



# Health-Related Quality of Life in Patients with Biliary Atresia: A Systematic Review and Meta-Analysis

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Received 2018 August 23; Revised 2019 April 09; Accepted 2019 April 12.

## Abstract

**Objectives:** In this systematic review and meta-analysis, for the first time, the existing evidence on health-related quality of life (HRQOL) was evaluated in patients with biliary atresia (BA) and compared with that of healthy population.

**Methods:** A systematic search was done on PubMed, Scopus, Embase, Cochrane Library and Web of Science from 1990 up to April 2018 in order to identify all articles that assess the HRQOL in patients with BA. Meta-analysis was done using comprehensive meta-analysis and the standard difference of mean (SDM) was calculated.

**Results:** A total of 188 publications were identified from the initial search. After removing duplicates and irrelevant studies, 32 articles remained for full-text evaluation. Out of this number, 22 articles were excluded due to non-relevance to the study scope leaving 10 studies for systematic review and three articles for meta-analysis. HRQOL was assessed using PedsQL4 in three studies, SF-36C in two studies and by assessing different parameters including social status, school, university, and/or sports performance in five studies. HRQOL in BA patients living with their own liver was significantly lower than that of the general population [SDM = -0.55 (95% CI: -0.69, -0.40)]. In the terms of PedsQL4 sub-scores, compared with healthy population, the levels of physical [SDM = -0.40 (95% CI: -0.55, -0.28)], social [SDM = -0.25 (95% CI: -0.40, -0.11)] and school functioning [SDM = -1.19 (95% CI: -2.35, 0.07)] were significantly lower in the group of biliary atresia.

**Keywords:** Quality of Life, Extra Hepatic Biliary Atresia, PedsQL4

## 1. Context

Biliary atresia (BA) is a rare inflammatory disease of the biliary tract. The progressive fibrosis of the biliary tree in this disease results in blockade of duct and subsequent cirrhosis (1). The symptoms of the disease include persistent jaundice, acholic stool and dark urine (2). The prevalence of this disease varies from 0.5 to 0.8 per 10,000 live births in western countries to 1.1 - 1.5 per 10,000 live births in Japan and Taiwan (2-5).

BA is the most common surgically correctable liver disease in infancy in which for returning normal bile flow, surgical treatment (Kasai operation) should be implemented urgently in the early weeks of life. However, in some infants this procedure may not be successful. Previous studies have showed that more than half of the infants born with this problem may need liver transplant (6-8). On the other hand, some patients live with their native liver for many years and may experience long-term complications such as cholangitis, portal hypertension, variceal bleeding and growth failure (9). These complications may lead to

frequent hospital admissions (10) and could have a great impact on the quality of life in these patients. Different studies have evaluated the health-related quality of life (HRQOL) in patients with BA and compared it with that of the healthy population. However, the results were controversial. To the best of our knowledge, no systematic review study and meta-analysis have been done to review these results up to the time of conducting this research study.

## 2. Objectives

Thus, in the present systematic review and meta-analysis, for the first time, the existing evidence on HRQOL was evaluated in patients with BA and compared with that of healthy population.

## 3. Data Sources

A systematic search was done on PubMed, Scopus, Embase, Cochrane Library and Web of Science from 1990 to

April 2018. The keywords were selected based on MESH terms and including: (I) population: “Biliary atresia” or “Extrahepatic Biliary Atresia”(II) outcome: “life quality” OR “health related quality of life” OR “health-related quality of life” OR “quality of life”(III) comparison: “healthy population” OR “general population”. The search strategy for each database is shown in Appendix 1 in Supplementary File. The reference list of included articles was also checked manually. The Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences approved the research protocol.

#### 4. Study Selection

The present systematic review included observational studies (descriptive and analytical studies) which assessed the HRQOL in patients with BA. The original articles or conference papers that had been published from 1990 to April 2018 were included if they reported the HRQOL in BA patients and/or compared the HRQOL between BA patients and the healthy population. All other types of articles including letters to the editors, review articles and articles published in any language other than English were excluded.

