The impact of percutaneous interatrial shunt closure

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Predictors of residual tricuspid regurgitation after percutaneous closure of atrial septal defect

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ABSTRACT

Aims: Functional tricuspid regurgitation (TR) associated with atrial septal defects (ASDs) is frequently present due to right-sided volume-overload. Tricuspid valve (TV) repair is often considered in candidates for surgical ASD closure, and percutaneous TV repair is currently under clinical investigation. In this study we develop a prediction model to identify patients with residual moderate/severe TR after percutaneous ASD closure.

Methods and results: In this observational study, 172 adult patients (26% male, age 49±17years) with successful percutaneous ASD closure had pre-and post-procedural echocardiography. Right heart dimensions/function were measured. TR was assessed semi-quantitatively. A prediction model for six-month post-procedural moderate/severe TR was derived from uni-and multivariable logistic regression. Clinical follow-up was updated and adverse events were defined as cardiovascular death or hospitalization for heart failure. Pre-procedural TR was present in 130(76%) patients (moderate/severe: n=64) of which 72(55%) had ≥1grade reduction post-closure. Independent predictors of post-procedural moderate/severe TR (n=36) were age ≥60y (OR=2.57;P=0.095), right atrial end-diastolic area ≥10cm2/m2 (OR=3.36;P=0.032), right ventricular systolic pressure ≥44mmHg (OR=6.44;P=0.001) and TAPSE ≤2.3cm (OR=3.29;P=0.037), producing a model with optimism-corrected C-index=0.82 (P<0.001). Sensitivity analysis excluding baseline ≤mild TR yielded similar results. Patients with moderate/severe TR at six-month follow-up had higher adverse event rates (hazard ratio=6.2[95%CI 1.5-26]; log-rank P=0.004) across a median of 45[30-76] months clinical follow-up.

Conclusion: This study shows that, parallel to reduction of volume-overload and reverse remodeling after percutaneous ASD closure, TR improved substantially despite significant TR at baseline. Our proposed risk model helps identify ASD patients in whom TR regression is unlikely after successful percutaneous closure.

INTRODUCTION

Secundum atrial septal defects (ASDs) are one of the most common adult congenital heart defects.[1] Functional tricuspid regurgitation (TR) can occur secondary to ASD-based volume-overload due to right heart- and tricuspid annular dilatation. Percutaneous ASD closure may improve functional TR by reverse remodeling and prevent further right heart deterioration from volume- and eventual pressure-overload.

Functional TR is the most prevalent tricuspid valve (TV) disease in the West and independently predicts cardiovascular morbidity and mortality,[1] especially if moderate/severe.[2-4] Following the recognition of the clinical relevance of functional TR, an active therapeutic strategy is currently advocated.[5-7] TV repair is considered in candidates for surgical ASD closure with annular diameter ≥40mm. However, current European[8] and American[9] guidelines recommend repair of functional TR as part of left-sided heart disease only, therefore management of ASD-based TR remains undetermined and simultaneous surgical ASD and TV repair is often performed.

Apart from a few studies reporting the frequency and risk factors of significant TR after ASD closure,[10,11] no risk stratification of moderate/severe TR at post-procedural follow-up exists for adult candidates of ASD closure. Our aim was to develop a clinical prediction model for the risk of persistent TR after percutaneous ASD closure to help identify patients in whom TR improvement may not occur.

METHODS

Study design

In this retrospective cohort study, all adult ASD patients from two university hospitals who underwent percutaneous closure were evaluated. The study cohort comprised consecutive patients who underwent successful percutaneous ASD closure (i.e. without device embolization/thrombosis or significant residual shunting) and who had transthoracic echocardiography (TTE) at baseline and at approximately six months follow-up (inclusion range of 3-18 months). Patient characteristics and echocardiographic studies were gathered from medical records, and clinical outcomes were updated from patient contact by telephone or alternatively gathered from the last medical follow-up. This study complies with the declaration of Helsinki and is in compliance with national legislation; each center's local medical ethical committee approved this study with a waiver and all patients provided informed consent.

ASD closure

The Grown-Up Congenital Heart disease (GUCH) heart team determined the indication for ASD closure according to recommendations of the current European guidelines, based on either hemodynamically significant left-to-right shunting with pulmonary vascular resistance <5 Woods units (Class I, level B) or suspicion of paradoxical embolism (Class IIa, level C).[12] Percutaneous ASD closure was performed under either general or local anesthesia and an Amplatzer Septal Occluder (St. Jude Medical, Minneapolis, MN, USA) of appropriate size was implanted. Post-procedural therapy included a six-month regimen of either dual antiplatelet therapy with aspirin 100mg and clopidogrel 75mg daily after a 600mg loading dose, or only aspirin 300mg daily, depending on the treating center's protocol.

