Transcatheter Pulmonary Valve Replacement in Middle and Late Adulthood

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Transcatheter pulmonary valve replacement (TPVR) is now frequently performed in patients with adult congenital heart disease. As the life expectancy of the population with adult congenital heart disease continues to improve, more patients will require pulmonary valve intervention. This study details the short-term and midterm clinical outcomes of patients aged ≥40 years who underwent TPVR. We performed an institutional retrospective cohort study that included patients aged ≥40 years who underwent TPVR (and clinical follow-up) from January 1, 2012 to January 1, 2024. Descriptive analyses, Kaplan-Meier survival analysis, and Cox proportional hazard modeling were used to determine outcomes and risk factors affecting survival. The study included 67 patients, and median age at TPVR was 48 years (43 to 57). Median hospital length of stay after TPVR was 1 day (1 to 3); periprocedural complications occurred in 5 patients, and acute kidney injury occurred in 1 patient. Median duration of follow-up was 3.5 years (0.1 to 9.7). There were 9 total deaths, and 1-, 3-, and 5-year Kaplan-Meier survival after TPVR was 95%, 91%, and 82%, respectively. Moderate or worse right ventricular dysfunction was present in 22 patients before TPVR and in 20 patients after TPVR. Inpatient status before TPVR negatively affected survival (hazard ratio 24.7, 3.3 to 186.1, p = 0.002). In conclusion, TPVR was performed in patients aged ≥40 years with favorable periprocedural and midterm follow-up outcomes including survival, but right ventricular dysfunction did not improve, and further exploration of the ideal timing of TPVR in this age group is warranted. **(Am J Cardiol 2024;229:36−46)**

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Right ventricular outflow tract (RVOT) abnormalities are present in approximately 20% of patients with congenital heart disease, and many of these patients require surgical or transcatheter palliative interventions early in infancy to survive.[1,2] Subsequent RVOT dysfunction in the form of pulmonary stenosis and/or pulmonary regurgitation eventually leads to right ventricular dysfunction as the patient ages.[2] This typically necessitates repeat surgical or transcatheter intervention that is almost inevitable during the life span of a patient with congenital heart disease.[3]

Over the past 20 years, the survival rate of the patient with congenital heart disease into adulthood has been reported to be >97%. Subsequently, the mortality rate of patients with congenital heart disease who require surgical or transcatheter procedures has significantly decreased.[4] Although this represents a great advancement, increasing numbers of sternotomies in adulthood are associated with increased mortality.[5,6] With 84% of the population with adult congenital heart disease (ACHD) now living >40 years, more patients with ACHD aged ≥40 years will require repeat intervention(s). RVOT dysfunction warranting pulmonary valve replacement comprises the most common procedure performed in patients with ACHD.[7,8]

Transcatheter pulmonary valve replacement (TPVR) is now being frequently performed in adult patients with RVOT dysfunction.[9,10] Indications for TPVR in the population with ACHD are similar to those of the pediatric population but remain somewhat unclear given the limited long-term data in this population.[3,11] However, in recent years, multiple studies have shown favorable short-term outcomes for young adult patients who undergo TPVR in terms of mortality and repeat valve intervention.[12−14] TPVR has been shown to require shorter length of stay (LOS), with similar short- and intermediate-term survival rates and rates of repeat valve intervention to those of surgical pulmonary valve replacement.[15−18] One recent study did show that increased age at the time of TPVR was associated with increased mortality and need for repeat valve intervention; however, this study did not outline the short- and midterm clinical outcomes in detail (except for survival and repeat pulmonary valve intervention rate) within the age of

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40 years and the older demographic.[18] This study adds to the literature by detailing the short- and midterm clinical TPVR outcomes and identifying risk factors affecting mortality within these patients with ACHD aged ≥40 years.

Methods

A retrospective chart review in all patients ≥40 years who underwent TPVR (and any clinical follow-up data) at a single, large volume institution from January 1, 2012 through January 1, 2024 was completed. Preprocedural, procedural, and outcome data for these patients were obtained through electronic medical record, and informed consent was waived as per the institutional review board. Congenital anatomy, previous valve/conduit type and size, history of endocarditis, previous permanent pacemaker/internal cardiac defibrillator, inotrope or extracorporeal membrane oxygen use, and inpatient status were noted. Baseline creatinine, post-TPVR creatinine at discharge, and the most recent creatinine obtained in follow-up were recorded. Pre- and post-TPVR New York Heart Association (NYHA) classifications, intubation/hospitalization days, electrocardiogram data, and rate utilization of guideline-directed medical therapy agents were also measured. Data from preprocedural and postprocedural transthoracic echocardiograms, in addition to advanced imaging in the form of cardiac computed tomography or magnetic resonance imaging spanning to any known clinical follow-up, were recorded for each patient. TPVR outcomes included endocarditis, repeat pulmonary valve intervention, death, and valve function at last clinical examination/follow-up.

All TPVR encounters were performed through a transfemoral, transjugular, or transapical approach under either general sedation or conscious sedation. Valves placed during the time frame included commercially available TPVR platforms spanning balloon-expandable valves (Edwards Sapien 3 or XT, Edwards Lifesciences, Irvine, California or Medtronic Melody, Medtronic, Minneapolis, Minnesota) systems and self-expandable valves (Medtronic Harmony, Medtronic). Appropriate pulmonary valve size was determined on the basis of RVOT anatomy and landing zone properties including previously placed conduit properties and sizes. All patients underwent advanced imaging in the form of either cardiac magnetic resonance imaging or computed tomography imaging before the procedure, in addition to echocardiography. Coronary compression testing was performed if concerns had been raised by previous advanced imaging. RVOT rehabilitation before valve placement in the form of stenting and/or fracture of native valve system was performed when deemed clinically appropriate. TPVR system after dilation was performed in select cases if the residual gradient across RVOT remained >15 mm Hg peak to peak. Hemodynamics including RVOT peak gradients before and after TPVR were obtained from cardiac catheterization reports. Intravascular contrast volume provided during TPVR was also recorded using these procedural reports. After TPVR, patients were discharged on aspirin therapy indefinitely in combination with a direct/novel oral anticoagulant for 3 months duration.

