The Quality of Life of Long Term Survivors of Patients with Biliary Atresia

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Research Article

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Abstract

Purpose: Advances in surgical techniques and perioperative care have improved patients' short-and mid-term postoperative outcomes with Biliary Atresia (BA). However, the long-term results of these patients have not been thoroughly investigated. This systematic review aims to determine the long-term outcomes and the patients' health-related Quality of life (HrQoL) with their native livers or liver transplantation.

Methods: A systematic literature-based search for relevant cohorts was performed using Pubmed/Medline, Cochrane Library from its inception to August 2021. Original studies reporting on BA, Hepatoportoenterostomie, portoenterostomy, Kasai, Liver transplantation, Quality of life, or HrQoL were included. Pooled prevalence has been calculated for cholangitis, secondary liver transplantation, or associated malformations using MetaXL (version 5.3). Subgroup analysis on HrQoL followed surgical treatment after BA was calculated by using RevMan (version 5.4).

Results: 12 articles were considered for data synthesis. Nine studies compared biliary atresia patients to an age-matched healthy reference group. 4/9 (n = 338) of these studies indicated lower scores for biliary atresia patients; 5/9 (n = 127) stated similar health status. A Forest plot analysis including all studies with total HrQoL showed a tendency of higher scores towards healthy controls (MD -0.79, 95% CI: -6.00-4.41). Comparing patients after Kasai Hepatoportoenterostomy with healthy controls demonstrated favorable outcomes for the control group (MD -3.22, 95% CI: -7.20-0.75) with no statistical significance (p = 0.11). The pooled estimation of the prevalence of cholangitis, secondary liver transplantation and associated malformations are 0.33 (95% CI: 0.06–0.66), 0.59 (95% CI: 0,42–0.75) and 0.13 (95% CI: 0,01–0.33).

Conclusion: Biliary atresia patients have an overall high prevalence of progressive liver-related complications and risk of lower HrQoL compared to their healthy peers. Furthermore, those patients who received liver transplantation appear to have the same Quality of life as those living with their native livers. Targeted and evidence-based follow-up procedures and transitional care are essential to meet these patients' long-term care needs. Prospective and multicenter research das focuses on the attributes and predictors of the long-term prognosis of patients with biliary atresia are necessary.

Introduction

Biliary atresia (BA) is a neonatal cholangiopathy of unknown cause. It leads if left untreated, to postinflammatory, fibrotic obliteration of the extrahepatic bile duct with consecutive liver cirrhosis and death [1]. BA occurs in 8000 – 18000 live births and is more common in Asians and Europeans in females than males [2]. Hepatoportoenterostomy (HPE; the Kasai procedure) permits bile flow after resection of the fibrotic tissue via a Roux-y-loop, therefore relieving extrahepatic biliary atresia obstruction [3]. However, it is not a curative procedure. Despite HPE being performed quickly, liver transplantation (LT) is ultimately required for most patients during childhood [4]. The disease is the leading indication for LT in the pediatric population with considerable morbidity and mortality, despite early detection [5].

Approximately one-half of affected infants will require LT in the first two years of life due to complications of cirrhosis and cholestasis, including severe malnutrition, ascites, portal hypertension, and coagulopathy [6]. The remainder of children with BA may live many years with their native livers, despite chronic, progressive cirrhosis. However, the long-term outcomes of children with BA surviving with or without LT has not been well documented. As with every chronic disease, assessing Health-related Quality of Life (HrQoL) is essential in providing comprehensive long-term care to children. One study revealed that children with BA and surviving with their native livers have a significantly impaired health-related quality of life, similar to that in patients with BA post-LT [7].

On the other hand, another study revealed that young adult BA survivors are experiencing a similar HrQoL compared with the reference population [8]. Because of the variety of the reported Quality of life in patients with BA, this systematic review aimed to clarify the conflicting results in the reported literature. Further, the present study's information will help facilitate evidence-based management and follow-up design and better care for patients with BA.

Methods

We conducted a meta-analysis according to the review protocol and Meta-analysis using PubMed/Medline, Cochrane Library as databases. For PubMed, the search string contained a combination of the following Medical Subject Heading terms, title/abstract, and topic field tags: "Biliary atresia," "Kasai," "portoenterostomy," "liver transplantation, "quality of life," "health-related quality of life." The reference lists of the included studies and existing systematic reviews were reviewed for additional relevant studies.

Selection criteria

Two reviewers independently scanned the titles and abstracts of the acquired articles for the initial screening. Original articles that reported the outcome or Quality of life of patients with BA surgical history were included. Only studies quantitatively measuring the Quality of life, i.e., using a scoring system, were included in this context. The exclusion criteria were as follows: 1) non-English language papers; 2) reviews, conference proceedings, and case reports or case series; 3) studies conducted on animal models or focused on analyzing the molecular biological or pathological mechanisms of biliary atresia; 4) studies focusing on parental stress and anxiety and 4) publication date prior to 2000. Studies were excluded if they did not meet eligibility criteria. After the initial screening, the full text of 87 included articles was retrieved and read by two reviewers to determine their eligibility for inclusion in the analysis. The structure of this systematic review followed the PRISMA guidelines (*Figure 1*).

Data extraction

The searches were performed in August 2021. A standardized Excel spreadsheet that included the study key characteristics, such as year of publication, geographical region, the study design, time of data collection, patients' age range, the age range of patients, gender, associated malformations, primary

surgical BA treatment (Kasai HPE or LT), age at surgery, cholangitis, portal hypertension, reoperations, and deaths was developed for data collection (*Table 1*). Another separate Excel spreadsheet was created for data concerning HrQoL of BA patients with a surgical history. *Table 2* presents the applied HrQoL assessment instruments of the respective papers, the number of patients enrolled for HrQoL assessment, HrQoL of patients with Kasai HPE/native liver and LT compared to healthy controls, HrQoL of patients who underwent Kasai HPE compared with LT, identified factors associated with HrQoL and the studies main findings. Two reviewers independently extracted information from the included articles. Discrepancies in the screening and data extraction process were discussed and resolved by the consensus of the two reviewers.

