Impact of moderate or severe mitral and tricuspid valves regurgitation after transcatheter aortic valve replacement

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ABSTRACT

Background Tricuspid regurgitation (TR) and mitral regurgitation (MR) are common valvular conditions encountered in patients undergoing transcatheter aortic valve replacement (TAVR). This retrospective study investigates the impact of moderate or severe TR and MR on all-cause mortality in 1-year post-TAVR patients.

Methods Consecutive patients who underwent TAVR at the 3 academic tertiary care centers in our health system between 2012 and 2018 were identified. Patients were stratified into 2 groups based on valvular regurgitation severity: moderate/severe MR vs no/mild MR, and moderate/severe TR vs no/mild TR. Primary outcome was all-cause mortality at 1-year and 5-year follow up, and secondary outcome was in-hospital death. Logistic regression analysis was conducted to assess the relationship between moderate/severe MR or TR and all-cause mortality at 1-year and 5-year follow-up.

Results We included a total of 1,071 patients who underwent TAVR with mean age 80.9 ± 8.6 years, 97% white, and 58.3% males. Moderate or severe MR group included 52 (4.88%) patients while mild or no MR group included 1,015 (95.12%) patients. There was no significant difference between both groups in TAVR procedure success rate (100% vs 97.83%, $P = .283$), in-hospital mortality (0 vs 1.08%, $P = .450$), or mortality at 1-year follow up (15.38% vs 14.09%, $P = .794$). At 5-year follow up, moderate/severe MR group had higher mortality (61.4% vs 49.5%, $P = .046$). In multivariable logistic regression analysis, moderate or severe MR did not show significant correlation with all-cause mortality at 1-year and 5-year follow up. Moderate or severe TR group included 86 (8.03%) patients while mild or no TR group included 985 (91.97%) patients. There was no difference between both groups in TAVR procedure success (98.8% vs 97.9%, $P = .54$) or in-hospital mortality (0% vs 1.1%, $P = .33$). At 1-year follow up, patients with moderate or severe TR had higher mortality (26.7% vs 13.2%, $P = .001$) compared to patients with mild or no TR. Same finding was noted with extended follow up at 5-years (68.3% vs 48.7%, $P < .001$). In multivariable cox regression analysis, moderate/severe TR was associated with higher all-cause mortality at 1-year (OR 1.94, 95% CI [01.09, 3.44], $P = .023$) and at 5-year (OR 1.46, 95% CI [1.092, 1.952], $P = .011$) follow up. Patients with combined moderate/severe MR and TR have even higher mortality compared to either moderate/severe valve regurgitation alone or mild/no valve regurgitation at 5-year follow up.

Conclusion At long term follow up, moderate/severe TR, but not MR, is associated with higher mortality in patients underwent TAVR. Combined moderate/severe TR and MR had even worse mortality. Careful assessment of multivalvular heart disease prior to the procedure is warranted. (Am Heart J 2025;280:79–88.)

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Background

The most common valve heart disease in the western world is degenerative aortic valve stenosis (AS).[1] A significant proportion of patients receiving transcatheter aortic valve replacement (TAVR) have moderate or severe mitral regurgitation (MR) and/or tricuspid regurgitation (TR). The combination of AS and significant other valvular regurgitation may impact the diagnosis, prognosis, and treatment.[2]

An improvement in MR severity after aortic valve (AV) surgery is linked to improved outcomes and decreased mortality.[2,3] However, a challenge arises due to the asynchronous progression of AS and MR, affecting the exact time of necessary intervention. Also, studies have revealed that up to 15% of patients diagnosed with severe AS also exhibit moderate or severe TR, underscoring the prevalence and clinical complexity of these concurrent conditions.[4,5] Addressing both conditions requires a thorough assessment of valve anatomy and function and understanding the underlying pathophysiological pathways to establish appropriate treatment methods and planning procedures.[6,7,8]

Traditional open-heart surgery manages both AS and significant valve regurgitation simultaneously. In contrast, recent transcatheter techniques present a more flexible approach, enabling customized intervention time, and offering less invasive options for staged or combined procedures, especially for elderly patients, avoiding the need for traditional surgery. The guidelines advise against surgery for nonsevere nonischemic MR without structural issues, as treating aortic stenosis might occasionally relieve the MR. However, a lack of specific guidance for more significant MR and TR remains a topic of ongoing discussion, lacking clear guideline-based recommendations.[6,9,10,11,12] The independent impact of concurrent MR and TR on clinical outcomes following TAVR is still being researched and debated. This study aimed to investigate the impact of concomitant significant valvular disease on patients undergoing TAVR.