Echocardiography

Two-dimensional transthoracic echocardiography was performed both at baseline and post-procedural follow-up as part of routine clinical outpatient visits. Echocardiographic views were acquired on a Vivid 7-9.5 (GE Healthcare, Horten, Norway) based on guideline recommendations,[13] and analyses were performed offline on EchoPAC PC v.201 (GE Healthcare, Horten, Norway). Right atrial (RA) and ventricular (RV) dimensions and maximal tricuspid annular diameter were obtained from the apical four-chamber view, and RV systolic function was assessed by fractional area change, tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular systolic motion velocity. Tricuspid regurgitation was semi-quantitatively scored based on valve morphology, visual assessment of color-flow TR jet, vena contracta width, shape and intensity of the continuous wave Doppler TR jet signal, and hepatic venous flow pattern.[14] In the absence of inferior vena cava measurements (n=64 baseline, n=54 follow-up), right atrial pressure was estimated at 8mmHg when RA area>18cm^2 and 3mmHg if smaller.[15] Peak TR jet velocity was obtained from multiple Doppler views, and right ventricular systolic pressure was calculated using the modified Bernoulli equation.[16]

Definition of outcomes

The main outcome measure of this study was moderate/severe TR on echocardiography at six-month post-procedural follow-up. Secondly, to assess the predictive value of the tricuspid valve severity on clinical outcome, all patients were contacted by telephone to update clinical information and assess symptomatology between June-November 2017. An adverse clinical event was defined as the composite of cardiovascular death or hospitalization for heart failure. All deaths were marked cardiovascular unless an

unequivocal non-cardiac cause could be established. Heart failure hospitalization was defined as hospital admission of ≥12 hours for worsening heart failure symptoms that required parenteral therapy. Time-to-event was time to first event, whichever came first. In addition, symptoms of dyspnea, peripheral edema, chest pain, palpitations, dizziness, syncope and fatigue were assessed at latest clinical follow-up.

Statistical analysis

Analyses were performed on R v.3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS v.23 (IBM Corp., Armonk, NY, USA). Baseline characteristics, hemodynamics and pulmonary function parameters are presented as mean ± standard deviation, median [25^{th}-75^{th} percentile], or frequency (percentage) according to variable type and distribution. The two-tailed paired- and independent t-tests were used for paired resp. between-group testing in continuous variables. Categorical variables were compared using the Chi-square test and the McNemar test in independent resp. paired testing. Correlations were linearly tested unless mentioned otherwise. A $P<0.05$ was considered statistically significant.

Two investigators (MN and MA), blinded to patient information and clinical outcome, assessed TR severity in 60 randomly selected cases. Inter-observer agreement was then analyzed using Cohen's kappa for TR grading.

Univariable logistic regression analyses were used to identify determinants of moderate/severe TR at post-procedural follow-up. Candidate risk factors were clinically relevant patient and ASD characteristics, and baseline echocardiographic parameters that statistically differed between the outcome and the non-outcome group. Continuous variables were dichotomized using the Youden index to facilitate potential use of this prediction model in clinical practice.

Variables with $P\leq0.10$ in univariable analysis were initially incorporated in three multivariable analyses; one with only clinical variables, another with additional echocardiographic parameters, and the third from a backward selection in which variables with $P<0.10$ by the Wald statistic were identified. The discriminative value of these models was compared using the C-index, Akaike Information Criterion, Net Reclassification Improvement and Integrated Discrimination Improvement.[17] The final model was defined as the simplest and highest discriminative model of these. Sensitivity analysis excluding patients with ≤mild TR was performed to validate the model specifically in patients with moderate/severe TR at baseline. Proportional to

their odds ratio (OR), independent predictors in the final model were assigned scores in which a higher cumulative score indicated higher estimated risk of moderate/severe TR at six-month follow-up.

Adverse event rates were based on Kaplan-Meier estimates in time-to-event analyses with a landmark at six months post-closure. Follow-up of patients was censored at the time of last telephone contact or, if not available, at the last medical contact. For time-to-event analyses between patients with and without moderate/severe TR at follow-up, the hazard ratio was determined by Cox regression analysis and Kaplan-Meier curves were compared using the log-rank test.

RESULTS

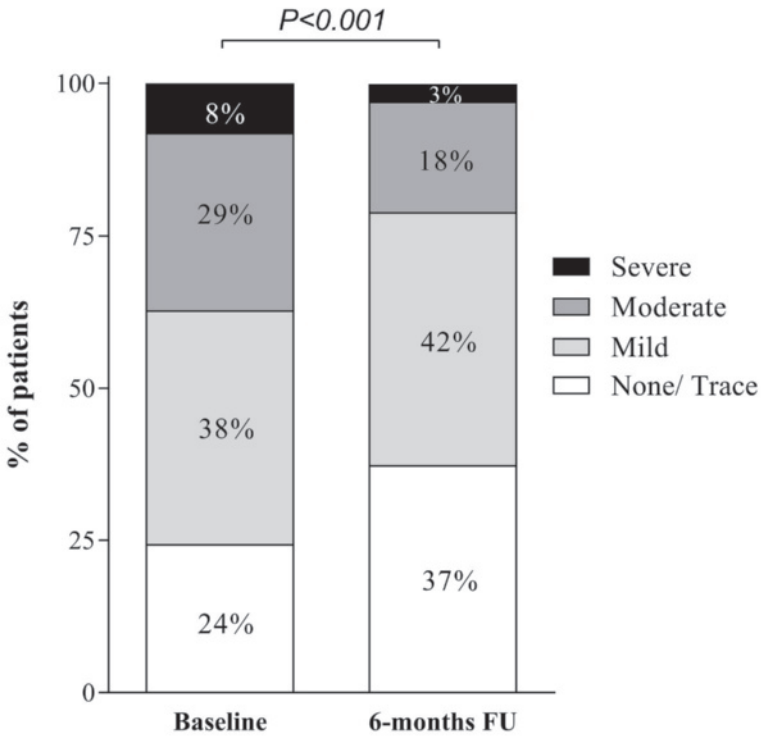
Study population

The total cohort consisted of 202 adult patients (see *Suppl. Figure 1*), of which 172 patients (74% female, mean age 49±17 years, range 18-84 years) were included in this study for having complete baseline (median 4.0[2.0-7.0] months before closure) and follow-up echocardiograms (median 6.0[5.0-7.0] months after closure). The indication for ASD closure was hemodynamically significant left-to-right shunting in 83%- and paradoxical embolism in 17% of patients. Patient characteristics and ASD-related measurements are shown in *Table 1*, and baseline cardiac medication is listed in *Suppl. Table 1*.

