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Review Article

Comparison of liver transplantation outcomes in biliary atresia patients with and without prior portoenterostomy: A meta-analysis

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ABSTRACT

Background: Portoenterostomy is currently the standard first procedure for biliary atresia, and liver transplantation is reserved as a complementary therapy for those with late diagnosis, rapid hepatic decompensation, or failed portoenterostomy. Many previous publications have analysed the impact of prior portoenterostomy on the clinical outcomes of liver transplantation and the conclusions are discordant.
Methods: PubMed and EMBASE were systematically searched for relevant articles, and studies published in Chinese were searched in the Wanfang China Medical Collections. The references of the retrieved studies were also reviewed. In addition, Google scholar was used to further confirm the literature search.
Results: Fourteen studies were included comprising 1560 patients, of which 1190 (76.3%) received portoenterostomy. Meta-analysis did not reveal significant differences in either patient survival rate (odds ratio, 0.82) or graft survival rate (odds ratio, 1.11) over a 5-year follow-up between biliary atresia patients with and without a portoenterostomy procedure prior to liver transplantation; patients who received a prior portoenterostomy procedure had a higher risk of postoperative infection (odds ratio, 2.02).
Conclusion: Accumulated literature suggested that a prior portoenterostomy did not adversely affect outcomes of liver transplantation in children with biliary atresia.

1. Introduction

Biliary atresia (BA), a liver disease with unknown aetiology, is the most common indication for paediatric liver transplantation [1]. Early diagnosis and a timely portoenterostomy (PE) procedure, especially Kasai's PE, are important for a favourable prognosis with the native liver. However, a minority of patients in whom inadequate management leads to an excessively late diagnosis or advanced cirrhosis may be considered for direct liver transplantation.

Studies suggest that PE may achieve immediate biliary drainage among up to 60% of BA patients [2,3]. The long-term outcome of PE has been previously studied and the findings indicate that most of the cases still progress to end-stage liver cirrhosis [4]. Concern has been raised for decades that the prior PE procedure may increase the likelihood of complications for the subsequent liver transplantation [5–7]. For instance, PE may cause abdominal adhesion and increase the difficulty of the recipient's hepatectomy. Also, some patients suffer from recurring cholangitis after PE, which may increase the risk of bacteremia, sepsis, chronic pylephlebitis, and portal vein thrombosis [8].

To evaluate whether a prior PE procedure affects liver transplantation outcomes, we systematically reviewed the literature and performed a meta-analysis. The information may be useful in the informed consent setting, both for the PE itself and for liver transplantation. In addition, the information contributes to the academic debate on the management of BA.

2. Materials and methods

2.1. Literature searches

PubMed (1966–April 2015) and EMBASE (1980–April 2015) were systematically searched by using terms "transplantation"

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and "hepatic or liver" and "biliary atresia" and "portoenterostomy;" studies published in Chinese were searched in the Wanfang China Medical Collections (1990–December 2014) by using the corresponding Chinese terms. Also, the references of the retrieved studies were reviewed. In addition, Google scholar was used to further confirm the literature search. No restriction was made for publication year.

2.2. Study selection and definitions

This systematic review and meta-analysis were conducted based on a pre-specified protocol (the PRISMA Statement) [9]. The titles and abstracts of all relevant studies were scanned independently by two authors (PW and PX). Publications including reviews, case reports, and letters to the editor were excluded. Studies were included if they met the following criteria: (1) the clinical studies involved BA patients with liver transplantation; (2) patients with or without prior PE therapy were included; and (3) patient survival rate, graft survival rate, or incidence of complications including postoperative infection and reoperation were reported or these data can be derived from the presented results.

PE is defined as the original Kasai hepatic PE or any of its variations [10], including any specialized PE such as hepaticoduodenostomy [11] and biliary appendicoduodenostomy [12]. Reoperation after liver transplantation includes re-anastomoses or interventional treatment for vascular thrombosis or stenosis, intra-abdominal haemorrhage and other conditions requiring abdominal exploration within one year after the transplantation. Infection is defined as local or systemic inflammation caused by bacteria, fungi, or viruses.

