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ORIGINAL ARTICLE

Tricuspid Annular Plane Systolic Excursion (TAPSE) correlates with mean pulmonary artery pressure especially 10 years after pediatric heart transplantation

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Abstract

Tricuspid annular plane systolic excursion (TAPSE) is important in the noninvasive echocardiographic assessment of right heart function. This retrospective observational study shows correlations of TAPSE with invasive right heart catheterization parameters after pediatric heart transplantation (HTx). The study included patients after pediatric HTx with cardiac catheterizations in 2018/2019 and measurement of TAPSE ($n = 52$ patients with 57 examinations; 50.9% adults, 52.6% female, median age: 18.54 years). TAPSE was compared with normal values. Stepwise, linear and multiple regression were used to show influencing variables on TAPSE. Mean TAPSE z-score was −3.48 (SD: 2.25) and 68.4% of HTx-recipients showed abnormally reduced TAPSE (z-score ←2) compared to normal values. Multiple regression (p-value <0.001; corrected $R^2 = 0.338$) showed significant correlations of time since HTx (p-value <0.001) and mPAP (p-value: 0.008) with TAPSE z-scores. Divided into subgroups (time since HTx <10 and ≥10 years), TAPSE and mPAP correlated only ≥10 years after HTx (p-value = 0.002). This study provides data of TAPSE even ≥10 years after pediatric HTx. Most patients showed a decreased TAPSE early after HTx, which improved over time. TAPSE z-scores correlated significantly with time since HTx and mPAP, especially ≥10 years post-HTx. Therefore, TAPSE must be used carefully in the early follow-up.

KEYWORDS
pediatric heart transplantation, pulmonary mean pressure, TAPSE

1 | INTRODUCTION

To monitor graft function after pediatric heart transplantation (HTx), comorbidities and possible complications such as acute or chronic rejection, a lifelong follow-up is required, including echocardiograms and heart catheterization.[1] Monitoring of heart transplant recipients also involves invasive hemodynamic measurements.[1,2]

Especially evaluation of right heart function plays an important role after HTx, because right ventricular dysfunction or failure is a severe complication and contributes to early morbidity and mortality in heart

transplant recipients.[1,3] In order to overcome the complex geometry of the right ventricle, tricuspid annular plane systolic excursion (TAPSE) can be used for quantitative assessment of right ventricular systolic function, because it does not require geometrical assumptions about the shape of the right ventricle.[4]

TAPSE is measured in M-mode by placing the cursor through the tricuspid annulus in apical four-chamber view and tracing longitudinal shortening of the right ventricle.[5] Advantages of TAPSE are its simple measurement and reproducibility, less dependency on optimal image quality and good correlation with right ventricular ejection fraction in healthy subjects.[5–8] In addition it is independent of heart rate, which makes it especially suitable for children.[9] But there are also disadvantages: TAPSE is angle and load dependent and furthermore, longitudinal shortening of a single segment may not represent the entire right ventricle.[5–7]

TAPSE has been correlated with qualitative assessment, it has shown positive correlations with right ventricular ejection fraction and fractional area change and a negative correlation with right ventricular end diastolic volume.[8,10–13] TAPSE has become a major echocardiographic parameter in pediatric pulmonary hypertension and other diseases such as Tetralogy of Fallot.[9–11,14,15] It even showed a strong correlation with right ventricular ejection fraction in children with pulmonary hypertension secondary to congenital heart disease and Tetralogy of Fallot.[10]

Nevertheless, this correlation could not be verified after pediatric surgeries, such as Fontan Palliation in children with hypoplastic left heart syndrome or repair of Tetralogy of Fallot.[16,17]

In patients after HTx, TAPSE has shown a significant correlation with right ventricular fractional area change, acute cellular rejection burden, cardiac allograft vasculopathy and mortality and is therefore an important prognostic parameter in heart transplant recipients.[12,13,18,19]

To what extent TAPSE correlates with the pulmonary artery pressure even ≥10 years after pediatric HTx and if TAPSE normalizes over the years after pediatric HTx is yet unknown. Thus, the purpose of this study was (1) to evaluate the potential difference of TAPSE between patients even ≥10 years after pediatric HTx and normal values of healthy children and (2) to analyze the correlation between TAPSE and invasively measured pulmonary artery pressure and right ventricular parameters after pediatric HTx.

2 | MATERIAL AND METHODS

2.1 | Study design

This observational study retrospectively analyzed echocardiographic and heart catheterization data of all heart transplant recipients, that received cardiac catheterization between January 2018 and December 2019 in the Department of Pediatric Cardiology and Intensive care medicine – Ludwig-Maximilians-University of Munich in Germany. The study was approved by the ethical review committee of the Ludwig-Maximilians-University Munich. The ethical review committee allowed a waiver of informed consent of the patients for the study because of an anonymized data elicitation.

2.2 | Inclusion/Exclusion criteria

All patients after pediatric heart transplantation who received heart catheterization with measurement of pulmonary artery pressure between January 2018 and December 2019 were included. Heart catheterization was either part of the standard follow-up monitoring, performed due to clinical suspicion of rejection or if the patients were clinically unstable.

Additionally, there had to be an echocardiogram with assessment of TAPSE within a maximum of 4 days before or after heart catheterization. Patients with poor quality of TAPSE examination were excluded from the study ($n = 4$). As a few patients had more than one check-up in 2018/2019, the study population consisted of 52 different patients with 57 individual measurements via heart catheterization and echocardiography (50.9% adults, mean age: 18.54 ± 7.88 years, 52.6% female).

