ORIGINAL ARTICLE

Progression of Tricuspid Regurgitation in Participants Undergoing Surgeries for Other Cardiac Diseases and Factors Influencing

Anand Ajaykumar,[1,*] Rajesh Sadanandan,[2] Sajiv Kunnuthukathil Paul,[1] Kudakkachira Mathew Kuriakose[3] and Najeeb Palakuzhiyil[4]

[1]*Assistant Professor, Department of Cardiovascular and Thoracic Surgery, Government Medical College, Kozhikode*
[2]*Professor & HOD, Department of Cardiovascular and Thoracic Surgery, Government Medical College, Kozhikode*
[3]*Professor & HOD, Department of Cardiovascular and Thoracic Surgery, KMCT Medical College, Mukkam, Kozhikode*
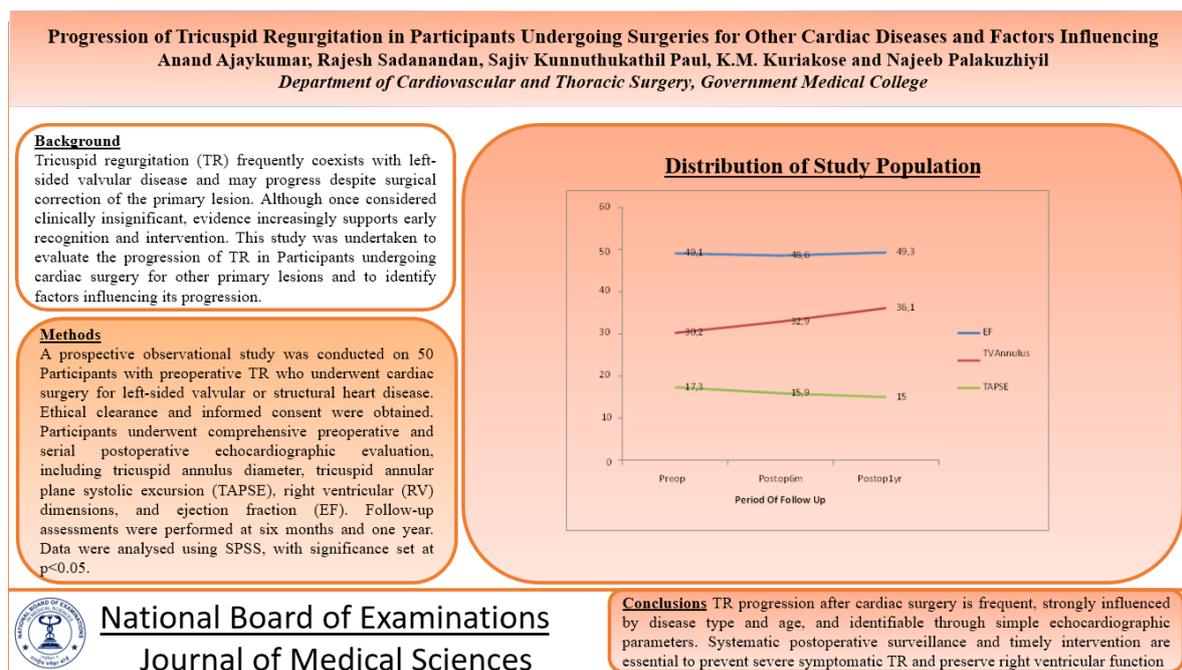[4]*Assistant Professor, Department of General Surgery, Government Medical College, Kozhikode*

Abstract
Introduction: Tricuspid regurgitation (TR) frequently coexists with left-sided valvular disease and may progress despite surgical correction of the primary lesion. Although once considered clinically insignificant, evidence increasingly supports early recognition and intervention. This study was undertaken to evaluate the progression of TR in Participants undergoing cardiac surgery for other primary lesions and to identify factors influencing its progression. **Materials and Methods:** A prospective observational study was conducted on 50 Participants with preoperative TR who underwent cardiac surgery for left-sided valvular or structural heart disease. Ethical clearance and informed consent were obtained. Participants underwent comprehensive preoperative and serial postoperative echocardiographic evaluation, including tricuspid annulus diameter, tricuspid annular plane systolic excursion (TAPSE), right ventricular (RV) dimensions, and ejection fraction (EF). Follow-up assessments were performed at six months and one year. Data were analysed using SPSS, with significance set at $p<0.05$. **Results:** The mean age was 45.8 ± 9.3 years, with 62% male predominance. Severe mitral stenosis was the most common primary lesion (56%). At baseline, mean tricuspid annulus was 30.2 mm and TAPSE 17.3 mm, with no RV dilatation. By one year, the mean annulus had increased to 36.1 mm ($p<0.001$), TAPSE declined to 15.0 mm ($p<0.001$), and RV dilatation was observed in 38% of Participants. Nineteen Participants (38%) developed severe TR, most commonly in mitral stenosis and CAD+MR subgroups. Advancing age was significantly associated with persistence of regional wall motion abnormalities ($p=0.020$), while gender showed no influence. **Conclusion:** TR progression after cardiac surgery is frequent, strongly influenced by disease type and age, and identifiable through simple echocardiographic parameters. Systematic postoperative surveillance and timely intervention are essential to prevent severe symptomatic TR and preserve right ventricular function.