#### 5. Data Extraction

Data extraction was done by two independent reviewers. Discrepancies were resolved by discussion and through involvement of a third reviewer. First, the results were screened to exclude duplicates and unrelated articles. Then, the full-texts of the remaining records were screened to select articles which met the inclusion criteria. Finally, for eligible studies, the data about the authors, publication date, methods used for assessing HRQOL, sample size, comparison group (if existed), participants’ characteristics and results were extracted using the predesigned checklist.

#### 6. Quality Assessment

The methodological quality of selected articles was done by two reviewers using JBI critical appraising checklist for descriptive and analytical studies. The following domains were assessed: clear research question, clear definition of population, subject selected based on inclusion criteria, reliable outcome assessment and using objective criteria for outcome assessment, comparison between responders and non-responders.

#### 7. Statistical Analysis

The comprehensive meta-analysis version 2.0 was used in this regard. The mean and standard deviation (SD) HRQOL (total score and domains scores including physical, emotional, social and school functioning) were extracted and then the standard difference of mean (SDM) was computed. Q statistic ( $P < 0.10$ ) and  $I^2$  ( $I^2 > 50\%$ ) were used for determination of heterogeneity (11). Based on heterogeneity analysis, fixed or random effect model was used. Publication bias was assessed with a visual inspection of funnel plots and with the Egger bias test (12). One study reported HRQOL scores (total score and domains scores) as median and inter quartile range (IQR) (13). For including these data in the meta-analysis, the median and IQR were converted to mean and SD using method introduced by Hozo et al. (14).

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) was used as the method of analysis in this research study.

#### 8. Results

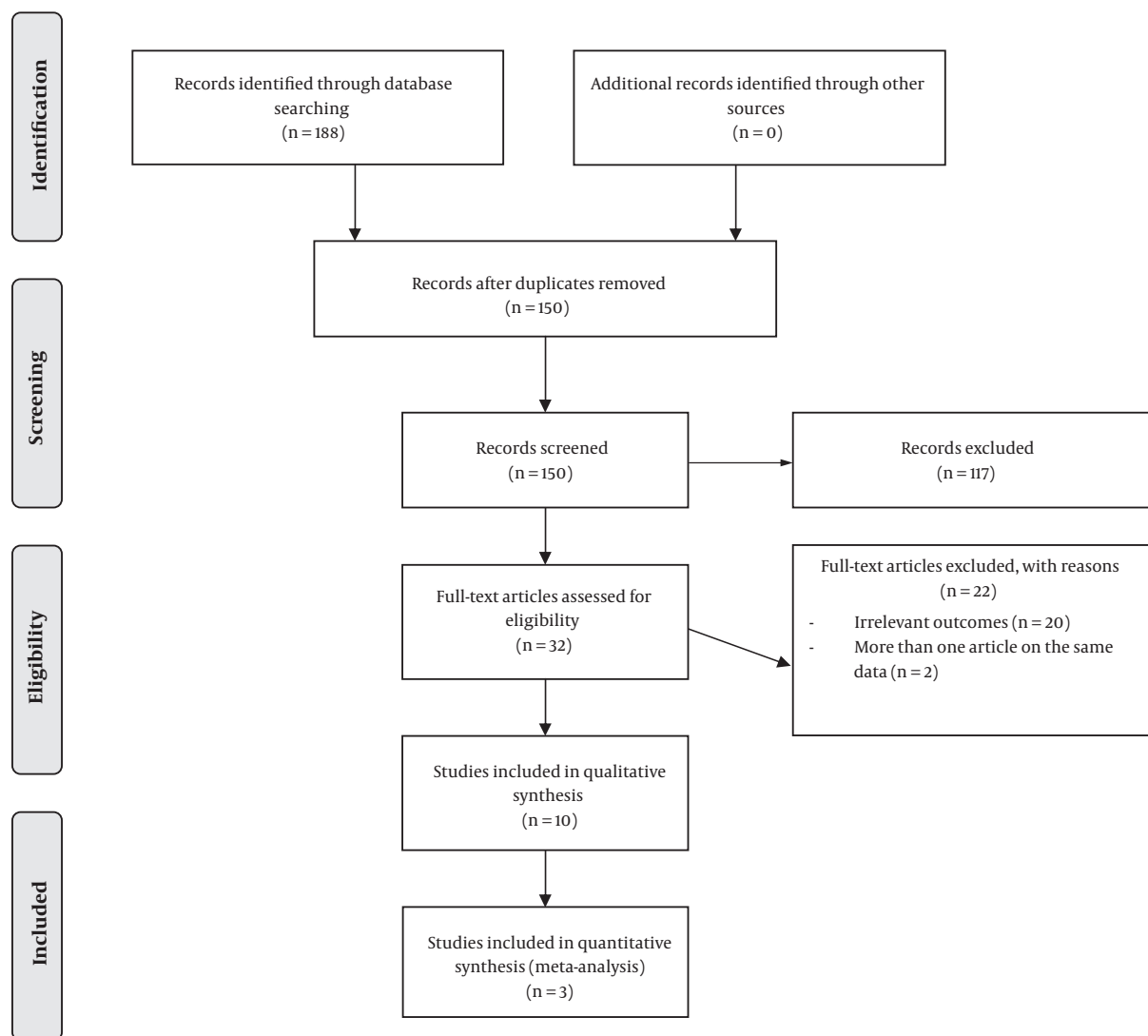
A total of 188 publications were identified after the initial systematic search of databases. Following the removal of duplicate records, 150 articles remained for review out of which 85 were excluded after title appraisal. Then the abstracts of the 65 remaining articles were reviewed and 32 articles were excluded. From the remaining 33 articles, 22 were excluded after appraisal of the full-texts, leaving 10 studies to be included for systematic review (Figure 1) and ultimately only three articles enrolled for meta-analysis. The detailed characteristics of the included studies are presented in Table 1.

