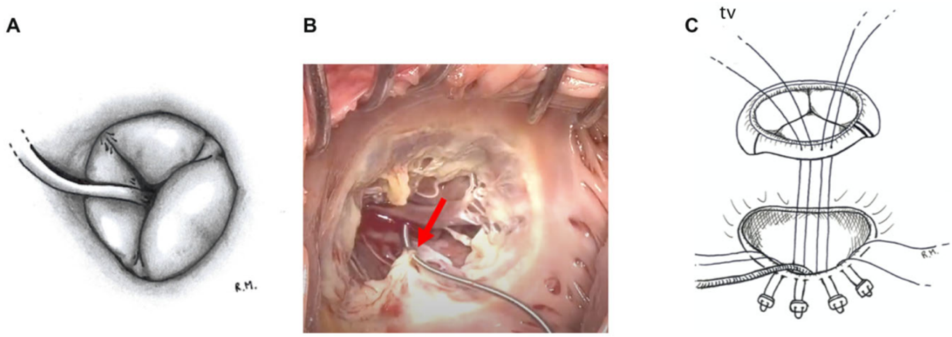

Figure 5: **(A)** Cardiac implantable electronic device-associated tricuspid regurgitation, with the lead in the centre of the valve not interfering with the motion of the leaflets. **(B)** Intraoperative image of cardiac implantable electronic device-induced tricuspid regurgitation. The red arrow indicates the lead impinging on the leaflets. Panel **(C)** Tricuspid valve replacement leaving the lead between the native annulus and the sewing ring of the prosthesis.

First, we noted that, in a variegated population of patients with CIEDs, undergoing surgical treatment of tricuspid regurgitation (either isolated or combined with left side valve surgery), more than 2/3 of the TR cases were CIEDs-induced, while CIEDs-associated TR was much less common. Several mechanisms of CIEDs induced TR have been described [4] with lead impingement being the most common in our own cohort. We did not notice any case of leaflet perforation and we noticed very few cases of sub-valvular entanglements.

Another important finding of our study is that, also in case of CIEDs induced TR, valve repair was still possible in 63% of the patients (N=65/103). Several techniques have been employed to repair the valve in case of CIEDs induced TR. In a number of cases, a fibrotic response causing encapsulation of the lead in the TV leaflet was noted and resected. Usually this was sufficient to allow an unrestricted motion of the leaflet and an annuloplasty (both using suture technique or a ring) was added to complete the repair, leaving the lead in the center of the valve. In other cases, the lead needed to be secured within the recess of the antero-posterior or postero-septal commissure to avoid further interference with the valve closure. Finally, in 1 peculiar case, a bespoke repair was necessary to prevent lead-induced tethering of the leaflet since there were no deep commissures in which to place the lead itself. In this case the posterior leaflet was divided in the middle, the lead was fixed at the base of this incision to the native annulus and the posterior leaflet was re-sutured to restore its continuity. We think that, whenever possible, it is worthwhile try to repair the tricuspid valve in case of CIEDs induced TR, limiting TV replacement only to patients with massive valve disruption or severe apical tethering. Being TV replacement a known risk factor for early and late mortality compared to TV repair [8, 19, 20] we strongly believe in this approach. Our data seem to give further confirmation to this known finding, with a significantly higher rate of cardiac death in the TV replacement group during the follow-up, although a word of caution is needed in the interpretation of this outcome considering that replacement was more common in patients with more advanced stage of the disease. In our series the attempted repair was not always successful and in 5 cases a second CPB run was necessary for residual severe TR and a TV replacement had to be performed.

Another finding of our study regards the absence of adverse events when the lead was left between the native annulus and the sewing skirt in case of valve replacement. No periprosthetic leaks were documented, all bio-prostheses showed no or mild regurgitation at follow-up and no cases of lead removal were documented. However, it must be kept in mind that after fixing the lead between the native annulus and the sewing skirt of the prosthesis in case of CIEDs infection the lead cannot be removed percutaneously.

Finally, in case of TV repair no difference in TR recurrence was noted between CIEDs induced and CIEDs associated TR. This is probably the most important finding of our study, and we are not aware of any other study reporting this data. The good durability of TV repair in case of CIEDs induced TR give further strength to our advice to reserve TV replacement only in case of extensive valve disruption. Sometimes this approach can be time consuming and in case of severe lead impingement the removal of fibrotic response of the leaflets to the lead, can be challenging. Nevertheless, in our experience in case of CIEDs induced TR the TV can still be repaired in more than 2/3 of the cases with good results, also in the long term and a low TR recurrence rate comparable to CIEDs TR associated cases. Again, these findings need to be confirmed by studies with more patients because the trend observed in our small series might possibly reach a statistical significance in population with larger sample sizes.

Limitations

The main limitations of our study are related to its retrospective nature and the related possible selection bias. Another limitation is the relatively small sample size. Particularly we cannot exclude that the lack of statistical significance in the recurrence TR rate between CIEDs induced and CIEDs associated TR is due to the relatively small size of the cohort. Finally, the follow-up is not 100% complete, and we cannot exclude that patients lost to follow-up died of cardiac causes or had recurrent TR. Nevertheless, the echocardiographic follow-up seems to be complete enough to provide meaningful information about the overall rate of TR recurrence.

Conclusion

In our experience about 2/3 of the patients undergoing TV surgery with a CIEDs have a CIEDs induced TR, whereas only in 1/3 of the case the TR was CIEDs associated. TV repair was still possible in 63% of the cases, with good long- term results and no significant durability difference between CIEDs-induced and CIEDs associated TR. Tricuspid valve replacement could not be avoided in 30% of the cases. In this series the policy of positioning the lead between the native annuls and the skirt of the prosthesis was simple and not associated to any complication.

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Chicago - 2017

Chapter 7

ISOLATED TRICUSPID VALVE SURGERY: BEYOND THE IDEA OF A HIGH MORTALITY SURGERY

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Eur J CardioThorac Surg 2022;62(2):1-2.

Management and treatment of patients with isolated tricuspid regurgitation (TR) remains a controversial issue. In patients with isolated TR, when should surgery be performed at a low risk, and when does it become a high-mortality intervention?

This issue of EJCTS contains a retrospective, single-centre study by Weiss et al. [1] assessing clinical outcome and functional capacity following isolated tricuspid valve (TV) surgery performed on 43 patients over a 6-year interval. Within the study, patients with severe right or left heart failure, severe pulmonary hypertension, end-stage renal disease and liver disease were excluded from open-heart surgery. No in-hospital mortality was reported, and, at one-year follow-up, 9% mortality was documented, with a significant improvement in functional capacity, together with a reduction of clinically apparent peripheral edema and daily oral furosemide therapy.

These findings strongly support the message that the cardiac surgery community has recently tried to deliver regarding "early referral and treatment" in TR. Indeed, it has now become evident that outcomes following isolated TV surgery are almost exclusively dependent on the baseline patient's profile [2]. The population of patients treated by Weiss and colleagues was highly selected and not extremely advanced in disease progression, resulting in good short-term outcomes and improved functional capacity [1]. Nevertheless, despite good prognosis, a small percentage of patients experienced rehospitalizations and death within a year, underlining the importance of thorough preoperative evaluation. These findings are in line with the surgical experience at San Raffaele Hospital, Milan, as well as those of other centres [3–5]. Patients operated upon in early stages of the disease, before the occurrence of prominent symptomatology, right ventricular dilation and dysfunction, and end-organ damage, most frequently receive tricuspid valve repair with no in-hospital mortality, fewer postoperative complications and shorter length-of-stay [6]. Furthermore, at 5 years, patients experience 100% survival and no further hospitalizations for right heart failure. On the contrary, patients medically managed for many years and referred late to tricuspid valve correction, when the disease is more advanced and the number of comorbidities grow, experience high morbidity and mortality after surgery [7,8]. This contributes to further supporting the erroneous belief that isolated TV surgery is always a high-risk procedure with a dismal outcome.

Recent knowledge should prompt to a change in attitude towards earlier referral and surgical treatment of patients with severe isolated TR. The European guidelines [9] have recognized that surgery might be considered in patients prior to development of right ventricular dysfunction and end-organ damage. Weiss et al. [1] have, in fact, demonstrated that isolated TV surgery can be performed with low surgical mortality and morbidity in patients at early stages of the disease, together with improvement in functional capacity. Such results support the importance of optimal surgical timing, thorough patient evaluation and correct selection. In this regard, a novel dedicated risk score aims at predicting the outcome of patients following isolated TV surgery [10] based not only on right and left ventricular function, but also kidney and liver involvement, as well as on medical therapy and preoperative clinical status. This should be of further help in guiding the clinical decision-making process of patients with severe isolated TR.

Therefore, it is of crucial importance to go beyond the misconception that isolated TV surgery is always associated with excessive in-hospital mortality and poor long-term outcomes. Timing is critical in this respect. Indeed, timely referral and early surgical treatment can be performed at low risk, and contribute to better short and long-term outcomes for these patients.

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Santorini -2018

Chapter 8

ISOLATED TRICUSPID VALVE DISEASE: TRANSCATHETER TREATMENT “FOR ALL”?

Alessandra Sala

Eur J CardioThorac Surg 2022;62(3):1-2.

Isolated tricuspid valve surgery has become a matter of great debate and great interest. Recently, the ultimate focus has been on patient selection, surgical indication, correct timing and identification of predictors of outcome following surgery in this population. Numerous studies have underlined the importance of early referral and early treatment, before the development of overt symptomatology, right heart dysfunction and failure, and end-organ damage [1–3]. This is also seen in the paper published within this issue of the European Journal of Cardio-Thoracic Surgery by Russo and colleagues [4]. The study is a retrospective, multi-centre study assessing early and long-term outcomes of patients undergoing isolated tricuspid valve surgery (ITVS) and comparing repair and replacement strategies. The study analysed 426 patients treated over an 18-year period in 13 different centres, with 52% of patients undergoing tricuspid valve replacement (TVR) and the remainder undergoing tricuspid valve repair (TVr). The greatest indication to ITVS was functional tricuspid regurgitation (TR), in 45% of cases. Results showed lower early and late mortality in patients undergoing TVr, with no difference at 10 years regarding reoperation rate when compared to replacement. Therefore, early intervention more frequently leads to TV repair, with associated better outcomes.

However, early referral is still far from common practice and currently more than 90% of patients with relevant isolated TR are not offered any treatment [5]. Efforts should be made to increase awareness within the medical community of the consequences of untreated severe TR [6] and the fact that early surgical correction can be safe and effective. Until then, is it reasonable to consider every available transcatheter treatment option for this heart valve disease? Can every disease stage and clinical scenario be effectively addressed by the percutaneous interventions?