2.3 | Data acquisition

All data were collected from the medical records of the patients. In addition to demographic and transplantation data, we documented prescribed medication and comorbidities at the time of admission for follow-up diagnostic at the clinic. For assessment of possible risk factors, confounders and influencing factors of right heart function we recorded complications since HTx (pacemaker, cardiac allograft vasculopathy and rejection episodes), current endomyocardial biopsy results (cardiac allograft vasculopathy (CAV) and acute rejection), laboratory parameters (high-sensitivity troponin T, HLA-antibodies), right bundle branch block and early signs of venous congestion. Most importantly, various echocardiographic measurements (TAPSE, TAPSE z-scores, ejection fraction using the Simpson method, aortic velocity time integral (VTI), VTI z-scores, pulmonary artery acceleration time) and catheterization parameters (central venous pressure, mean pulmonary artery pressure (mPAP), right ventricular systolic pressure, left ventricular systolic pressure, cardiac index) were documented.

2.4 | Definition

Cardiac allograft vasculopathy was defined as a pathological result in the angiography according to the ISHLT CAV classification[20] or a pathological result in the optical coherence tomography. Acute rejection was defined as any kind of acute rejection (cellular or humoral) with positive endomyocardial biopsy or clear clinical symptoms.

2.5 | TAPSE acquisition

TAPSE was measured in M-Mode. To reduce inter-observer variability, in addition to the information in medical records TAPSE was remeasured by two independent observers and an overall mean was calculated. These two observers measured TAPSE twice per patient and

calculated the mean (two-beat averaging) to decrease intra-observer variability.

2.6 | Age adjustment

TAPSE can vary highly in different age groups, so TAPSE mean values of the patients were converted into z-scores using age-specific normal values for healthy children and adults[7,21]: $z = (x - \mu)/\sigma$, with x being the TAPSE mean value, μ being the mean normal value and σ its standard deviation. VTI can also show great differences between age groups, so they were also converted into z-scores using age-specific normal values.[22]

2.7 | Statistical analysis

For statistical analysis we used IBM SPSS ® Statistics version 27 (June 2020) for Microsoft Windows.

Continuous data are presented as mean ± standard deviation (SD) and categorial data are shown as absolute values with percentages. *P*-values <0.05 were considered statistically significant.

We compared mean values of two groups using independent *t*-test if normal distribution applied and Mann-Whitney-*U*-test if not. We used Kolmogorov-Smirnov-Test, histograms and Q-Q plots to check for normal distribution.

To identify main factors influencing TAPSE z-scores and possible confounders, stepwise regression using backwards elimination (removal criteria: probability of F <0.10) was performed. Multicollinearity was detected using Pearson correlation coefficients and only the most important ones of intercorrelating variables were included in stepwise regression. Scatterplot matrix was used to identify variables correlating with TAPSE z-scores that have been missed by stepwise regression.

Remaining parameters after stepwise regression were put into the final multiple regression model. This model was graphically checked for multicollinearity, homogeneity of variance (homoscedasticity) and normal distribution of residuals.

Linear regression outcomes were used to show correlations graphically. To explore the results even further, the population was divided into two groups (time since HTx <10 years and ≥10 years) and two separate linear regression models were calculated. Because of intercorrelations between heart catheterization parameters, three separate linear regression models were used additionally to show correlations between right heart function and TAPSE z-scores.

3 | RESULTS

3.1 | Population

Half of the 57 patients were female (52.6%) and half were adults (≥18 years at the time of heart catheterization; 50.9%) attending follow-up inspection after HTx. Median age at HTx was 9.4 years (range: 0.04–18.7 years) and mean time since HTx was 10.17 (±6.89) years with 47.4% of patients having been transplanted for ≥10 years. All demographic, transplantation and medication data as well as comorbidities are provided in Table 1.

3.2 | TAPSE

The vast majority of echocardiographic measurements were performed within 48 h of catheterization. Median TAPSE was 14.0 mm (detailed echocardiographic and catheterization data shown in Table 2), mean TAPSE z-score was −3.48 (SD: 2.25). 68.4% of heart transplant recipients in this study showed abnormally reduced TAPSE values (z-score ≤2) compared to age-specific normal values despite mostly normal invasive hemodynamic parameters. Divided into subgroups 83.3% ($n = 25$) of the patients <10 years post-HTx had an abnormally reduced TAPSE compared to only 51.9% ($n = 14$) of the patients ≥10 years post-HTx.

Comparison of mean values showed significantly lower mean TAPSE z-scores in patients <10 years since HTx in comparison to patients ≥10 years since HTx ($p = < 0.001$) (Figure 1).

Mean TAPSE z-scores were compared in several subgroups but neither gender nor endomyocardial biopsy results (cardiac allograft vasculopathy and acute rejection) nor cardiac allograft vasculopathy (according to the angiography or the optical coherence tomography) nor rejection events since transplantation revealed a significant difference.

3.3 | Stepwise regression

Stepwise regression in form of backwards elimination (removal criteria: probability of F <0.10) was used to explore and detect confounders and important factors influencing TAPSE z-scores. Beforehand variables were tested for intercorrelations, and age was excluded from the stepwise regression model because of its high correlation with time since HTx (Pearson's correlation coefficient: 0.693, *p*-value <0.001). The following variables were put into stepwise regression and backwards elimination: TAPSE z-scores, ejection fraction by Simpson method, VTI z-scores, pulmonary artery acceleration time, tissue doppler, fractional shortening, wall motion abnormalities, tricuspid regurgitation, central venous pressure, mPAP, right ventricular systolic pressure, left ventricular systolic pressure, cardiac index, time since HTx, sex, high sensitive troponin T, HLA-antibodies, arterial hypertension, diabetes mellitus, hyperlipidemia, prescription of statins, pacemaker, biopsy results for CAV and acute rejection, cardiac allograft vasculopathy, rejection episodes, right bundle branch block and early signs of venous congestion.

Stepwise regression results showed that only time since HTx and mPAP correlated significantly with TAPSE z-scores (final regression model after stepwise regression: *p*-value <0.001; corrected R^2 = 0.338).