Out of 10 included studies, three were conducted in Japan (19, 20, 22), two in France (18, 21), and others in Finland (13), Netherlands (17), Canada (15), and Malaysia (10). Moreover, one study included the participants from two different populations, namely UK and Japan (16). The study design of all articles was cross-sectional.

The methodological quality assessment of the studies is presented in Table 2. Reliable method for the assessment of HRQOL was used in only five studies. Inclusion criteria for sample recruitment were clarified in all studies except for two papers.

##### 8.1. HRQOL Assessment

HRQOL was assessed using PedsQL4 in three studies (10, 13, 15), SF-36C in two studies (16, 17) and by assessing different parameters including social status, school, university and/o sports performance in five studies (18-22). The HRQOL and their sub-scores were compared in patients with BA and healthy population in five studies using SF-36C (two studies) (16, 17) and PedsQL4 (three studies) (10, 13, 15).



**Figure 1.** Flow diagram of studies for inclusion in the systematic review and meta-analysis

## 8.2. Outcomes

Three studies assessed HRQOL in BA patients using PedsQL4 and compared the results with healthy control groups. Two of the studies (10, 13) showed that there was no significant difference between BA patients and healthy population regarding HRQOL total score. However, Lampela et al. reported a significantly lower level of school domain in BA patients ( $P < 0.004$ ) (13). Sundaram et al. reported a low level of HRQOL total score and all the sub-scores in BA patients compared with healthy population (15).

Two studies used SF-36C questionnaire to evaluate the HRQOL in BA patients and compared total score and sub-scores with those of the healthy population. Howard et

al. studied the QOL in two populations, namely Japan and UK (16). According to the results, there was no significant difference in the HRQOL scores of BA patients and healthy control group in the UK population. However, in Japanese population, general health and social functioning sub-scores were significantly lower in BA patients compared to the general healthy population of Japan (16). De Vries et al. reported HRQOL in population of the Netherlands and showed that there was no significant difference between BA patients and the general Dutch population regarding all domains of SF-36C except for general health which was significantly lower ( $P < 0.004$ ) (17).

