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Abstract

Introduction We aimed to assess health-related quality of life (HrQoL) in biliary atresia (BA) patients, based on original data and a literature review, and to determine factors associated with their HrQoL.

Materials and Methods We reviewed available studies describing HrQoL in BA patients. We assessed HrQoL in Dutch BA patients (6–16 years) using the validated Child Health Questionnaire. We compared HrQoL scores in BA patients with healthy peers and with children who had undergone major surgery in infancy or children with chronic conditions. We determined the relationship between specific patient-related factors and HrQoL.

Results Literature data indicated that HrQoL in children with BA is lower than in healthy peers. In Dutch BA patients ($n = 38$; age 10 ± 3 years), parent-proxy physical HrQoL (48 ± 11) was significantly lower compared with two reference groups of healthy peers (59 ± 4 and 56 ± 6, respectively, each $p < 0.001$), and lower than in children with attention deficit hyperactivity disorder (60 ± 5), asthma (54 ± 6), attending a cardiology clinic ($52 \pm n/r$), congenital diaphragmatic hernia (53 ± 7) or D-transposition of the great arteries (54 ± 6; all $p < 0.05$). Psychosocial HrQoL (50 ± 9) was lower than in healthy peers (54 ± 6, $p = 0.02$, and 53 ± 6, $p = 0.07$) and children with asthma (54 ± 6, $p = 0.02$), and largely comparable to children with other chronic conditions. Parent-proxy physical HrQoL was adversely related to adverse medical event in the past year, special education, and motor impairments; psychosocial HrQoL was adversely related to behavioral problems.

Conclusion Children with BA are at risk of impaired HrQoL. Special attention is warranted for children with adverse medical events and special education.

Keywords
- biliary atresia
- health-related quality of life
- liver transplantation
- childhood

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Introduction

The increased survival in children with biliary atresia (BA) has allowed a shift in research focus from survival to a more holistic approach, including long-term functional outcomes and quality of life (QoL). Health-related quality of life (HrQoL) reflects the perceived impact of a disease and its treatment on well-being and functioning of the patient.[1] Several studies have shown a significantly impaired HrQoL in children with a chronic condition[2] or after major surgery for complex disease in infancy, such as, congenital heart disease, necrotizing enterocolitis, omphalocele, and esophageal atresia.[3] Recently, Parmar et al described impaired HrQoL in a systematic review on pediatric liver transplantation (LTx) recipients, in which the proportion of BA etiology per study ranged between 20 and 98%.[4] These studies did not describe HrQoL in patients transplanted for BA specifically, although congenital disease was associated with lower HrQoL in transplant recipients.[4,5]

Knowledge on factors associated with HrQoL in BA patients is scarce. Devine et al described that the HrQoL in LTx recipients is influenced more by behavioral indicators of adherence and family conflict, than by medical or surgical events.[6] In children who underwent surgery for congenital heart disease, neurodevelopmental deficits are associated with worse psychosocial health status in adolescence.[7] Recently, we described significantly impaired neurodevelopmental outcomes in Dutch school-aged children with BA.[8] As impaired neurodevelopment might influence daily functioning we hypothesized that neurodevelopmental impairments in children with BA might affect their HrQoL.

In this study, we first aimed to provide an overview of recent literature on HrQoL in children with BA, both with native liver and those who had undergone an LTx. Second, we aimed to assess HrQoL in Dutch school-aged children with BA, to determine differences in HrQoL as perceived by BA patients and their parents, and to compare HrQoL of children with BA with their healthy peers and with children who had undergone other major surgery in infancy or with a chronic condition. Third, we explored factors associated with HrQoL in children with BA.

Materials and Methods

Literature Search

To provide an overview of literature on HrQoL in BA patients we used the following predefined search terms in PubMed: *("biliary atresia"[Mesh] OR biliary atresia [tiab]) AND ("Quality of life"[Mesh] OR Health-related quality of life [tiab])*. We searched the reference lists of the included studies for additional studies that were eligible for inclusion. Inclusion criteria were studies that reported on HrQoL in patients with BA specifically, either with native liver or after having undergone LTx, published between January 1, 2010 and November 31, 2019. Exclusion criteria were unavailability of full text articles, duplicates, manuscripts that were not available in English language, review articles or case reports/series, or studies that assessed HrQoL in LTx recipients in general but that do not stratify on BA etiology.

As we hypothesized that neurodevelopmental outcomes affect HrQoL in BA patients, we added search terms related to neurodevelopment, i.e., cognition, motor skills and behavior. However, this new search did not reveal studies on the relation between neurodevelopmental outcomes and HrQoL in BA patients.

We searched for studies on HrQoL in children who underwent major surgery in infancy or with a chronic condition, that used the Child Health Questionnaire, (CHQ), using the following predefined search terms in PubMed: *("Child"[Mesh] OR "Infant, Newborn"[Mesh] OR child*[tiab] OR youth[tiab] OR infant*[tiab] OR newborn*[tiab]) AND ("surgery"[tiab] OR chronic condition [tiab] OR chronic disease[tiab]) AND ("Quality of life"[Mesh] OR Health-related quality of life[tiab]) AND (child health questionnaire [tiab] OR CHQ [tiab])*. Inclusion criteria for reference groups were studies that reported the CHQ parent-proxy physical or psychosocial HrQoL summary scores of children with a mean age between 7 and 13 (within 1 standard deviation [SD] of the mean age in the BA group).

Studies were independently and blindly screened by two authors, L.H.R. and E.M.W.S. Observer agreement was calculated and interpreted by means of Cohen's Kappa.[9] In case of discrepancies a third author (J.L.M.B.) was consulted. Data extraction was performed by L.H.R. and crosschecked by E.M.W.S.