Statistical analysis

Pooled prevalence has been calculated using MetaXL (version 5.3) software add-in for Microsoft Excel. For the estimation of pooled prevalence, the double arcsine transformation was used. Results were calculated with a 95% CI. Expecting a high heterogeneity, a random-effects model was selected, and heterogeneity was assessed using the I^2 statistic, which describes the percentage of variation across studies not only resulting from sampling error. An I^2 value above 75% was defined as an indicator for high heterogeneity. Since this analysis aimed to estimate the pooled effect size without testing a hypothesis, there was no p-value calculation for the pooled prevalence analysis. Subgroup analysis on HrQoL after surgical treatment of BA was calculated by using RevMan (version 5.4). A p-value < 0.05 was defined as statistically significant for this analysis, and results were presented with a 95% CI.

Results

Study characteristics

The systematic literature review resulted in the identification of 1647 publications *(Figure 1)*. Of these, 156 were duplicates, 1404 records were excluded following title and abstract screening, and 87 articles were selected for full-text review. Finally, 12 articles were considered for data synthesis, among which eight were multicentred studies [9–16], and the remaining four were single-centered studies [17–20]. *Table 1* presents an overview of the study characteristics of the included paper. Estimates of HrQoL of patients with biliary atresia were found for samples from a total of 6 countries (China, Canada, Netherlands, Finland, Japan, Italy) and three continents (Europe, North America, and Asia). The studies included patient data ranging from the year 1951 to the year 2016. Most of the included studies had HPE as the primary surgical approach (10 of 12) [9, 10, 12–19]. Only two studies presented liver transplantation as the primary surgical treatment of BA [11, 20]. A total of 1183 patients were enrolled when adding up the total number of patients of all included studies.

HrQoL Measurement

In total, ten HrQoL assessment instruments were used. In 42% (5 of 12) of the identified publications, HrQoL was measured using the **Pediatric Quality of Life Inventory 4.0 Generic Core Scales** (PedsQL™ 4.0

GCS), making it the most commonly utilized Quality life instrument. The PedsQL™ 4.0 GCS are child self-report, and parent proxy-report scales developed to measure health-related Quality of life in children and adolescents ages 2-18, including physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). These scales produce a Total, Psychosocial, and Physical Summary score. The **Short Form-36 Health Survey** (SF-36), **RAND-36** for Health Status (RAND-36), and **WHOQOL-100** for QoL (WHOQOL-100) were each utilized twice in the identified publications. The SF-36 questionnaire consists of eight scaled sections: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The score of each section results in a scale from zero to 100, with 100 being the highest score and highest function attainable [21]. The WHOQOL-100 is a generic, cross-cultural multidimensional questionnaire. It consists of 100 items assessing 24 aspects of QoL within six domains (physical health, psychological health, level of independence, social relationships, environment, and spirituality) and a general evaluative aspect (overall QOL and general health). This 100-item questionnaire has a 5-point response scale from 1 to 5. Scores are calculated for each domain, with a maximum possible score of 20 per domain [22]. RAND-36 comprises 36 items that assess eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions. Physical and mental health summary scores are also derived from the eight RAND-36 scales. The scores were converted to a 1 to 100 scale, with higher scores indicating better levels of functioning or well-being [23]. The child self-reported **Child Health Questionnaire™** (CHQ-CF87), applied by one study, is a full-length 87-item self-report. Per scale, the items are summed up and transformed into a 0 (worst possible score) to 100 (best possible score) scale [24]. Both studies that included listed liver transplantation as the primary procedure applied an additional disease-specific questionnaire, respectively: Pediatric Liver Transplant Quality of Life (PeLTQL) and PedsQL™ Transplant Module.

HrQoL Outcome

Complete results of quantitative analysis are provided in *Table 2*. In total, 811 BA patients were evaluated for HrQoL.

HrQoL compared to the healthy population

Of 12 included studies, nine studies compared BA patients to an age-matched healthy reference group. 4/9 of these studies (n = 338) indicated lower scores for BA patients after surgical treatment when compared to healthy peers [9, 11, 15, 17]; 5/9 studies (n = 127) stated similar health status in both groups [12–14, 16]. *Figure 2* displays the HrQoL of all BA patients compared to healthy peers, including all studies which provided total scores of HrQoL (mean and standard deviation) with a scale from zero to 100, with 100 being the highest score. Therefore, this forest plot analysis only includes seven studies (n = 502) since Lind et al., and Parolini et al. failed to include HrQoL total scores. Comparing both groups for HrQoL, there was a tendency towards healthy controls (MD -0.79, 95% CI: -6.00-4.41, p = < 0.000, I^2 =

93%). Although there was a tendency for higher scores in healthy peers, no significant difference was found for both groups (Z = 0.30, p = 0,76).

Kasai HPE/Liver transplantation vs. healthy population

Eight studies compared HrQoL of patients surviving with their native liver after Kasai HPE with healthy controls. Of these studies, 3/8 studies (n = 268) reported lower scores, and 5/8 studies (n = 127) demonstrated comparable HrQoL for BA patients compared to healthy peers, with the only significant difference found in "missing school or daycare for hospital visits" and "general health perception" for patients with BA [12, 13]. One study even revealed significantly higher scores for the social domain in the BA group compared with healthy peers [12]. *Figure 3* compares non-transplanted BA patients against healthy peers. Again, only studies with sufficient HrQoL data were included for the forest plot analysis. The forest plot demonstrates favourable outcome for the control group (MD -3.22, 95% CI: -7.20-0.75, p = 0.000, I^2 = 77%). However, no statistical significance was found for the tendency of higher HrQoL towards disease-free controls (Z = 1.59, p = 0.11). Only three studies included data comparing transplanted patients with healthy controls [11, 17] [14]. Miserachs et al. reported significantly lower HrQoL scores in liver transplant recipients with biliary atresia (p < 0.001), whereas Wong et al. described no statistically significant difference in HrQoL scores between the transplanted and the disease-free group. Likewise, De Vries et al. stated largely comparable HrQoL for both groups. Kikuchi et al. evaluated HrQoL of biliary atresia after a living donor liver transplant in Japan but did not compare HrQoL data with the healthy or general Japanese population [20]. With only three studies providing data regarding HrQoL of LT vs. healthy controls, no reliable statement was possible.

