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Quality of Life and its Determinants in a Multi-Center Cohort of Children with Alagille Syndrome

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Abstract

Objectives—To assess health-related quality of life (HRQOL) in children with Alagille syndrome (ALGS) in comparison with healthy and other liver disease cohorts, and to identify determinants of HRQOL in patients with ALGS.

Study design—Within the Childhood Liver Disease Research Network prospective study of cholestasis, Pediatric Quality of Life Inventory™ (PedsQL) questionnaires were administered to 70 ALGS, 95 alpha-1-antitrypsin deficiency (A1ATD) and 49 children with other causes of chronic intrahepatic cholestasis (IHC) aged 5-18 years. Parent-proxy PedsQL scores were recorded for children aged 2-18 (98 ALGS, 123 A1ATD, 68 IHC).

Results—Mean ages and total bilirubin (mg/dL) were: ALGS 9.4y; 4.4, A1ATD 9.5y; 0.7, IHC 10.3y; 2.9. ALGS child PedsQL scores were lower than in healthy children and children with A1ATD (mean 73 vs. 83 p=0.001). Children with ALGS and IHC were similar, except in physical scores (73 vs. 79 p=0.05). ALGS parents perceived their children to have worse HRQOL than A1ATD (p<=0.001) and marginally lower compared with IHC. Univariate analysis revealed ALGS child-reported scores were positively associated with better growth and inversely with total bilirubin. Growth failure, elevated INR and an intra-cardiac defect were predictive of poor parental scores (p<=0.05). In multivariate analysis, only weight z-score remained significant for child and parent-reported scores.

Conclusions—HRQOL is impaired in ALGS compared with healthy and children with A1ATD, similar to IHC and is associated with growth failure, which is a potentially treatable cause of impaired HRQOL.

Keywords

health-related quality of life; cholestasis

Alagille syndrome (ALGS) is an autosomal dominant disorder that affects the liver, heart, eyes, face, skeleton, kidneys and vasculature (1, 2). Children with chronic disease in any one of these systems alone may have impairment of their health-related quality of life (HRQOL), however investigations of HRQOL in ALGS, as well as other causes of chronic pediatric liver disease, have been limited. Most studies have focused on HRQOL in liver transplant (LT) recipients (3-9) or biliary atresia (10) and have demonstrated that pediatric LT recipients have lower HRQOL outcomes than healthy children. There is scant literature regarding HRQOL in specific pediatric liver diseases and very few patients with ALGS have been captured in the transplant studies.

ALGS has unique manifestations that may affect HRQOL. The cholestasis-related pruritus of ALGS is amongst the most severe of all liver disease resulting in cutaneous mutilation and disrupted sleep and school activities. Children with cholestatis and ALGS often have disfiguring xanthomas, and linear growth retardation, poor weight gain, and decreased bone

mineral density are common. Finally significant cardiac involvement or renal dysfunction may independently impact exercise tolerance and school attendance. As each of these factors may impact HRQOL across multiple domains, there is a rationale for studying HRQOL in ALGS.

One prior study of HRQOL in ALGS utilized the CHQ-PF50 questionnaire. This documents parental responses only (11), but provides preliminary insight into the problem. Parents of children with ALGS reported substantially lower HRQOL than parents of healthy children. Significant cardiac disease, a mental health diagnosis and sleep problems were associated with lower CHQ scores. These data reinforce the need to systematically characterize HRQOL in ALGS.

The objectives of the current study were to capitalize on a large ongoing prospective multi-centered study of childhood cholestatic liver diseases, further characterize HRQOL in ALGS, and identify its determinants. We compared HRQOL in children with ALGS with liver disease to previously published normative data, and to two other groups of pediatric liver diseases, one with minimally cholestatic chronic liver disease, alpha-1-antitrypsin deficiency (A1ATD), and one that included children with other forms of chronic intrahepatic cholestasis (IHC) including patients with progressive familial intrahepatic cholestasis (PFIC). The significance of understanding HRQOL and its determinants in ALGS lies in identifying treatable causes of impaired HRQOL.

Methods

This is a cross-sectional study of HRQOL in a cohort of patients with ALGS with liver disease. Subjects in this study were enrolled in the Longitudinal Study of Genetic Causes of Intrahepatic Cholestasis (LOGIC) protocol organized under the Childhood Liver Disease Research Network (ChiLDReN), an NIDDK/National Institutes of Health-funded network of 16 pediatric academic medical centers across North America. This study was approved by Institutional Review Boards at each center and informed consent was obtained from parents/guardians or subjects 18 years or older, and assent from children 7 years and older.

