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Review Article

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Peri-Operative Liver Fibrosis and Native Liver Survival in Pediatric Patients with Biliary Atresia: A Systematic Review and Meta-Analysis

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ABSTRACT

No systematic review to date has examined histopathological parameters in relation to native liver survival in children who undergo the Kasai operation for biliary atresia (BA). A systematic review and meta-analysis is presented, comparing the frequency of native liver survival in peri-operative severe vs. non-severe liver fibrosis cases, in addition to other reported histopathology parameters. Records were sourced from MEDLINE, Embase, and CENTRAL databases. Studies followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and compared native liver survival frequencies in pediatric patients with evidence of severe vs. non-severe liver fibrosis, bile duct proliferation, cholestasis, lobular inflammation, portal inflammation, and giant cell transformation on peri-operative biopsies. The primary outcome was the frequency of native liver survival. A random effects meta-analysis was used. Twenty-eight observational studies were included, 1,171 pediatric patients with BA of whom 631 survived with their native liver. Lower odds of native liver survival in the severe liver fibrosis vs. non-severe liver fibrosis groups were reported (odds ratio [OR], 0.16; 95% confidence interval [CI], 0.08–0.33; I^2=46%). No difference in the odds of native liver survival in the severe bile duct destruction vs. non-severe bile duct destruction groups were reported (OR, 0.17; 95% CI, 0.00–63.63; I^2=96%). Lower odds of native liver survival were documented in the severe cholestasis vs. non-severe cholestasis (OR, 0.10; 95% CI, 0.01–0.73; I^2=80%) and severe lobular inflammation vs. non-severe lobular inflammation groups (OR, 0.02; 95% CI, 0.00–0.62; I^2=69%). There was no difference in the odds of native liver survival in the severe portal inflammation vs. non-severe portal inflammation groups (OR, 0.03; 95% CI, 0.00–3.22; I^2=86%) or between the severe giant cell transformation vs. non-severe giant cell transformation groups (OR, 0.15; 95% CI, 0.00–175.21; I^2=94%). The meta-analysis loosely suggests that the presence of severe liver fibrosis, cholestasis, and lobular inflammation are associated with lower odds of native liver survival in pediatric patients after Kasai.

Keywords: Native liver; Pathology; Liver fibrosis; Biliary atresia; Pediatric patients; Liver transplantation; Cholestasis; Inflammation

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Conflict of Interest
The authors have no financial conflicts of interest.

INTRODUCTION

Biliary atresia (BA) is an idiopathic neonatal obstructive cholangiopathy, characterized by a progressive, fibrosclerosing obliteration of large bile ducts, usually manifesting in the first months of life [1,2]. The incidence of BA is approximately 1:20,000 newborns vs. 1:8,000 in European vs. Asian countries, respectively [3,4].

Presently, the standard of care is surgical management with initial hepatic portoenterostomy (i.e., Kasai operation), and liver transplantation, in pediatric cases with end-stage liver disease [5]. Moreover, early diagnosis leading to earlier age at Kasai can significantly improve immediate and long-term outcomes, such as jaundice clearance rates, native liver survival (NLSR), and mortality [6-9]. In contrast, delaying Kasai can increase the odds of needing a liver transplant (Ltx) [10,11].

Histopathological parameters obtained during pre or peri-operative liver biopsy, including degree of liver fibrosis, can predict patients at risk for early failure of Kasai (i.e., the need for Ltx before one year of age or BA-related death) [12]. Moreover, bile duct proliferation, giant cells, and fibrosis have shown significant changes in fibrosis progression in BA over time [13].

Current systematic reviews (SR) of pediatric patients with BA examine the accuracy of biomarkers in early BA diagnosis. Specifically, interleukin (IL)-33 has shown good evidence in distinguishing BA from healthy controls, serum IL-18 for prognosis of post-Kasai persistent jaundice, and serum hyaluronic acid and serum matrix metallopeptidase-7 (MMP-7) for prognosis of post-Kasai significant liver fibrosis [14,15]. Further, radiological parameters such as triangular cord sign, abnormal morphologic gallbladder characteristics, and the presence of hepatic subcapsular flow have all shown to be strong diagnostic indicators of BA [16]. Hinojosa-Gonzalez et al. [17] determined that laparoscopic portoenterostomy decreased operative time and time to normal diet vs. open portoenterostomy. However, no differences were observed in mean length of stay, complications, postoperative cholangitis, or NLSR between the two surgical approaches.

Despite these SRs, data from published literature originate from single-centers with reduced sample size [18,19] or based on long-term results from multiple institutions, before pediatric liver transplantation became regularly available [20-22]. Further, no SR to date has examined histopathological parameters, such as degree of liver fibrosis, in relation to NLSR in children who undergo Kasai for BA. Therefore, the objective of this review is to examine if histopathology parameters on pre-operative liver biopsies can predict NLSR in pediatric patients who undergo the Kasai procedure. Specifically, if the presence of severe vs. non-severe liver fibrosis can predict NLSR.

MATERIALS AND METHODS

This review followed the Cochrane Methodology to identify and select the studies [23] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to guide the reporting of this SR [24].

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Search strategy and selection criteria

The following databases were searched: MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946-May 31, 2021) and Embase (1947 to May 30, 2021) and the CENTRAL Trials Registry of the Cochrane Collaboration (April 2021 Issue) using the Ovid interface. Searches were limited to English or French. Searches were developed and conducted by a librarian and research coordinator experienced in SR, using a method designed to optimize term selection [25]. Search strategies are presented in the **Supplementary Table 1**. The study protocol has been registered in PROSPERO (CRD 42021281066). All duplicate records were removed online, records retrieved by the electronic search were downloaded and imported into Mendeley-a citation database, and then uploaded to a SR software InsightScope (www.InsightScope.com) for title and abstract screening and full text review. Five reviewers (AJ, IO, NI, YN, AW) screened at title/abstract level and full text review stages, citations were excluded if at least two reviewers agreed to exclude; disagreements were reviewed and resolved by the study leads, where necessary (DED & JDN). The study co-lead (IO) reviewed all eligible citations to confirm eligibility.

Inclusion criteria

Cohort and case control studies examining liver histopathology in pediatric patients aged less than 18 years diagnosed with BA, and reported NLSR, were included.

Exclusion criteria

Studies were excluded if they did not capture frequencies of NLSR, histopathology parameters characterized into severe vs. non-severe types, study population (i.e., adults only) or absence of the Kasai surgical intervention. Case studies, literature reviews, SR, editorials, letters to the editor, conference abstracts, and commentaries were excluded in addition to studies not written in English or French.