All statistical analysis was performed using SPSS version 28 (IBM, New York, New York). Continuous variables were reported using means with SDs, and ordinal variables were reported using medians with interquartile ranges. Additional descriptive data were reported with numerical counts and percentages. Kaplan-Meier survival analysis was used to illustrate freedom from death after TPVR over time. Univariate Cox proportional hazards regression models were used to identify mortality risk factors to include in a multivariate Cox hazards regression. Risk factors included male gender, tetralogy of Fallot anatomy, previous pulmonary valve replacement, history of endocarditis, previous pacemaker/intracardiac defibrillator, baseline moderate or greater tricuspid regurgitation, baseline moderate or greater pulmonary regurgitation, baseline moderate or greater pulmonary stenosis, baseline moderate or greater right ventricular dysfunction, baseline moderate or greater left ventricular dysfunction, inpatient status, prestenting, and use of Melody valves. Risk factors with a p value ≤0.2 in univariate regression were included in the multivariate Cox hazards regression. Risk factors with a p value ≤0.05 in the multivariate regression were deemed to be statistically significant mortality risk factors. Cox regression hazard ratios were reported with 95% confidence intervals.

Results

This study included 67 patients who underwent TPVR who were aged ≥40 years during the study period. Table 1 lists the baseline characteristics, and Supplementary Table 1 shows pre-TPVR medication usage within this cohort. The median age at the time of TPVR in this cohort was 48 years [43, 57]. Anatomic diagnosis was dominated by 33 patients (49%) who held a diagnosis of tetralogy of Fallot and 14 patients (21%) who had a diagnosis of congenital pulmonary stenosis; 36 patients (54%) underwent valve-in-valve TPVR in the setting of a previously placed bioprosthetic valve, valved conduit, or Contegra conduit, and 8 patients (12%) had a medical history of endocarditis. Functional assessment of this cohort was primarily performed using NYHA classification, and the median baseline NYHA classification was III [II, III]. Table 1 also outlines other preprocedural data including medication usage, QRS duration, indexed right ventricular end-diastolic volume (RVEDV), and indexed left ventricular end-diastolic volume (LVEDV). The preprocedure indexed RVEDV/LVEDV ratio was 1.8 ± 0.7.

Table 2 outlines TPVR intraprocedural data. TPVR was performed in most of the patients under general anesthesia (n = 65; 97%) through transfemoral access (n = 63; 94%). RVOT rehabilitation in the form of prestenting was performed in 43 patients (64%). Prestenting was performed on the basis of the preferences of the interventional team to rehabilitate the entirety of the landing zone (regions that may be distal/proximal to TPVR) before placing the valve despite the ultimate choice of valve system. Intentional fracture of previous prosthetic pulmonary valves was also routinely performed by the interventional team to help facilitate placement of the new valve with a nominal diameter. TPVR platforms used included Sapien valves in 59 patients (88%), Melody valves in 7 patients (10%), and a Harmony valve in 1 patient (2%). After TPVR, system balloon dilation was completed in 17 patients (25%) owing to

Table 1
Study cohort demographics

Variable	Patient Number (%; median IQR)
Congenital Heart Defect:	
Tetralogy of Fallot	33 (49%)
Congenital Pulmonary Stenosis	14 (21%)
Double Outlet Right Ventricle	4 (6%)
Aortic Stenosis status post Ross	3 (4%)
Carcinoid Syndrome with Pulmonary Stenosis or Regurgitation	3 (4%)
Pulmonary Atresia	1 (2%)
Other	9 (14%)
Age (years)	52 ± 10
Weight (kg)	81 ± 20
Height (cm)	167 ± 10
Sex	
Male	29 (43%)
Female	38 (57%)
Race	
White	43 (66%)
Black	20 (30%)
Hispanic	2 (3%)
Asian	1 (1%)
Chronic Kidney Disease	20 (30%)
Hypertension	39 (58%)
Hyperlipidemia	31 (46%)
Diabetes	20 (30%)
Smoking	11 (16%)
Heart Failure Reduced Ejection Fraction	7 (10%)
Heart Failure Preserved Ejection Fraction	16 (24%)
Coronary Artery Disease	12 (18%)
Coronary Artery Disease Revascularization	3 (5%)
Peripheral Artery Disease	3 (5%)
Permanent Pacemaker	9 (13%)
Chronic Obstructive Pulmonary Disease	5 (8%)
Atrial Fibrillation	27 (40%)
Conduit/Valve Type:	
Bioprosthetic valve	24 (36%)
Homograft	3 (4%)
Native RVOT-valve annulus	22 (33%)
Valved conduit	8 (12%)
Contegra conduit	4 (6%)
Unknown/other	6 (9%)
Original Conduit/Valve Size:	
20-22mm	7 (11%)
23-25mm	11 (16%)
26-28mm	9 (13%)
29-31mm	10 (15%)
Unknown/other	30 (45%)
Valve-in-valve Transcatheter Pulmonary Valve	36 (54%)
Prior history of endocarditis	8 (12%)
Baseline NYHA Classification	3 [2, 3]
Class I	3 (4%)
Class II	20 (30%)
Class III	41 (61%)
Class IV	3 (5%)
ASA Classification	4 [3, 4]
Baseline Creatinine (mg/dL)	1.1 ± 1.2
Baseline eGFR	80 ± 21
Pacemaker/ICD presence	15 (22%)
Inpatient status	4 (6%)
Extracorporeal Membrane Oxygenation/Inotrope Support	1 (2%)
Pre-Procedure Echo Tricuspid Regurgitation	
None or Trace	7 (10%)
Mild	20 (30%)
Moderate	36 (54%)
Severe	4 (6%)
Pre-Procedure Echo Pulmonary Stenosis	
None or Trace	13 (19%)
Mild	14 (21%)
Moderate	24 (36%)
Severe	16 (24%)
Pre-Procedure Echo Pulmonary Regurgitation	
None or Trace	8 (12%)
Mild	6 (9%)
Moderate	17 (25%)
Severe	36 (54%)
Pre-Procedure Echo Right Ventricular Function	
Normal	30 (45%)
Mildly Depressed	15 (22%)
Moderately Depressed	12 (18%)
Severely Depressed	10 (15%)
Pre-Procedure Echo Left Ventricular Function	
Normal	49 (73%)
Mildly Depressed	11 (16%)
Moderately Depressed	3 (5%)
Severely Depressed	4 (6%)
Pre-Procedure Indexed RVEDV (mL/m^2)	145 ± 56
Pre-Procedure Indexed LVEDV (mL/m^2)	92 ± 79
Pre-Procedure QRS duration (ms)	149 ± 35