TABLE 1 Demographic data

	Demographic data	
		n **(percentage) ormean ± SD ormedian (range)**
Patient data	Study population	57 (100.0%)
	Female	30 (52.6%)
	Adults (≥18 years)	29 (50.9%)
	Age at baseline[a] (years)	18.54 ± 7.88
	Body weight (kg)	52.0 ± 20.7
	Body length (cm)	165.0 (84.0–193.0)
	BMI (kg/m^2)	19.8 (12.5–27.1)
Transplant data	Age at HTx (years)	9.4 (0.04–18.7)
	Time since HTx (years)	10.17 ± 6.89
	Time since HTx ≥10 years	27 (47.4%)
	HLA mismatch	2 (3.5%)
Cause for HTx	DCM	41 (71.9%)
	RCM	5 (8.8%)
	Congenital heart defect	6 (10.5%)
	Other[b]	5 (8.8%)
Medication	Immunosuppressants	57 (100.0%)
	Tacrolimus	43 (75.4%)
	Everolimus	42 (73.7%)
	Mycophenolate	22 (38.6%)
	Azathioprine	3 (5.3%)
	Ciclosporin	3 (5.3%)
	Prednisolone	3 (5.3%)
	Antihypertensives	48 (87.2%)
	Statins	45 (78.9%)
	Antidiabetics	4 (7.0%)
	Diuretics	9 (15.8%)
	Anticoagulants	8 (14.0%)
Comorbidities	Arterial hypertension	46 (80.7%)
	Pulmonary hypertension	0 (0.0%)
	Diabetes mellitus	4 (7.0%)
	Hyperlipidemia	17 (29.8%)
	Chronic renal failure	16 (28.1%)
	Post-Transplant Lymphoproliferative Disorder	2 (3.5%)
	Myopathy	4 (7.0%)
	Acute rejection[c]	19 (33.3%)
	CAV[d]	50 (87.7%)

Abbreviations: BMI, Body-Mass-Index; CAV, cardiac allograft vasculopathy; DCM, dilated cardiomyopathy; HLA, human leukocyte antigen; HTx, heart transplantation; RCM, restrictive cardiomyopathy.

[a]Age at baseline: age at time of heart catheterization.

[b]Other causes for HTx include Re-transplantation, Kawasaki disease, intrauterine myocardial infarction and arrhythmogenic or ischemic cardiomyopathy.

[c]Acute rejection: all patients who had been diagnosed at least once with acute rejection since their last HTx.

[d]CAV: all patients who had been diagnosed with cardiac allograft vasculopathy in coronary angiography or optical coherence tomography since their last HTx.

TABLE 2 Echocardiographic and cardiac catheterization data

	Echocardiographic and cardiac catheterization data		
		Mean ± SD or *n* (percentage) or median	Range
Echocardiographic data	TAPSE (mm)	14.0	6-24
	TAPSE z-scores[a]	−3.48 ± 2.25	−8.93–0.00
	Abnormal TAPSE[b]	39 (68.4%)	
	LV EF (Simpson) (%)	63.1	24.0–87.3
	Aortic VTI (cm)	23.50 ± 7.08	12.1–44.0
	Aortic VTI z-scores[c]	−0.60 ± 2.05	−3.86–5.56
	PAAT (s)	132.14 ± 25.96	60–174
Cardiac catheterization data	CVP (mmHg)	3.0	0–16
	mPAP (mmHg)	13.0	7–30
	RVSP (mmHg)	26.4 ± 6.5	14–40
	RAP (mmHg)	3.0	0–16
	RVEDP (mmHg)	4.0	0–14
	LVSP (mmHg)	105.0 ± 14.8	74–145
	Cardiac index (L/min/m^2)	3.9	0.9–10.0

Abbreviations: CVP, central venous pressure; LV EF, left ventricular ejection fraction; LVSP, left ventricular systolic pressure; mPAP, mean pulmonary arterial pressure; PAAT, pulmonary artery acceleration time; RAP, richt atrial pressure; RVEDP, right ventricular end diastolic pressure; RVSP, right ventricular systolic pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; VTI, velocity-time-integral.

[a]TAPSE z-scores show deviation of TAPSE from age-specific mean normal values.[7,21]

[b]According to age specific mean normal values[7,21]: abnormal: ≤2 standard deviations.

[c]Aortic VTI z-scores show deviation of aortic VTI from age-specific mean normal values.[22]

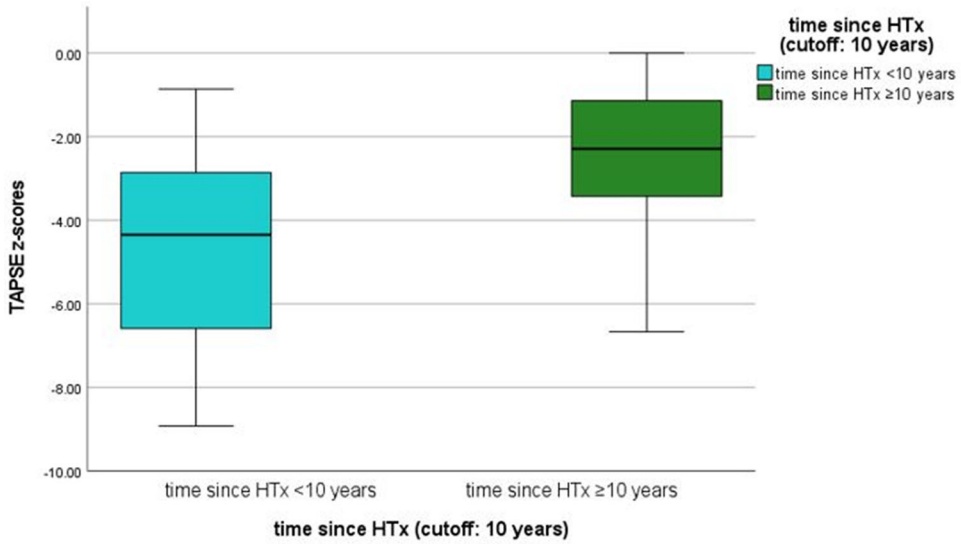

FIGURE 1 Boxplot: TAPSE z-scores sorted by time since transplantation (cutoff: 10 years)