Data extraction and outcomes

Four authors (AJ, IO, NI, AW) extracted patient frequencies using a pre-designed and piloted data abstraction sheet in Excel version 14·7·7 (Microsoft, Redmond, WA, USA). The extracted information included: author details; fibrosis instrument applied; frequency of NLSR in severe vs. non-severe liver fibrosis groups; frequency of total patients who underwent Kasai operation; follow-up length; and presence of histopathology parameters of interest (defined below).

Our primary clinical outcome, NLSR, was calculated using actuarial survival calculations (like Kaplan–Meir survival curves) using two end-points (death or transplantation). Consequently, we extracted the actuarial survival rate at the designated follow-up period (2-, 5-, 10- or 20-years) [26]. For studies that did not explicitly state NLSR, we extracted data based on how the authors defined “favourable outcome” or “success of operation.” Hence, we extracted the frequency of patients with normal living function without cholangitis or portal hypertension [27], patients with good quality of life without jaundice relapsing [28], normal lab parameters and no evidence of medical chronic liver disease [29], absence of cirrhosis [30,31] or serum total bilirubin <2 mg/dL at follow-up post-Kasai operation [32-36].

The primary exposure variable, fibrosis severity, was usually reported on a semi-quantitative scoring scale. For example, 0 -no fibrosis; 1 - mild portal fibrosis with no septa; 2 - porto-septal (rare fibrous septa) and non-bridging fibrosis; 3 - bridging fibrosis with many fibrous septa; and 4 - cirrhosis [26,37]. Liver fibrosis could be assessed via the Ohkuma’s classification from grades I to IV [38], Metavir system where F1–F3 implied non-severe

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fibrosis, and F4 as severe fibrosis (cirrhosis), or the Ishak score where non-severe indicated F1 to F5 while severe was F6 [32].

In order to differentiate "severe" from "non-severe" liver fibrosis, we collapsed the 0–3 categories and labelled them as "non-severe" while any value exceeding 3 was deemed "severe." The method for collapsing differed based on the definition for severe fibrosis in the included studies (e.g., grade IV represented severe, using Ohkuma's classification).

We followed a similar method for organizing all other histopathological features, where 0 indicated absence of that feature and 1–3 as increasing intensity [26,39]. Bile duct proliferation/destruction was defined as: (1) mild, 5–9 bile ducts per portal tract; (2) moderate, ≥10 bile ducts per portal tract; and (3) severe, ≥10 bile ducts per portal tract and the ducts are elongated attenuated and angulated [30,33,40]. Cholestasis was defined as: (1) absent; (2) mild, accumulation of bile in centrilobular hepatocytes; (3) moderate, accumulation of bile in centrilobular and periportal hepatocytes or even in portal tracts; and (4) severe, presence of bile infarcts. Portal inflammation was defined as: (1) mild, cells are present in <1/3 portal tracts; (2) moderate, cells are present in >1/3–2/3 portal tracts; and (3) severe, dense packing of cells present in >2/3 portal tracts. Giant cell transformation was grouped into positive vs. negative categories [30,33,40].

Overall, the majority of histopathological parameters were assessed on liver biopsy, ultrasound or magnetic resonance imaging. The diagnosis of BA could have been proven by abdominal ultrasound, hepatobiliary iminodiacetic acid scan, liver biopsy, and intraoperative cholangiogram [41]. See the **Supplementary Table 1** for additional information regarding histopathological measurements.

Assessment of risk of bias within studies

AJ and IO independently assessed risk of bias (ROB) using the Ottawa–Newcastle Scale to evaluate the quality of nonrandomized studies in meta-analyses [42,43]. Three factors were considered to score the quality of included studies: (1) selection, including representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that at the start of the study the outcome of interest was not present; (2) comparability, assessed on the basis of study design and analysis, and whether any confounding variables were adjusted for; and (3) outcome, based on the follow-up period and cohort retention, and ascertained by independent blind assessment, record linkage, or self-report. We rated the quality of the studies (good, fair, and poor) by awarding stars in each domain following the guidelines of the Ottawa–Newcastle Scale. A "good" quality score required 3 or 4 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A "fair" quality score required 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A "poor" quality score reflected 0 or 1 star(s) in selection, or 0 stars in comparability, or 0 or 1 star(s) in outcomes.

Statistical analysis

All statistical analysis were performed using Review Manager 5 (RevMan 5.3) [44]. Categorical variables were expressed as numbers and percentages. Data was meta-analyzed using a random effects model in RevMan 5.3 software. Pooled odds ratios (OR) were generated using Mantel–Haenszel test, using a random effects model. Statistical heterogeneity was determined using I^2 tests. I^2 is the proportion of total variation observed between studies attributable to differences between studies rather than sampling errors. We considered high heterogeneity if I^2>75%.

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RESULTS

Study selection

The initial search yielded 905 studies of which 28 met the inclusion criteria and were included after full-text review. Thirteen of these studies were used in the meta-analysis (**Fig. 1**).

Study characteristics and individual results

Characteristics of the 28 studies with 1,171 pediatric patients who had BA and underwent Kasai operation are located in **Table 1**. Briefly, there were 25 cohort [26-34,36,37,39-41,45-55] and 3 case control studies [35,56,57]. Six hundred and thirty-one patients survived with their native liver, while 573 required Ltx and 99 reportedly died after Kasai during follow-up. The majority of studies were conducted in the United States of America or Japan. Median age at Kasai was 75 days. Median follow-up for the NLSR group was 7.8 years vs. 5.6 years for the Ltx group. Documented histopathological parameters included: severe liver fibrosis (28.6% [164/573] in Ltx vs. 7.4% [47/631] NLSR patients), giant cells (18.5% [106/573] Ltx vs. 11.3% [71/631] NLSR), lobular inflammation (4.9% [28/573] vs. 4.0% [25/631]), focal necrosis (2.4% [14/573] vs. 2.7% [17/631]), bridge necrosis (2.4% [14/573] vs. 2.7% [17/631]), bile duct destruction or proliferation in 15.7% (90/573) Ltx vs. 13.2% (83/631) NLSR patients, portal inflammation in 40.1% (230/573) Ltx vs. 13.8% (87/631) NLSR patients, and cholestasis in LTx vs. NLSR patients (52.5% [301/573] vs. 21.0% [131/631]), respectively. The Metavir fibrosis staging system was the most common tool used to assess liver fibrosis severity (**Table 1**).

