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Identifying the determinants of health–related quality of life in children after heart transplant

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congential heart disease;
ecological systems

BACKGROUND: Pediatric heart transplant (PHT) recipients have impaired health–related quality of life (HRQOL) that is not fully explained by cardiac limitations. Environment is known to influence HRQOL in other chronic disease populations but is less understood in PHT. Understanding the determinants of HRQOL is a necessary step in identifying high-risk groups and designing actionable interventions.

METHODS: This cross-sectional study includes 8- to 18-year heart transplant (HT) recipients and their families. Generalized estimating equations were used to evaluate the associations of individual characteristics (diagnosis, pulmonary capillary wedge pressure [PCWP], cardiac index [CI]), microenvironment (parent education level, financial security, parental stress [PSI], assessment of child anxiety) and macroenvironment [Child Opportunity Index (COI)] with HRQOL.

RESULTS: Of 31 participants, 32% self-identified as Black, and 40% had congenital heart disease. On cardiac catheterization, 61% had a CI ≥3 liter/min/m^2 and PCWP ≤10 mm Hg. Most households had ≥1 parent who had completed college (58%); 28% of households expressed difficulty paying bills. The PSI showed elevated parental stress [64.5 (interquartile range [IQR] 52.0, 77.8)], while the COI was low [73.0 (IQR 44.5, 89.0)] as was HRQOL [Pediatric Quality of Life 4.0 Core Scales 71.7 (IQR 64.2-82.5), Pediatric Cardiac Quality of Life Index 61.8 (IQR 55.7-74.8)]. Higher parental stress (p = 0.036), higher parental perception of child anxiety (p = 0.058), lower Max VO_2 (p = 0.059), and higher PCWP (p = 0.006) were independently associated with worse quality of life.

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CONCLUSIONS: HRQOL in children after heart transplant is reduced and determined not only by traditional measures of cardiovascular function, but also by patient psychology and their household environment, highlighting the utility of using an adapted ecological systems framework to understand HRQOL.

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Background

Heart transplant restores normal cardiac function in severely ill children, with the potential to not only relieve fatigue, dyspnea, and exercise intolerance due to diminished cardiac function but also malnutrition and chronic gut ischemia due to poor perfusion of end-organs. This leaves most pediatric heart transplant recipients free of symptoms attributable to cardiac disease.[1-3] However, health–related quality of life (HRQOL) is significantly lower than in "cardiac normal" peers[4-8] and psychosocial comorbidities are prevalent.[4,9-13] In fact, despite the fact that children after heart transplant report significantly fewer cardiac symptoms than children after other types of cardiac surgery, they have quality of life (QOL) scores similar to children with residual or palliated heart disease, with nearly one-third showing significant deficits in psychosocial measures.[14]

HRQOL, which measures how a person's health affects their physical, psychological, and social functioning, is an important patient-reported outcome (PRO) providing information about overall health that is not available in the conventional medical record.[15] It is potentially influenced by a diverse range of factors. Adapting Bronfenbrenner's ecological systems framework,[16] we can divide potential factors associated with HRQOL into 3 inter-related levels based on their proximity to the patient (Figure 1): characteristics of the individual (i.e., age, initial diagnosis, time since heart transplant, illness severity as well as mood disorders, anxiety, and positive psychological traits such as resilience and optimism), the microenvironment (i.e., household level factors such as parental stress, educational background, and household income), and the macroenvironment (i.e., neighborhood level factors such as educational, social, and economic opportunity.) Using this conceptual framework helps to understand how factors in each of these