ASA = American Society of Anesthesiologists; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter defibrillator; LVEDV = left ventricular end diastolic volume; NYHA = New York Heart Association; RVEDV = right ventricular end diastolic volume; RVOT = right ventricular outflow tract.

a residual gradient noted immediately after intervention(s) despite baseline intentional fracture previously outlined. For the patients who underwent TPVR for pulmonary stenosis, the right ventricular/systemic pressure percentage ratio on average before and after TPVR was 55% and 46%, respectively. For the patients with pulmonary stenosis, the RVOT gradient on average before and after TPVR was 29 mm Hg and 7 mm Hg, respectively. For the patients who underwent TPVR for indications other than pulmonary stenosis, the right ventricular/systemic pressure percentage ratio on average before and after TPVR was 42% and 45%, respectively. For these patients, the RVOT gradient on average before and after TPVR was 9 mm Hg and 3 mm Hg, respectively.

Contrast use on average was 197 ml, and contrast per unit mass on average was 5 ml/kg for the entire cohort. Complications after TPVR included large-volume bleeding from peripheral vascular injury in 3 patients (5%), arrythmia (high-grade heart block) requiring intracardiac defibrillator/pacemaker placement in 1 patient (2%), and cardiac arrest in 1 patient (2%). The 1 patient requiring intracardiac defibrillator/pacemaker had a preexisting right bundle branch block and tolerated TPVR well without immediate complication. However, an atrio-ventricular dissociation

Table 2
Procedural details

Variable	Number (%; median IQR)
Years since prior valve/palliation	30 ± 22
Transcatheter Approach:	
Femoral vein	63 (94%)
Jugular vein	3 (5%)
Transapical	1 (1%)
General Anesthesia	65 (97%)
Pre-stent placed	43 (64%)
Valve Placed	
Sapien	59 (88%)
Melody	7 (10%)
Harmony	1 (2%)
Valve Diameter	
18mm	0 (0%)
20mm	2 (3%)
22mm	6 (9%)
23mm	8 (12%)
25mm	1 (2%)
26mm	19 (28%)
29mm	31 (46%)
Concomitant Procedure	
Percutaneous Coronary Intervention	1 (2%)
Pulmonary Artery stenting	0 (0%)
Post-valve system dilatation performed	17 (25%)
Volume Contrast Used (mL)	197 ± 208
Contrast per mass (mL/kg)	5 ± 2
Complications	
Bleeding	3 (4.5%)
Vessel injury	0 (0%)
Arrythmia Requiring ICD/CRT/Pacemaker	1 (2%)
Cardiac arrest	1 (2%)

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator.

with a ventricular escape rhythm (approximately 40 beats/min) developed in the patient in the postanesthesia care unit. The electrophysiology team was consulted, and the patient underwent cardiac resynchronization therapy-defibrillator placement the day after TPVR was performed. At the patient's last clinical examination, there was pacing 99% of the time, and the underlying rhythm was normal sinus rhythm with ventricular pacing.

Table 3 lists hospitalization and discharge outcomes. The median hospital LOS was 1 day (1 to 3), and the median number of intubation days was 1 (1 to 1). Acute kidney injury occurred in 1 patient (2%). RVOT peak gradient at the time of discharge was 19 mm Hg ± 10 mm Hg based on echocardiogram data.

Table 4 outlines medium-term outcomes plus clinical follow-up data, and Supplementary Table 1 shows post-TPVR medication use for the patient cohort. Median duration of follow-up was 3.5 years (0.1 to 9.7), and median NYHA classification at most recent follow-up was 2 (1 to 2). Endocarditis was diagnosed in 4 patients (6%) after TPVR; repeat pulmonary valve intervention occurred in 4 patients (6%), and death occurred in 9 patients (13%). Of the patients in whom endocarditis developed, 3 patients had Sapien valves placed during TPVR, and 1 patient had a Melody valve placed. Data on postprocedural QRS duration

Table 3
Hospitalization and discharge outcomes

Variable	Number (%; median IQR)
Hospitalization days	1 [1,3]
Intubation days	1 [1,1]
Creatinine on discharge (mg/dL)	1 ± 1
Acute Kidney Injury prior to discharge	1 (1.5%)
Echo RVOT peak gradient (mmHg)	19 ± 10
Discharge Echo Right Ventricular Function	
Normal	31 (46%)
Mildly Depressed	14 (21%)
Moderately Depressed	15 (22%)
Severely Depressed	7 (11%)
Discharge Echo Left Ventricular Function	
Normal	52 (78%)
Mildly Depressed	6 (9%)
Moderately Depressed	5 (7%)
Severely Depressed	4 (6%)

RVOT = right ventricular outflow tract.

