Original Article

Effect of Kasai procedure on liver transplantation in children with biliary atresia: a systematic review and updated meta-analysis

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Contributions: (I) Conception and design: S Liu; (II) Administrative support: J Zhan; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: S Liu, Q Yang, Q Ji; (V) Data analysis and interpretation: S Liu, Z Wang, R Sun; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Kasai procedure and liver transplantation are effective ways to save the life of children with biliary atresia (BA). However, with the gradual development of liver transplantation technology, scholars have questioned the necessity of the Kasai procedure. Therefore, we conducted a meta-analysis to evaluate the effect of previous Kasai procedures on liver transplantation in children with BA.

Methods: Seven databases were searched and screened from the establishment of the database to May 3, 2023. The data in the included literature were extracted for meta-analysis to compare the differences between the Kasai group and the non-Kasai group. Finally, a publication bias test, sensitivity analysis, subgroup analysis, and systematic review were performed.

Results: A total of 26 studies were included in which 6,522 children with BA underwent liver transplantation, including 4,989 in the Kasai group. Compared with the non-Kasai group, the Kasai group had older age [standardized mean difference (SMD) =0.64; 95% confidence interval (CI): 0.46, 0.82; $P<0.001$] ($I^2=78.6\%$), heavier weight (SMD =0.41; 95% CI: 0.33, 0.48; $P<0.001$) (after sensitivity analysis, $I^2=0.0\%$), lower pediatric end-stage liver disease (PELD) (SMD =−0.41; 95% CI: −0.48, −0.35; $P<0.001$) ($I^2=20.1\%$), longer operation time (SMD =0.33; 95% CI: 0.01, 0.65; $P<0.001$) ($I^2=83.2\%$), more intraoperative blood loss (SMD =0.26; 95% CI: 0.06, 0.46; $P=0.012$) ($I^2=19.1\%$), shorter intensive care unit (ICU) stay (SMD =−0.09; 95% CI: −0.34, 0.15; $P=0.027$) ($I^2=68.6\%$) and higher incidence of intestinal perforation [odds ratio (OR) =1.96; 95% CI: 1.20, 3.18; $P=0.007$] ($I^2=7.4\%$) and biliary complications (OR =1.41; 95% CI: 1.05, 1.89; $P=0.024$) ($I^2=31.4\%$). In the "Asia" subgroup, the Kasai group was older (SMD =0.68; 95% CI: 0.52, 0.84; $P<0.001$) ($I^2=28.2\%$). In the "Cases since 2000" subgroup, there was no significant difference in operation time between the two groups ($I^2=28.5\%$). In the "Other" and the "non-Asia" subgroup, there was no significant difference in length of intensive care unit (ICU) stay between the two groups ($I^2=0.0\%$). However, there were no significant differences in other postoperative complications and prognostic indicators between the two groups.

Conclusions: For children with BA undergoing liver transplantation, although previous Kasai procedure may increase the risk of intraoperative bleeding, biliary complications, and intestinal perforation, it does not affect the main clinical outcomes, and can even delay the timing of liver transplantation and improve the preoperative status of children. Therefore, when BA children have no obvious contraindications to Kasai procedure, the sequential treatment of Kasai procedure-liver transplantation should be supported first.

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Keywords: Biliary atresia (BA); Kasai procedure; liver transplantation; meta-analysis; review

Submitted Oct 11, 2023. Accepted for publication Dec 10, 2023. Published online Jan 24, 2024.
doi: 10.21037/tp-23-504
View this article at: https://dx.doi.org/10.21037/tp-23-504

Introduction

Biliary atresia (BA) is a progressive, inflammatory, and fibrosclerosing disease of the bile ducts. It occurs predominantly during the neonatal period, and surgical treatment is the only effective way to save lives. Without treatment, most patients will die in the first two years of life (1). The current surgical methods include Kasai procedure and liver transplantation. According to various countries, the 5-year survival rate of the native liver after the Kasai procedure in children with BA is about 50% (2-4). Intestinal adhesions caused by previous Kasai procedures are a major concern for surgeons during liver resection in recipients (5). With the development of pediatric liver transplantation, the efficacy of BA liver transplantation has been significantly improved, and scholars have begun to rethink the role of Kasai procedure in the treatment of BA. However, liver transplantation is also not perfect, and long-term use of immunosuppressive drugs after liver transplantation may increase the risk of infection and malignant tumors. Therefore, we systematically reviewed the literature and performed a meta-analysis to evaluate the effect of previous Kasai procedure on liver transplantation in children with BA. This may contribute to the selection of clinical treatment options and the resolution of academic controversies on this issue. The researchers followed the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-504/rc) (6).

