



Comparison of laparoscopic portoenterostomy and open portoenterostomy for the treatment of biliary atresia

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Abstract

Background Although open portoenterostomy (OPE) is considered the standard treatment for biliary atresia (BA), laparoscopic portoenterostomy (LPE) is conducted and reported by many investigators. Data on the safety and efficacy of LPE remain controversial. The aim of this meta-analysis is to compare the safety and efficacy of LPE and OPE for the treatment of BA.

Methods Three electronic databases were searched: PubMed, Embase, and the Cochrane Library. The eligible studies were limited to those published in English. The following keywords were used: “biliary atresia,” “laparoscopic portoenterostomy,” “Kasai portoenterostomy,” “open portoenterostomy,” “surgery,” and “treatment.”

Results Nine studies, including 434 patients, were analyzed. The operative time of LPE was significantly longer than that of OPE (MD=40.55 min, 95% CI 4.83–76.27 min, $P=0.03$). There was no significant difference between the two groups in terms of the time of hospital stay, the volume of intraoperative blood loss, or the rates of cholangitis, early clearance of jaundice or two-year survival with the native liver. The subgroup analyses revealed that the rate of early clearance of jaundice in the LPE group was significantly higher than that in the OPE group in studies published after 2016 (95% CI 1.04–1.75; $P=0.02$).

Conclusions The present meta-analysis provides evidence that LPE is a feasible option for patients with BA. LPE should be reevaluated by further studies and longer follow-up.

Keywords Pediatric · Biliary atresia · Laparoscopy · Portoenterostomy

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Biliary atresia (BA) is one of the most common cholestatic childhood diseases, with an estimated incidence of 1 in 8000–18,000 live births [1]. BA is a progressive cholangiopathy with fibro-obliterative obstruction of the bile duct. The exact pathogenesis and etiology of BA have not been fully elucidated. The hypothesis that is most widely recognized states that injury to the biliary duct is caused by an initial infection and then an autoimmune response is induced by infection, leading to progressive damage to the biliary duct [2]. Typical clinical manifestations of BA include persistent jaundice, acholic stools, and pigmented urine in the first months after birth. Unfortunately, the presentation time of the clinical features can be delayed in BA, which may lead to misdiagnosis. The average diagnostic age of BA is 60 days in many countries [3, 4].

Currently, effective management for BA is the Kasai portoenterostomy (KPE), which was originally reported by Morio Kasai in 1959 [5]. Serum bilirubin < 2 mg/dL and jaundice clearance in three months after KPE are the main

predictive indicators of transplant-free survival in patients with BA. In the literature, 47–65% of patients with BA achieved jaundice clearance after standard open portoenterostomy (OPE) [6–9]. In many institutions, OPE is the first-line treatment for BA.

With the development of minimally invasive surgery, Esteves et al. [10] reported the first laparoscopic portoenterostomy (LPE) for the treatment of BA in 2002. Subsequently, some investigators indicated that LPE was feasible and safe [11, 12]. However, several centers [13, 14] reported that the outcome in patients who underwent LPE was inferior compared with that in patients who underwent OPE. The International Pediatric Endosurgery Group (IPEC) discouraged the use of LPE in 2007 [15]. Recently, with the improvement of instrumentation and technology, some investigators restarted LPE, and they have achieved good results [11, 12, 16–19]. However, the sample sizes of these reports were relatively small. The safety and efficacy of LPE are still controversial issues in the management of BA. The aim of the present systematic review was to compare LPE and OPE for the treatment of BA.

Methods

Search strategy

This study was undertaken at the West China Hospital of Sichuan University with the approval of the human ethics review committee. The search of the online databases was performed independently by two investigators (YNL and CW). The electronic databases of PubMed, Embase, and the Cochrane Library were searched to identify the literature comparing LPE and OPE for the treatment of BA until January 2019. The literature was limited to being published in English. The following keywords were used: “biliary atresia,” “laparoscopic portoenterostomy,” “Kasai portoenterostomy,” “open portoenterostomy,” “surgery,” and “treatment.”

Inclusion and exclusion criteria

The inclusion criteria were (1) randomized clinical trials or prospective/retrospective controlled studies comparing LPE and OPE for the treatment of BA; (2) studies that included at least one of the following outcomes: “cholangitis,” “early clearance of jaundice,” or “two-year survival with the native liver.” Case reports, meeting abstracts, review articles, letters, and opinions were excluded.

Study selection

All titles, abstracts, and full texts were searched and reviewed independently by two investigators (YNL and

CW) based on predefined criteria. Titles and abstracts were examined first, and then full texts were obtained for final eligibility. The most recent and comprehensive reports were identified. Duplicate publications were excluded.