Keywords: Tricuspid Regurgitation, Mitral Stenosis, Cardiac Surgery, Echocardiography, Right Ventricular Function

*Corresponding Author: Anand Ajaykumar
Email: dranandajay171@gmail.com

Graphical Abstract

Progression of Tricuspid Regurgitation in Participants Undergoing Surgeries for Other Cardiac Diseases and Factors Influencing
Anand Ajaykumar, Rajesh Sadanandan, Sajiv Kunnuthukathil Paul, K.M. Kuriakose and Najeeb Palakuzhiyil
Department of Cardiovascular and Thoracic Surgery, Government Medical College

Background
Tricuspid regurgitation (TR) frequently coexists with left-sided valvular disease and may progress despite surgical correction of the primary lesion. Although once considered clinically insignificant, evidence increasingly supports early recognition and intervention. This study was undertaken to evaluate the progression of TR in Participants undergoing cardiac surgery for other primary lesions and to identify factors influencing its progression.

Methods
A prospective observational study was conducted on 50 Participants with preoperative TR who underwent cardiac surgery for left-sided valvular or structural heart disease. Ethical clearance and informed consent were obtained. Participants underwent comprehensive preoperative and serial postoperative echocardiographic evaluation, including tricuspid annulus diameter, tricuspid annular plane systolic excursion (TAPSE), right ventricular (RV) dimensions, and ejection fraction (EF). Follow-up assessments were performed at six months and one year. Data were analysed using SPSS, with significance set at p<0.05.

Distribution of Study Population

Conclusions TR progression after cardiac surgery is frequent, strongly influenced by disease type and age, and identifiable through simple echocardiographic parameters. Systematic postoperative surveillance and timely intervention are essential to prevent severe symptomatic TR and preserve right ventricular function

National Board of Examinations
Journal of Medical Sciences

Introduction

Pathology of the left-sided heart valves is frequently associated with significant tricuspid regurgitation (TR), which may not always resolve after correction of the left-sided lesion. The latest European guidelines [1] recommend tricuspid valve surgery in Participants with severe TR, or when the annular diameter is ≥40 mm, regardless of regurgitation severity, highlighting the need for prophylactic intervention even in less advanced disease [1,2]. Despite these recommendations, concomitant correction of functional TR in Participants undergoing left heart surgery remains underutilised. Pulmonary arterial hypertension, right ventricular dilatation, tricuspid annular enlargement, and right-sided heart failure are common contributors to worsening TR [3,4]. Nearly half of Participants undergoing mitral valve surgery are reported to have associated TR [5], and the majority of those with right ventricular dilatation and annular enlargement develop functional TR [6]. Additional causes include iatrogenic injury such as pacing leads, rheumatic heart disease, infective endocarditis, and rare conditions such as carcinoid syndrome [7].

Although literature on tricuspid annuloplasty and repair techniques in this setting remains relatively limited, evidence indicates that concomitant tricuspid valve repair, particularly ring annuloplasty, is a safe and effective option. A recent meta-analysis demonstrated that performing tricuspid valve repair during left-sided valve surgery in Participants with moderate TR improves survival and reduces the progression of regurgitation without increasing operative mortality [8]. Similarly, a 2024 study confirmed that tricuspid ring annuloplasty at the time of mitral surgery significantly decreased late TR progression while maintaining acceptable perioperative risk [9]. Long-term follow-up data from a Japanese cohort

also showed excellent survival and durable freedom from recurrent TR following combined procedures, though preoperative right heart condition was an important predictor of outcome [10].

With the growing recognition that TR is often overlooked despite being clinically significant, there has been a rising trend in the incidence of severe symptomatic disease that might have been prevented with timely intervention. Structural changes such as a 5.9 mm increase in annular diameter and a 2.2 mm decline in TAPSE represent meaningful deterioration, corresponding to TR progression and emphasising the importance of systematic post-operative surveillance in high-risk Participants. Hence, this study was undertaken to evaluate the progression of tricuspid regurgitation in Participants undergoing other cardiac surgeries and to identify the factors influencing its progression.

Materials and Methods

This prospective observational study was conducted after obtaining approval from the Institutional Human Ethics Committee. The study adhered to the principles outlined in the Declaration of Helsinki. Participants who were scheduled to undergo cardiac surgery for left-sided valve or other structural heart diseases in the cardiothoracic unit of the Institute were screened for eligibility. Those with associated congenital heart disease, prior tricuspid valve intervention, or significant structural abnormalities of the right heart valves unrelated to functional tricuspid regurgitation were excluded.