Highlight box

Key findings
- For liver transplantation in children with biliary atresia (BA), the previous Kasai procedure may increase the risk of intraoperative bleeding, biliary complications, and intestinal perforation, but it does not affect the main clinical outcomes.
- Previous Kasai procedure can delay the timing of liver transplantation and improve the preoperative condition of patients.

What is known and what is new?
- Previous Kasai procedure did not influence the primary outcome of liver transplantation.
- Compared with previous studies, we included more studies (n=26), collected more comprehensive data, used more appropriate analysis methods, and reached slightly different conclusions.

What is the implication, and what should change now?
- It is recommended that the sequential treatment of the Kasai procedure-liver transplantation is the first choice for BA children in the absence of contraindications to the Kasai procedure, and the Kasai procedure should be standardized.

Methods

The study followed a protocol registered with the international review registration platform PROSPERO (International Prospective Register of Systematic Reviews) with PROSPERO ID: CRD42023423232.

Search strategy

PubMed, Embase, Web of Science, Cochrane, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM), and Wanfang Database were searched from the establishment of the database to May 3, 2023. The MeSH keywords were "Biliary Atresia", "Portoenterostomy, Hepatic" and "Liver Transplantation", and the corresponding free words were searched. We used the Boolean operator "OR" to connect the subject words with the free words to extend the search criteria, and then the individual subject words were connected through the Boolean operator "AND" to exact the search range. The search strategy for the seven databases is available at https://cdn.amegroups.cn/static/public/TP-23-504-1.docx. There were no restrictions on the language and publication status of the papers.

Literature searches

The inclusion and exclusion criteria were prespecified according to PRISMA, and the PICOS approach was used to define study eligibility. Studies selected in our meta-analysis must meet all the following inclusion criteria: Inclusion criteria: (I) clinical studies involving BA patients undergoing liver transplantation. (II) Patients with or without previous Kasai procedure were included. (III) Any one of these indicators was reported: age at surgery, weight at surgery, pediatric end-stage liver disease (PELD) score, operation time, intraoperative blood loss, intraoperative blood transfusion, length of hospital stay, length of intensive care unit (ICU) stay, infection, reoperation, retransplantation, hepatic artery complications, portal vein complications, hepatic vein complications, biliary complications, rejection, intestinal perforation, intestinal obstruction, bleeding, lymphatic fistula, survival of patients and grafts or other data available from the article. (IV) If there were studies with duplicate cases from the same center, the studies with larger number of cases, more recent publications, and complete data were preferentially included. Meanwhile, the criteria used to exclude studies were as follows: (I) lack of necessary information or obvious errors in the data. (II) Case reports, expert consensus, conference abstracts with no valid information, clinical trials, comments, questions and reflections, guidelines, reviews, letters, meta and systematic reviews, and proposals. (III) No comparisons were made between Kasai and non-Kasai groups. (IV) Non-BA or combined with other related diseases. (V) Non-human studies. (VI) Repeated data.

Study selection and definitions

All authors independently removed duplicate entries from the seven databases. Subsequently, each author independently screened the titles and abstracts of the retrieved results for relevance. Finally, the full text of the remaining results was assessed separately by two authors according to prespecified criteria, with discrepancies resolved by a third author. The final list of included articles was determined by careful discussion among the authors.

Data extraction

According to the inclusion criteria, all data were recorded independently by three authors, and discrepancies were resolved by discussion with the research team (raw data are available at https://cdn.amegroups.cn/static/public/TP-23-504-1.docx). A self-designed extraction table was used to extract the following information from the included literature:

(I) Literature characteristics (first author's name, publication year, country).
(II) Baseline data of previous Kasai group and non-Kasai group (number, gender, liver source, study type, follow-up time).
(III) Preoperative indicators of the two groups (age at surgery, weight at surgery, PELD score).
(IV) Perioperative data of the two groups (operation time, intraoperative blood loss, intraoperative blood transfusion, length of hospital stay, length of ICU stay).
(V) Postoperative indicators of the two groups (infection, reoperation, retransplantation, hepatic artery complications, hepatic vein complications, portal vein complications, biliary complications, rejection, lymphatic fistula, bleeding, intestinal perforation, intestinal obstruction).
(VI) Survival data of patients and grafts in the two groups.