Data Collection in Dutch Children with BA

Children between 6 and 16 years eligible for inclusion were identified using the *Netherlands Study Group on Biliary Atresia Registry (NeSBAR)*, a prospective database that contains information of all children with BA in the Netherlands.[10] Exclusion criteria were presence of chronic disease unrelated to BA and insufficient knowledge of the Dutch language. Ethical approval was obtained from the UMCG Medical Ethics Committee and the study was performed in accordance with the Declaration of Helsinki.

Invitation letters were sent to all eligible children and their parents, followed by a phone call to further explain the goal of this study. After obtaining informed consent from either parents or caregivers, and from children aged 12 years or older, participants were asked to fill out the questionnaires. Information on the health status of the children was obtained from the electronic patient registry systems or the NeSBAR database. These data included gender, age at LTx, and whether the child had an adverse medical event related to BA in the past year. Adverse medical events, directly or indirectly related to liver disease or LTx included, but were not limited to, cholangitis, gastrointestinal hemorrhage, portal hypertension, hepatopulmonary syndrome, posttransplant lymphoproliferative disorder, portal vein thrombosis, stenosis of the biliary anastomosis, and spontaneous bacterial peritonitis.

Measurements

A short questionnaire on demographic status was used. Questions included educational level of the child, household income, marital status, and highest educational level or work status of parents or caregivers. Educational levels were classified in accordance with the International Standard Classification of Education Fields of Training and Education.[11]

To assess HrQoL in children with BA, we used the internationally validated CHQ.[12,13] This questionnaire has been developed to test both physical and psychosocial HrQoL of children aged 5 years and older.[14] The CHQ consists of a 50-item parent-proxy form (CHQ-PF50), and an 87-item child-reported form (CHQ-CF87) for children aged 10 years or older.[15,16] The CHQ assesses HrQoL on 15 different domains. Higher domain scores indicate a better HrQoL. Reliability and validity of the Dutch version of the CHQ are good.[15–18]

We used proportions of our previously published data from partly the same patient cohort on IQ (Wechsler Intelligence Scale for Children-III-NL), motor skills (Movement-ABC), and behavior (Child Behavioral Checklist) to explore the association of possible neurodevelopmental impairments with HrQoL in children with BA.[8]

Reference Data

To compare HrQoL domain scores of children with BA with a norm population of Dutch schoolchildren (aged 5–13) we used reference data as reported by Raat et al.[17,19] We also compared the parent-proxy physical and psychosocial summary scores to more recently collected reference data on Dutch schoolchildren (aged 4–11) without a chronic condition as described by Bai et al.[2] These data were collected using the shortened version of the CHQ parent-report form (CHQ-PF28), of which the summary score is an acceptable alternative for the longer version of the questionnaire (CHQ-PF50).[20] We compared the parent-proxy CHQ summary scores of children with BA with children with major surgery in infancy or chronic conditions as follows: attention-deficit hyperactivity disorder,[2] asthma,[2] children attending a cardiology clinic,[21] chronic recurrent rhinosinusitis,[22] congenital diaphragmatic hernia,[23] D-transposition of the great arteries,[7,24] esophageal atresia,[25] history of cancer,[26] symptomatic epilepsy,[27] and tetralogy of Fallot.[28] These reference data were retrieved from studies that were identified by the previously reported literature search. We included all studies that used the CHQ to assess HrQoL in any chronic disease or major surgery in infancy.

Data Analysis

Distribution of data is reported as number (%), mean ± SD, or median [range]. In case of >20% missing data on the CHQ questionnaire the patient was excluded for analyses. In case of nonunique answers, where a participant circled two answers for one question, the least extreme answer was registered. Per questionnaire, domain scores and summary or final scores were calculated in accordance with the questionnaire manuals.[29] We reported the percentage of children with the maximum score to provide additional information about the distribution of scores. We defined children with a summary score of more than 1 SD below the population mean as "poor HrQoL," in accordance with previous publications from the Childhood Liver Disease Research Network.[30,31]

Parametric and nonparametric analyses were applied as appropriate. One-sample *t*-tests for normally distributed data and one-sample Wilcoxon signed rank tests for non-normally distributed data were used to compare children with BA to the reference population. Intraclass correlation coefficients (ICC) between parent- and child-reported domain scores were calculated using one-way random effects models, based on absolute agreement. ICCs were designated as poor (≤0.50), moderate (0.50–0.75), good (0.75–0.90), and excellent agreement (≥0.90).[32]

Effect sizes were calculated for differences between the study and reference population by means of a Cohen's *d* ([Mean of reference data − Mean of BA group]/SD^{pooled}), where SD^{pooled} is the pooled estimate of the SD in the reference population and study population. When there were substantial differences between the study sample size and that of the reference population, Hedges' *g* effect size was calculated (with pooling of weighted *SD*). Effect sizes are interpreted as small (0.20), moderate (0.50), or large (0.80).[33,34]

Either independent *t*-test for normally distributed data or Mann-Whitney U test for non-normally distributed data was used to compare outcomes between subgroups, e.g., children with native liver versus LTx. Chi-square or Fisher Exact analysis were used to compare proportions. Univariable linear regression analysis was performed to determine factors that were associated with HrQoL. Any factor associated with HrQoL with a *p*-value <0.2 was included in a multivariable generalized linear regression model. Backward selection method was applied to select the most significant variables throughout consecutive regression models. The regression models were checked for regression assumptions, as well as for multicollinearity and interaction terms. The effect of outliers on regression performance was checked using sensitivity analysis (by comparing model performance before and after exclusion of outliers). Data were captured in Redcap[35] and analyzed using IBM SPSS version 23. Throughout analyses, *p*-value <0.05 was considered statistically significant.