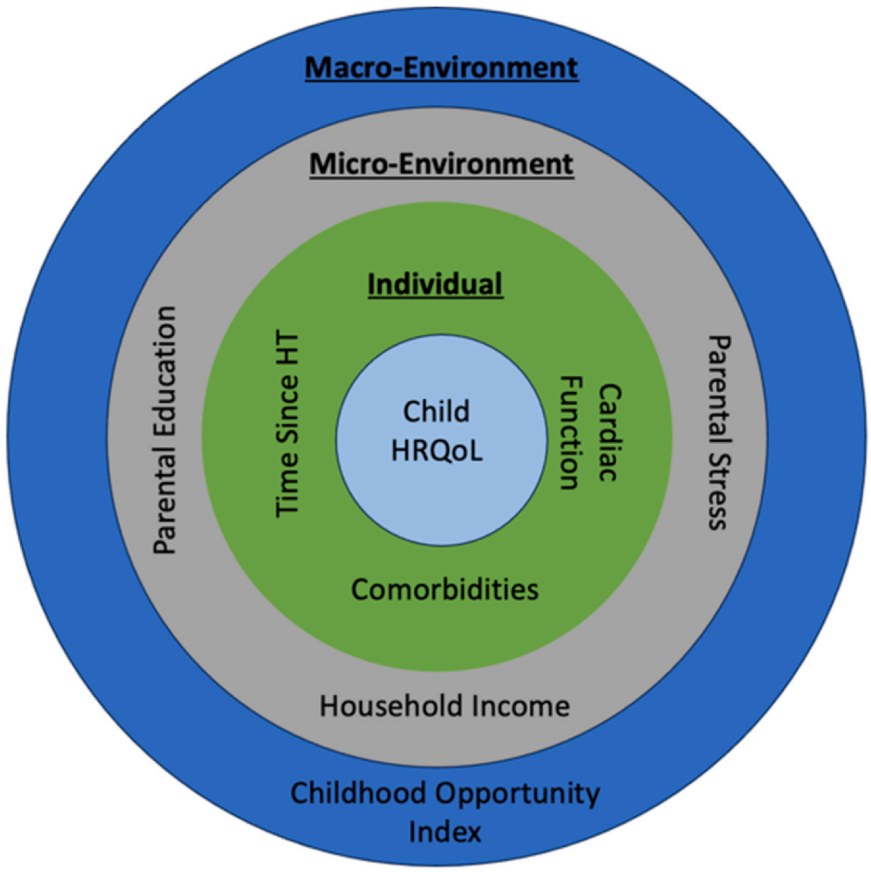

Figure 1 Conceptual model. HRQOL, health–related quality of life.

levels interact and ultimately influence the individual's health and well-being. Analogous conceptual frameworks have been used to study how environmental factors influence HRQOL in other pediatric chronic illness populations.[17]

Disentangling the ways in which these various factors influence HRQOL requires a large diverse sample, which is logistically challenging. As a first step, we performed a single–center cohort study to begin to identify which aspects of the individual, microenvironment, and macroenvironment are associated with HRQOL. Ultimately, improving HRQOL and functional status in pediatric heart transplant recipients is critical both as an end unto itself but also as a potential means of improving adherence and graft durability. A clearer understanding of the determinants of HRQOL may identify modifiable factors that may be targets for intervention. Identifying nonmodifiable factors will, at a minimum, help identify children who may benefit from other forms of support.

Methods

Study design and population

A single–center cross-sectional study with prospective data collection was performed at a free-standing tertiary care children's hospital between January 2019 and December 2021. Child-parent/guardian dyads were eligible if the child was between ages 8 and 18 years and had previously received a heart transplant. Exclusion criteria included recent transplant (within 6 months) because this period is characterized by intensive hospitalization and frequent medical procedures. For similar reasons, children were not eligible for enrollment while admitted to the hospital. If either the patient or their parent/guardian was unable to complete study instruments due to cognitive disability or inability to answer English language questionnaires, they were excluded because the primary study end-points depended on responses to study instruments. At the time of this study, some instruments were not available in other languages.

Potentially eligible child/adolescent participants were identified through review of a clinical database of heart transplant patients and upcoming outpatient clinic visits. To avoid selection bias, all eligible patients and their families who followed as outpatients were approached during planned clinic visits. Consent was obtained from parents/guardians and assent was obtained from patients before enrollment. All study procedures were approved by the Institutional Review Board of The Children's Hospital of Philadelphia. Deidentified study data and statistical methods will be shared on request after execution of a data use agreement. This study affirms compliance with the International Society for Heart and Lung Transplantation's Statement on Transplant Ethics.

Study measures

This study includes measurements from both PRO and extractions from the patient's medical record. The primary outcomes were cardiac-specific HRQOL measured using the Pediatric Cardiac Quality of Life Index (PCQLI)[18,19] and general HRQOL measured by the Pediatric Quality of Life 4.0 Core Scales (PedsQL).[20,21] The PCQLI was chosen because it incorporates both cardiac disease–specific symptoms and treatments into its assessment and therefore was thought to be a useful complement to the more general evaluation of the PedsQL. Reliability, construct validity, and generalizability have been demonstrated for both PCQLI and PedsQL.[21-23] Both parents reported and the subject reported PROs were collected.

Other PROs obtained were participant and parent-proxy measures of anxiety (Multidimensional Anxiety Scale for Children [MASC] and P-MASC[24,25]), resilience (Connor-Davidson[26]), and parent/guardian stress (PSI-4-SF[27]). Anxiety was chosen as an exposure of interest given its known prevalence in heart transplant patients and established association with post-transplant complications and adherence to immunosuppressive medications.[28] Given the promising development of interventional programs aimed at promoting resilience in children with cardiac disease and mitigating parental stress, measuring these characteristics in this population is an important step toward building effective interventions.[29,30] Impaired QOL has traditionally been defined as a score ≥1 standard deviation below normal,[31] and this threshold was used to assess QOL scores in our population. While QOL values vary by age, gender, and race, a score of >80 is generally consistent with normal QOL. MASC scores are translated into 1 of 6 hierarchical categories of anxiety, ranging from lower than average (T-score <40) to very elevated (T-score >70). Additionally, parents/guardians completed an investigator-designed survey to assess microenvironmental exposures, and included questions related to household income, education level, employment status, and perceived difficulties with paying monthly bills.