TR and reverse remodeling

At baseline, 130(76%) patients had ≥mild TR (see *Figure 1A*) and of these, 72(55%) patients experienced ≥1 TR grade reduction at post-procedural follow-up. Of the 64 patients who had moderate/severe TR at baseline, 34(53%) patients improved to none/mild at follow-up (see *Figure 1B*). Six patients were classified from baseline mild TR to post-procedural moderate TR, thus 36 patients eventually had moderate/severe TR at six-month post-procedural follow-up. Mild residual shunting was present in three patients (n=2 with none/mild TR), one of which had a small second ASD not intended for closure. The inter-observer variability in TR severity assessment yielded a very good agreement (n=56 out of n=60) with Cohen's kappa= 0.830 (95%CI 0.669-0.991), P<0.001.

A



B

		TR grade at 6-month FU				
N		None/trace	Mild	Moderate	Severe	Total
Baseline TR grade	None/trace	27	14	1	0	42
	Mild	33	28	5	0	66
	Moderate	3	24	20	3	50
	Severe	2	5	5	2	14
Total		65	71	31	5	172

Figure 1. Pre-and post-closure tricuspid regurgitation. Pre- and post-procedural tricuspid regurgitation grades in percentages (**A**) and number of patients (**B**). Percentages may not sum to 100% due to rounding. FU= follow-up; TR= tricuspid regurgitation.

Table 1. Baseline patient characteristics.

	n=172
Demographics	
Age, y	49 ±17
Female	128 (74)
BSA, m2	1.8 ±0.2
Medical history	
Hypertension	58 (34)
Dyslipidemia	34 (20)
Diabetes mellitus	13 (8)
Coronary intervention	4 (2)
Cerebrovascular accident	29 (17)
Atrial arrhythmia	40 (23)
Paroxysmal atrial fibrillation	27 (16)
Persistent atrial fibrillation	10 (6)
Atrial flutter	3 (2)
Pulmonary hypertension*	14 (8)
Right ventricular systolic pressure, mmHg	37 ±12
Symptoms	
Palpitations	50 (29)
NYHA class I	87 (52)
NYHA class II	59 (34)
NYHA class III	22 (13)
NYHA class unknown	4 (2)
ASD-related characteristics	
TEE max. defect size, mm (n=161)	19 ±7.5
Device size, mm	21 ±7.3
Qp:Qs ratio†	1.9 ±0.6

Data are presented as mean ± SD or frequencies (%). BSA=Body surface area; NYHA= New York Heart Association; TEE= transesophageal echocardiography; Qp:Qs= pulmonary to systemic flow ratio.
** Right ventricular systolic pressure ≥50mmHg by TTE.[15]*
† By echocardiography or CMR (n=74).

The echocardiographic parameters of reverse remodeling are given in *Table 2*. Overall, RA and RV dimensions and RV systolic pressure regressed, even more significantly in patients with baseline moderate/severe TR, possibly explained by larger right-sided dimensions and a higher RV systolic pressure at baseline. Right ventricular systolic function parameters RV fractional area change and TAPSE significantly reduced after closure, which reflect the volume-load dependency of these variables together with the volume reduction that results from the shunt closure. Left ventricular ejection fraction was ≥50% in all patients and remained unchanged after closure.

Table 2. Baseline and post-procedural change in hemodynamic parameters stratified to TR severity at baseline.

	None/ mild TR				Moderate/ severe TR				P-value*
	n	baseline	Δ (%)	P-value (paired)	n	baseline	Δ (%)	P-value (paired)	
Chamber dimensions									
RA end-systolic area, cm2/m2	106	12 ±3.6	-16 ±27	<0.001	61	16 ±6.1†	-26 ±17	<0.001	0.006
RA end-diastolic area, cm2/m2	106	7.5 ±3.0	-14±35	<0.001	61	11 ±5.9†	-24 ±19	<0.001	0.04
RV end-systolic basal diameter, cm	107	3.8 ±0.8	-3 ±38	0.05	62	4.0 ±0.7	-2 ±50	0.46	0.92
RV end-systolic length, cm	107	6.3 ±1.0	0.5 ±19	0.54	62	6.2 ±0.7	-1 ±17	0.36	0.60
RV end-systolic area, cm2	107	19 ±6.2	-10 ±29	<0.001	62	20 ±5.0	-16 ±27	<0.001	0.24
RV end-diastolic basal diameter, cm	107	4.3 ±1.0	-14 ±16	<0.001	62	4.4 ±0.9	-12 ±12	<0.001	0.54
RV end-diastolic length, cm	107	8.1 ±1.1	-3 ±18	0.02	62	7.8 ±0.9	-5 ±16	0.004	0.54
RV end-diastolic area, cm2	107	31 ±9.2	-18 ±23	<0.001	62	32 ±6.3	-26 ±16	<0.001	0.009
Tricuspid valve									
TV annular diameter, cm	108	3.7 ±0.7	-8 ±17	<0.001	64	3.9 ±0.6	-11 ±13	<0.001	0.28
Vena contracta, mm	108	2.1 ±1.5	-12 ±84	0.21	64	5.1 ±0.02†	-21 ±61	<0.001	0.003
RV systolic pressure, mmHg	81	32 ±8.5	-2 ±42	0.01	62	44 ±13†	-15 ±21	<0.001	0.03
Right ventricular systolic function									
RV fractional area change, %	107	38 ±14	-13 ±47	0.005	62	38 ±15	-16 ±62	0.01	0.73
TAPSE, cm	93	2.8 ±0.5	-6 ±21	<0.001	50	2.6 ±0.06‡	-6 ±23	0.01	1.00
RV S´, cm/s	36	14 ±3.0	-5 ±15	0.08	21	17 ±0.2	-14 ±27	0.26	0.24