Methods

We performed a retrospective observational study utilizing the Mayo Clinic National Cardiovascular Diseases Registry database, which included patients from 3 major academic medical centers in Rochester, MN, Phoenix, AZ, and Jacksonville, FL. We included all consecutive patients who underwent TAVR for severe aortic valve stenosis from January 2012 to December 2018. We used the last available preprocedure transthoracic or transesophageal echo to identify other concomitant valvular abnormalities. Moderate or severe MR was defined as regurgitation volume >45 ml/beat, regurgitation fraction >40%, and/or effective regurgitation orifice area >0.30 cm^2. Moderate or severe TR was defined as regurgitation jet area >5 cm^2, vena contracta width >0.4 cm, and hepatic vein systolic flow blunting or reversal. We retrospectively collected data on the baseline characteristics of the included patients, echocardiographic parameters prior to the TAVR procedure, and the outcomes of interest. Our data included patients aged 18 years or older who underwent TAVR with available preprocedural transthoracic or transesophageal echo data. We excluded patients with prior MR/TR intervention to minimize any sources of bias. We used the Valve Academic Research Consortium (VARC-3) criteria to define technical procedure success which include successful access delivery and retrieval, appropriate positioning of the prosthetic heart valve, freedom from death, and no surgery or interventions related to the prosthesis or procedure complications. The primary outcome was all-cause mortality at 1-year and 5-year follow up, and the secondary outcome was in-hospital death.

We used STATA software version 17 for the statistical analysis. We reported categorical variables as numbers and percentages, and the continuous variables as mean ± standard deviation (SD). Categorical variables were analyzed using Pearson's Chi-square or Fisher's exact tests. Continuous variables were analyzed using 2-sample t test or Mann-Whitney U test. *P* values were 2-sided and $P <$ .05 was considered. Multivariable cox regression analysis was conducted to identify variables associated with all-cause mortality at 1-year and 5-year follow up. We included all known variables that may affect mortality such as age, sex, diabetes, hypertension, and prior MI. The Mayo Clinic institutional review board approved the study with patients' consent waiver (ID 21-011977).

Result

Comparing moderate/severe MR vs mild/no MR

We included a total of 1,067 patients who underwent TAVR, 52 patients (4.88%) had moderate/severe MR, and 1,015 patients (95.12%) had mild/no MR. Table 1 summarizes the demographics and baseline patients characteristic of the 2 groups. Patients with moderate/severe MR were more likely to have prior myocardial infarction (38.5% vs 23.6%, P = .014) and end-stage renal disease (9.6% vs 3.3%, P = .016) compared to those with mild/no MR. On the other hand, they had less diabetes mellitus (19.2% vs 36.3%, P = .012) and were less likely to receive balloon-expandable aortic valve prosthesis (63.5% vs 79%, P = .009). Outcomes of the study are summarized in (Table 2). There was no significant difference between the moderate/severe MR and mild/no MR groups in procedure success rate, and in-hospital all-cause mortality. At 1-year follow up, there was no difference in mortality between both groups (15.4% vs 14.1%, P = 794) (Figure 1). However, at 5-year follow up all-cause mortality was higher in moderate/severe MR group compared to mild/no MR group (61.4% vs 49.5%, P = .046) (Figure 2). In multivariable cox regression analysis, moderate/severe MR was not associated with higher all-cause mortality at 1-year follow up (OR 0.88, 95% CI [0.39, 1.99], P = .761) (Table 3) or at 5-year follow up (OR 1.277, 95% CI [0.877, 1.86], P = .201) (Table 4).

Comparing moderate/severe TR vs mild/no TR

The baseline demographics and patient characteristics were summarized in (Table 5). The moderate/severe TR group included 86 patients (8%), and the mild/no TR

Table 1. Baseline characteristics of the study patients stratified according to MR severity