LOGIC is a longitudinal observational study of the natural history of several genetic causes of intrahepatic cholestasis, including ALGS, A1ATD and PFIC. Defined data elements are collected in a prescribed fashion at yearly intervals for up to 10 years, or until death. Pertinent data about past history including major illness, hospitalizations, and surgery, along with growth parameters and standard laboratory evaluations are recorded annually. Upon enrollment into the study, and annually thereafter, the Pediatric Quality of Life Inventory™ (PedsQL™) 4.0 Generic Core Scale is administered to children ages 5 and older and to the parents of children 2 years to 18 years of age (12).

Study subjects were between 2 and 18 years of age, had not undergone liver transplantation, had confirmed ALGS, A1ATD or chronic intrahepatic cholestasis (IHC) by set diagnostic criteria, and had evidence of liver disease. Cholestasis was defined by either fasting total serum bile acid greater than three times the upper limit of normal for age; direct bilirubin > 2 mg/dL; fat-soluble vitamin deficiency otherwise unexplainable; gamma glutamyl transferase

greater than three times the upper limit of normal for age; and/or intractable pruritus explainable only by liver disease.

Subjects were confirmed as ALGS by standard clinical criteria and/or the presence of a disease-causing mutation in *JAGGED1* or *NOTCH2*. The clinical criteria were at least 3 of the following: bile duct paucity on liver biopsy, heart murmur or cardiac anomaly; posterior embryotoxon or other anterior chamber defect; butterfly vertebrae; characteristic facial features and renal anomalies. Patients with A1ATD had low alpha-1 antitrypsin concentrations, and PIZZ or PISZ phenotype or genotype, and evidence of liver disease. Patients with IHC were defined by biochemical evidence of cholestasis for greater than six months, or two mutant alleles of *ATP8B1*, *ABCB11* or *ABCB4*, without another definable cause of cholestasis. By definition this group of patients was heterogeneous with broad inclusion criteria to capture those with unknown causes of PFIC and others with chronic cholestasis for which the genetic cause was yet to be identified. At the time of data analysis , the total number of patients for each disease in LOGIC were ALGS: n=146; IHC: n=126; and A1AT: n=169.

Measurement of HRQOL

The PedsQL™ 4.0 Generic Core Scale (PedsQL) is a validated, 23-item modular instrument designed to measure HRQOL in children and adolescents. The PedsQL includes parallel child self-report and parent proxy–report versions. The PedsQL assesses child HRQOL across 4 domains: Physical Functioning, Emotional Functioning, Social Functioning and School Functioning. The PedsQL also yields 3 summary scores: Total scale score, Physical Health Summary and Psychosocial Health Summary (12). Items are reverse scored and linearly transformed to a scale of 0-100, with higher scores indicating better HRQOL. The published validation study identified a value one standard deviation below the population mean for the PedsQL Total Score (69.7 for child self-report and 65.4 for parent-proxy) as a threshold score for an at-risk status for impaired HRQOL relative to the population sample (13). HRQOL scores were examined by age group and in aggregate for both child self-report and parent proxy-report.

Statistical Analyses

Mean and median PedsQL 4.0 Generic Core Scale and Summary scores were calculated for the ALGS, A1ATD and IHC cohorts. Wilcoxon two sample tests were used to compare scores between patients with ALGS and A1ATD, and then between patients with ALGS and IHC. Differences in mean scores and effect sizes were calculated to determine the magnitude of difference by subtracting the ALGS mean from the A1ATD or IHC mean and then dividing by the pooled standard deviation (14). Aggregate data including mean and standard deviation for the healthy population were cited from the literature (13). Effect sizes were calculated by subtracting the ALGS mean from the healthy mean and then dividing by the standard deviation for the healthy population. Effect sizes are designated as small (0.20 – 0.49), medium (0.50-0.79), or large (0.80 or >) in magnitude (14).

Agreement between child self-report and parent proxy-report was examined by Intra-class Correlation Coefficient (ICCs) with the 95% confidence intervals (15). ICCs are designated

as poor to fair (<=0.40), moderate (0.41-0.60), good (0.61-0.80), or excellent (0.81-1.00) in agreement (16).

For the subjects with ALGS, univariate regression analysis was employed to identify demographic and health status variables that were associated with impairments in HRQOL in total, physical, and psychosocial summary scores. Factors identified in univariate analysis at the $p < 0.1$ level as potential predictors of HRQOL entered a multivariate model. Effect selection procedure was used to finalize the multivariate model with the significant effects. Model diagnosis was checked to ensure the model assumptions were satisfied in the framework of general linear models. Separate analyses were conducted for the child self-report and parent proxy-report scores, given the possibility that different predictors could emerge. All statistical analyses and plots were performed in SAS 9.2 for Windows (SAS Inc., Cary, NC).

