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Residual Tricuspid Regurgitation following Tricuspid Valve Repair during Concomitant Valve Surgery Worsens Late Survival

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ABSTRACT

Background: Concomitant tricuspid valve repair (TVr) for functional tricuspid regurgitation (TR) at the time of left-sided valve surgery has become increasingly more common over the past decade. The impact of residual post-repair TR on late outcomes remains unclear.

Methods: All patients undergoing TVr during concomitant left-sided valve surgery at our institution from 2005-2012 were retrospectively reviewed. Patients were stratified into 2 groups according to the degree of post-cardiopulmonary bypass TR observed on intraoperative transesophageal echocardiography; 0-1+ TR (No TR, n = 246) and ≥2+ TR (Residual TR, n = 26). Primary outcomes of interest were 30-day survival, 4-year survival, and follow-up TR grade. A propensity-matched subgroup analysis was performed in addition to the overall cohort analysis.

Results: Mean age for all patients was 70.3 ± 13.0 years and 107 (39%) patients were male. There was no difference in 30-day survival between groups (92% No TR versus 96% Residual TR, $P = .70$). Kaplan-Meier analysis of overall 4-year survival showed a trend toward worsened survival in the Residual TR group (log rank $P = .17$) and propensity-matched subgroup analysis showed significantly worse 4-year survival for Residual TR (log rank $P = .02$). At mean echocardiographic follow up of 11.9 ± 22.5 months, TR grade was significantly worse in the Residual TR group compared to No TR (1.5 ± 0.8 Residual TR versus 0.9 ± 0.9 No TR, $P = .005$), although TR severity was significantly improved from immediately post-bypass.

Conclusions: Patients left with residual TR following TVr during concomitant left-sided valve surgery have significantly decreased late survival compared to patients left with no post-repair TR.

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INTRODUCTION

Functional tricuspid regurgitation (TR) most commonly occurs in the context of left-sided valvular or myocardial disease leading to right ventricular (RV) dilation, tricuspid annular dilatation, leaflet tethering, and ultimately, malcoaptation [Rogers 2009; Mahesh 2013]. Prior studies have shown that TR negatively impacts survival, with TR severity correlating to mortality, which has led to a doubling of tricuspid valve (TV) procedures over the last decade [Nath 2004; Vassileva 2012]. Although it is frequently believed that correction of left-sided valvular abnormalities alone will improve functional TR, growing evidence suggests that patients with functional TR undergoing concomitant valve surgery nonetheless benefit from tricuspid valve repair (TVr) [Benedetto 2012; Desai 2013; Teman 2014; Matsunaga 2005]. Given these findings, the current American Heart Association/American College of Cardiology guidelines recommend TV surgery in patients with severe TR undergoing left-sided valve surgery as a class I indication [Nisimura 2014].

Despite the growing enthusiasm for tricuspid intervention in this population, few studies have addressed the fate of early residual TR following TVr [Fukuda 2006]. Furthermore, no studies have directly addressed the effect of residual TR on patient survival. Therefore, the aim of the current study is to determine 1) the impact of residual TR after left-sided valve surgery and TVr on overall survival and 2) the progression of post-procedure residual TR after surgical repair.

METHODS

Patient Selection

All patients undergoing left-sided valve surgery with concomitant TV surgery from 2005 to 2012 at our center were reviewed. Patients undergoing TVr were selected for inclusion and stratified according to the severity of residual TR on intra-operative post-cardiopulmonary bypass transesophageal echocardiography (TEE); 0-1+ TR (No TR, n = 246) and ≥2+ TR (Residual TR, n = 26). Post-bypass TEE was selected as the basis for stratification due to the fact that it is the primary modality used to determine if further re-intervention is necessary prior to weaning of bypass and chest closure. Patients who underwent TV replacement were excluded from the study.