Data extraction and quality assessment

For each selected study, the following information was extracted: first author, year of publication, country, study type, number of patients, gender, age, operative time, hospital stay, follow-up, mean blood loss, cholangitis, the rate of long-term survival with the native liver, and the rate of early clearance of jaundice. The quality of the selected studies was assessed using the Newcastle–Ottawa criteria. This scale system ranges from 0 to 9 stars for cohort studies, with a score of at least 6 stars being considered high quality.

Statistical analysis and exploration of heterogeneity

RevMan software (version 5.3, Cochrane collaboration) was used for the analyses. A fixed-effects model (Mantel–Haenszel method) or a random-effects model (DerSimonian–Laird method) was used to analyze the data. The I^2 method was used to assess heterogeneity among studies, with higher I^2 values indicating higher heterogeneity. If the I^2 value was less than 50%, a fixed-effects model of analysis was used. If not, a random-effects model of analysis was used. Pooled results were expressed as the risk ratio (RR) with 95% confidence intervals (CIs) for all end points. Subgroup analyses were also used to assess independent variables.

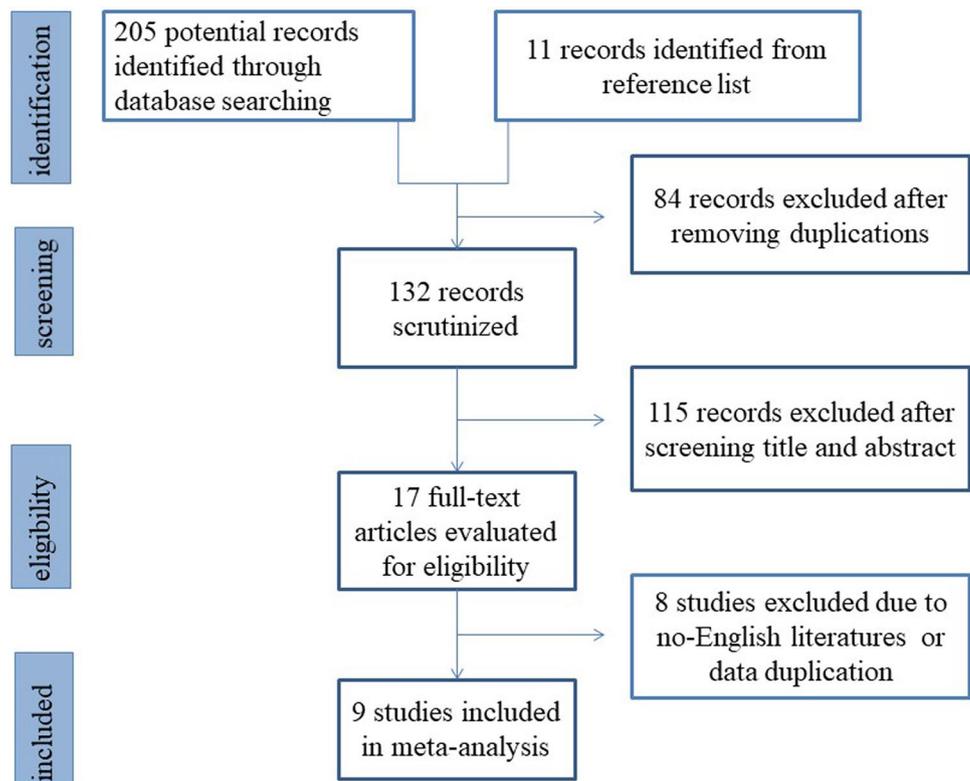
Results

Search results

The flowchart of the search results is shown in Fig. 1. In total, 216 potential records were identified and evaluated by two investigators independently. One hundred fifteen studies were excluded after screening the titles and abstracts. Eighty-four records were excluded after removing duplicates. In addition, 8 studies were excluded because they used the same data or were non-English documents. Finally, 9 studies met the inclusion criteria and were included in the meta-analysis (Table 1). All of the studies scored at least 6 stars, which were evaluated using the quality assessment (the Newcastle–Ottawa criteria).

Study characteristics

The detailed characteristics of the selected studies are summarized in Table 1. Nine studies published between 2007 and 2018 were analyzed. These 9 studies included

Fig. 1 Flowchart of the study selection process

two prospective and seven retrospective studies. The studies were from different geographic locations: China (4), Japan (3), Germany (1), and Canada (1). In these studies, 172 patients underwent LPE and 262 patients underwent OPE.

