Assessment of quality of life in pediatric patients with pulmonary hypertension

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Abstract
The aim of this study is to evaluate quality of life in four domains (physical, emotional, social, and school) in pediatric patients with pulmonary hypertension (PH) using a validated survey (PedsQL). This is a prospective cohort study of pediatric patients aged 2–18 years with PH. Parents of all children and patients aged 8–18 years with appropriate developmental capacity completed the PedsQL survey in the clinic. Results were compared with published norms for pediatric patients, those with congenital heart disease (CHD) and cancer. Thirty-three children were enrolled yielding 32 parent and 18 patient self-reports: seven patients were aged 2–4 years; three were aged 5–7 years; 11 were aged 8–12 years, and 12 were aged 13–18 years. Twenty-one patients were classified as World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH), 11 WHO Group III PH due to lung disease, and one WHO Group V with segmental PH. Thirteen patients were NYHA functional class (FC) 1, 12 were FC 2, eight were FC 3, and none were FC 4. The PH cohort had significantly lower scores than healthy children in all domains on both parent and self-report. The PH cohort also had significantly lower scores than patients with CHD (parent report: total, physical, social, school; patient self-report: total, physical, school) and cancer (parent report: school; patient self-report: physical, school). Close to 50% of participants reported at risk scores in each domain. The quality of life in pediatric PH patients assessed by PedsQL revealed functional impairment in multiple domains. Administration of the PedsQL during outpatient encounters may provide an easy, reproducible method to assess quality of life and direct referral for interventional services.

Keywords
functional ability/impairment/quality of life/physical activity, pediatric cardiovascular disease, pulmonary hypertension

Introduction
Pulmonary hypertension (PH) is a progressive disease characterized by elevation of pulmonary vascular resistance (PVR), ultimately leading to right ventricular (RV) failure and premature death. In the NIH Primary Pulmonary Hypertension registry, median adult survival before advent of pulmonary vasodilator therapy was 2.8 years, with even worse outcomes in pediatric patients.¹ Reflecting current practice, the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) reported five-year survival in childhood pulmonary hypertension of 74±6%.² With more widespread use of prostacyclin therapy, even the sickest patients now approximate this improved survival.³,⁴

Interest in pediatric PH has grown, with expansion of the World Health Organization (WHO) Group classification system for PH to include pediatric-specific forms and the development of the Panama classification system for pediatric PH specific to pediatric disorders.⁵,⁶ Clinical trials are focusing on pediatric patients and use of FDA-approved therapies for adults with PH known to improve functional status. Appropriately, with improved survival and treatment...
options, clinicians start to focus on improvements in quality of life (QOL) as well as quantity of life.

Mullen et al. recently described QOL and parental adjustment in pediatric PH using parent-reported measures, concluding that decreased QOL negatively impacted parents and warranted intervention to support families.1 No previous studies, however, have examined QOL as reported by pediatric patients with PH or compared patient perception of QOL to parents or their age-matched healthy and disease cohorts.

The purpose of this study is to assess QOL in pediatric patients with PH using a validated survey to compare PH patients to published norms for healthy children and those with other chronic illness. In addition, patient- and parent-administered surveys allow comparison of patient- and parent-perceived QOL. We hypothesize that pediatric patients with PH will have a lower QOL across four domains of functioning (physical, emotional, social, school) compared to healthy children and those with congenital heart disease (CHD) and cancer. In addition, we hypothesize that parents and patients will differ, particularly in the emotional functioning domain, with patients reporting more emotional problems than their parents.

Methods

This is a prospective, cohort study approved by the Children’s Hospital of Wisconsin Institutional Review Board. Patients aged 2–18 years with a diagnosis of PH requiring medical therapy were eligible for inclusion in the study. Written parental consent and patient assent (when applicable) were obtained during routine outpatient clinic visits in the Pediatric Pulmonary Hypertension Program at the Herma Heart Institute.