Results

Literature Search on HrQoL in Children with BA

We included nine studies on HrQoL in BA patients ($n = 984$ children, $n = 102$ adults). Four studies assessed patients who survived with their native liver,[36–39] two studies assessed LTx recipients with BA specifically,[40,41] and three studies assessed both[30,42,43] (►Table 1). There was a moderate agreement (Kappa 0.77) between the two screening authors L.H.R. and E.M.W.S. as one author included three more studies than the other. After discussion with the third author (J.L.M.B.), those three articles were also included. We were unable to obtain the full article of one abstract and, therefore, excluded that study.[44]

All studies on self-reported HrQoL in children with BA described lower HrQoL compared with healthy peers.[30,39,41] Parent-proxy based studies reported somewhat controversial results, with one study describing similar HrQoL as healthy peers[37]; however, the majority of parents also reported impaired HrQoL in children.[30,39,41] Four studies included adult BA patients,[36,38,42,43] who scored their HrQoL as similar to healthy peers, except for general health perception or physical QoL in studies on patients who still had their native liver.[38,42] Five studies investigated the difference between children with native liver and LTx

Table 1 Data from the last decade (2010–2020) on health-related quality of life in patients with biliary atresia, surviving with native liver or after liver transplantation

Authors, year	Country	Participants (native liver vs. LTx, number, age in years)	Tool (self-report or parent-proxy)	Reference group	HrQoL BA vs. reference (effect size)	Predictors of HrQoL
Rodijk et al, this paper	Netherlands	Native liver and LTx: 35 children Age 10 ± 3 y	CHQ *Self-report and parent-proxy*	Healthy peers	*Physical HrQoL*: Parent-proxy: ↓ (*g* 1.21–2.69) *Psychosocial HrQoL*: Parent-proxy: ↓ (*g* 0.76–0.99) *Native liver* vs. *LTx:* NS	*Physical HrQoL*: Parent-proxy: ↓ adverse medical event in past year, special education, motor impairments *Psychosocial HrQoL*: Parent-proxy: ↓ special education, motor impairments, behavioral problems.
Miserachs et al, 2019	Canada, Spain, Poland, Italy, Germany, France, Switzerland	LTx: 70 children Age 10 y (IQR 9–11)	PedsQoL 4.0 PeLTQL *Self-report and parent-proxy*	Healthy peers	*Overall HrQoL, physical health, emotional functioning and school functioning*: Self-report and parent-proxy: ↓ (*d* 0.20–0.79)	*Transplant-specific HrQoL*: Self-report: ↑ immunosuppression monotherapy *Overall QoL*: Parent-proxy: ↑ sports participation (No significant predictors after multivariable analysis).
Parolini et al, 2019	Italy	Native liver: 11 adults Age not reported	WHOQOL-BREF *Self-report*	Healthy peers	*Overall QoL*: Self-report: NS (10/11 patients) ↓ (1 patient)	Not studied
Wong et al, 2018	China	Native liver and LTx: 26 adults Native liver: 27 (22–34) LTx: 26 (20–37)	Short Form-36 Health Survey version 2.0 *Self-report*	Healthy peers	*General health and overall physical QoL:* Self-report: Native liver: ↓ LTx: NS *Native liver* vs. *LTx:* NS	*Vitality score*: ↓ Active complications.
Kikuchi et al, 2018	Japan	LTx: 75 children Age 10 ± 4 y	PedsQoL 4.0 PeLTQL *Self-report and parent proxy*	Ref 1: USA BA patients Ref 2: USA solid organ transplant recipients (e.g. liver, kidney and heart)	*Overall HrQoL*: Self-report: vs. ref 1: ↑ (*d* 0.96) vs. ref 2: ↑ (*d* 0.80) Parent-proxy: vs. ref 1: ↑ (*d* 0.13) vs. ref 2: ↑ (*d* 0.30) *Total transplant specific*: Self-report: vs. USA 1: ↑ (*d* 0.55) Parent-proxy: vs. USA 1: ↓ (*d* 0.26)	*Overall HrQoL*: Self-report: ↑ in older children Parent-proxy: ↑ marital status: married *Total transplant specific HrQoL*: Self-report: ↑ consultation frequency, commuting time to hospital, ↓ number of types prescribed drugs Parent-proxy: ↑ in older children, post-LTx complications, ↓ number of types prescribed drugs.
Lampela et al, 2017	Finland	Native liver: 20 children Age 6 y (IQR 5–9)	PedsQoL 4.0 *Parent-proxy*	Healthy peers	*Overall HrQoL: NS* *School domain*: ↓ (effect size not reported) Native liver vs. LTx: NS	*Total HrQoL*: ↓ if "symptoms" were present (e.g., sleeping difficulties, nocturnal wetting, abdominal distention) *School domain*: ↓ if parents expressed more worry.
de Vries et al, 2016	Netherlands	Native liver and LTx: 40 adults Age: not reported Native liver:	RAND-36 *Self-report*	Healthy peers	*General Health* Native liver vs. LTx ↓ (*d* 0.63) Native liver vs. ref ↓ (*d* 0.69) *Mental HrQoL:*	*General health perception*: ↓ in women with native liver.