Percutaneous tricuspid valve interventions are a growing field. Patients undergo leaflet-to-leaflet repair, incomplete ring annuloplasty, receive coaptation devices, caval valve implantations and percutaneous tricuspid valve replacement. Overall, these procedures are safe and recent evidence support such solutions in patients considered inoperable. Retrospective studies have reported a reduction in TR grade and symptomatic improvement (with reduced right heart failure hospitalization rates) in patients undergoing percutaneous repair procedures [7]. However, the amount of TR reduction has been variable among studies and devices, with many patients remaining with at least moderate TR despite a successful procedure [8]. Surgical literature has underlined that residual TR is a marker for poor outcomes. Therefore, the clinical impact of these incomplete TR repairs is still in question and will need to be better established in the upcoming years. Among the various factors identified as responsible for non-optimal repairs, anatomical aspects, linked both to the underlying disease etiology and to the duration of TR/disease stage, seem to play a major role, such as important coaptation gaps (>7mm) due to excessive annular dilation, marked leaflet tethering or restricted leaflet mobility and presence of pacemaker leads. The presence of such anatomical factors upon preoperative evaluation may tip the scales in favour of transcatheter valve replacement. In fact, valve performance and absence of residual TR seem superior in patients undergoing transcatheter tricuspid valve replacement. However, in spite of worse procedural safety, higher rates of major adverse events and higher reported mortality (up to 10% in some series) [9]. These “surgical-like” results should be carefully considered for each single patient in a case-specific scenario, evaluating the feasibility and expected results of the various repair techniques. Another treatment option considered for inoperable and strongly symptomatic patients consists in caval valve implantations. These interventions solely aim at reducing congestion and end-organ involvement, while TR is not addressed. As a result, right ventricular dilation and dysfunction will progress, making these devices merely palliative.

Regardless optimal repair results, most studies have also demonstrated a clinical benefit following transcatheter repair interventions, with an improvement in New York Heart Association (NYHA) functional class and reduction in hospitalizations for right heart failure [10]. These results are of utmost importance, especially in patients deemed inoperable and that would therefore be denied any surgical correction.

Nevertheless, a control group treated with optimal medical therapy is lacking and most studies report exclusively early outcomes following device implantation, while mid- and long-term data are still not available.

In an era of great fervour for the development and application of transcatheter tricuspid treatment options, all the aforementioned aspects should be well considered. Just as for surgical correction, transcatheter tricuspid valve interventions require correct timing, indication and optimal patient selection. Multiple factors should be taken into account, including patients' clinical characteristics and disease stage, end-organ function and anatomical considerations. Percutaneous procedures are, matter of factly, not "for all" but may result futile in candidates with end-stage heart failure, untreated pulmonary hypertension and end-organ damage. Therefore, a comprehensive evaluation by the Heart Team is mandatory, in order to determine the surgical risk, thoroughly assess both anatomical and clinical characteristics, carefully weigh the expected results and clinical benefits versus the potential risk factors, and finally identify the most appropriate treatment strategy for every patient.

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Morocco - 2018

Chapter 9

TRANSCATHETER AND SURGICAL TREATMENT OF TRICUSPID REGURGITATION: PREDICTING RIGHT VENTRICULAR DECOMPENSATION AND FAVOURABLE RESPONDERS

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Front Cardiovasc Med 2022;9:980639

Abstract

Isolated tricuspid regurgitation (TR) has gained increasing recognition in recent years both in the surgical and in the cardiological community. Left untreated, isolated TR significantly worsens survival. Despite being a strong predictor of negative prognosis, interventions to correct TR are rarely performed due to increased surgical risk and late patient presentation. Recently, the ultimate focus has been on patient selection, surgical or transcatheter indication, and correct timing. Furthermore, of paramount importance is the identification of predictors of outcome following treatment, in order to discriminate between favorable and unfavorable responders and guide the decision-making process of the most adequate treatment for every patient.

Introduction

Isolated tricuspid regurgitation (TR) has gained increasing recognition in recent years both in the surgical and in the cardiological community. Initially considered benign, isolated severe TR has been found to be a strong predictor of prognosis (1,2). Furthermore, when left untreated, TR significantly worsens survival, with a mortality rate at 5 years of approximately 50% (3–5). Despite such strong evidence in the literature, management of patients with severe isolated TR remains controversial. Current guidelines (6,7) provide specific indications for treatment of TR; while surgical correction of TR concomitantly to left-sided heart diseases has been accepted and is commonly performed, reluctancy remains regarding treatment of isolated TR. This is mainly related to the fact that even if severe, TR can be clinically well tolerated for many years. Patients, in fact, tend to be asymptomatic, with a good quality of life, and whenever minor symptoms arise, they can be initially easily managed with an adequate medical therapy (8). However, following many years of tolerating TR, patients tend to develop organ failure difficult to manage with medical therapy, requiring a structural intervention on the valve which becomes high risk for the multimorbid status of the patient (9–11). For this reason, for years, an extremely high in-hospital mortality following surgery has been reported in the literature, together with great uncertainty regarding long-term outcomes (12–14).

Therefore, despite being a disabling condition, a very low percentage of patients affected by isolated TR (approximately 5%) are currently receiving treatment, resulting in significant undertreatment of the disease (5,15). This large unmet clinical need has favored the development and exponential growth of transcatheter devices for the treatment of TR. However, regardless the treatment strategy, whether surgical or transcatheter, patient selection and correct timing play the most important role in determining a favorable outcome following TR treatment (16). Recently, the ultimate focus has been trying to identify predictors of outcome following tricuspid valve (TV) treatment.

In the present article we aim at reviewing the currently available results in the literature regarding isolated TR treatment, both surgical and transcatheter, with particular attention to outcomes and predictors of a favorable versus an unfavorable response.

Surgical treatment

The majority of tricuspid valve operations are performed concomitantly to left-sided valve surgeries, while only a minority, approximately 14%, are performed in isolation (17–19). This likely occurs in response to the historically reported high in-hospital mortality rates following isolated TV surgery and poor long-term outcomes, that have remained relatively stable during the last decade. Previous studies have indeed reported an in-hospital mortality ranging from 8.8 to 37%, associated to a 30 day all-cause death rate ranging from 3.2 to 16% and a 5-year mortality rate of 55% (18,20–22). Furthermore, these studies reported a trend towards increasing patient complexity over time, and a significant impact on outcomes of factors associated with disease duration and late clinical presentation (17,19). Recent data has underlined how early referral for surgical correction results in excellent both short and long-term outcomes (23–27). These findings support the message that the cardiac surgery community has recently tried to deliver regarding "early referral and treatment" in TR. The surgical act of TV repair or replacement is not technically demanding in itself and the outcome is therefore almost exclusively dependent on the baseline patient's profile, and in particular, on right ventricular (RV) function (28) and the overall right heart physiological status. While American guidelines (6) tend to be more conservative, and suggest waiting for the development of signs or symptoms of right heart failure (RHF) before recommending TV repair or replacement (Class IIa), European guidelines (7) have recognized that surgery might be considered in patients prior to development of RV dysfunction and end-organ damage, even in asymptomatic patients, whenever there is evidence of ongoing right heart remodeling.

However, to date, the questions of when to perform isolated TV surgery for severe TR, when is referral considered "early" and when is late referral considered "too late" are of crucial importance.

Quite a few authors have tried to identify predictors of a favorable outcome in order to better aid in the stratification of surgical risk (***Table 1***).

Table 1. Characteristics of the surgical studies in the literature

Study	n. of patients	Age (years)	Procedure TVR	NYHA III/IV	REDO	RHF episodes	RHF signs	End-organ involvement	LVEF (%)	≥moderate RV dysfunction	sPAP (mmHg)	Outcomes
Dreyfus (28)	466	60±16	57%	47%	24%	35%	57%	33% CKD 12% liver disease	58±9%	17%	40±11	10% in-hospital mortality 38% 5-years all-cause death
Sala (26,27)	172	66[55-74]	75%	62.2%	57.6%	34.3%	21.5%	22.7% CKD	60% [55-60]	13.6%	40 [35-48]	5.8% in-hospital mortality 15% 5-years all-cause death
Weiss (31)	43	65.2±13.8	41.9%	72.1%	27.9%	-	34.9%	14% CKD	60% [IQR 2.5]	7%	-	0% in-hospital mortality 9.3% 1-year all-cause death
Kawsara (24)	1513	55.7±16.6	36.5%	-	-	85.9%	41%	36.2% CKD 36% liver disease	-	-	-	8.7% in-hospital mortality 26.8% cardiogenic shock

CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RHF: right heart failure; RV: right ventricle; sPAP: systolic pulmonary artery pressure; TVR: tricuspid valve replacement

Dreyfus and colleagues (28) analysed patients treated with TV surgery in 12 French tertiary centres. Only a minority (8%, 466) underwent isolated TV surgery, and were mainly older (mean age 60 years), 24% had had previous left-sided valve surgery, approximately 50% presented with New York Heart Association (NYHA) class III and IV heart failure symptoms and 35% experienced heart failure within the year prior to surgery. Moreover, >50% presented with RHF, 8% with ascites and chronic kidney and liver disease were present in 33% and 12% of patients, respectively. Regarding echocardiographic data, approximately 20% of patients had moderate and severe RV dysfunction and a systolic pulmonary artery pressure (sPAP) ≥ 50mmHg. More than half of patients received TV replacement.

In terms of outcomes, in-hospital mortality was 10%, and at 1- and 5-years follow-up the rates of all-cause death and cardiovascular readmissions were 25% and 38%, respectively. Independent predictors associated to in-hospital mortality and mid-term follow-up were NYHA III/IV heart failure symptoms, low prothrombin time and moderate and severe RV dysfunction. These data underline the importance of timely referral. In fact, chronic severe TR leads to RV dilation and dysfunction, and when patients present with symptoms despite medical therapy it is often too late for intervention (29).

These results were further confirmed by a single-centre retrospective study published by our group (26,27). The 172 patients analysed were divided according to a new classification based not only on TR grade, but also symptoms, RV remodeling and function, RHF episodes and medical therapy (30), ranging from Stage 1 (less than moderate TR, no symptoms) to Stage 5 (severe TR, RHF episodes despite maximal medical therapy, organ damage, severe RV dysfunction). In our experience, patients operated upon in early stages of the disease (Stage 2 and 3), without prominent symptomatology, RV dilation or dysfunction, and without organ involvement, most frequently received TV repair with no in-hospital mortality, fewer postoperative complications and shorter postoperative length-of-stay. Moreover, patients at early stages of the disease, following TR treatment, experienced 100% survival at 5 years and no further hospitalizations for RHF. On the contrary, patients in more advanced stages (Stage 4 and 5) experienced higher in-hospital mortality (15.3%), postoperative complications (such as acute kidney injury and low cardiac output syndrome), and longer both intensive care unit and hospital lengths-of-stay. In these stages, survival at 5 years was 60.5% and 20% of patients experienced at least one hospitalization for RHF following surgery.