Variables collected included age, sex, body surface area (BSA), preoperative comorbidities (coronary artery disease [CAD], prior myocardial infarction [MI], stroke/transient ischemic attack, hypertension [HTN], chronic kidney disease [CKD, creatinine > 2 mg/dL], need for hemodialysis [HD], atrial fibrillation [Afib], peripheral arterial disease [PAD], diabetes mellitus [DM], chronic obstructive pulmonary disease [COPD], prior cardiac surgery), preoperative echocardiographic variables (left ventricular ejection fraction [EF], left ventricular end-diastolic dimension [LVEDD], RV function [0 = severe dysfunction to 4 = normal function], and TR grade [0-4+]), preoperative mean pulmonary artery pressure, concomitant valve operation, intraoperative variables (TVr technique, bypass and cross-clamp time, post-bypass TR grade), postoperative complications (reoperation for bleeding, need for new permanent pacemaker, stroke, myocardial infarction, respiratory failure, need for new dialysis), mortality, and echocardiographic follow-up (most recent echocardiogram). TV annular dimension was collected for propensity-matched patients by measurement in the apical 4-chamber view as previously described [Fukuda 2006]. The study was approved by the Institutional Review Board of Columbia University and need for informed consent was waived.

Tricuspid Repair Technique

The decision to repair the tricuspid valve was based on preoperative and intraoperative pre-bypass grade of TR, tricuspid annular dimension, and right and left ventricular function, but was ultimately left to the discretion of the operating surgeon. Approach to the tricuspid valve was via either median sternotomy or right mini-thoracotomy. Techniques for repair included ring annuloplasty, Kay annuloplasty (bicuspidization), or a "complex" repair that included a combination of techniques. Tricuspid repair was performed both under full cardioplegic arrest or following removal of the cross-clamp at the discretion of the operating surgeon. In cases where application of a cross-clamp was contraindicated, the entire procedure was performed on the warm, beating heart. Patients with a failed repair requiring immediate TV replacement or re-repair intraoperatively were excluded from this analysis.

Statistical Analysis

Data was analyzed using SPSS version 21 (IBM, Armonk, NY). Continuous variables are reported as mean ± standard deviation and compared using independent samples t tests. Categorical variables are reported as frequency and percentage of total group and compared using Pearson chi-squared test or Fisher exact test where applicable. Kaplan-Meier analysis was used to compare 4-year survival between groups and statistical significance was determined using the log rank test. Finally, a propensity-matched subgroup analysis was performed using the nearest-neighbor Greedy 5 to 1 digit matching algorithm (MatchIt package in R 3.0.2, R Foundation for Statistical Computing, Vienna, Austria) in order to control for differences in preoperative characteristics between groups. Covariates included in the algorithm were age, sex, left ventricular ejection fraction, preoperative TR grade, concomitant valve procedure, presence of concomitant coronary artery bypass grafting, and history of stroke, MI, CAD, Afib, CKD, DM, or HD. Matching was done in 2:1 fashion and matched 52 patients in the No TR group with 26 patients in the Residual TR group. All *P* values ≤ .05 are considered statistically significant.

Table 1. Baseline Characteristics

	No TR	Residual TR	*P*
Demographics			
Total, n	246	26	–
Age, years (mean ± SD)	70.5 ± 12.5	68.5 ± 17.1	.57
Male, n (%)	100 (41)	7 (27)	.17
BSA, m^2 (mean ± SD)	1.85 ± 0.25	1.82 ± 0.23	.66
Comorbidities, n (%)			
Coronary artery disease	90 (37)	11 (42)	.57
Myocardial infarction	26 (11)	4 (15)	.51
Stroke/TIA	33 (13)	4 (15)	.76
Hypertension	159 (65)	17 (65)	.94
Chronic kidney disease	25 (10)	2 (8)	1.00
Atrial fibrillation	152 (62)	20 (77)	.13
Peripheral arterial disease	21 (9)	0 (0)	.24
COPD	39 (16)	4 (15)	1.00
Diabetes	53 (22)	5 (19)	.78
Dialysis	13 (5)	1 (4)	1.00
Prior cardiac surgery	86 (35)	12 (46)	.26
Echo and hemodynamics (mean ± SD)			
TR grade	2.9 ± 0.9	3.2 ± 0.8	.12
RV function*	2.9 ± 1.1	2.7 ± 1.2	.42
LVEF, %	47.6 ± 12.7	49.4 ± 10.7	.49
LVEDD, cm	5.2 ± 0.8	5.4 ± 0.6	.63
Mean PAP, mmHg	35.2 ± 11.6	36.8 ± 12.0	.66

BSA indicates body surface area; COPD, chronic obstructive pulmonary disease; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; PAP, pulmonary arterial pressure; RV, right ventricle; TIA, transient ischemic attack; TR, tricuspid regurgitation (0 to 4+).
*RV function scale: 0 = severe dysfunction to 4 = normal function.