Validity assessment

The quality of the included studies was independently evaluated by two authors using the Newcastle-Ottawa Quality Assessment Scale. The checklist covered essential items on the quality of the included studies, including (I) patient selection. (II) Comparability of study groups. (III) Outcome assessment. Each item was assigned a score of one for meeting the criteria, and zero for not meeting the criteria or being unclear whether the criteria were met. Then a total score was calculated for each study, a score greater than five indicated a high-quality study. Discrepancies needed to be resolved by the third author.

Statistical analysis

Statistical analyses were performed with Review Manager 5.4 (Cochrane Collaboration, Oxford, UK) and STATA 16.0 (StataCorp LP, College Station, TX, USA). An odds ratio (OR) with a 95% confidence interval (CI) was used to compare binary variables. The standardized mean difference (SMD) and 95% CI were calculated for continuous outcomes. For all meta-analyses, the Cochrane Q P value and I^2 statistic were applied to check heterogeneity. When $P<0.05$ or $I^2>50\%$, there was a significant heterogeneity, a random-effect model was used to merge the results. Otherwise, a fixed-effect model was used. $P<0.05$ was considered statistically significant. Egger's test and funnel plot were used to assess publication bias, and $P<0.05$ was considered as the existence of publication bias. Sensitivity analysis ("leave-one-out" method) and subgroup analysis were used to find the sources of heterogeneity. The method