In five studies the HRQOL in BA patients was assessed using different parameters including social status, school,

**Table 2.** Methodological Quality of Included Studies

Authors, Year	Study Design	Clear Research Question	Clear Definition of Population	Subject Selected Based on Inclusion Criteria	Reliable Outcome Assessment	Using Objective Criteria for Outcome Assessment	Compare Responders and Nonresponders
Lampela et al., 2017 (13)	Cross sectional	y	y	y	y	N	y
Sundaram et al., 2013 (15)	Cross sectional	y	y	y	y	N	y
Lee et al., 2016 (10)	Cross sectional	y	y	y	y	N	N
Howard et al., 2001 (16)	Cross sectional	y	y	y	y	N	Y
de Vries, et al., 2015 (17)	Cross sectional	y	y	y	y	N	Y
Valayer, 1996 (18)	Cross sectional	y	y	y	N	N	N
Nio et al., 1997 (19)	Cross sectional	y	y	ND	N	N	N
Ohi et al., 1990 (20)	Cross sectional	y	y	y	N	N	N
Lykavieris et al., 2005 (21)	Cross sectional	y	y	y	N	N	N
Nio et al., 1996 (22)	Cross sectional	y	N	ND	N	N	N

university, and/or sports performance. In four out of five studies, more than 70% of BA patients had a normal life and satisfactory rate of HRQOL (19-22). In addition, in Valayer's study that was conducted in France, only 31% of BA patients had normal school performance (18).

### 8.3. Meta-Analysis

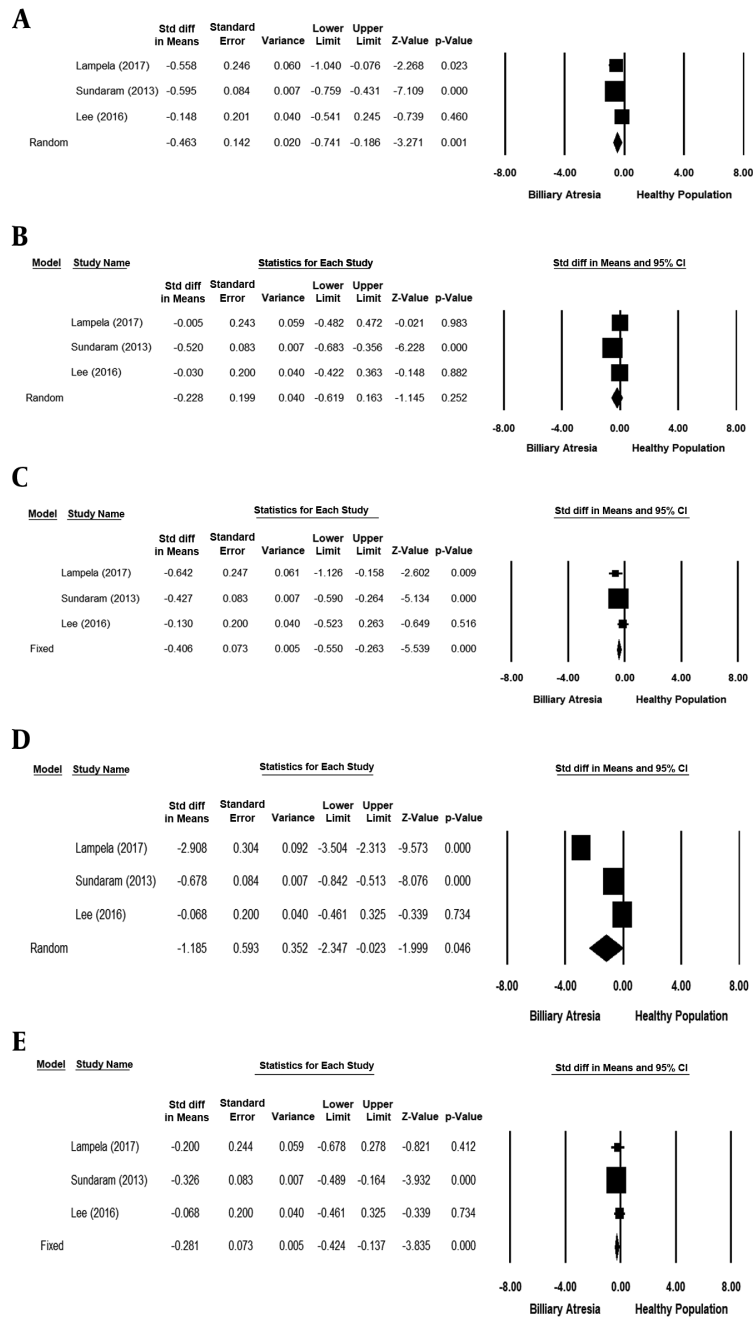
According to Figure 2, the extracted data enables five separate meta-analysis to compare the HRQOL assessed using PedsQL4 between BA patients and the healthy control group (10, 13, 15). No publication bias was observed in the HRQOL score and subscores (Egger test P value > 0.05). Considering the presence of heterogeneity in HRQOL total score ( $I^2 = 52.65$ ,  $Q = 4.23$ ,  $P = 0.12$ ) random effect model was used. The results of meta-analysis indicated that the HRQOL in BA patients living with their own liver was significantly lower than general population [SDM = -0.46 (95% CI: -0.74, -0.18),  $P = 0.001$ ].