All eligible Participants were contacted and Participant Information sheet was issued. After adequate time and counselling for the doubts they had, Written informed consent was obtained. Baseline demographic data including age, sex, height, weight, body surface area, and relevant clinical characteristics were recorded. A detailed medical history was obtained, with particular attention to comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, pulmonary arterial hypertension, and prior cardiac interventions. Clinical examination focused on signs of right-sided heart failure and jugular venous distension.

Comprehensive preoperative evaluation was carried out using transthoracic echocardiography (TTE). Parameters assessed included severity of tricuspid regurgitation graded according to American Society of Echocardiography recommendations, tricuspid annular diameter, right ventricular basal diameter, right atrial size, right ventricular systolic pressure, and tricuspid annular plane systolic excursion (TAPSE). In addition, left ventricular ejection fraction, left atrial diameter, and severity of associated left-sided valve disease were documented. In selected Participants with suboptimal transthoracic windows, transesophageal echocardiography (TEE) was employed for confirmation. Baseline laboratory investigations, electrocardiography, and chest radiography were also performed as part of preoperative assessment.

All Participants underwent standard cardiac surgical procedures under cardiopulmonary bypass according to the indication, which included mitral valve replacement or repair, aortic valve replacement, or combined procedures. The tricuspid valve was inspected intraoperatively and managed according to the discretion of the operating surgeon in line with current guidelines. Participants

who underwent concomitant tricuspid valve annuloplasty were documented separately. Intraoperative data including cardiopulmonary bypass time, aortic cross-clamp time, type of surgical procedure performed, and immediate operative complications were recorded.

Postoperatively, Participants were monitored in the intensive care unit with standard hemodynamic and biochemical surveillance. Echocardiographic reassessment was carried out before discharge, and follow-up evaluations were performed at six months and one year. The severity of tricuspid regurgitation, annular dimensions, TAPSE values, right atrial and right ventricular dimensions, and pulmonary pressures were serially compared to determine progression. Any need for subsequent tricuspid valve intervention, occurrence of right heart failure, or all-cause mortality were noted during follow-up.

Data were compiled systematically and entered into Microsoft Excel using appropriate coding and analysed in SPSS (IBM SPSS Statistics, version 27) . Continuous variables such as annular diameter, TAPSE, and ventricular dimensions were expressed as Mean ± Standard Deviation, and categorical variables such as sex, comorbidities, and severity grades of TR were presented as Proportions Or Percentages. Comparison of means between groups was done using the T-test or ANOVA as appropriate. Categorical variables were analysed using the chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant.

Results

The baseline characteristics of the study population are summarized in **Table 1**. The mean age of Participants was 45.8 ± 9.3 years (range 25–63 years), with a male predominance (62%). Mitral stenosis was the most common primary cardiac lesion (56%), followed by aortic stenosis (16%), mitral regurgitation (12%), combined CAD with MR (10%), and aortic regurgitation (6%).

Table 1. Baseline Characteristics of the Study Population (N=50)

Characteristic	Value
Age, years (mean ± SD)	45.8 ± 9.3
Age range	25–63
Male, n (%)	31 (62.0)
Female, n (%)	19 (38.0)
Primary Cardiac Disease	
- MS / AS / MR / CAD+MR / AR	28 / 8 / 6 / 5 / 3

At baseline, the mean ejection fraction (EF) was 49.1 ± 7.5%, the mean tricuspid annulus diameter was 30.2 ± 3.4 mm, and the mean tricuspid annular plane systolic excursion (TAPSE) was 17.3 ± 1.4 mm. Six Participants (12%) demonstrated regional wall motion abnormalities (RWMA), while none showed right ventricular (RV) dilatation (Table 2).

Table 2. Echocardiographic Parameters at Baseline, 6 Months, and 1 Year

Parameter	Baseline (Mean ± SD)	6 Months	1 Year	p-value
EF (%)	49.1 ± 7.5	48.6 ± 6.3	49.3 ± 6.2	0.71 (NS)
TV Annulus (mm)	30.2 ± 3.4	32.9 ± 3.6	36.1 ± 4.7	<0.001
TAPSE (mm)	17.3 ± 1.4	15.9 ± 1.3	15.0 ± 1.5	<0.001
RV Dilatation (%)	0	20	38	<0.001
RWMA (%)	12	12	12	NS

At six months after surgery, EF remained stable at 48.6 ± 6.3% (p=0.49 vs baseline). However, significant structural and functional changes were evident on the right side. The mean tricuspid annulus diameter increased to 32.9 ± 3.6 mm (p<0.001 compared to baseline), and TAPSE declined to 15.9 ± 1.3 mm (p<0.001). Ten Participants (20%) developed new-onset RV dilatation, whereas the prevalence of RWMA remained unchanged at 12%.