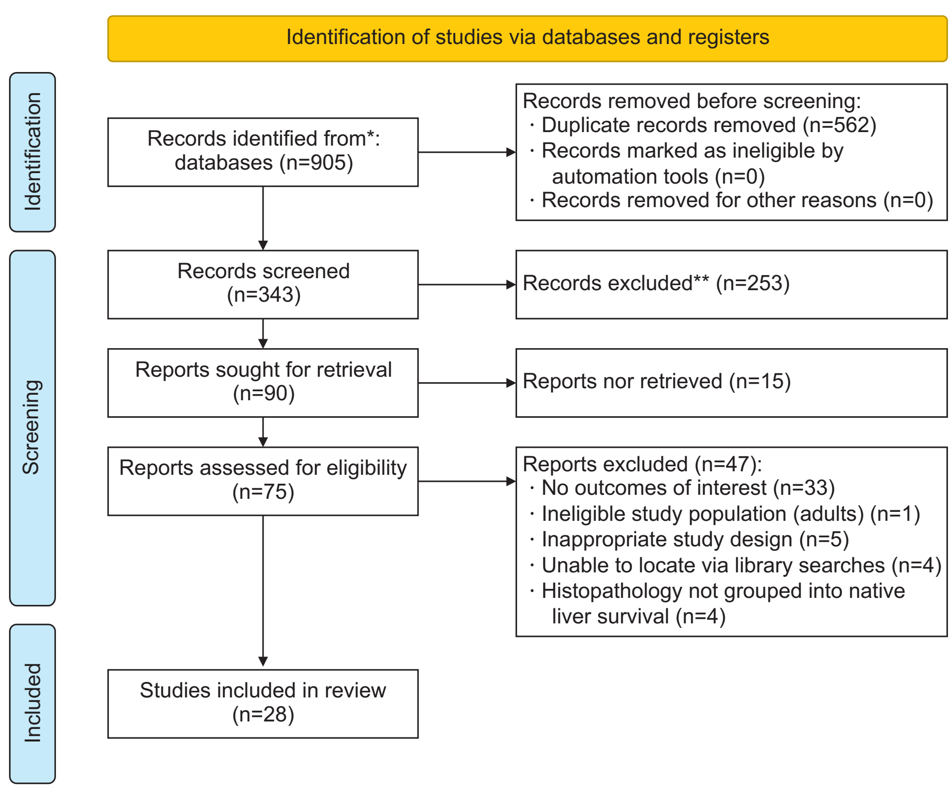

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for included studies.
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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Table 1. Study characteristics

	Author, year	Country	Total patients*	Age at Kasai (d)†	Severe liver fibrosis	Non-severe‡	Liver fibrosis§	Giant cells	Lobular inflammation	Focal necrosis	Bridge necrosis	Bile ducts‖	Portal inflamma-tion	Cholesta-sis¶	Follow-up**
Cohort studies (retrospective or prospective)															
	Davenport et al., 2004 [26]	UK	26	133						††					
NLSR					4	4		7	8			8		8	9
Ltx					7	7		15	14			14		14	1
	Lang et al., 2000 [41]	Germany	36												
NLSR				50.4	1	4		1				15	15		
Ltx				67.9	4	15		4				21	21		
	Azarow et al., 1997 [39]	Canada	31	65.8			31								
NLSR				61.6				17	17	17	17			17	
Ltx				70.7				14	14	14	14			14	1
	Meyers et al., 2003 [45]	USA	28	112			25								3.8
NLSR (steroid vs. standard)								5			3	1 vs. 7			
Ltx (steroid vs. standard)								2 vs. 4			1 vs. 2	2 vs. 9			
	Oh et al., 1995 [46]	USA	59	60.2			59								
NLSR															5
Ltx															5
	Okazaki et al., 1999 [27]	Japan	34				22								
NLSR				79.5	1	5							0	0	
Ltx				62	1	15							17	22	10
	Serinet et al., 2006 [47]	France	255				21								
NLSR															7
Ltx					17	4									
	Shteyer et al., 2006 [48]	USA	33				22								
NLSR				47	3	4									10
Ltx				59	12	3									10
	Uchida et al., 2004 [28]	Japan	30												
NLSR				63	5	15	30						0		23
Ltx				68	4	6									23
	Volpert et al., 2001 [49]	USA	9				7								
NLSR															
Ltx				20.8	3	3						7		1	15
	Apostu et al., 2021 [50]	Romania	14	70			14								
NLSR					4										6
Ltx															6
	Caruso et al., 2020 [29]	Italy	24												
NLSR (US vs. MRI)												3 vs. 2	0	0	9.7
Ltx (US vs. MRI)												1 vs. 3	8	5	7.7
	Ferreira et al., 2019 [32]	Brazil	117				Metavir: 87 Ishak: 91								
NLSR (Metavir vs. Ishak)					8 vs. 8	26 vs. 26		20						25	
Ltx (Metavir vs. Ishak)					12 vs. 8	61 vs. 65		33						49	

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Table 1. (Continued) Study characteristics

	Author, year	Country	Total patients*	Age at Kasai (d)†	Severe liver fibrosis	Non-severe‡	Liver fibrosis§	Giant cells	Lobular inflammation	Focal necrosis	Bridge necrosis	Bile ducts‖	Portal inflamma-tion	Cholesta-sis¶	Follow-up**
	Gunadi et al., 2020 [30]	Indonesia	50	102.5											
NLSR								18				18	18	18	
Ltx								32				32	32	32	
	Hukkinen et al., 2019 [31]	Finland	41												
NLSR				54	0	16	36							5	5.2
Ltx				61	4	16								10	5.2
	Jaramillo et al., 2020 [51]	USA	21												
NLSR				64	3	4	15					3		4	8.5
Ltx				67	2	9						12		12	8.5
	Lemoine et al., 2020 [52]	USA	6	75			4								
NLSR															
Ltx					1							1	3	6	
	Nguyen et al., 2021 [33]	Vietnam	85												17.8
NLSR				81.3	8	31	85					39	39	39	19.4
Ltx				79.9	10	36							46	46	
	Patel et al., 2020 [53]	USA	14				11								
NLSR															
Ltx							2					3	14	1	
	Ramachandran et al., 2019 [34]	India	30	83			30								
NLSR				78	2	11		8							
Ltx				91	6	11		8							
	Santo et al., 2021 [40]	Japan	63	62			63								
NLSR (left vs. right biopsy)															
Ltx (left vs. right biopsy)					58 vs. 43	5 vs. 20							63 vs. 63	63 vs. 63	
	Suda et al., 2019 [54]	Japan	34	66.6											
NLSR															8.6
Ltx															10.3
	Ueno et al., 2021 [55]	Japan	35				35								
NLSR					13	22									
Ltx															
	Wu et al., 2018 [36]	Taiwan	15	50.5			15								
NLSR															0.5
Ltx															0.5
	Zhou et al., 2021 [37]	China	11	73			10								
NLSR					3	8									2
Ltx															
Case-control studies															
	Kobayashi et al., 2005 [56]	Japan	22	57.3											12.4

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Table 1. (Continued) Study characteristics