Similar results were also reported by Weiss et al (31) in their single-centre study assessing clinical outcome and functional capacity following isolated TV surgery. Within the study, patients with severe right or left heart failure, severe pulmonary hypertension, end-stage renal disease and liver disease were excluded. No in-hospital mortality was reported and at 1-year follow-up 9% mortality was documented together with a significant improvement in functional capacity, reduction in clinically apparent peripheral edema and daily oral furosemide therapy. The population treated by Weiss and colleagues was highly selected and not advanced in disease progression resulting in good short-term outcomes and improved functional capacity.

On the same line are results reported by Kawsara et al (24) that studied 1513 patients from the Nationwide Readmissions Database, that underwent isolated TV surgery. Surrogates of late referral in the patient population were frequent, such as admission with decompensated heart failure (41%), non-elective surgery (44%), and advanced liver disease (17%). These factors were the strongest predictors of in-hospital mortality, further supporting the idea that the poor outcomes of isolated TV surgery are related to the late referral for intervention.

Even though all the recent data in the literature regarding surgical treatment of isolated TV disease stress the importance of early referral and treatment, no specific parameter and cut-off value had been identified in order to guide the decision-making process of optimal patient management. In this regard, a novel dedicated risk score has been recently made available that aims at predicting the outcome of patients following isolated TV surgery (32). The TRI-SCORE managed to identify eight parameters not only related to right and left ventricular function, but also end-organ involvement (both liver and kidney), medical therapy and clinical status. More specifically, age, NYHA functional class, RHF signs, daily dose of furosemide, renal insufficiency determined by glomerular filtration rate, elevated total bilirubin, left ventricular ejection fraction and moderate/severe RV dysfunction, were all found to be independent predictors of in-hospital mortality. Even though this scoring system still requires external validation, the TRI-SCORE, based on eight easy to ascertain parameters, is the first example of an attempt to predict favorable versus non favorable responders to isolated TV surgery.

Transcatheter treatment

Transcatheter treatment of severe isolated TR is becoming an accepted option for the management of patients considered high-risk or surgically ineligible. Available transcatheter treatment options mimic surgical techniques and include leaflet approximation, incomplete ring annuloplasty, heterotopic valve implantation (caval valve devices) and percutaneous tricuspid valve replacement. At present, the most widely applied technique is edge-to-edge repair of the tricuspid valve (33). Retrospective analyses have reported a reduction in TR grade, symptomatic improvement (reduced RHF hospitalizations) and lower mortality at 1 year with various devices compared to medical therapy alone (34–36). In fact, results from the TRILUMINATE trial have shown that, despite residual TR being associated with worse outcomes, reduction of at least one degree of TR is associated with improved symptoms at follow-up. Furthermore, reverse remodeling of the right ventricle, improved cardiac output and reduction of liver enzymes were also reported following TV treatment using the TriClip device (Abbott Vascular, Chicago, USA) (37–39). Results are further improving with the advent of new platforms. Despite these promising and encouraging results, it has recently emerged that, just as for surgical correction, indication and timing of any transcatheter tricuspid valve intervention (TTVI) are of paramount importance and should take into consideration multiple aspects, such as patients' clinical characteristics, disease stage, end-organ function and anatomical factors (***Table 2***).

According to current guidelines, in patients undergoing evaluation for TR treatment, a comprehensive RV assessment should be performed, including measures of RV size and morphology, RV function and tissue remodeling (7). Non-invasive assessment of the RV is a complex task, requiring the integrated evaluation of multiple parameters, and taking advantage of emerging imaging modalities, such as speckle-tracking and 3D echocardiography or cardiac computed tomography and magnetic resonance (CMR). Nevertheless, RV dilatation and systolic function are key determinants in the evaluation and management of patients with significant TR owing to their prognostic relevance. Patients presenting with RV systolic dysfunction irrespective of RV size experience 5-years survival rates (29). Similarly, the presence of RV dysfunction has been shown to be a risk factor associated with adverse outcome in patients with TR and in tricuspid valve surgery, as

Table 2. Characteristics of the transcatheter studies in the literature

Study	n. of patients	Age (years)	Procedure	NYHA III/IV	RHF episodes	End-organ involvement	LVEF (%)	≥moderate RV dysfunction	sPAP (mmHg)	Outcomes
Schlotter (41)	TTVI: 288 Control: 562	78 [74-82] 76 [69-82]	MitraClip, PASCAL, Trialign, Cardioband etc None	261 (90.6%) 520 (92.5%)	- -	eGFR 42 [30-58] eGFR 52 [37-71]	55 [43-61] 50 [35-60]	54% 49%	43 [34-53] 48 [37-60]	13.1% 1-year mortality 25.4% 1-year mortality
Orban (43)	75	77 [74-82]	67 MitraClip 8 PASCAL	100%	-	-	55 [49.9-62.4]	3D-RVEF 41±7.8%	-	33% 1-year mortality
Brener (44)	444	76.7±9.1	MitraClip, PASCAL, Trialign, Cardioband, FORMA, Tricinch, Navigate	91.4%	72.3%	eGFR 46.1±20.1	50.6±13.3	TAPSE 16.4±4.6mm	40.8±15.3	2.3% in-hospital mortality 14.2% 1-year mortality
Lurz (49)	243	77±9	MitraClip	92%	76%	eGFR 48±22	51±14	TAPSE 17±5mm	49±15	19% 1-year morality
Stocker (50)	236	78 [74-82]	MitraClip, PASCAL	89%	-	eGFR 46 [33-59]	55 [50-60]	TAPSE 17 [13-20]mm	41 [32-49]	8% 1-year mortality with no PH; 22% 1-year mortality with post-capillary PH; 62% 1-year mortality with pre-capillary PH
Muntané-Carol (51)	300	77±9	MitraClip, PASCAL, Trialign, Cardioband, FORMA, Tricinch, Navigate	93%	68.7%	eGFR 44.7±20.3	49±13	TAPSE 15±4mm	44±17	3% in-hospital mortality 18% 6-months mortality

eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PH: pulmonary hypertension; RHF: right heart failure; RV: right ventricle; RVEF: right ventricular ejection fraction; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TTVI: transcatheter tricuspid valve interventions

underlined previously (29,40). Schlotter and colleagues (41) decided to analyze the clinical impact of RV dysfunction in patients undergoing TTVI from the TriValve registry, in order to try and shed some light on favorable responders and patient selection. Patients from the TTVI cohort were compared to patients treated conservatively, and the whole population was further stratified in three subgroups according to longitudinal RV function expressed by the tricuspid annular plane systolic excursion (TAPSE): preserved (TAPSE >17mm), mid-range (TAPSE 13-17mm) and reduced RV function (TAPSE <13mm). Not surprisingly, TTVI was associated with reduced mortality in patients with severe TR as compared to conservative treatment (13% vs 25.4%, respectively). However, this survival benefit was not seen in cases of procedural failure. Even more importantly, TTVI was associated with a survival benefit solely in patients with

mid-range RV function, improving their outcome to the level of patients with preserved RV function. No improvement was instead reported for patients with preserved or reduced RV function, and the latter was associated with impaired outcome in both patients treated conservatively and with TTVI. These findings may seem in contrast with those reported by Miura et al (42), who identified RV dysfunction as an independent predictor of all-cause mortality and RHF hospitalizations in patients treated with TTVI. However, these results underline the importance of adequate timing and patient selection also in patients undergoing percutaneous procedures: patients treated in late stages of the disease, with pronounced RV dysfunction, may not benefit from the reduction in venous congestion and reverse remodeling, ultimately impacting on clinical events.
Orban et al (43) investigated the prognostic impact of global RV function assessed using 3-dimensional (3D) echocardiography in 75 patients undergoing transcatheter tricuspid edge-to-edge repair, stratified according to preprocedural 3D RV ejection fraction (3d-RVEF). Patients in the highest tertile (3D-RVEF 44.6-61.8%) had a better survival than those in the intermediate or lower tertiles. Furthermore, at follow-up, patients in the highest RVEF tertile were more likely to be in NYHA class ≤ II and experienced greatest improvement in 6-minute walking distance. Both pre-procedural RVEF and NYHA functional class IV were independent predictors of all-cause

mortality. Interestingly, RV function identified by TAPSE was not predictive of outcome in these patients.

These discordant findings emphasize the complexity of non-invasive assessment of RV function by the adoption of single parameters and the need for a comprehensive evaluation. Indeed, both TAPSE and 3D-RVEF might fail to capture the actual relationship between RV contractility and afterload, leading to overestimation of RV systolic function in patients with severe TR. RV-pulmonary artery (PA) coupling helps to determine whether RV function is adequately compensated for specific loading conditions. In compensated states, RV contractile function increases together with the increase in afterload to maintain a steady RV-PA ratio. On the other hand, in decompensated states, RV contractile function does not rise together with the afterload, resulting in lower RV-PA coupling ratios. Brener et al (44) evaluated the prognostic value of non-invasively derived RV-PA coupling in patients from the TriValve registry undergoing TTVI for severe TR. A high baseline TAPSE/systolic pulmonary artery pressure (sPAP) ratio was found to be independently associated to lower all-cause mortality with respect to lower baseline TAPSE/sPAP ratios. Furthermore, patients with higher baseline TAPSE/sPAP ratios experienced fewer hospitalizations for RHF within 12 months from TTVI treatment. Interestingly enough, the benefits associated to a high RV-PA coupling ratio were irrespective of baseline TAPSE and sPAP values, implying that this coupling measurement takes into account a contractile reserve that the single parameters are not capable of assessing.

The RV contractile reserve in response to pharmacological or physical stress has shown prognostic relevance in patients with pulmonary hypertension and severe baseline RV dysfunction, however, further studies are warranted to explore the role of stress imaging in severe TR (45).

Finally, detection of myocardial fibrosis by CMR or by speckle-tracking echocardiography has recently demonstrated prognostic importance in RV failure and might represent a promising tool to define the optimal timing of intervention in severe TR (46).
Right ventricular function and pulmonary hypertension are not the only factors responsible for an unfavorable outcome in patients undergoing TTVI. Indeed, pulmonary circulation status plays a relevant role in determining the prognosis of patients with severe TR and the outcome of TTVI. Right heart catheterization is the gold standard for the invasive assessment of the right heart, providing information regarding the severity and mechanism of pulmonary hypertension (PH), pulmonary vascular resistance, preload conditions, RV function and RV-PA coupling.