RESULTS

Baseline Characteristics

A total of 272 patients were included in the study, with 26 identified as Residual TR and 246 with No TR. Patient demographics, comorbidities, and preoperative echocardiographic variables are presented in Table 1. Mean age for all study participants was 70.3 ± 13.0 years and 107 (39%) patients were male. There was no significant difference in age, sex, or comorbidities between groups. Additionally, there

Table 2. Operative Characteristics

	No TR	Residual TR	P
Concomitant valve operations, n (%)			
AVR	31 (13)	5 (19)	.36
MVR	99 (40)	16 (62)	.04
MVr	60 (24)	1 (4)	.02
AVR/MVR	44 (18)	3 (12)	.59
AVR/MVr	12 (5)	1 (4)	1.00
MAZE*	45 (18)	6 (23)	.60
CABG*	37 (15)	5 (19)	.57
Tricuspid repair details			
Ring annuloplasty	232 (94)	18 (69)	<.001
Kay annuloplasty	8 (3)	5 (19)	.004
Complex valve repair	6 (2)	3 (12)	.04
Cardiopulmonary bypass details			
Bypass time, min (mean ± SD)	153 ± 49	160 ± 59	.50
XCL time, min (mean ± SD)	98 ± 34	103 ± 39	.47
Beating heart procedure, n (%)	12 (5)	0 (0)	.61
Intraoperative echocardiography			
Post-bypass TR grade (mean ± SD)	0.2 ± 0.4	2.0 ± 0.2	<.001

AVR indicates aortic valve replacement; MVR, mitral valve replacement; MVr, mitral valve repair; TR, tricuspid regurgitation; XCL, cross-clamp.
*In addition to concomitant valve procedure.

was no difference in baseline echocardiographic and hemodynamic parameters between groups, including RV function and degree of pulmonary HTN.

Operative Characteristics

Concomitant valve procedures, tricuspid repair details, bypass variables, and post-bypass residual TR grade are presented in Table 2. Overall, there were 36 (13%) concomitant aortic valve replacements (AVR), 115 (42%) mitral valve replacements (MVR), 61 (22%) mitral valve repairs (MVr), 47 (17%) AVR/MVRs, and 13 (5%) AVR/MVr procedures. Patients in the Residual TR group had significantly more MVRs and significantly less MVrs than the No TR group. The vast majority (92%) of patients in both groups underwent TV ring annuloplasty, which was associated with a low rate of Residual TR (18/250, 7%). In contrast, Kay annuloplasty and complex valve repair were associated with a much higher rate of Residual TR (38% and 33% [*P* = .004 and *P* = .04], respectively) compared to ring repair. The 9 cases with complex valve repair included 5 ring annuloplasty/Kay annuloplasties, 2 ring annuloplasty/patch augmentation, 1 ring annuloplasty/left cleft closure, and 1 ring annuloplasty/artificial chord implant. There were no differences in cardiopulmonary bypass or cross-clamp times, and 12 cases were done on a beating heart. Post-bypass TR grade was 0.2 ± 0.4

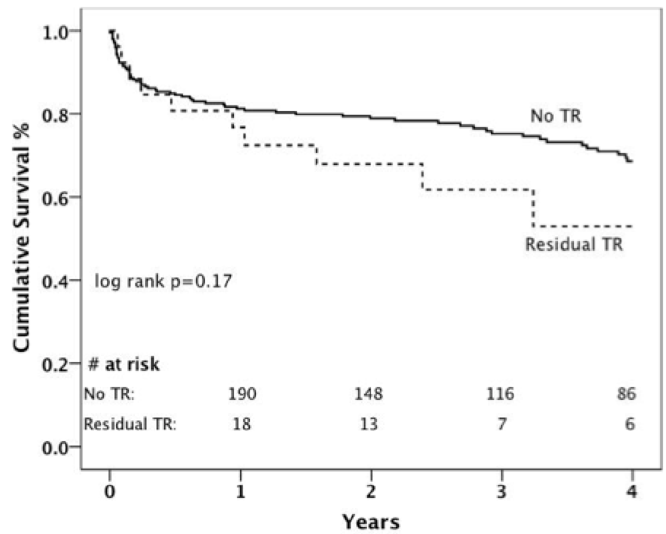

Figure 1. Kaplan-Meier analysis of 4-year survival stratified by post-repair tricuspid regurgitation.

in the No TR group and 2.0 ± 0.2 in the Residual TR group (*P* < .001).