	Author, year	Country	Total patients*	Age at Kasai (d)†	Severe liver fibrosis	Non-severe‡	Liver fibrosis§	Giant cells	Lobular inflammation	Focal necrosis	Bridge necrosis	Bile ducts‖	Portal inflamma-tion	Cholesta-sis¶	Follow-up**
	Kerola et al., 2019 [57]	Finland	28	61			24								
NLSR						15							15	15	3
Ltx						9							9	9	3
	Udomsinprasert et al., 2020 [35]	Thailand	20	91.1			20								
NLSR															8.5
Ltx															8.5

NLSR: native liver survival, Ltx: liver transplant, US: ultrasound, MRI: magnetic resonance imaging, UK: United Kingdom, USA: United States of America.
*Total pediatric patients with biliary atresia who underwent Kasai/hepatoportoenterostomy operation.
†Provided as mean or median age at Kasai operation.
‡Pediatric patients with non-severe liver fibrosis at peri-operative biopsy.
§Presence of liver fibrosis in total sample (not defined into severe or non-severe).
‖Bile duct destruction.
¶Cholestasis or cholangitis.
**Follow-up in years.
††Empty cells indicate no data for that parameter.

Risk of bias across studies

A detailed quality appraisal of case-control and cohort studies is summarized in **Table 2**. After formally assessing ROB for all studies based on limitations in their study design, we rated 22 studies as "poor", 5 studies as "fair", and 1 study as "good". All studies consulted secure records and/or liver histology for ascertainment of histopathological parameters and BA, and participants were truly or somewhat representative of the average pediatric patient with BA. Apart from 11 studies that were based on a selected group of users limited to a small sample size, patients were identified via electronic health records or referred to as a consecutive sample later subdivided into ideal vs. non-ideal outcomes [28,29,32,35-37,39,40,51,54,57]. Fourteen studies described pathologists being independently blinded to NLSR status [29,31-36,39,40,48,49,51,54,57]. Length of follow-up was 12 months for capturing survival outcomes in 17 studies [26-29,31,34-37,46-48,50,51,54,56,57]. The studies were mainly scored as 'poor' because they did not describe adjusting for confounders in a regression model, such as age at Kasai operation, anatomical pattern, polysplenia syndrome, level of centre experience, sex, albumin, total or direct bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and/or degree of liver failure.

Primary analysis outcome

There were lower odds of NLSR in the severe liver fibrosis vs. non-severe liver fibrosis groups (OR, 0.16; 95% confidence interval [CI], 0.08–0.33; I^2=46%) (**Fig. 2**).

Secondary analysis outcomes

There was no difference in the odds of NLSR in the severe bile duct destruction vs. non-severe bile duct destruction groups (OR, 0.17; 95% CI, 0.00–63.63; I^2=96%) (**Fig. 3**). In contrast, lower odds of NLSR were documented in the severe cholestasis vs. non-severe cholestasis (OR, 0.10; 95% CI, 0.01–0.73; I^2=80%) (**Fig. 4**) as well as severe lobular inflammation vs. non-severe lobular inflammation groups (OR, 0.02; 95% CI, 0.00–0.62; I^2=69%) (**Fig. 5**). There was no difference in the odds of NLSR in the severe portal inflammation vs. non-severe portal inflammation groups (OR, 0.03; 95% CI, 0.00–3.22; I^2=86%) (**Fig. 6**) or between the severe giant cell transformation vs. non-severe giant cell transformation groups (OR, 0.15; 95% CI, 0.00–175.21; I^2=94%) (**Fig. 7**).

Table 2. Risk of bias assessment (Newcastle–Ottawa quality assessment scale criteria)[††]

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort*	Selection of the non-exposed cohort from same source as exposed cohort[†]	Ascertainment of exposure[‡]	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis[§]	Assessment of outcome[∥]	Follow-up long enough for outcome to occur[¶]	Adequacy of follow-up**	Quality score
Davenport et al., 2004 [26]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia. A total of 422 infants had BA diagnosed and underwent confirmatory laparotomy and portoenterostomy or hepaticojejunostomy from January 1980 to December 2000	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	Yes, at least 12 months. Twelve (34%) children were alive at last follow-up with their native liver (median, 9 [range, 2 to 18] years); 9 (28%) children had undergone liver transplantation (median, 1 [range, 0.18 to 12] years postoperatively), and 13 children have died (median, 0.75 [range, 0.3 to 6] years postoperatively) ★	Complete follow-up; all subjects accounted for. Twenty-six infants underwent a KP. The whole group then was followed up for a median of 2.2 (0.45 to 18) years ★	Poor
Lang et al., 2000 [41]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia. 36 consecutive children with biliary atresia, diagnosed between 1989 and 1996 were included. All patients underwent HPE performed by the same surgeon as described by Kasai ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	No	No statement about follow-up of cohorts	Poor
Azarow et al., 1997 [39]	Selected group of users. The charts of 31 patients who underwent portoenterostomy for biliary atresia at our hospital were reviewed	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	Independent blind assessment ★	No	No statement about follow-up of cohorts	Poor
Kobayashi et al., 2005 [56]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	Drawn from a different source. Six histologically normal wedge liver biopsies from four patients with choledochal cyst and two patients with prolonged jaundice were used as controls ★	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	Yes, at least 12 months. We classified 22 long-term follow-up postoperative BA patients (mean age 12.4±5.4 years; eight boys, 14 girls) ★	No statement about follow-up of cohorts	Poor
Meyers et al., 2003 [45]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	Yes, at least 12 months ★	Follow-up rate less than 95% 1/13 patients lost to follow-up in steroid group (7%)	Poor
Oh et al., 1995 [46]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	Yes, at least 12 months. Seventeen patients (28.8%) had follow-up for 5 or more years, 13 patients (22.0%) for 2 to 5 years, and 29 patients (49.2%) for less than 2 years ★	Follow-up rate less than 95% and no description of those lost 12 patients were lost to follow-up within 2 years of surgery (12 of 59 represents 20% loss to follow-up)	Poor

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Table 2. (Continued) Risk of bias assessment (Newcastle–Ottawa quality assessment scale criteria)††