	Moderate or Severe MR (n = 52)	Mild or no MR (n = 1015)	*P*-value
Age, Y (mean ± SD)	80.5 ± 9.7	81 ± 8.5	.796
Male (%)	71.2	57.6	.054
White race (%)	94.2	97.1	**.001**
Smoking (%)	3.9	3	.713
Diabetes mellitus (%)	19.2	36.3	**.012**
Hypertension (%)	80.8	84.7	.441
MI (%)	38.5	23.6	**.014**
PCI (%)	48.1	34.5	**.045**
CABG (%)	36.5	26.7	.120
Prior stroke (%)	17.3	9.4	.059
PAD (%)	50	49.9	.983
Pacemaker/ICD (%)	28.9	15.1	**.008**
ESRD (%)	9.6	3.3	**.016**
Atrial fibrillation/flutter (%)	51.9	41.7	.144
Previous AV intervention (%)	41.2	15	< **.001**
Prior MV intervention (%)	0	1.8	.333
Prior TV intervention (%)	0	0	
Baseline echo parameters			
LV Ejection fraction (%) (mean ± SD)	43 ± 17	57 ± 12	< **.001**
AV area (cm^2) (mean ± SD)	1 ± 0.6	0.9 ± 0.4	.28
AV mean gradient (mmHg) (mean ± SD)	38 ± 17	43 ± 13	< **.001**
AV peak velocity (m/sec) (mean ± SD)	3.8 ± 0.8	4.2 ± 0.7	< **.001**
Aortic valve regurgitation			< **.001**
Trivial to mild (%)	39.1	56.5	
Mild to moderate (%)	13	11.8	
Moderate to severe or severe (%)	8.7	1.5	
Valve type			**.009**
Balloon-expandable (%)	63.5	79	
Self- expandable (%)	36.5	21	

AV, aortic valve; CABG, coronary artery bypass graft; ESRD, end stage renal disease; ICD, implantable cardioverter-defibrillator; LV, left ventricle; MI, myocardial infarction; MR, mitral regurgitation; MV, mitral valve; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TV, tricuspid valve.

Table 2. Outcomes of moderate/severe valvular regurgitation

	Moderate or Severe MR (n= 52)	Mild or no MR (n= 1015)	*P*-value
TAVR procedure Success (%)	100	97.8	.283
In-hospital all-cause mortality (%)	0	1.1	.450
1-year all-cause mortality (%)	15.4	14.1	.794
5-year all-cause mortality (%)	61.4	49.5	**.046**
	Moderate or Severe TR **(n = 86)**	Mild or no TR **(n = 985)**	*P*-value
TAVR procedure Success (%)	98.8	97.9	.543
In-hospital all-cause mortality (%)	0	1.1	.325
1-year all-cause mortality (%)	26.7	13.2	**.001**
5-year all-cause mortality (%)	68.3	48.7	< **.001**

MR, mitral regurgitation; TAVR, transcatheter aortic valve replacement; TR, tricuspid regurgitation.

group included 985 patients (92%), with a total of 1,071 patients. The mild/no TR group had a greater proportion of males (59.39% vs 45.35%, $P = .011$) compared to moderate/severe TR group. Patients with moderate/severe TR had lower incidence of diabetes mellitus (19.8% vs 36.8%, $P = .002$), and percutaneous coronary interventions (24.4% vs 35.9%, $P = .032$), but higher incidence of atrial fibrillation (80.2% vs 38.8%, $P < .001$), and prior mitral valve intervention (5.8% vs 1.4%, $P = .03$). There was no difference in procedural success rate or in-hospital all-cause mortality between both groups (Table 2). At 1-year follow up, all-cause mortality was significantly higher in moderate/severe TR group compared to mild/no TR group (26.7% vs 13.2%, $P = .001$) (Table 2, Figure 3). Same finding was noted with extended follow up at 5-years (68.3% vs 48.7%, $P < .001$) (Figure 2). In multivari-

Figure 1. Impact of moderate/severe mitral regurgitation in all-cause mortality during hospitalization and at 1-year follow up post TAVR.