Clinical factors that we hypothesized with the potential to influence HRQOL were collected via manual review of the medical record. These included hemodynamic data from cardiac catheterizations, metabolic data from exercise stress tests, and information about clinical course such as initial diagnosis, time since transplant, medication burden, and current comorbidities. At our institution, it is the standard of care to perform cardiac catheterizations and exercise stress tests annually, and to have clinic visits with lab monitoring at least every 3 months. After a post hoc analysis, a pulmonary capillary wedge pressure (PCWP) of 10 mm Hg was determined to be the best cut point when evaluating wedge pressure in categorical form.

To collect information about the macroenvironment, participants' address was geocoded and spatially linked to their neighborhood tract (a geospatial unit of between 300 and 6,000 people) from the US Census, which was then linked to the Child Opportunity Index 2.0 (COI). COI is a composite index of child health and well-being that measures inequities across US communities.[32-34] It is available at the census tract level and is comprised of 29 indicator variables across 3 domains: education, health/environment, and social/economic. For each census tract, the COI provides a single metric (scored 1-100) and 5 categories of neighborhood opportunity from very low to very high. For

this exploratory analysis, COI was deliberately chosen based on its comprehensive nature and because of its organization into 3 distinct domains. We anticipated potentially identifying different associations of the education, health/environment, and social economic domains with HRQOL that could guide the next steps in this investigative pathway.

Statistical analysis

Traditional descriptive statistics were calculated. To generate the most accurate evaluation of factors potentially influencing HRQOL, a parameterized outcome variable of HRQOL was developed, accounting for correlations between PedsQL and PCQLI scores. This approach, combining cardiac-specific and general HRQOL into a single metric, has been modeled in other studies of HRQOL in children with cardiac disease.[22] Next, to evaluate the associations between individual, microenvironmental, and macroenvironmental exposures with HRQOL, generalized estimating equations (GEE) were calculated, including prespecified covariates. GEE models are well-suited for analyzing data with correlated observations and provide population-averaged estimates without strong distributional assumptions. A univariate regression model was used to screen a wide range of candidate predictors for total scores of HRQOL, encompassing microenvironmental and macroenvironmental determinants, as well as demographic and disease-specific characteristics. Multicollinearity among predictors was assessed using Pearson's correlation, which quantifies the strength and direction of a linear relationship between 2 continuous variables. For variables with measures of strong correlation, clinical judgment was used to determine which variable to include in the adjusted analysis. Candidate variables with a significance level of $p < 0.20$ were subsequently included in a multivariable regression model. Quasi-likelihood under the independence model criterion was utilized to evaluate the goodness of fit of the model and determine the best working correlation structure for GEE. Given that this study was inherently limited by sample size, and that the results are intended to be hypothesis-generating, a significance level of $p < 0.10$ was chosen a priori as the threshold for statistical significance.

Results

Study population

Over the study period, 59 heart transplant patients and their families were screened (Figure 2). Of the 50 potential patient-guardian dyads approached, 32 enrolled (64% enrollment). One patient's surveys were never returned and they were therefore excluded from analysis. Of the 31 patients included in the study, 52% were female, 32% self-identified as Black, 55% received public insurance, and 40% had congenital heart disease before undergoing heart transplant.

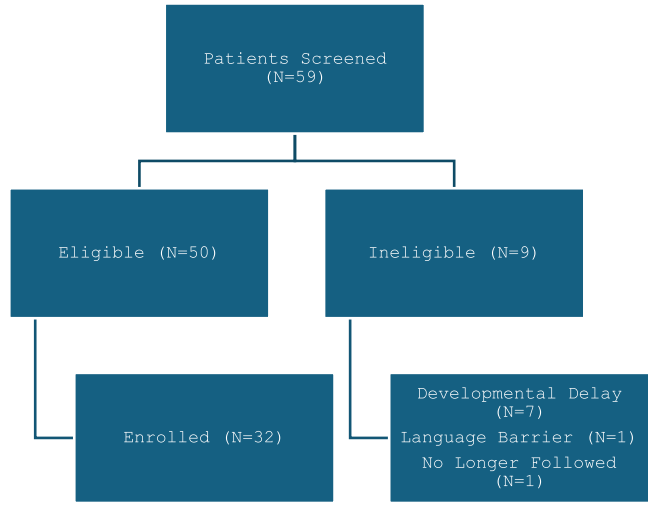

Figure 2 Cohort development.