Data are presented as mean±SD of both absolute values (baseline) and percentages (delta of post-versus pre-procedural values). RA= right atrial; ES= end-systolic; ED= end-diastolic; RV= right ventricular; TV= tricuspid valve; TR=tricuspid regurgitation; TAPSE= Tricuspid annular plane systolic excursion; RV S'=Tricuspid annular systolic motion velocity.

** Comparison of percentage change stratified by baseline TR severity.*

† P<0.001; ‡ P<0.05; for all comparisons of baseline value stratified by TR severity.

Tricuspid annular diameter showed modest association with TR grade, both at baseline and at follow-up (r=0.32 resp. r=0.37; P<0.001), see *Suppl. Figure 2*. Tricuspid annular diameter reduction was more significant in patients who had ≥1 TR grade improvement (Δ-13±13% vs. Δ-8±16%; P=0.018).

Predictors of post-procedural TR

Univariable predictors of moderate/severe TR at post-procedural follow-up are shown in *Table 3*. After comparing three multivariable models (see *Suppl. Table 2*), the final model included age ≥60 years (OR 2.57; P=0.10), RA end-diastolic area index ≥10cm2/m2 (OR 3.36; P=0.03), RV systolic pressure ≥44mmHg (OR 6.44; P=0.001) and TAPSE ≤2.3cm (OR 3.29; P=0.04) as independent predictors. This model was statistically significant (χ2[4]=35.57; P<0.001), and correctly classified 82% of cases by internal validation (C-index=0.85 [95%CI 0.76-0.93]; P<0.001). In a sensitivity analysis including only patients with baseline moderate/severe TR (n=64), this model remained significantly predictive of residual moderate/severe TR (C-index=0.72 [95%CI 0.58-0.86]; P=0.008). *Figure 2* shows a simplified risk stratification using OR-based risk score, along with corresponding predicted and observed rate of moderate/severe TR at six-month follow-up. A risk score of ≥4 yielded a predicted probability of ≥75% for moderate/severe TR at FU, see *Figure 2B*. In patients with a risk score of ≥4 (n=12), 9 patients (75%) actually had moderate/severe TR at post-procedural FU.

Clinical outcomes

The median clinical post-procedural follow-up duration was 45[30-76] months (range 9-146 months). Six patients died during follow-up; three in each outcome group, i.e. with and without moderate/severe TR at six-months follow-up, and in each two cardiovascular deaths occurred. One patient died of ovarian carcinoma (outcome group) and another of bladder cancer (non-outcome group).

Between June-November 2017, 155(93%) of the surviving patients could be contacted by telephone to update clinical follow-up. The unavailable patients had a median follow-up of 33[24-54] months. Patients with moderate/severe TR at follow-up had significantly higher adverse event rates (see *Figure 3*) with a hazard ratio of 6.2 (95%CI 1.5-26) and log-rank P=0.004. This was mainly driven by a higher rate of heart failure hospitalizations (n=3 in outcome group, n=1 in non-outcome group).

Table 3. Uni- and multivariable logistic regression for moderate/severe tricuspid regurgitation at follow-up.

	Variable present	Variable absent	Univariable			Multivariable		
			OR	95%CI	P-value	OR	95%CI	P-value
Patient characteristics								
Age at closure ≥60 years	**38%** (19/50)	**14%** (17/122)	3.8	1.8-8.2	0.001	2.6	0.9-7.6	0.10
Female gender	**23%** (30/128)	**14%** (6/44)	1.9	0.8-5.0	0.17			
Hypertension	**29%** (17/58)	**17%** (19/114)	2.1	1.0-4.4	0.06			
Atrial arrhythmia	**38%** (15/40)	**16%** (21/132)	3.2	1.4-7.0	0.004			
NYHA class ≥III	**45%** (10/22)	**17%** (26/150)	4.0	1.6-10.2	0.004			
ASD characteristics								
TEE max. defect size ≥24 mm	**29%** (12/41)	**19%** (23/120)	1.8	0.8-3.9	0.18			
Device size ≥26 mm	**29%** (13/45)	**18%** (23/127)	1.8	0.8-4.0	0.14			
Qp:Qs ratio ≥2.3	**26%** (5/19)	**16%** (9/55)	1.8	0.5-6.3	0.34			
Baseline echocardiography								
RA ES area ≥15 cm2/m2	**35%** (18/51)	**15%** (17/116)	3.2	1.5-6.9	<0.001			
RA ED area ≥10 cm2/m2	**45%** (19/42)	**13%** (16/125)	5.7	2.5-12.6	<0.001	3.4	1.1-10.1	0.03
RV ES basal diameter ≥4 cm	**31%** (23/75)	**13%** (12/94)	3.0	1.4-6.6	0.005			
RV ED basal diameter ≥5 cm	**30%** (10/33)	**18%** (25/136)	1.9	0.8-4.6	0.13			
TV annular diameter ≥4 cm	**36%** (20/55)	**14%** (16/117)	3.6	1.7-7.7	0.001			
Vena contracta ≥5 mm	**50%** (20/40)	**12%** (16/132)	7.7	3.4-17.6	<0.001			
RV systolic pressure ≥44 mmHg	**54%** (20/37)	**14%** (15/106)	7.1	3.1-16.6	<0.001	6.4	2.1-19.7	0.001
RV fractional area change ≤30%	**25%** (8/32)	**20%** (27/137)	1.4	0.6-3.4	0.51			
TAPSE ≤2.3 cm	**35%** (13/37)	**15%** (16/106)	3.1	1.3-7.2	0.01	3.3	1.1-10.1	0.04