Results

Health-related Quality of Life in ALGS

Ninety-eight children with ALGS were studied, including 70, aged 5 - 17.4 years, for whom child-self reports were obtained. Their demographic and medical characteristics are summarized in Table IV (available at www.jpeds.com). Parent-proxy PedsQL scores were obtained from 98 parents of children with ALGS aged 2 – 17.4 years. Demographic variables were similar between the 70 patients with ALGS that completed the self-report and 28 younger children in whom there were parent-proxy reports only. Seven of the parents (7%) were themselves affected by ALGS (by self-report). As expected, the study cohort was cholestatic with a mean ± SD total bilirubin 4.4 ± 6.2 mg/dL. The group did not have of end-stage liver disease, broadly defined by INR levels <1.5 and platelet count >150,000/mm^3 and only 1 patient had undergone a biliary diversion.

ALGS HRQOL scores were compared with aggregated healthy pediatric population data (13). The 2 groups had similar ages; 9.4±3.1 (ALGS) and 7.9±4.0 years (healthy). Children with ALGS demonstrated significant impairments in HRQOL reporting lower scores with almost universal large effect sizes (Total scores: ALGS 69.86 ± 16.09 vs. Healthy 83.91 ± 12.47, effect size 1.12) (Table I). The largest effect size was seen in the physical domain. The parent-proxy scores were also significantly lower in ALGS across all measured domains, but with mostly moderate effect sizes.

Intra-class correlation coefficients (ICCs) were used to assess differences in perceptions of HRQOL between 62-paired child and parent reports. There was variation in the ICCs across different scales and age groups (Table V; available at www.jpeds.com). Among 5-7 year olds, there was poor to fair agreement between child and parent. The ICCs appeared to be better for the teenage group, but this class also had the fewest subjects (n=8 out of 62).

Health-related Quality of Life in Alpha-1-antitrypsin deficiency

Ninety-five children with A1ATD were enrolled with a mean age of 9.5 years (SD 3.9) and mean total bilirubin 0.7mg/dL (SD 0.8). In comparison with healthy population data (13) children with A1ATD self-reported lower HRQOL scores with medium effect size, (mean

77 vs. 84, effect size 0.56) though parent-proxy data were similar between the groups (83 vs. 82).

Health-related Quality of Life in Chronic Intrahepatic Cholestasis

49 patients with IHC with a mean age of 10.3 years (SD 3.9) and mean total bilirubin 2.9 mg/dL (SD 5.2) were enrolled. 25/49 patients with IHC had a known genetic diagnosis (6 PFIC1, 12 PFIC2, 7 PFIC3). In comparison with healthy population data, children with IHC had lower total self-report scores with large effect size (73 vs. 84, effect size 0.87). The parent scores were similar in both groups (79 vs. 82).

Determinants of Health-Related Quality of Life in Alagille Syndrome

Univariate linear regression analysis was performed to understand the relationship between HRQOL summary scores and demographic and clinical factors among patients with ALGS (Table II). The degree of cholestasis, as measured by elevated total bilirubin, was associated with lower summary scores of HRQOL by child self-report. Weight and height z-scores were also positively associated with these summary scores revealing that better growth was associated with higher QOL scores. Different predictors emerged from the analysis of parent-proxy reports. In this analysis INR was inversely associated with parental total and physical scores. Cardiac defects were broadly stratified according to severity, namely intra-cardiac versus peripheral pulmonary stenosis, whereby the latter is more benign. The presence of an intra-cardiac defect was found to be predictive of lower QOL as measured by the parental total and physical scores with remarkable statistical significance. Growth z-scores were inversely related to parent-proxy HRQOL scores. Of note pruritus was not associated with either child-self or parent-proxy reports scores.

Risk factors found to be significant at the $p < 0.1$ level in the univariate analysis were entered into a multivariate linear regression model. Adjusting for other risk factors significant in the univariate analysis, only the weight z-score was positively associated with Total and Physical HRQOL summary scores by both child self and parent proxy reports.

Comparison of Patients with Alagille syndrome with Other Chronic Liver Disease Populations

ALGS vs. A1ATD—Participants with ALGS had generally worse HRQOL scores than children with A1ATD, although with mostly small to medium effect sizes (Table III). For the child-report scores, the largest difference was seen in the physical domain (73 vs. 83, effect size 0.63). The parent-proxy reports showed significantly lower scores with higher effect sizes in patients with ALGS across all scores.