Patient Outcomes

Survival, length of stay, postoperative complications, and echocardiographic follow-up are presented in Table 3. There was no difference in 30-day survival between groups. Kaplan-Meier analysis of 4-year survival showed no significant difference between groups, although there was a visual trend towards decreased survival in the Residual TR group (Figure 1, log rank *P* = .17). Patients in the Residual TR group had more severe TR at a mean follow-up of 11.9 ± 22.5 months than patients in the No TR group (1.5 ± 0.8 Residual TR versus 0.9 ± 0.9 No TR, *P* = .005). It is notable that a significant reduction in TR occurred in the Residual TR cohort from post-repair TEE to the most recent echo follow-up, presumably due to the effect of the primary valvular surgery (*P* = .004 for paired t test). There was no difference in postoperative complication rates or postoperative length of stay between groups.

Propensity Matched Subgroup

A comparison of propensity-matched cohorts is presented in Table 4. At baseline, patients in the Residual TR group had a trend towards higher mean pulmonary pressures, but no differences in other preoperative echo measurements including grade of TR, TV annular dimension, or RV function. Similar to the overall analysis, significantly more patients underwent ring annuloplasty in the No TR group compared to the Residual TR group (90% No TR versus 69% Residual TR, *P* = .03). In comparison, significantly more patients in the Residual TR group underwent Kay annuloplasty (19% Residual TR versus 4% No TR, *P* = .04). There was no difference in 30-day survival, however, Kaplan-Meier analysis of 4-year survival revealed significantly worse outcomes for patients in

Table 3. Outcomes

	No TR	Residual TR	*P*
Survival/hospital stay			
30-day survival, n (%)	227 (92)	25 (96)	.70
Postop LOS, days (mean ± SD)	16 ± 16	18 ± 18	.43
Follow-up, years (mean ± SD)	3.2 ± 2.5	2.6 ± 2.5	.22
Postoperative complications, n (%)			
Reoperation for bleed	10 (4)	0 (0)	.61
New PPM	25 (10)	1 (4)	.49
Stroke/TIA	6 (2)	2 (7.7)	.17
Myocardial infarction	0 (0)	0 (0)	1.00
Respiratory failure	46 (19)	5 (19)	1.00
Need for dialysis	27 (11)	4 (15)	.51
Echocardiographic follow-up			
TR grade (mean ± SD)	0.9 ± 0.9	1.5 ± 0.8	.005
LVEF, % (mean ± SD)	50.4 ± 15.2	51.8 ± 12.8	.70
Echo follow-up, months (mean ± SD)	11.9 ± 22.6	12.1 ± 22.6	.97

LOS indicates length of stay; LVEF, left ventricular ejection fraction; PPM, permanent pacemaker; TIA, transient ischemic attack; TR, tricuspid regurgitation (0 to 4+).

Table 4. Propensity Matched Subgroup

	No TR	Residual TR	*P*
Demographics			
Total, n	52	26	–
Age, years (mean ± SD)	68.6 ± 13.4	68.5 ± 17.1	.98
Male, n (%)	18 (35)	7 (27)	.49
Baseline echo and hemodynamics (mean ± SD)			
TR grade	3.1 ± 0.9	3.2 ± 0.8	.85
TV annular dimension, cm	3.2 ± 0.5	3.5 ± 0.5	.21
RV function*	3.0 ± 1.1	2.7 ± 1.2	.25
LVEF, %	50.0 ± 12.1	49.4 ± 10.7	.87
LVEDD, cm	5.1 ± 1.0	5.4 ± 0.6	.49
Mean PAP, mmHg	30.1 ± 9.8	36.8 ± 12.0	.09
Intraoperative variables			
Ring annuloplasty, n (%)	47 (90)	18 (69)	.03
Kay annuloplasty, n (%)	2 (4)	5 (19)	.04
Complex repair, n (%)	3 (6)	3 (12)	.39
Post-repair TR grade (mean ± SD)	0.3 ± 0.5	2.0 ± 0.2	<.001
Survival			
30-day, n (%)	50 (96)	25 (96)	1.00
Overall, n (%)	38 (73)	16 (62)	.30
Follow-up, years (mean ± SD)	3.9 ± 2.6	2.6 ± 2.5	.05
Echocardiographic follow-up (mean ± SD)			
TR grade	0.9 ± 0.8	1.5 ± 0.8	.01
Echo follow-up, months	12.3 ± 22.5	12.1 ± 22.6	.97