The Pediatric Quality of Life Inventory Generic Core Scales (PedsQL 4.0™) is a validated QOL survey that assesses four domains: Physical Functioning; Emotional Functioning; Social Functioning; and School Functioning.8 The Psychosocial Health Score is calculated as the mean of the sum of the items from the Emotional, Social, and School Functioning Scales. The PedsQL 4.0 – Parent Report was administered in clinic to available parents. Patients aged 8–18 years with the appropriate developmental capacity completed the PedsQL 4.0™ Child or Teen Report. Both the parent report and child/teen self-report survey questions utilize a 5-point Likert (0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = always). Items are reverse-scored and linearly transformed, resulting in a score of 0–100; higher scores represent better child QOL. Patients were categorized based on age for comparison: 2–4 years (toddlers); 5–7 years (young children); 8–12 years (children); and 13–18 years (adolescents); based on the ages used in the versions of the PedsQL 4.0 Generic Core Scales.8

Responses were collected in a HIPAA-secure REDCap database along with demographic and clinical information to grade disease severity, including prior studies (echocardiogram, cardiac catheterization) and medication treatment (drug therapy specifically for PH).9

Z-tests were used to compare patient and parent-proxy scores to national norms.10 The percentage of scores reported in each domain lower than one standard deviation below the mean for healthy children were defined as “at risk.”8 Responses by patients versus parent-proxy to the same questions were compared using paired t-tests (or Wilcoxon signed rank tests). Mann–Whitney and Kruskal–Wallis tests were performed to compare QOL measurements between groups based on categorical characteristics, such as gender, race, or diagnosis. Spearman rank correlations were used to investigate the relationship between QOL and quantitative variables (such as PVR) or ordinal characteristics (such as WHO functional class [FC]). A P value < 0.05 was considered statistically significant. IBM SPSS Statistics v.20 was used for analysis.

Results

Patient characteristics

Thirty-three pediatric patients with PH were enrolled in this study between April and September 2017. One parent of an 18-year-old was unable to complete the survey after consent was obtained, rendering 32 parent surveys and 18 self-report surveys. Five patients aged 8–18 years (four aged 8–12 years and one aged 13–18 years) did not complete the self-report survey due to developmental delay. Demographic information including age, sex, ethnicity, age at diagnosis, and classification of PH are shown in Table 1. Treatment characteristics are shown in Table 2.

PedsQL survey

QOL scores for the PedsQL surveys for the cohort are shown in Fig. 1 along with published values for healthy children and those with CHD and cancer.10 Overall, the PH cohort scored significantly lower than healthy children in total score and all domains, as reported by both parents and patients.

In the parent report, PH patients scored significantly lower compared to those with CHD in total score as well as physical, social, and school functioning. PH patients also scored significantly lower in school functioning in the parent report compared to those with cancer.

In the patient self-report, PH patients scored significantly lower compared to those with CHD in total score as well as physical and school functioning. PH patients also scored significantly lower in physical and school functioning in the patient self-report compared to those with cancer.

Scores for the PH cohort are plotted against scores for healthy children and those with congenital heart disease and cancer in Fig. 1a (parent report) and Fig. 1b (patient self-report). There were no domains in which PH patients scored better than the disease controls.
Scores for each age group are shown in Fig. 2a (parent report) and Fig. 2b (patient self-report). There were no significant differences between parent and patient report in any domain. Overall, close to 50% or more of survey participants reported at risk (lower than one standard deviation below mean for healthy children) scores in each domain (Table 3). Most notably, 69% of parents reported at risk scores for school function while 66.7% of patients reported at risk scores for physical function.

Overall, PedsQL scores were not associated with sex, ethnicity, or WHO or Panama group diagnostic classification. Several markers of severity of disease including physician assessment of FC, number of medications and mean pulmonary artery pressure were associated with lower QOL score in the parent and/or patient self-report as shown in Table 4. RV systolic function by echocardiogram, cardiac index by catheterization, 6-min walk test distance, and NT-proBNP were not associated with differences in the distribution of QOL scores.

### Table 1. Demographics.

| Age (years) | Median (range) or n (%) |
|-------------|------------------------|
| Toddlers (2–4) | 7 (21.2) |
| Young children (5–7) | 3 (9.1) |
| Children (8–12) | 11 (33.3) |
| Adolescents (13–18) | 12 (36.4) |

**WHO Nice classification**

1. Pulmonary arterial hypertension
   - PAH associated with congenital heart disease (n = 10)
   - PAH associated with connective tissue disease (n = 1)
2. PH due to lung disease and/or hypoxemia
3. PH with unclear/multifactorial mechanisms (segmental PH)

**Panama classification**

1. Prenatal or developmental PH vascular disease
2. Pediatric cardiovascular disease
   - Systemic to pulmonary shunts (n = 2)
   - Post-operative PAH (n = 6)
   - PVD following staged palliation for single ventricle physiology (n = 1)
   - PVD association with congenital abnormalities of the pulmonary veins (n = 2)
3. Bronchopulmonary dysplasia
4. Isolated pediatric PAH
5. Pediatric lung disease
6. PVD associated with other system disorders