2.3. Data extraction

Two authors (PW and PX) independently reviewed the literature and extracted the following data from the included studies: first author, publication year, country where the study was conducted, number and age of participants, the ratio of boys to girls, type of liver transplantation, pediatric end-stage liver disease (PELD) score prior to transplantation, operation time, amount of blood loss during operation, rate of reoperation and postoperative infection, and 1- and/or 5-year patient and graft survival rates after the transplantation.

If the required data were not available in the primary article, we contacted the authors and requested *de novo* data. Disagreement on data extraction was resolved by group discussion.

2.4. Statistical analysis

All analyses were performed using STATA statistical software (Version 13.0, STATA Corp, College Station, Texas, US). All statistical tests were two-sided, and a P-value ≤ 0.05 was considered statistically significant, if not otherwise specified.

The 1-year or 5-year survival rate after transplantation was compared between the BA patients with and without prior PE therapy. The odds ratio (OR) and 95% confidence interval (CI) were calculated based on the presented information on outcome of interest, including patient survival rate, graft survival rate, overall complication, and its two main components (i.e., infection and reoperation) by comparing the two groups with and without prior PE therapy. The pooled ORs and 95% CIs were estimated by using a fixed-effects model if the test for heterogeneity across studies was not significant or by a random-effects model if heterogeneity existed. Cochran's Q test was used to determine heterogeneity, and I^2 was computed to assess the degree of inconsistency across studies. Egger's regression asymmetry test was performed to detect any potential publication bias in this meta-analysis. A P-value ≤ 0.10 was considered statistically heterogeneous. In addition, the major complications (i.e., postoperative infection and reoperation) were compared between the two groups with and without prior PE therapy using an approach similar to that used to examine survival rates. Moreover, weighted mean differences (WMDs) and 95% CIs were computed to compare the differences in a few factors (i.e., age, PELD score, transplantation operation time and blood loss during the operation) that may affect the clinical outcomes of liver transplantation between the two groups.

In addition, we stratified the data by study region (e.g., USA vs. non-USA) based on the available data. Sensitivity analyses were conducted to evaluate: (1) if the results were robust to using a fixed- or random-effects model; and (2) if the pooled results were driven by any single study.

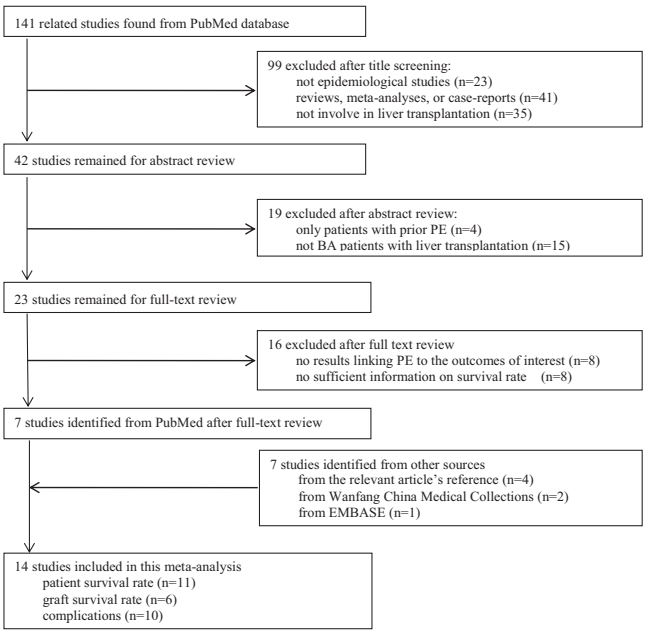

Fig. 1. Flow chart of study screening and selection. BA, biliary atresia; PE, portoenterostomy.