The median age at the time of the study was 14.1 years (interquartile range [IQR] 11.8, 15.9) with a median duration from transplant of 6.3 years (IQR 1.4-11.8). There were 18 dyads approached who declined enrollment.

Clinical characteristics

On most recent annual surveillance cardiac catheterizations, the median cardiac index (CI) was 3.2 liter/min/m^2 (IQR 2.8, 3.6) and the median PCWP was 10.0 mm Hg (IQR 7.0, 12.0). The CI was low (< 3 liter/min/m^2) and the PCWP > 10 mm Hg in 39% of participants. Performance on annual surveillance exercise stress tests revealed low exercise capacity compared to cardiac normal peers; the peak maximum oxygen consumption (max VO_2) was low (27.6 ml/kg/min, IQR 21.9, 33.0) as was the median peak physical working capacity (1.9 W/kg, IQR, 1.5, 2.0) (Table 1).

HRQOL and other PRO

As shown in Figure 3, measures of both general and cardiac-specific HRQOL were low [PedsQL 71.7 (IQR 64.2-82.5), PCQLI 61.8 (IQR 55.7-74.8)], Table 4. In terms of anxiety, 67% of patients exhibited above-average levels by self-report. When evaluating resilience, patients showed scores reflecting slightly below average resilience, with room for improvement with a median score of 70 compared to a median score of 82 in the general population[25] (Table 2a).

Microenvironment

Most households had at least 1 parent/guardian who had completed college (58%) and were employed full time (52%). Three households had a combined annual income of ≤$40,000, while 10 had a combined annual income of > $150,000. More than one-fourth of parents/guardians (28%) expressed difficulties paying bills. Study instruments

Table 1 Demographics and Clinical Characteristics

Variable	N (%) or median [IQR25, IQR75]
Age	14.1 [11.8, 15.9]
Time since HT (years)	6.3 [1.4, 11.8]
Female sex	16 (51.6%)
Ethnicity	
Not Hispanic or Latino	30 (96.8%)
I prefer not to answer	1 (3.2%)
Race	
Asian	1 (3.2%)
Black or African American	10 (32.3%)
White	20 (64.5%)
Insurance coverage: government	16 (55.1%)
Initial diagnosis	
Cardiomyopathy	18 (60.0%)
Congenital heart disease	12 (40.0%)
LV systolic function (ejection fraction)	64.0 [60.0, 68.0]
Cardiac index	
≥3 liter/min/m^2	19 (61.3%)
(liter/min/m^2)	3.2 [2.80, 3.6]
Wedge pressure	
> 10 mm Hg	12 (38.7%)
(mm Hg)	10.0 [7.0, 12.0]
Max VO_2 (ml/kg/min)	27.6 [21.9, 33.0]
Peak physical working capacity (W/kg)	1.9 [1.5, 2.0]

Abbreviations: HT, heart transplant; IQR, interquartile range; LV, left ventricle.

showed elevated levels of parental stress and perceived levels of child anxiety (Table 2b).

Macroenvironment

The median overall neighborhood COI score was 73.0 (IQR 44.5, 89.5), though the results skewed toward areas with increased childhood opportunity, with > 60% of participants coming from high or very high COI neighborhoods. COI domains followed similar trends to the overall COI (Table 3, Figure 4).

Table 2a Participant Instruments

Variable	N (%) or median [IQR25, IQR75]
Connor-Davidson	70.0 [53.8, 85.3]
MASC: *t*-score	62.5 [54.0, 70.0]
MASC: *t*-score	
Average	10 (33.3%)
High average	4 (13.3%)
Slightly elevated	2 (6.7%)
Elevated	5 (16.7%)
Very elevated	9 (30.0%)

Abbreviations: IQR, interquartile range; MASC, Multidimensional Anxiety Scale for Children.

Associations with QOL

The results of the GEE univariate analysis are included in Table S1. An elevated PCWP, elevated parental stress level, and increased parental perceptions of child anxiety were all associated with lower HRQOL, while higher maximum oxygen consumption on cardiopulmonary exercise testing and increased measures of resilience were associated with better HRQOL. There were no detected associations between overall neighborhood COI or COI domains with HRQOL.