Table 4
Last clinical follow-up evaluation outcomes

Variable	Number (%; median IQR)
Last outpatient follow-up interval (years from procedure)	3.5 [0.1, 9.7]
Follow-up NYHA Classification	2 [1, 2]
Class I	20 (30%)
Class II	34 (51%)
Class III	7 (10%)
Class IV	6 (9%)
Follow-up Echo Tricuspid Regurgitation	
None or Trace	11 (17%)
Mild	27 (40%)
Moderate	27 (40%)
Severe	2 (3%)
Follow-up Echo Pulmonary Stenosis	
None or Trace	25 (37%)
Mild	36 (54%)
Moderate	6 (9%)
Severe	0 (0%)
Follow-up Echo Pulmonary Regurgitation	
None or Trace	54 (81%)
Mild	10 (15%)
Moderate	2 (3%)
Severe	1 (2%)
Follow-up Echo Right Ventricular Function	
Normal	23 (34%)
Mildly Depressed	24 (36%)
Moderately Depressed	14 (21%)
Severely Depressed	6 (9%)
Follow-up Echo Left Ventricular Function	
Normal	50 (75%)
Mildly Depressed	10 (15%)
Moderately Depressed	2 (3%)
Severely Depressed	5 (7%)
Post-Procedure Indexed RVEDV (mL/m^2)	152 ± 48
Post-Procedure Indexed LVEDV (mL/m^2)	86 ± 29
Post-Procedure QRS Duration (ms)	146 ± 33
QRS Duration Change (ms)	-0.3 ± 20

LVEDV = left ventricular end diastolic volume; NYHA = New York Heart Association; RVEDV = right ventricular end diastolic volume.

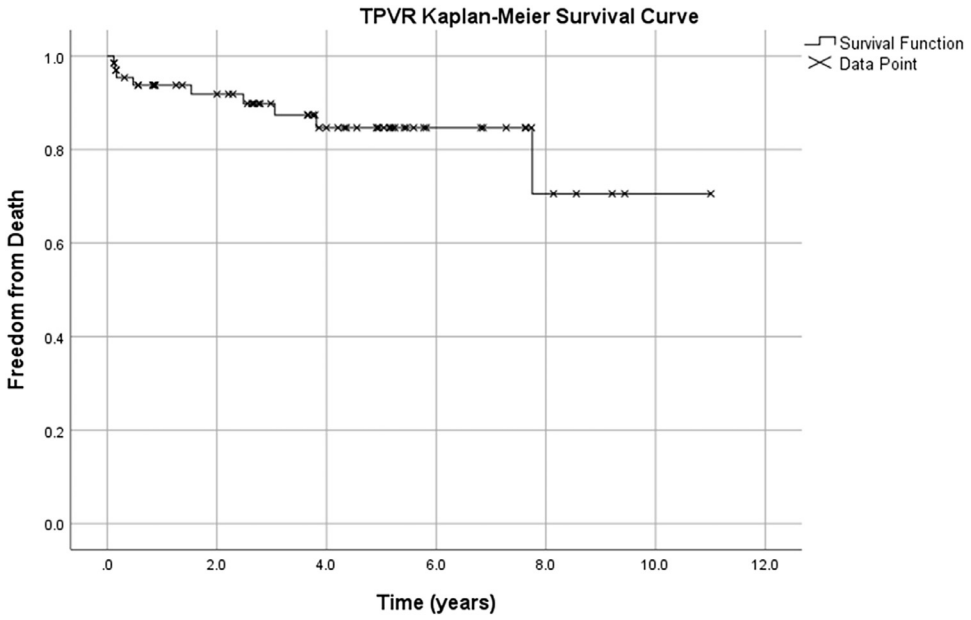

Figure 1. Kaplan-Meier survival curve after TPVR.

on electrocardiogram are listed in Table 4. QRS duration change before and after TPVR was −0.3 ± 19.9 milliseconds. The postprocedural RVEDV and LVEDV values listed in Table 4 can be compared with the preprocedural values outline in Table 1. Of note, however, only 17 patients (25%) underwent repeat advanced imaging scans after TPVR. Death at 1 year after TPVR occurred in 3 patients (5%), and Figure 1 shows the Kaplan-Meier survival curve for TPVR. The 1-, 3-, and 5-year Kaplan-Meier survival after TPVR was 95%, 91%, and 82%, respectively. The 10-year Kaplan-Meier survival after TPVR was 70%.

The entire cohort was divided into 3 subgroups based on the following indication: TPVR for a primary indication of pulmonary regurgitation, TPVR for pulmonary stenosis, and TPVR for mixed disease of both pulmonary regurgitation and stenosis. TPVR for pulmonary regurgitation primarily was defined by presence of pulmonary regurgitation of at least moderate severity without pulmonary stenosis of at least moderate severity. TPVR for pulmonary stenosis primarily was defined by presence of pulmonary stenosis of at least moderate severity without pulmonary regurgitation of at least moderate severity. Finally, TPVR for a combination of pulmonary regurgitation and stenosis was defined by presence of both pulmonary regurgitation and stenosis of at least moderate severity. Table 5 presents the pulmonary regurgitation subgroup, Table 6 the pulmonary stenosis subgroup, and Table 7 the combined pulmonary regurgitation and stenosis subgroup. Tables 5 to 7 note ventricular dimensions before and after TPVR, QRS durations before and after TPVR, and hemodynamics before and after TPVR in addition to transthoracic echocardiogram findings before and after TPVR in the 3 subgroups.

Table 8 lists the univariate Cox proportional hazard ratios for each risk factor. Table 8 also outlines the multivariate Cox proportional hazards regression that includes risk factors based on the univariate Cox regression results. Inpatient status negatively affected survival, with a hazard ratio of 24.7 (3.3 to 186.1), (p = 0.002). Figure 2 illustrates the impact of inpatient status on survival after TPVR. In inpatients, the 1-, 3-, and 5-year survival after TPVR determined from Cox regression was 60%, 39%, and 23%, respectively.