Results of the meta-analysis

Hospital stay

Three studies [20–22] with a total of 143 patients (LPE = 59, OPE = 84) described the time of hospital stay. The pooled result was -0.47 days (95% CI -1.84 – 0.91 days; $P = 0.51$), with no heterogeneity ($I^2 = 0\%$) (Fig. 2A). There was no significant difference between LPE and OPE.

Operative time

Three studies [20–22] with a total of 143 patients (LPE = 59, OPE = 84) compared the operative time between LPE and OPE. High heterogeneity was detected among the studies ($I^2 = 65\%$), so a random-effects model of analysis was used. The pooled results showed that the operative time of LPE was significantly longer than that of OPE (MD = 40.55 min, 95% CI 4.83–76.27 min; $P = 0.03$) (Fig. 2B).

Intraoperative blood loss

Two studies [21, 22] with a total of 114 patients (LPE = 54, OPE = 60) recorded the volume of intraoperative blood loss. A high heterogeneity was revealed ($I^2 = 74\%$). A random-effects model of analysis showed that the pooled result was -2.77 (95% CI -8.05 – 2.52 ; $P = 0.3$). In terms of intraoperative blood loss, there was no significant difference between the two groups (Fig. 2C).

Cholangitis

Five studies [13, 21–24] comprising 269 patients (LPE = 131, OPE = 138) reported cholangitis after LPE or OPE. The pooled result indicated that the incidence of cholangitis was not discernibly significantly different between the two groups (RR = 1.03, 95% CI 0.85–1.24; $P = 0.75$), with no heterogeneity ($I^2 = 0\%$) (Fig. 2D).

Early clearance of jaundice

Seven studies [13, 21–26], including a total of 377 patients (LPE = 160, OPE = 217), reported early clearance of jaundice. The heterogeneity among the studies was high ($I^2 = 52\%$), and a random-effects model of

Table 1 Characteristic of the included studies

References	Region	Year	Study type	Sample size	Age (day)	Sex m/f	Operative time (mean, min)	Hospital stay (mean, day)	Follow-up (mean, month)	Mean blood loss (mL)	Cholangitis	JC	SNL
Asplund et al. [20]	Canada	2007	Re	LPE:5 OPE:24	N N	N N	329±65 301±77	9.2±4.0 11±5.6	9.9 40	N N	3 4	N N	N N
Ure et al. [14]	Germany	2011	Pr	LPE:12 OPE:28	57±27 57±21	6/6 14/14	N N	N N	24 24	N N	N N	N N	1 9
Wada et al. [24]	Japan	2014	Re	LPE:12 OPE:11	65.8 (29–119) 64.7 (29–100)	N N	546 (414–662) 468 (375–576)	N N	35.3 45.1	11.9 (3–21) 12.4 (7–32)	6 3	12 9	10 9
Chan et al. [13]	China	2014	Re	LPE:16 OPE:27	65.6 (45–106) 58.9 (39–135)	5/11 9/18	N N	N N	24 24	N N	7 11	8 25	8 22
Sun et al. [22]	China	2015	Pr	LPE:44 OPE:47	61.5±22.75 67±16.5	23/21 23/24	169.5±30.25 146±27.5	12.5±3.25 13.±4	12 12	10±5 15±5	26 28	19 24	N N
Murase et al. [36]	Japan	2015	Re	LPE:12 OPE:65	53 (41–77) 66 (32–144)	3/9 26/39	307 (253–448) 281 (163–395)	N N	N N	25 (5–58) 50 (5–363)	N N	8 41	N N
Nakamura et al. [16]	Japan	2016	Re	LPE:17 OPE:14	65.5 69.3	N N	N N	N N	30 30	N N	N N	16 10	13 10
Huang et al. [21]	China	2018	Re	LPE:10 OPE:13	67.75±42.50 57.15±20.14	4/6 5/8	285±38.82 209.62±60.4	18.0±6.35 14.62±9.4	20.38 54.62	4.85±5.52 4.36±6.92	7 9	5 4	7 9
Li et al. [23]	China	2018	Re	LPE:49 OPE:40	87.3 (42–125) 92.0 (59–135)	16/33 18/22	263 (210–420) 188 (120–240)	23.9 (14–30) 22.2 (12–30)	76.7 79.4	N N	36 30	30 18	18 10

Re, retrospective; Pr, prospective; m, male; f, female; LPE, laparoscopic portoenterostomy; OPE, open portoenterostomy; N, not clear; JC, jaundice clearance; SNL, survival with native liver