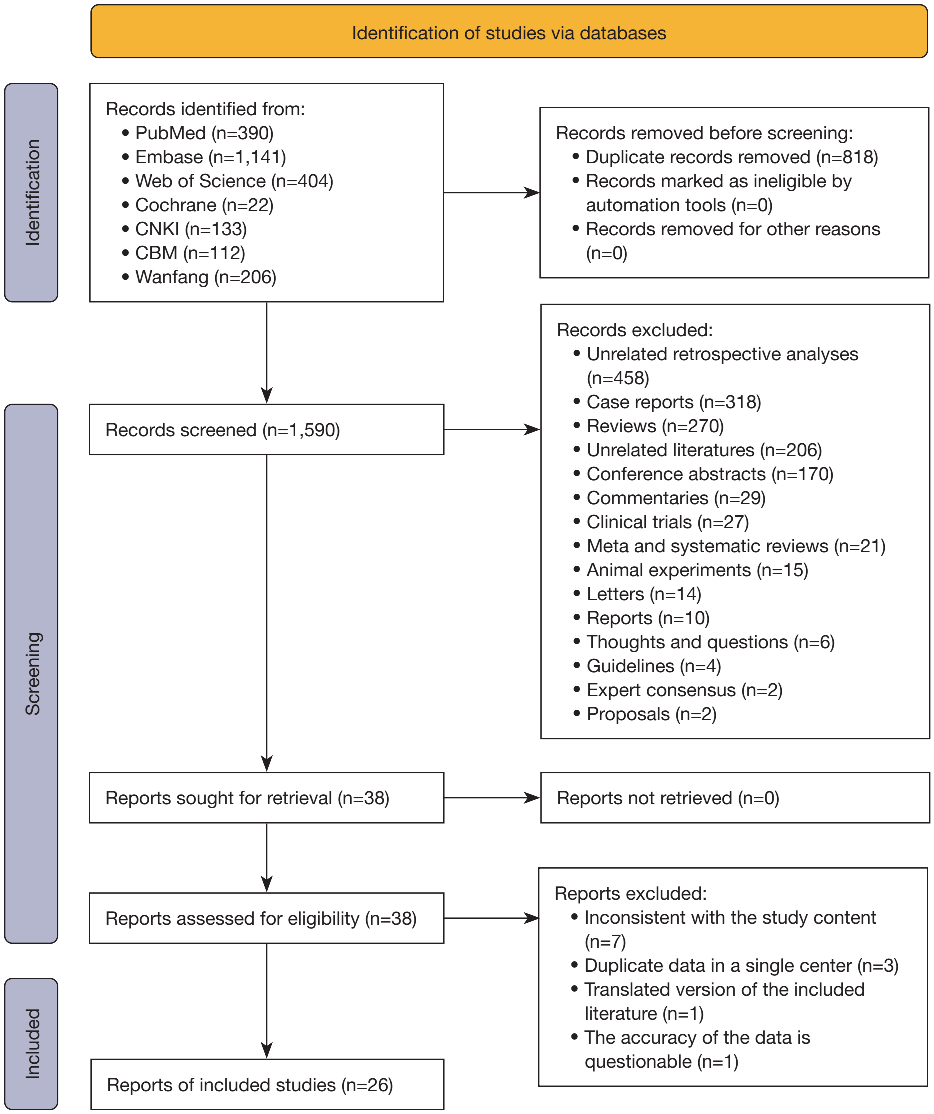

Figure 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases only. CNKI, China National Knowledge Infrastructure; CBM, China Biology Medicine.

of combining the mean and standard deviation of two or more groups of data can be referred to the study of Higgins *et al.* (7). In contrast, the method of transforming the interquartile range into the mean and standard deviation can be referred to the study of Shi *et al.* (8) and Wan *et al.* (9).

Results

Search process

The literature screening flow chart is shown in *Figure 1*. Firstly, the first step identified 2,408 articles by database search, of which 818 duplicate articles existed. In the second step, we removed 1,552 articles based on reading the title and abstract of the articles, leaving only 38 articles. In the third step, we conducted a close reading of the full text of 38 articles and removed 12 of them. In the fourth step, the remaining 26 studies were included, and subsequent data extraction and meta-analysis were performed. Among 26 studies, five studies (10-14) were published before 2000, and 21 studies (15-35) were published after 2000.

Quality assessment of studies included in the meta-analysis

The quality of the 26 included studies was evaluated based on the Newcastle-Ottawa quality assessment scale (Table S1). Four studies had a score of nine, six studies had a score of eight, 12 studies had a score of seven, and four studies had a score of six.

Study baseline data

The 26 included studies were all retrospective studies, 22 studies were published in English and four studies were published in Chinese (*Table 1*). Among them, the study population included China (n=10), USA (n=8), Belgium (n=2), India (n=2), Canada (n=1), France (n=1), Turkey (n=1), Brazil (n=1). A total of 6,522 children with BA were included in the meta-analysis, and 4,989 of them had undergone the Kasai procedure. In the studies with gender information, boys accounted for 42.8% (1,988/4,643) and girls accounted for 57.2% (2,655/4,643). Among the studies with available liver source information, 64.8% (1,283/1,980) received living donor (LD) liver and 35.2% (697/1,980) received deceased donor (DD) liver. Table S2 provides data summary information on the indications for transplantation in children from each study.

Preoperative indicators

There was large heterogeneity in the age at surgery between the 17 studies (I^2=78.6%, P<0.001), so the random effect model was used. The results of the meta-analysis showed that the age at surgery in the Kasai group was older, and the difference was statistically significant (SMD =0.64; 95% CI: 0.46, 0.82; P<0.001) (*Figure 2A*).

There was large heterogeneity in the weight at surgery between the 13 studies (I^2=78.6%, P<0.001), so the random effect model was used. The results of the meta-analysis showed that the weight at surgery of the Kasai group was heavier. The difference was statistically significant (SMD =0.58; 95% CI: 0.38, 0.79; P<0.001) (*Figure 2B*).

There was no significant heterogeneity in the PELD score between the 14 studies (I^2=20.1%, P=0.235), so the fixed effect model was used. The results of the meta-analysis showed that the PELD score of the Kasai group was lower, and the difference was statistically significant (SMD =−0.41; 95% CI: −0.48, −0.35; P<0.001) (*Figure 2C*).

Perioperative indicators

There was large heterogeneity in the operation time between the 12 studies (I^2=83.2%, P<0.001), so the random effect model was used. The results of the meta-analysis showed that the operation time of the Kasai group was longer, and the difference was statistically significant (SMD =0.33; 95% CI: 0.01, 0.65; P<0.001) (*Figure 3A*).

There was no significant heterogeneity in intraoperative blood loss between the seven studies (I^2=19.1%, P=0.284), so the fixed effect model was used. The results of the meta-analysis showed that the Kasai group had more intraoperative blood loss, and the difference was statistically significant (SMD =0.26; 95% CI: 0.06, 0.46; P=0.012) (*Figure 3B*).