Pulmonary hypertension frequently coexists with severe TR, being a marker of poor prognosis and high operative risk (47). Furthermore, it has been shown to be responsible for adverse outcomes in patients with heart failure and patients undergoing TV surgery (48). To date, PH is often solely assessed by echocardiography. However, recent data have shown that the diagnostic sensitivity of echocardiography in accurately detecting PH is only 55%, since the determination of sPAP might be limited in severe TR (49). Lurz et al (49) analyzed the impact of PH on clinical outcomes of 243 patients with severe TR undergoing transcatheter tricuspid edge-to-edge repair. Invasive PH (iPH) and echocardiographic PH (ePH) were defined as sPAP≥50mmHg. The presence of iPH resulted associated with the primary composite endpoint of death, heart failure hospitalization and re-intervention at 1 year. The echocardiographic diagnostic accuracy to detect iPH was low (55%). A discordance between non-invasive and invasive RHC assessments (iPH+/ePH-) and an impaired invasive RV-PA coupling resulted as independent predictors of the primary composite endpoint at 1 year.

The invasive cardiopulmonary hemodynamic profile predicts survival in patients undergoing TTVI, allowing risk stratification and identification of those patients that could benefit the most from intervention. Stocker et al (50) decided to analyze RHC data of 238 patients with severe TR undergoing transcatheter tricuspid valve repair. Authors identified mean PAP, diastolic

PAP, transpulmonary gradient (TPG), pulmonary vascular resistance (PVR) and right ventricular stroke work as significant hemodynamic predictors of 1-year mortality. On the other hand, pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), cardiac output (CO), and pulmonary artery pulsatility index were not associated with one year mortality following TTVI. The following cutoff values were identified: mPAP >30mmHg, sPAP >50mmHg, dPAP >20mmG, TPG >17mmHg and PVR >5WU. Moreover, stratification of patients according to mPAP and TPG resulted associated with 1 year mortality following TTVI: patients with pre-capillary dominant PH (high mPAP>30mmHg and high TPG>17mmHg) had an unfavorable prognosis (38% 1-year survival), while patients without or with post-capillary PH (mPAP>30mmHg and TPG <17mmHg) had a favorable outcome (92% and 78% survival at 1-year, respectively). These data suggest that echocardiography alone might not be sufficient in accurately detecting PH and, even more importantly, they highlight the need for a comprehensive, multimodality assessment of PH and RV function in patients undergoing TTVI. Therefore, RHC should be performed systematically as a pre-procedural assessment tool in order to better characterize TR and PH and consequently stratify patients and define their prognosis.

Recently, Muntané-Carol et al (51) reported the outcome of a cohort of 300 patients undergoing TTVI with RV dysfunction (TAPSE <17mm) or pulmonary hypertension (sPAP ≥ 50mmHg) from the TriValve registry. Reported procedural success was 80% with 3% in-hospital mortality following TTVI. At 6 months follow-up, there was an improvement in NYHA functional class, with more than two thirds of patients in NYHA class I-II. However, at follow-up approximately 20% of patients died. Factors identified as independent predictors of outcome were hepatic congestion, renal dysfunction and lack of procedural success. Furthermore, the estimated 1-year mortality in patients with more advanced heart failure, with both renal dysfunction and significant hepatic congestion at baseline, was close to 50%. Therefore, transcatheter procedures may result futile in candidates with end-stage heart failure, untreated pulmonary hypertension and end-organ damage.

The grey zones and the future

Long forgotten, the tricuspid valve has now gained great momentum. Isolated tricuspid valve treatment, both surgical and transcatheter, is matter of great debate. Even though surgery is the only definitive treatment for isolated TR, it is rarely performed in response to the historically reported high in-hospital morbidity and mortality and poor long-term outcomes (18,52). These results have led to lengthy medical management and late referral for surgery. However, severe TR can precede right heart failure by many years until late in the natural history of the disease. This is responsible for a vicious circle that further delays or even rejects the referral for surgery. Transcatheter tricuspid treatments have therefore emerged as treatment options for severe symptomatic TR in patients considered ineligible for cardiac surgery (53). Despite numerous devices and increasing awareness of early intervention, when and in whom to perform surgical or transcatheter procedures remains a clinical conundrum. In fact, regardless the type of intervention, the ultimate focus has been on patient selection, surgical or transcatheter indication, timing of intervention and identification of predictors of outcome following treatment in order to identify favorable and non-favorable responders to treatment. The less invasive nature of transcatheter procedures, however, allow to investigate more appropriately the influence of baseline predicting factors by eliminating the influence of the surgical insult, as well as by including more patients. Transcatheter interventions will therefore help a better understanding of right heart physiology and support decision making in the future. In the future, earlier referral will also increase the rate of surgical procedures on isolated TR patients (a trend already happening in high volume centers offering transcatheter procedures).

In both treatment options, specific parameters capable of predicting outcome have been of difficult identification.

The cardiac surgery community has stressed the idea of early referral following recent data published in the literature. Early referral and early treatment, before the development of overt symptomatology, right heart dysfunction and failure and end-organ damage, are associated to excellent in-hospital outcomes, with a higher rate of TV repair versus replacement, and good long-term outcomes, with low-to-none mortality at 5 years and significant improvement in symptomatology (24,26,27). To better define early referral and therefore aid in the stratification of surgical risk, the TRI-SCORE was recently developed (32). The most relevant predictors of outcome, and as a consequence of favorable and unfavorable responders, are symptomatology (NYHA class and medical therapy), end-organ involvement (hepatic congestion and renal dysfunction) and RV function (TAPSE and tissue doppler imaging (TDI)). Interestingly enough, what has emerged in the literature, is that patient selection and optimal timing are crucial also in percutaneous tricuspid procedures. The same above-mentioned parameters were also identified as independent predictors of outcome of patients undergoing TTVI. In particular, the greatest attention in recent years was entirely directed towards the identification of the most appropriate parameter capable of defining RV function (54). Adequate assessment of RV function is extremely complex and many parameters, such as TAPSE, have given contradictory results. RV-PA coupling appears to be a powerful predictor of outcome, by assessing whether RV function is correctly compensated for specific loading conditions. Preoperative echocardiographic data concerning both right ventricular size and function are of paramount importance in order to guide when to intervene and how to treat patients with severe TR. Relevant parameters have been identified: surgery should be considered in patients with mild RV dysfunction, while transcatheter procedures result beneficial in patients with moderate RV dysfunction. However, more thorough assessment of RV function is still required, especially with the new approaches in transcatheter tricuspid valve replacement (55). In this setting, misdiagnosis of RV dysfunction may result in acute right heart failure due to sudden increase in afterload and development of afterload mismatch.

In this moment of great enthusiasm for the treatment of TR, a comprehensive evaluation by the Heart Team is mandatory, in order to thoroughly assess clinical characteristics, define the surgical and percutaneous risks and identify the most appropriate treatment strategy for each patient. However, in order to define whether either intervention is truly beneficial and in which populations, randomized controlled trials analysing optimal medical therapy versus surgical treatment versus transcatheter interventions are necessary.

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Paris - 2019

Chapter 10

TRI-SCORE: A SINGLE CENTRE VALIDATION STUDY

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Submitted for publication

Abstract

Background and Aims: The TRI-SCORE is a recently published risk score for predicting in-hospital mortality in patients undergoing isolated tricuspid valve surgery (ITVS). The aim of this study is to externally validate the ability of the TRI-SCORE in predicting in-hospital and long-term mortality following ITVS.

Methods: A retrospective review of our institutional database was carried out to identify all patients undergoing isolated tricuspid valve repair or replacement from March 1997 to March 2021. The TRI-SCORE was calculated for all patients. Discrimination of the TRI-SCORE was assessed using receiver operating characteristic curves. Accuracy of the models was tested calculating the Brier score. Finally, a COX regression was employed to evaluate the relationship between the TRI-SCORE value and long-term mortality.

Results: A total of 176 patients were identified and the median TRI-SCORE was 3 (1-5). The cut-off value identified for increased risk of isolated ITVS was 5. Regarding in-hospital outcomes, the TRI-SCORE showed high discrimination (area under the curve 0.82), and high accuracy (Brier score 0.054). This score showed also very good performance in predicting long-term mortality (at 10 years HR: 1.47, 95% CI [1.31-1.66], $p<0.001$), with high discrimination (area under the curve >0.80 at 1-5 and 10 years) and high accuracy values (Brier score 0.179).

Conclusions: This external validation confirm the good performance of the TRI-SCORE in predicting in-hospital mortality. Moreover, the score showed also very good performance in predicting the long-term mortality.

Introduction

Isolated tricuspid valve regurgitation (TR) has gained increasing recognition in recent years. Initially considered benign, isolated severe TR has been found to be a strong predictor of poor prognosis (1,2). If left untreated, isolated TR significantly decrease survival at short and long-term (3–5). Despite such dismal prognosis, treatment of patients with severe isolated TR remains controversial, with reported high in-hospital mortality rates and great uncertainty regarding long-term outcomes (6–8). For these reasons surgical treatment is often delayed or even rejected (9). Therefore, a very low percentage of patients are currently receiving surgical treatment, resulting in undertreatment of the disease (5,9).

Patient selection and correct timing have emerged as key factors in determining favorable outcome following TR treatment (10). However, the most commonly available surgical scores do not reliably predict outcomes of patients undergoing isolated tricuspid valve surgery (ITVS) (11). Recently, a dedicated risk score, named the TRI-SCORE, was specifically developed to predict in-hospital mortality in patients undergoing ITVS (12). Even though results are extremely interesting and the usefulness is evident, this new score still lacks external validation. The aim of this study is to validate the discriminatory ability of the TRI-SCORE in predicting in-hospital mortality following ITVS. Furthermore, we sought to evaluate the ability of the score to predict long-term results following ITVS.

Materials and Methods

Study Population and follow-up

A retrospective review of our institutional database was carried out to find all patients who underwent ITVS in our department from March 1997 to March 2021. 199 patients fulfilled the inclusion criteria and were initially included in the study cohort. Charts were analyzed to identify preoperative characteristics, laboratory values, and echocardiographic parameters in order to determine the TRI-SCORE value. Postoperative results and echocardiographic data were also analyzed, and all data were inserted within a second dedicated database. The Ethical Committee of our Institution approved the Study and waived individual informed consent for this retrospective analysis. Survival and echocardiographic follow-ups were carried out using the informatics hospital system for outpatient clinic visits and echocardiographic examinations. If follow-up information was not retrieved through the hospital system, patients, or their referring cardiologists, were reached via telephone calls and asked to provide recent laboratory and echocardiographic data (<6 months). Cause of death was determined by death certificates or information from family members or referring physicians. Clinical follow-up was 94% complete.

Statistical analyses

Statistical analyses were performed using Stata Software (Statacorp, LLC; TX, USA; version 15). Analyses were exploratory in nature. Categorical variables were expressed as absolute number and percentages. Normal distribution of continuous variables was assessed with the Shapiro-Wilk test. Continuous normal distributed variables were expressed as mean± standard deviation (SD), whereas continuous not-normal variables were reported as median [25th percentile; 75th percentile].