3. Results

3.1. Flow of the included studies

Our literature search resulted in an initial set of 141 publications from the PubMed database. Of these, 118 articles were excluded during title/abstract review due to at least one of the following reasons: (1) they were not epidemiological studies, e.g., studies on mechanism or introduction to PE surgery ($n = 23$); (2) not original studies, e.g., reviews, meta-analyses or case reports ($n = 41$); (3) did not involve liver transplantation ($n = 35$); (4) only included patients with prior PE ($n = 4$); or (5) not BA patients with liver transplantation ($n = 15$). Among the remaining 23 studies, 16 were further excluded after full text screening because of: (1) no results relating prior PE to the outcomes of interest; or (2) insufficient information to retrieve survival rate for either the treatment or control group. Furthermore, seven additional studies were found in other resources, including 4 from the references of the relevant articles [13–16], 2 from the China Medical Collections (Wanfang), and 1 from EMBASE (Fig. 1). Finally, a total of 14 clinical studies were included in the meta-analysis [8,11–23].

Of the 14 included studies (Table 1), 12 were published in English and 2 in Chinese [18,21]. The study populations were from the USA ($n = 6$), China ($n = 3$), Taiwan ($n = 1$), Canada ($n = 1$), France

Table 1
Characteristics of the included studies of 1213 biliary atresia patients who underwent liver transplantation, according to prior portoenterostomy status (yes vs. no).

Source (first-author, year, study region)	PE	*N*	Age (months)	LT type (LD:DD)	PELD Score	LT operation time (min)	Blood loss during surgery
Millis, 1988, USA	Yes	28	32	0:28	–	–	5.6 (0.44–33) Vol
	No	8	20	0:8	–	–	4.1 (1.2–13) Vol
Wood, 1990, USA	Yes	46	–	–	–	–	–
	No	2	–	–	–	–	–
Meister, 1993, USA	Yes	32	–	0:32	–	–	–
	No	7	–	0:7	–	–	–
Sandler, 1996, Canada	Yes	49	27.6 ± 4.8	0:49	–	593.9 ± 29.3	–
	No	8	8.4 ± 2.4	0:8		476.8 ± 53.3	–
Chardot, 1999, France	Yes	208	–	–	–	–	–
	No	17	–	–	–	–	–
Diem, 2003, Belgium	Yes	285	–	–	–	–	–
	No	43	–	–	–	–	–
Visser, 2004, USA	Yes	53	29 ± 49	24:29	9.7 ± 9.2	395 ± 106	1400 ± 2900 mL
	No	13	12 ± 8	7:6	13.7 ± 6.4	400 ± 110	500 ± 200 mL
Cowles, 2008, USA	Yes	61	8.6	–	14.0	–	–
	No	10	7.9	–	15.5	–	–
Tiao, 2008, Taiwan	Yes	60	66.0 ± 75.6	0:60	–	–	–
	No	46	19.2 ± 13.2	0:46	–	–	–
Guo, 2010, China	Yes	9	10.2 ± 4.3	9:0	12.3 ± 6.8	460 ± 75	260 (150–900) mL
	No	13	6.8 ± 3.1	13:0	19.8 ± 8.5	513 ± 118	155 (50–650) mL
Alexopoulos, 2012, USA	Yes	112	20.3 ± 31.1	–	8.9 ± 9.1	396 ± 108	–
	No	22	11.1 ± 4.9	–	13.6 ± 6	408 ± 120	–
Wang, 2013, China	Yes	10	8.4 ± 3.4	10:0	11.9 ± 9.2	534 ± 150	197 ± 132 mL
	No	18	7 ± 4	18:0	16 ± 7.4	558 ± 252	208 ± 148 mL
Sui, 2014, China	Yes	28	12.5 (6.6–82.5)	28:0	12.3 ± 10.9	521.5 ± 65.6	351.8 ± 208.8 mL
	No	25	7.5 (5.8–43)	25:0	22.1 ± 19	573.2 ± 98.5	277.6 ± 133.9 mL
Neto, 2015, Brazil	Yes	209	23 ± 28.3	189:12	15.5 ± 8.6	–	–
	No	138	10.8 ± 5	120:10	19.2 ± 7.6	–	–

Continuous variables are expressed as mean ± standard deviation.
PE, portoenterostomy; LT, liver transplantation; LD, living donor graft; DD, deceased donor graft; PELD, pediatric end-stage liver disease.

