Original Article

Health-Related Quality of Life in Children with Biliary Atresia Living with Native Livers

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Abstract

Introduction: This study aimed to quantify and investigate factors affecting the health-related quality of life (HRQoL) in children with biliary atresia (BA) living with their native livers. Materials and Methods: A cross-sectional study on the HRQoL using the PedsQL4.0 generic core scales in children with BA aged between 2 to 18 years followed up at the University Malaya Medical Centre (UMMC) in Malaysia was conducted. Two groups, consisting of healthy children and children with chronic liver disease (CLD) caused by other aetiologies, were recruited as controls. Results: Children with BA living with their native livers (n = 36; median (range) age: 7.4 (2 to 18) years; overall HRQoL score: 85.6) have a comparable HRQoL score with healthy children (n = 81; median age: 7.0 years; overall HQRoL score: 87.4; *P* = 0.504) as well as children with CLD (n = 44; median age: 4.3 years; overall score: 87.1; *P* = 0.563). The HRQoL of children with BA was not adversely affected by having 1 or more hospitalisations in the preceding 12 months, the presence of portal hypertension, older age at corrective surgery (>60 days), a lower level of serum albumin (≤34 g/L) or a higher blood international normalised ratio (INR) (≥1.2). Children who had liver transplantation for BA did not have a significantly better HRQoL as compared to those who had survived with their native livers (85.4 vs 85.7, *P* = 0.960). Conclusion: HRQoL in children with BA living with their native livers is comparable to healthy children.

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Key words: Chronic liver disease, Survivors

Introduction

Biliary atresia (BA), a progressive obliterative fibro-inflammatory cholangiopathy, usually presents with jaundice in infancy.[1] The definitive therapy for BA in the majority of infants is liver transplantation (LT).[2,3] The creation of a portoenterostomy (Kasai surgery) is now considered by many as a bridge to eventual LT.[3] Infants who have surgery before 60 days of age had a more than 80% chance of re-establishing bile flow and clearance of jaundice.[2-6] Without surgery, BA is a fatal disease for which children rarely survive beyond 3 years of age.[5] LT is indicated in those who have unsuccessful surgery.[5] In Malaysia, the overall 2-year survival rate (with native liver and after LT) of BA was 40%.[7] The outcome was adversely affected by late referral for surgery and a lack of timely LT in those who had unsuccessful surgery.[7]

Many patients with BA develop progressive liver disease with ongoing cirrhosis after surgery.[7-9] Complications include recurrent cholangitis, portal hypertension and variceal bleed, as well as bone fractures.[7,9] Therefore, lifelong follow-up is necessary to detect the complications of biliary cirrhosis. With the improvement in survival, greater attention is now being given to the assessment of quality of life (QoL) in children living with chronic illness.[10] In addition to assessing the effect on physical and mental health, QoL also assesses the impact of an underlying chronic illness on the cultural, environmental and economic well-being of the affected individual.[10]

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Health-related QoL (HRQoL) refers to the impact that health and illness may have on the well-being of an individual, and on his/her ability to function in daily life with regard to physical health as well as emotional, social and school functioning.[11] It is a multidimensional construct that assesses the physical, psychological (including emotional and cognitive) and social health dimensions, and has been used widely in the paediatric population.[12] The objective of the present study was to measure the HRQoL in children with BA who survived with their native livers and to compare them with healthy children as well as children with chronic liver disease (CLD) due to aetiologies other than BA.

Materials and Methods

This was a cross-sectional study conducted among children with BA attending our institution's paediatric gastroenterology and nutrition unit. Patients with BA who were diagnosed between January 1993 and June 2012 were identified from the hospital database. Patients were recruited and interviewed when they attended the children's liver clinic from December 2011 to March 2013. The present study was approved by the institutional ethic review committee (MEC reference: 902.15). Parental consent was obtained before the distribution of research questionnaire.

Inclusion Criteria

All children with a diagnosis of BA who attended the children's liver clinic during the study period were recruited. The diagnosis of BA was confirmed via an operative cholangiogram. Patients younger than 2 years or older than 18, or those without parental consent, were excluded.

Data Collection

Demographic, medical and laboratory data were collected. Interview and physical examination were conducted by one of the co-authors throughout the study. Medical and laboratory data were collected via chart review. No additional laboratory tests were performed for the purpose of the present study. Medical events in the preceding 12 months were collected through chart review as well as parental and patient's recall.