Discrimination of a test indicates the extent to which the model distinguishes between patients who will die or survive in the perioperative period. Discrimination was assessed with receiver operating characteristic (ROC) curves. ROC area under the curve (AUC) values vary between 0.5 and 1, where 0.5 denotes a bad diagnostic test and 1 denotes an excellent diagnostic test (13,14). Another index used to evaluate the discrimination was the Somers' D_{xy} rank correlation between predicted probabilities and observed responses. When $D_{xy} = 0$, the model is making random prediction, when $D_{xy} = 1$, the prediction is perfect (15). The accuracy of the models was tested calculating the Brier score (quadratic difference between predicted probability and observed outcome for each patient; when the prediction of the model is perfect, the Brier score is 0.

Finally, a Cox regression model was employed to evaluate the relationship between the TRI-SCORE value and long-term mortality.

Results

Out of the 199 patients who underwent ITVS at our center during the study period, 23 were excluded due to lack of sufficient preoperative data and, therefore, inability of calculating the risk score. The main parameters that were lacking were specific echocardiographic data regarding right ventricular function and specific laboratory values. A total of 176 patients have been considered for the purpose of this study, among which 131 (74.4%) underwent isolated TV replacement (ITVR) and 45 (25.6%) underwent TV repair (ITVr).

Table 1. Baseline clinical and echocardiographic parameters

	N=176
CLINICAL	
• Age (years)	67.5 [56-74.5]
• Sex (M)	62 (35.2%)
• EuroSCORE II (%)	5.5 [2.1-10.4]
• NYHA III-IV	110 (62.5%)
• AFib	120 (68.2%)
• Permanent Pacemaker	32 (18.2%)
• Insulin-dependent diabetes	25 (14.2%)
• eGFR (ml/min)	63.8 [47-84.5]
• Total bilirubin (mg/dL)	1 [0.6-1.4]
• REDO	103 (58.5%)
• REDO > 1	29 (16.5%)
• Diuretics dose (mg)	50 [0-100]
• Ascites	38 (21.6%)
• Previous RHF	60 (34.1%)
ECHOCARDIOGRAPHIC	
• TR 3-4+	176 (100%)
• LVEF (%)	60 [55-60]
• Basal RVEDD (mm)	46.6±8.48
• sPAP (mmHg)	40 [35-48]
• TAPSE (mm)	20.1±5.39
• S'TDI (cm/s)	10 [9-13]
TRI-SCORE	3 [1-5]

AFib: atrial fibrillation; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RHF: right heart failure; RVEDD: right ventricular end diastolic diameter; sPAP: systolic pulmonary artery pressure; s'TDI: peak systolic velocity tissue doppler imaging; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation

Baseline clinical and echocardiographic parameters of the study cohort are summarized in **Table 1**. Median TRI-SCORE at baseline was 3 [interquartile range (IQR) 1-5]. In-hospital mortality was 6.3%. Death was due to low cardiac output syndrome (LCOS) leading to multiorgan failure in 7 patients, septic shock in 1 patient, cerebral hemorrhage in 1 patient and other causes in the remaining 2 patients. Intraoperative variables and post-operative complications are listed in **Table 2**.

Table 2. Intraoperative characteristics and postoperative complications

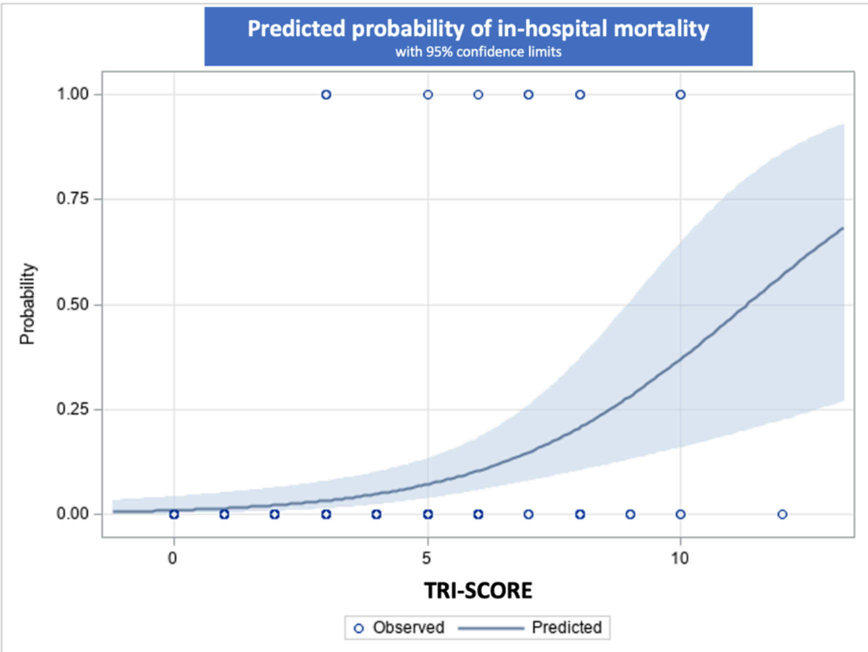
	N=176
Beating Heart	114 (64.8%)
CPB time (min)	57 [47-75]
Cross-clamp time (min)	0 [0-30]
Low cardiac output syndrome	24 (13.6%)
Acute Kidney Injury	40 (22.7%)
Re-exploration for bleeding	19 (10.8%)
New permanent pacemaker	19 (10.8%)
Permanent neurologic damage	14 (8%)
Length-of-stay (days)	8 [6-15]
In-hospital mortality	11 (6.3%)

CPB: cardiopulmonary bypass

The TRI-SCORE value emerged as a significant predictor of in-hospital mortality ($p<0.001$), with an exponential growth of the risk of in-hospital mortality as the TRI-SCORE increases above the value 5 (**Fig.1**). The TRI-SCORE showed high discrimination with an area under the ROC curve of 0.82 (**Fig.2**). The Somers' D_{xy} index was 0.639. The Brier score was 0.054 indicating high accuracy in predicting in-hospital mortality.

There were 33 late deaths at 10 years follow-up (20%). Overall survival was 96.7±1.43% at 1 year, 81±3.72% at 5 years and 60±6.63% at 10 years (**Fig. 3**). Finally, and most importantly, the TRI-SCORE showed very good performance in predicting mortality during follow-up (Hazard Ratio: 1.47. 95% confidence

Figure 1. Predicted probability of in-hospital mortality. This figure highlights the exponential growth of the risk of in-hospital mortality as the TRI-SCORE increases above the value 5.



interval [1.31-1.66], p<0.001). The time-dependent area under the ROC curve was >0.80 in all stages of follow-up, as shown in **Fig. 4**. Furthermore, the Brier score was 0.179. These values indicate a high discrimination and high accuracy of the TRI-SCORE not only for in-hospital mortality but also for predicting mortality at 10-years following ITVS.

Figure 2. Receiver operating characteristic curves for patients undergoing isolated tricuspid valve surgery. The value of the area under the curve was 0.82 indicating a high discrimination of the TRI-SCORE in these patients. AUC: area under the curve.

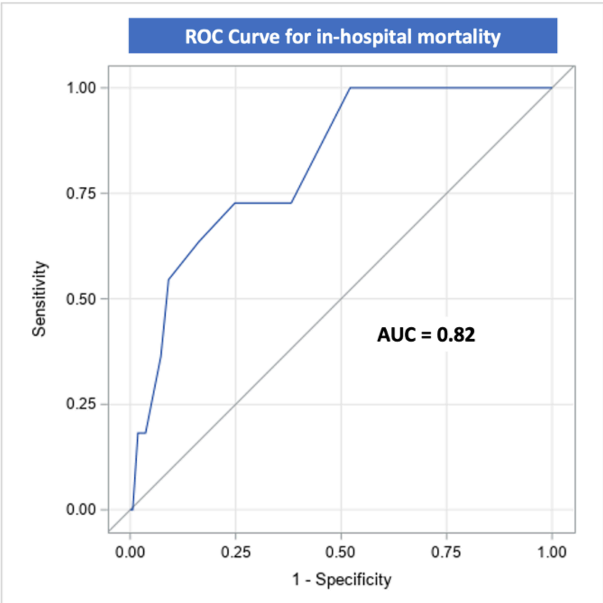


Figure 3. Kaplan Meier curve for all-cause death at follow-up in patients undergoing isolated tricuspid valve surgery.

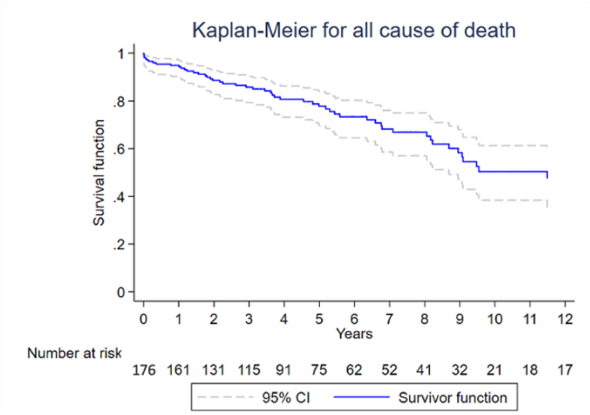
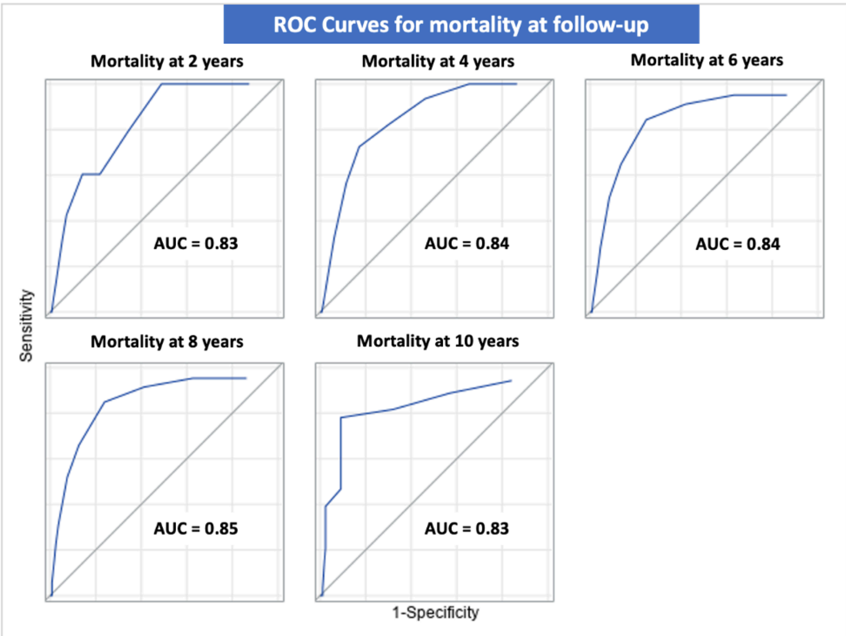


Figure 4. Receiver operating characteristic curves regarding mortality at follow-up in patients undergoing isolated tricuspid valve surgery. The area under the curve was >0.8 at all time-frames indicating high discrimination of the TRI-SCORE also at mid- and long-term follow-up.