(*n* = 1), Belgium (*n* = 1), and Brazil (*n* = 1). When the required data were not available in the primary article, we contacted the corresponding authors for the missing information. Unfortunately, these attempts were unsuccessful.

A total of 1560 BA patients were included in this meta-analysis. Among them, 1190 patients received PE (76.3%). According to the available data, 45.8% were boys, and the average follow-up time was 48 months (range, 1–144 months). Approximately 44.7% patients with PE and 31.7% patients without PE received a deceased donor graft.

Factors affecting the clinical outcomes of liver transplantation including age, PELD score, transplantation operation time, and blood loss during the operation were collected and the WMDs between patients with and without prior PE are summarized in Table 2. Compared to PE patients, those who did not receive PE prior to liver transplantation were younger in age (12.2 vs. 27 months, $P < 0.01$) and had a higher PELD score (18.4 vs. 12.6, $P < 0.01$). Patients with a prior PE had a longer transplantation operation time, though statistically it did not reach significance ($P = 0.06$), while there was no difference in blood loss during operation ($P = 0.09$) between these two groups.

3.2. Measures of clinical outcome after liver transplantation

3.2.1. Patient survival rate

Eight studies reported 1-year patient survival rate [8,15–17,19–21,23] and 6 studies presented 5-year patient survival rate [8,13–15,20,22]. The pooled OR was 0.73 (95% CI: 0.44–1.20) for 1-year patient survival rate and 0.82 (95% CI: 0.54–1.25) for 5-year patient survival rate (Fig. 2). Heterogeneity was not found ($I^2 = 0\%$ and $P = 0.80$ for 1-year survival rate; and $I^2 = 0\%$ and $P = 0.95$ for 5-year survival rate). No evidence of publication bias was found (Egger's test: $P = 0.79$ for 1-year survival rate; and $P = 0.76$ for 5-year survival rate). The associations were not appreciably modified by the study region (USA vs. non-USA).

Table 2
Weighted[a] mean differences in clinical variables of biliary atresia patients with and without portoenterostomy before liver transplantation.

Factors	No. of included studies	Heterogeneity test	WMD (95% CI)	Model	*P* value
Age	8	$I^2 = 95\%$, $P < 0.01$	10.92 (3.79 to 18.05)	Random-effects	<0.01
PELD score	6	$I^2 = 0\%$, $P = 0.68$	−4.26 (−5.59 to −2.92)	Fixed-effects	<0.01
LT operation time	6	$I^2 = 88\%$, $P < 0.01$	−1.16 (−70.8 to 68.48)	Random-effects	0.06
Blood loss during operation	5	$I^2 = 42\%$, $P = 0.14$	56.25 (−8.87 to 121.38)	Fixed-effects	0.09

[a] Weighted by meta-analysis.
PELD, pediatric end-stage liver disease; LT, liver transplantation; WMD, weighted mean difference; CI, confidence interval.