In a GEE multivariate model, including the variables identified above, a mean PCWP > 10 mm Hg (beta: −9.6 95% −16.3, −2.8 $p = 0.006$), an elevated level of parental stress (beta −0.2 95% confidence interval [CI] −0.4, −.01 $p = 0.036$), and increased parental perceptions of their

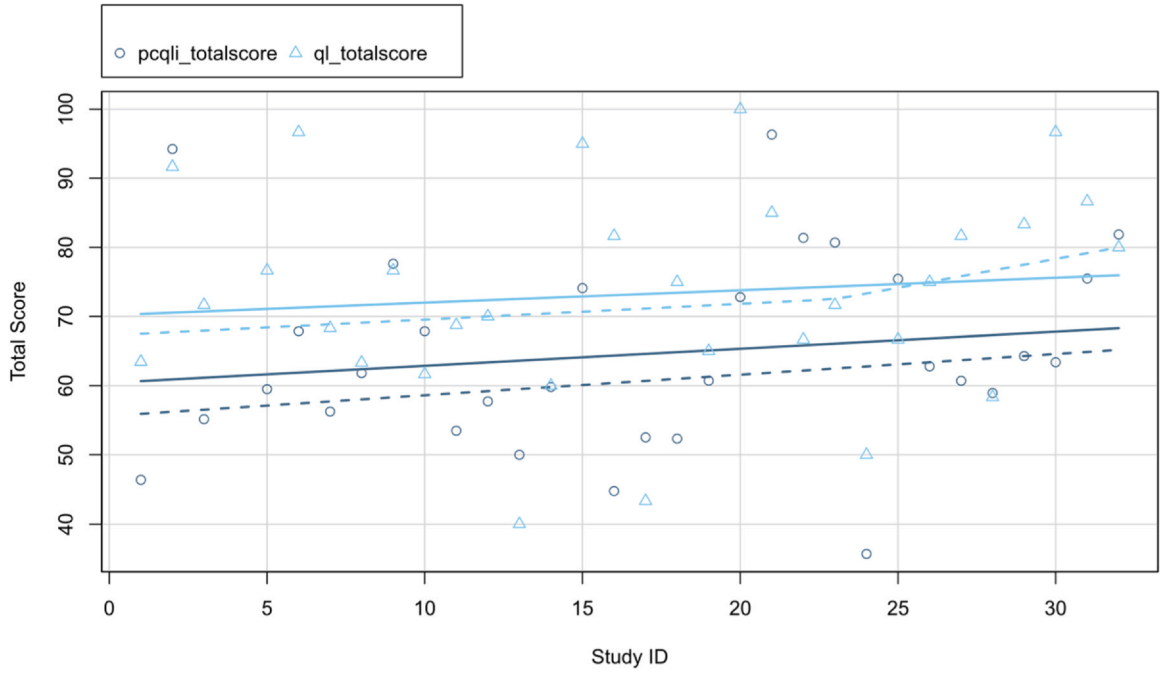

Figure 3 Patient quality of life scores.

Table 2b Parent/Guardian Instruments

Variable	N (%) or median [IQR25, IQR75]
Highest level of education	
Completed high school or GED	2 (6.9%)
Some college, technical, or trade school	3 (10.3%)
Completed 2-year degree with an associate's degree	6 (20.7%)
Completed 4-year college degree	7 (24.1%)
Some graduate schools	3 (10.3%)
Completed a master's or professional degree	7 (24.1%)
Prefer not to answer	1 (3.4%)
Employment status	
Employed full time	15 (51.7%)
Employed part time	5 (17.2%)
Not employed	3 (10.3%)
Homemaker	6 (20.7%)
Household income	
$40,000 or less per year	3 (10.2%)
$40,001-$90,000 per year	6 (20.6%)
$90,001- $150,000 per year	3 (10.2%)
More than $150,000 per year	10 (34.5%)
Prefer not to answer	7 (24.1%)
Difficulty paying bills over prior 6 months	8 (27.6%)
P-MASC: *t*-score	48.5 [43.3, 63.8]
Parental stress	64.5 [52.0, 77.8]

Abbreviations: IQR, interquartile range; GED, General Education Development Test.

child's anxiety (beta −0.2 95% CI −0.4, 0.1 $p = 0.058$) were associated with worse patient-reported HRQOL. An increased max VO_2 on Exercise Stress Test was associated with better patient-reported HRQOL (beta 0.4 95% CI −0.02, 0.9 $p = 0.059$) (Table 5, Figures 5 and 6).

Discussion

Pediatric heart transplantation remains the ultimate therapy for heart failure in children that is refractory to maximum medical care. The scarcity of transplantable pediatric hearts and persistent rate of death, while waiting for a transplant, underscore the importance of efforts to improve the lifespan of transplanted organs and the QOL of childhood heart transplant survivors. The current study identifies modifiable factors that may improve the health and well-being of these children, and which should be further evaluated in future research. In particular, these results reinforce that traditional measures of cardiopulmonary function (i.e., higher PCWP and worse performance on exercise testing), patient psychopathology (anxiety by parent-proxy report), and household environment (parental stress) were all associated with worse/lower HRQOL in models adjusting for measurable confounding. Even in a relatively small sample of patients, this underscores the importance of considering these factors in the health and well-being of this vulnerable population.