There was large heterogeneity in the length of ICU stay between the six studies (I^2=68.6%, P=0.007), so the random effects model was used. The results of the meta-analysis showed that the length of ICU stay of the Kasai group was shorter. The difference was statistically significant (SMD =−0.09; 95% CI: −0.34, 0.15; P=0.027) (*Figure 3C*).

There was no significant heterogeneity in the length of hospital stay between the nine studies (I^2=40.8%, P=0.095), so a fixed effect model was used. The results of the meta-analysis showed that there was no significant difference in the length of hospital stay between the two groups (SMD =−0.03, 95% CI: −0.13, 0.07; P=0.514) (*Figure 3D*).

There was large heterogeneity in the intraoperative blood transfusion between the four studies (I^2=71.9%, P=0.014). The results of the meta-analysis showed that there was no significant difference in intraoperative blood transfusion between the two groups (SMD =0.12; 95% CI: −0.30, 0.53; P=0.536) (*Figure 3E*).

Postoperative indicators

The results of the meta-analysis showed that the incidence of intestinal perforation and biliary complications in the Kasai group was higher than that in the non-Kasai group, and the differences were statistically significant. However, there were no significant differences in postoperative infection, reoperation, retransplantation, hepatic artery complications, portal vein complications, hepatic vein complications, bleeding, intestinal obstruction, rejection, and lymphatic fistula between the two groups (*Table 2*, Figures S1,S2).

Table 1 Baseline data from 26 studies

First author	Year	Country	Data coverage time	Kasai	N	Gender (male:female)	LT type (LD:DD)†	Follow-up (months)	Type of study
Millis (10)	1988	USA	1984–1987	Yes	28	–	0:28	–	Retrospective study
				No	8	–	0:8	–	
Wood (11)	1990	USA	1985–1989	Yes	46	–	–	–	Retrospective study
				No	2	–	–	–	
Meister (12)	1993	USA	1988–1991	Yes	32	–	0:32	–	Retrospective study
				No	7	–	0:7	–	
Sandler (13)	1997	Canada	1986–1996	Yes	49	24:25	0:49	–	Retrospective study
				No	8	3:5	0:8	–	
Chardot (14)	1999	France	1986–1996	Yes	208	–	–	–	Retrospective study
				No	17	–	–	–	
Diem (15)	2003	Belgium	1984–2000	Yes	285	–	–	–	Retrospective study
				No	43	–	–	–	
Visser (16)	2004	USA	1988–2002	Yes	42	–	22:20	–	Retrospective study
				No	13	–	7:6	–	
Cowles (17)	2008	USA	1998–2006	Yes	61	–	–	58.00 (6.00–111.00)‡	Retrospective study
				No	10	–	–	58.00 (6.00–111.00)‡	
Tiao (18)	2008	China	1996–2004	Yes	60	–	–	–	Retrospective study
				No	46	–	–	–	
Guo (19)	2010	China	2006–2009	Yes	9	–	9:0	18.50 (1.00–36.00)‡	Retrospective study
				No	13	–	13:0	18.50 (1.00–36.00)‡	
Alexopoulos (20)	2012	USA	1995–2008	Yes	112	–	–	–	Retrospective study
				No	22	–	–	–	
Wang (21)	2013	China	2008–2011	Yes	10	2:8	10:0	31.00 (12.00–44.50)‡	Retrospective study
				No	18	10:8	18:0	31.00 (12.00–44.50)‡	
Celik (22)	2014	Turkey	2006–2013	Yes	28	–	–	–	Retrospective study
				No	12	–	–	–	
Neto (23)	2015	Brazil	1995–2013	Yes	209	90:119	189:20	–	Retrospective study
				No	138	51:87	120:18	–	
Chung (24)	2015	China	1993–2015	Yes	74	–	–	–	Retrospective study
				No	7	–	–	–	
Safwan (25)	2016	India	2010–2015	Yes	33	–	–	18.00 (3.00–61.00)‡	Retrospective study
				No	25	–	–	18.00 (3.00–61.00)‡	
Mohan (26)	2016	India	2004–2015	Yes	38	20:18	–	45.12§	Retrospective study
				No	20	–	–	45.12§	