*significant comparison of means with *p*-value <0.001 time since transplantation <10 years: mean: −4.53 (SD: ± 2.30; range: −8.93 to −0.86), median: −4.35 time since transplantation ≥10 years: mean: −2.32 (SD: ± 1.54; range: −6.67 to 0.00), median: −2.29. HTx, heart transplantation; TAPSE, tricuspid annular plane systolic excursion

Notes: Boxplot, sorted by time since HTx: ≥10 years (*n* = 27) or <10 years (*n* = 30)

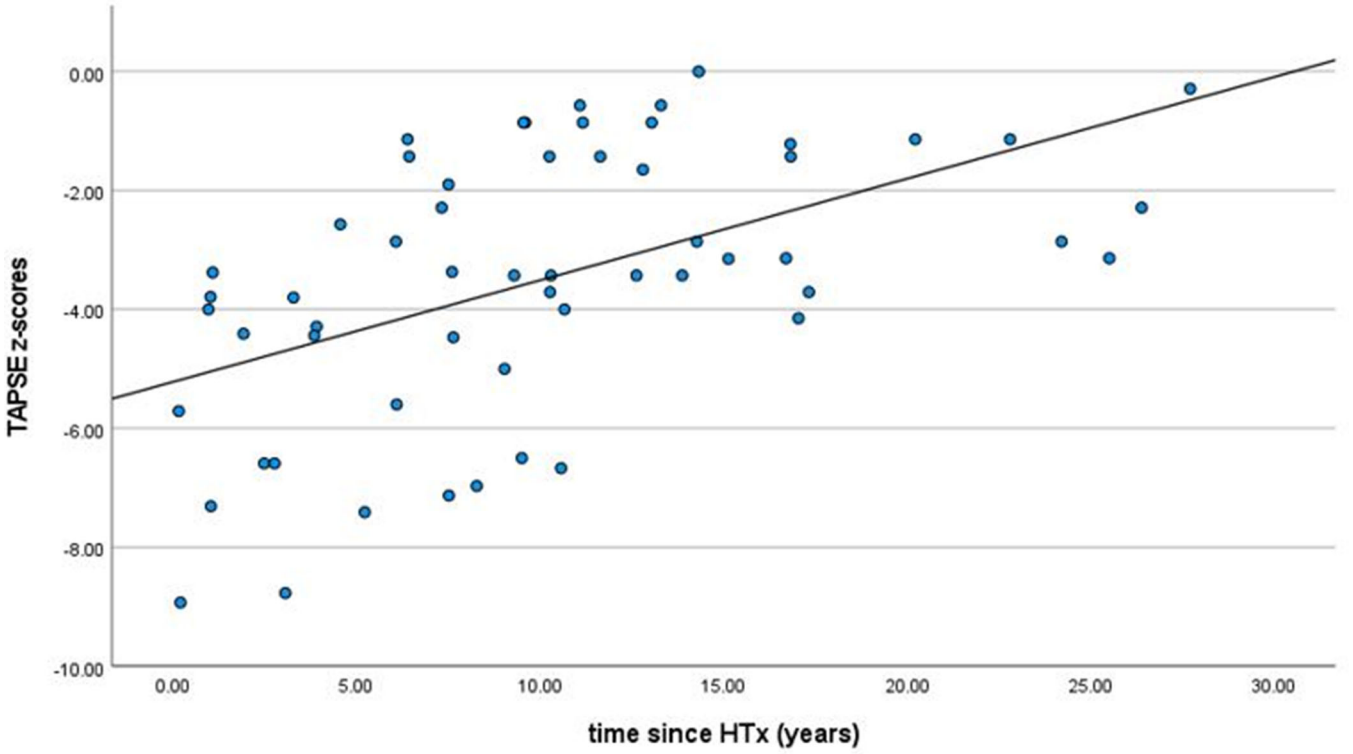

FIGURE 2 Scatterplot: correlation between time since HTx and TAPSE z-scores
Regression coefficient: 0.171 (p-value <0.001). HTx, heart transplantation; TAPSE, tricuspid annular plane systolic excursion
Notes: Scatterplot; linear regression model (p-value <0.001; corrected R^2: 0.259)

3.4 | Linear regression models

Linear regression analysis of the correlation between TAPSE z-scores and time since HTx showed that every year after transplantation TAPSE z-score would increase 0.171 (p-value <0.001), which would be equivalent to 0.60 mm per year for adult patients as one TAPSE z-score translates to 3.5 mm for adults according to normal values[7] (Figure 2). Correlation between TAPSE z-scores and mPAP in a linear regression model indicated that TAPSE z-score would be reduced by −0.165 for every additional mmHg of mPAP (p-value = 0.010), which would be a decrease of 0.58 mm per mmHg for adult patients (Figure 3).

Additionally, we performed a second linear regression excluding all multiple examinations of patients (n = 5) to make sure the multiple examinations were not influencing the results. This analysis also showed a correlation between TAPSE and time since HTX (p-value < 0.001; regression coefficient 0.175) as well as TAPSE and mPAP (p-value 0.014, regression coefficient −0.164).