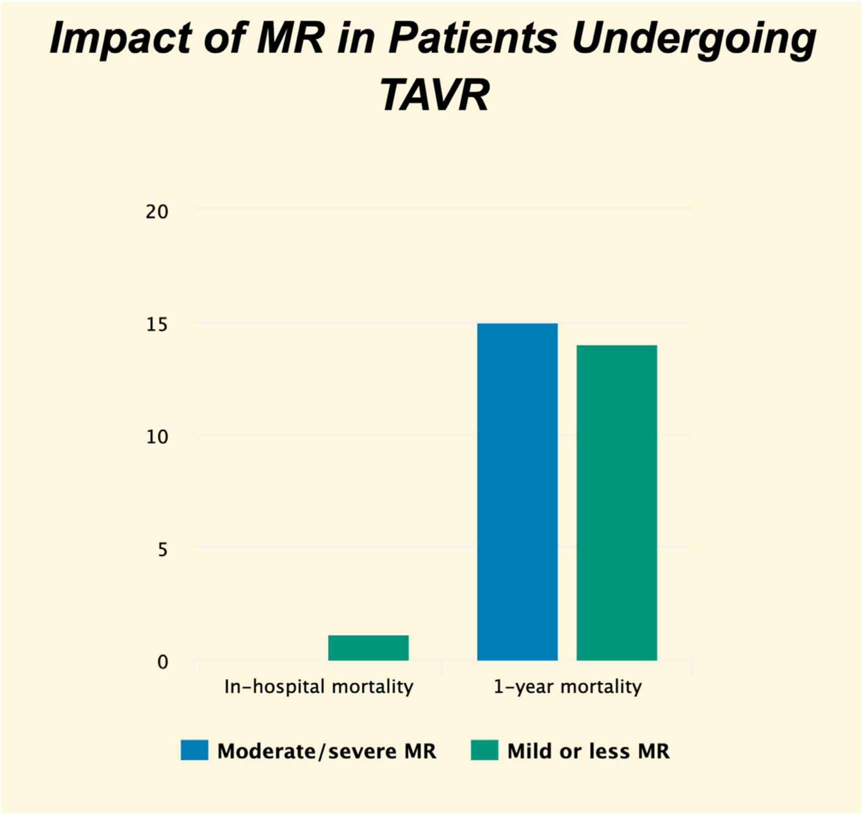


Table 3. Multivariable cox regression analysis in patients underwent TAVR at 1-year follow-up

	Odds ratio	Standard error	*P*-value	95% Confidence interval
Moderate/severe TR	**1.944607**	**0.5675503**	**.023**	**1.097492-3.44558**
Moderate/severe MR	0.880866	0.3675831	.761	0.3887815-1.995787
Gender	1.030002	0.2076312	.883	0.6938252-1.529065
Age	1.016118	0.0117927	.168	0.9932659-1.039496
Prior MV intervention	1.406484	0.850043	.573	0.4302195-4.598109
Hypertension	0.8124038	0.2149982	.432	0.4836221-1.364702
Diabetes mellitus	1.053106	0.208657	.794	0.714199-1.552833
ESRD	**4.505258**	**1.675088**	**< .001**	**2.173885-9.336898**
Prior MI	1.031806	0.2429494	.894	0.6503901-1.6369
Atrial fibrillation/flutter	**2.062502**	**0.413216**	**< .001**	**1.392703-3.054429**
Prior CABG	1.019374	0.2342097	.933	0.6497747-1.599205
Pacemaker/ICD	0.8736883	0.2215863	.594	0.5314634-1.436282
TAVR procedure success	**0.1817218**	**0.0847071**	**< .001**	**0.0728839-0.4530882**

CABG, coronary artery bypass graft; ESRD, end stage renal disease; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; MR, mitral regurgitation; MV, mitral valve; TAVR, transcatheter aortic valve replacement; TR, tricuspid regurgitations.

able cox regression analysis, moderate/severe TR was associated with higher all-cause mortality at 1-year follow up (OR 1.94, 95% CI [01.09, 3.44], $P = .023$) (Table 3) and at 5-year follow up (OR 1.46, 95% CI [1.092, 1.952], $P = .011$) (Table 4).

Combined moderate/severe MR and moderate/severe TR

We identified a small group of patients (n = 11) that had combined moderate/severe MR and moderate/severe TR. Patients with combined moderate to

Figure 2. Impact of moderate/severe tricuspid regurgitation in all-cause mortality during hospitalization and at 1-year follow up post TAVR.