At one-year follow-up, progression of tricuspid regurgitation was more pronounced. The mean tricuspid annulus diameter further increased to 36.1 ± 4.7 mm, with 19 Participants (38%) crossing the threshold for severe TR (≥40 mm). TAPSE declined further to 15.0 ± 1.5 mm, with 19 Participants (38%) showing values <14 mm, indicating poor RV function. RV dilatation was documented in 38% of the cohort, while EF remained unchanged at 49.3 ± 6.2% (p=0.71 vs baseline) (Table 2 and Figure 1).
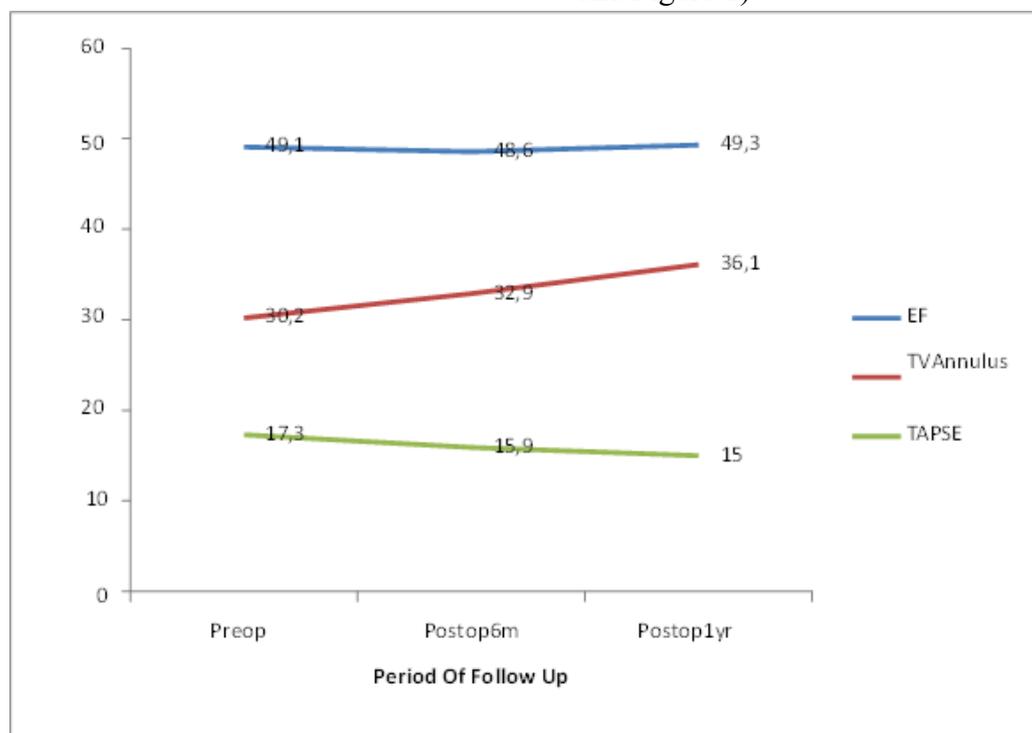

Figure 1. Serial echocardiographic changes in EF, TV annulus, and TAPSE at baseline, 6 months, and 1 year.