Discussion

TPVR has recently been shown to be safe in the age ≥40 years demographic in the short- and midterm time frames.[19] Similarly to that work, our study cohort's age and anatomic diagnoses were equivalent. Our study adds to the literature for this specific age group in that there were only 5 periprocedural complications (7.5%), and there were low rates of acute kidney injury with creatinine, on average remaining similar before and after TPVR. Median intubation duration and hospital LOS were both 1 day, reflective of TPVR outcomes across all age groups.[20,21] We noted a significant reduction in moderate or greater pulmonary stenosis at midterm follow-up after TPVR from 39 patients (58%) to 6 patients (9%) and a reduction in moderate or greater pulmonary insufficiency at last follow-up from 52 patients (78%) to 2 patients (3%). These findings agree with other studies examining patients of all ages.[22,23] Moreover, tricuspid regurgitation of moderate or greater severity was seen in 31 patients (46%) before TPVR whereas only 14 patients (21%) had tricuspid regurgitation of moderate or greater severity after TPVR. This improvement in tricuspid function after TPVR reflects other publications surrounding TPVR in younger patient cohorts.[24]

Of particular interest, there were 22 patients (33%) in this cohort with moderate or greater right ventricle (RV) dysfunction at baseline and 20 patients (30%) who had moderate or greater RV dysfunction at last clinical follow-up after TPVR. The average preprocedural indexed RVEDV was 145 ml/m^2 whereas the follow-up postprocedural indexed RVEDV was 152 ml/m^2. In addition, QRS

Table 5
Transcatheter pulmonary valve replacement for pulmonary regurgitation (n =24) subgroup

Variable	Patient Number (%; median IQR)
Pre-Procedure Indexed RVEDV (mL/m^2)	157 ± 56
Pre-Procedure Indexed LVEDV (mL/m^2)	114 ± 124
Pre-Procedure QRS duration (ms)	139 ± 33
Baseline RVp (mmHg)	48/16 ± 16/5
Baseline Systolic RVp: Systolic Aortic Pressure (%)	39 ± 15
Baseline Pulmonary Arterial Pressure (mmHg)	42/16 ± 13/5
Baseline RVOT gradient (mmHg)	8 ± 10
Pre-Procedure Echo Tricuspid Regurgitation	
None or Trace	2 (8%)
Mild	11 (46%)
Moderate	6 (25%)
Severe	5 (21%)
Pre-Procedure Echo Pulmonary Stenosis	
None or Trace	11 (46%)
Mild	13 (54%)
Moderate	0 (0%)
Severe	0 (0%)
Pre-Procedure Echo Pulmonary Regurgitation	
None or Trace	0 (0%)
Mild	0 (0%)
Moderate	1 (4%)
Severe	23 (96%)
Pre-Procedure Echo Right Ventricular Function	
Normal	12 (50%)
Mildly Depressed	6 (25%)
Moderately Depressed	1 (4%)
Severely Depressed	5 (21%)
Pre-Procedure Echo Left Ventricular Function	
Normal	15 (63%)
Mildly Depressed	6 (25%)
Moderately Depressed	1 (4%)
Severely Depressed	2 (8%)
Post-Procedure Indexed RVEDV (mL/m^2)	147 ± 47
Post-Procedure Indexed LVEDV (mL/m^2)	91 ± 34
Post-Procedure QRS Duration (ms)	142 ± 30
QRS Duration Change (ms)	3 ± 11
Post-Procedure RVp (mmHg)	53/17 ±19/6
Post-Procedure Systolic RVp: Systolic Aortic Pressure (%)	41 ± 14
Post-Procedure Pulmonary Arterial Pressure (mmHg)	45/22 ± 13/7
Post-Procedure RVOT gradient (mmHg)	2 ± 4
Follow-up Echo Tricuspid Regurgitation	
None or Trace	3 (12%)
Mild	9 (38%)
Moderate	6 (50%)
Severe	6 (50%)
Follow-up Echo Pulmonary Stenosis	
None or Trace	11 (46%)
Mild	13 (54%)
Moderate	0 (0%)
Severe	0 (0%)
Follow-up Echo Pulmonary Regurgitation	
None or Trace	16 (67%)
Mild	8 (33%)
Moderate	0 (0%)
Severe	0 (0%)
Follow-up Echo Right Ventricular Function	
Normal	4 (17%)
Mildly Depressed	11 (46%)
Moderately Depressed	6 (24%)
Severely Depressed	3 (13%)
Follow-up Echo Left Ventricular Function	
Normal	15 (63%)
Mildly Depressed	6 (25%)
Moderately Depressed	1 (4%)
Severely Depressed	2 (8%)

LVEDV = left ventricular end diastolic volume; RVEDV = right ventricular end diastolic volume; RVOT = right ventricular outflow tract; RVp = right ventricular pressure.

durations and RVEDV/LVEDV ratios were similar before and after TPVR. These results contradict other studies, performed in younger populations, that have indicated a reduction in RV dysfunction and remodeling after TPVR.[25] Within each of the 3 indication subgroups (pulmonary regurgitation, pulmonary stenosis, and mixed disease), there were improvements in tricuspid and pulmonary valve function without significant change in RV function and size. Altogether, this indicates that RV function and size remain similar despite TPVR intervention in this demographic. On the basis of our findings, although improvement in valve (pulmonary/tricuspid) function is attainable, RV remodeling and function recovery just may represent a limited capability of this age group. This raises the question whether earlier TPVR intervention (at younger ages or even when mild RV dysfunction develops) would protect against irreversible effects on RV function and hemodynamics.