### Table 2. Patient characteristics.

| Medical therapy | Median (range) or n (%) |
|-----------------|------------------------|
| PDE-5 inhibitor | 30 (90.9) |
| Endothelin receptor antagonist | 15 (45.5) |
| Prostacyclin | 16 (48.5) |
  | Parenteral (n = 11) |
  | Inhaled (n = 3) |
  | Oral (n = 2) |

**WHO FC**

| FC | Median (range) or n (%) |
|----|------------------------|
| 1 | 13 (39.4) |
| 2 | 12 (36.4) |
| 3 | 8 (24.2) |
| 4 | 0 |

**Panama FC**

| FC | Median (range) or n (%) |
|----|------------------------|
| I | 12 (36.4) |
| II | 12 (36.4) |
| IIIa | 8 (24.2) |
| IIIb | 1 (3.0) |
| IV | 0 |

**RV function (by echocardiogram)**

| RV function | Median (range) or n (%) |
|-------------|------------------------|
| Normal | 19 (57.6) |
| Mild dysfunction | 8 (24.2) |
| Moderate dysfunction | 5 (15.2) |
| Severe dysfunction | 1 (3.0) |

**Cardiac index (most recent catheterization)**

| Cardiac index | Median (range) or n (%) |
|---------------|------------------------|
| >3 L/min/m²² | 26 |
| <3 L/min/m²² | 4 |
| Not available | 3 |

**6-min walk test (m) (n = 18)**

| 6-min walk test | Median (range) or n (%) |
|-----------------|------------------------|
| 348.6 (176.3–546.5) | 156 (15–4770) |

### Discussion

By assessing QOL in pediatric patients with PH using a validated tool to compare to healthy children and those with CHD and cancer, this study demonstrated worse perceived QOL by both parents and patients with PH. Specifically, when compared to healthy children, the patients with PH scored significantly lower in all assessed domains of functioning. In addition, patients with PH had significantly lower QOL in several domains of functioning, based on parent and patient self-report, when compared to...
those with CHD and cancer. This is consistent with a previous study evaluating QOL and parental adjustment in caretakers of pediatric patients with PH, in which parents reported significantly lower patient QOL than healthy norms in total, psychosocial, and physical domains.

Interestingly, there was no difference in any domain between the parent and patient reports of patient QOL in this study, which is in contrast to previous studies that have shown limited agreement between parent and patient self-report of QOL, particularly in the areas that are less observable, such as social support and emotional functioning. It is possible that there is more agreement between parents and patients with PH because the degree of impairment in functioning seen in PH compared to other chronic illnesses is more significant, making it more obvious to both parents and patients what domains are affected.

As expected, several markers of disease severity were significantly associated with lower PedsQL scores. Based on correlation with WHO and Panama FCs, there appears to be good correlation between physician and parent/patient assessment of global function. There were also differences in responses from parents of toddlers compared to children and adolescents, perhaps demonstrating worse functioning in older patients with more advanced disease.

As survival with pediatric PH has improved with the advent of new medical therapy for adults with PH, there is a greater focus on improving QOL. As clinicians caring for children, it seems obvious that physical, emotional, social, and school functioning should be addressed during routine medical care, although there are few data to suggest what impairments exist in these domains of functioning in this population. This study illustrates that as a chronic illness, PH affects QOL even more so than other types of pediatric chronic illness. This is likely related to the progressive and fatal nature of PH with progressive decline in exercise tolerance and inability to keep up with peers as evidenced by the majority of patients in NYHA FC II and III.

Impairment may also be related to the therapy for PH, which involves frequent medications and for the majority of our patients on prostacyclin therapy, continuous parenteral therapy. This reflects our practice strategy, to be more aggressive up front with parenteral therapy in those with heart failure, syncope, or severely abnormal hemodynamics. It also represents a bias in this study population as the short duration of the study allowed more opportunity for enrollment of patients on parenteral therapy who are seen more frequently. We do our best to empower families to make a decision together when recommending prostacyclin therapy with the goal being to optimize QOL for the child, which may start with aggressive treatment of the disease to improve FC. As new oral medications become available for PH, certainly consideration of transition from parenteral therapy for those with improvement in hemodynamics to improve QOL is an option that should be considered.