Discussion

Prediction models and risk scores play an extremely important role in current cardiac surgery practice. However, the most commonly available surgical risk scores do not reliably predict outcomes in patients undergoing ITVS. In an era of great fervor for the surgical and transcatheter treatment of isolated TV disease, the need of a dedicated risk score has become evident.

The main findings of our study are the following:

- in patients undergoing ITVS the TRI-SCORE shows high discrimination (AUC 0.82) and high accuracy (Brier score 0.054) for predicting in-hospital mortality.
- The TRI-SCORE also shows very good discrimination (AUC >0.80) and high accuracy (Brier score 0.179) in predicting mid- and long-term outcomes.
- Based on our experience, a TRI-SCORE value of 5 was identified as the cut-off for an increased risk in ITVS.

Recent studies have paved the way to the idea that ITVS can be performed with a reasonable surgical risk and good long-term outcomes in selected patients (16–18). Particularly, whenever surgical correction of isolated TR is performed early in the disease course, mainly before the occurrence of overt symptomatology, of RV dilation or dysfunction, and of end-organ involvement, it is associated with no in-hospital mortality, fewer postoperative complications and shorter postoperative lengths-of-stay (19,20). Moreover, patients at early stages of the disease, following TR treatment, experience 100% survival at 5 years and no further hospitalizations for right heart failure (21). These findings are in strong contrast with the ingrained belief that ITVS is always associated with high in-hospital mortality and uncertain long-term outcomes (22–24). Therefore, it has become evident that adequate patient selection and correct timing are of paramount importance in order to obtain good surgical results (19,21).

Although some risk scores for ITVS have been proposed, they are very rarely used in daily clinical practice (25,26). The TRI-SCORE is a novel surgical risk score that aims at predicting in-hospital mortality of patients undergoing ITVS. It was developed analyzing a cohort of 466 patients operated on in 12 French centers. The score is an additive score, based on eight easy to ascertain parameters related to right and left ventricular function, end-organ involvement, medical therapy and clinical status. More specifically the variables used to calculate the score are summarized in **Table 3** (12). Observed and predicted in-hospital mortality rates increased from 0% to 60% and from 1% to 65% respectively, as the score increased from 0 up to ≥9 points (12). Despite the promising results and the extreme simplicity in the calculation of the score, external validation of a risk model is crucial in order to effectively assess its validity. Moreover, the performance of the score in predicting the long-term mortality was not evaluated, and to the best of our knowledge this is the first report analyzing this aspect.

Table 3. Variables used to calculate the TRI-SCORE

Variables
Age ≥ 70 years
New York Heart Association ≥ III
Presence of right heart failure signs *(severe jugular venous distension, ascites and/or marked peripheral edema)*
Daily dose of furosemide ≥ 125mg
Glomerular filtration rate < 30ml/min
Elevated total bilirubin
Left ventricular ejection fraction < 60%
Moderate/severe right ventricular dysfunction *(TAPSE < 17mm and/or s'TDI < 9.5cm/sec)*

TAPSE: tricuspid annular plane systolic excursion; s'TDI: tissue doppler imaging

Furthermore, among the findings of our study, a TRI-SCORE cut-off value of 5 is in-line with results of the French group, as the predicted in-hospital mortality grows exponentially when the score points go from 5 to ≥9 (12). But probably the main finding of our study is the very good performance of the score also in predicting mortality at mid- and long-term follow-up after surgery.

Up to now, management of patients with isolated TV disease was controversial and, despite recent guidelines (27) support the idea of early referral and treatment, the questions of "who" and "how" to treat this population remains. In this light, the external validation of the TRI-SCORE and its good performance also in predicting long term outcomes could increase its value in the daily clinical practice.

Finally, the TRI-SCORE could have an important role in the decisions whether a patient should be considered for surgical correction, or whether the surgical risk is too high and an alternative trans-catheter approach should be pursued (28). It would be interesting to assess the performance of the TRI-SCORE in patients undergoing transcatheter interventions. This step could be crucial in the future and dedicated studies are warranted in this respect.

Limitations

The main limitation of the study is the retrospective, single-centre nature of the design, which may have led to selection bias. Furthermore, the sample size is relatively small due to the few isolated TV surgeries performed.

Conclusions

Our report externally validates the TRI-SCORE performance in predicting 30-day mortality with an overall good performance with high discrimination and high accuracy. Furthermore, this scoring model also showed very good performance in predicting mortality at mid- and long-term follow-up with high discrimination and high accuracy.

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Lanzarote - 2019

Chapter 11

GENERAL DISCUSSION

Tricuspid valve (TV) pathology has been disregarded for a very long time due to established belief that treatment of left-sided heart disease would lead to resolution or significant improvement of tricuspid regurgitation. Initially considered benign, severe TR has been found to be a strong predictor of prognosis[1,2], with 50% mortality rate at 5 years in untreated patients[3,4]. Despite the increasing prevalence, the disabling nature of this disease and the bad prognosis, to date most patients (>90%) are not offered any treatment, also due to the fact that management of patients with TV disease remains controversial[5]. Medical treatment can be effective in early stages, while TV surgery is only occasionally considered, but often too late in the course of the disease. This attitude arises as a result that, even if severe, TR is initially well tolerated, patients have a good quality of life and minor symptoms are effectively controlled with medical treatment[6]. In addition, most symptoms of severe chronic TR can be subtle and misdiagnosed, such as dyspepsia, venous incompetence, aging. As a consequence of the late referral, data in the literature regarding surgical outcomes are discouraging, reporting high in-hospital mortality rates[7–9]. On these premises, to overcome the limitations of surgical invasiveness, numerous devices for transcatheter treatment of TR have been developed[10]. The only effective treatment is, nonetheless, surgical correction[11].

However, what has emerged in the literature in recent years, is that the outcome of patients undergoing isolated TV correction is nearly completely dependent on baseline clinical presentation and duration of disease[12–14]. Furthermore, our daily clinical practice was constantly faced with doubts regarding treatment of patients with isolated TR due to the great uncertainty of the outcomes.

Latib and colleagues had proposed a classification based on both clinical and functional aspects of patients affected by TR[15,16]. Based on the stage of disease, authors recommended the best treatment strategy. In this scenario, we decided to review our surgical experience of patients undergoing isolated TV surgery (ITVS), either repair or replacement, in order to assess factors that may have played a major role in the outcome of our patients[17,18]. We analysed in-hospital outcomes, therefore in-hospital mortality, postoperative complications and postoperative length-of-stay, of patients undergoing isolated TV surgery divided in Stages according to the preoperative characteristics. Even though retrospective in nature, results of our study confirmed the most recent surgical evidence: the reported poor early outcomes following ITVS are related to clinical status (symptomatology, medical treatment), right ventricular function and timing of referral. In fact, surgical treatment of TR in early stages of the disease (Stages 2-3), without prominent symptomatology, RV dilation or dysfunction, and without organ involvement, more frequently leads to TV repair with no in-hospital mortality, fewer postoperative complications, shorter intensive care unit length-of-stay and shorter overall postoperative length-of-stay. On the contrary, patients treated in more advanced stages (Stages 4-5) experience higher in-hospital mortality (15.3%), postoperative complications (such as acute kidney injury and low cardiac output syndrome), longer intensive care unit and hospital lengths-of-stay[17,18]. Furthermore, based on our experience, patients operated upon in early stages experience 100% survival at 5 years with no further hospitalizations for right heart failure. Instead, at 5 years, in late stages, survival is approximately 60% and one out of 5 patients experience at least one hospitalization for right heart failure[19]. Therefore, surgery for isolated TR can be performed with a reasonable risk in selected patients and in experienced centres.

A specific subgroup of patients with TR that are constantly increasing are those undergoing de novo implantation of cardiac implantable electronic devices (CIEDs). It is well established that in patients with CIEDs, moderate or severe TR occurs frequently, up to 45% of cases[20,21], and it is associated with increased mortality and hospitalization for heart failure[22,23]. Despite its increased recognition and the always growing requirement of CIEDs, there is limited data regarding outcomes of TV surgery in patients with CIEDs[3]. Furthermore, a clear distinction between CIED-induced or CIED-associated TR is not present. We performed a retrospective analysis of our surgical cohort, and results showed that CIED-induced TR accounts for two-thirds of patients surgically treated. In our experience, TV repair was still possible in 63% of cases with no significant durability difference between CIED-induced and CIED-associated[24]. Therefore, once again, a more aggressive approach towards TV surgery also in this specific setting should be adopted, in order to avoid worse long-term outcomes.

As a result, the cardiac surgery community has, in recent years, stressed the idea of timely referral and early treatment. This is reflected in the most recent European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines[25], that strongly support an earlier surgical referral to achieve low in-hospital mortality and better postoperative outcomes. What has emerged in the “desperate” attempt to develop new transcatheter treatment options as an alternative to the high-risk surgical option, is that also in these cases early referral and adequate patient selection are of paramount importance. In fact, initially considered “for all”, transcatheter treatment for isolated TR also requires a careful analysis, correct timing and indication and may result futile in patients with end-stage heart failure, untreated pulmonary hypertension and end-organ damage[26–28].

Despite the recent data in the literature all emphasize the importance of early referral and treatment, no specific parameter or cut-off value had been identified until recently. A novel dedicated risk score has been made available that aims at predicting the outcome of patients following isolated TV surgery[29]. The TRI-SCORE is based on eight parameters, easy to obtain, related to right and left ventricular function, end-organ involvement (both kidney and liver), medical therapy and clinical status. The identification of specific predictors of in-hospital mortality together with threshold values allows to guide the decision-making process of optimal patient management. In order to assess its validity, we decided to review our patients undergoing isolated TV surgery and calculate the TRI-SCORE for every patient. The discriminatory ability of the TRI-SCORE in predicting both in-hospital mortality and also long-term results was evaluated. Based on our experience, this novel and dedicated risk score is capable of predicting both in-hospital and long-term follow-up outcomes, with high discrimination and high accuracy [submitted for publication]. Therefore, the TRI-SCORE should be implemented in the routine work-up of patients who are candidates for isolated TV surgery, either repair or replacement.

Conclusions

The management of patients with severe symptomatic isolated TR remains extremely challenging. Little awareness still remains within the clinical and scientific communities of when and how to treat severe TR. Results of our studies show that isolated TV surgery can be performed with a reasonable risk and good both short- and long-term outcomes whenever correct timing and adequate patient selection are respected. Therefore, timely referral and evaluation by a multidisciplinary heart team is nowadays of utmost importance; thorough preoperative assessment and early surgical treatment are associated with close to zero surgical risk and improved outcomes. Furthermore, the recently published TRI-SCORE may further help in risk stratification and may provide a tailored therapeutic approach based on patient's characteristics and disease stage.