Our study details midterm clinical outcomes that corroborate symptomatic improvement in this middle/late adulthood demographic given the median NYHA improved from III to II at last follow-up, as in other reported post-TPVR outcomes across all age groups.[26,27] Within our cohort, repeat pulmonary valve intervention was warranted in 4 patients (6%), and endocarditis developed in 4 patients (6%). Interestingly, there were 8 patients (12%) with a history of endocarditis before TPVR intervention, but endocarditis developed in only 1 of these patients after TPVR. Furthermore, the usage of β blockers, angiotensin-converting enzyme/angiotensin receptor blockers/angiotensin receptor blocker with neprilysin inhibitors, mineralocorticoid receptor antagonists, sodium/glucose cotransporter 2 inhibitors, and diuretic medication was similar before and after TPVR. Finally, 1-, 3-, and 5-year survival outcomes were favorable in this demographic, with 10-year Kaplan-Meier survival shown to be 70%. This is similar to 10-year survival outcomes after surgical pulmonary valve replacement in patients aged ≥40 years.[28]

Although most patients received a Sapien valve (88%) during TPVR, valve type did not significantly affect outcomes in this demographic, although admittedly, the cohort without a Sapien implant represents small numbers. Prestenting and RVOT rehabilitation were performed in 43 patients (64%), and the need for this intervention did not significantly affect midterm outcomes. History of endocarditis did not significantly affect survival in our cohort but

Table 6
Transcatheter pulmonary valve replacement for pulmonary stenosis (n = 13) subgroup

Variable	Patient Number (%; median IQR)
Pre-Procedure Indexed RVEDV (mL/m^2)	129 ± 33
Pre-Procedure Indexed LVEDV (mL/m^2)	76 ± 18
Pre-Procedure QRS duration (ms)	160 ± 30
Baseline RVp (mmHg)	77/21 ± 28/7
Baseline Systolic RVp: Systolic Aortic Pressure (%)	64 ± 29
Baseline Pulmonary Arterial Pressure (mmHg)	51/24 ± 17/8
Baseline RVOT gradient (mmHg)	29 ± 16
Pre-Procedure Echo Tricuspid Regurgitation	
None or Trace	2 (15%)
Mild	4 (31%)
Moderate	3 (23%)
Severe	4 (31%)
Pre-Procedure Echo Pulmonary Stenosis	
None or Trace	0 (0%)
Mild	0 (0%)
Moderate	6 (46%)
Severe	7 (54%)
Pre-Procedure Echo Pulmonary Regurgitation	
None or Trace	6 (46%)
Mild	7 (54%)
Moderate	0 (0%)
Severe	0 (0%)
Pre-Procedure Echo Right Ventricular Function	
Normal	4 (31%)
Mildly Depressed	3 (23%)
Moderately Depressed	4 (31%)
Severely Depressed	2 (15%)
Pre-Procedure Echo Left Ventricular Function	
Normal	11 (84%)
Mildly Depressed	1 (8%)
Moderately Depressed	0 (0%)
Severely Depressed	1 (8%)
Post-Procedure RVp (mmHg)	67/20 ± 30/7
Post-Procedure Systolic RVp: Systolic Aortic Pressure (%)	61 ± 33
Post-Procedure Pulmonary Arterial Pressure (mmHg)	56/26 ± 26/10
Post-Procedure RVOT gradient (mmHg)	11 ± 10
Post-Procedure Indexed RVEDV (mL/m^2)	136 ± 22
Post-Procedure Indexed LVEDV (mL/m^2)	77 ± 6
Post-Procedure QRS Duration (ms)	161 ± 22
QRS Duration Change (ms)	0.2 ± 30
Follow-up Echo Tricuspid Regurgitation	
None or Trace	1 (8%)
Mild	8 (61%)
Moderate	1 (8%)
Severe	3 (23%)
Follow-up Echo Pulmonary Stenosis	
None or Trace	4 (31%)
Mild	6 (46%)
Moderate	2 (15%)
Severe	1 (8%)
Follow-up Echo Pulmonary Regurgitation	
None or Trace	12 (92%)
Mild	1 (8%)
Moderate	0 (0%)
Severe	0 (0%)
Follow-up Echo Right Ventricular Function	
Normal	5 (38%)
Mildly Depressed	4 (31%)
Moderately Depressed	4 (31%)
Severely Depressed	0 (0%)
Follow-up Echo Left Ventricular Function	
Normal	9 (69%)
Mildly Depressed	1 (8%)
Moderately Depressed	0 (0%)
Severely Depressed	3 (23%)

LVEDV = left ventricular end diastolic volume; RVEDV = right ventricular end diastolic volume; RVOT = right ventricular outflow tract; RVp = right ventricular pressure.

has been shown to affect survival in other demographics.[7] Inpatient status was the only risk factor that was associated with increased mortality after TPVR in this cohort. There were 4 patients with inpatient status before TPVR, and 3 of these patients died within 1 year of TPVR being performed; these 3 patients comprised 1/3 of all deaths seen in the entire cohort. Before TPVR, all 4 of these patients revealed at least moderate tricuspid regurgitation, moderate pulmonary stenosis and/or regurgitation, and at least moderate RV dysfunction. In general, these inpatients held much greater severity of cardiac disease preceding TPVR. Moreover, these inpatients also required management of other preceding co-morbidities including previous stroke, previous endocarditis, obesity, carcinoid disease, liver failure, end-stage renal disease, restrictive lung disease, and atrial fibrillation. If a patient was hospitalized for heart failure and/or co-morbidities before TPVR, there was a huge disadvantage in terms of longer-term clinical outcomes. In reviewing the documented multidisciplinary consensus discussions, TPVR may have truthfully represented a salvage procedure to alter their clinical course despite their advanced cardiac disease and various co-morbidities.

This study holds several limitations in that it is a single-center, retrospective cohort without a control group to serve as a comparison. Our group was unable to effectively compare TPVR outcomes with surgical pulmonary valve replacement outcomes at this institution for the same age demographic because of limited numbers within the surgical group. Along these lines, this study does not account for patients who did not meet the clinical criteria for TPVR owing to various exclusion criteria and for those in whom a TPVR was believed by the congenital interventional team to be infeasible (proximity of coronary arteries, limitations of landing zone, and so on). Institutionally, our general clinical approach has been to refer patients for TPVR if there are surgical candidacy concerns or if they have already undergone surgical pulmonary valve replacement as an adult, which may skew study cohort characteristics. It should also be pointed out that most patients (54%) in this cohort underwent valve-in-valve TPVR, and although this did not significantly affect survival according to multivariate regression, stratifying the cohort using this criterion potentially could affect the additional studied outcomes.