Table 1 (*Continued*)

Authors, year	Country	Participants (native liver vs. LTx, number, age in years)	Tool (self-report or parent-proxy)	Reference group	HrQoL BA vs. reference (effect size)	Predictors of HrQoL
		23 (19–30) LTx: 22 (19–31)			Native liver: NS (*d* 0.04) LTx: NS (*d* 0.28) *Physical HrQoL*: Native liver: NS (*d* 0.02) LTx: NS (*d* 0.36) *Native liver* vs. *LTx:* NS (*d* 0.28)	
Lind et al, 2015	Netherlands	Native liver: 25 adults Age 23 ± 3 y	WHOQOL-100 RAND-36 *Self-report*	Healthy peers	*Health status*: NS (*d* n/a) *General health perception*: ↓ (*d* 0.67) *Overall QoL*: NS (*d* n/a) *Social domain*: ↑ (*d* 0.74)	Not studied
Ng et al, 2014	North America	Native liver: 161 children Age 11 ± 4 y	PedsQoL 4.0 *Self-report and parent-proxy*	Healthy peers	*Overall HrQoL*: 47% ≤1 SD below population mean	Not studied
Sundaram et al, 2013	North America	Native liver: 221 children, age 10 ± 5 y LTx: 437 children, age 7 ± 4 y	PedsQoL 4.0 *Self-report and parent-proxy*	Healthy peers	*Overall HrQoL native liver*: Self-report: ↓ (*g* 0.62) Parent-proxy: ↓ (*d* 0.50) *Overall HrQoL LTx*: Self-report: ↓ (*g* 0.76) Parent-proxy: ↓ (*g* 0.46) *Native liver* vs. *LTx: NS*	Native liver patients: *Overall HrQoL*: Self-report: ↑ absence of hepatopulmonary syndrome, higher hemoglobin level Parent-proxy: ↓ black race, elevated total bilirubin level *Social domain*: Self-report: ↑ in older children *School and psychosocial functioning*: Parent-proxy: ↓ in older children.

Abbreviations: CHQ, Child Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HrQoL, health-related quality of life; IES, impact event scale; IQR, interquartile range; LTx, liver transplantation; n/a, not applicable; NS, nonsignificant; PedsQoL, pediatric quality of life inventory; PeLTQL, Pediatric Liver Transplant Quality of Life questionnaire; RAND-36, research and development-36; USA, United States of America; WHOQOL, World Health Organization Quality of Life questionnaire.
Note: Effect sizes were calculated by means of a Cohen's *d* or Hedges *g*, both interpreted as small (0.20), moderate (0.50), or large (0.80). ↑ higher, ↓ lower compared with reference data.

recipients and all described similar HrQoL in both groups[30,37,39,42,43] (►Table 1).

HrQoL in Dutch Children with BA

For the analysis of HrQoL in Dutch children, 38 children with BA were included (►Fig. 1). The CHQ parent-proxy form was filled out for 35 children and 21 children filled out the child-report form. Data of nine children (14%) were excluded from analysis due to excessive missing data (accepted participation but no completion of questionnaires, or >20% of missing answers). In- and excluded patients did not significantly differ with regard to gender (respectively 56% vs. 53% boys, $p = 0.80$) or history of LTx (respectively 76% vs. 88%, $p = 0.17$). ►Table 2 shows the characteristics of the 38 included children and their parents.

The parent-proxy physical HrQoL summary score in children with BA (48 ± 11), was significantly ($p = 0.001$) lower compared with reference data from healthy peers (56 ± 6, effect size g 1.21),[19] as 43% of the BA children scored 1 SD or more below the population mean, which we defined as poor HrQoL. The parent-proxy psychosocial summary score of 50 ± 9 in children with BA seemed ($p = 0.06$) to be lower than in healthy peers (53 ± 6, effect size g 0.76),[19] as 31% of children scored 1 SD or more below the population mean. Compared with more recently collected reference data of Dutch schoolchildren without a chronic condition, children with BA scored significantly lower on both physical (48 ± 11 vs. 59 ± 4, $p < 0.001$, effect size g 2.69) and psychosocial HrQoL (50 ± 9 vs. 54 ± 6, $p = 0.02$, effect size g 0.99).[2] Sensitivity analysis (i.e., exclusion of outlier) revealed comparable results (data not shown).

Results on parent-proxy and child self-reported HrQoL are presented in ►Table 3. All children aged 10 year or older were asked to self-report their HrQoL. Overall parent–child agreement was moderate to excellent for health perception, physical functioning, emotional role functioning, self-esteem, and family activities. There was poor to moderate agreement on behavior, behavioral/physical role functioning, bodily pain, mental health, and family cohesion.

Compared with reference data of healthy Dutch children, almost all parent-proxy HrQoL domains were lower in BA.[19] Two parents (5%) rated the global health of their child as poor, and six parents (16%) as fair. The majority of parents ($n = 25$, 66%) rated the health of their child to be similar to 1 year ago, nine parents (23%) as improved, and four parents (11%) as somewhat worse. None of the parents rated their child's current health to be much worse than 1 year earlier. Children themselves reported significantly lower scores on physical functioning and emotional role functioning than their healthy peers (►Table 3). None of the children rated their global health as poor and only three children (15%) as fair.

The comparison of parent-proxy physical and psychosocial HrQoL summary scores in Dutch BA patients and children with other major surgery in infancy or chronic condition is reported in ►Table 4.