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Country	Data coverage time	Kasai	N	Gender (male:female)	LT type (LD:DD)†	Follow-up (months)	Type of study
Yang (27)	2018	China	2014–2015	Yes	58	24:34	40:18	–	Retrospective study
				No	45	24:21	34:11	–	
Li (28)	2019	China	2006–2014	Yes	89	53:36	–	19.70§	Retrospective study
				No	61	38:23	–	14.60§	
Chang (29)	2021	China	2010–2016	Yes	38	–	–	36.00§	Retrospective study
				No	36	–	–	36.00§	
Tambucci (30)	2021	Belgium	1993–2018	Yes	296	–	–	–	Retrospective study
				No	97	–	–	–	
Li (31)	2022	China	2013–2020	Yes	51	31:20	14:37	22.00 (1.00–88.00)‡	Retrospective study
				No	54	30:24	25:29	22.00 (1.00–88.00)‡	
Zhang (32)	2022	China	2014–2019	Yes	542	245:297	334:208	38.00 (26.90, 55.40)¶	Retrospective study
				No	338	149:189	251:87	38.00 (26.90, 55.40)¶	
Lemoine (33)	2022	USA	1997–2020	Yes	97	–	39:58	–	Retrospective study
				No	14	–	4:10	–	
Yoeli (34)	2022	USA	2002–2021	Yes	2,340	963:1,377	–	12.57±7.84††	Retrospective study
				No	436	151:285	–	8.26±2.97††	
Liu (35)	2022	China	2017–2019	Yes	154	81:73	117:37	–	Retrospective study
				No	43	19:24	37:6	–	

†, LD:DD = living donor:deceased donor; ‡, median (minimum–maximum); §, median; ¶, median (P25, P75); ††, mean ± standard deviation.

Patient survival rate

There was no significant heterogeneity in the 1-year survival between the 14 studies (I^2=0.0%, P=0.988), so the fixed effect model was used. The results of the meta-analysis showed that the difference was not statistically significant (OR =1.10; 95% CI: 0.82, 1.47; P=0.546) (*Figure 4A*).

There was no significant heterogeneity in the 3-year survival between the six studies (I^2=0.0%, P=0.873), so the fixed effect model was used. The results of the meta-analysis showed that the difference was not statistically significant (OR =0.71; 95% CI: 0.49, 1.01; P=0.053) (*Figure 4B*).

There was no significant heterogeneity in the 5-year survival between the nine studies (I^2=0.0%, P=0.550), so the fixed effect model was used. The results of the meta-analysis showed that the difference was not statistically significant (OR =0.86; 95% CI: 0.67, 1.10; P=0.219) (*Figure 4C*).

Graft survival rate

There was no significant heterogeneity in 1-year graft survival between the eight studies (I^2=0.0%, P=0.686), so a fixed effect model was used. The results of the meta-analysis showed that there was no statistically significant difference (OR =1.06; 95% CI: 0.83, 1.34; P=0.660) (*Figure 4D*).

There was no significant heterogeneity in 5-year graft survival between the five studies (I^2=0.0%, P=0.555), so the fixed effect model was used. The results of the meta-analysis showed that there was no statistically significant difference (OR =0.87; 95% CI: 0.70, 1.08; P=0.207) (*Figure 4E*).

Publication bias

To make the included studies more persuasive, we used the funnel plot and Egger's test to detect publication bias.