3.5 | Multiple regression model

The final multiple regression model included TAPSE z-scores as a dependent variable and time since HTx and mPAP as independent variables. It was able to explain 33.8% of variance (corrected R^2 = 0.338; p-value <0.001). Regression coefficients for time since HTx and mPAP varied only slightly compared to linear regression results and are provided in Table 3 as well as details of multiple regression analysis and the equivalents for TAPSE in mm for adult patients. The multiple regression model proved to be homoscedastic. It showed normal distribution of residuals and no multicollinearity was detected.

3.6 | Subgroups

We divided the population into subgroups (time since HTx <10 years and ≥10 years) and calculated two separate linear regression models describing the relation between TAPSE z-scores and mPAP (Figure 4). While the linear regression model for patients who had been transplanted for ≥10 years proved to be significant (p-value = 0.002), the linear regression model for those whose transplantation had taken place less than 10 years ago could not be significantly validated (p-value = 0.153). These results can also be seen graphically as most of the patients who had a highly abnormal TAPSE but normal mPAP were transplanted less than 10 years ago.

3.7 | Right ventricular parameters

Because of intercorrelations between mPAP and other heart catheterization parameters, the correlation between TAPSE z-scores and right heart function was displayed in three separate linear regression models. Right atrial pressure (RAP) seemed to correlate graphically with TAPSE z-scores, but neither systolic function represented by right ventricular systolic pressure (RVSP) nor diastolic function represented

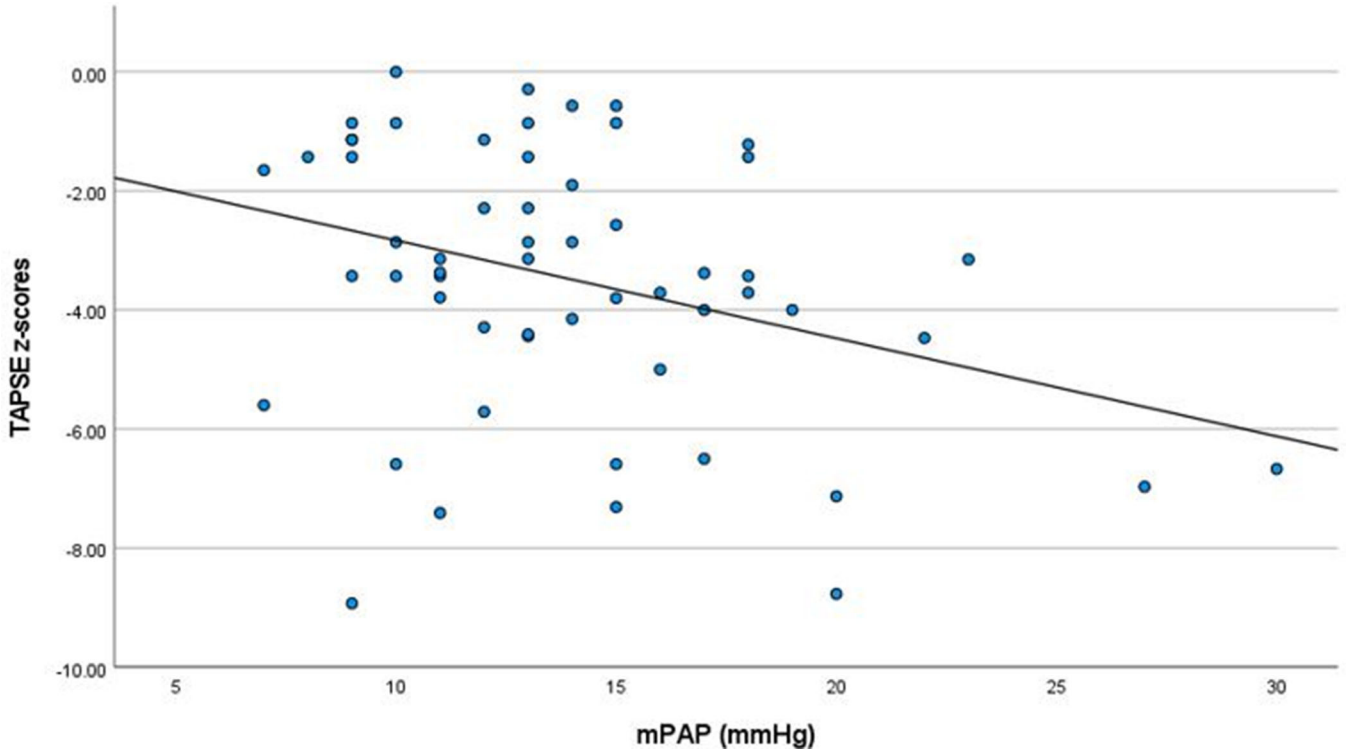

FIGURE 3 Scatterplot: correlation between mPAP and TAPSE z-scores
Regression coefficient: −0.165 (*p*-value: 0.010). mPAP, mean pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion
Notes: Scatterplot; linear regression model (*p*-value: 0.010; corrected R^2: 0.099)

TABLE 3 Multiple regression analysis for TAPSE z-scores

Multiple regression analysis for TAPSE z-scores					
Variable	Regression coefficient B	Standard error	Standardized coefficient Beta	Equivalent for adults[a] (mm)	*p*-value
Time since HTx	0.163	0.036	0.499	0.571	<0.001*
mPAP	0.146	0.053	−0.300	−0.511	0.008*

Abbreviations: HTx, heart transplantation; mPAP, mean pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.
Results from multiple regression analysis: regression model significance: *p*-value <0.001; corrected $R^2 = 0.338$.
*Significant values: *p*-value <0.05.
[b]Calculation for equivalent for adults in mm: 1 TAPSE z-score translates to 3.5 mm for adults according to normal values.[7]

by right ventricular end diastolic pressure (RVEDP) and RAP showed a significant correlation with TAPSE z-scores using linear regression (Figure 5).