Data are presented as frequencies (%). Cut-off values correspond to the 75th percentile. Abbreviations as in Table 1.

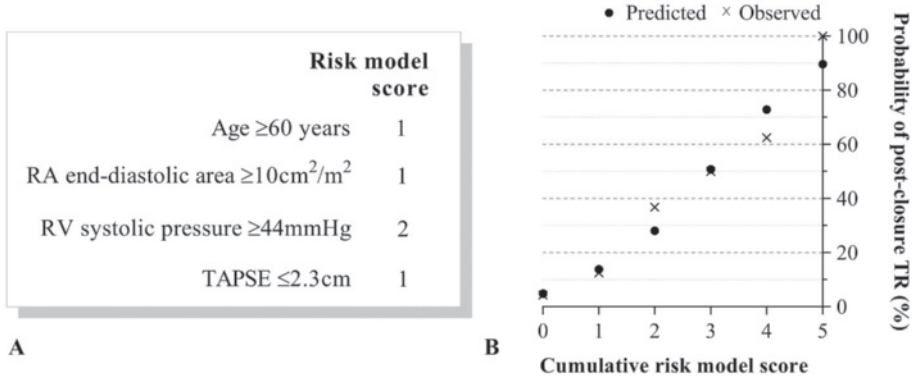


Figure 2. Prediction model for moderate/severe TR after percutaneous ASD closure in adults. (**A**) Risk model scores per independent predictor, weighted according to respective odds ratios. (**B**) Plotted cumulative risk score against predicted and observed probability of moderate/severe TR six months after ASD closure. A higher cumulative risk score (range 0-5) indicated a higher predicted probability (5%, 14%, 29%, 52%, 75% resp. 90%) and showed a higher observed rate (4%, 13%, 37%, 50%, 63% resp. 100%) of post-closure moderate/severe TR; C-index=0.85 (95%CI 0.76-0.93), P<0.001. Abbreviations as in *Table 1*.

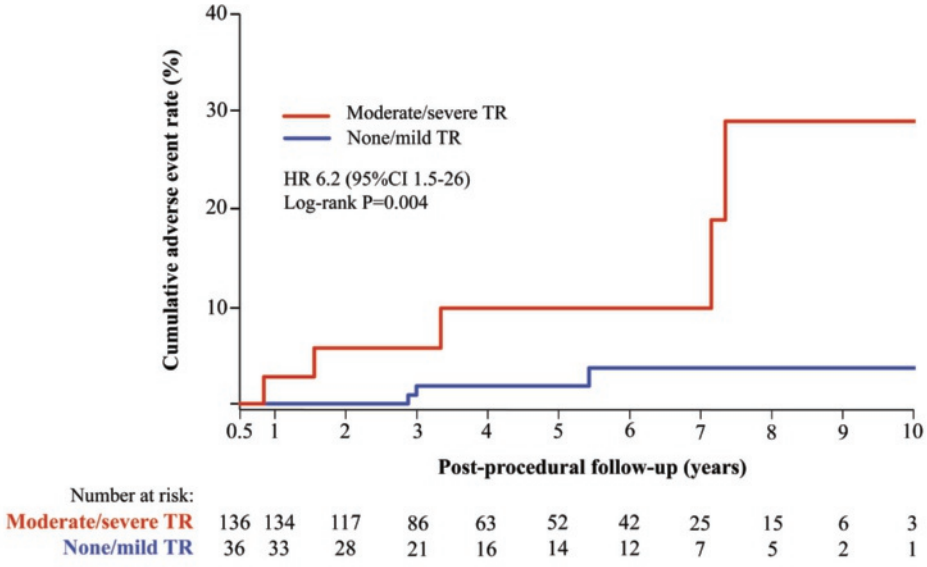


Figure 3. Adverse event rate during post-procedural follow-up. Event rates of cardiovascular mortality or hospitalization for heart failure in patients with none/mild and moderate/severe TR, with a landmark at six-month post-procedural follow-up.