From a procedural standpoint, there was mild variation in approach in terms of intervention access sites, deployed

Table 7
Transcatheter pulmonary valve replacement for mixed pulmonary regurgitation and stenosis (n = 30) subgroup

Variable	Patient Number (%; median IQR)
Pre-Procedure Indexed RVEDV (mL/m^2)	141 ± 63
Pre-Procedure Indexed LVEDV (mL/m^2)	80 ± 28
Pre-Procedure QRS duration (ms)	143 ± 37
Baseline RVp (mmHg)	66/16 ± 22/6
Baseline Systolic RVp: Systolic Aortic Pressure (%)	52 ± 16
Baseline Pulmonary Arterial Pressure (mmHg)	40/16 ± 12/6
Baseline RVOT gradient (mmHg)	29 ± 24
Pre-Procedure Echo Tricuspid Regurgitation	
None or Trace	3 (10%)
Mild	7 (23%)
Moderate	15 (50%)
Severe	5 (17%)
Pre-Procedure Echo Pulmonary Stenosis	
None or Trace	0 (0%)
Mild	0 (0%)
Moderate	22 (73%)
Severe	8 (27%)
Pre-Procedure Echo Pulmonary Regurgitation	
None or Trace	0 (0%)
Mild	0 (0%)
Moderate	10 (33%)
Severe	20 (67%)
Pre-Procedure Echo Right Ventricular Function	
Normal	14 (47%)
Mildly Depressed	6 (20%)
Moderately Depressed	7 (23%)
Severely Depressed	3 (10%)
Pre-Procedure Echo Left Ventricular Function	
Normal	22 (74%)
Mildly Depressed	6 (20%)
Moderately Depressed	1 (3%)
Severely Depressed	1 (3%)
Post-Procedure RVp (mmHg)	51/17 ± 11/5
Post-Procedure Systolic RVp: Systolic Aortic Pressure (%)	42 ± 13
Post-Procedure Pulmonary Artery Pressure (mmHg)	48/22 ± 10/6
Post-Procedure RVOT gradient (mmHg)	6 ± 4
Post-Procedure Indexed RVEDV (mL/m^2)	161 ± 74
Post-Procedure Indexed LVEDV (mL/m^2)	82 ± 21
Post-Procedure QRS Duration (ms)	143 ± 38
QRS Duration Change (ms)	-3.4 ± 21
Follow-up Echo Tricuspid Regurgitation	
None or Trace	8 (27%)
Mild	11 (37%)
Moderate	10 (33%)
Severe	1 (3%)
Follow-up Echo Pulmonary Stenosis	
None or Trace	25 (84%)
Mild	4 (13%)
Moderate	1 (3%)
Severe	0 (0%)
Follow-up Echo Pulmonary Regurgitation	
None or Trace	10 (33%)
Mild	17 (57%)
Moderate	3 (10%)
Severe	0 (0%)
Follow-up Echo Right Ventricular Function	
Normal	14 (47%)
Mildly Depressed	9 (30%)
Moderately Depressed	4 (13%)
Severely Depressed	3 (10%)
Follow-up Echo Left Ventricular Function	
Normal	25 (84%)
Mildly Depressed	4 (13%)
Moderately Depressed	0 (0%)
Severely Depressed	1 (3%)

LVEDV = left ventricular end diastolic volume; RVEDV = right ventricular end diastolic volume; RVOT = right ventricular outflow tract; RVp = right ventricular pressure.

Table 8
Risk factors: univariate and multivariate risk adjusted models for adverse event

Variable	Hazard Ratio [95% CI]	p-value
Univariate Risk Adjusted Model		
Male Sex	1.5 [0.4, 5.7]	0.54
Tetralogy of Fallot Anatomy	1.1 [0.3, 4.2]	0.88
Previous PVR	0.3 [0.1, 1.3]	0.11
Endocarditis History	3.0 [0.6, 15.1]	0.19
Previous PPM or ICD Placement	1.6 [0.4, 6.5]	0.50
Baseline Tricuspid Regurgitation ≥ Moderate	4.0 [0.8, 19.1]	0.09
Baseline Pulmonary Regurgitation ≥ Moderate	0.8 [0.2, 3.9]	0.79
Baseline Pulmonary Stenosis ≥ Moderate	0.5 [0.1, 2.0]	0.30
Baseline RV Dysfunction ≥ Moderate	1.8 [0.8, 3.9]	0.17
Baseline LV Dysfunction ≥ Moderate	3.0 [0.8, 11.2]	0.11
Inpatient status	19.2 [4.5, 82.8]	**<0.001**
TPVR with Pre-stent	4.2 [0.5, 33.6]	0.18
TPVR with Melody valve	1.3 [0.2, 7.3]	0.78
Multivariate Risk Factor Model		
Previous PVR	0.3 [0.02, 2.8]	0.26
Endocarditis History	2.5 [0.3, 18.2]	0.37
Baseline Tricuspid Regurgitation ≥ Moderate	0.9 [0.1, 6.2]	0.88
Baseline RV Dysfunction ≥ Moderate	4.8 [0.5, 49.2]	0.18
Baseline LV Dysfunction ≥ Moderate	1.3 [0.2, 12.2]	0.79
Inpatient	24.7 [3.3, 186.1]	**0.002**
Pre-stent	1.0 [0.1, 17.9]	0.99

ICD = implantable cardioverter defibrillator; LV = left ventricle; PPM = permanent pacemaker; PVR = pulmonary valve replacement; RV = right ventricle; TPVR = transcatheter pulmonary valve replacement.