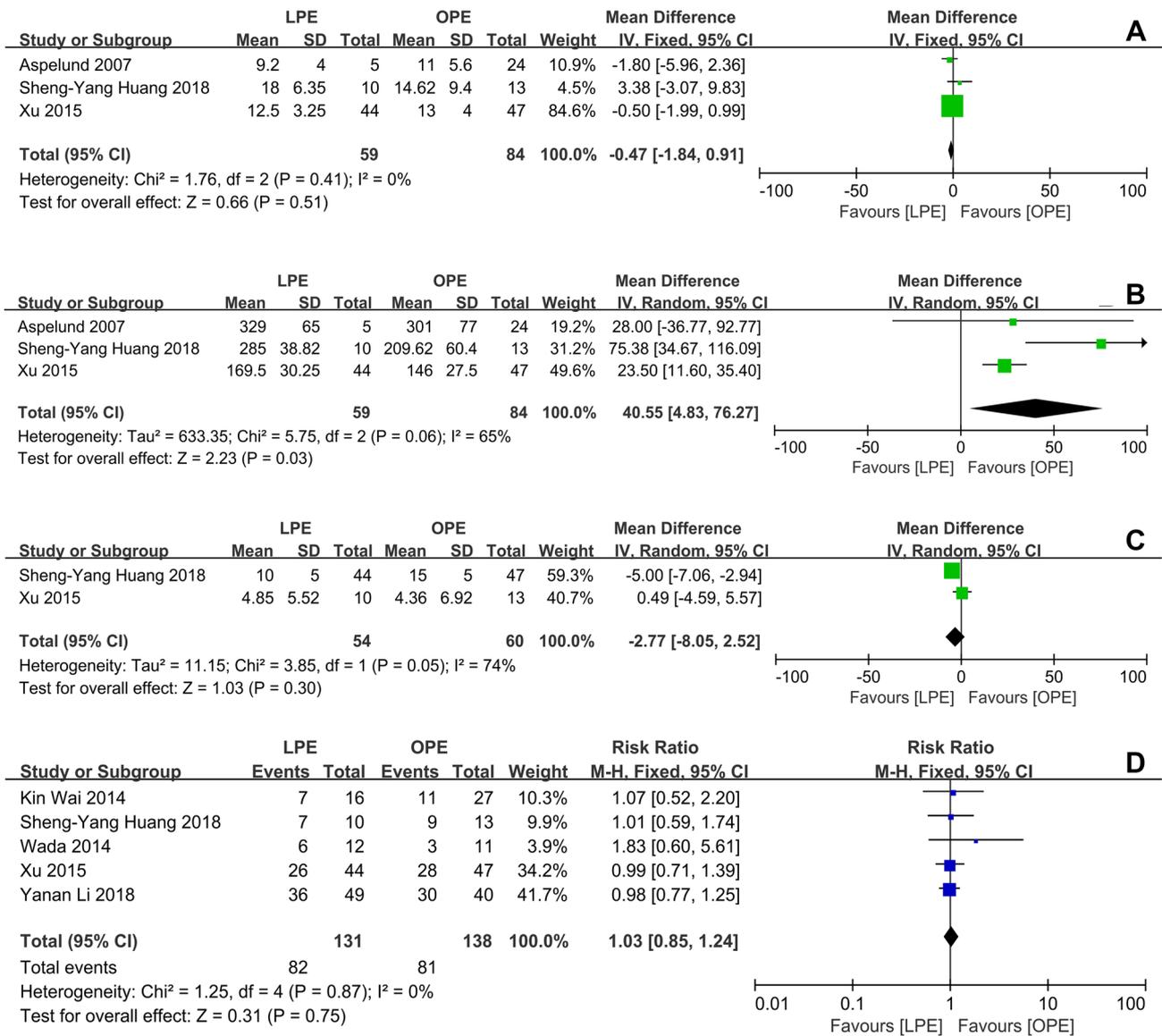


Fig. 2 Forest plots of the outcome of open portoenterostomy versus laparoscopic portoenterostomy according to **A** hospital stay; **B** operative time; **C** intraoperative blood loss; and **D** cholangitis

analysis was conducted. The pooled result showed no significant difference in early clearance of jaundice between the two groups (RR = 1.06, 95% CI 0.84–1.35, $P = 0.61$) (Fig. 3C).

In the subgroup analyses, the pooled RR was 0.90 (95% CI 0.63–1.29, $P = 0.57$) for studies published before 2016 and 1.35 (95% CI 1.04–1.75; $P = 0.02$) for studies published after 2016 (Fig. 3B). In addition, the pooled RR was 0.95 (95% CI 0.59–1.51, $P = 0.81$) for studies conducted in China compared to 1.21 (95% CI 0.99–1.49; $P = 0.07$) for studies conducted in Japan (Fig. 3A).