4 | DISCUSSION

4.1 | TAPSE

This study showed an overall decreased TAPSE in heart transplant recipients early as well as late after HTx. The mean deviation from normal values was −3.48 SDs and no patient reached a TAPSE greater than the age-specific mean normal value even more than 10 years post-transplant. Nonetheless, we saw TAPSE improving over the years as TAPSE correlated significantly with time since HTx (*p*-value <0.001) and there was a significant difference of means between subgroups regarding time since HTx <10 years and ≥10 years (*p*-value <0.001). But as mentioned previously TAPSE did not fully recover in most of the patients as 68.4% of HTx recipients showed abnormally reduced TAPSE with z-scores less than −2 compared to age-specific normal values.

Various studies have shown a similar decrease in TAPSE and other parameters of right heart function in heart transplant recipients. Early after pediatric HTx, Harrington et al., White et al. and Moñivas Palomero et al. described significantly impaired TAPSE, which improved over the first 1–2 years after HTx, but overall remained

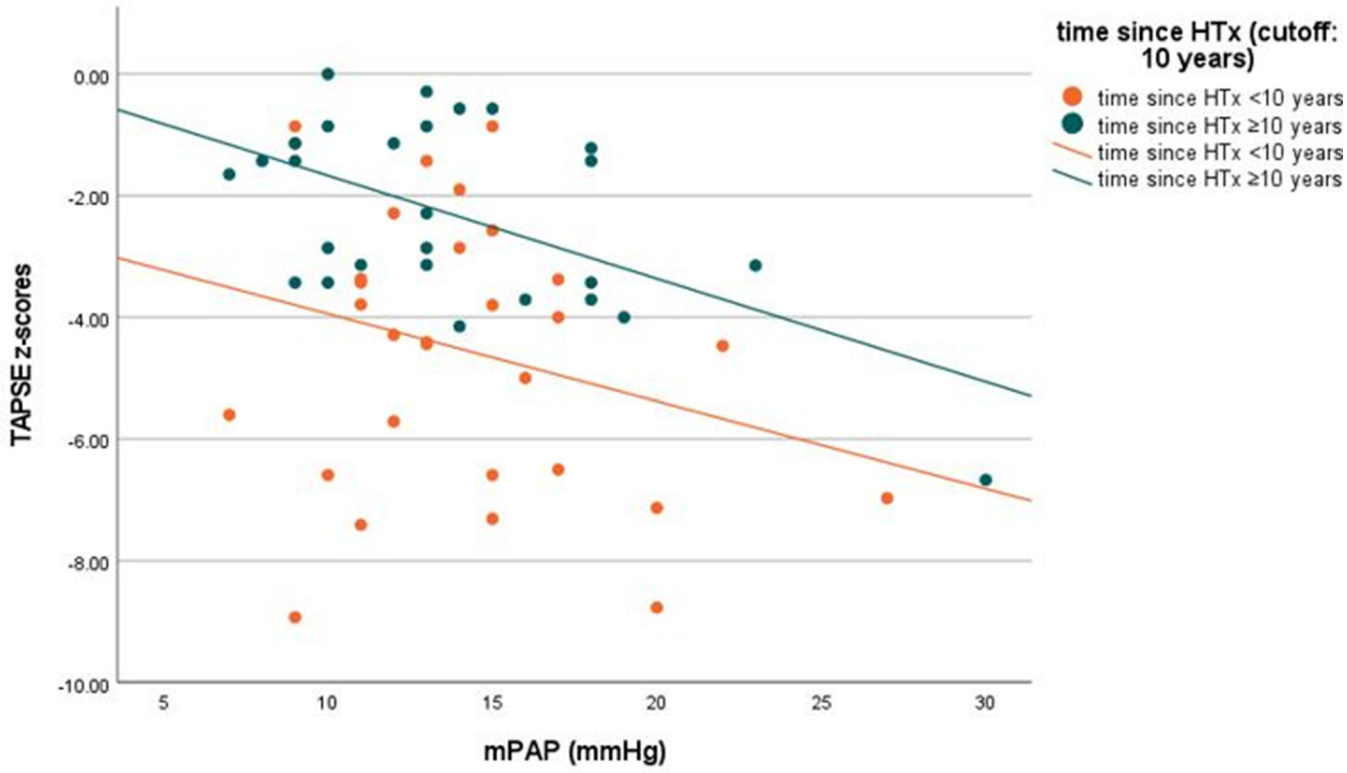

FIGURE 4 Scatterplot: correlation between mPAP and TAPSE z-scores sorted by time since HTx (cutoff: 10 years)

Notes: Scatterplot sorted by time since HTx: ≥10 years or <10 years; separate linear regression model for each subgroup linear regression model time since HTx <10 years (not significant with *p*-value >0.05: $p = 0.153$; corrected R^2: 0.039); regression coefficient B: −0.144 (*p*-value = 0.153) linear regression model time since HTx ≥10 years (significant with *p*-value <0.05: $p = 0.002$; corrected R^2: 0.284); regression coefficient B: −0.170 (*p*-value = 0.002). HTx, heart transplantation; mPAP, mean pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion

abnormal.[3,23,24] Consequently, TAPSE may not be a reliable parameter for the assessment of right ventricular function very early after HTx.

The suggestion that TAPSE might recover completely over time could not be confirmed in this study as lots of patients showed abnormal TAPSE even ≥10 years after HTx. TAPSE rarely reached age-specific normal values, but it did improve and stabilize ≥10 after HTx.

This study provides data of TAPSE even ≥10 years after pediatric HTx, which is important for the interpretation of the follow-up results as there are yet no normal values available for TAPSE late after pediatric HTx.

Clemmensen et al. and Ingvarsson et al. showed a decreased TAPSE (−2.25 SD) in stable adult patients years after HTx.[25,26] We found similar results for pediatric heart transplant recipients (mean TAPSE z-score: −2.32 ≥10 years post-HTx).