TPVR systems, and procedural techniques (including use of prestenting and balloon dilation after TPVR). These differences can be attributed to the heterogenous cohort, intraprocedural findings, and operator preference, but this variability may have affected this study's outcomes. Our study cohort also only contained 1 patient with a new self-expandable TPVR platform owing to the limited follow-up not yet available in this population. Although our cohort had strong echocardiographic and clinical post-TPVR follow-up, the advanced imaging rate after TPVR was low despite provider recommendations (17 patients; 25% of this

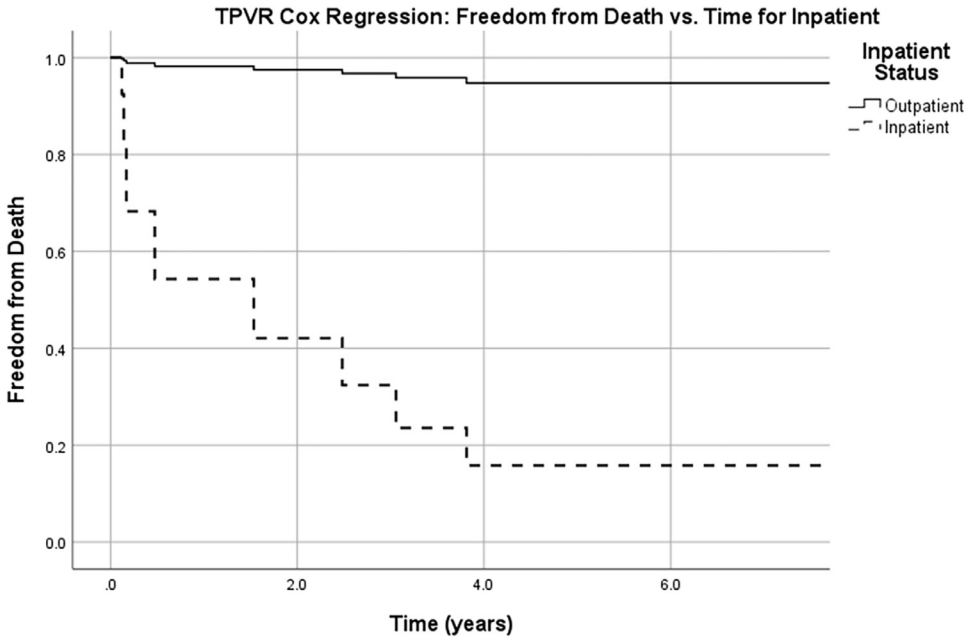

Figure 2. The impact of inpatient status on survival after TPVR. Cox regression: freedom from death versus time for inpatients.

patient cohort), limiting a comprehensive assessment of interventions effects on ventricular remodeling and function. Furthermore, this cohort was limited in the rate of functional testing (cardiopulmonary exercise testing) performed before and after TPVR, which limits functional outcome assessment after TPVR. Cardiopulmonary exercise testing has recently been adopted as a standard practice (expectation communicated to the patient before the procedure) at our institution to better assess functional outcomes.

Although implantation of TPVR spanned over 10 years, the median follow-up duration was limited owing to the large referral base and catchment region provided by this institution. There may be unaccounted clinical outcomes within this cohort that limit the comprehensiveness of the follow-up data. Some patients were previously observed at this institution for multiple years, which limits generalizability to other centers where patients are less known to the institution. Moreover, many patients referred to this institution already held significant RV or tricuspid valve dysfunction, which suggests that they may have been past the "critical time frame window" for the intervention previously suggested. A significant portion of the cohort (22 patients, 33%) showed moderate or greater right-sided cardiac dysfunction at baseline, and this may limit generalizability to other patient populations with less severe right-sided cardiac dysfunction. Recent publications outline proactive criteria (indexed RVEDV >160 ml/m^2, QRS duration >160 ms, LVEF <55%, and so on) and novel imaging criteria (right atrial reservoir strain, right atrial pressure, RV global longitudinal strain, and so on) for patient selection that we now are aiming to use institutionally along with education to our referral base.[29,30]

In summary, this study shows that patients aged ≥40 years who undergo TPVR have similar outcomes to those of younger patients who undergo TPVR. Periprocedurally, there were few complications, and only 1 event of acute kidney injury was noted on discharge. Hospital LOS was relatively short and comparable to LOS after TPVR in younger-age demographics. There were significant decreases in pulmonary regurgitation and pulmonary insufficiency, but RV dysfunction persisted in this cohort, suggesting that this might be irreversible in older patients and that TPVR possibly should be performed earlier in adulthood to improve RV function. For midterm outcomes, there was significant improvement in symptomatology and favorable 1-, 3-, and 5-year survival after TPVR, with rates of endocarditis and repeat intervention comparable to those in younger demographics. Inpatient status before TPVR negatively affected survival, which was likely related to the severity of their preexisting cardiac disease and co-morbidities. Overall, TPVR can be performed in middle and late adulthood with good short-term and midterm clinical outcomes, but further investigation into ideal timing of TPVR is warranted to optimize outcomes. It remains critical that we advocate for "lifelong" management of any patient with ACHD, planning not only for the present intervention but possibly also the subsequent intervention. This warrants a multidisciplinary approach, spanning surgical and transcatheter considerations along with extensive discussions surrounding the optimal timing of interventions for this medically complex patient population.

Declaration of competing interest

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CRediT authorship contribution statement

John D'Angelo: Writing − review & editing, Writing − original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **John Lisko:** Writing − review & editing, Writing − original draft, Data curation, Conceptualization. **Vasilis C. Babaliaros:** Writing − review & editing, Writing − original draft, Conceptualization. **Adam Greenbaum:** Writing − review & editing, Writing − original draft. **Dennis W. Kim:** Writing − review & editing, Writing − original draft, Conceptualization. **Fred H. Rodriguez:** Writing − review & editing, Writing − original draft, Investigation, Conceptualization. **Joshua M. Rosenblum:** Writing − review & editing, Writing − original draft, Formal analysis, Conceptualization. **Nikoloz Shekiladze:** Writing − review & editing, Writing − original draft. **Hiroki Ueyama:** Writing − review & editing, Writing − original draft, Data curation. **R. Allen Ligon:** Writing − review & editing, Writing − original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.08.007.

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