Lower exercise capacity, as measured by max VO_2, was associated with worse HRQOL in our cohort. The relationship between exercise and HRQOL is likely bidirectional, as opposed to causal. However, exercise interventions with adult heart transplant patients have demonstrated decreased rates of depression and anxiety and improved HRQOL,[35,36] and similar efforts are underway in pediatric patients.[37] Although most children have normal cardiac function after heart transplant (HT), they routinely have deficits in their exercise performance and physical activity levels.[38,39] The findings of this study suggest that targeting these deficits may be an important mechanism by which to improve not only cardiovascular well-being, but also QOL and mental health.

As transplanted hearts age, they all develop a gradual and progressive worsening of diastolic function, and our study showed that diastolic dysfunction was negatively associated with HRQOL. Diastolic dysfunction and elevated filling pressures drive many of the cardiac symptoms that are most

Table 3 Neighborhood Childhood Opportunity Index of Study Population

Variable name	N or median [IQR25, IQR75]
Neighborhood Child Opportunity Level: education	72.0 [50.5, 94.0]
Very low	4 (12.9%)
Low	3 (9.7%)
Moderate	5 (16.1%)
High	4 (12.9%)
Very high	15 (48.4%)
Neighborhood Child Opportunity Level: health and environment	63.0 [35.0, 84.5]
Very low	4 (12.9%)
Low	6 (19.4%)
Moderate	4 (12.9%)
High	7 (22.6%)
Very high	10 (32.3%)
Neighborhood Child Opportunity Level: social and economic	76.0 [45.5, 86.0]
Very low	4 (12.9%)
Low	4 (12.9%)
Moderate	3 (9.7%)
High	11 (35.5%)
Very high	9 (29.0%)
Neighborhood Child Opportunity Level: overall (N = 31)	73.0 [44.5, 89.5]
Very low	4 (12.9%)
Low	2 (6.5%)
Moderate	6 (19.4%)
High	7 (22.6%)
Very high	12 (38.7%)

Abbreviation: IQR, interquartile range

Table 4 HRQOL Scores

Variable	Median [IQR25, IQR75]
PedsQL	71.7 [64.2, 82.5]
PCQLI subject: total score	61.8 [55.7, 74.8]

Abbreviations: HRQOL, health–related quality of life; IQR, interquartile range; PCQLI, Pediatric Cardiac Quality of Life Index; PedsQL, Pediatric Quality of Life 4.0 Core Scales.

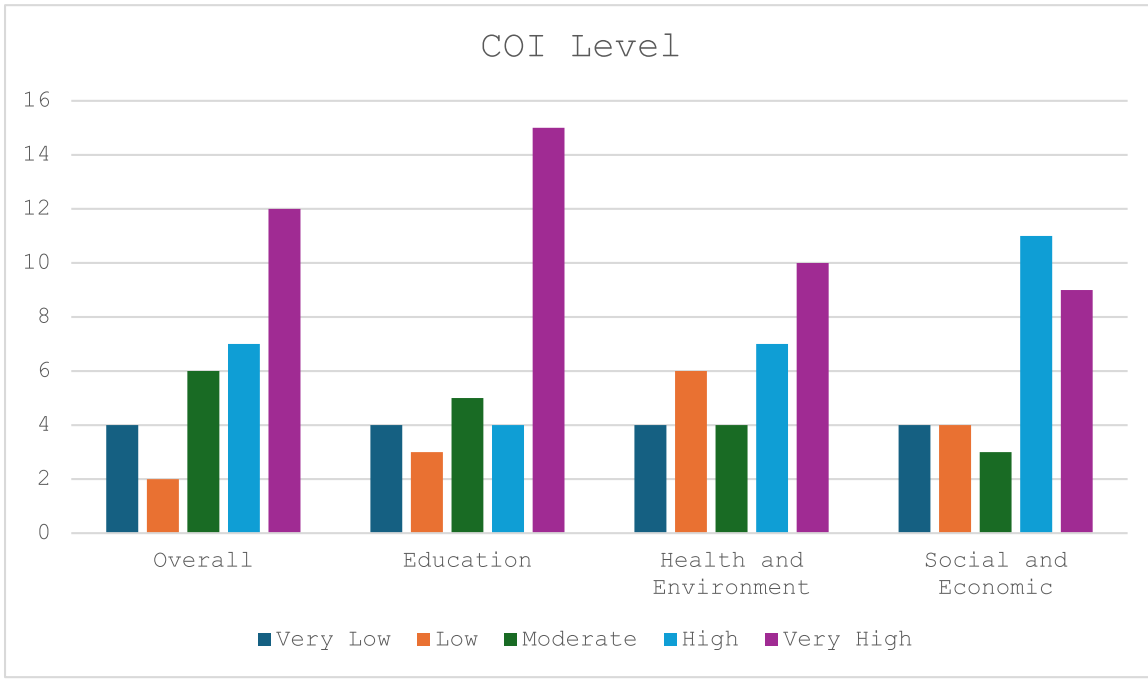

Figure 4 COI levels. COI, Child Opportunity Index.