Definitions

Age at Kasai surgery was considered as early if the surgery was performed at or before 60 days of age. Portal hypertension was defined as presence of variceal bleed due to a documented oesophageal or gastric varices and/or splenomegaly.

Controls

A cohort of healthy children with no intercurrent or chronic illnesses was recruited as controls. They were siblings of other patients accompanying their parents to the hospital. This was a convenient sample and no attempts were made to match for age or sex with the patients with BA. Consent was obtained from their parents before the interview. A second group control consisted of children who were attending the children's liver clinic and were diagnosed with CLD caused by conditions other than BA. Similarly, this was a convenient sampling and no attempts were made to match for age or sex with patients with BA.

Survey Instrument

The HRQoL was assessed using PedsQLTM 4.0 generic core scales.[12,13] Written permission for the use of the questionnaire was obtained from the MAPI Research Institute in Lyon, France. PedsQLTM is a 23-question instrument which has been validated in healthy children aged between 2 and 18 years. It measures the core dimensions of health and includes the following domains: physical (8 items), emotional (5 items), social (5 items) and school functioning (5 items).[13] The PedsQL 4.0 generic core scales has a parallel parent proxy-report and child self-report versions. The reported internal consistency between child self-report and parent proxy-report is excellent.[13] The items in the PedsQL 4.0 are reversely scored and linearly transformed to a scale of 0 to 100 with higher scores indicating better HRQoL. Age-appropriate questionnaires were used for different age groups (2 to 4, 5 to 7, 8 to 12 and 13 to 18 years). Both English and Malay language versions were available upon request. Parents completed the questionnaire while children aged ≥5 years were offered the child self-report version.

Demographic and Medical Factors Affecting HRQoL

Age at Kasai surgery, presence of portal hypertension, the number of hospital admissions, failure to thrive (defined as weight ≤ third centile for age and sex), serum bilirubin and albumin levels, as well as blood international normalised ratio (INR) were analysed to ascertain factors affecting the HRQoL in children with BA. We did not include the presence of visible change in skin colour (visible jaundice), as the children in the present study were from various ethnic backgrounds and had different skin colours. Thus, it was difficult to standardise the change in skin colour. Similarly, the presence of skin itchiness was not included as a factor because it was difficult to standardise the presence and the degree of itchiness in children from different sociocultural backgrounds.

Statistical Methods

Statistical Products for Social Services (SPSS; Chicago, Illinois) for Windows (version 16.0) was used. Chi-square tests were used for categorical data, while continuous data were checked for normality via Kolmogorov-Smirnov testing. To determine the agreement between child self-report and parent proxy-report, interclass correlation coefficients (ICCs) were used.[13] ICCs <0.40 were designated as poor-to-fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as good and 0.81 to 1.00 as excellent agreement.[13] One-way ANOVA was applied when comparison of more than 2 groups were made. Univariate analysis was conducted to identify demographic and clinical factors associated with impairment in the HRQoL scores in children with BA. Multivariate analysis was performed by conducting linear regression to identify significant demographic or clinical data which may influence the HRQoL. For all the statistical tests used, a *P* value of ≤0.05 was considered to be statistically significant.

Results

A total of 144 patients with a diagnosis of BA were identified (Fig. 1). Of these, the case notes of 24 patients were unavailable for review, and efforts to contact them were unsuccessful. Of the remaining 120 patients, 61 had died (55 with native liver, 6 after LT; overall survival rate 49%; Fig. 1). The overall survival rate with native liver was 46%.

Fifty-nine patients with BA (48 with native liver, 11 after LT) were identified. Of these, 44 patients (8 had LT, 18% of 44) fulfilled the inclusion criteria of the present study. Reasons for excluding the remaining 15 patients were: beyond the age limit of the study (younger than 2 years of age, n = 5; older than 18 years, n = 3), parental refusal to participate (n = 1), transferred to another hospital for care (n = 4) or defaulted on follow-up (n = 2). Eight of the 44 with BA had a successful LT and were still alive at the time of review.

Biliary Atresia

Thirty-six (median age: 7.4 years; range, 2 to 18 years) of the 44 patients with BA survived with their native livers. Of these, 25 (69%) had early Kasai surgery (≤60 days of life). Fifteen patients (42%) had portal hypertension and 3 (8%) had failure to thrive (Table 1).