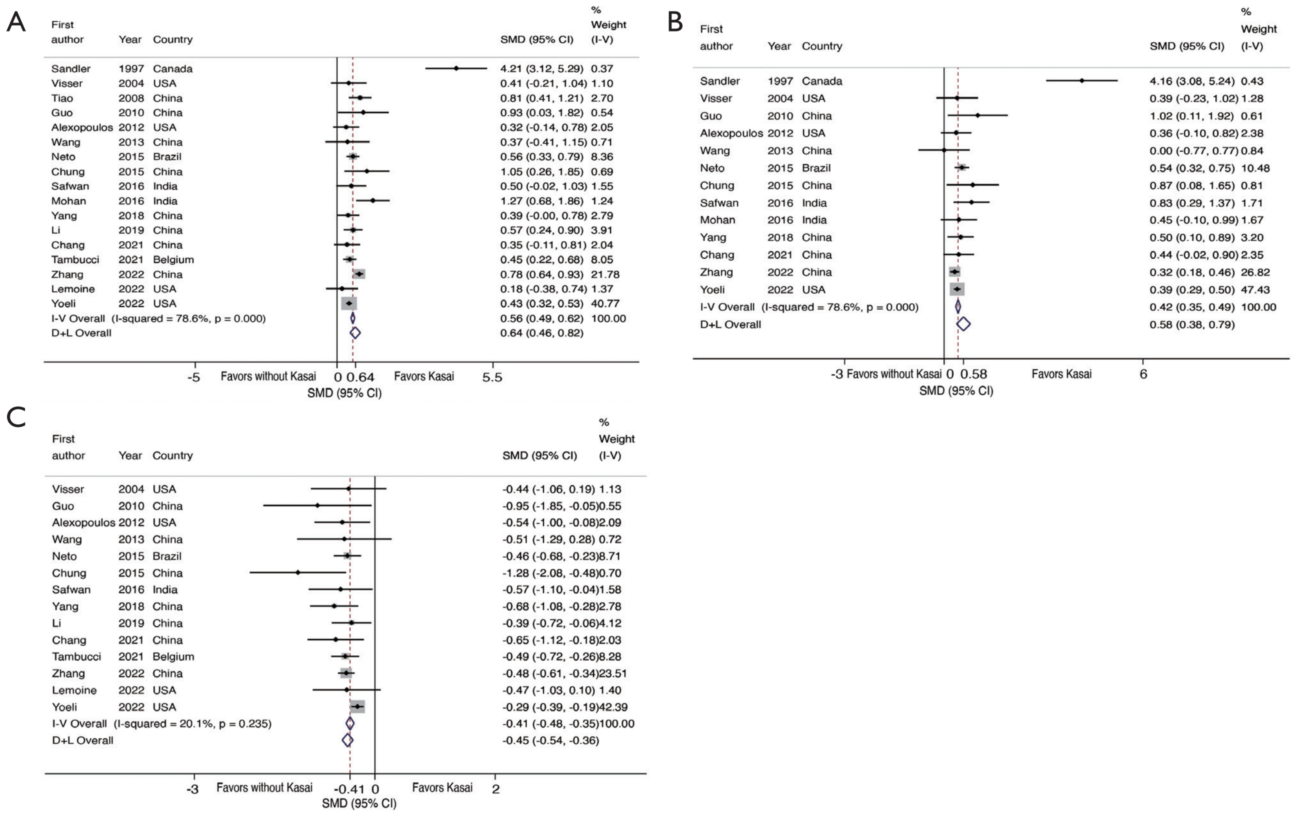

Figure 2 Forest plot of the meta-analysis of preoperative indicators. (A) Age at surgery. (B) Weight at surgery. (C) PELD score. Fixed effects model: I-V overall, random effects model: D + L overall. SMD, standardized mean difference; CI, confidence interval; I-V, Inverse-Variance; D + L, DerSimonian and Laird; PELD, pediatric end-stage liver disease.

When the funnel plot is used to detect publication bias, the number of studies in the meta-analysis should be at least 10, and if the number of studies is too small, it is difficult to detect the cause of asymmetry (36). The results showed that the Egger's test of PELD score was less than 0.05, indicating that there may be publication bias, and the reliability of its conclusions still needs to be confirmed by more studies (*Table 3*, Figure S3).

Sensitivity analysis

To determine the source of heterogeneity, we performed a sensitivity analysis of studies in which heterogeneity was present, including age at surgery, weight at surgery, operation time, intraoperative blood transfusion, and length of ICU stay. Excluding any one study under each indicator, the results showed that the study of Sandler *et al.* (13) was the main source of heterogeneity in the weight at surgery (Figure S4A). After exclusion, there was no significant heterogeneity among the remaining 12 studies (I^2=0.0%, P=0.563), so the fixed effect model was used. The results of the meta-analysis showed that the weight at surgery of the Kasai group was heavier. The difference was statistically significant (SMD =0.41; 95% CI: 0.33, 0.48; P<0.001) (Figure S4B,S4C). However, the exclusion of any study in the other indicators did not have a significant effect on heterogeneity, and further search for the source of heterogeneity is needed (Figure S4D-S4G).

Subgroup analysis

To further search for sources of heterogeneity, subgroup analyses were performed. All studies were divided into "Asia" and "non-Asia" groups according to region. According to the time of case reporting, the Cases after 2000 were divided into the "Cases since 2000" group, and the studies involving cases before 2000 were divided into the "Other" group.