Table 5 GEE Multivariate Model

Variable	Estimate	95% Confidence interval	*p*-value
Pulmonary capillary wedge pressure > 10 mm Hg	−9.56	−16.32, −2.79	0.006
Parental stress	−0.22	−0.42, −0.01	0.036
Max VO_2	0.42	−0.02, 0.9	0.059
P-MASC *t*-score	−0.20	−0.41, 0.01	0.058
Cardiac index	2.3	−3.23, 7.80	0.416
Self-blame score	−0.40	−2.31, 1.52	0.686

Covariates adjusted in the multivariate model include pulmonary capillary wedge pressure > 10 mm Hg, parental stress, self-blame score, P-MASC *t*-score, Max VO_2, and cardiac index.

limiting and intrusive for children after transplant, including dyspnea, and studies of adults with heart failure show that QOL is more impacted by diastolic than systolic dysfunction.[40] Unfortunately, there is a lack of medical therapies to address the impaired functional capacity that accompanies diastolic heart failure, which is a major clinical gap for children with elevated filling pressures. Recent trials of sodium-glucose contransporter-2 inhbitor (SGLT2i) have shown a positive impact on QOL in adults with heart failure with preserved ejection fraction (HFpEF),[41] and whether these results can be replicated in HT patients remains to be seen but is worthy of further investigation.

In addition to the potential physiologic contributions of diastolic performance to QOL, we identified that patient mental health independently impacts HRQOL. The anxiety identified in this population may be secondary to the

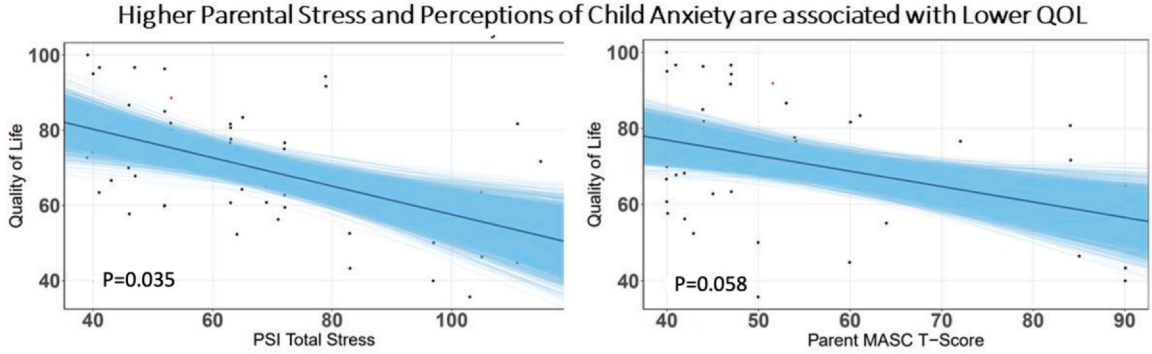

Figure 5 Higher parental stress and perceptions of child anxiety are associated with lower QOL. QOL, quality of life.

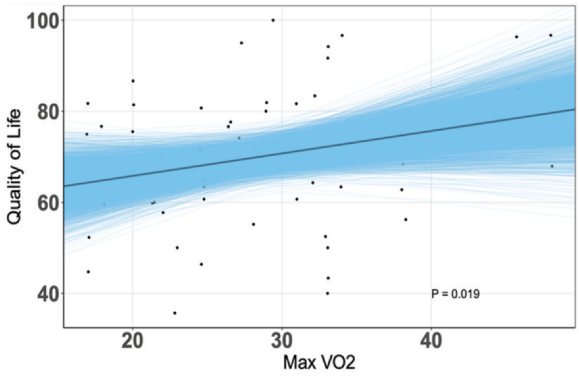

Figure 6 Higher exercise capacity is associated with higher QOL. QOL, quality of life.

stressors of adolescence but is potentially compounded by the psychological distress that develops as children get older and they are confronted with the finite survival of their graft. Our findings highlight that in addition to emphasizing long–term physical health, we must also address mental health comorbidities if the ultimate goals of heart transplant, improved quality, and quantity of life are to be achieved.