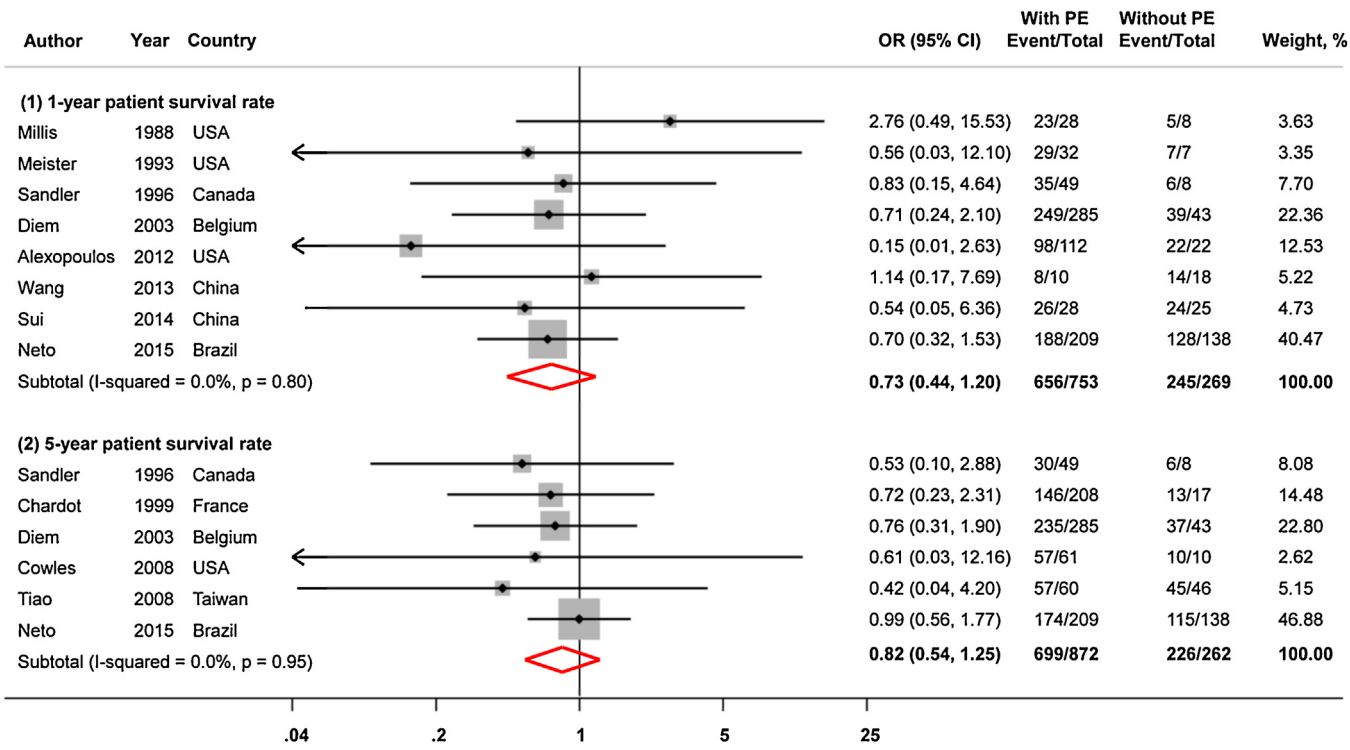

Fig. 2. Odds ratios and 95% confidence intervals of patient survival rate (1-year and 5-year) after liver transplantation in biliary atresia patients with and without prior portoenterostomy. The overall estimate is from a fixed-effects model. The dots indicate the point estimates and the horizontal lines represent 95% confidence intervals. The size of the shaded square is proportional to the weight of each study. PE, portoenterostomy; OR, odds ratio; CI, confidence interval.

3.3. Graft survival rate

Five studies reported 1-year graft survival rate [8,15,17,20,23]. The pooled OR was 0.85 (95% CI: 0.54–1.34) without significant heterogeneity (I^2 = 0%; P = 0.47). No publication bias was found (Egger's test: P = 0.60).

Three studies reported 5-year graft survival rate [14,15,20]. The pooled OR was 1.11 (95% CI: 0.74–1.67) with no significant heterogeneity (I^2 = 29.8%; P = 0.24) (Fig. 3). No evidence of publication bias was detected (Egger's test: P = 0.52).

3.4. Complications

Reoperation and postoperative infection were the two main complications considered in the analysis. The pooled OR for the overall complications was 1.24 (95% CI: 0.91–1.70). The heterogeneity was not significant (I^2 = 29.9%; P = 0.14) (Fig. 4). The observed association was not appreciably modified by the study region (USA vs. non-USA; data not shown).