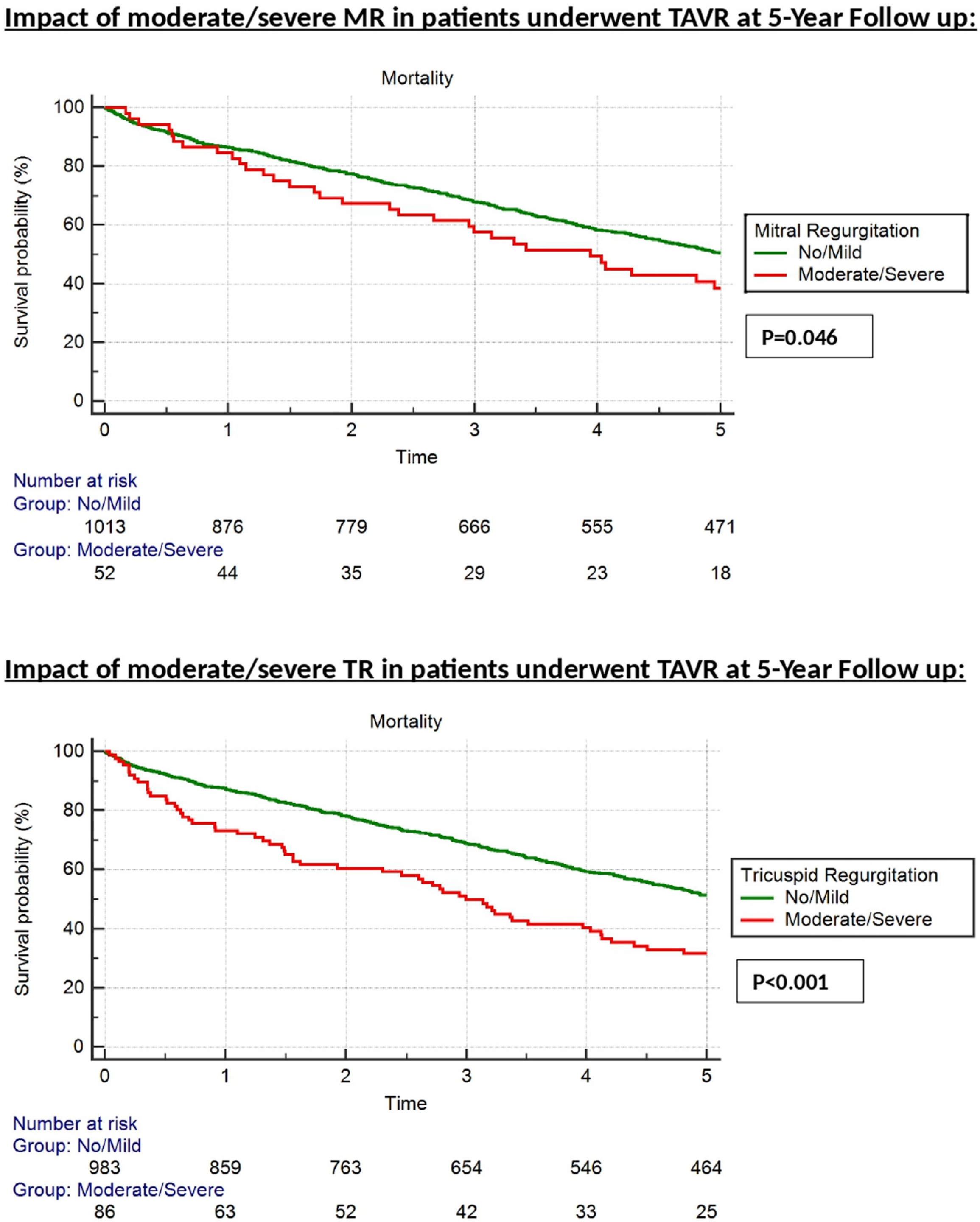


Table 4. Multivariable cox regression analysis in patients underwent TAVR at 5-year follow-up

	Odds ratio	*P*-value	95% Confidence interval
Moderate/severe TR	**1.460**	**.011**	**1.092-1.952**
Moderate/severe MR	1.277	.201	0.877-1.860
Gender	1.010	.914	0.837-1.220
Age	1.008	.154	0.997-1.020
Prior MV intervention	0.982	.959	0.499-1.934
Hypertension	0.962	.768	0.745-1.242
Diabetes mellitus	1.170	.100	0.970-1.410
ESRD	**2.623**	**< .001**	**1.754-3.923**
Prior MI	**1.243**	**.047**	**1.003-1.540**
Atrial fibrillation/flutter	**1.846**	**< .001**	**1.535-2.220**
Prior CABG	0.986	.901	0.795-1.224
Pacemaker/ICD	1.025	.827	0.820-1.281
TAVR procedure success	**0.487**	**.007**	**0.290-0.820**

TAVR, transcatheter aortic valve replacement; TR, tricuspid regurgitations; MR, mitral regurgitation; MV, mitral valve; ESRD, end stage renal disease; MI, myocardial infarction; CABG, coronary artery bypass graft; ICD, implantable cardioverter-defibrillator.

Table 5. Baseline characteristics of the study patients stratified according to TR severity

	Moderate or severe TR (n = 86)	Mild or no TR (n = 985)	*P*-value
Age, Y (mean ± SD)	81 ± 8.6	81 ± 8.6	.933
Male (%)	45.4	59.4	**.011**
White race (%)	97.7	97	.897
Smoking (%)	0	3.3	**.09**
Diabetes mellitus (%)	19.8	36.8	**.002**
Hypertension (%)	84.9	84.4	.899
MI (%)	20.9	24.5	.463
PCI (%)	24.4	35.9	**.032**
CABG (%)	29.1	26.9	.665
Prior stroke (%)	11.6	9.5	.531
PAD (%)	41.9	50.5	.126
Pacemaker/ICD (%)	30.2	14.4	**< .001**
ESRD (%)	2.3	3.8	.497
Atrial fibrillation/flutter (%)	80.2	38.8	**< .001**
Previous AV intervention (%)	26.7	15.4	**.006**
Prior MV intervention (%)	5.8	1.4	**.03**
Prior TV intervention (%)	0	0	
Baseline echo parameters			
LV Ejection fraction (%) (mean ± SD)	45 ± 17	55 ± 12	**< .001**
AV area (cm^2) (mean ± SD)	0.9 ± 0.5	0.9 ± 0.4	.28
AV mean gradient (mmHg) (mean ± SD)	39 ± 17	42 ± 13	**< .001**
AV peak velocity (m/sec) (mean ± SD)	3.9 ± 0.8	4.2 ± 0.7	**< .001**
Valve type			**.012**
Balloon-expandable	67.4	79.1	
Self-inflatable	32.6	20.9	