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort*	Selection of the non-exposed cohort from same source as exposed cohort†	Ascertainment of exposure‡	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis§	Assessment of outcome‖	Follow-up long enough for outcome to occur¶	Adequacy of follow-up**	Quality score
Okazaki et al., 1999 [27]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	Yes, at least 12 months. Assessed post-surgical outcome at the end of 1997. Therefore, maximum follow-up of 11 years in the time period from 1986 to 1997	Complete follow-up; all subjects accounted for. There were three survivors from 34 patients treated in period I (9% survival rate), 16 survivors from 81 patients treated in period II (20% survival rate; three of whom had LT), and 29 survivors from 48 patients treated in period III (60% survival rate; 11 of whom had LT). Twenty-nine percent. The denominators match with the number of patients outlined in the methods	Poor
Serinet et al., 2006 [47]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	Study controls for any additional confounder statistically. **Table 1** survival with native liver provides multivariate analysis, including age at Kasai operation, anatomical pattern, polysplenia syndrome, and level of center experience as factors. **Table 2** survival after liver transplantation analyzes age at liver transplant, degree of liver failure, and level of center experience as their variables ★	No description	Yes, at least 12 months. Median follow-up in survivors was 7 years (range 0.2–18.1 years)	Follow-up rate less than 95% and no description of those lost. Two hundred and twenty-two out of 271 patients had at least two years follow-up. Therefore, 18% were lost to follow-up	Fair
Shteyer et al., 2006 [48]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	Independent blind assessment ★	Yes, at least 12 months. Availability of clinical details and at least 2 year follow-up after Kasai was part of the inclusion criteria	No statement about follow-up of cohorts	Poor
Uchida et al., 2004 [28]	Select group of users. 55 consecutive children with biliary atresia were treated at the Second Department of Surgery. Among them, records were reviewed of 35 long-term jaundice-free (at least 5 years) survivors. These patients were divided into 2 groups based on QOL (group A consisted of 10 patients with bad QoL who underwent liver transplantation and group B with good QoL whose jaundice did not relapse)	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	Study controls for age at Kasai at operation, sex, albumin, total or direct bilirubin, ALT, AST, ALP, and GGT in an adjusted regression model or other statistical technique ★	No description	Yes, at least 12 months. Records were reviewed retrospectively of 35 long-term (at least 5 years) and jaundice-free survivors	No statement about follow-up of cohorts	Poor

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Table 2. (Continued) Risk of bias assessment (Newcastle–Ottawa quality assessment scale criteria)††

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort*	Selection of the non-exposed cohort from same source as exposed cohort†	Ascertainment of exposure‡	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis§	Assessment of outcome‖	Follow-up long enough for outcome to occur¶	Adequacy of follow-up**	Quality score
Volpert et al., 2001 [49]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	Independent blind assessment ★	Not applicable	Not applicable	Poor
Apostu et al., 2021 [50]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	Yes, at least 12 months. Follow-up was performed at 1, 3, 6, and 12 months and afterward annually or when complications occurred	Complete follow-up; all subjects accounted for. **Table 2** clearance rate after surgery provides the same number of patients (n=14) as from the onset of the study. patients). Patients had a median follow-up of six years (4.5–10 years)	Poor
Caruso et al., 2020 [29]	Selected group of users. We reviewed imaging examinations (US, SWE, and MRI), performed between January 2012 and December 2017, of 49 native liver survivor patients with BA after KP referred to the Pediatric Hepatology Unit of the University Hospital "Federico II". Patients were divided into two groups according to medical outcome: ideal or non-ideal. These were defined based on clinical and laboratory parameters	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	Independent blind assessment ★	Yes, at least 12 months. Median follow-up timing was 9.7 years (range 5–14 years) for ideal medical outcome patients and 7.7 years (range 5–25 years) for non-ideal medical outcome patients	Complete follow-up; all subjects accounted for. The final population consisted of 24 patients (15 boys/men, 9 girls/women; median age 9 years; age range 5–25 years), of which 15 had an ideal medical outcome while nine had a non-ideal outcome	Poor
Ferreira et al., 2019 [32]	Selected group of users	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	Study controls for age at Kasai at operation, sex, albumin, total or direct bilirubin, ALT, AST, ALP, and GGT in an adjusted regression model or other statistical technique ★	Independent blind assessment	Not applicable	No statement about follow-up of cohorts	Poor

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Table 2. (Continued) Risk of bias assessment (Newcastle–Ottawa quality assessment scale criteria)[††]

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort[*]	Selection of the non-exposed cohort from same source as exposed cohort[†]	Ascertainment of exposure[‡]	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis[§]	Assessment of outcome[‖]	Follow-up long enough for outcome to occur[¶]	Adequacy of follow-up[**]	Quality score
Gunadi et al., 2020 [30]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/ or liver histology ★	Yes ★	No description of statistical adjustment	No description	Not applicable	No statement about follow-up of cohorts	Poor
Hukkinen et al., 2019 [31]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/ or liver histology ★	Yes ★	Study controls for any additional confounder statistically. Statistically significant variables from simple regression were adjusted for in multiple regression. Liver function tests with higher odds ratios (OR) in simple regression were chosen if significant both 3 and 6 months after portoenterostomy (PEostomy). Conjugated instead of total bilirubin at PEostomy was chosen for the model because of its greater OR in simple regression, and conjugated bilirubin at 6 months was chosen because of its greater OR compared with other postoperative bilirubin measurements. ORs are reported with 95% confidence intervals (CI) ★	Independent blind assessment	Yes, at least 12 months. After median follow-up of 5.2 years (interquartile range 1.6–10.2) after portoenterostomy, liver biopsies showed cirrhosis in 53% of patients, and the Metavir stage remained stable or decreased in 38%	Complete follow-up; all subjects accounted for. **Table 1** includes characteristics of all patients (n=41) having cleared their jaundice according to the presence of cirrhosis at last follow-up. The sample sizes of the two groups are identical to the sample size of the total population. Patients without cirrhosis at follow-up (n=19) and patients with cirrhosis at follow-up (n=22) is equivalent to a total of 41 patients assessed	Good
Jaramillo et al., 2020 [51]	Selected group of users. We retrospectively reviewed the medical records of patients diagnosed with BA who underwent KP at our institution from 2006 to 2016. In order to pilot this novel technique, only patients with available wedge biopsies from time of KP were included for CHP assessment	No description of the derivation of the non-exposed cohort	Secure record and/ or liver histology ★	Yes ★	Study controls for any additional confounder statistically. For the multivariable analysis, a backward-elimination approach using the Cox proportional hazard model was performed, using a cutoff *p*-value of <0.10 to be included in the model. Hazard ratios and *p*-values were reported for each factor alone and for the factors found to be significant from the backward elimination ★	Independent blind assessment	Yes, at least 12 months. Exclusion criteria included lack of a wedge biopsy or <2 years follow-up post-KP	Complete follow-up; all subjects accounted for. Follow-up time provided for the liver transplant (n=14) and non-liver transplant (n=7) group, which is equivalent to the total sample size (n=21) who underwent percutaneous liver biopsy before KP	Fair
Kerola et al., 2019 [57]	Selected group of users. Of 51 BA patients operated in Helsinki University Hospital (Finland) between 1991 and 2013, 30 patients (59%) cleared their jaundice after PE, and 28 of them (93%) were enrolled	Drawn from a different source. Healthy nonfibrotic control liver biopsies were obtained from 19 pediatric donor livers (median age 14.2 years [interquartile range 8.0–16.2 years]) and from 10 children (age 11.4 years [7.8–14.8 years]) undergoing cholecystectomy for cholecystolithiasis. Fibrotic control liver tissue was obtained from 11 patients with intestinal failure (age 4.7 years [3.5–9.7 years])	Secure record and/ or liver histology ★	Yes ★	No description of statistical adjustment	Independent blind assessment	Yes, at least 12 months. After median follow-up of 3.0 years, histologic cholestasis resolved, whereas fibrosis had progressed only in isolated biliary atresia	Subjects lost to follow-up unlikely to introduce bias – number lost less than or equal to 5%. **Table 2** shows 28 patients at the median follow-up of 3 years. However, one patient was lost to follow-up (n=27) under ductal reaction, TGF-beta1, CTGF, and three patients lost to follow-up under decorin	Poor