ALGS vs. IHC—HRQOL for subjects with ALGS was modestly impaired compared with the IHC cohort (Table VI; available at www.jpeds.com). The ALGS child self-reports were similar across all domains to IHC and only significantly lower in physical domain (ALGS 73 vs. IHC 79, effect size 0.37) and marginally lower in social functioning domain. For the parent-proxy reports, the ALGS PedsQL scores were lower in almost all domains with small to medium effect sizes.

ALGS vs. A1ATD and IHC—Overall in terms of summary PedsQL scores, subjects with ALGS had consistently worse scores than both patients with A1ATD and IHC in the parent proxy reports (Figure, B). In the patient reports, these differences were less pronounced with subjects with ALGS and IHC both scoring more poorly than A1ATD individuals, but with little difference between ALGS and IHC self-reports (Figure, A).

Discussion

This multi-center study of HRQOL in ALGS and other chronic intrahepatic cholestatic liver diseases of childhood comprehensively assessed child and parental perspectives. This study demonstrates that HRQOL is impaired in children with cholestatic ALGS, as compared with a healthy population. HRQOL scores were significantly lower in ALGS across all domains with the largest difference seen in physical health, for child self-report scores. This is not unexpected as ALGS is a complex disorder with disease in multiple organ systems.

One of the hallmark features of ALGS is variable expressivity so that multiple disease manifestations may impact HRQOL. This cohort was defined by the presence of cholestasis, but the involvement of other organs varied. In this cohort, growth failure was a major determinant of impaired HRQOL in ALGS. This is interesting as growth failure is a pervasive feature of ALGS and short stature, in particular, is a lifelong issue. Growth failure may simply be a marker of poor overall health or frailty or there may be specific effects of short stature that impact QOL. This is in contrast to other manifestations of ALGS, such as cholestasis, pruritus and xanthomas, which often improve with age. Surprisingly, in this cohort, pruritus was not a major determinant of HRQOL. This may be explained by the fact that this ALGS cohort was ascertained on the basis of the presence of cholestatic liver disease and therefore was skewed towards higher pruritus scores with insufficient variability to demonstrate an association. This finding may also be an indicator of the weakness of currently available tools to assess pruritus.

Other factors that emerged from the univariate analyses as potential predictors of HRQOL were the degree of cholestasis It is not clear if it is the presence of jaundice that stigmatizes children with cholestatis or that serum bilirubin is a biomarker for other disabling features and complications of ALGS, all of which could impair their HRQOL. For the parents, the presence of a cardiac defect and INR were predictors of HRQOL. It is possible that parents have a different perception of a cardiac defect as being of more concern as compared with a child’s perception. Other studies do support the concept of impaired HRQOL in children and parents with complex cardiac disease (17). Similarly, children are unlikely to understand the implications of a high INR (poorer liver synthetic function and hence a poorer prognosis) as parents do.

Our data indicate that children with ALGS have only poor to moderate agreement with their parents in reporting HRQOL. This is consistent with previous reports in chronic disease states demonstrating that information obtained by child self-report and parent proxy report is not equivalent (18). There was a trend towards the lowest correlation in the perception of emotional and social functioning between self and parent proxy reports. This is frequently

observed for internalized constructs such as self-esteem, anxiety and for areas unobserved by parents, like peer relationships.

This study is strengthened by the comparison of HRQOL in ALGS with other chronic liver diseases as disease control groups. Children with ALGS were more impaired in HRQOL as compared with patients with A1ATD. This is understandable as most children with A1ATD do not have significant cholestasis nor do they have extrahepatic physical limitations in childhood, except for a possible predisposition to asthma. In contrast, HRQOL by child self-report was similarly impaired between ALGS and IHC. These groups had similar degrees of cholestasis, as measured by total bilirubin, suggesting a significant effect across diseases. Parental perceptions of HRQOL were more impaired in ALGS than in IHC, which may reflect a better adult appreciation of the multisystem nature of ALGS. For both parents and children there were significant differences in the physical domain. Although both cohorts may have physical limitations due to pruritus or short stature, it is likely that children with ALGS carry additional burdens due to cardiac disease, xanthomas and facial dysmorphism. There was also a large difference in parental perception of social functioning between ALGS and IHC. This may be explained by the overt physical manifestations of ALGS, which may result in them being teased or left out of activities by other children. It must be pointed out that the IHC group was quite heterogeneous, including children with PFIC type 1, 2 and 3, both with and without partial biliary diversion procedures, and other children with chronic intrahepatic cholestasis. Thus the results should not be interpreted to represent each specific PFIC group; the numbers of participants in each PFIC type were too small for this interpretation.