Ingvarsson et al. reported normal values for TAPSE in adults after HTx (TAPSE: 14 mm; SD: 4 mm).[26] Harrington et al. already provided normal values for pediatric heart transplant recipients up to one year after HTx.[3] This study emphasizes that because of the significant difference to healthy patients normal values of TAPSE are needed for pediatric heart transplant recipients long-term ≥10 years after HTx.

Geometrical changes in the contractile pattern have been suggested as explanation for impaired TAPSE after HTx.[3,27] These changes might be caused by cardiac surgery, which can lead to a relative loss of longitudinal shortening and gain in transverse shortening despite normal global right ventricular function.[28,29]

Streeter et al. found that right ventricular ejection fraction remains stable more than one year after HTx in adults and thus especially changes of individual values are abnormal and should be clinically evaluated.[30] This could translate to TAPSE as it might stabilize over time and deviations from individual values of the patients should be investigated further.

4.2 | Left ventricular function

Aortic VTI z-scores and LV EF (Simpson) showed no significant correlation with TAPSE z-scores after stepwise regression, which could mean that TAPSE values are not dependent on the left ventricular function. But as there were only five patients in our study who showed abnormal LV EF ≤55%, this result may not represent the entire population of pediatric heart transplant recipients.[31] There are studies showing the correlation between left ventricular EF and TAPSE in adults with

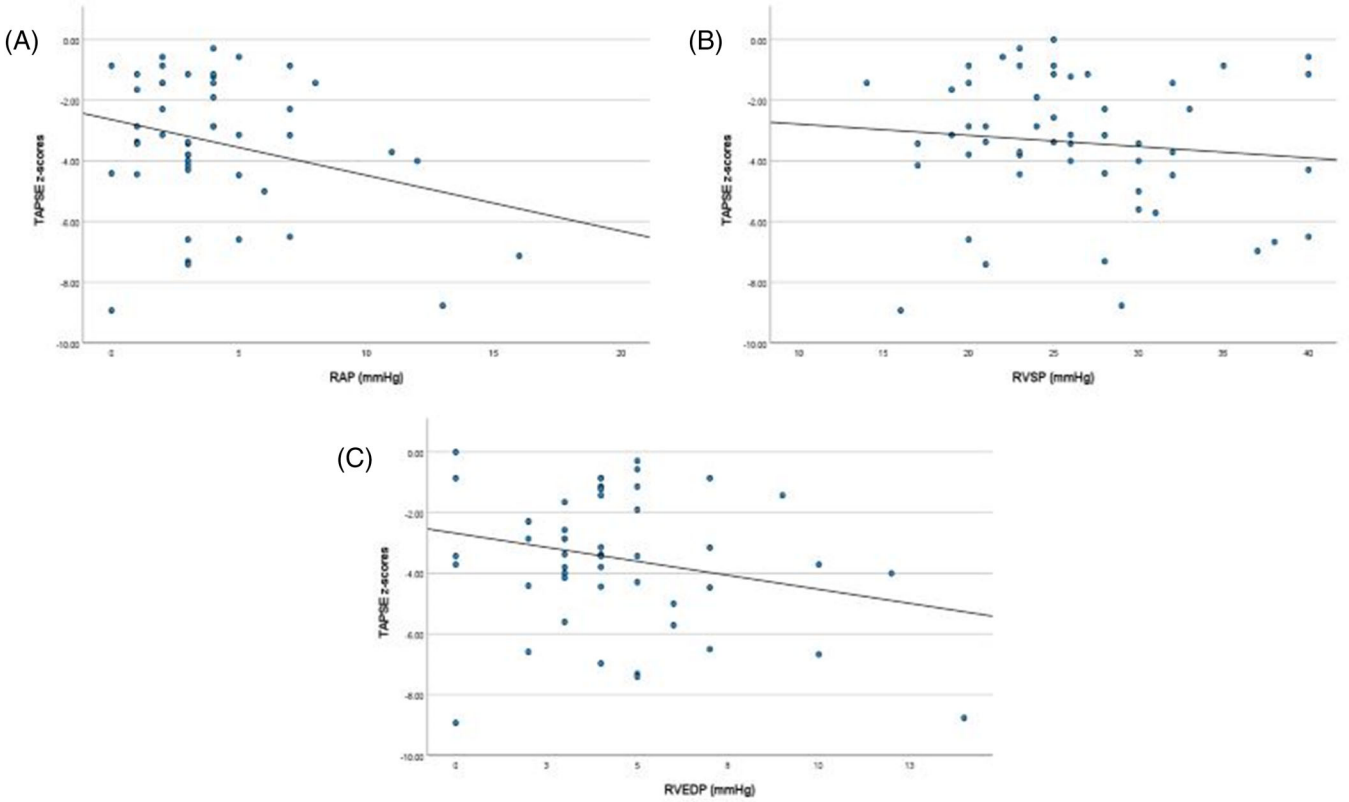

FIGURE 5 Scatterplots: correlations between right ventricular parameters (RAP, RVSP, RVEDP) and TAPSE z-scores
(a) linear regression model RAP and TAPSE z-scores: not significant with *p*-value >0.05: $p = 0.058$; corrected R^2: 0.057; regression coefficient B: −0.184 (*p*-value = 0.058)
(b) linear regression model RVSP and TAPSE z-scores: not significant with *p*-value >0.05: $p = 0.437$; corrected R^2: −0.007; regression coefficient B: −0.037 (*p*-value = 0.437)
(c) linear regression model RVEDP and TAPSE z-scores: not significant with *p*-value >0.05: $p = 0.093$; corrected R^2: 0.038; regression coefficient B: −0.185 (*p*-value = 0.093)
RAP, right atrial pressure; RVEDP, right ventricular end diastolic pressure; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion

Notes: Scatterplots; separate linear regression model for each parameter

severe systolic left ventricular dysfunction, end-stage renal disease, severe aortic stenosis or heart failure, but there is as of yet no data on the interdependence of TAPSE and left ventricular parameters in children after HTx.[32–35]

4.3 | Right ventricular function

Three separate linear regression models showed no significant correlations between TAPSE z-scores and RVSP, RAP and RVEDP. This might be a sign that TAPSE does not correlate with right ventricular systolic or diastolic function after pediatric HTx. However, for better evaluation of the correlation between right ventricular function and TAPSE an assessment of the right ventricular ejection fraction with cardiac magnetic resonance would be important. Additionally, it seems unlikely that TAPSE would only correlate with mPAP but not with right ventricular hemodynamic pressure. Larger studies including cardiac magnetic resonance are needed to verify these results considering that due to the small size of the study they might not apply to the whole population of pediatric heart transplant recipients.

4.4 | mPAP

TAPSE z-scores correlated significantly with mPAP in linear regression (*p*-value = 0.010) and multiple regression (*p*-value = 0.008). However, early after HTx mPAP did not significantly correlate with TAPSE z-scores, which leads to the assumption that during the first years after HTx TAPSE may not be a reliable parameter to predict invasively measured hemodynamics.

Furthermore, in agreement with this result, Ingvarsson et al. showed that TAPSE did not correlate with invasively measured pulmonary pressures up to one year after HTx in adult patients.[36]

TAPSE z-scores and mPAP showed a significant correlation ≥10 years after HTx in linear regression (*p*-value = 0.002). This new finding means that TAPSE might stabilize over time and regain its

reliability in the assessment of right heart function after pediatric HTx.

There are no other studies describing the correlation between TAPSE and mPAP in heart transplant recipients, but Domingo et al. has been able to show a significant correlation between TAPSE and mPAP in adults with pulmonary arterial hypertension.[37] TAPSE also correlated with pulmonary vascular resistance and cardiac output and was able to predict survival in patients with pulmonary hypertension.[15,38]

In our study overall TAPSE values deviating up to -3 SD from mean normal values were not associated with abnormal mPAP, which means that TAPSE values close to age-specific normal values might indicate normal right ventricular function and normal or only slightly increased mPAP. If TAPSE values are normal, elevated mPAP seems to be unlikely and frequency of catheterization and invasive hemodynamic measurement might be reduced, especially in younger children and if there is no other clinical or diagnostical indication for catheterization.

Nonetheless, highly abnormal values of TAPSE (z-score ←3) can be accompanied by normal or abnormal mPAP. Therefore, abnormal TAPSE should always be investigated further using other echocardiographic measurements or even catheterization if necessary. Especially upon suspicion of acute rejection catheterization including an endomyocardial biopsy is still considered gold standard.[1,2]

4.5 | Limitations

The size of the study was limited due to the rareness of pediatric heart transplantation. Five patients had more than one check-up in 2018/2019, which means that this might influence the results, but all of the measurements were carried out during different hospital stays partially for standard follow-up and partially upon suspicion of acute rejection and no catheterization or echocardiographic data was used twice. To make sure the multiple examinations were not influencing the results we performed an additional linear regression excluding all multiple examinations of patients which then showed very similar results to the first linear regression.

Consequently, it might not be possible to generalize these results and more studies are required in order to prove our findings. Especially the number of patients who showed abnormal pulmonary artery pressure was very small as mPAP ≥22mmHg was measured in only four patients.[39] Larger studies addressing the correlation between mPAP and TAPSE are therefore required to verify the correlation we found.

The multiple linear regression model could only explain 33.8% of variance, which means there might be other influencing factors on TAPSE that we did not include in this study.

As age and time since HTx correlated significantly, the correlation between time since HTx and TAPSE might be a correlation between age and TAPSE. Therefore, we tried to adjust TAPSE for age by calculating TAPSE z-scores using age-specific normal values and interpreted the remaining variable time since HTx as the main influencing factor.

5 | CONCLUSION

This study provides data of TAPSE even ≥10 years after pediatric HTx with the majority of patients showing a decreased TAPSE even ≥10 years after HTx. Still, TAPSE improved with an increasing amount of time between measurement and HTx. Normal values of TAPSE in children more than one year after HTx have yet to be determined.

There was no significant correlation between TAPSE z-scores and invasively assessed right heart function or echocardiographically assessed left heart function.

TAPSE z-scores correlated significantly with time since HTx and mPAP, especially ≥10 years post-HTx. TAPSE can therefore be a useful tool in the individual noninvasive follow-up diagnostics in HTx recipients as it can indicate a decreased right heart function or elevated mean arterial pulmonary pressure. It seems that normal TAPSE values are unlikely to coincide with elevated mPAP, but abnormal values should be investigated further. TAPSE must be used carefully, because it may not be sufficiently reliable early after HTx. TAPSE should always be interpreted individually and compared to normal values or previously measured TAPSE in the same patient.

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AUTHOR CONTRIBUTIONS

Morgana Michalski, Dr. Sarah M. Ulrich, Prof. Dr. Nikolaus Haas: participated in study design and enrolling patients; Morgana Michalski and Dr. Sarah Ulrich: participated in the performance of the research, in data collection and analysis; Morgana Michalski, Prof. Dr. Nikolaus Haas, Prof. Dr. Robert Dalla Pozza, PD Dr. Sebastian Michel, Dr. Marcus Fischer, Dr. Anja Lehner, Dr. Laura Rosenthal, PD Dr. André Jakob, Dr. Madeleine Orban, Dr. Sarah M. Ulrich: participated in invasive and echocardiographic data acquisition, analysis and interpretation and the writing of the paper.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

CONFLICTS OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose as described by *Clinical Transplantation*.

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