Subgroup analysis revealed significant variability in progression patterns according to the underlying cardiac disease. Table 3 shows the disease-specific outcomes at one year following surgery. Participants with mitral stenosis (MS) demonstrated the most severe deterioration, with mean annular dilatation of +8 mm and TAPSE decline of –2.5 mm; 50% developed severe TR and RV dilatation. CAD+MR Participants were also at very high risk, with 40% developing severe TR and RV dilatation, despite showing improvement in LV function. In contrast, Participants with aortic regurgitation and pure MR exhibited minimal annular enlargement and TAPSE decline. These patterns are illustrated in Figures 2–4, where MS and CAD+MR groups showed the steepest deterioration compared to other subgroups.
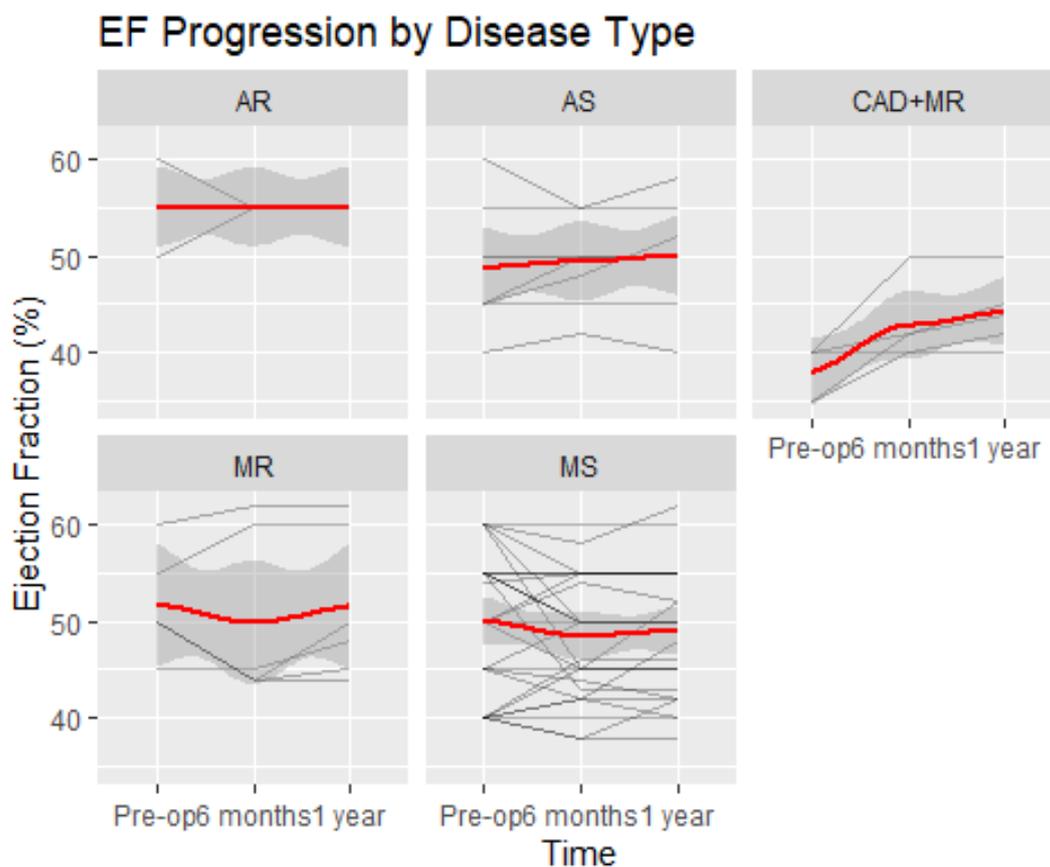
Figure 2. Disease-specific EF trajectories over one year following surgery.
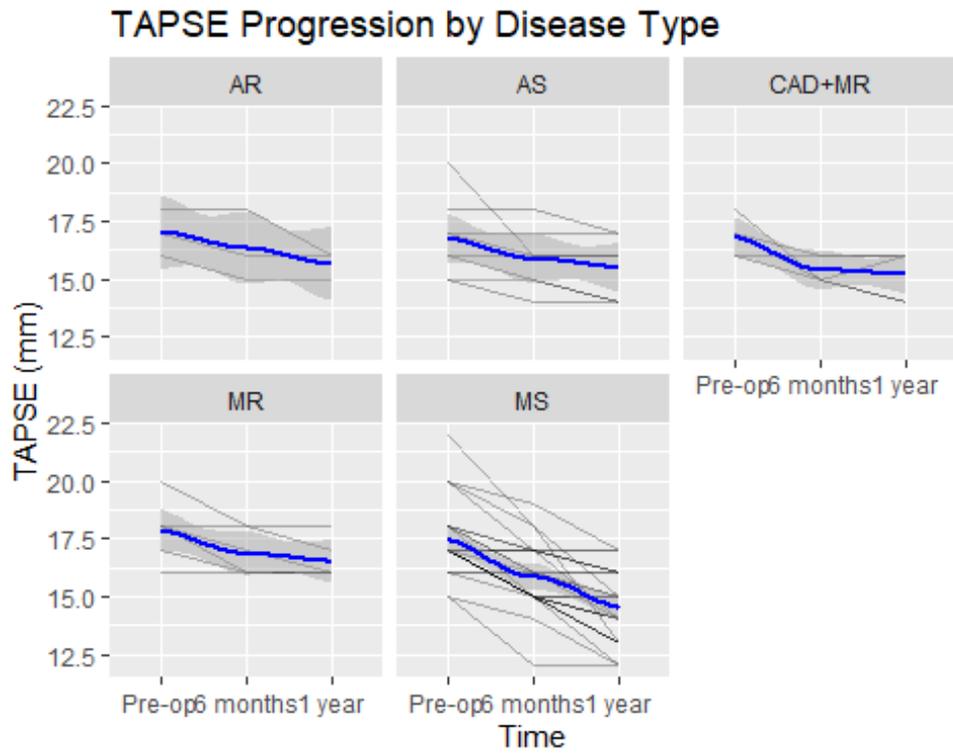
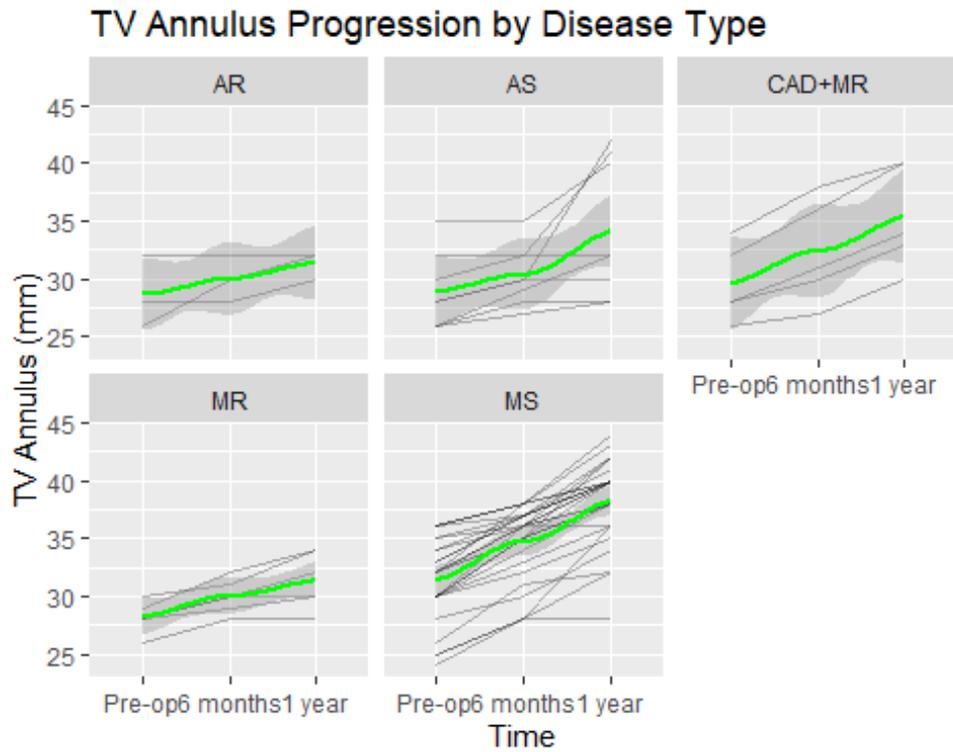Figure 3. Disease-specific TAPSE decline over one year following surgery.