LVEDD indicates left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; RV, right ventricle; TR, tricuspid regurgitation (0 to 4+); TV, tricuspid valve.
*RV function scale: 0 = severe dysfunction to 4 = normal.

the Residual TR group (Figure 2, log rank $P = .02$). Finally, at a mean echo follow-up of 12.2 ± 22.3 months, there was a significant difference in TR grade between groups (0.9 ± 0.8 No TR versus 1.5 ± 0.8 Residual TR, $P = .01$).

DISCUSSION

Functional TR from left-sided valvular or myocardial disease remains a common entity affecting approximately 30% of patients undergoing mitral valve surgery [Shinn 2013]. The belief that functional TR will resolve once left-sided valvular pathology is corrected has recently been challenged, and there is increasing evidence that patients with significant TR at the time of aortic or mitral valve surgery benefit from concomitant tricuspid repair [Benedetto 2012; Desai 2013; Teman 2014; Matsunaga 2005]. Despite the increasing frequency of tricuspid interventions, no studies have evaluated post-repair residual TR and its impact on medium or long-term survival. In this report, we show for the first time that there is a significant medium-term survival difference between patients left with moderate residual TR compared with those with no TR at the conclusion of TVr with left-sided valve surgery. Although the severity of TR in patients left with post-repair residual TR appears to lessen over time, these patients continue to have more severe TR at late follow-up than patients left with no residual TR. Finally, we observed a small but statistically significant correlation in the type of repair and the severity of residual TR, suggesting a potential benefit of ring annuloplasty over other methods. The impact of these findings for surgeons may affect both the extent to which a "perfect repair" is pursued in the operating room, and have implications on intraoperative decision-making to convert a failed repair to a TV replacement.

It is generally accepted that TR severity negatively correlates with long-term survival. In 2004, Nath and colleagues published a study evaluating the survival impact of TR in over 5,000 patients in the Veterans Affairs system [Nath 2004]. They found that there was little difference in 1-year survival between patients with no and mild TR (91.7% versus 90.3%, respectively), but that moderate or greater TR was an independent predictor of death after adjustment for age, EF, vena cava size, and RV function. In our Residual TR group, mean TR grade at an average follow-up of 1 year post-surgery was mild-to-moderate compared to the No TR group whose mean TR grade was trace-to-mild. Thus, given the conclusions

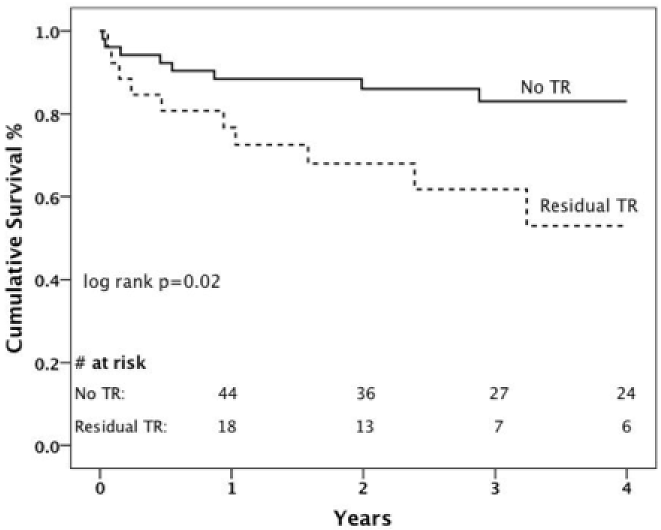

Figure 2. Kaplan-Meier analysis of 4-year survival in propensity matched subgroups.

that suggest any TR greater than mild significantly impacts late survival, it is not surprising to find that patients left with moderate or greater TR at the time of TV repair suffer from increased late mortality, as these patients persistently demonstrate a significant amount of TR even at late echo follow-up.