Symptoms at latest clinical follow-up are shown in *Table 4*. Patients with persistent moderate/severe TR had more symptoms of dyspnea and peripheral edema than patients in whom TR had reduced to none/mild (30% vs. 16% resp. 41% vs. 16%). The latter were comparable to patients who maintained none/mild TR (15% resp. 20%). Regardless of TR severity at follow-up, palpitations and fatigue were the most frequently reported symptoms post-closure.

DISCUSSION

This study is the first to propose a clinical prediction model for residual TR after successful percutaneous ASD closure in adults. Age ≥60 years, RA end-diastolic area index ≥10cm2/m2, RV systolic pressure ≥44mmHg and TAPSE ≤2.3cm each independently predicted moderate/severe TR at six-month post-procedural follow-up, and together yielded a highly predictive model. Patients with persistent significant TR at six-month post-closure had a higher adverse event rate during long-term follow-up.

Table 4. Patient symptoms at latest clinical follow-up.

	Moderate/severe TR before and after closure	Moderate/severe TR reduced to none/mild TR	None/mild TR before and after closure
	n=27	n=32	n=101
Dyspnea	8 (30)	5 (16)	15 (15)
Peripheral edema	11 (41)	5 (16)*	20 (20)
Chest pain	2 (7)	0 (0)	6 (6)
Palpitations	12 (44)	16 (50)	42 (42)
Dizziness	9 (33)	7 (22)	32 (32)
Syncope	3 (11)	2 (6)	5 (5)
Fatigue	9 (33)	10 (31)	31 (31)

*Data are presented as frequencies (%) of surviving patients' reported symptoms at median 45[30-76] months post-procedural follow-up. * P<0.05 for moderate/severe TR that persisted vs. reduced to none/mild TR.*

TR and reverse remodeling

Functional TR in patients with ASD and left-to-right shunting is mainly the result of RV dilatation and free wall stretch causing both tricuspid annular dilatation as well as leaflet malcoaptation and tethering.[6,18] Atrial tachyarrhythmia and/or increased pulmonary artery pressures contribute to this pathophysiology. In turn, functional TR can further contribute to RA and RV dilatation irrespective of pulmonary artery pressure.[19]

In line with previous studies,[10,11,20] our study reports significant TR reduction at six-month follow-up post ASD closure despite significant TR at baseline. Successful closure unloads the right heart and initiates a reduction of right heart dimensions, occurring mostly within one-month post-closure[21] followed by slow additional improvement up to six to 24 months.[4,22] Our observed improvement of functional TR was parallel to significant reduction of the tricuspid annulus diameter and RV reverse remodeling. In line with previous studies,[20,23] post-procedural decrease in RV systolic pressure (RVSP) also contributed to TR improvement and took place even in patients with mildly elevated pulmonary pressures. Six patients had increase from baseline none/trace to post-procedural moderate TR. Fang et al.[10] reported similar observations and suggested a mechanical influence of the ASD occluder.

Predictors of post-procedural TR

Despite general TR improvement after ASD closure, persistent moderate/severe TR was observed in 30/64(47%) patients, consistent with previous reports.[10,11] The predicted probability of post-closure moderate/severe TR was translated into a more practical 6-point cumulative risk score which performed satisfactorily in all risk strata (see *Figure 2*). For example, patients with the highest cumulative score (≥4) had a predicted and observed probability of 75% for post-closure moderate/severe TR.

In line with our findings, most studies investigating ASD-based TR agree that in a subgroup of patients with significantly elevated RVSP, post-closure TR regression is less likely.[11,20,24] Toyono et al.[11] even recommend TV repair to be considered in all ASD patients with concomitant pulmonary hypertension. Rather than maintaining TR intrinsically, elevated RVSP provokes RV dysfunction by pressure-overload[22,24-26] causing leaflet tethering and further annular dilatation.[6,18,27] Leaflet tethering is therefore expected to be a stronger predictor than RVSP, which Fang et al.[10] demonstrated indeed. Although TV geometry assessment is an appealing approach to predict post-closure TR, this is difficult to measure from 2D echocardiographic images,[18] and high-quality 3D echocardiographic techniques were yet unavailable when most of this patient cohort underwent ASD closure.

Older age increases the risk of atrial fibrillation among others, and RA dilatation cannot be seen separately from atrial arrhythmia; it induces atrial arrhythmia and vice versa.[18,28] Therefore, we found a strong collinearity between the presence of atrial arrhythmia and both age and end-diastolic RA size, which explains its exclusion from our model. Older age is also associated with higher pulmonary artery pressure,[20] yet

although the latter is the strongest predictor in our model, age does independently contribute to significant TR since it remained significant in the multivariable model.

Atrial fibrillation and NYHA class, which are previously reported predictors of moderate/severe TR,[4] were eliminated in the final multivariable model because of strong associations with RA size and TAPSE respectively. Exclusion of these clinical variables provided a higher discrimination in our final model based on the optimism-corrected C-index and Akaike Information Criterion (see *Suppl. Table 2*). Although it can be argued that a model comprising only clinical variables would facilitate its use in daily practice, such a model also lowers its discriminative properties (see *Suppl. Table 2*) compared to the combination of age with echocardiographic parameters that are still routinely collected in candidates for ASD closure.