Figure 4. Disease-specific TV annulus progression over one year following surgery.

Table 3. Disease-Specific Progression at 1-Year Follow-up (Post-surgery)

Disease Type	n	Severe TR (≥40mm), n (%)	RV Dilatation, n (%)	Mean Annular Increase (mm)	Mean TAPSE Decline (mm)	Risk Category
Mitral stenosis	28	14 (50.0)	14 (50.0)	+8.0	–2.5	High
CAD + MR	5	2 (40.0)	2 (40.0)	+6.0	–1.5	Very High
Aortic stenosis	8	3 (37.5)	3 (37.5)	+4.0	–1.5	Moderate
Mitral regurgitation	6	0 (0.0)	0 (0.0)	+4.0	–1.0	Low
Aortic regurgitation	3	0 (0.0)	0 (0.0)	+2.0	–1.0	Low

Age-related analysis demonstrated that RWMA incidence was significantly higher in Participants above 50 years (p=0.020). As shown in Figure 5, RWMA prevalence reached 66.7% in Participants aged 61–70 years, compared to <6% in those younger than 50 years. No significant association was found between gender and TR progression.
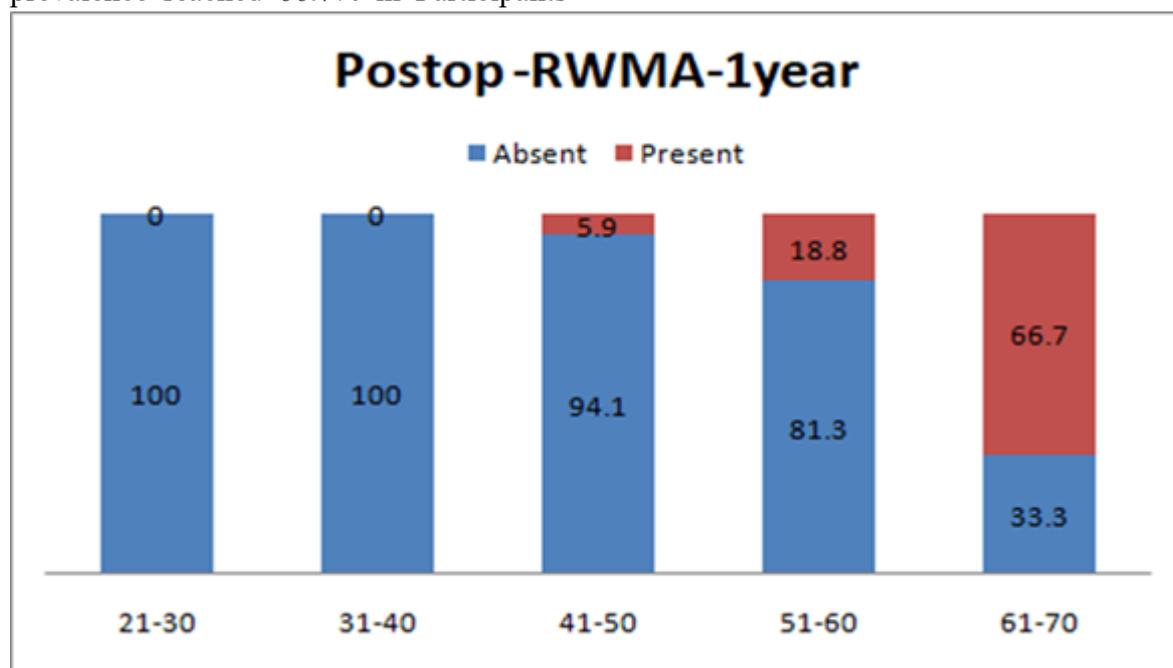

Figure 5. Age-stratified RWMA prevalence at one-year follow-up.