Kasai vs. liver transplantation

Five studies compared HrQoL of native liver patients with liver transplant recipients (n = 327). [9, 13–15, 17]. All five studies described similar/comparable scores for both groups. However, even though De Vries et al. described comparable scores for both groups, non-transplanted BA patients had significantly lower scores on general health perception than transplanted patients. Furthermore, native liver patients tended to have lower physical role functioning than the reference and transplanted patient groups [14].

Factors associated with HrQoL

The included studies identified several factors associated with HrQoL. Concerning patient characteristics, children's higher age at survey was significantly related to higher generic HrQoL [20]. Furthermore, patients with and without associated anomalies had no significant difference in HrQoL scores [13]. Regarding gender, females tend to report lower HrQoL than males [14]. Interestingly, "age at surgery" revealed no significant difference between patients with good and impaired Quality of life (p = 0.56) [18]. However, four studies failed to include age at operation in data. The number of drugs for immunosuppression was stated in two studies to be related to a lower transplant-specific HrQoL [11, 20]. Miserachs et al. defined immunosuppression polytherapy as more than two immunosuppressant drugs at a time. Three studies tested laboratory-based parameters for correlation with HrQoL. De Vries et al. found no significant correlations for "serum Aspartate-Aminotransferase," "bilirubin," "albumin levels," "age at LT,"

or "time elapsed since LT" with HrQoL. Then again, another study described "Aspartate-Aminotransferase level at one year" after Kasai HPE to be a significant independent predictor for HrQoL (p=0.03) [18]. Sundaram et al. described "higher total bilirubin" associated with poorer HrQoL in patients with BA. Uchida et al. ought to determine clinical predictors for Quality of Life in long-term jaundice-free survivors after the Kasai operation [18]. As a result, the first onset and frequency of postoperative cholangitis was no significant predictor of high HrQoL (p = 0.25). De Vries et al. reported liver disease-associated symptoms, such as itch, jaundice, decreased appetite, as essential determinants of HrQoL [14].

Pooled Prevalence

All in all, as studies with HrQoL as the primary outcome, the included studies only provided very little data regarding long-term clinical outcomes after surgical biliary atresia treatment.

Only three studies included data corresponding to prevalence of cholangitis (n = 614) [9, 10, 19]. The pooled estimation of the prevalence of cholangitis is 0.33 (95% CI: 0.06–0.66, Cochran Q test = 124.55, P = 0.00, I^2 = 98.%, see *Figure 4A*). The largest study of Sundaram et al. (n = 221) reported a cholangitis prevalence of 0.13 (95% CI: 0.09-0.18), being the study with the lowest cholangitis prevalence of all three included studies (0.13 vs. 0.32 vs. 0.62). In this study, BA patients were shown to have significantly poorer HrQoL than healthy children and similar scores to children with post-LT. With a cholangitis frequency of 2.0 ± 0.6 in patients with bad Quality of life and 1.6 ± 0.7 in patients with good Quality of life, Uchida et al. showed that the frequency of postoperative cholangitis was not a significant indicator for the prediction of high HrQoL [18]. Five studies added reoperations after primary surgical treatment in their follow-up. Of these, 3/5 studies with Kasai HPE as primary treatment reported secondary liver transplantation in their follow-up [15, 17, 19]. The pooled prevalence of secondary LT was 0.59 (95% CI: 0,42–0.75, Cochrane Q test = 17.72, I^2 = 89% see *Figure 4B*), which is largely in line with current literature. Four studies provided data regarding associated malformations [10, 11, 13, 19]. Pooled prevalence of associated malformations was 0.13 (95% CI: 0,01–0.33, Cochrane Q test = 60.61, I^2 = 95%, see *Figure 4C*), with the largest study (n = 219) reporting an associated malformation prevalence of 0.24 (95% CI: 0.19-0.30). Overall, our data showed high study heterogeneity (I^2=98%; I^2=89%; I^2= 95%).

Discussion

Overall, children with BA are at risk of impaired HrQoL, both physically and psychologically, significantly when younger, whether they are native liver survivors or received an LT during disease progression (*Figure 2*). Whereas bilirubin levels, the number of cholangitis episodes, variceal bleeding, and nutritional status mainly define the pretransplant HrQoL, the HrQoL posttransplant is mainly affected by the number of prescribed immunosuppressive medications. Interestingly, age at surgery and associated malformations seem not to affect the HrQoL (*Figure 4*). However, children at higher ages score higher in HrQoL than their younger peers. This might be a result of their long-term adaption to their disease. This phenomenon is known as "response shift," a change in individuals' perceptions of their HrQoL based on their individual experiences[25] Moreover, children who already had reached school age are clinically stable, with a

similar or even improved health status compared with the years before, most likely score their HrQoL higher. Also, the score can be affected by the reporter. Parents might tend to report a lower HrQoL because of the intense years after their child was diagnosed with BA and their experience coping with the disease[20].

An important finding is the often neglected aspect of gender difference in HrQoL. In our study, we found that females had lower scores in all domains of HrQol questionnaires. Especially in bodily pain, females show increased sensitivity to nociceptive stimuli [26]. Studies reported that the hormones like estrogen or testosterone had a direct impact on perceived pain. For instance, estrogen increases the nervous system activity, which increases the transmission of pain stimuli and pain sensitivity of a woman [27].

On the other hand, testosterone has an analgesic effect and can reduce pain sensitivity in men [26, 27]. Also, in another study concerning "fatigue" after LT, Berg-Emons et al. concluded that the female gender perceives "fatigue" with greater severity, suggesting impaired HrQol [28]. However, although females score lower in "physical function" and "physical role functioning," studies are suggesting that females score higher in domains "emotional role functioning" and "mental health," suggesting females have a better ability to manage stress and psychosocial demands in the posttransplant setting [26]. However, these findings could not be substantiated in the present study.