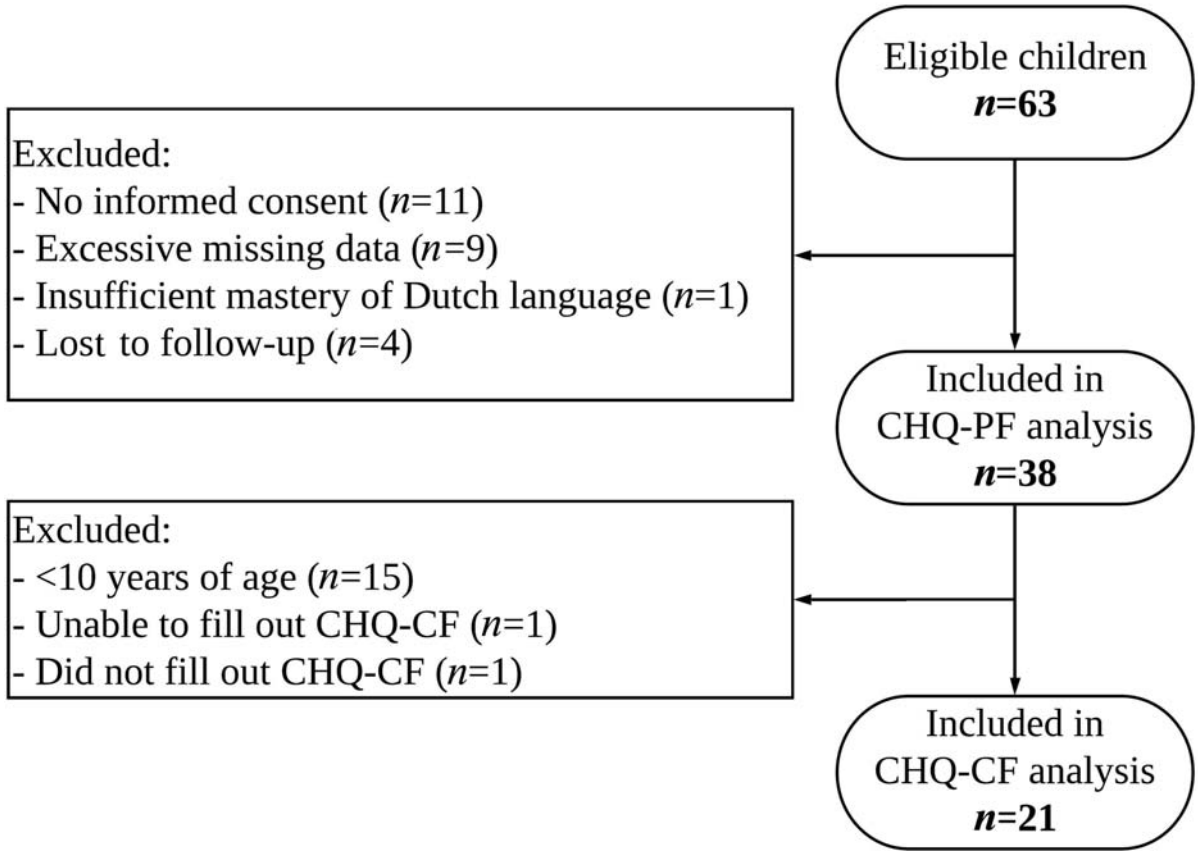

Fig. 1 Flowchart of the inclusion process in Dutch school-aged children with biliary atresia. CHQ-CF, Child Health Questionnaire Child Form; CHQ-PF, Child Health Questionnaire Parent Form.

Table 2 Child characteristics

Child characteristics ($n = 38$)	*N*	*n* mean median	% ± SD min–max
Male gender	38	20	53%
Age child at time of assessment (y)	38	10	± 3
Special education	38	8	21%
Liver transplantation	38	29[d]	76%
Time passed since liver transplantation (y)	28	9	1–14
Adverse medical event in the past year[a]	38	10	26%
Most recent bilirubin measurement (μmol/L)[b]	30	8	3–34
Total intelligence quotient (norm 100 ± 15)	37	91	± 17
Motor impairments (norm 10 ± 3)	36	13	± 8
Behavioral problems (norm 50 ± 10)	30	33	0–113
Marital status parents	37		
Married/living together		31	84%
Separated/divorced		4	11%
Widowed		2	5%
Employed (fulltime or part-time)	34	32	94%
Highest completed parental educational level per household[c]	31		
Low/intermediate		10	32%
High		21	68%
Household income (euros per year)	33		
< 35.000		8	24%
> 35.000		25	76%

[a]Adverse medical events included cholangitis, gastrointestinal hemorrhage, portal hypertension, hepatopulmonary syndrome, post-transplant lymphoproliferative disorder, portal vein thrombosis, stenosis of the anastomosis and spontaneous bacterial peritonitis.
[b]Normal value <17 μmol/L.
[c]Educational level according to the International Standard Classification of Education Fields of Training and Education (ISCED).
[d]One child was on the waiting list for liver transplantation at time of health-related quality of life assessment.

Factors Associated with HrQoL in Children with BA

The most frequently reported factors in literature, that are adversely associated with self-reported or parent-proxy HrQoL in children with BA, include adverse medical events,[30,40,42] higher number of types of prescribed drugs,[40,41] and younger age of child[30,40] (►Table 1).

In multivariable regression analysis, parent-proxy physical HrQoL in Dutch children with BA was on average (β) 10.95 points (95% confidence interval [CI] 16.91, −4.99, $p = 0.001$) lower in children who had an adverse medical event in the past year, 9.34 points (95% CI −16.90, −1.79, $p = 0.02$) lower in children who received special education, 0.55 points (95% CI −0.93, −0.17, $p = 0.007$) lower per point increase on motor impairments, and 11.54 points (95% CI 6.13, 16.94, $p < 0.001$) higher in children of whom at least one parent completed a high household educational level, while adjusted for gender (►Table 5). One child, who had an adverse medical event in the past year, had a score of 10 on the physical HrQoL summary scale and was considered an outlier. Sensitivity analysis, by excluding this outlier, showed a change in the magnitudes of the factors "adverse medical event in the past year" (β −4.93 [−10.56, 0.70], $p = 0.08$) and "time passed since LTx" (β 0.78 [0.01, 1.55], $p = 0.05$).

After multivariable regression analysis, parent-proxy psychosocial HrQoL significantly ($p = 0.002$) decreased with 0.17 points (95% CI −0.28, −0.07) per every point increase on child behavioral problems, while adjusted for gender (►Table 5).

There were no statistically significant differences in HrQoL between children with native liver and children who had undergone a LTx.