In terms of PedsQL4 sub-scores, heterogeneity was found in emotional ( $I^2 = 75.29$ ,  $Q = 8.09$ ,  $P = 0.01$ ) and school functioning ( $I^2 = 93.33$ ,  $Q = 8.09$ ,  $P < 0.001$ ) subscores. The results of random model meta-analysis showed that the level of school functioning [SDM = -1.18 (95% CI: -2.34, -0.02),  $P = 0.03$ ] was significantly lower in BA patients compared with those of the normal population. However, in the case of emotional subscore, there was no significant difference between BA patients and the general population [SDM = -0.22 (95% CI: -0.61, 0.16),  $P = 0.25$ ]. In the case of physical ( $I^2$

= 30.38,  $Q = 2.87$ ,  $P = 0.2$ ) and social functioning ( $I^2 = 0.00$ ,  $Q = 1.53$ ,  $P = 0.4$ ), fixed effect model was used since heterogeneity was not observed between studies. The results of meta-analysis showed that the levels of physical [SDM = -0.40 (95% CI: -0.55, -0.26),  $P < 0.001$ ] and social functioning [SDM = -0.28 (95% CI: -0.42, -0.13),  $P < 0.001$ ] were significantly lower in BA patients compared with those of the normal population.

## 9. Conclusions

There has been much advancement in the management of children with BA and accordingly the survival rate of these children has been improved. Nowadays, a great attention is being paid to the HRQOL of these patients. Although there have been numerous studies to analyze the HRQOL of children with BA, to the best of our knowledge, this study is the first systematic review and meta-analysis aimed to investigate the HRQOL in BA patients who survived with their own liver comparing the results with those of the healthy population. Out of 10 studies that assessed HRQOL in patients with BA, only five studies used valid methods for evaluating HRQOL (using PedsQL4 (3 studies), SF-36 (two studies)) (10, 13, 15-17). These studies compared the HRQOL between BA patients and healthy populations. Of these, only two studies specifically selected the healthy control groups for the study (10, 13). All these studies were conducted on children and adolescents (< 18 years) except



**Figure 2.** Meta-analysis of comparison the quality of life between biliary atresia and healthy population. A, total score; B, emotional domain; C, physical functioning domain; D, school functioning domain; E, social domain.

for one study that evaluated the HRQOL in BA patients over 18 (17).

Two of the three studies that used PedsQL4 reported a low level of HRQOL total score in BA patients compared with healthy control groups with the greatest difference in school functioning domain (10, 13). Also, two studies used

SF-36C questionnaire for outcome assessment (16, 17). According to the results of these studies, there was no significant difference between BA patients and healthy populations in all domains of SF-36 except for general health (in Japanese and Dutch populations) and social functioning (in Japanese population).

Moreover, the results of meta-analysis also showed the lower level of overall score of HRQOL in BA patients compared with healthy populations. In the case of HRQOL domains, we also showed the lower level of HRQOL in all domains except for emotional functioning domain. According to the results, BA patients had a lower HRQOL in psychological domain. The parents of children with chronic diseases had a high distress that was associated with higher depressive symptoms in children (23). A previous study showed that about 85% of parents had been extremely worried when they heard about the diagnosis of BA in their children (13). So, it seems that there is a need for providing psychological counseling sessions for both parents and children, and also developing peer support groups for improving psychosocial functioning.