Nevertheless, gender differences also exist in response to painful situations in teenagers and adolescents. Males would primarily seek out distracting behaviors while females use social support and positive self-statements [26, 29]. Hence, it is essential to recognize gender differences in the setting of chronic liver disease to direct attention to being active, thinking positively, and expressing emotions positively, which will be correlated with higher scores in HrQol questionnaires. However, among all pretransplant clinical covariates, serum bilirubin following HPE appears to be the most predictive biomarker of the outcome [30]. With increasing levels of bilirubin, the likelihood of the need for LT increases. For example, children with Bilirubin levels > 50 µl/ml at 2- and five years had a transplant-free survival of 4.8 % and 0, respetively [31]. Cholangitis is one factor that has a direct impact on HrQol in patients with BA. In the present study, the pooled prevalence of cholangitis was 33% which correlates with the incidence of cholangitis reported in the literature (40 % and 90 %)(*Figure*). In general, most patients experience at least one episode prior to 2 years of age. Recurrent cholangitis may predict the need for LT as it can lead to progressive cirrhosis [30, 32]. On the other hand, one episode of cholangitis does not predict early LT [30]. Also, other liver disease-associated symptoms like therapy refractory ascites with accompanying risk of spontaneous bacterial peritonitis or increased portal hypertension with the risk of gastrointestinal hemorrhage, which is present throughout the lives of children with BA, are often correlated with a poor outcome and early liver transplantation needs. However, HrQol is mainly dependent on whether adequate bile drainage is achieved after HPE [33][30, 34].

A significant common clinical problem in BA is poor nutrition and, along nondrainage of the HPE, the most common indication for LT. Unfortunately, nutritional problems in BA are challenging to overcome. Children with BA have a constant caloric deficit and need to be supplemented with extra calories, fat-

soluble vitamins, and medium-chain triglycerides (MCT) to prevent weight loss and failure to growth [35]. The perceived dependency from external nutritional support is also reflected by the correlation of a low HrQoL and the number of prescribed drugs. We found that immunosuppression polytherapy and the number of prescribed medications were associated with a significantly lower HrQoL [11, 20]. Immunosuppressive medications are necessary post-LT because of the risk of organ rejection and graft loss, and the need for re-transplantation is a lifelong danger. However, those drugs produce side effects that need to be monitored. First, early post-transplant use of corticosteroids raises the risk of post-transplant hyperglycemia and diabetes. The weight gain may result in long-standing post-transplant metabolic syndrome as well. The most common side effects are nephrotoxicity and hypertension because of Calcineurin inhibitors such as tacrolimus or ciclosporin. To reduce nephrotoxicity, other immunosuppressive drugs like the antimetabolites mycophenolate mofetil, azathioprine, or mTOR inhibitors like sirolimus and everolimus increased the armamentarium of immunosuppressive drugs [36].

In one study, the ideal survivor after liver transplantation was on single-agent immunosuppression, not receiving prednisone, antihypertensive or antiseizure medications with no impact on linear growth or immunosuppression-related comorbid conditions [37]. A condition that is barely achieved in those patients who received an LT. So, it is not a surprise that Miserachs et al. reported significantly lower HrQoL scores in liver transplant recipients with biliary atresia ($p < 0.001$) than healthy peers in physical, psychosocial, social, and family functioning domains [11]. Despite the constant improvement of the survival rates following LT, future research on immunosuppression withdrawal will be necessary to improve the HrQoL of children with BA.

Although we found that the HrQoL of those who lived with their native livers and BA patients who received an LT is comparable to healthy peers, the survival of BA patients with their native liver is poor and reported in the literature between 30% - 55%, 30% - 40%, and 20% - 40% at 5, 10, and 20 years respectively [38]. Most patients will develop chronic liver disease and require an LT. In the present study, the pooled prevalence of having an LT after a "failed HPE" was 59 %,which is in line with the reported literature [39]. It has been suggested that LT as a primary approach for managing patients with BA is possible. However, HPE remains to be the most reasonable initial approach. If the patient is stable, it is better to delay the LT to increase the chances of a successful liver transplant [38].

One often-overlooked factor is that patients with BA often show a history of neurodevelopmental delay, especially in early childhood [37]. Also, motor impairments or behavioral problems are common. Additionally, up to 25 % f the patients are suffering from anxiety and depression. While addressing the numerous liver disease complications, it is essential to identify patients with neurodevelopmental and psychological issues as early as possible for timely referral to a psychosocial health care provider [12].

Conclusion

The development of preventive and therapeutic modalities in treating patients with BA depends on understanding the disease. Although considerable progress has been made in basic research and the

clinical setting, the disease remains a dark chapter in pediatric hepatology [38]. The present study underscores the urgent need to improve the various factors influencing the HrQoL in patients with BA. This includes individualized patient-specific immunosuppression, including withdrawal from polydrug immunosuppressive regimes if possible, modifying psychoemotional problems, and recognizing the differences in disease burden and treatment between males and females.

Abbreviations

BA	Biliary atresia
CHQ	Child Health Questionnaire
CI	Confidence Interval
HPE	Hepatoportoenterostomy
HrQoL	Health-related Quality of Life
LT	Liver transplantation
MD	Mean deviation
MCT	Medium-chain triglycerides
PedSQL	Pediatric Quality of Life
PeLTQL	Pediatric Liver Transplant Quality of Life
QoL	Quality of Life

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CT designed the study and drafted the manuscript. CT and ML screened and evaluated the Quality of studies and extracted data. CT and ML interpret the results. KR reviewed the manuscript. All authors read and approved the manuscript.