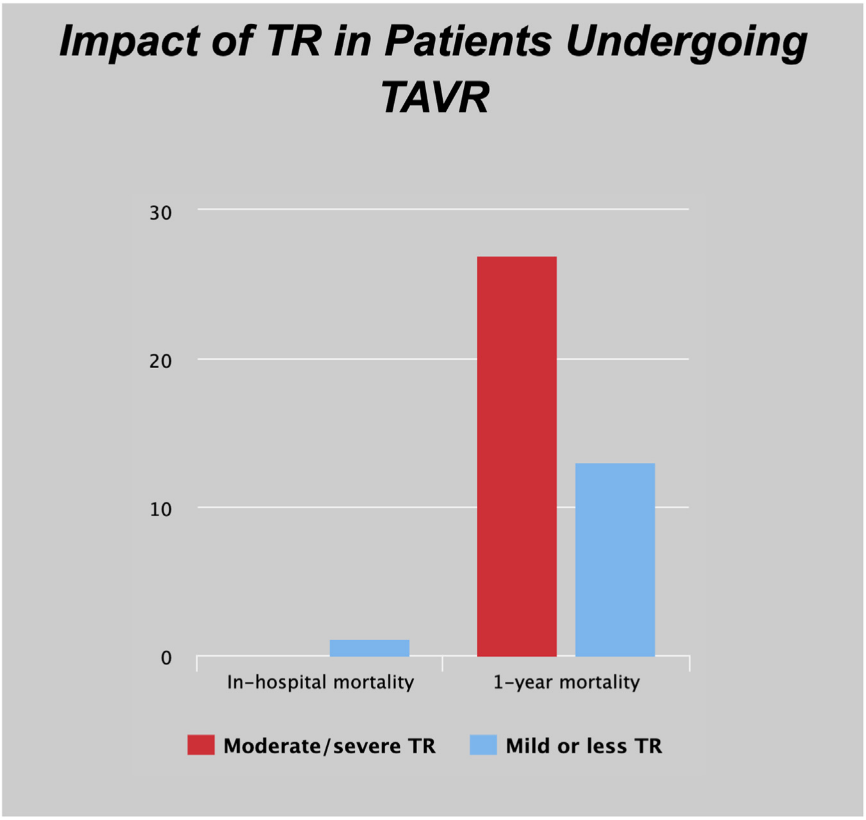
AV, aortic valve; CABG, Coronary artery bypass graft; ESRD, end stage renal disease; ICD, implantable cardioverter-defibrillator; LV, left ventricle; MI, myocardial infarction; MV, mitral valve; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TR, tricuspid regurgitation; TV, tricuspid valve.

severe MR and TR had significantly higher mortality (72.7%) compared to moderate/severe MR alone (58.5%), moderate/severe TR alone (67.7%), and mild/no valve involvement (48.3%) ($P < .001$) (Figure 4).

Discussion

Aortic stenosis is notably prevalent in the elderly population, as evidenced by a prospective study highlighting a notable rise in its incidence from 0.2% among individuals in their 50s to a significant 9.8% among those in their 80s.[13] The etiology of concomitant valvular dysfunction in patients with severe AS is frequent and often multifactorial. Significant aortic stenosis obstructs blood flow and reduces forward flow causing left ventricular pressure build-up, and subsequently elevated filling pressures in left ventricle and left atrium which in-turn causes pulmonary hypertension, right sided heart failure and significant functional MR and TR. In addition, cardiac remodeling induced by severe AS leads to functional MR.[14] Smoking, hypertension, diabetes, peripheral

Figure 3. Impact of moderate/severe MR and moderate/severe TR in patients underwent TAVR at 5-year follow up.