Certain limitations of this study should be noted. Firstly there is an ascertainment bias in the whole cohort as they were enrolled in LOGIC based on the presence of liver disease. In some patients with ALGS, liver disease is a very minor component with cardiac or renal disease dominating. Thus, ALGS is a complex disorder with multiple potential confounders of HRQOL. Therefore this study addresses questions regarding HRQOL in cholestatic ALGS only and does not fully delineate the spectrum of quality of life in all individuals with ALGS. It should also be noted that the assessment of HRQOL in families with an autosomal dominant condition requires careful consideration. In this cohort only 7% of the parents were themselves affected by ALGS, though this was by self-report and not genetically determined. This is a surprisingly low frequency as approximately 30% of ALGS cases are reportedly inherited (19). In an exploratory analysis (data not shown), there were no marked differences in HRQOL scores between the affected and non-affected parents. It is possible that there was some selection bias by families who participated in this study and families with more than one affected individual are under-represented in the dataset.

Children with ALGS are particularly vulnerable to psychosocial deficits and require careful evaluation and targeted interventions to support their functional health. In this cohort, growth failure was a major determinant of HRQOL. This provides a rationale for addressing growth aggressively in children with ALGS. Recent data indicate that after LT, children with ALGS demonstrate catch-up growth (20). This suggests that growth failure is not an inevitable feature for all patients with ALGS and there is potential for intervention that may improve growth and possibly improve HRQOL. This study underscores the importance of

including HRQOL measurements in the assessment of patients with ALGS to advocate for early educational interventions and support social integration. These data also support the need for a longitudinal study of HRQOL in ALGS in order to evaluate the potential benefit of medical and surgical therapies.

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Appendix 1

Members of ChiLDReN include (principal investigator followed by co-investigators for each institution):

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Appendix 2

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Abbreviations

ALGS	Alagille syndrome
HRQOL	health-related quality of life
PedsQL	Pediatric Quality of Life Inventory™
A1ATD	alpha-1-antitrypsin deficiency
IHC	chronic intrahepatic cholestasis
QOL	quality of life
ICC	Intra-class correlation coefficients
PFIC	progressive familial intrahepatic cholestasis

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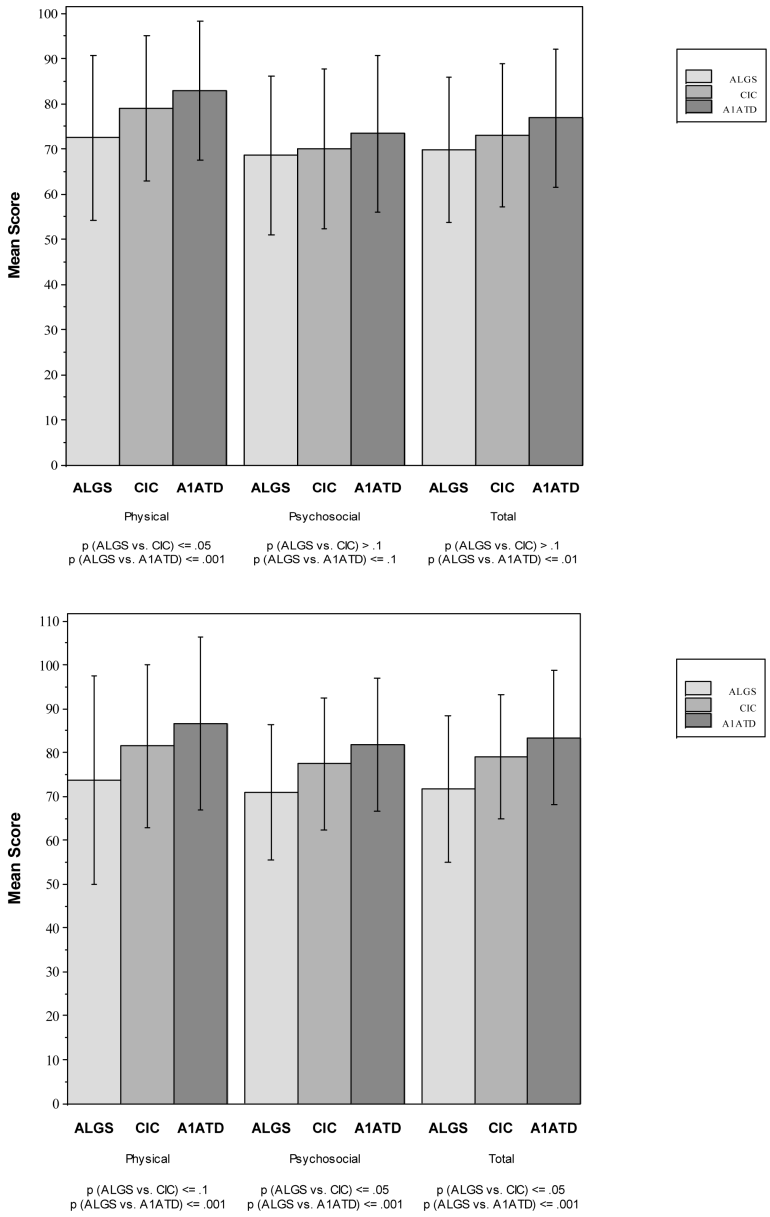