Each complication was also examined separately: among 6 studies with data available on postoperative infection rate [16–19,21,23], the pooled OR was 2.02 (95% CI: 1.14–3.56) without significant heterogeneity (I^2 = 0.0%; P = 0.78). Eight studies reported reoperation rate after liver transplantation [8,11,12,16,17,19,20,23]. The pooled OR was 1.00 (95% CI: 0.69–1.45) with no significant heterogeneity (I^2 = 39.5%; P = 0.12). No evidence of publication bias was found (Egger's test: P = 0.11 for infection; P = 0.25 for reoperation).

3.5. Sensitivity analyses

After replacing the fixed-effects model with the random-effects model for the pooled analyses, the findings were generally consistent (Supplemental Table S1). After omitting 1 study each time in the pooled analyses we found that no single study substantially influenced the pooled results in the main analyses (Supplemental Table S2).

4. Discussion

Findings from this meta-analysis suggest that a prior PE procedure may increase the risk of postoperative infection after liver transplantation, but did not affect the major clinical outcomes liver transplantation, including 1-year or 5-year patient and graft survival rates and the overall complications. Based on our results, there is no doubt about the rationality of the current consensus for sequential use of PE as a first step for BA followed by liver transplantation.

The advantage of BA patients initially receiving the PE procedure is mainly based on the fact that bile flow may be restored through PE, while patients considered for transplantation suffer high surgical risk, and the long term use of immunosuppressive drugs may increase the risk of infection and malignancy.

The presence of adhesions and other anatomic alterations caused by prior abdominal surgery for patients who subsequently undergo liver transplantation after a failed PE is the major concern of surgeons during the recipient's hepatectomy, and is thought to cause greater intraoperative blood loss, more frequent post-transplant complications, and an overall poorer survival [24,25]. Of note, this meta-analysis indicated that a prior PE procedure did not cause statistically significant longer operation time nor significantly increase blood loss during liver transplantation. There are a few possible explanations. First, the majority of liver transplantations that follow PE are performed when children are younger than 2 years of age, with coagulation function based on platelet counts and values of the international normalized ratio [17]. Second, liver transplantation was performed right after PE in some of the included studies [17,18,21,23]. Therefore epigastric adhesion