Clinical implications

ASD patients are at high risk of functional TR, therefore it is essential not to overlook the improvement of TR as an important target of ASD closure. TR regression is however not guaranteed in all patients, which prevents it from being an indication for ASD closure itself. Our predictive model may help in identifying patients in whom TR may remain after successful percutaneous ASD closure. Among other factors such as anatomical suitability, the likelihood of moderate/severe TR to persist after ASD closure should be considered by the interventional heart-team when deciding between surgical and percutaneous ASD closure. The debate as to whether a high likelihood of moderate/severe TR post ASD closure justifies that surgical closure be favored over percutaneous closure merely to facilitate simultaneous TV repair, is far from being settled.[29] The optimal strategy has yet to be explored in future studies, particularly in light of the rapidly evolving less-invasive percutaneous TV repair techniques which currently show promising results.[30,31]

Limitations

This study has a retrospective design, therefore we cannot account for all potential confounders in our prediction model despite multivariable analysis. Given the relatively low frequency of moderate/severe TR even with our multicenter data, predictors' regression coefficients may be overestimated even after optimism-correction. The limited number of adverse clinical events did not allow for additional multivariable analysis. Our study did not validate our prediction model in a second patient cohort so future studies are needed to externally validate our model. Finally, echocardiographic follow-up duration was limited to six months, however as shown in previous studies,[4,21]

the largest reverse remodeling and consequent TR change occurs within six months post-closure.

CONCLUSIONS

This study is the first to provide a practical prediction model for the risk of residual TR after percutaneous ASD closure. TR significantly improved in some patients despite significant TR at baseline, and moderate/severe TR post-closure is best predicted by the combination of age, RA size, RV systolic pressure and the extent of RV dysfunction. This model may help identify a subgroup of patients in whom TR regression after ASD closure is unlikely.

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SUPPLEMENTARY DATA

Suppl. Table 1. Cardiac medication at baseline.

	n=172
Diuretics	
Hydrochloorthiazide	6 (3)
Furosemide	12 (7)
Spironolacton	6 (3)
Bumetanide	6 (3)
β-blocking agents	
Metoprolol	18 (10)
Bisoprolol	6 (3)
Propranolol	1 (1)
Nebivolol	2 (1)
Atenolol	2 (1)
Calcium channel blockers	
Verapamil	3 (2)
Amlodipine	4 (2)
Nifedipine	2 (1)
Barnidipine	1 (1)
Renin-angiotensin system agents	
Perindopril	6 (3)
Lisinopril	6 (3)
Enalapril	3 (2)
Fosinopril	1 (1)
Irbesartan	3 (2)
Candesartan	2 (1)
Losartan	1 (1)
Antiarrhythmics	
Sotalol	5 (3)
Amiodaron	2 (1)
Digoxin	6 (3)
Flecainide	2 (1)
Anticoagulation	
Acenocoumarol	15 (9)
Fenprocoumon	5 (3)
Rivaroxaban	1 (1)
Dabigatran	2 (1)

Data are presented as frequencies (%). Medication remained unchanged at six-month post-closure follow-up.

Suppl. Table 2. Comparison of three prediction models for moderate/severe TR at six-month follow-up.

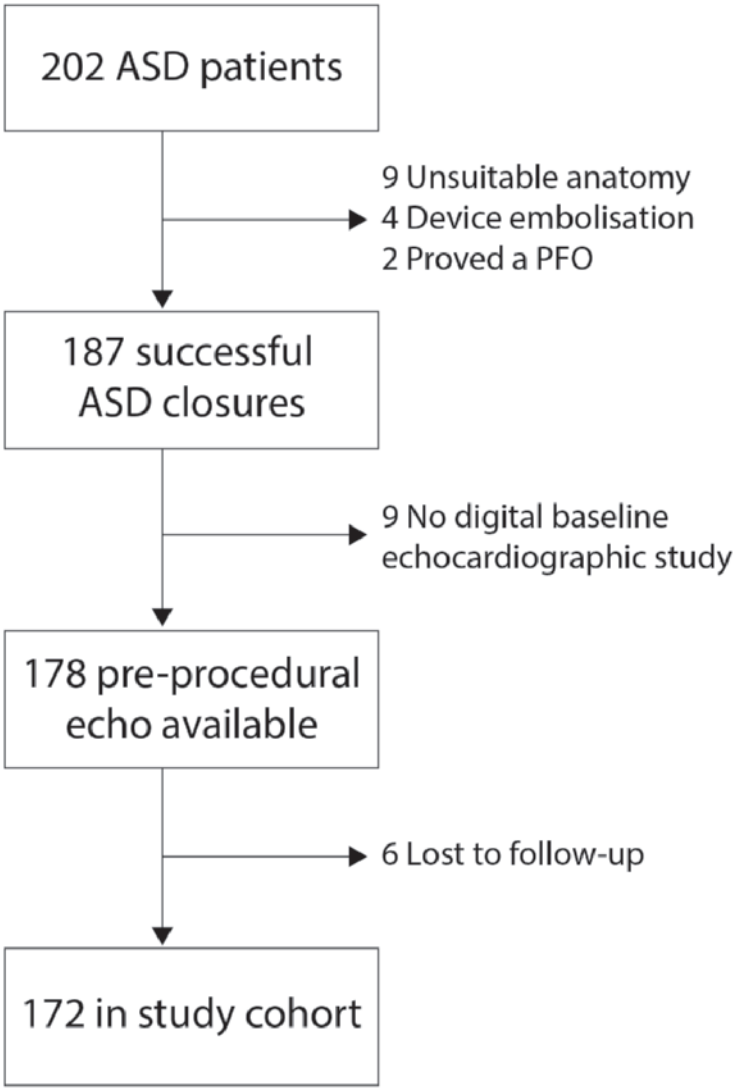
	Model containing only clinical variables			Model of both clinical and echocardiographic variables			Final simplified model of clinical and echocardiographic variables		
	n=172			n=119			n=119		
Model predictors	**B**	**SE**	**P-value**	**B**	**SE**	**P-value**	**B**	**SE**	**P-value**
Age ≥60 years	0.871	0.439	0.048	0.888	0.583	0.128	0.942	0.564	0.095
Atrial arrhythmia	0.796	0.451	0.078	0.229	0.702	0.744			
NYHA class ≥III	1.096	.515	0.033	0.216	0.756	0.775			
RAEDA≥10cm2/m2				1.096	0.646	0.090	1.212	0.564	0.032
RVSP ≥44 mmHg				1.779	0.620	0.004	1.863	0.572	0.001
TAPSE ≤2.3 cm				1.164	0.578	0.044	1.192	0.572	0.037
Model properties									
C- index		0.707			0.846			0.845	
Optimism-corrected C-index*		0.690			0.803			0.820	
Nagelkerke's R^2		0.160			0.395			0.393	
Hosmer-Lemeshow		0.999			0.980			0.991	
Model comparison									
Akaike Information Criterion		166			106			102	
Net Reclassification Improvement†		Reference			0.310; P<0.001			0.310; P<0.001	
Integrated Discrimination Improvement‡		Reference			0.167; P<0.001			0.165; P<0.001	