Figure 1.

Histograms depicting mean PedsQL Summary Scores for cohorts with Alagille syndrome (ALGS), chronic intrahepatic cholestasis (CIC) and alpha-1-antitrypsin deficiency (A1ATD). The error bar represents the standard deviation. Panel (a) reveals scores for child self-reports and panel (b) for parent proxy reports.

Figure 1a. Child Self-Reports of PedsQL 4.0 Summary Scores in ALGS, CIC and A1ATD (Mean Score with Standard Deviation Error Bar)

Figure 1b. Parent Proxy Reports of PedsQL 4.0 Summary Scores in ALGS, CIC and A1ATD (Mean Score with Standard Deviation Error Bar)

Table 1

A Comparison of PedsQL™ 4.0 Generic Core Scale Scores in Patients with Alagille Syndrome and Healthy Children, Child Self and Parent Proxy Reports

	Alagille Syndrome N Mean (SD)	Healthy* N Mean (SD)	Differences	Effect Size ^
Child Self-Report				
Total Score	70 69.86 (16.09)	5079 83.91 (12.47)	14.05	1.12
Physical Health	69 72.52 (18.28)	5070 87.77 (13.12)	15.25	1.16
Psychosocial Health	70 68.56 (17.63)	5070 81.83 (13.97)	13.27	0.95
Emotional Functioning	70 69.13 (20.61)	5068 79.21 (18.02)	10.08	0.56
Social Functioning	70 69.11 (23.84)	5056 84.97 (16.71)	15.86	0.94
School Functioning	67 67.28 (19.98)	5026 81.31 (16.09)	14.03	0.87
Parent Proxy-Report				
Total Score	98 71.63 (16.72)	8713 82.29 (15.55)	10.66	0.69
Physical Health	98 73.81 (23.73)	8696 84.08 (19.70)	10.27	0.52
Psychosocial Health	97 70.94 (15.36)	8714 81.24 (15.34)	10.30	0.67
Emotional Functioning	98 67.70 (18.11)	8692 81.20 (16.40)	13.50	0.82
Social Functioning	97 75.22 (18.61)	8690 83.05 (19.66)	7.83	0.40
School Functioning	81 68.11 (20.42)	7287 78.27 (19.64)	10.16	0.52

*Healthy population data from Varni et al, 2003. Items are reverse scored and linearly transformed to a scale of 0-100, with higher scores indicating better HRQOL. A value 1 SD below the population mean for the PedsQL Total Score (69.7 for child self-report and 65.4 for parent-proxy) is a threshold score for an at-risk status for impaired HRQOL relative to the population.

^Effect sizes are designated as small (.20-49), medium (.50-79), and large (.80 and >)

Table 2

Univariate Regression Analysis of Predictors of Quality of Life, Child Self and Parent Proxy Report Scores in Patients with Alagille Syndrome

Risk Factor^	Total Score β (SE) N(total=70 for child and 98 for parents)	Physical Score β (SE)	Psychosocial Score β (SE)
Child Self Report			
Total Bilirubin (mg/dl)	−0.82 (0.35) ** 55	−1.1 (0.4) **	−0.67 (0.38) *
Weight Z-Score	4.5 (1.6) *** 70	4.4 (1.8) **	4.5 (1.7) **
Height Z-Score	4.1 (1.6) ** 70	3.9 (1.9) **	4.2 (1.7) **
Parent Proxy Report			
Age at Survey (years)			−0.9 (0.4) **
INR	−16.6 (7.4) ** 84	−22.9 (10.3) **	
Weight Z-Score	3.4 (1.5) ** 98	4.8 (2.1) **	2.4 (1.4) *
Height Z-Score	2.6 (1.4) * 98	4.4 (2.0) **	
Cardiac Defect			
None vs. PPS	3.6 (5.6)	7.6 (7.8)	
Other vs. PPS	−9.5 (3.6) *** 94	−14.4 (5.0) ***	