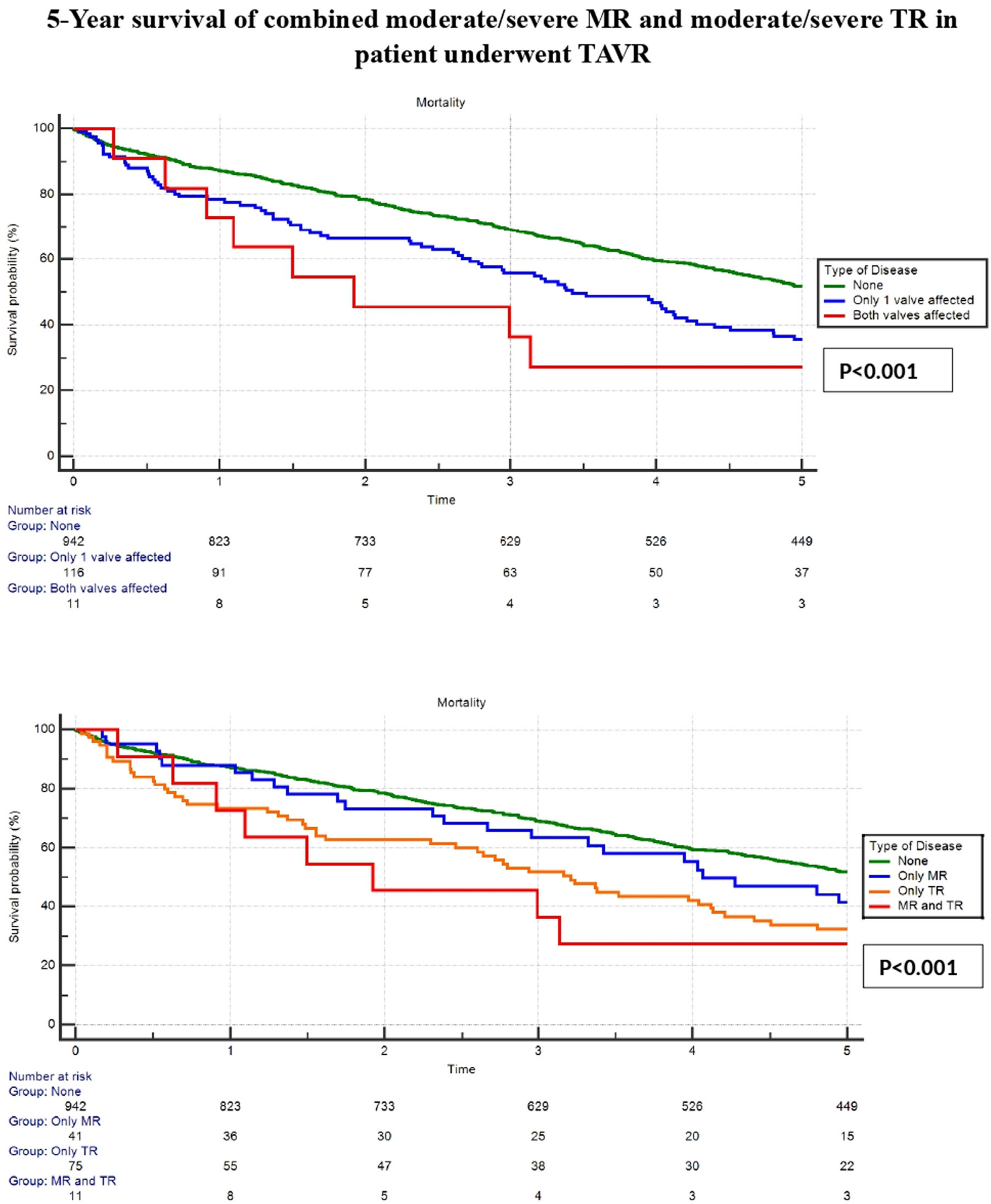
arterial diseases, and ESRD, significantly impact the progression of AS, MR, and TR. AS advances rapidly in individuals with ESRD due to increased metabolic and hemodynamic stress on the aortic valve, resulting in an accelerated disease course and a poorer prognosis even with mild-to-moderate AS in ESRD.[15] Current guidelines incorporate multiple factors in risk stratifying patients with severe AS such as: echocardiographic parameters, presence of AS-related symptoms, and multiple other comorbidities.[16] However, concomitant other valvular dysfunction was not one of the factors. Genereux et al.[17] proposed AS staging based on the extent of cardiac damage, giving moderate/severe MR stage 2 and moderate/severe TR stage 3. The higher the stage, the worse the prognosis after TAVR.

In this retrospective observational study, we investigated the impact of concomitant moderate/severe MR and TR in patients who underwent TAVR. In our cohort, 4.9% of the patients had concomitant moderate/severe MR and 8% had concomitant moderate/severe TR. The key findings of our analysis are summarized in the following:[1] Moderate to severe MR was not associated with higher mortality at follow up, however was associated with higher mortality at 5-year follow up;[2] Moderate/severe TR was associated with higher all-cause mortality at 1-year and 5-year follow up;[3] In multivariable cox regression analysis, moderate/severe TR was associated with higher mortality at 1-year and 5-year follow up, however, moderate/severe MR was not;[4] combined moderate/severe MR and moderate/severe TR had higher mortality compared to either valve alone or mild/no regurgitation.