School functioning is the most affected domain in BA children. This may be due to the frequent hospital or daily care visits (13). This problem may be partially solved by designating a contact person to liaise regularly with families and also children to provide medical and psychological support, and at the same time, lessen the number of hospital visits. Moreover, the motor and language skills may be impaired in these children that affect the school functioning (24, 25).

Social functioning in BA patients was also lower in three studies. This might be due to the growth impairment in BA patients. Previous studies showed that impaired social functioning in BA children was higher than in older adolescents. This might be due to the fact that with increasing age, BA patients accommodate to BA and their negative perception of adverse impact of this disease on social function decreases (26, 27).

The other five studies reported the HRQOL rate based on some information about educational level, sport performance and employment status (18-22). Most of these studies reported that more than 70% of patients had a normal life or satisfactory HRQOL rate. However, the methodological quality of these studies was low. Two studies had not used a valid method for assessing HRQOL and the inclusion criteria had not been reported in them. In addition, there was no complete definition of population in one of the studies. None of these studies compared the characteristics of responders and non-responders.

### 9.1. Strengths and Limitations

In the present systematic review and meta-analysis, we did a comprehensive search using multiple databases and extracted all English language studies conducted on the HRQOL in BA patients. This reduced the risk of subjective data selection. All the process of conducting this systematic review including the searching phase, quality assessment of articles and data extraction was fulfilled by two

reviewers (ShN, ZN) independently using predefined inclusion criteria and valid tools.

Regarding the limitation of this study, as negative findings are published with lower probability the publication bias could not be fully excluded. Second, the quality of systematic review depends on the quality of the included studies. Only some of the included studies in the present systematic review seemed methodologically sound.

In the present study, some of the included studies had not used valid tools for assessing HRQOL, and they had not selected specific control groups, as well. Moreover, due to variety of methods used in different studies, meta-analysis could be done only on three studies using PedsQL4 for assessing HRQOL. One of these studies (13) reported median and IQR. So, these figures were converted to mean and SD using the method introduced by Hoza et al. (14).

In summary, this systematic review demonstrates that the HRQOL of BA patients who lived with native liver was lower than the HRQOL of healthy population especially in the domains of physical, school and social functioning. But it is still believed that there is need for conducting large-scale studies using valid tools for assessing HRQOL in BA patients.

### Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

### Acknowledgments

The authors would like to thank the authorities of Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences for financial support.

### Footnotes

**Authors' Contribution:** Shahnaz Naghashy developed the original idea and the protocol, article selection, data extraction, and co-wrote the paper. Zeinab Nikniaze was the third reviewer in data extraction, abstracted and analyzed data, and co-wrote the paper. Mandana Rafeey contributed to the development of the protocol, abstracted data, prepared the manuscript, and guaranteed it. Nazanin Hazhir: searching of paper, selection of article, and data extraction.

**Conflict of Interests:** Authors declare no conflict of interest.

**Ethical Considerations:** IR.TBZMED.REC.1395.539.

**Funding/Support:** Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences financially supported this study.

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Table 1. Characteristics of the Included Studies in the Systematic Review and Meta-Analysis