Discussion

In this study we determined HrQoL in BA patients, based on results from recent literature and from a cohort of Dutch children with BA. Literature from the past decade shows significantly lower HrQoL in children with BA compared with their healthy peers. All studies on self-reported HrQoL and the majority of studies on parent-proxy HrQoL reported impaired HrQoL compared with healthy peers. Our findings on HrQoL in Dutch children with BA are in line with previous literature, with lower HrQoL than in healthy peers, with a

Table 3 Parent-proxy and child-reported HrQoL and family functioning of children with biliary atresia ($n = 38$), compared with reference data of Dutch schoolchildren ($n = 353$), using either the one-sample *t*-test or the one-sample Wilcoxon signed rank test

		Reference	HrQoL in children with biliary atresia					
Domain	**Parent-proxy (P) or Child-reported (C)**	**Mean ± SD Median (range)**	**% max score**	**n**	**Mean ± SD Median (range)**	**% max score**	***p*-Value**	**Parent vs. child ICC (95% CI)**
Global health	P	n/r		38	73 (0–100)	11	n/a	
	C	n/r		20	85 (30–100)	25	n/a	0.82 (0.54, 0.93)
Physical functioning	P	100 (39–100)	91	38	100 (56–100)	68	0.002 ↓	
	C	100 (56–100)	60	21	96 (74–100)	48	0.003 ↓	0.87 (0.69, 0.95)
Role functioning								
Emotional/ behavioral	P	100 (33–100)	86	37	100 (33–100)	70	0.003 ↓	
Emotional	C	100 (0–100)	73	21	100 (33–100)	62	0.01 ↓	0.82 (0.55, 0.93)
Behavioral	C	100 (33–100)	63	21	100 (44–100)	76	0.04 ↓	0.62 (0.06, 0.85)
Physical	P	100 (0–100)	91	38	100 (0–100)	76	0.007 ↓	
	C	100 (0–100)	86	20	100 (67–100)	80	0.06 =	0.72 (0.32, 0.89)
Bodily pain	P	90 (10–100)	46	36	80 (0–100)	39	0.007 ↓	
	C	80 (10–100)	30	21	100 (10–100)	52	0.87 =	0.77 (0.45, 0.91)
General behavior	P	80 (25–100)	5	36	73 (51–98)	0	0.03 ↓	
	C	84 ± 10	2	20	79 ± 12	0	0.08 =	0.71 (0.31, 0.88)
Global behavior	P	n/r		36	73 (30–100)	8	n/a	
	C	n/r		20	73 (30–100)	15	n/a	0.55 (-0.11,0.82)
Mental health	P	81 ± 12	7	38	75 ± 13	5	0.008 ↓	
	C	80 (19–100)	1	21	83 (52–97)	0	0.90 =	0.75 (0.39, 0.90)
Self-esteem	P	79 ± 11	6	38	76 ± 15	5	0.20 =	
	C	75 (25–100)	2	21	79 (52–100)	5	0.22 =	0.87 (0.70, 0.95)
General health	P	83 ± 13	12	38	48 ± 23	3	<0.001 ↓	
	C	75 ± 16	3	21	64 ± 24	5	0.06 =	0.78 (0.46, 0.91)
Family activities	P	95 (30–100)	48	38	88 (8–100)	32	0.001 ↓	
	C	n/r		21	88 (50–100)	33	n/a	0.93 (0.84, 0.97)
Family cohesion	P	60 (30–100)	16	36	73 (30–100)	14	0.03 ↓	
	C	85 (60–100)	30	21	85 (30–100)	24	0.39 =	0.73 (0.34, 0.89)
Parental impact								
Emotional	P	92 (25–100)	34	38	83 (17–100)	18	<0.001 ↓	
Time	P	100 (0–100)	71	38	100 (0–100)	58	<0.001 ↓	n/a
Summary score								
Physical	P	56 ± 6	n/a	35	48 ± 11	n/a	<0.001 ↓	
Psychosocial	P	53 ± 6	n/a	35	50 ± 9	n/a	0.06 =	n/a

Abbreviations: ↑ significantly higher; ↓ significantly lower than the reference population; C, child-reported; HrQoL, health-related quality of life; ICC, intraclass correlation coefficient; n/a, not applicable; n/r, not reported in reference data; P, parent-proxy; SD, standard deviation.
Note: Higher scores represent better outcomes. The percentage of children with the maximum score (% max score) is reported to provide additional information about the distribution of scores. ICCs were designated as poor (≤0.50), moderate (0.50–0.75), good (0.75–0.90) and excellent agreement (≥0.90).

large effect size in physical HrQoL and a moderate to large effect size in psychosocial HrQoL.

In our cohort of Dutch children with BA, parents reported stronger family cohesion than parents of healthy peers. Previously, Lind et al found that adults with BA report higher scores on the social domain.[38] These findings might be explained by a higher involvement of family members or friends, or by adapted expectations due to a patient's chronic disease.[38]

Another aim of this study was to determine patient-related factors that are associated with HrQoL in BA patients.