Two-year survival with the native liver

Six studies [13, 14, 21, 23–25], including a total of 249 patients, described the rates of two-year survival with the native liver (LPE = 116, OPE = 133). The pooled result indicated that there was no significant difference between the two groups in the rates of two-year survival with the native liver (RR = 0.93, 95% CI 0.73–1.19, $P = 0.57$), with moderate heterogeneity ($I^2 = 25%$) (Fig. 4C).

In the subgroup analyses, the pooled RR was 0.64 (95% CI 0.44–0.94; $P = 0.02$) for studies published before 2016

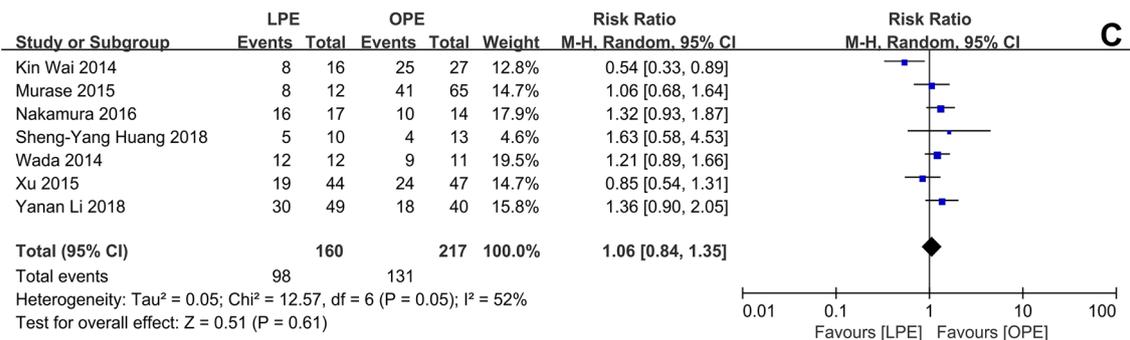
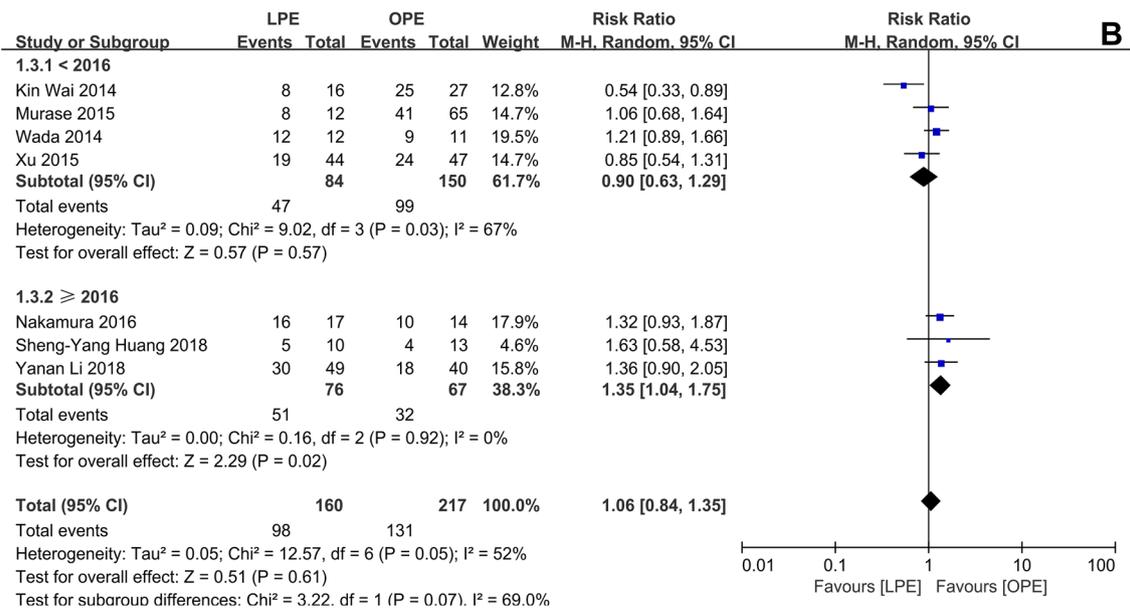
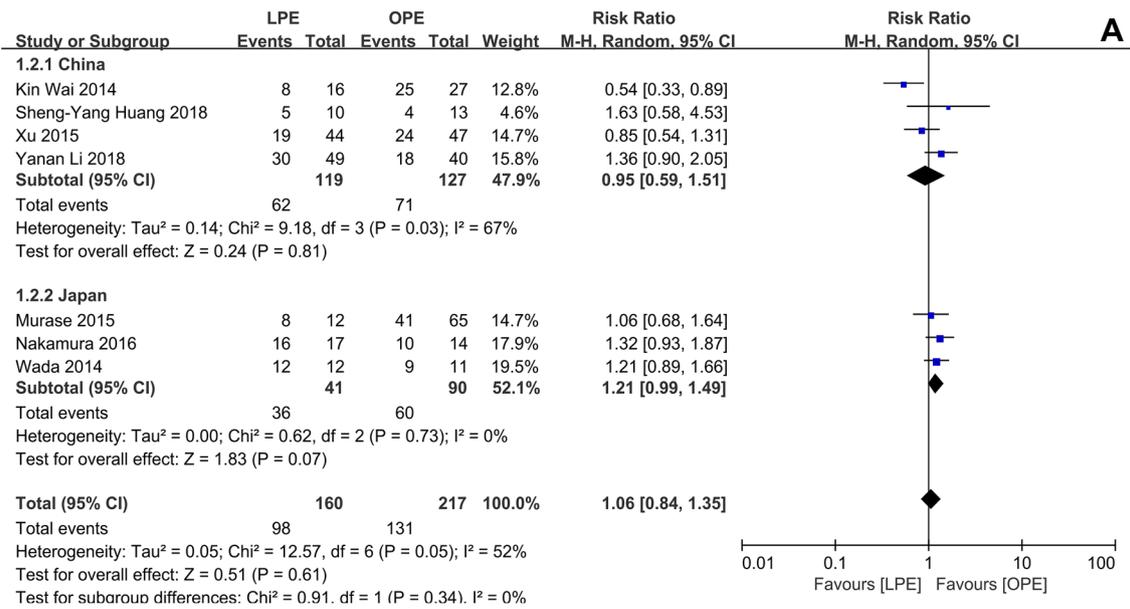