* Note for βs: p ≤0.1,

** p≤0.05,

*** p≤0.01

^ Only significant risk factors with a p value at above levels were reported in the table; the risk predictors considered in univariate analysis included gender, age at survey, total bilirubin, total cholesterol, conjugated bilirubin, INR, platelets, pruritus score, xanthomas, weight Z-score, height Z-score, weight-for-height Z-score, and cardiac defect

PPS = peripheral pulmonary artery stenosis

Table 3

A Comparison of the PedsQL 4.0™ Generic Core Scale Scores in Patients with Alagille Syndrome and A1ATD, Child Self and Parent Proxy Reports

	Alagille Syndrome N Mean (SD)	A1ATD N Mean (SD)	Differences #	Effect Size ^
Child Self-Report				
Total Score*	70 69.86 (16.09)	94 76.84 (15.22)	6.98***	0.45
Physical Health	69 72.52 (18.28)	95 82.92 (15.39)	10.40****	0.63
Psychosocial Health	70 68.56 (17.63)	94 73.42 (17.33)	4.86*	0.28
Emotional Functioning	70 69.13 (20.61)	94 72.91 (19.57)	3.78	0.19
Social Functioning	70 69.11 (23.84)	94 76.66 (22.05)	7.55**	0.33
School Functioning	67 67.28 (19.98)	91 70.38 (22.03)	3.10	0.15
Parent Proxy-Report				
Total Score	98 71.63 (16.72)	123 83.44 (15.23)	11.81****	0.75
Physical Health	98 73.81 (23.73)	123 86.58 (19.80)	12.77****	0.59
Psychosocial Health	97 70.94 (15.36)	123 81.76 (15.14)	10.82****	0.71
Emotional Functioning	98 67.70 (18.11)	123 78.10 (17.10)	10.40****	0.60
Social Functioning	97 75.22 (18.61)	123 87.60 (16.65)	12.38****	0.71
School Functioning	81 68.11 (20.42)	110 78.27 (19.04)	10.16****	0.52

*Items are reverse scored and linearly transformed to a scale of 0-100, with higher scores indicating better HRQOL. A value 1 sd below the population mean for the PedsQL Total Score (69.7 for child self-report and 65.4 for parent-proxy) is a threshold score for an at-risk status for impaired HRQOL relative to the population.

#Note:

*p ≤0.1,

**p≤0.05,

***p≤0.01,

****p≤0.001 from Wilcoxon two-sample test

^Effect sizes are designated as small (.20-.49), medium (.50-.70), and large (.80 and >) A1ATD = alpha 1 antitrypsin deficiency

Table 4

Demographic and Medical Characteristics of Patients with Alagille Syndrome, A1ATD, and CIC Completing Child Self-Report of HRQOL

Characteristics	ALGS (N=70)		A1ATD (N=95)		CIC (N=49)	
	n	descriptive statistics*	n	descriptive statistics*	n	descriptive statistics*
Female	27	39%	40	42%	28	57%
White	53/62 (missing=8)	85%	90/90 (missing=5)	100%	35/46 (missing=3)	76%
Age at survey (in years)	70	9.4 (3.1)	95	9.5 (3.9)	49	10.3 (3.9)
Weight (Z score) adjusted for age	70	−1.5 (1.2)	93	0.5 (1.1)	49	−0.8 (1.6)
Height (Z score) adjusted for age	70	−1.6 (1.2)	93	0.1 (3.0)	49	−1.2 (1.6)
Listed for Liver Transplant	6	9%	6	6%	10	20%
Total Bilirubin (mg/dL)	55	4.4 (6.2)	77	0.7 (0.8)	42	2.9 (5.2)
ALT (U/L)	66	160.3 (96.9)	94	65.1 (53.5)	45	75.0 (56.4)
Albumin (g/dL)	67	4.2 (0.5)	92	4.4 (0.5)	45	4.3 (0.7)
GGTP (U/L)	55	386.2 (351.6)	77	61.8 (85.0)	40	94.1 (169.1)
INR	60	1.0 (0.2)	66	1.1 (0.1)	37	1.1 (0.2)
WBC ($10^3/mm^3$)	62	7.0 (3.6)	85	7.0 (5.5)	38	5.8 (2.3)
Platelet ($10^3/mm^3$)	61	234.7 (98.9)	86	249.3 (116.4)	38	256.8 (155.6)