Controls

Forty-four children with other aetiologies of CLD (median

Table 1. Demographic Data and Family Background of Children with Biliary Atresia, Chronic Liver Disease and Healthy Controls

Parameters	Biliary Atresia (n = 36)	Chronic Liver Diseases (n = 44)	Healthy Controls (n = 81)	All Groups (n = 161)
Age (year)				
2 – 4	14	11	26	51
5 – 7	7	5	15	27
8 – 12	7	19	19	45
13 – 18	8	9	21	38
Median ± SD	7.4 ± 4.2	9.3 ± 4.1	7.0 ± 4.4	
Gender				
Male	13	19	34	66
Female	23	25	47	95
Respondent's relationship with patient				
Father	8	17	16	41
Mother	28	27	65	120
Failure to thrive*				
Present	3 (8%)	4 (9%)‡		
Absent	33	40		
Portal hypertension†				
Present	15 (32%)	8 (18%)§		
Absent	21	36		

SD: Standard deviation
*Defined as weight ≤ third centile for age and sex.
†Defined as presence of variceal bleed due to a documented esophageal or gastric varices and/or splenomegaly.
‡*P* value = 1.0 (Fisher's exact test).
§*P* value = 0.027 (Fisher's exact test).

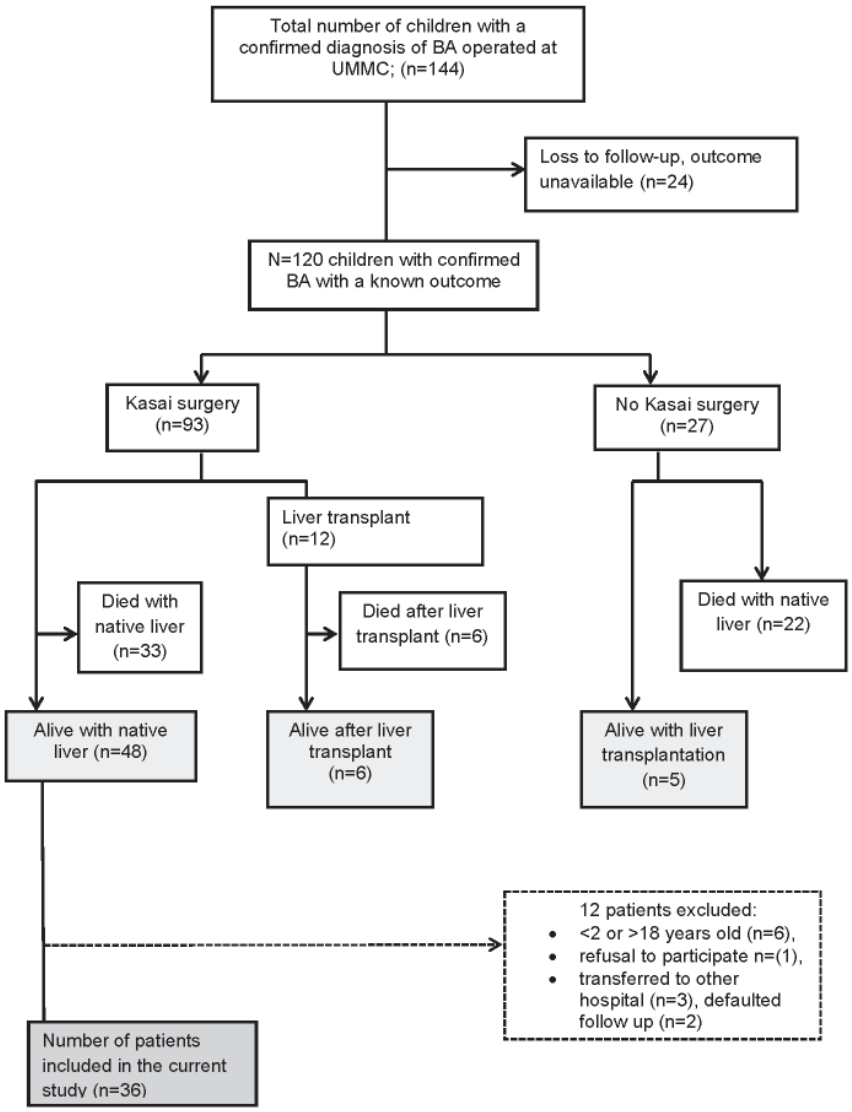

Fig. 1. Flowchart showing the recruitment process for children with a diagnosis of biliary atresia in the current study.

age ± SD = 9.3 ± 4.1 years) were recruited as controls (Table 1). The controls were recruited as a convenient sample. The diagnoses were: autoimmune hepatitis (n = 14), chronic hepatitis B (n = 14), Alagille syndrome (n = 3), idiopathic portal hypertension (n = 2), progressive familial intrahepatic cholestasis (n = 2), cystic fibrosis liver disease (n = 2), glycogen storage disease (n = 2), non-alcoholic steatohepatitis (n = 1), and idiopathic neonatal hepatitis (n = 1). Four have other medical conditions (one each for Ehler Danlos, bronchiectasis, atrial septal defect not in failure and solitary kidney). Eight of the 44 (18%) children with CLD have portal hypertension and 44 (9%) have failure to thrive. A second group of 81 healthy children (median ± SD = 7.0 ± 4.4 years) were recruited as controls.