Fig. 1. PedsQL scores PH vs. other pediatric populations (reported as mean) by parent report (a) and patient self-report (b). *P < 0.05 compared to healthy; †P < 0.05 compared to CHD; ‡P < 0.05 compared to cancer.
Fig. 2. PedsQL scores by age (reported as mean) by parent report (a) and patient self-report (b). *$P < 0.05$ compared to children; $\circ P < 0.05$ compared to adolescents.

Table 3. Percentage of at risk scores by domain (lower than one standard deviation below mean for healthy).

| Parent report | Patient self-report |
|---------------|---------------------|
|              | Total (%) | Physical (%) | Psychosocial (%) | Emotional (%) | Social (%) | School (%) | Total (%) | Physical (%) | Psychosocial (%) | Emotional (%) | Social (%) | School (%) |
| Total (%)     | 59.4      | 46.9         | 69               | 46.9          | 69         |           |           | 61.1         | 66.7         | 61.1        | 50         | 50         | 61.1        |

Table 4. Relationship of PedsQL scores with patient characteristics (correlation coefficient: all noted statistically significant with $P < 0.05$, others non-significant [NS]).

| Parent report | Patient self-report |
|---------------|---------------------|
|              | Total | Physical | Psychosocial | Emotional | Social | School | Total | Physical | Psychosocial | Emotional | Social | School |
| ↓ WHO FC     | $-0.551$ | $-0.418$ | $-0.420$ | NS | $-0.446$ | $-0.564$ | $-0.559$ | $-0.617$ | $-0.633$ | $-0.585$ | $-0.567$ |
| ↓ Panama FC  | $-0.572$ | $-0.497$ | $-0.380$ | NS | $-0.468$ | $-0.488$ | $-0.711$ | $-0.685$ | $-0.644$ | $-0.469$ | $-0.742$ | $-0.557$ |
| ↑ Medications (n) | NS | NS | NS | $-0.378$ | NS | NS | NS | NS | NS | NS | NS | NS |
| ↑ Pulmonary artery pressure (mean) | $-0.501$ | NS | $-0.414$ | $-0.532$ | NS | NS | $-0.615$ | NS | NS | NS | NS | NS |
In patients with CHD, routine PedsQL assessment was completed in 176 patients aged 8–18 years, with 38% reporting significant problems in at least one domain and 30% of patients receiving intervention, such as counseling or referral to a specialist.13 Health-related QOL has become important as survival with complex CHD continues to improve, with research focused on not only physical and neurodevelopmental outcomes but psychosocial morbidity as well.14 The high percentage of parent and patient self-reports with at risk scores in every domain in this study highlight this importance in our patient population.

While this was a prospective study, there are several limitations to the study design. First, the small sample size may limit the ability to detect statistical differences in certain domains of functioning. Even so, we were able to show statistically significant differences in many areas, likely highlighting the significant impairment in functioning in this chosen patient population. Second, several of our patients (especially those with Group III PH due to lung disease) have co-morbidities that may also affect their QOL. However, we included these patients in order to capture a representative sample of patients seen in pediatric PH centers to allow for better external validity. Third, assessment of RV function by echocardiography was subjective but still included as few patients in the study group had cardiac magnetic resonance imaging. Finally, as this study was cross-sectional in nature, we did not have the ability to assess changes over time.

Interestingly, we recognized important deficiencies in functioning in several encounters leading to immediate intervention. One parent was found to be illiterate and two patients were having difficulties with school function and were referred to our school liaison. This highlights the importance of incorporating an assessment of QOL (be it a formal survey or direct questioning about these domains of functioning) into routine clinic encounters to identify problems early in order to make needed referrals, for example, for psychological counseling.

QOL screening has been shown to be practical and feasible to perform in a pediatric cardiology clinic,13 and is consistent with recommendations from the American Heart Association and American Academy of Pediatrics14 to assess psychosocial morbidity in these patients. Future directions include developing a formal referral process for various specialty programs (school intervention, neurodevelopmental assessment, psychology, cardiac rehabilitation) based on specific results of the PedsQL surveys.

In conclusion, this study demonstrates decreased QOL in pediatric PH patients compared to healthy children, and even those with CHD and cancer. PH teams have the opportunity to improve QOL in these patients by incorporating multidisciplinary specialists that can address problems in physical, emotional, social, and school functioning.

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