*% reported for categorical variables; mean (SD) reported for continuous variables

ALGS = Alagille syndrome; A1ATD = alpha-one antitrypsin deficiency; CIC = chronic intrahepatic cholestasis; HRQOL = health related quality of life; ALT = alanine aminotransferase; GGTP = gamma glutamyl transpeptidase; INR = international normalized ratio; WBC = white blood count

Table 5

Age Based Intra-Class Correlations (ICCs) between Child Self and Parent Proxy-Report of the PedsQL™ 4.0 Generic Core Scales for Scales for Patients with Alagille Syndrome

PedsQL™ Scale	Parent-Child Agreement ICCs All Ages (N=62)	Parent-Child Agreement ICCs 5-7 years (N=20)	Parent-Child Agreement ICCs 8-12 years (N=34)	Parent-Child Agreement ICCs 13-18 years (N=8)
Total Score	0.51(0.33, 0.68)	0.31 (0.07, 0.74)	0.52 (0.29, 0.74)	0.78 (0.42, 0.94)
Physical Health	0.59 (0.42, 0.74)	0.38 (0.11, 0.76)	0.64 (0.42, 0.81)	0.76 (0.39, 0.94)
Psychosocial Health	0.46 (0.28, 0.65)	0.17 (0.01, 0.80)	0.54 (0.31, 0.75)	0.69 (0.30, 0.93)
Emotional Functioning	0.29 (0.12, 0.55)	0.18 (0.01, 0.80)	0.24 (0.05, 0.64)	0.56 (0.16, 0.90)
Social Functioning	0.34 (0.16, 0.58)	0.19 (0.02, 0.78)	0.40 (0.17, 0.68)	0.33 (0.03, 0.89)
School Functioning	0.55 (0.38, 0.71)	0.17 (0.01, 0.82)	0.71 (0.52, 0.85)	0.77 (0.41, 0.94)

ICCs: Intra-class Correlations

ICC (95% confidence interval) were reported

ICCs are designated as poor to fair (<=0.40), moderate (0.41-0.60), good (0.61-0.80), and excellent (0.81-1.00) in agreement

Table 6

A Comparison of the PedsQL 4.0™ Generic Core Scale Scores in children with Alagille syndrome and Chronic Intrahepatic Cholestasis (CIC), child self and parent proxy reports

	Alagille Syndrome N Mean (SD) Median (IQR)	CIC N Mean (SD) Median (IQR)	Differences #	Effect Size ^
Child Self-Report				
Total Score	70 69.86 (16.09) 70.55 (20.65)	49 73.04 (15.80) 72.83 (21.74)	3.18	0.20
Physical Health	69 72.52 (18.28) 75.00 (18.75)	49 78.91 (16.06) 81.25 (15.63)	6.39**	0.37
Psychosocial Health	70 68.56 (17.63) 67.26 (26.67)	49 69.92 (17.69) 71.67 (20.00)	1.36	0.08
Emotional Functioning	70 69.13 (20.61) 70.00 (35.00)	49 67.35 (21.56) 65.00 (25.00)	−1.78	−0.09
Social Functioning	70 69.11 (23.84) 70.00 (35.00)	49 76.26 (20.81) 80.00 (30.00)	7.15*	0.32
School Functioning	67 67.28 (19.98) 65.00 (35.00)	48 65.94 (19.75) 62.50 (27.50)	−1.34	−0.07
Parent Proxy-Report				
Total Score	98 71.63 (16.72) 73.81 (21.63)	68 79.02 (14.22) 79.46 (26.09)	7.39**	0.47
Physical Health	98 73.81 (23.73) 82.81 (37.50)	68 81.47 (18.67) 85.94 (23.44)	7.66*	0.35
Psychosocial Health	97 70.94 (15.36) 71.15 (20.00)	68 77.50 (15.06) 77.50 (25.00)	6.56**	0.43
Emotional Functioning	98 67.70 (18.11) 67.50 (25.00)	68 74.10 (17.11) 77.50 (27.50)	6.40**	0.36
Social Functioning	97 75.22 (18.61) 75.00 (30.00)	68 84.78 (16.76) 90.00 (25.00)	9.56****	0.54
School Functioning	81 68.11 (20.42) 70.00 (25.00)	55 70.52 (21.87) 70.00 (35.00)	2.41	0.12

#Note:

*p ≤0.1,

**p≤0.05,

***p≤0.01,

****p≤0.001 from Wilcoxon two-sample test

^Effect sizes are designated as small (.20-.49), medium (.50-.79), and large (.80 and >)

CIC – chronic intrahepatic cholestasis