Table 4 Parent-proxy CHQ summary scores of children with biliary atresia compared with children with other major surgery in infancy or chronic condition

				Physical HrQoL			Psychosocial HrQoL		
Subjects	**Authors, year**	**Country**	**Age (y)**	**n**	**Mean ± SD**	***p*-Value**	**n**	**Mean ± SD**	***p*-Value**
Biliary atresia	Rodijk et al, this paper	Netherlands	10 ± 3	35	48 ± 11	Reference	35	50 ± 9	Reference
Healthy children	Bai et al, 2017	Netherlands	8 ± 2	*4,539*	59 ± 4	**<0.001**	*4,539*	54 ± 6	**0.02**
	Raat et al, 2002	Netherlands	9 (5–13)	*353*	56 ± 6	**<0.001**	*353*	53 ± 6	0.07
Children with									
ADHD	Bai et al, 2017	Netherlands	8 ± 2	*51*	60 ± 5	**<0.001**	*51*	47 ± 6	**0.03**
Asthma	Bai et al, 2017	Netherlands	8 ± 2	*235*	54 ± 6	**0.003**	*235*	54 ± 6	**0.02**
Children attending cardiology clinic	Walker et al, 2004	USA	11 (n/r)	*368*	52 ± n/r	**0.04**	*368*	52 ± n/r	0.26
Chronic recurrent rhinosinusitis	Cunningham et al, 2000	USA	10 ± 4	*21*	35 ± 6	**<0.001**	*21*	47 ± 6	**0.03**
Congenital diaphragmatic hernia	Peetsold et al, 2009	Netherlands	10 ± 3	*33*	53 ± 7	**0.01**	*33*	53 ± 7	0.07
D-transposition of the great arteries	Robson et al, 2019	USA	8 ± 0	*135*	54 ± 6	**0.003**	*135*	51 ± 9	0.64
D-transposition of the great arteries	Dunbar-Masterson et al, 2001	USA	8 (8–10)	*155*	54 ± 6	**0.003**	*155*	50 ± 10	0.68
Esophageal atresia	Peetsold et al, 2010	Netherlands	11 ± 1	*24*	50 ± 9	0.32	*24*	52 ± 8	0.26
History of cancer	Speechley, et al, 2006	Canada	(6–16)	*763*	50 ± 10	0.32	*763*	49 ± 10	0.38
Symptomatic epilepsy	Sabaz et al, 2003	Australia	(4–18)	n/r	41 ± 12	**<0.001**	n/r	34 ±11	**<0.001**
Tetralogy of Fallot[a]	Goldmuntz et al, 2017	USA	12 ± 3	*122*	50 ± 9	0.27	*122*	51 ± 11	0.50

Abbreviations: ADHD, attention-deficit hyperactivity disorder; BA, biliary atresia; HrQoL, health-related quality of life; n/r, not reported; USA, United States of America.

Note: Effect sizes of differences between children with BA and reference groups are calculated by means of a Cohen's *d* or Hedges' *g* (with pooling of weighted *SD*), interpreted as small (0.20), moderate (0.50), or large (0.80). *P*-values <0.05 are considered as statistically significant and presented in bold values.

[a]Without 22q11.2 deletion.

In our cohort, we did not find significant differences in HrQoL between children who survived with their native liver and children post-LTx. Our findings correspond with previous studies, which also did not find significant differences between children with native liver or post-LTx.[30,37,42,43] One study found similar HrQoL in adult LTx recipients with BA compared with healthy peers, but lower HrQoL in patients who still had their native liver, although the differences between the two patient groups did not reach statistical significance.[42] One has to bear in mind the small proportion of children who survive with their native liver, which might have masked any statistically significant differences between the two patient groups. Both patient groups are at risk of adverse medical events. However, native liver survivors might be more frequently hospitalized due to ongoing liver cirrhosis and portal hypertension, compared with LTx recipients, which may influence their HrQoL.

The most frequent reported factors in literature that are adversely associated with HrQoL include higher number of prescribed drugs,[40,41] adverse medical events,[30,40,42] and younger age of child.[30,40] Although adult patients with BA still report an impaired general health,[38] several studies showed that young adult BA patients, either with native liver or after LTx, did not experience an impaired HrQoL compared with their healthy peers.[36,38,43] The findings of our literature analysis support the concept that the negative effect of a disease on HrQoL reduces as patients age. This phenomenon might be explained by the "response shift," a change in an individuals' perception of their QoL, based on their individual experiences, which might have changed their internal standards or values.[45] In a group of young LTx recipients (<5 years of age), Cole et al showed that their physical abilities and HrQoL improved in the first year after LTx.[46] In our Dutch cohort of BA patients, we did not find a significant association between age and HrQoL. Another explanation could be that the number of LTx-related complications decreases after a certain period of time, which might cause an improvement in HrQoL since data from our cohort showed a significant association between adverse medical events in the past year and physical HrQoL. Nevertheless, longitudinal studies describing HrQoL trajectories in children with BA, with native liver or transplantation, are scarce.[4] Another possible explanation for the differences in HrQoL as perceived by children and adults with BA might be the different questionnaires that

Table 5 Linear regression analysis on factors associated with parent-proxy physical and psychosocial health-related quality of life in children with biliary atresia