Respondents of Questionnaire

All the parents (74% were mothers, Table 1) recruited in the 3 study groups completed the questionnaire. Child self-report version of the questionnaire was offered to the 115 children (in all 3 groups) aged 5 years and above and 106 (92% of 115) completed the questionnaire (5 to 7 years, n = 21; 8 to 12 years, n = 43; 13 to 18 years, n = 42).

Comparison of Patients with BA with CLD and Healthy Controls

For the purpose of comparing PedsQL data (Tables 2, 3 and 4), the parent proxy-report scores were used. Generally, children with BA living with their native livers were reported

Table 2. PedsQL 4.0 Generic Core Scale Scores in Children with Biliary Atresia, Chronic Liver Disease and Healthy Controls

Domains	Biliary Atresia (n = 36)		Chronic Liver Disease (n = 44)		Healthy Controls (n = 81)		All (n = 161)		*P* Value
	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)	
Physical functioning	88.7 ± 21.1	(82.3, 95.1)	89.7 ± 15.1	(85.1, 94.3)	90.8 ± 13.4	(87.8, 93.8)	90.0 ± 16.1	(87.6, 92.5)	0.776
Psychological functioning	85.2 ± 15.1	(80.6, 89.8)	87.0 ± 13.0	(83.0, 90.9)	86.0 ± 12.9	(83.2, 88.9)	86.0 ± 13.5	(84.0, 88.1)	0.829
Emotional functioning	83.4 ± 16.4	(78.4, 88.4)	86.7 ± 18.2	(81.2, 92.2)	83.9 ± 17.0	(80.1, 87.6)	84.5 ± 17.1	(81.9, 87.1)	0.600
Social functioning	90.2 ± 18.5	(84.5, 95.9)	92.5 ± 14.6	(88.1, 96.9)	91.2 ± 12.7	(88.3, 93.9)	91.2 ± 14.8	(89.0, 93.5)	0.770
School functioning	90.2 ± 18.5	(84.5, 95.9)	92.5 ± 14.6	(88.1, 96.9)	91.2 ± 12.7	(88.3, 93.9)	91.2 ± 14.8	(89.0, 93.5)	0.770
Overall score	85.6 ± 15.4	(80.91 90.3)	87.1 ± 12.6	(83.3, 91.0)	87.4 ± 11.5	(84.8, 89.9)	86.9 ± 12.8	(84.9, 88.8)	0.752

CI: Confidence interval; SD: Standard deviation

by their parents to have the lowest score in the school and emotional functioning domains and the highest score in the social functioning domain. However, healthy children and children with CLD were reported to have the highest scores in the physical and social functioning domains, and the lowest score in the school functioning domains (Table 2). As compared to healthy controls, children with BA surviving with their native livers have no significant difference in the overall PedsQL 4.0 generic core scale score (85.5 ± 15.4 vs 87.4 ± 11.5; differences in means: -1.8; $P = 0.465$; Tables 2 and 3). Analysis of the individual components of the scores yielded no significant difference as well (Table 3).

There was no significant difference in the PedsQL 4.0 generic core scale scores (both overall and subscale scores) between healthy children and children with CLD (Table 3). Similarly, no significant difference in PedsQL 4.0 generic core scale scores (both overall and subscale scores) was observed between children with BA living with their native livers and those with other forms of CLD (Table 3).

Comparison of Child Self-report and Parent Proxy-report Scores

A total of 106 child self-report and parent proxy-report pairs were available in all the 3 study groups for comparison (Table 4). There was excellent correlation between the parent proxy-report and child self-report scores in the overall score (ICC 0.844), with good correlation in the emotional, social and school functioning domains, and excellent correlation in the physical and psychosocial functioning domains. Both the parents and children reported higher scores for physical functioning as compared to the psychosocial domain.

Medical Predictors of HRQoL in Children with BA

Table 5 shows the influence of age at Kasai surgery, number of hospital admissions in the preceding 12 months, presence of portal hypertension, serum albumin and blood INR on the HRQoL scores in children with BA. Children with more hospital admissions in the preceding 12 months had significantly worse HRQoL scores.