The regression in TR severity we found in the Residual TR group is likely multifactorial. Following a cardiopulmonary bypass run, in the absence of major bleeding, most patients are volume overloaded due to the volume challenge required for cardioplegia administration and crystalloid pump prime. In this setting, RV dilation is increased above baseline and may lead to more leaflet tethering, and therefore, more TR. Upon diuresis and return to euvolemia, one would predict the severity of TR to improve, which we have observed in this study to a certain extent. In addition to volume status, longer-term RV remodeling has been shown to take place following tricuspid repair [Bertrand 2014]. With resolution of left-sided valve disease and potential improvement in pulmonary pressures, RV pressure overload should improve with remodeling, leading to reduced RV and tricuspid annular dilation, and therefore, improved tricuspid leaflet coaptation. This remodeling process likely occurs to some extent after TVr, however, our study shows that while there is some regression in TR grade from the immediate post-bypass period in patients with residual TR, in reality, TR does not regress to an acceptably low level even in patients who have undergone TVr. The current data refutes the notion that repair of left-sided valvular lesions will lead to the significant improvement in TR in patients presenting with both entities. The implication of these findings suggests that a surgical strategy to monitor moderate residual TR after TVr surgery may be inappropriate. Rather, re-repair with a smaller ring or TV replacement may be warranted to prevent mortality associated with a poor repair. Although beyond the scope of this study, clinical benefit with a good repair likely improves RV function, reduces venous and hepatic congestion, and facilitates volume management. These concepts become even more critical in elderly, sicker patients with concurrent liver and lung disease. Further research will be needed to identify the detailed physiology that dictates these mechanisms.

Only one prior group has evaluated residual TR following tricuspid repair [Fukuda 2006]. Fukuda et al determined predictors of functional TR after tricuspid annuloplasty in 39 patients. Preoperative leaflet tethering height (>0.51 cm) and area (>0.80 cm2) were found to be predictors of early and medium-term postoperative TR severity. Predictors of late (>1 year) TR greater than 1+ included low left ventricular EF and severity of early postoperative TR. Although quite provocative, this study is difficult to compare with our results because TR severity is measured in different units (%TR = maximal TR area/right atrial area) and this group did not evaluate survival based on residual TR. Nonetheless, it is notable in our study that severity of post-repair TR did affect late TR grade in both the overall analysis and the propensity-matched subgroup analysis.

The main limitation of our study is its retrospective, single-center nature, which reflects the treatment biases of our cardiologists and surgeons. Although the overall size of our cohort was acceptable, the number of patients in the Residual TR group was small. It is clear that the immediate post-bypass echocardiography may not be reflective of hemodynamic conditions at euvolemia, and thus it may be less accurate in determining the true post-repair level of TR severity. However, residual TR, as evaluated immediately post-CPB, was studied due to its utility in the intraoperative decision-making process, and thus, we felt this was most appropriate for data analysis. Overall, the number of patients receiving a Kay repair versus ring annuloplasty was slightly different, which complicates interpretation of the propensity analysis. In the future, analysis must focus on patient groups with similar repair techniques to fully understand the appropriate effect of residual TR on long-term RV function and outcomes. The vast majority of preoperative echocardiograms at our facility do not include detailed measurements of tricuspid valve area or RV size variables. These measures would have been beneficial for a more detailed analysis. With regard to echo follow-up, 71% of patients in the cohort had follow-up echocardiograms in our electronic medical record. Additionally, we were unable to track functional or clinical status other than all-cause mortality. These outcomes are important, particularly in this population, and would have enabled us to draw more robust conclusions. Finally, the number of patients in the Residual TR group was not large enough to perform an accurate multivariable regression analysis in order to determine independent predictors of residual TR.

In conclusion, we have shown that there is a significant survival difference between patients with residual TR following tricuspid repair during concomitant left-sided valve surgery and those with no TR at the conclusion of the procedure. We also demonstrate that, while residual TR often improves in the short and medium-term, patients left with residual TR will consistently have worse TR than their counterparts without TR at the conclusion of their repair. With increasing numbers of tricuspid valve operations being performed, this is an important observation suggesting that significant reduction in TR severity in the operating room is required in order to confer a survival benefit of undergoing a concomitant TVr. Close attention should be given to using appropriate repair techniques, preferably with a ring repair, and considering re-repair or tricuspid replacement in the setting of residual TR. In the future, larger cohorts and longer echocardiography follow-up are warranted to further delineate the impact of residual TR following tricuspid valve repair.

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