	Physical HrQoL		Psychosocial HrQoL	
Univariable analysis	*n*	*β* [95% CI]	*n*	*β* [95% CI]
Gender				
Boys	*17*	*Reference*	*17*	*Reference*
Girls	*18*	2.11 [−5.28, 9.51]	*18*	5.40 [−0.34, 11.14][e]
Age at assessment (y)	*35*	−0.23 [−1.58, 1.12]	*35*	−0.15 [−1.24, 0.95]
Special education				
No	*28*	*Reference*	*28*	*Reference*
Yes	*7*	−11.44 [−19.59, −3.29][d]	*7*	−12.12 [−18.16, −6.07][d]
Highest household education[a]				
Low/intermediate	*8*	*Reference*	*8*	*Reference*
High	*20*	6.43 [−2.20, 15.06][e]	*20*	3.80 [−3.37, 10.98]
Biological parents living together				
No	*4*	*Reference*	*4*	*Reference*
Yes	*30*	−1.15 [−11.38, 9.08]	*30*	−0.94 [−9.27, 7.39]
Household income (euros per year)				
< 35.000	*7*	*Reference*	*7*	*Reference*
> 35.000	*24*	−4.93 [−14.00, 4.15]	*24*	−1.16 [−8.69, 6.38]
Adverse medical event in past year				
No	*26*	*Reference*	*26*	*Reference*
Yes	*9*	−10.91 [−18.40, −3.42][d]	*9*	−1.12 [−7.97, 5.73]
LTx				
No	*8*	*Reference*	*8*	*Reference*
Yes	*27*	−0.73 [−9.45, 8.09]	*27*	−0.16 [−7.27, 6.95]
Time passed since LTx (y)	*26*	1.12 [−0.35, 2.59][e]	*26*	−0.47 [−1.71, 0.77]
Total IQ (norm 100 ± 15)[b]	*34*	0.17 [−0.04, 0.38][e]	*34*	0.14 [−0.30, 0.31][e]
Motor impairments (norm 10 ± 3)[c]	*33*	−0.72 [−1.10, −0.33][d]	*33*	−0.53 [−0.86, −0.20][d]
Behavioral problems (norm 50 ± 10)[c]	*28*	−0.13 [−0.28, 0.02][e]	*28*	−0.22 [−0.31, −0.12][d]
Final multivariable model	*28*		*28*	
Female gender		−6.95 [−12.72, −1.18][d]		2.60 [−2.99, 8.20]
Special education		−9.34 [−16.90, −1.79][d]		−5.59 [−13.21, 2.03][e]
High household education		11.54 [6.13, 16.94][d]		n/i
Adverse medical event in past year		−10.95 [−16.91, −4.99][d]		n/i
Motor impairments (norm 10 ± 3)[c]		−0.55 [−0.93, −0.17][d]		n/i
Behavioral problems (norm 50 ± 10)[c]		n/i		−0.17 [−0.28, −0.07][d]

Abbreviations: CI, confidence interval; HrQoL, health-related quality of life; LTx, liver transplantation; n/i, not included in the final model.
Note: Variables with a *p*-value <0.2 were included in multivariable analysis. The final model after manual backward multivariable regression is reported.
[a]Educational level according to the International Standard Classification of Education Fields of Training and Education (ISCED).
[b]Higher scores represent better outcomes.
[c]Higher scores represent worse outcomes.
[d]*p*-Value <0.05.
[e]*p*-Value <0.2.

are used to assess HrQoL. For example, the WHOQOL (World Health Organization Quality of Life questionnaire) is used in adult patients and assesses QoL in general, whereas the CHQ assesses HrQoL in children.

Several studies reported the lowest scores on school functioning domains.[30,37,40,41] Recently, we described significantly impaired neurodevelopmental outcomes in school-aged children with BA and we hypothesized that these impairments are

associated with impaired HrQoL.[8] In our present study, we report strong support for this hypothesis and show that children with BA who receive special education and children who have impaired motor skills score lower on parent-proxy physical HrQoL. In the Netherlands, special education is provided for those children who cannot participate in regular education. The majority of children at special education suffer from cognitive deficits, psychiatric or serious behavioral problems (e.g., autism) or have physical disabilities, or a chronic illness that hinders regular education.[47] We showed that behavioral problems in children with BA are associated with lower parent-proxy psychosocial HrQoL. This might be explained by more limitations in schoolwork and activities with friends due to behavioral difficulties. Our data implicate that children with neurodevelopmental impairments are indeed at increased risk of impaired HrQoL. Furthermore, both children and their parents reported limitations due to emotional difficulties which might be caused by symptoms of anxiety and depression.

Compared with children with other major surgery in infancy or chronic conditions, children with BA scored predominantly lower on physical HrQoL and largely comparable on psychosocial HrQoL. An explanation for the lower physical HrQoL in children with BA compared with other chronic conditions might be the higher burden on a daily basis that accompanies BA. For example, children with BA might suffer from more complications, experience more bodily pain, or require a higher number of prescribed drugs.

Previously, Sundaram et al assessed parent–child agreement per age category and found higher agreement between parents and older children (age >7 years) than between parents and younger children.[30] In our cohort, agreement (measured as ICC) on HrQoL domains between parents and their child was moderate to high, with poorest agreement on the behavioral scales. A systematic review of studies comparing parent-proxy and child self-reported HrQoL showed that there are only moderate correlations between parent- and child-reported domains, with a much greater agreement in observable functioning (physical HrQoL), than in reports of social or emotional HrQoL.[48] Differences between parent and child might be explained by the "disability paradox," the concept that having a chronic disease does not necessarily mean that someone is unsatisfied with life, in contrast to what others may anticipate.[49]

We are aware that our study has some limitations. First of all, as BA is a rare disease, the sample size in the majority of studies on HrQoL in BA patients was small. HrQoL summary scores of children with BA were compared with summary scores from children with chronic diseases as reported by other studies, using *t*-tests. When performing multiple *t*-test, the risk of a cumulative type I error increases. Therefore, the comparison between the different patients' groups has to be interpreted cautiously. The majority of the studies on other chronic diseases that used the CHQ were executed in the United States or the Netherlands, which might have somewhat limited the representativeness of those studies. Currently, there is no validated summary score of the self-reported CHQ domains. This hindered the exploration of patient-related factors that might be associated with self-reported HrQoL, and the comparison of self-reported HrQoL between patients' groups. We feel that international collaboration is warranted to confirm our findings in a larger and longitudinal cohort of children with BA.

Conclusion

Children with BA are at risk of impaired HrQoL, especially physical HrQoL. Special attention is warranted for children with adverse medical events, motor impairments, or behavioral problems, whom might be at increased risk of impaired HrQoL. The results of this study will allow physicians to provide patients and their caregivers/parents with information on the long-term effects of BA. The development of an intervention program to support children with BA at risk of impaired HrQoL is warranted.

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Conflict of Interest

None declared.

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