Authors, Year	Country	Sample Size	Median Age of BA Patients, y	Results						
<b>Method of Quality of Life Assessment: PedsQL4</b>										
<b>Lampela et al., 2017 (13)</b>	Finland		≥ 2 (5-6)	<b>Total Score</b>	<b>Physical Domain</b>	<b>Emotional Domain</b>	<b>Social Domain</b>	<b>School Domain</b>		
BA		20		81.22 ± 5.82	86.35 ± 4.30	76.27 ± 8.12	87.5 ± 6.25	72.92 ± 8.32		
HP		108		83.4 ± 3.46	82.5 ± 6.25	76.25 ± 2.5	90.00 ± 3.33	87.5 ± 4.16		
<b>Sundaram et al., 2013 (15)</b>	USA		≥ 8 (9.75)	<b>Total Score</b>	<b>Physical Domain</b>	<b>Emotional Domain</b>	<b>Social Domain</b>	<b>School Domain</b>		
BA		173		76.36 ± 16.40	82.04 ± 21.50	73.74 ± 17.08	80.94 ± 18.37	68.35 ± 20.39		
HP		945		84.58 ± 13.30	87.28 ± 16.35	81.86 ± 16.01	86.49 ± 16.75	80.64 ± 17.69		
<b>Lee et al., 2016 (10)</b>	Malaysia		2 - 18 (7.4)	<b>Total Score</b>	<b>Physical Domain</b>	<b>Emotional Domain</b>	<b>Social Domain</b>	<b>School Domain</b>		
BA		36		85.5 ± 15.4	88.6 ± 21.1	83.4 ± 16.4	90.2 ± 18.5	90.2 ± 18.5		
HP		81		87.4 ± 11.5	90.8 ± 13.4	83.9 ± 17	91.2 ± 12.7	91.2 ± 12.7		
<b>Method of Quality of Life Assessment: SF36C</b>										
<b>Howard et al., 2001 (16)</b>	England and Japan		ND	<b>Body Pain</b>	<b>General Health</b>	<b>Mental Health</b>	<b>Physical Function</b>	<b>Role Emotional</b>	<b>Role Physical</b>	<b>Social Functioning</b>
BA		UK population: 21/japanese population: 25		82.0/81.5	66.0/73.5	71.0/73.8	90.5/88.4	84.1/82.9	76.2/85.8	83.6/88.0
HP		UK population: 9338/japanese population: 1078		79.6/87.6	60.8/72.5	76.6/81.6	93.2/94.2	81.2/94.5	83.0/95.5	81.0/93.8
<b>de Vries et al., 2015 (17)</b>	Netherlands		23.5 ± 3.3	84/87						
BA		25		63 ± 21	76 ± 17	81 ± 35	91 ± 17	73 ± 40	88 ± 19	64 ± 23
HP		500		75 ± 15	76 ± 15	87 ± 29	93 ± 14	87 ± 27	87 ± 18	65 ± 17
<b>Valayer, 1996 (18)</b>	France	71	ND	<b>Method of Quality of Life Assessment: School, University, and/or Sports Performance<sup>a</sup></b>						
				School performance <sup>a</sup>						



<b>Nio et al., 1997 (19)</b>	Japan	21	20 to 39	Professional activity <sup>b</sup> Satisfactory: 16 of 21 Unsatisfactory: 5 of 21 - Liver dysfunction (16 patient) - intrahepatic stones (13 patient) - Cholangitis (14 patient) - Cholangitis with hypersplenism (17 patient) - Turner's syndrome (1 patient)
<b>Ohji et al., 1990 (20)</b>	Japan	48	More than 10	Normal lives: 37 patients - 31 patients were doing well without any problems throughout their postoperative courses. - 6 patients, were enjoying their lives after overcoming sequelae.
<b>Lykavieris et al., 2005 (21)</b>	France	52	at least 20	Unsatisfactory quality of life: 11 patients Normal life: 38 patients Regularly employed: 21 University students: 17. Married or have a stable partnership: 20 Normal life: 22 patients
<b>Nio et al., 1996 (22)</b>	Japan	30	at least 20	Normal life: 22 patients

<sup>a</sup>As related to age was normal for eight, 1 year below normal for 11, and 2 or 3 years below normal for seven. In patients with serum bilirubin 18 - 36, 11 of 14 are leading a near normal life, with excellent school performance for at least three of them. Of the 16 patients over 15 years of age, school performance was judged satisfactory for three and poor for 3.

<sup>b</sup>For those in their twenties, it appeared normal for age, but with no outstanding achievement. With respect to extracurricular activities, 12 teenagers with serum bilirubin < 18 were shown to be adept at sports (skiing, soccer, tennis, cycling; the eldest in the series is an amateur cycling champion). Of the 16 patients over 15 years of age, professional activity was reported for seven patients, with no outstanding accomplishments or intellectual feats, however.