B= Regression coefficient; SE= Standard error; NYHA= New York Heart Association; RAEDA= Right atrial end-diastolic area in cm2/m2; RVSP= Right ventricular systolic pressure; TAPSE= Tricuspid annular plane systolic excursion.

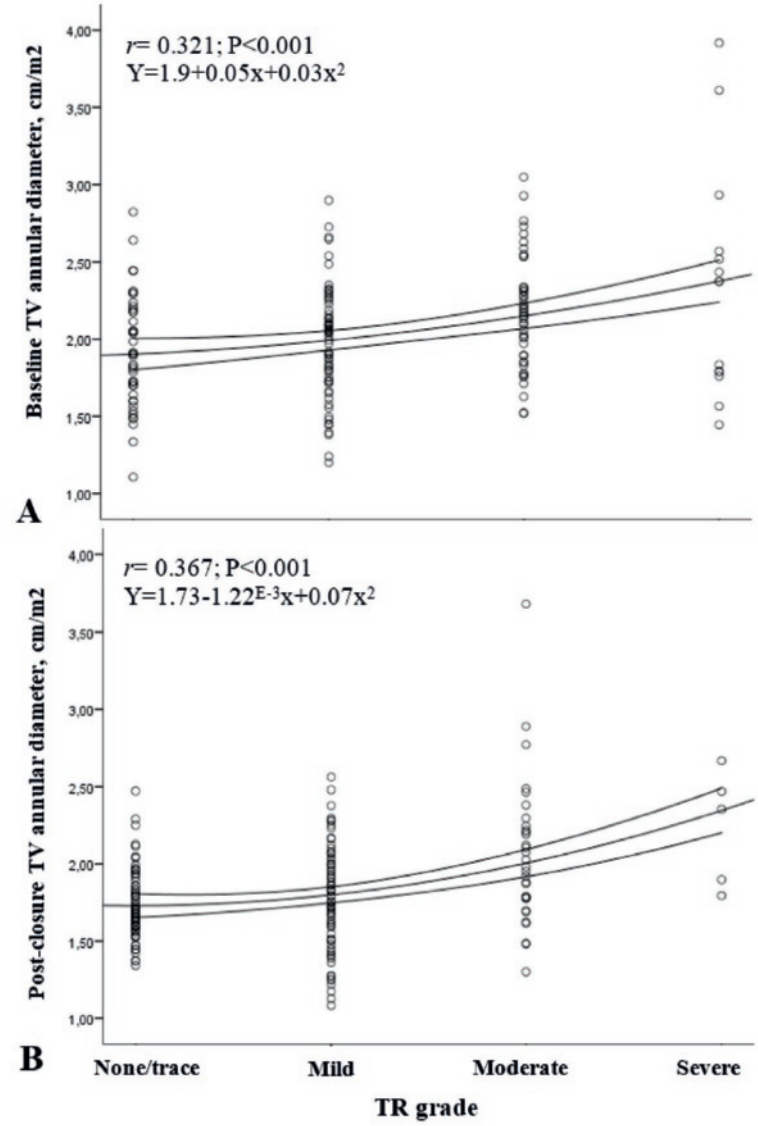
** By n=1000 bootstrapping of the model.*

† Defined as (Pimproved_prediction_among_outcome + Pimproved_prediction_among_no_outcome) – (Pworse_prediction_among_outcome + Pworse_prediction_among_no_outcome) for continuous predicted probabilities with P= proportion of patiens.

‡ Defined as (Σ^ioutcome(Pnew(i) – Pold(i)) / n(outcome)) - (Σ^jno_outcome(Pnew(j) – Pold(j)) / n(no_outcome)) with P= predicted probability for the outcome.



Suppl. Figure 1. Study flow chart. ASD= atrial septal defect; PFO= patent foramen ovale.



Suppl. Figure 2. BSA-indexed tricuspid annular diameter shows a moderate association with increasing TR grade at baseline (A) and six-month follow-up (B).