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Tables

Table 1: Characteristics of included studies

Author	Year of Publication	Title	Country	Study Design	Time of data collection	Total number of patients	Age range of patients	male	female
Rodijk et al.	2020	Health-Related Quality of Life in Biliary Atresia Patients with Native Liver or Transplantation	Netherlands	multicenter study	/	38	mean: 10 ± 3 years	20	18
Miserachs et al.	2018	Health-related Quality of life in pre-adolescent liver transplant recipients with biliary atresia: A cross-sectional study	Canada	cross-sectional, multicenter study	2014-2016	70	8.9-10.9 years	31	39
Parolini et al.	2018	Biliary atresia: 20–40-year follow-up with native liver in an Italian centre	Italy	retrospective, single-center study	1975-1996	174	/	91	83
Wong et al.	2018	Long-term Results and Quality of Life Assessment in Biliary Atresia Patients: A 35-Year Experience in a Tertiary Hospital	China	single-center study	1980-2015	141	mean: 21.8-34.3 years (native liver); 20.0-37.1 years (liver transplant); 22.0-32.0 years (control)	/	/
Kikuchi et al.	2017	Quality of life of biliary atresia after living donor liver transplant in Japan	Japan	cross-sectional, single-center study	April-July 2015	75	mean: 9.6 ± 3.7	27	48
Lampela et al.	2017	Quality of Life and parental worrying in a National Cohort of biliary atresia children living with their native livers	Finland	longitudinal, cross-sectional multicenter study	1996-2011	20	median: 5.9 years (IQR: 4.7–8.6)	/	/
De Vries et al.	2015	Overall Quality of Life in Adult Biliary Atresia Survivors with or without Liver Transplantation: Results from a National Cohort	Netherlands	retrospective, cross-sectional multicenter	1977-1992	25	/	13	12
Lind et al.	2015	Health Status and Quality of Life in Adult Biliary Atresia Patients Surviving with Their Native Livers	Netherlands	retrospective, multicenter study	/	30	mean: 23.2 ± 3.3 years	13	12
Lee Ng et al.	2014	Medical Status of 219 Children with Biliary Atresia Surviving Long-Term with their Native Livers: Results from a North American Multicenter Consortium	North America	retrospective, cross-sectional, multi-center study	2006-2012	219	mean: 5.1-17.9 years	95	124
Sundaram et al.	2013	Health Related Quality of Life in Patients with Biliary Atresia Surviving with their Native Liver	North America	cross-sectional, multicenter study	2005-2010	221	mean: 9.75 ± 5.25 years	102	119
Uchida et al.	2004	Predicting Factor of Quality of Life in Long-Term Jaundice-Free Survivors After the Kasai Operation	Japan	retrospective, single center study	1978-2001	55	/	/	/
Howard et al.	2001	Survival Patterns in Biliary Atresia and Comparison of Quality of Life of	Japan, UK	multicenter study	1951-1998	115	14-24 years	/	/

Associated malformations, congenital disease or syndrome	Primary surgical treatment		Age at surgery	Time of follow up	Cholangitis	Reoperations		Deaths
	Procedure	number				Procedure	number	
/	Kasai HPE Liver transplantation	9 29	/	/	/	Liver transplantation	29	/
Associated structural malformations (n=2)	Liver transplantation	70	median: 8.9 months (IQR: 7-11.9 months)	8,9 years	/	Retransplantation	4	/
5 patients (1.8%): Biliary Atresia Splenic Malformation Syndrome (BASM) (n=4), intestinal malrotation (n= 1), congenital short bowel (n=1)	Kasai portoenterostomy Porto-cholecystostomy Porto-jejunostomy Cholecysto-jejunostomy	162 10 1 1	median: 60.4 (range 26–154) days	22 years	32%	Liver transplantation	104	32
/	Kasai HPE	141	mean: 65 ± 19 days	20 years	/	Liver transplantation	60	13
/	Liver transplantation	75	/	/	/	/	/	/
Heart defects (n=2), intestinal malrotation (n=2), multilobular spleen (n=1), annular pancreas (n=1), Meckel diverticulum (n=1), plagiocephaly (n=1), Sotos syndrome (n=1)	Kasai HPE	16	/	/	/	Cystojejunostomy for biliary lakes Incisional hernia Laparotomy for adhesional ileus Sclerotherapy for esophageal varices	2 2 1 11	/
/	Kasai HPE Kasai HPE + secondary liver transplantation	25 15	median: 58 (35–117) days Kasai median: 60 (43–126) days	/	/	/	/	/
/	Kasai HPE	25	mean: 58.4 ± 18.3 days	/	/	/	/	/
Polysplenia (n=5), congenital heart disease (n=23), and other gastrointestinal malformations (n=25)	Kasai HPE	183	mean: 56.4 ± 23.19 days	> 5 years	136 (62,1%)	Liver transplantation *(exclusion criteria)*	0	/
/	Kasai HPE	221	mean: 30.43 ±	/	13,4%	/	/	/

			278.19 days					
/	Kasai HPE (bad QoL group) Kasai HPE (good QoL group)	10 25	mean: 68 ± 22 days mean: 63 ± 16 days	/	frequency of cholangitis (bad QoL group): 2.0 ± 0.6 (range 1-5); frequency of cholangitis (good QoL group): 1.6 ± 0.7 (range 0-12)	bad QoL group: Liver transplantation Endoscopic infusion sclerotherapy good QoL group: Endoscopic infusion sclerotherapy	3 7 3	/
/	Kasai HPE	46	/	/	/	/	/	/

Table 2: Health-related Quality of Life of included studies.