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Table 2. (Continued) Risk of bias assessment (Newcastle–Ottawa quality assessment scale criteria)[††]

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort*	Selection of the non-exposed cohort from same source as exposed cohort†	Ascertainment of exposure‡	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis§	Assessment of outcome‖	Follow-up long enough for outcome to occur¶	Adequacy of follow-up**	Quality score
Lemoine et al., 2020 [52]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	Not applicable	No statement about follow-up of cohorts	Poor
Nguyen et al., 2021 [33]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	Study controls for any additional confounder statistically. Group comparison was carried us ing the Mann–Whitney–Wilcoxon-test, Fisher's exact test or logistic regression analysis. Histology data in the good and poor outcome group are reported by grade for each of the variables of hepatocellular injury, inflammation, cholestasis, ductal proliferation and fibrosis and the corresponding frequency ★	Independent blind assessment	No	Complete follow-up; all subjects accounted for. **Table 1** reports follow-up (months) of the good outcome (n=39) and poor outcome group (n=46), which is the same number of patients included at study onset	Fair
Patel et al., 2020 [53]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	Drawn from a different source. Appropriate age matched controls from both cirrhotic and noncirrhotic explants were used to compare the vascular abnormalities	Secure record and/or liver histology ★	Yes ★	Study controls for any additional confounder statistically adjusted for age. Appropriate age matched controls from both cirrhotic and noncirrhotic explants ★	No description	Not applicable	No statement about follow-up of cohorts	Poor
Ramachandran et al., 2019 [34]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	Independent blind assessment	Yes, at least 12 months. Ten children who cleared jaundice and had mild expression of α-SMA are alive with native liver 6–27 months after KP	No statement about follow-up of cohorts	Poor

(continued to the next page)

Table 2. (Continued) Risk of bias assessment (Newcastle–Ottawa quality assessment scale criteria)[††]

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort*	Selection of the non-exposed cohort from same source as exposed cohort[†]	Ascertainment of exposure[‡]	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis[§]	Assessment of outcome[‖]	Follow-up long enough for outcome to occur[¶]	Adequacy of follow-up**	Quality score
Santo et al., 2021 [40]	Selected group of users. Among the 116 patients with BA underwent LT at the National Center for Child Health and Development (NCCHD) between January 2014 and December 2018, 69 had failed KP. Six patients were excluded, including 3 with situs inversus and 3 with missing samples from both lobes. Of these patients, 63 were selected for this study	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	Independent blind assessment	Not applicable	No statement about follow-up of cohorts	Poor
Suda et al., 2019 [54]	Selected group of users. The present study was a retrospective analysis that included 34 patients with BA treated at Ibaraki Children's Hospital between 1986 and 2015. All patients underwent KP	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	Independent blind assessment	Yes, at least 12 months. The follow-up duration was not significantly different between the two groups (p=0.52; 8.6±5.2 vs. 10.3±5.5 years, respectively)	Complete follow-up; all subjects accounted for. Table 3 provides the same sample size numbers for the NLS vs. non-NLS group at follow-up	Poor
Udomsinprasert et al., 2020 [35]	Selected group of users. Perioperative liver biopsies of 20 BA infants who underwent KP and 7 non-BA patients who underwent liver biopsies with no signs of fibrosis were obtained at the Department of Surgery, King Chulalongkorn Memorial Hospital. Infants diagnosed with BA or non-BA were included based on clinical, cholangiographic, and histologic findings	Drawn from a different source. All non-BA patients that served as controls included 7 patients with choledochal cysts	Secure record and/or liver histology ★	Yes ★	Study controls for age at Kasai at operation, sex, albumin, total or direct bilirubin, ALT, AST, ALP, and GGT in an adjusted regression model or other statistical technique ★	Independent blind assessment	Yes, at least 12 months. The duration of follow-up after KP ranged from 1 year to 14 years (median 8.5 years)	Complete follow-up; all subjects accounted for. We conducted Kaplan–Meier analysis to examine the relationships between high expressions of these molecules and poor survival of BA patients (n=12). The duration of follow-up after KP ranged from 1 year to 14 years (median 8.5 years). One patient underwent liver transplantation after KP	Fair
Ueno et al., 2021 [55]	Participants were truly or somewhat representative of the average pediatric patient with biliary atresia ★	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	No statement about follow-up of cohorts	No statement about follow-up of cohorts	Poor

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Table 2. (Continued) Risk of bias assessment (Newcastle–Ottawa quality assessment scale criteria)[††]

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort*	Selection of the non-exposed cohort from same source as exposed cohort†	Ascertainment of exposure‡	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis§	Assessment of outcome‖	Follow-up long enough for outcome to occur¶	Adequacy of follow-up**	Quality score
Wu et al., 2018 [36]	Selected group of users. We recruited 48 cholestatic infants (31 males and 17 females) from the Department of Pediatrics of National Taiwan University Hospital (NTUH) from May 2015 to December 2017 to this study prospectively. All patients presented with cholestasis (serum direct bilirubin level >1 mg/dL and direct to total bilirubin ratio >20%). Subjects with ascites, septic shock, and previous abdominal surgery were excluded	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	Study controls for any additional confounder statistically. p-value<0.017 was regarded as statistically significant, and between 0.017–0.035 as a trend in the univariate logistic regression analysis after Bonferroni correction. Only factors that achieved a trend (<0.034) were included into the multivariate model analysis. The variables included in the models included sex, GGT, and LSM ★	Independent blind assessment	Yes, at least 12 months. In subjects with BA post-HPE, we performed an abdominal sonogram every 6 months since 6 months of age or at the presence of palpated splenomegaly at physical examination	Complete follow-up; all subjects accounted for. The clinical data of the 15 subjects with BA are summarized in Table 3 at follow-up (3 months post-Kasai) is provided	Fair
Zhou et al., 2021 [37]	Selected group of users. Between January 2012 and November 2020, a total 437 patients with BA who underwent liver US scan during follow-up after KP were initially assessed. Patients were included in this study if they (a) presented obvious liver segmental deformation, (b) underwent SWE examination and (c) had serum biochemical tests within one week of US examination	No description of the derivation of the non-exposed cohort	Secure record and/or liver histology ★	Yes ★	No description of statistical adjustment	No description	Yes, at least 12 months. 33 patients were known to survive with native liver for more than 2 years while one patient was lost after 1 year of follow-up due to parents' non-cooperation	No statement about follow-up of cohorts	Poor