Table 3. Comparison of PedsQL Generic Core Scale Scores in Children with Biliary Atresia, Chronic Liver Disease and Healthy Controls

Domains	BA vs Healthy Controls		BA vs CLD		CLD vs Healthy Controls	
	Mean Difference	*P* Value	Mean Difference	*P* Value	Mean Difference	*P* Value
Physical functioning	-1.2	0.702	+0.1	0.977	-1.1	0.615
Psychological functioning	-0.8	0.781	-1.8	0.463	+1.0	0.524
Emotional functioning	-1.2	0.715	-3.3	0.280	+2.8	0.346
Social functioning	+1.0	0.991	-2.3	0.483	+1.3	0.322
School functioning	+2.1	0.802	+3.0	0.744	-0.9	0.910
Overall score	-1.7	0.504	-1.5	0.563	-0.3	0.961

BA: Biliary atresia; CLD: Chronic liver disease

Table 4. Comparison of PedsQL Generic Core Scale Scores Between Parent Proxy-Report and Child Self-Report

Domains	n	Child Self-Report (Mean ± SD)	Parent Proxy-Report (Mean ± SD)	Interclass Correlation Coefficient* (*P* Value)
Physical functioning	106	87.9 ± 13.1	90.2 ± 15.7	0.776 (<0.001)
Psychosocial functioning	105	83.6 ± 12.7	86.3 ± 13.3	0.688 (<0.001)
Emotional functioning	106	82.4 ± 17.5	84.4 ± 17.4	0.613 (<0.001)
Social functioning	104	89.0 ± 12.8	91.7 ± 13.8	0.643 (<0.001)
School functioning	104	79.3 ± 17.0	81.7 ± 18.6	0.594 (<0.001)
Overall score	106	84.2 ± 14.0	87.0 ± 12.7	0.670 (<0.001)

SD: Standard deviation

*Interclass correlation coefficient <0.40 were designated as poor-to-fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as good and 0.81 to 1.00 as excellent agreement.

HRQoL Scores in Children with BA Surviving with Native Liver and After LT

There was no significant difference in the parent proxy-report HRQoL scores between the 8 children with BA surviving after LT as compared to the HRQoL scores of the 36 children with BA surviving with their native livers groups (Table 6), although the number of children who had LT in the present study was small (n = 8).

Discussion

Advances in the management of children with gastrointestinal and hepatic diseases have led to an increased survival in this group of children. Attention is now given to the QoL in children living with chronic gastrointestinal and liver disorders.[10] Cholangitis, portal hypertension, bleeding and bone fractures are important complications in children with BA surviving long-term with their native livers.[8,9] Lee et al observed that 24% of children with BA who had a successful surgery have major morbidities.[7] In those who survived for more than 20 years with their native livers, up to 61% have complications.[8]

There have been several studies on the HRQoL in children with BA, both living with their native livers and after LT.[14-17]

Table 5. Medical Variables Affecting the Overall Parent Proxy-Report PEDSQL Generic Core Scale Scores in Children with Biliary Atresia Living with their Livers

Factors	n	Overall Parent Proxy-Report Score (Mean ± SD)	Mean Difference	*P* Value
Age at surgery				
≤60 days	25	82.8 ± 16.6	-10.2	0.076
>60 days	11	93.0 ± 9.5		
Hospitalisations*				
No hospitalisation	28	86.6 ± 14.8	5.3	0.37
At least 1 hospital admission	8	81.4 ± 13.4		
Portal hypertension				
Present	15	80.9 ± 20.1	-8.2	0.166
Absent	21	89.1 ± 10.5		
Serum bilirubin level (μmol/L)				
>85 μmol/L	6	80.6 ± 14.5	-6.5	0.37
≤85 μmol/L	33	87.0 ± 16.3		
Serum albumin level (g/L)				
≤34 g/L	13	82.8 ± 15.8	-4.4	0.458
>34 g/L	19	87.2 ± 16.4		
International normalised ratio				
≤1.2	18	87.9 ± 16.6	17.4	0.094
>1.2	3	70.5 ± 5.1		

SD: Standard deviation

*In the preceding 12 months.