Author	Questionnaire	Patients enrolled for HrQoL-analysis	Kasai HPE vs. healthy controls	Liver transplantation vs. healthy controls	Kasai HPE vs. Liver transplantation	Factors associated with HrQoL	Main findings
Rodijk et al.	CHQ-CF87 for children aged 10 years or older	35	BA patients reported significantly lower on physical and emotional functioning.	/	No significant differences between children who survived with their native liver and children post-LT.	“Adverse medical events”, “motor impairments”, or “behavioral problems” increase the risk of impaired HrQoL.	Children with BA are at risk of impaired HrQoL, especially physical HrQoL.
Miserachs et al.	PedsQL™ 4.0 Generic Core Scale Pediatric Liver Transplant Quality of Life (PeLTQL)	70	/	Significantly lower QoL ($p < 0.001$) in liver transplant recipients with biliary atresia compared to the healthy.	/	"Immunosuppression polytherapy (≥ 2 immunosuppressant drugs)" at the time of HRQOL assessment was associated with lower PeLTQL. The psychosocial health benefits of “sports participation”.	Pre-adolescents who underwent LT as an infant self-report low HrQoL on both disease-specific and generic HrQoL tools especially in the area of school function.
Parolini et al.	WHOQOL-100 for QoL	11	QoL was comparable with the healthy Italian population in all but one patient.	/	/	/	Kasai HPE as the cornerstone BA treatment. Lifelong post-operative follow-up should be guaranteed.
Wong et al.	Short Form-36 Health Survey version 2.0	26	Native liver scored lower vs. disease free control in general health and overall physical component ($p=0.029$), ($p=0.037$).	No statistically significant difference in the scores between the transplanted group and the disease-free control group.	No statistically significant difference of the scores between native liver and transplant group.	/	QoL of the long-term survivors are impaired. Despite the apparent impairment of physical condition in BA patients, their social functioning ability appeared to be relatively preserved.

Author	Questionnaire	Patients enrolled for HrQoL-analysis	Kasai HPE vs. healthy controls	Liver transplantation vs. healthy controls	Kasai HPE vs. Liver transplantation	Factors associated with HrQoL	Main findings
Kikuchi et al.	Pediatric Quality of Life Inventory™ PedsQL™ Transplant Module	75 75	/	/	/	"Children's higher age" at survey was significantly related to higher generic HrQoL "More number of types of prescribed drugs" was significantly related to lower transplant-specific HrQoL	Japanese patients rated higher HrQoL than that rated by the American patients. HrQoL of Japanese pediatric and adolescent patients with BA after LT varied with each reporter (i.e., patients or parents).
Lampela et al.	PedsQL™ 4.0	20	Comparable HrQoL for both groups. Except: significant difference in "missing school or day care for hospital visits" for patients with native liver vs control.	/	Similar HrQoL scores for native liver and patients with liver transplant.	Patients "with and without associated anomalies" had no significant difference in HrQoL scores. Patients with "optimal health" had no significant differences in HrQoL scores.	/

Author	Questionnaire	Patients enrolled for HrQoL-analysis	Kasai HPE vs. healthy controls	Liver transplantation vs. healthy controls	Kasai HPE vs. Liver transplantation	Factors associated with HrQoL	Main findings
De Vries et al.	RAND-36 Liver Disease Symptom Index 2.0 (LDSI)	25	/	HrQoL of transplanted young adult patients with BA is largely comparable to that of an age-matched reference group.	HrQoL of transplanted and non-transplanted young adult patients with BA is largely comparable. Except: native liver patients with significantly lower scores on general health perception than transplanted patients.	Females tend to report a lower HrQoL than males. No significant correlations between RAND-36 with "serum Aspartate-Aminotransferase", "bilirubin" or "albumin levels", "age at LT" or "time elapsed since LT". "Liver disease–associated symptoms" seem to be an important determinant of HrQoL.	BA patients manage to overcome the medical challenges involved with Kasai HPE and/or LT, they can achieve an HrQoL similar to age-matched peers. The non-transplanted patients did not require an LT before reaching adult age suggesting that the disease had a relatively benign course.
Lind et al.	RAND-36 for Health Status WHOQOL-100 for QoL Hospital Anxiety and Depression Scale Impact Event Scale for posttraumatic stress disorder symptom dimensions (intrusion and avoidance)	25	BA patients with native liver have comparable QoL with healthy peers. Except: social domain significantly higher in the BA group; general health perception being significant lower in BA patients (p=0.002).	/	/	/	Adult BA patients surviving with their native livers had a similar Heath status and QoL as compared with healthy peers. 25% of the patients are suffering from anxiety and/ or depression. These patients should be identified as early as possible.

Author	Questionnaire	Patients enrolled for HrQoL-analysis	Kasai HPE vs. healthy controls	Liver transplantation vs. healthy controls	Kasai HPE vs. Liver transplantation	Factors associated with HrQoL	Main findings
Lee Ng et al.	PedsQL™ Total Scale Score	161	/	/	/	/	Despite over 98% of subjects with BA living with native livers after Kasai HPE have evidence of chronic liver diseases, over one-half of patients rated their quality of life as good.
Sundaram et al.	PedsQL™ 4.0 Generic Core Scale	221	Poorer HrQoL in native liver vs. disease-free across all measured domains ($p < 0.001$). 29.5% of self-reported PedsQL Total Scale scores were at least 1 SD below the population mean of 76.96.	/	HrQoL in native livers and post-LT were similar across all measured domains.	"Higher total bilirubin" was associated with poorer HrQoL in patients with biliary atresia.	Psychosocial functioning in children with biliary atresia surviving with their native livers was significantly impaired. HrQoL in BA patients with native liver is significantly poorer than healthy children and similar to BA patients with post-LT.

Author	Questionnaire	Patients enrolled for HrQoL-analysis	Kasai HPE vs. healthy controls	Liver transplantation vs. healthy controls	Kasai HPE vs. Liver transplantation	Factors associated with HrQoL	Main findings
Uchida et al.		Group A: 10 patients with bad QoL Group B: 25 patients with good QoL	/	/	/	No significant difference between both groups for "age at surgery" (good vs. bad QoL; p=0.56). No significant difference between both groups for "postop cholangitis frequency or first onset" (good vs. bad QoL; p=0.25). "Aspartate-Aminotransferase level at 1 year" after Kasai seems to be an independent predictor for QoL (good vs. bad QoL; p=0.03).	The “serum Aspartate-Aminotransferase level at 1 year” is a simple predicting factor of QoL and liver dysfunction in long-term jaundice-free survivors after Kasai operation.
Howard et al.	“Short Form 36” (SF-36) Questionnaire	21 UK patients 25 Japanese patients	The Japanese sample did not differ significantly from the Japanese normative population in Physical function and Vitality. Patients in Japan and UK showed only a small degree of underperformance in comparison with normative data from Japan and UK. Except: UK patients significantly overperformed the UK normative population in Vitality; UK patients underperformed in General Health, Social functioning, Role limitations due to physical problems (not statistically significant).	/	/	/	The QoL measurements were comparable between patients in Japan and UK except for small reductions in the Japanese scores for general health and vitality. Continue to use portoenterostomy as the primary treatment for biliary atresia.