Fig. 3 Forest plots of early clearance of jaundice of open portoenterostomy versus laparoscopic portoenterostomy according to **A** country; **B** year of publication; and **C** overall effect

and 1.20 (95% CI 0.86–1.67; $P=0.27$) for studies published after 2016 (Fig. 4B). In addition, the pooled RR was 0.97 (95% CI 0.69–1.36; $P=0.86$) for studies conducted in China, 1.00 for studies conducted in Japan (95% CI 0.74–1.35; $P=1.00$), and 0.26 for studies conducted in Germany (95% CI 0.04–1.83; $P=0.18$) (Fig. 4A).

Sensitivity analysis

In this meta-analysis, when excluding the study of Chan et al. [13], the value of I^2 was obviously reduced. Exclusion of other studies did not influence the results.

Discussion

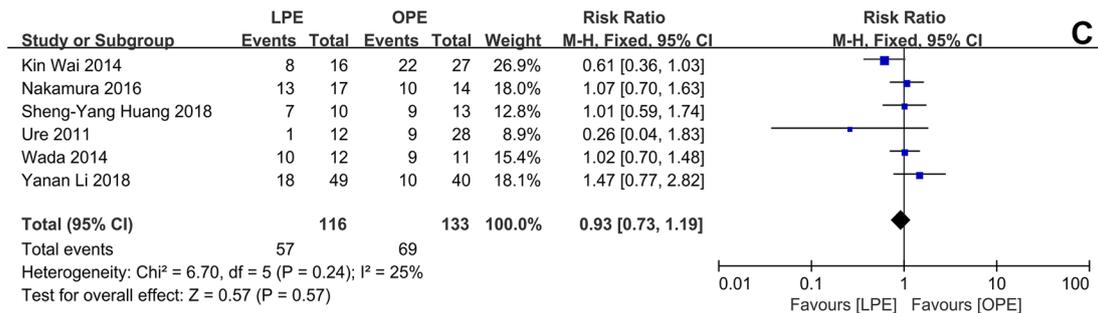
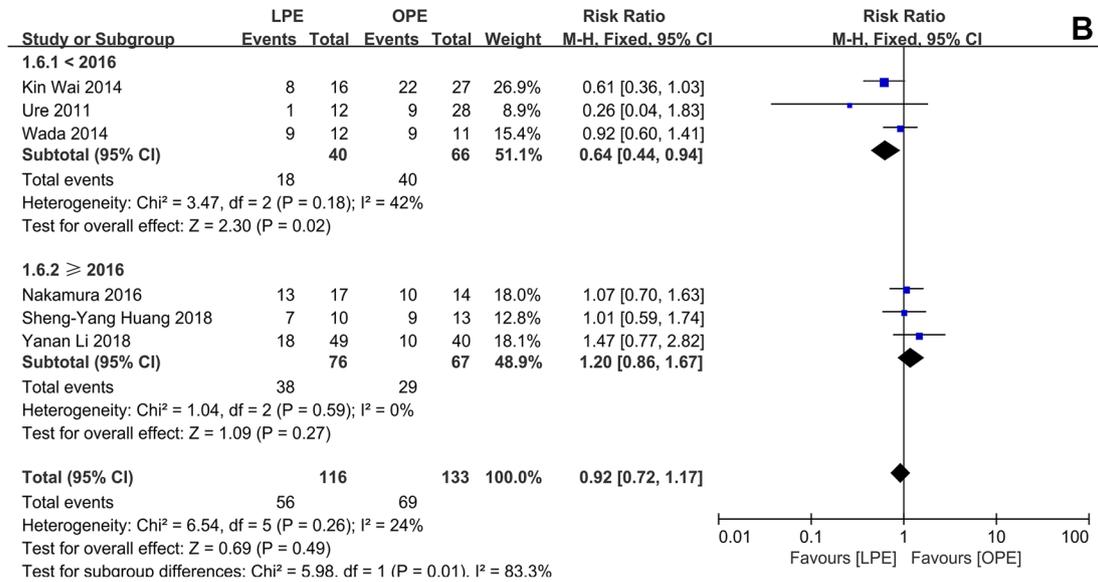
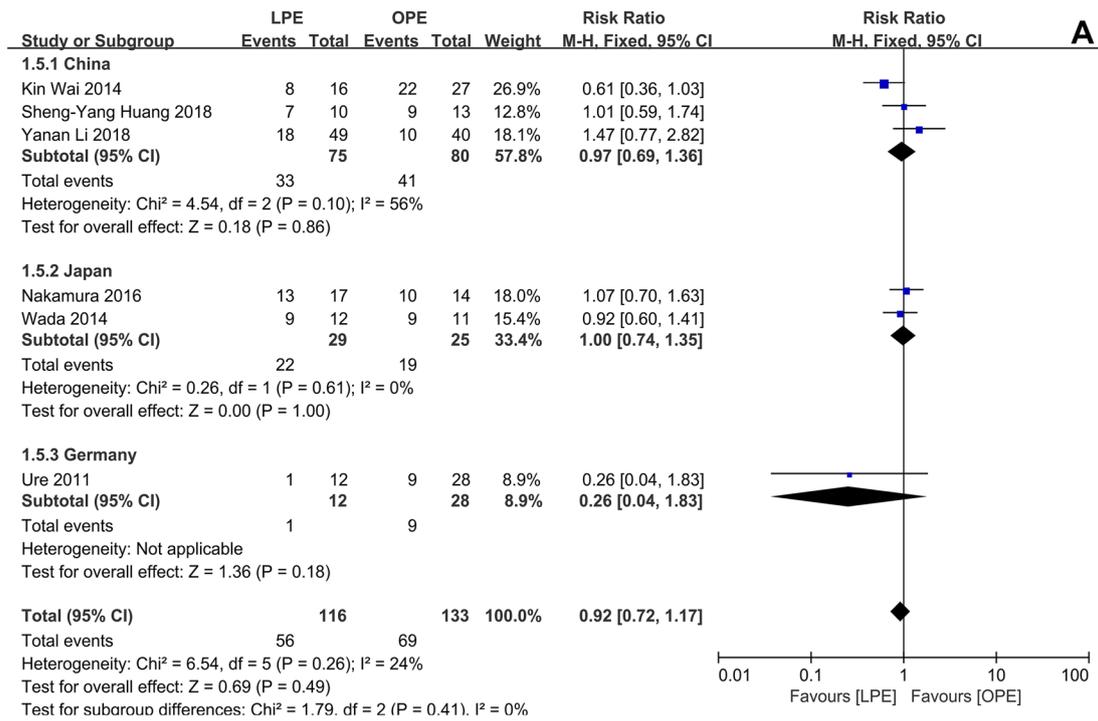
The current meta-analysis showed that there was no significant difference between patients with BA who underwent OPE and patients with BA who underwent LPE in hospital stay, intraoperative blood loss, cholangitis, early clearance of jaundice, or two-year survival with the native liver. Compared with LPE, the operative time was shorter in OPE.

BA is a fibro-obliterative disorder that progresses to end-stage liver disease [27]. KPE is considered the standard initial therapy for BA [7], although the majority of patients will eventually receive liver transplantation. Previously, several studies have reported that compared with OPE, LPE had a higher postoperative complication rate and poorer outcome [14, 22, 28, 29]. Until now, OPE has been regarded as the standard therapy for BA [30]. However, recent studies have shown that the efficacy of LPE was as good as that of OPE [21, 23, 25]. Interestingly, in the present meta-analysis, the data revealed that the efficacy of LPE was not significantly different from that of OPE. Moreover, LPE has many advantages, including less tissue injury, no mobilization of the liver, much better visualization of the porta hepatis, smaller wounds, improved cosmesis, decreased pain, and fewer abdominal adhesions [11, 31]. Murase et al. [26] reported that the adhesion around the porta hepatis after OPE was more serious than that after LPE, which resulted in a longer time of hepatectomy through liver transplantation in patients who had undergone OPE than in patients who had undergone LPE.