In summary, within one year of follow-up, more than one-third of Participants developed severe TR after cardiac surgery, characterized by annular dilatation ≥40 mm and TAPSE <14 mm. The degree of deterioration (mean annular increase of 5.9 mm and TAPSE decline of 2.2 mm) was clinically meaningful and strongly influenced by the type of primary cardiac disease and age at presentation.

The progression of tricuspid regurgitation was not uniform across the cohort but was significantly influenced by patient-specific factors. Disease type emerged as the strongest determinant, with mitral stenosis and CAD+MR Participants

showing the most severe deterioration in annular dilatation and TAPSE decline (Figures 2–4). Advancing age (>50 years) was also associated with higher prevalence of RWMA (p=0.020), suggesting reduced myocardial reserve in older Participants (Figure 5). In contrast, gender showed no significant association with TR progression. These findings indicate that both underlying cardiac pathology and age are important modifiers of disease trajectory.

Discussion

Tricuspid regurgitation is frequently encountered in Participants undergoing surgery for cardiac disease, particularly those with valvular heart pathology, with severe mitral stenosis being the most common substrate [11-13]. Historically, the tricuspid valve was neglected, and surgical attention was primarily directed at the left-sided lesions. However, long-term studies such as those by Dreyfus et al. [14] and Topilsky et al. [15] demonstrated that untreated TR can progress over time, often leading to symptoms and eventual need for surgical or medical management. In support of this, Kilic et al. [16,17] and Navia et al. [18] reported symptomatic improvement and stabilization of right ventricular function when concomitant tricuspid repair was performed.

In our study of 50 Participants with preoperative TR undergoing surgery for primary cardiac disease, serial echocardiographic evaluation was performed to document progression. The mean age was 45 years, with a male predominance (62%). Severe mitral stenosis accounted for over half of the cases, whereas only a small proportion (6%) had aortic regurgitation as the primary lesion. Regional wall motion abnormalities

(RWMA) were documented in 12% of Participants preoperatively, without any new cases during follow-up. Left ventricular ejection fraction (EF) remained largely stable, with a minor decrease at six months followed by recovery at one year.

Importantly, right heart parameters showed progressive deterioration. No patient had right ventricular dilatation preoperatively, but 20% developed RV dilatation at six months, increasing to 38% at one year. Tricuspid annular diameter increased from 30.2 mm at baseline to 36.1 mm at one year, with 19 Participants (38%) crossing the threshold of ≥40 mm, consistent with severe TR. Similarly, TAPSE declined from a mean of 17.3 mm to 15.0 mm over one year, with 38% demonstrating TAPSE <14 mm, signifying impaired RV function. These findings confirm that TR progression after left-sided cardiac surgery is both structural and functional, aligning with previously published literature [16-18].

The second objective of our study was to identify factors influencing the progression of tricuspid regurgitation. Our results demonstrate that progression is strongly dependent on the type of primary cardiac disease, with mitral stenosis and CAD+MR Participants at the highest risk for developing severe TR within one year of follow-up. In addition, older age (>50 years) was significantly associated with persistence of RWMA, further contributing to adverse remodeling. Conversely, gender did not appear to affect outcomes. Thus, disease type and advancing age represent key determinants of TR progression that should be taken into account in clinical decision-making. These findings are consistent with contemporary data indicating that rheumatic mitral pathology and ischemic substrates impose significant

load on the right heart, accelerating TR progression [19,20].

Our results also suggest that echocardiographic markers such as annular dilatation (>40 mm) and TAPSE <14 mm should be considered red flags during follow-up. These parameters reflect clinically meaningful deterioration and may warrant earlier intervention before the onset of irreversible right ventricular dysfunction. Recent multicentric analyses confirm that proactive tricuspid valve repair during left-sided surgery is safe and may prevent late symptomatic TR, reducing the need for high-risk reoperations [21,22].

Conclusion

Our study highlights that tricuspid regurgitation, often overlooked during left-sided cardiac surgery, shows frequent progression within one year of follow-up, particularly in Participants with mitral stenosis and CAD with MR. Simple echocardiographic parameters such as tricuspid annular diameter, TAPSE, and right ventricular dimensions provide reliable markers for monitoring severity and progression. In our cohort, 38% of Participants developed severe TR (annulus ≥40 mm, TAPSE <14 mm, and RV dilatation) within one year, underscoring the importance of systematic surveillance and timely surgical correction. Early recognition and intervention in high-risk Participants may prevent irreversible right ventricular dysfunction and improve long-term outcomes.

Statements and Declarations
Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

References

1. Nath J, Foster E, Heidenreich P. Impact of tricuspid regurgitation on long term survival. J Am Coll Cardiol 2004;43:405–409.