Impact of moderate to severe MR

Data about prognostic significance of MR post TAVR is controversial. In our analysis, baseline significant MR was not associated with higher mortality either in-hospital or at 1-year follow up. At 5-year follow-up, moderate/severe MR was associated with higher mortality. However, in the multivariable cox regression analysis, moderate/severe MR was not an independent factor of mortality at 1-year or 5-year follow-up. TAVR may improve LV stroke volume and unload the LV, as result it may improve MR after the procedure. In 1 study, 59% of patients with significant MR regressed after TAVR.[18] In the SWEDEHEART registry, the persistence or worsening of significant MR was associated with higher mortality post TAVR. However, MR improvement post TAVR offset this effect.[19] In Baz et al.[20] persistent significant MR at 6-months post TAVR was an independent predictor of mortality at 2-years. However,

Figure 4. Five-year survival of combined moderate/severe MR and moderate/severe TR in patient underwent TAVR.



in our analysis we did not include transthoracic echo data post TAVR and at follow up.

Impact of moderate to severe TR

In our analysis, baseline moderate to severe TR was associated with 2-folds higher mortality at 1-year follow up and 1.5-folds higher mortality at 5-year follow up post TAVR procedure. In multivariable cox regression analysis, moderate/severe TR was recognized as independent factor of mortality at 1 and 5 years follow up. In other analysis, progression of mild or less to moderate or higher TR post TAVR was also associated with higher mortality at 2-year follow-up, likely related to worsening RV function and pulmonary hypertension.[21] In addition, previous meta-analyses had linked significant TR, RV dysfunction, and pulmonary hypertension with higher mortality and worse prognosis post TAVR.[22,23]

Multivariate analysis results

In the multivariate analysis, moderate/severe TR was an independent factor of mortality at 1 and 5 years follow up. However, the moderate/severe MR was not.

Impact of combined moderate/severe MR and moderate/severe TR

We identified a small group of patients (n = 11) that had baseline moderate/severe MR and moderate/severe TR. Despite, the small sample size, this group of patients had higher mortality and less survival in the long term follow up at 5-year. This was noted in comparison to patients with only 1 moderate/severe valve regurgitation (mitral or tricuspid) and/or mild/no valve regurgitation. As a result, a careful transthoracic echo assessment pre and post TAVR is warranted as it may affect patients' prognosis and risk stratification.

Limitations

Our study has few limitations, including those inherent to retrospective observational study design. In addition, dependence on the Mayo enterprise database adds further restrictions. Our data included patients from 2012 to 2018. There were multiple differences in the demographics and baseline patients' characteristics between the 2 arms of our study, which may affect the outcomes, but we conducted a multivariable cox regression analysis to correct for the differences and demonstrate the independent predictors of mortality at 1-year follow up post TAVR. Also, the data in the etiology of moderate to severe MR was not available.

Conclusion

Our study reveals that moderate or severe TR is associated with a significant increase in all-cause mortality at 1 and 5 years after TAVR. However, at the same period, moderate or severe MR did not demonstrate a significant association with mortality. Combined moderate/severe MR and TR had even worse mortality that either one alone. These findings emphasize the importance of thorough assessment and consideration of multivalvular disease in TAVR patients to optimize long-term outcomes. Future research should address these limitations to enhance treatment strategies and refine clinical decision-making.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Bishoy Abraham: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Mustafa Suppah:** Formal analysis, Data curation. **Juan Farina:** Formal analysis, Data curation. **Michael Botros:** Formal analysis, Data curation. **Ayman Fath:** Formal analysis, Data curation. **Sara Kaldas:** Formal analysis, Data curation. **Michael Megaly:** Writing – review & editing, Formal analysis. **Chieh-Ju Chao:** Writing – review & editing, Formal analysis. **Reza Arsanjani:** Writing – review & editing, Methodology. **Chadi Ayoub:** Writing – review & editing, Methodology. **F. David Fortuin:** Writing – review & editing, Methodology. **John Sweeney:** Writing – review & editing, Methodology. **Patricia Pellikka:** Writing – review & editing, Methodology. **Vuyisile Nkomo:** Writing – review & editing, Conceptualization. **Mohamad Alkhouli:** Writing – review & editing. **David Holmes Jr:** Writing – review & editing. **Amr Badr:** Formal analysis, Data curation. **Said Alsidawi:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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