Table 6. Comparison of Parent Proxy-Report PEDSQL Scores in Children with Biliary Atresia Surviving with Native Liver After Liver Transplantation

	Liver Transplant	n	Mean ± SD	Mean Difference	*P* Value
Physical functioning	Yes	8	84.7 ± 24.6	5.0	0.553
	No	36	89.6 ± 20.5		
Psychosocial functioning	Yes	8	85.0 ± 15.9	0.3	0.964
	No	36	85.3 ± 15.2		
Emotional functioning	Yes	8	86.9 ± 12.8	-4.3	0.513
	No	36	82.6 ± 17.2		
Social functioning	Yes	7	85.7 ± 27.0	5.4	0.487
	No	36	91.1 ± 16.8		
School functioning	Yes	6	87.5 ± 14.1	-4.8	0.565
	No	25	82.7 ± 18.7		
Overall score	Yes	8	85.4 ± 15.7	0.3	0.960
	No	36	85.7 ± 15.6		

SD: Standard deviation

Sundaram et al observed that HRQoL in children with BA living with their native livers was significantly poorer as compared to healthy children but was similar to children who had LT,[17] although children with BA living with native livers were generally healthy with up to 62% having a state of optimal health. The most significant difference observed was in school functioning.[17] Another study comparing 30 Japanese and 25 English adolescents with BA living with their native livers showed significant impairment in general, physical, social and emotional health in patients with BA as compared with healthy children.[18]

In the present study, we observed that the overall HRQoL scores in children with BA living with their native livers were not significantly different from that of healthy children. In addition, there was no significant difference in all the measured domains of the HRQoL scores.

LT for children with end-stage liver disease or those with unacceptable QoL in Malaysia is limited.[7] The cohort of children with BA living with their native livers in the present study has significant morbidity with one-third having portal hypertension and 7% having had failure to thrive. It is therefore somewhat unexpected that based on parental proxy-report, the HRQoL in these children were found to be similar to those reported by healthy children.

However, a recent study on adults with BA living with their native livers from the Netherlands also showed a comparable health status and QoL with their healthy peers.[19] However, the number of patients enrolled was small (25 patients), and the instrument of study used was different.[19]

We observed that the overall HRQoL score in children with BA was 85.6, while the score noted in the study by Sundaram et al was 76.9.[17] The scores for healthy controls in both studies were comparable (87.4 in the present study; 84.7 in the study by Sundaram et al).[17] Possible explanation for the difference in the HRQoL scores between the 2 studies included differences in the age of the patients studied. The median age of children with BA in the present study was younger than that reported by Sundaram et al (7.4 years vs 9.75 years).[17] We postulated that HRQoL in children with BA deteriorated with age. However, neither of the studies compared the HRQoL in different age groups.

We found good-to-excellent correlation between the parent proxy-report and child self-report in the HRQoL scores across all domains in all the 3 study groups. Other authors have also observed good-to-excellent correlation between parent and child report.[20,21] Children as young as 5 years have been found to be reliable in reporting the HRQoL scores.[21] In addition to comparing between children with BA and healthy children, we were also unable to observe any differences in the HRQoL between children with BA living with their native livers and those with CLD caused by conditions other than BA.

Sundaram et al reported no difference in the HRQoL in children with BA living with native livers and after LT.[17] We did not observe any significant difference in the HRQoL in children with BA living with their native livers or after LT, although the number of children with BA after LT in the present study was small.

There are several limitations in the present study. Firstly, the number of patients with BA and CLD recruited for the present study was small. Only 36 patients with BA living with their native livers were recruited for the present study. We were unable to match the healthy controls selected for the present study with children with BA. In addition, we were unable to include a significant number of children with a diagnosis of BA.

We have previously reported that the overall survival rate among patients with BA with their native liver was 40% at 2 years after surgery.[7] Reasons for this unfavourable outcome was a delay in referral for timely diagnosis and surgery in infants with neonatal cholestasis. For those with unsuccessful surgery, a lack of timely liver transplant surgery also contributed to a poor overall survival rate.[7]

We did not find the presence of any medical factors significantly affecting the HRQoL scores in children with BA living with their native livers. Having a serum bilirubin level above 85 μmol/L or hospitalisation in the preceding 12 months did not adversely affecting the HRQoL of children with BA.

Conclusion

With good medical care, children with BA surviving with their native livers can enjoy a good QoL that is comparable with their healthy peers. Nevertheless, careful long-term follow-up, with particular attention on the various issues affecting the QoL in these children, is necessary. Strategies to prevent recurrent cholangitis leading to frequent hospital admissions is needed to further improve the QoL in children with BA living with their native livers. Children with BA surviving after LT do not necessarily have a better QoL than their peers living with their native livers.

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