2. Matsuyama K, Matsumoto M, Sugita T, Nishizawa J et al. Predictors of residual tricuspid regurgitation after mitral valve surgery. Ann Thorac Surg 2003;75:1826–1828.

3. Lancellotti P, Moura L, Pierard LA, Agricola E et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Eur J Echocardiogr 2010;11:307–332.

4. Badano LP, Muraru D, Enriquez-Sarano M. Assessment of functional tricuspid regurgitation. Eur Heart J. 2013;34(25):1875-85. doi: 10.1093/eurheartj/ehs474.

5. Matsunaga A, Duran CM. Progression of tricuspid regurgitation after repaired functional ischemic mitral regurgitation. Circulation 2005;112(Suppl. I):I453–I457.

6. Mangoni AA, DiSalvo TG, Vlahakes GJ, Polanczyk CA et al. Outcome followingisolated tricuspid valve replacement. Eur J Cardiothorac Surg 2001;19(1):68–73.

7. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS); Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk

V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012 Oct;33(19):2451-96. doi: 10.1093/eurheartj/ehs109.

8. Barua A, Wong N, Jain S, Uzzaman M, Nanjaiah P, Jeeji R, Balacumaraswami L. Concomitant tricuspid surgery for moderate tricuspid regurgitation improves survival in left-sided valve surgery - a meta-analysis. J Cardiothorac Surg. 2025 Jul 12;20(1):294. doi: 10.1186/s13019-025-03464-0.

9. David TE. Tricuspid valve annuloplasty at the time of mitral valve surgery: is it justified in all cases? Indian J Thorac Cardiovasc Surg. 2020 Mar;36(2):88-90. doi: 10.1007/s12055-019-00907-x.

10. Noda K, Kawamoto N, Kainuma S, Tadokoro N, Ikuta A, Fukushima S. Predictors of late outcomes after concomitant tricuspid valve repair with left-sided valve surgery. Gen Thorac Cardiovasc Surg. 2024 Dec;72(12):755-762. doi: 10.1007/s11748-024-02033-x.

11. Singh JP, Evans JC, Levy D, Larson MG et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol 1999; 83:897–902.

12. Braunwald NS, Ross J Jr, Morrow AG. Conservative management of tricuspid regurgitation in Participants undergoing mitral valve replacement. Circulation 1967;35(4 Suppl.):I63–169.

13. Sadeghi HM, Kimura BJ, Raisinghani A, Blanchard DG et al. Does lowering pulmonary arterial pressure eliminate severe functional tricuspid regurgitation? Insights from pulmonary thromboendarterectomy. J Am Coll Cardiol 2004; 44: 126–132.

14. Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg. 2005 Jan;79(1):127-32. doi: 10.1016/j.athoracsur.2004.06.057.

15. Topilsky Y, Khanna AD, Oh JK, Nishimura RA et al. Preoperative factors associated with adverse outcome after tricuspid valve replacement. Circulation 2011;123:1929–1939.

16. De Vega NG. [Selective, adjustable and permanent annuloplasty. An original technic for the treatment of tricuspid insufficiency]. Rev Esp Cardiol 1972; 25:555–556.

17. Zhu TY, Wang JG, Meng X. Is a rigid tricuspid annuloplasty ring superior to a flexible band when correcting secondary tricuspid regurgitation? Interact Cardiovasc Thorac Surg 2013; 17:1009–10

18. Navia JL, Nowicki ER, Blackstone EH, Brozzi NA et al.Surgical management of secondary tricuspid valve regurgitation: annulus, commissure, or leaflet procedure? J Thorac Cardiovasc Surg 2010; 139:1473–1482 e5.

19. Mangieri A, Montalto C, Pagnesi M, Jabbour RJ, Rodés-Cabau J, Moat N, Colombo A, Latib A. Mechanism and Implications of the Tricuspid Regurgitation: From the Pathophysiology to the Current and

Future Therapeutic Options. Circ Cardiovasc Interv. 2017 Jul;10(7):e005043. doi: 10.1161/CIRCINTERVENTIONS.117.005043.

20. Pettinari M, De Kerchove L, Van Dyck M, Pasquet A, Gerber B, El-Khoury G, Vanoverschelde JL. Tricuspid annular dynamics, not diameter, predicts tricuspid regurgitation after mitral valve surgery: Results from a prospective randomized trial. JTCVS Open. 2023 Feb 15;14:92-101. doi: 10.1016/j.xjon.2023.02.005.

21. Mahboobi SK, Sharma S, Ahmed AA. Tricuspid Valve Repair. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559179/

22. Blitzer D, Bouhout I, Al Haddad E, Lewis M, Farooqi K, Shah A, Zemer-Wassercug N, Singh H, Anderson B, Bacha E, Kalfa D. Outcomes and risk analysis after tricuspid valve surgery for non-Ebstein 2-ventricle congenital tricuspid valve diseases. JTCVS Open. 2022 Jul 5;11:351-362. doi: 10.1016/j.xjon.2022.06.017.