The disadvantage of LPE was the long operative time related to the instruments used and a steep learning curve [12, 32]. In addition, Ure et al. [14] reported that pneumoperitoneum could cause liver cell damage and result in poor prognosis in the LPE group. In this regard, Nakamura et al. [16] suggested that the main cause was a high flow rate,

which was detrimental for patients with impaired liver function. The authors recommended a 0.5–1.0 L/min flow rate to maintain the pneumoperitoneum pressure at 8 mmHg.

Huang [21] proposed that the poor outcome in studies reporting LPE may be due to the steep learning curve for the complicated laparoscopic biliary procedures and the inconsistency of treatment protocols. The former includes optimal port placement, full exposure of the porta hepatis, hemostasis, and portoenterostomy. The latter includes the dissection of the hepatic hilar, the diversity of postoperative steroid therapy, and the use of adjuvant antibiotics. Remarkably, improved outcomes have been reported in studies with large patient volumes and laparoscopic-modified portoenterostomy techniques, including shallow dissection of the biliary remnant and shallow but deep sutures for the anastomosis [16, 19, 21, 25, 33]. To decrease the training time and overcome the bottleneck of the learning curve, Li et al. [34] presented some improvements: (1) clearly exposing the operation site by suspending the liver edge and ligamentum teres hepatis; (2) using a 3-mm laparoscopic electric hook to dissect along the lower edge of the fibrous tissue of porta hepatis without cauterizing the right and left sides of the fibrous tissue; (3) using laparoscopic scissors to cut the fibrous tissue along the visceral surface of the liver without leaving too much tissue or damaging the liver parenchyma; (4) using a high-resolution laparoscope to obtain a clear image of the fibrous tissue; and (5) using teamwork, which is one of the most important recommendations. Continuous practice and rewatching operation videos are helpful to train surgeons and improve the skill and speed of LPE. As highlighted in our previous report [33], animal experiments were able to help surgeons shorten the learning curve of LPE. Training devices, such as laparoscopic boxes and virtual reality laparoscopic simulators, can also help surgeons improve their proficiency. In addition, it may be very important to establish standardized surgical procedures, strengthen academic exchanges, and promote multicenter research. In our meta-analysis, subgroup analyses were used to assess potential heterogeneity, including the contributing factors of country and year of publication. The results showed that in terms of two-year survival with the native liver, the outcome in the studies published before 2016 was inferior in the LPE group. However, there was no significant difference between the two groups in the studies published after 2016. Interestingly, the outcome of early clearance of jaundice in the LPE group was much better than that in the OPE group in the studies published after 2016. Perhaps with the modification of techniques, the outcome of LPE has improved. Several studies [21, 25, 35–37] with large sample sizes have reported favorable outcomes with the laparoscopic-modified portoenterostomy technique, including shallow dissection and sutures of hepatic hilum using a ligature device for hemostasis and customized Roux limb. In our experiences [33],



◀**Fig. 4** Forest plots of two-year survival with the native liver of open portoenterostomy versus laparoscopic portoenterostomy according to **A** country; **B** year of publish; and **C** overall effect

the dissection site of the fibrous cone should be between the first bifurcation of the portal vein, and the dissection should be gradually pushed deeper until the leakage or oozing of bile-like liquid emerges on the surface of the fibrous stump. Keeping the fibrous cone intact is vital. The seams of the anastomoses should be as far as possible from the surface of the stump during the portoenterostomy. The management after the operation also determines the prognosis. The rigorous use of steroids and prophylactic antibiotic treatment for cholangitis after operation is vital to achieve better long-term results.

This meta-analysis has several limitations. One of the major limitations of this study is the lack of RCT studies. Second, the sample size of several studies is small, with a lack of rich detail in the information. Third, these studies have reported a relatively short period of follow-up evaluation. Only two-year survival with the native liver was compared in the present study.

Conclusion

In conclusion, the results of this meta-analysis indicate that LPE is a feasible option for the treatment of patients with BA. Future prospective, randomized, and controlled trials are needed to extend our conclusions toward improving the care of patients with BA.

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Compliance with ethical standards

Disclosures Yanan Li, Chuan Wang, Jinran Gan, Zhicheng Xu, Yiyang Zhao, and Yi Ji have no conflicts of interest or financial ties to disclose.

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