Figures

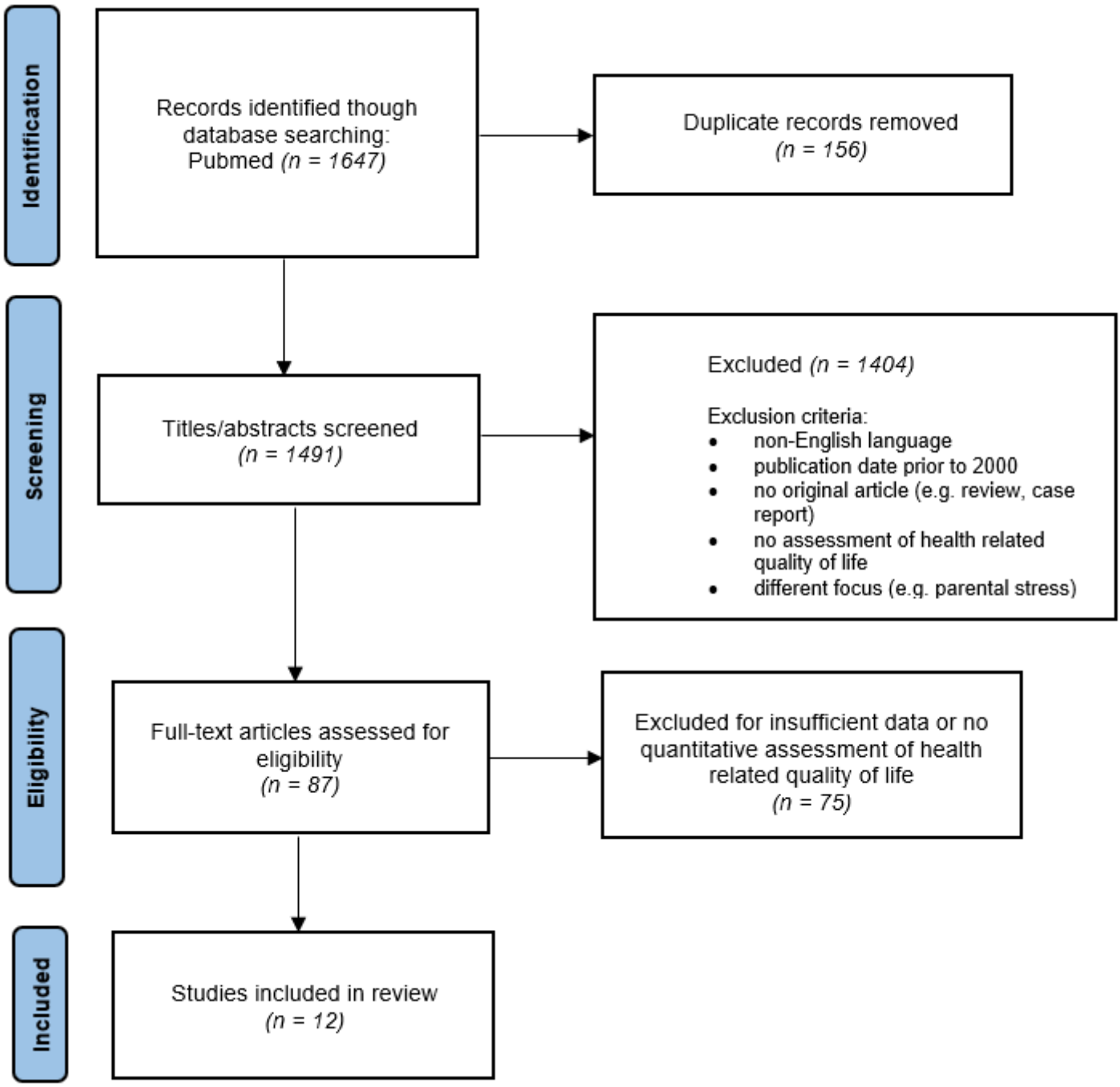

Figure 1

PRISMA Flow Diagram

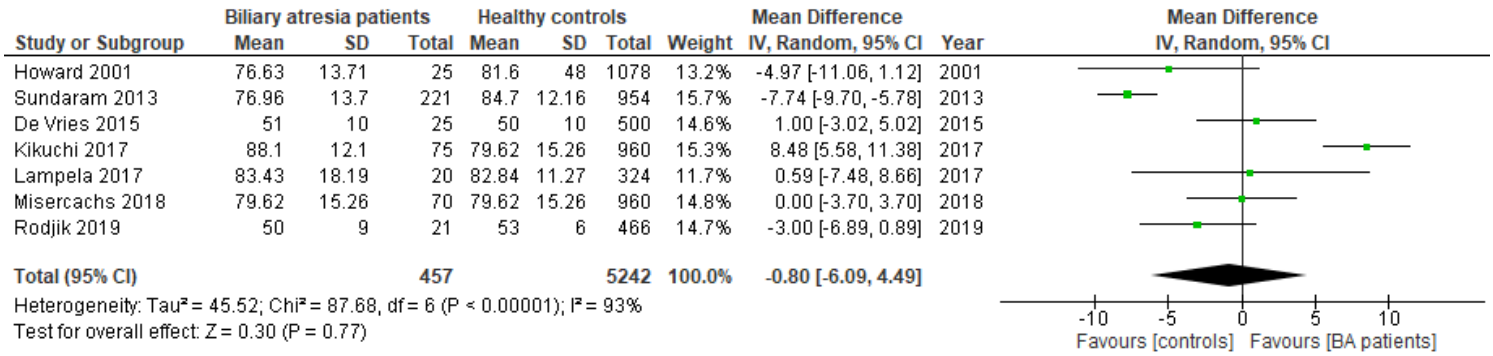

Figure 2

Forest Plot comparing Health-related Quality of Life (scale 0-100) of biliary atresia patients with age-matched healthy peers