LT: liver transplant, QOL: qulaity of life, US: ultrasound, SWE: shear wave elastography, MRI: magentic reaseanace imaging, KP: kasai portoenterostomy, CHP: collagen hybridizing peptide, PE: portoenterostomy, CTGF: connective tsiiue growth factor expression, SMA: smooth muscle antigen, NLS: non liver transplants, LSM: liver stiffness measurement, HPE: hepatoportoenterostomy.

*Truly or somewhat representative of the average pediatric patient with biliary atresia (BA) (i.e., random or all sequential admissions); somewhat representative of the average pediatric patient with BA (i.e., only selected pediatric patients based on location, type of medical insurance, living in a certain urban or rural area etc.); selected group of users (pediatric patients with BA who underwent Kasai/HPE operation); no description of the derivation of the cohort.

†Draw from same sample as the exposed cohort; drawn from a different source (children with liver diseases other than biliary atresia); no description of the derivation of the non-exposed cohort.

‡Secure record and/or liver histology; structured interview; written self-report; no description.

§Study controls for age at Kasai operation, sex, albumin, total or direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) in an adjusted regression model or other statistical technique; study controls for any additional confounder statistically; no description of statistical adjustment.

‖Independent blind assessment (e.g., pathologist blinded to clinical status, diagnosis – biliary atresia – and outcome of the patient after Kasai when evaluating liver histology); record linkage (population-level databases); self-report (survey or interview response); no description.

¶Follow-up of at least one year in length to assess the outcomes of native liver survival or liver transplant.

**Complete follow-up, all subjects accounted for; subjects lost to follow-up unlikely to introduce bias – number lost ≤5%; Follow-up rate <95% and no description of those lost; not applicable; no statement about follow-up of cohorts.

††Good quality: 3 or 4 stars (F) in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

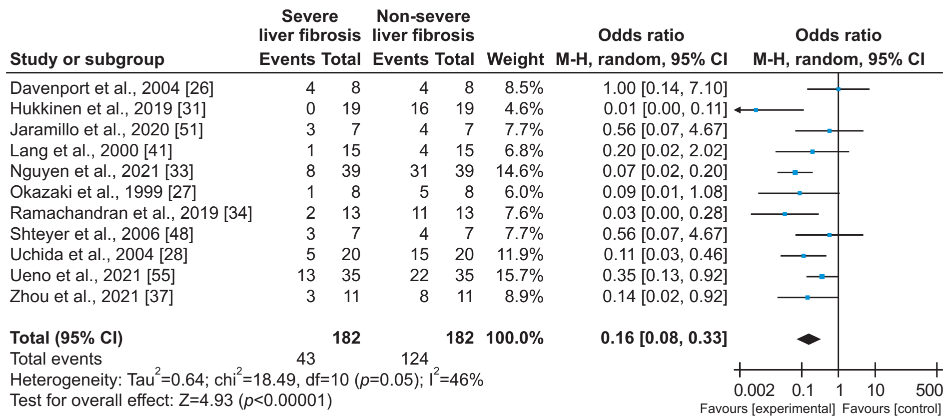

Fig. 2. Meta-analysis plot of the pooled odds ratio comparing native liver survival in severe fibrosis ('experimental') vs. non-severe fibrosis ('control') groups.
CI: confidence interval.

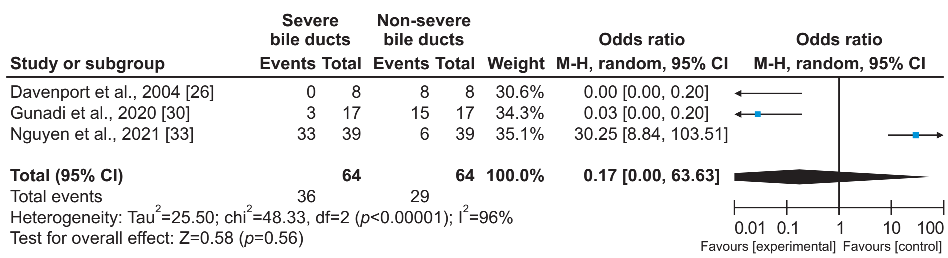

Fig. 3. Meta-analysis plot of the pooled odds ratio comparing native liver survival in severe bile duct destruction ('experimental') vs. non-severe bile duct destruction ('control') groups.
CI: confidence interval.

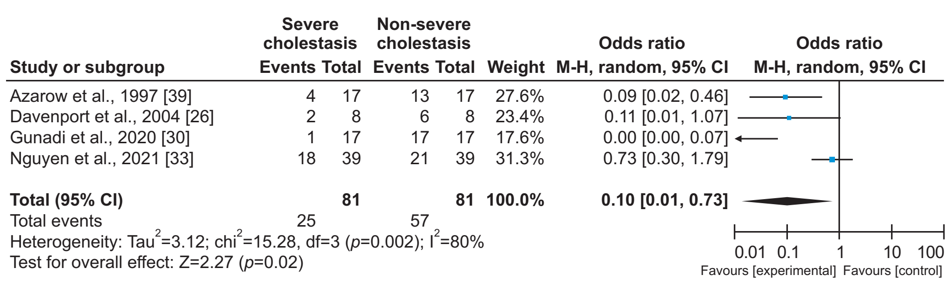

Fig. 4. Meta-analysis plot of the pooled odds ratio comparing native liver survival in severe cholestasis ('experimental') vs. non-severe cholestasis ('control') groups.
CI: confidence interval.

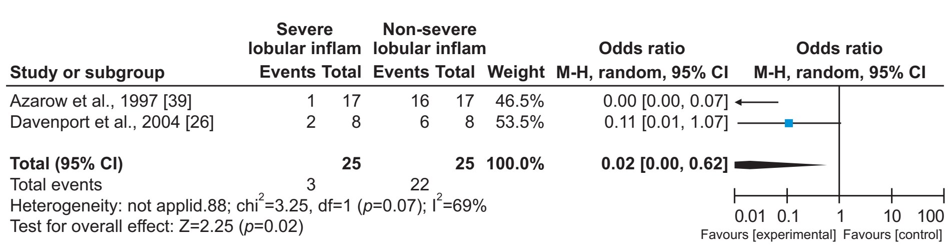

Fig. 5. Meta-analysis plot of the pooled odds ratio comparing native liver survival in severe lobular inflammation ('experimental') vs. non-severe lobular inflammation ('control') groups.
CI: confidence interval.