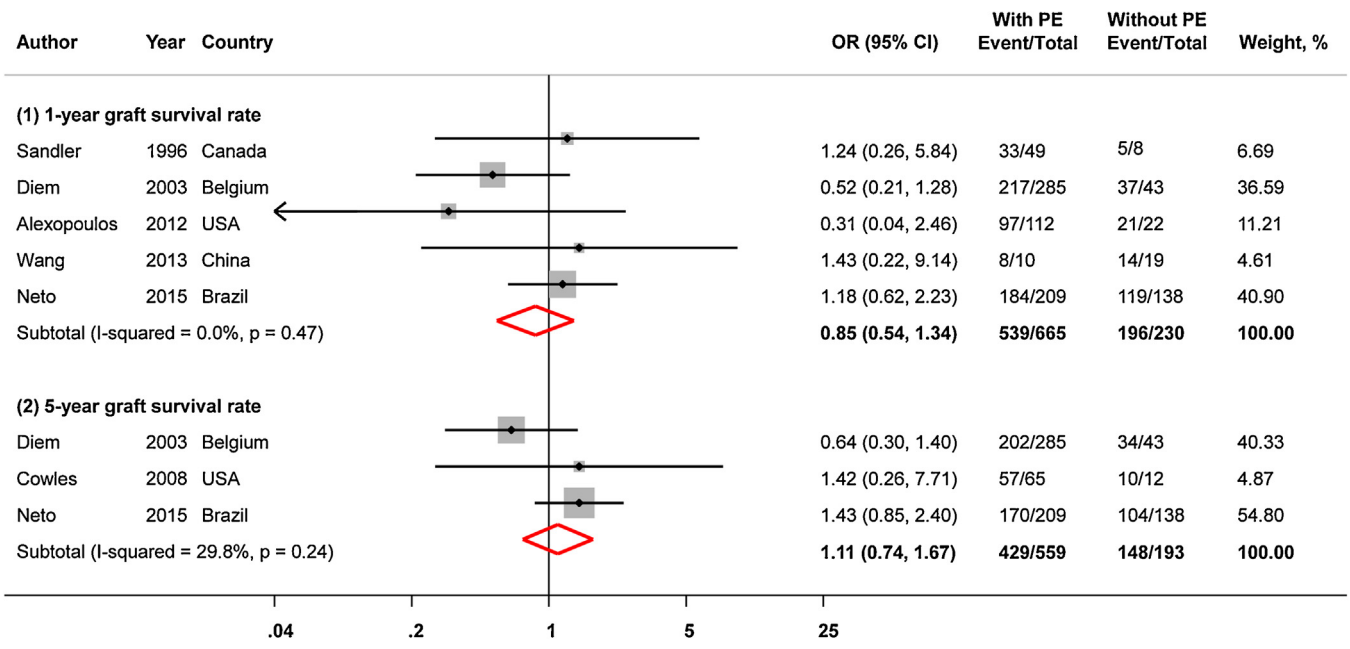

Fig. 3. Odds ratios and 95% confidence intervals of graft survival rate (1-year and 5-year) after liver transplantation in biliary atresia patients with and without prior portoenterostomy. The overall estimate is from a fixed-effects model. The dots indicate the point estimates and the horizontal lines represent 95% confidence intervals. The size of the shaded square is proportional to the weight of each study. PE, portoenterostomy; OR, odds ratio; CI, confidence interval.

might have not become a serious problem when performing liver transplantation. Third, adhesions might cause problems primarily in opening the abdomen and dissecting the hepatic hilus, ligaments, and soft tissues around the liver, not when dissecting the secondary porta hepatis.

Cholangitis is the most controversial complication after a Kasai procedure. Repeated cholangitis may cause bacteremia and sepsis as well as portal vein thrombosis [26] and is likely to increase the risk of infection following liver transplantation, and thus significantly affects transplantation outcomes [27]. Consistently, our