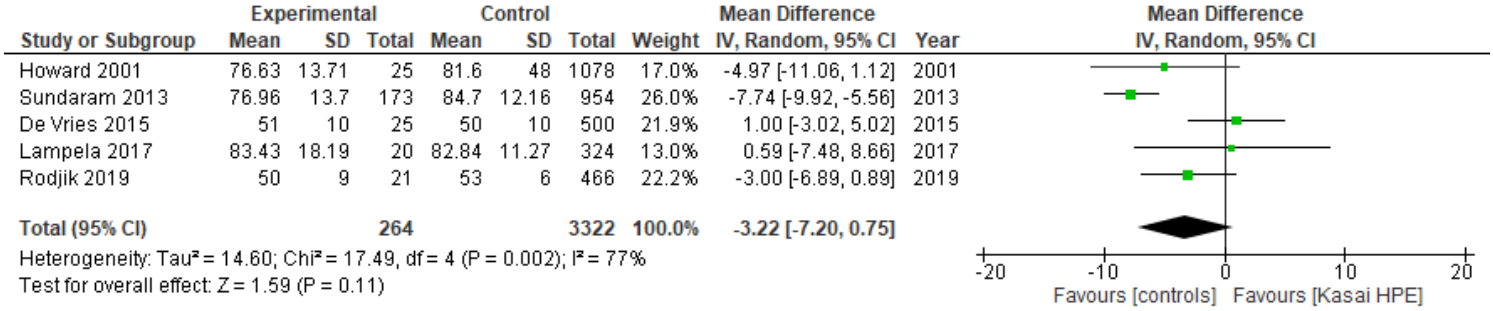

Figure 3

Health-related Quality of Life: Kasai hepatoportoenterostomy vs. healthy controls

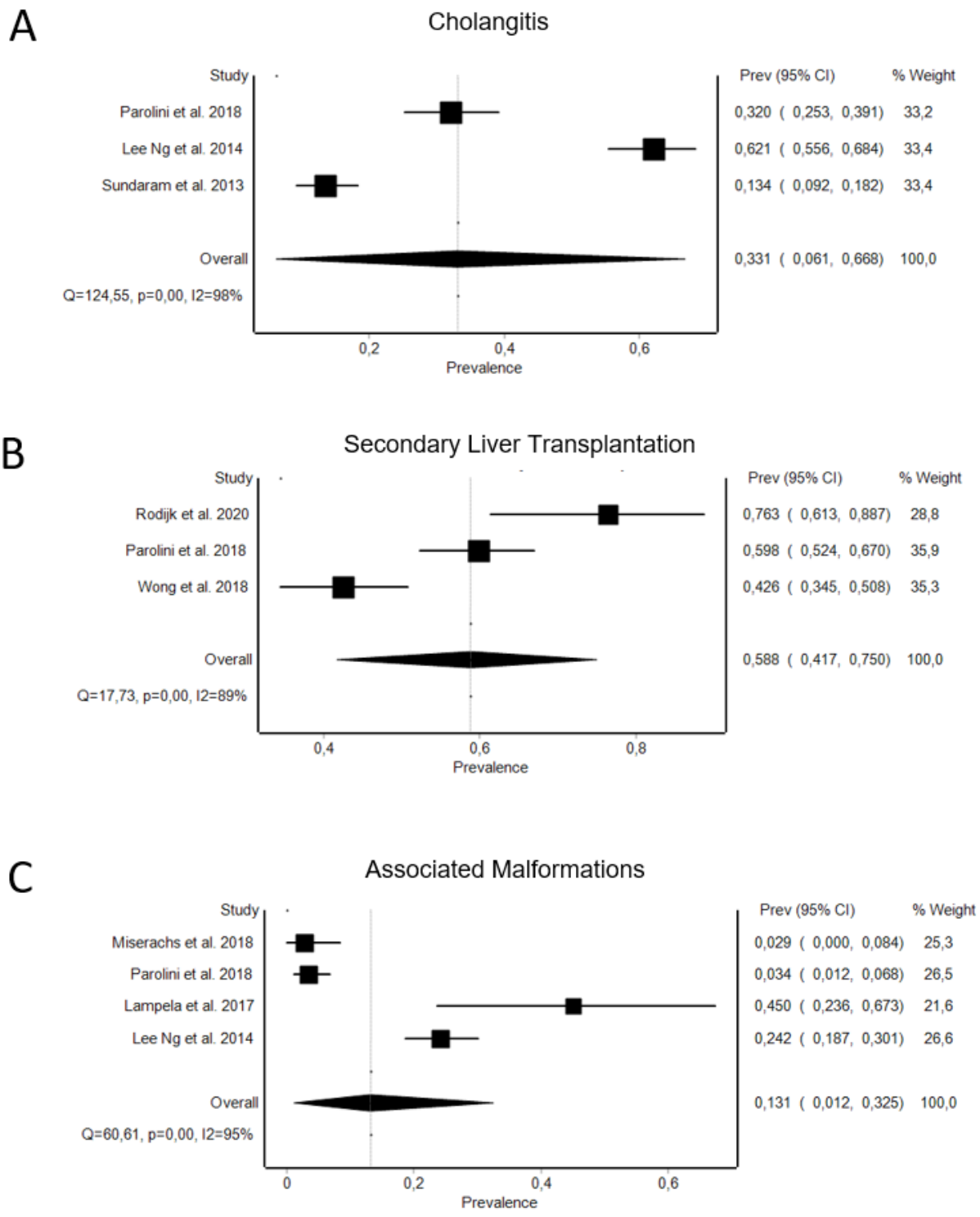

Figure 4

Pooled prevalence (A: Cholangitis; B: Secondary Liver Transplantation after Kasai hepatoportoenterostomy; C: Associated Malformations in patients with biliary atresia)