Anxiety is a pervasive issue in chronically ill children, and the current research highlights both its prevalence in pediatric transplant recipients and the potential influence it has on HRQOL. This underscores the importance of effective screening in these patients. In the current study, a discrepancy was identified in parent and patient-reported anxiety with respect to the association of anxiety and HRQOL. These discordances are common and emphasize the importance of capturing both child and parent-proxy measures.[42] Higher parent–reported child anxiety was associated with worse child HRQOL, but child self-reported anxiety was not. This finding is important; parental perception of child anxiety may reflect parental psychological distress, or parents may be identifying anxiety in their child that their children are either not aware of or reluctant to report due to perceived stigma. While the mechanism of this finding is uncertain, it emphasizes the importance of including parents in the assessment of their children's emotional well-being after transplant.

Heart transplant is a state of chronic disease characterized by daily medication use, frequent doctor visits and procedures, and intermittent bouts of acute illness. Caring for a medically complex child with chronic illness places tremendous emotional and financial stress on the family, which in turn influences QOL and emotional functioning in the child/patient.[43-45] Unlike other forms of chronic childhood disease such as inflammatory bowel[44] and chronic kidney disease,[45] the stress of caring for children after transplant is compounded by its inherently palliative nature; children transplanted in their early childhood are unlikely to survive into their fourth decade of life without a second heart transplant,[46] and our study demonstrates the significance of this impact on the family unit, with parents reporting markedly elevated levels of stress, and those increased ratings associating with worse HRQOL in their children.

Given the associations between parent and family factors and child QOL, a family-centric approach to care is warranted. A first step in identifying parental stress could include screening of parents at clinic visits. If high levels of stress are identified, parents should be referred for psychological counseling as appropriate and resources that may mitigate stress (transportation and food assistance, employment, and financial services) made available. Chronic childhood illness affects the entire family, and the impact of the disease on caregivers and the ensuing effect on the child should be taken into account when building effective care models.

While the results of this investigation did not show an association between macroenvironmental factors and QOL in children after transplant, we cannot disregard the possibility of type II error. In this fixed sample with inherent selection bias, we should not assume that the absence of associations is evidence of the absence of influence. Furthermore, the instruments used are not able to capture certain more granular details such as health care access or job flexibility. Both larger studies and mixed methods are necessary to explore the potential relationship.

Long–term graft survival relies on the patient to take their immunosuppression on a consistent basis. Even a slight lapse can precipitate an episode of rejection, with resultant effects on long-term survival. The association between mental well-being and adherence further emphasizes the importance of this investigation and raises the possibility that interventions that leverage the mechanisms identified to improve HRQOL could lead to improvements not only in QOL (an important end unto itself), but also in adherence and ultimately survival.

Limitations

In addition to those already addressed, we acknowledge that, as a cross-sectional study, causal inference is limited. As a single-center study, generalizability is limited, and multi-institutional studies are an important next step in better understanding these issues. Also, despite our best efforts, unmeasured confounding is possible. In addition, as a fixed sample, type II error is possible. The results from the eligible dyads who did not participate may have been different from those who did, and our population skewed toward high COI, which may have limited our ability to detect macroenvironmental associations. Finally, though a panel of PRO sought to capture salient aspects of patient experience, complementing this approach with a mixed-methods approach could help determine what aspects of patient experience are most relevant.

Conclusion

HRQOL in children after heart transplant is influenced not only by traditional measures of cardiovascular function, but also by patient psychology and their household environment, highlighting the utility of using an adapted ecological systems framework to more completely understand

HRQOL. Additional work in a larger and more heterogeneous cohort is necessary. Ultimately, improving health and well-being in this population will require a proactive approach that addresses both clinical and nonclinical factors.

CRediT authorship contribution statement

Jonathan B. Edelson: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Jing Huang:** Methodology, Software, Data curation, Visualization, Formal analysis. **Zi Wang:** Methodology, Software, Data curation, Visualization, Formal analysis. **Vicky Tam:** Conceptualization, Methodology, Writing – review & editing. **Debra Lefktowitz:** Conceptualization, Writing – review & editing. **Matthew J. O'Connor:** Writing – review & editing. **Rachel White:** Conceptualization, Writing – review & editing. **Lynne Ha:** Resources, Writing – review & editing. **Carol A. Wittlieb-Weber:** Writing – review & editing. **Joseph W. Rossano:** Writing – review & editing. **Kimberly Lin:** Conceptualization, Writing – review & editing. **Melissa K. Cousino:** Conceptualization, Methodology, Writing – review & editing. **Meghan Lane-Fall:** Supervision, Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Michael L. O'Byrne:** Supervision, Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2025.100250.

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