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Baia di Campi - 2020

Chapter 12

IMPACT

Tricuspid regurgitation (TR) is a common echocardiographic finding that is present in 70-90% of the general population. While a trivial form is often seen in healthy individuals, with structurally normal valves and no clinical impact, moderate or severe TR is associated to excess cardiac morbidity and mortality[1]. The incidence of moderate-severe TR is higher in women and increases with advancing age, with an age-adjusted prevalence of 0.55%. Approximately 4% of subjects aged 75 years or more have clinically relevant TR[2]. Epidemiological studies suggest that moderate or severe TR affects approximately 1.6 million individuals in the United States[2–4]. Furthermore, amongst patients with heart failure and reduced ejection fraction, the prevalence of moderate-severe TR is 26% and independently affects prognosis[5,6].

Even though surgery is the only definitive treatment for severe TR, it is rarely performed. The majority of tricuspid valve operations are performed concomitantly to left-sided valve surgeries, while only approximately 14% are performed in isolation[7–9].

The main objective of the thesis was to analyse patients undergoing isolated tricuspid valve surgery, either repair or replacement, and identify predictors of outcome, as well as provide further proof that early tricuspid valve surgery is feasible, with a low associated risk and good outcomes.

The surgical impact is the common thread throughout the thesis, which mainly deals with the challenges in isolated TR.
The main challenges in the field of isolated TR are surgical timing and patient selection. The great reluctancy in performing isolated TV surgery is a consequence of the reported high in-hospital mortality rates and poor clinical short and long-term outcomes. Older studies have in fact reported an in-hospital mortality ranging from 8 to 37%, associated to 55% mortality at 5 years[7,10]. However, the baseline clinical presentation of such patients and the stage of disease may have negatively impacted on the outcome[11]. In our research we addressed this issue and analysed outcomes of patients treated in early stages of disease, therefore patients referred to treatment with adequate timing, versus patients treated in late stages due to lengthy medical management. Both in-hospital and mid-term results were assessed and results strongly support the current train of thought of early referral and surgical correction. We demonstrated that patients treated before the occurrence of overt symptomatology, RV dilation or dysfunction, and without end-organ involvement, experienced no in-hospital mortality and fewer postoperative complications. Furthermore, at follow-up, survival was approximately 100% with no further hospitalizations for right heart failure.
Regarding adequate patient selection, we decided to provide external validation of a risk score recently made available, specific for isolated TV surgery. The TRI-SCORE, based on our

experience, will allow risk stratification of every single patient and as a consequence appropriate patient selection for surgical treatment. It will be interesting to assess its validity in patients candidates for transcatheter interventions, in order to choose between every treatment option.

Finally, another rarely investigated aspect of TR is valve incompetence due- or related-to the presence of intracardiac leads. In our experience, tolerating moderate or severe TR in these settings is not a favourable attitude for the patient. A more aggressive surgical approach should be kept since valve repair is still feasible in more than two-thirds of patients, with no durability difference between lead-induced and lead-associated TR.

All these considerations taken together may contribute to a clearer indication to management and treatment of patients with isolated tricuspid regurgitation. All the explored topics will need further data, from multicentric and prospective studies, in order to further build and expand the knowledge and practice of isolated tricuspid valve surgery. all the studies collected in this thesis were initial stepping stones for this long research journey.

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Sardegna - 2020

Chapter 13

SUMMARY

Chapter 2. In this retrospective study, the applicability of a novel classification of patients with tricuspid regurgitation based on 5 stages and the in-hospital outcomes following isolated tricuspid valve surgery were investigated. Patients in earlier stages of the disease (Stage 2) more frequently received tricuspid valve repair. Hospital mortality was 5.8%, in particular 0% in Stages 2-3 and 15.3% in Stages 4-5. Both intensive care unit and hospital lengths-of-stay were longer in more advanced stages ($p<0.001$). Furthermore, patients in stages 4-5 developed more postoperative complications, such as acute kidney injury (3.7-10% in Stages 2-3 vs 44-100% in Stages 4-5) and low cardiac output syndrome (15-50% in Stages 2-3 vs 71-100% in Stages 4-5).

Chapter 3. This study aimed at defining the profile of patients with a complicated versus a non-complicated postoperative course following isolated tricuspid valve surgery. Patients with a negative postoperative course had worse baseline clinical and echocardiographic characteristics. At univariate analysis, chronic kidney disease, ascites, previous right heart failure hospitalizations, right ventricular dysfunction, previous cardiac surgeries, tricuspid valve replacement and higher MELD scores were identified as predictors of negative outcome. At multivariate analysis, liver enzymes and diuretics' dose were predictors of complicated postoperative course.

Chapter 4. We reviewed the literature regarding isolated tricuspid regurgitation. Management of patients with severe isolated TR remains controversial and stand-alone surgery is rarely performed. Isolated TR is present in different clinical scenarios, and in all cases, if left untreated, is a strong predictor of prognosis. In fact, this pathology has a poor natural history due to the negative effects of TR on right ventricular function and as a consequence end-organ function. Analysing the available therapeutic options, it appears evident that surgery remains the only definitive treatment, whenever the surgical risk is acceptable. Therefore, awareness is necessary in order to obtain optimal timing for surgical referral and improve outcome for these patients.

Chapter 5. In this study, the mid-term outcomes of patients previously studied according to the 5 Stages classification undergoing isolated tricuspid valve surgery were investigated. At 5 years, overall survival was 100% in Stage 2, 88% in Stage 3 and 60% in Stages 4-5. Furthermore, cumulative incidence function of re-hospitalization for right heart failure was 0% for Stage 2 and 20% for Stages 3, 4 and 5. Therefore, both short and mid-term outcomes support early referral for surgery in isolated tricuspid regurgitation, with excellent survival at 5 years and no further hospitalizations for right heart failure.

Chapter 6. This study aimed at assessing a subgroup of patients affected by tricuspid regurgitation due to the presence of an intracardiac lead. Long-term results of the surgical treatment of tricuspid regurgitation in this setting are not extensively studied. More than 60% of patients were diagnosed with cardiac implantable electronic device (CIED)-induced tricuspid regurgitation, while the remining 32% with CIED-related tricuspid regurgitation. Tricuspid valve repair was still possible in 63% of patients, with good long-term results and no durability difference between CIED-induced and CIED-associated cases.

Chapter 7. A commentary was written in response to a retrospective single-centre study published in the European Journal of Cardio-Thoracic Surgery, assessing clinical outcome of patients undergoing isolated tricuspid valve surgery. The study reported good outcomes but had excluded from their cohort all patients with severe right or left heart failure, severe pulmonary hypertension, end-stage renal disease and liver disease. Once again, this underlines the importance of early referral and timely treatment to obtain good surgical results.

Chapter 8. Another commentary was published to accompany a multi-centre, retrospective study regarding short and long-term outcomes of patients undergoing isolated tricuspid valve surgery submitted to the European Journal of Cardio-Thoracic Surgery. This commentary wants to highlight how the widespread idea that all patients affected by isolated tricuspid regurgitation and at high risk for surgery can be effectively treated with transcatheter options is not truthful. In fact, just as for surgery, also in the case of transcatheter treatment optimal timing and adequate patient selection are crucial for outcome.

Chapter 9. We reviewed the literature regarding transcatheter and surgical treatment of tricuspid regurgitation in order to identify all factors capable of predicting right ventricular decompensation or favourable responders. The most relevant predictors of outcome for both treatment strategies are symptomatology (NYHA functional class and medical therapy), end-organ involvement (hepatic congestion and renal dysfunction), and right ventricular function (TAPSE and tissue doppler imaging). In transcatheter treatment studies, right ventricular function has been particularly analysed. Right ventricle-pulmonary artery (RV-PA) coupling has been found to be a powerful predictor of outcome, assessing whether RV function is correctly compensated for specific loading conditions. As a result, right heart catheterization should be considered as part of the preoperative workup of patients.

Chapter 10. In this study, we performed a retrospective review of our surgical experience in isolated tricuspid valve surgery based on a novel dedicated risk score, the TRI-SCORE. The aim of the study was to validate the ability of the TRI-SCORE in predicting in-hospital mortality and long-term follow-up outcomes following isolated tricuspid valve surgery. in our experience, the risk score showed high discrimination and high accuracy regarding both in-hospital outcomes and also long-term mortality. A cut-off value for increased risk of isolated TV surgery was 5.

Chiesa di San Colombano - 2021

Chapter 14

SAMENVATTING

Hoofdstuk 2. In deze retrospectieve studie werd de toepasbaarheid van een nieuwe classificatie van patiënten met tricuspidalisregurgitatie op basis van 5 stadia en de ziekenhuisresultaten na geïsoleerde tricuspidalisklepchirurgie onderzocht. Patiënten in eerdere stadia van de ziekte (fase 2) kregen vaker tricuspidalisklepreparatie. De ziekenhuissterfte was 5,8%, met name 0% in de fasen 2-3 en 15,3% in de fasen 4-5. Zowel de opnameduur op de intensive care als in het ziekenhuis was langer in meer gevorderde stadia ($p < 0,001$). Bovendien ontwikkelden patiënten in de stadia 4-5 meer postoperatieve complicaties, zoals acuut nierletsel (3,7-10% in de stadia 2-3 versus 44-100% in de stadia 4-5) en het lage hartminuutvolume-syndroom (15-50% in de Fase 2-3 versus 71-100% in Fase 4-5).

Hoofdstuk 3. Deze studie was gericht op het definiëren van het profiel van patiënten met een gecompliceerd versus een niet-gecompliceerd postoperatief beloop na geïsoleerde tricuspidalisklepchirurgie. Patiënten met een negatief postoperatief beloop hadden slechtere klinische en echocardiografische kenmerken bij aanvang. Bij univariate analyse werden chronische nierziekte, ascites, eerdere ziekenhuisopnames voor hartfalen, rechterventrikeldisfunctie, eerdere hartoperaties, tricuspidalisklepvervanging en hogere MELD-scores geïdentificeerd als voorspellers van een negatieve uitkomst. Bij multivariate analyse waren leverenzymen en de dosis van diuretica voorspellers van gecompliceerd postoperatief beloop.

Hoofdstuk 4. We hebben de literatuur over geïsoleerde tricuspidalisregurgitatie beoordeeld. De behandeling van patiënten met ernstige geïsoleerde TR blijft controversieel en op zichzelf staande chirurgie wordt zelden uitgevoerd. Geïsoleerde TR is aanwezig in verschillende klinische scenario's en is in alle gevallen, indien onbehandeld, een sterke voorspeller van de prognose. In feite heeft deze pathologie een slechte natuurlijke geschiedenis vanwege de negatieve effecten van TR op de rechterventrikelfunctie en als gevolg daarvan de functie van het eindorgaan. Als we de beschikbare therapeutische opties analyseren, lijkt het duidelijk dat chirurgie de enige definitieve behandeling blijft, wanneer het chirurgische risico acceptabel is. Daarom is bewustzijn noodzakelijk om een optimale timing voor chirurgische verwijzing te verkrijgen en de uitkomst voor deze patiënten te verbeteren.