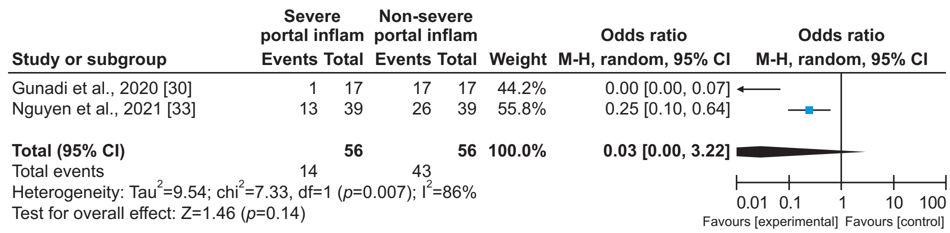

Fig. 6. Meta-analysis plot of the pooled odds ratio comparing native liver survival in severe portal inflammation ('experimental') vs. non-severe portal inflammation ('control') groups.
CI: confidence interval.

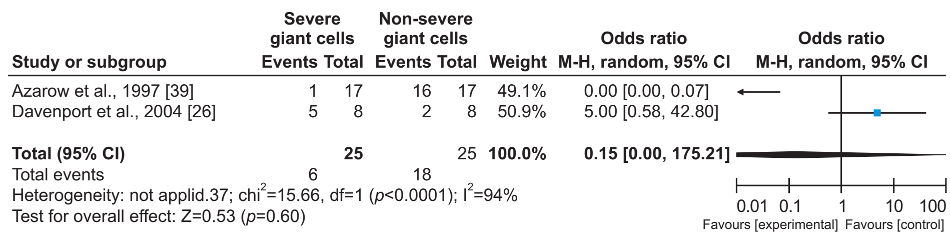

Fig. 7. Meta-analysis plot of the pooled odds ratio comparing native liver survival in severe giant cell transformation ('experimental') vs. non-severe giant cell transformation ('control') groups.
CI: confidence interval.

DISCUSSION

The aim of this SR was to identify if certain histopathological parameters could predict NLSR in pediatric patients with BA who underwent the Kasai/hepatoportoenterostomy operation. Our meta-analysis findings loosely suggest that the presence of severe liver fibrosis, cholestasis, and lobular inflammation are associated with lower odds of NLSR after Kasai. However, caution should be exercised due to considerable levels of heterogeneity and wide or imprecise confidence intervals.

No similar SR within the past five years has incorporated the severity of liver fibrosis, cholestasis, and lobular inflammation as predictors of NLSR. We do know that preoperative biopsies are highly specific and sensitive in diagnosing BA before operation [58], but a meta-analysis into particular peri-operative histopathological parameters for comparison is lacking.

Despite this, fibrosis is a crucial factor predicting NLSR outcomes [59-61], and a successful Kasai operation can slow down the progression of fibrosis and inflammation [62,63]. Moreover, cirrhosis imaging findings, including diminished portal flow, as well as advanced fibrosis, increased liver expression of collagen, and smooth muscle actin, are correlated with decreased NLSR [64,65]. Results are conflicting with respect to severe fibrosis and postoperative outcomes. Certain large, cohort studies suggest that fibrosis stage, and Ishak scores, are not related to postoperative outcome and fewer patients present with advanced fibrosis [60,62,66-68], while others support a correlation between fibrosis degree and absence of bridging fibrosis, in relation to jaundice free NLSR [59,69].

Severe cholestasis was associated with poor NLSR in our review, characterized by the progression of fibrosis and irregular expansion of intrahepatic bile ducts [65]. Presently, a specific marker of cholangiocyte, known as cytokeratin-7, is involved in the ductular reaction at Kasai and has predicted NLSR, as well as accelerates fibrosis after operation [62,66,70]. Though we did not measure this parameter in our study, upregulated liver MMP-7 expression presents in cholangiocytes, and is a marker for bile duct injury and reactions [71]. MMP-7 does indicate cholangiopathy and decreased NLSR six months after Kasai; however, there is no association with liver survival at Kasai [72].

Lastly, our review found no impact of portal inflammation, but an adverse effect of severe lobular inflammation, on NLSR. In contrast, Hukkinen et al. [62,65] determined that high grade histological portal tract inflammation at Kasai is correlated with improved NLSR. In fact, active inflammation may indicate early and adaptable liver disease stage [65]. Currently, the association between inflammatory markers (like lobular inflammation) and NLSR is poorly understood [73]. Present knowledge suggests that an altered immune response and inflammatory cytokines precipitate bile duct injury in BA [65]. Specifically, IL-8 leads to bile duct injury, and decreased NLSR is associated with elevated circulating IL-8 levels at two months post Kasai [73]. Contrastingly, IL-12p40 or IL-12B, activate natural killer cells in proinflammatory cytokine IL-12p70, and this process is hypothesized to predict NLSR at Kasai [74,75].

This review is not without limitations. The levels of heterogeneity were quite high across all meta-analyses; as such, results should be interpreted with caution. We decided not to pursue a subgroup analysis to investigate sources of heterogeneity (instrument type, age at Kasai, length of follow-up). According to the Cochrane Handbook for Systematic Reviews, investigations of heterogeneity when there are very few studies are not worth pursuing due to questionable value [76]. In light of previous literature [77-79], we initially wanted to explore the efficacy of treatment-related factors such as steroids in improving NLSR outcome, including among cholestasis cases, yet insufficient numbers of studies provided this information. Moreover, pre-cirrhotic liver fibrosis has not been well correlated with NLSR. Possible reasons include sampling error and various quantitative tools of liver fibrosis. Thus, comparing our findings to previous literature proves difficult, since there is no universally implemented histological grading system for changes in the liver of BA patients [65]. Lastly, biomarkers of fibrosis, inflammation, and cholestasis are inconsistent and not well reproduced in multiple patient cohorts. Hence, findings have been contradictory [65,80].

Overall, our review determined that severe fibrosis, cholestasis, and lobular inflammation are all associated with reduced NLSR in pediatric patients with BA after Kasai operation. Consistency in definitions for histopathology are needed for reproducibility by pathologists in the future. While also considering the patient's age, pathologists can communicate histopathological findings to surgeons who are deciding the optimal time for Kasai intervention.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Histopathological parameters and method of assessment per study

Click here to view

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