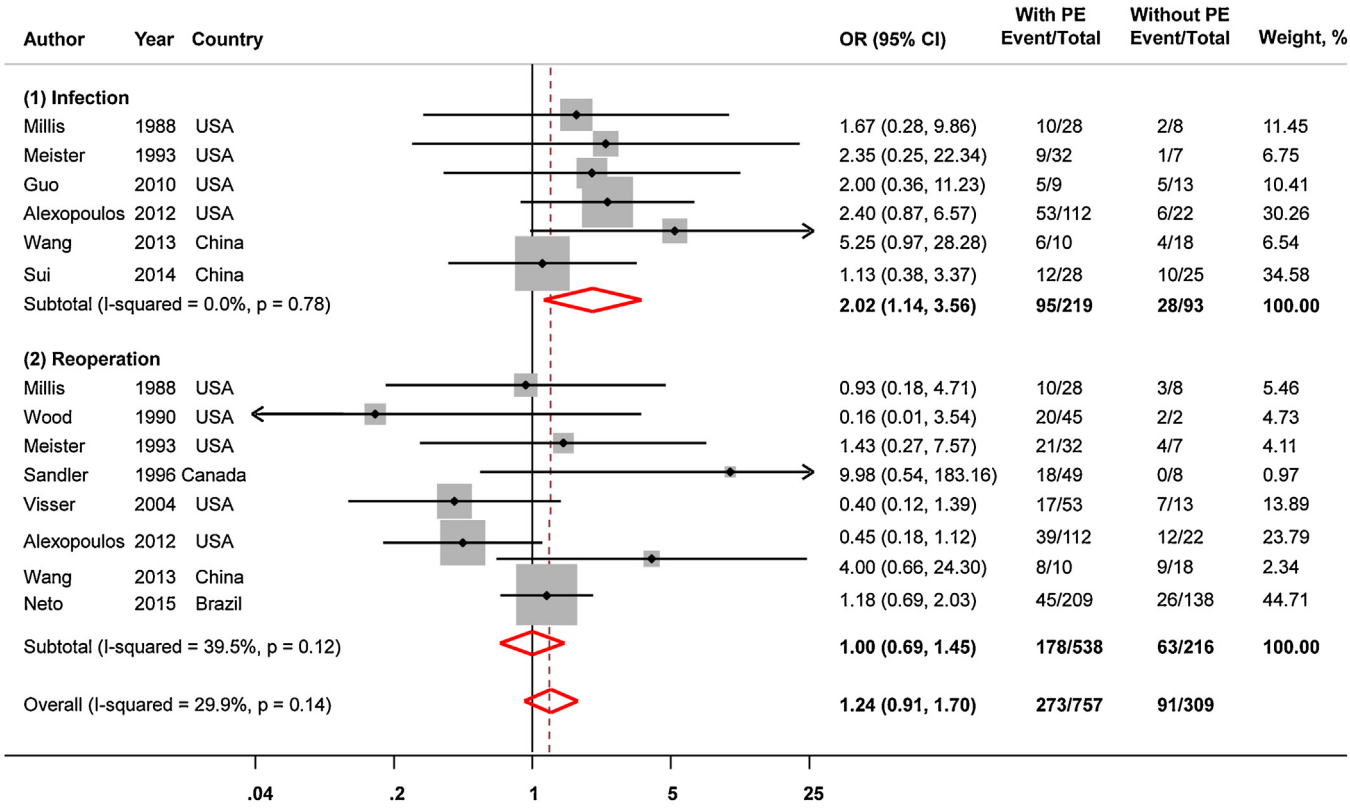

Fig. 4. Odds ratios and 95% confidence intervals of complication rates (postoperative infection and reoperation) after liver transplantation in biliary atresia patients with and without prior portoenterostomy. The overall estimate is from a fixed-effects model. The dots indicate the point estimates and the horizontal lines represent 95% confidence intervals. The size of the shaded square is proportional to the weight of each study. PE, portoenterostomy; OR, odds ratio; CI, confidence interval.

meta-analysis showed that patients who underwent PE prior to liver transplantation were more likely to have postoperative infection compared with those who did not have a PE. Nevertheless, the prior PE procedure did not significantly affect patient and graft survival rate over 5 years of follow-up. Presumably, this is due to the advancement of surgical techniques and postoperative management, which make life-threatening infection preventable and controllable.

Furthermore, two studies subdivided the patients of the PE group into early failure (those who ultimately received transplantation within the first year of life following PE) and late failure (those who need transplantation beyond the first year of life), and drew different conclusions [17,20]. Alexopoulos et al. [17] reported that early failure patients had a significantly higher incidence of post-operative infection and lower survival rates. Neto et al. [20] showed there was no difference in survival rates between early failure patients and those patients without PE, but late failure patients had a higher survival rate. Due to the limited data, a detailed analysis could not be performed, and future studies may provide more comprehensive evidence.

A few limitations need to be considered. One concern is that the priority for BA is an early diagnosis and immediate PE; the fact that children not selected for PE are in general those in whom the diagnosis was too late (and who experience more rapid hepatic decompensation) represents an intrinsic, unavoidable selection bias. Second, confounding from unknown or unmeasured factors cannot be completely excluded. Third, important factors such as liver function after PE and the interval between PE and transplantation cannot be analysed due to data deficiency. Any inherent limitation in the included studies may bias our results.

In summary, this meta-analysis shows that, though a PE procedure may increase the risk of postoperative infection, there were no significant differences between BA patients with and without a prior PE procedure in terms of patient and graft survival rates or overall complications after liver transplantation. Prior PE does not appear to adversely affect outcomes of liver transplantation, and there is no doubt that PE is the first choice procedure for biliary atresia.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2015.11.021.

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