Hoofdstuk 5. In deze studie werden de resultaten op middellange termijn onderzocht van patiënten die eerder waren onderzocht volgens de 5 Stadia-classificatie en die een geïsoleerde tricuspidalisklepoperatie ondergingen. Na 5 jaar was de totale overleving 100% in stadium 2, 88% in stadium 3 en 60% in stadium 4-5. Bovendien was de cumulatieve incidentiefunctie van heropname voor rechterhartfalen 0% voor stadium 2 en 20% voor stadium 3, 4 en 5. Daarom ondersteunen zowel resultaten op korte als middellange termijn een vroege verwijzing voor chirurgie bij geïsoleerde tricuspidalisregurgitatie, met uitstekende overleving na 5 jaar en geen verdere ziekenhuisopnames voor rechterhartfalen.

Hoofdstuk 6. Deze studie was gericht op het beoordelen van een subgroep van patiënten die lijden aan tricuspidalisregurgitatie als gevolg van de aanwezigheid van een intracardiale lead. Langetermijnresultaten van de chirurgische behandeling van tricuspidalisregurgitatie in deze setting zijn niet uitgebreid bestudeerd. Bij meer dan 60% van de patiënten werd de diagnose CIED-geïnduceerde tricuspidalisregurgitatie gesteld, terwijl de resterende 32% CIED-gerelateerde tricuspidalisregurgitatie had. Tricuspidalisklepreparatie was nog steeds mogelijk bij 63% van de patiënten, met goede resultaten op lange termijn en geen verschil in duurzaamheid tussen CIED-geïnduceerde en CIED-geassocieerde gevallen.

Hoofdstuk 7. Er is een commentaar geschreven naar aanleiding van een retrospectieve single-center studie gepubliceerd in het European Journal of Cardio-Thoracic Surgery, waarin de klinische uitkomst werd beoordeeld van patiënten die een geïsoleerde tricuspidalisklepoperatie ondergingen. De studie rapporteerde goede resultaten, maar had alle patiënten met ernstig rechter- of linkerhartfalen, ernstige pulmonale hypertensie, terminale nierziekte en leverziekte van hun cohort uitgesloten. Dit onderstreept nogmaals het belang van vroegtijdige verwijzing en tijdige behandeling voor het verkrijgen van goede chirurgische resultaten.

Hoofdstuk 8. Een ander commentaar werd gepubliceerd ter begeleiding van een multicenter, retrospectief onderzoek naar de korte en lange termijn resultaten van patiënten die een geïsoleerde tricuspidalisklepoperatie ondergingen, ingediend bij het European Journal of Cardio-Thoracic Surgery. Dit commentaar wil benadrukken hoe het wijdverbreide idee dat alle patiënten die getroffen zijn door geïsoleerde tricuspidalisregurgitatie en met een hoog risico op chirurgie effectief kunnen worden behandeld met transkatheter-opties, niet waarheidsgetrouw is. In feite zijn, net als bij chirurgie, ook bij transkatheterbehandeling optimale timing en adequate patiënten selectie cruciaal voor de uitkomst.

Hoofdstuk 9. We hebben de literatuur over transkatheter en chirurgische behandeling van tricuspidalisregurgitatie beoordeeld om alle factoren te identificeren die in staat zijn om rechterventrikeldecompensatie of gunstige responders te voorspellen. De meest relevante voorspellers van uitkomst voor beide behandelstrategieën zijn symptomatologie (NYHA functionele klasse en medische therapie), betrokkenheid van eindorganen (levercongestie en nierdisfunctie) en rechterventrikelfunctie (TAPSE en weefseldopplerbeeldvorming). Bij transkatheterbehandelingsonderzoeken is met name de rechterventrikelfunctie geanalyseerd. Linker ventrikel-pulmonale arterie (RV-PA) koppeling is een krachtige voorspeller van de uitkomst gebleken, waarbij wordt beoordeeld of de RV-functie correct wordt gecompenseerd voor specifieke belastingscondities. Als gevolg hiervan moet rechterhartkatheterisatie worden overwogen als onderdeel van de preoperatieve opwerking van patiënten.

Hoofdstuk 10. In deze studie hebben we een retrospectieve beoordeling uitgevoerd van onze chirurgische ervaring bij geïsoleerde tricuspidalisklepchirurgie op basis van een nieuwe speciale risicoscore, de TRI-SCORE. Het doel van de studie was om het vermogen van de TRI-SCORE te valideren bij het voorspellen van sterfte in het ziekenhuis en de resultaten van de follow-up op lange termijn na geïsoleerde tricuspidalisklepchirurgie. in onze ervaring vertoonde de risicoscore een hoge discriminatie en een hoge nauwkeurigheid met betrekking tot zowel de resultaten in het ziekenhuis als de mortaliteit op de lange termijn. Een afkapwaarde voor een verhoogd risico op geïsoleerde tv-chirurgie was 5.

Monte Solena - 2021

Chapter 15

ACKNOWLEDGEMENTS

University of Maastricht Medical Center, leading institution in medicine, research and innovation.

Prof. Dr. Roberto Lorusso, Promotor. Dear Professor Lorusso, I am extremely thankful for all the help, support and advice received since the beginning of my PhD. Thank you for your interest and supervision of my research development. These years have been unusual for everyone and we didn't have the chance to meet often in person, however I am honored to have received your guidance and suggestions throughout the project.

Prof. Dr. Jos G Maessen, Promotor. Dear Professor Maessen, I would like to thank you for the attention you reserved to this project.

Prof. Dr. Michele De Bonis, Supervisor. Dear Professor De Bonis, we met many years ago, when I was still a medical student. You saw me grow both from a professional and from a personal/human point of view. I would like to thank you for always being there for me, for supporting my choices, and for teaching me day after day how to become a good doctor, both in the clinical and in the research field. You constantly pushed me to do better and you managed to guide me all the way to the end of this PhD project, which I wouldn't have even started if it wasn't for you. Therefore, thank you, thank you a thousand times!

Prof. Dr. Ottavio Alfieri, Mentor. Dear Professor Alfieri, this is the biggest acknowledgement of all. You showed great faith in my regards, in every single moment of these long eight years. You dedicated precious time in teaching me our profession, in listening to my doubts and concerns, in providing important advice and always facing every situation in a critical and constructive way. You have walked by my side always, with your encouragements and reproaches, and you have made me the cardiac surgeon I am today. Thank you for your time and support, I really hope you will continue to guide me in future years.

Stefano, my life companion. Thank you for showing and teaching me how to appreciate and enjoy life in all its wonderful facets. Our life together is interlocking. It has always been until now, in an unpredictable way, full of surprises and amazing Tetris. Our life together will be interlocking, but I am up for the adventure because you make me feel the happiest and luckiest girl ever.

Viola, my little tortella. Who would have thought that this year, 2022, would have been so special to me? You are the most amazing and incredible gift I could receive, and I can’t wait to see you grow day by day.

Lauretta, Wonder-woman. Dear Mama, you are the most incredible woman I have ever met. You have been a role model, and you constantly surprise me with your strength and toughness. Thank you for your support all these years, both in the ups and in the lows. You managed to keep me going and you kept the mood high for both of us, with your decision but most of all with your love. I am a mum myself, and only now I fully understand the infinite love of a mother towards her sons and daughters. I really hope I'll manage to become a tenth of the woman you are.

Giorgio, loving father. Dear Dad, thank you for being such an incredible example throughout all my life. You taught me most of the things I know and have made me the human I am today. You taught me to be loving, caring, generous, determined, patient, and you made me love sports, and nature. You always believed in me, in my abilities, and pushed me to follow my dreams with courage and sacrifice. Without your support I would have never made it anywhere. Most of all, you always told me not to be afraid as long as you were by my side. Thank you for still being here today!

Andrea e Paolo, amazing brothers. You have both taught me important lessons in life and have helped me grow as a sister, as a daughter, as a friend, as a doctor and as a mother. You have been there for me in every situation, encouraging me in difficult

moments, always finding the time for me and my doubts (and some sport!), pushing me to do better but also to enjoy life, and always managing to bring back a smile and a laugh, with love, affection and great sense of humor. You are my heroes, the examples to which I thrive, you are my "people". I know that I will never be alone. You are the most wonderful brothers anyone could ask for, and I am beyond lucky to have you both!

Francesca e Erica, sisters more than in law. Thank you for always being there for me, in every situation. You always make the time to spend time together and have given me incredible support and advice in life and recently as a mum. I am grateful to have found two sisters, it really means a lot and fills my heart!

Tommaso, Giulia, Olivia e Filippo, the fantastic Four. You are the most incredible kids I have ever met, in all your different and particular ways. I can't wait to see you all grow in the amazing people you will become!!

I would also like to thank with great love and affection all my friends for their support, for having shared intense years and experiences with me. I owe you all!

Pizzo Tresero - 2021

Chapter 16

ABOUT THE AUTHOR

Alessandra Sala was born in Milan (Italy) on the 24th of August 1991. Her childhood and her adolescence mostly rotated around the tennis court. She played tennis at a professional level and traveled in most countries in the world to play tournaments. She later decided to put aside the sporting life and follow the medical career, following a couple of experiences as a volunteer in hospitals in Tanzania (Africa) and Pokhara (Nepal). She studied Medicine at the Vita-Salute San Raffaele University in Milan, MD Degree, and graduated with Honors in 2016 with a thesis on a new percutaneous technique for the treatment of functional tricuspid regurgitation, the TriCinch device. During her last year of University Alessandra spent 6 months in New York, United States, in order to increase her experience in cardiac surgery departments. Later she attended the residency program in Cardiac Surgery at the San Raffaele Hospital in Milan under the supervision of Prof. Michele De Bonis. She is currently in her last year of residency. Dr. Sala's interests include all aspects of adult cardiac surgery, especially mitral and tricuspid valve disease, their surgical treatment and postoperative management. Throughout these years she has particularly taken at heart the issue of the tricuspid valve and has gone into depth of the disease, preoperative assessment, surgical and transcatheter treatment options.
Outside of the hospital, Alessandra is a sports lover. She enjoys running, trail running, skiing and hiking. She absolutely loves to be outdoor, immersed in nature, surrounded by wilderness. She

adores traveling, seeing new places, coming into contact with new cultures and different people. She can’t wait to travel the world with her family, Stefano and Viola.

My incredible family

Chapter 17

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Milano - Bormio