In the "Asia" subgroup, the age at surgery of Kasai

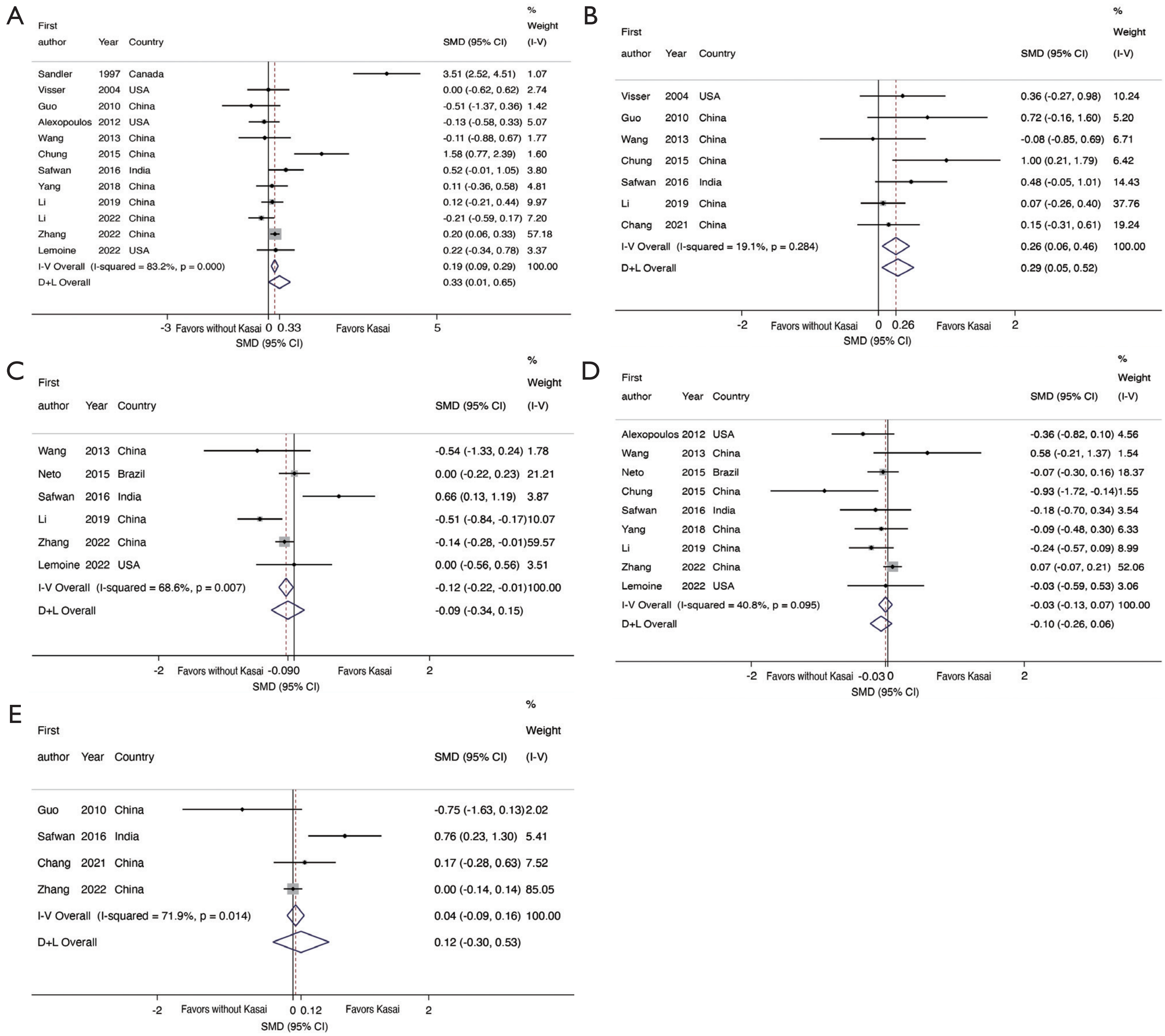

Figure 3 Forest plot of the meta-analysis of perioperative indicators. (A) Operation time. (B) Intraoperative blood loss. (C) Length of ICU stay. (D) Length of hospital stay. (E) Intraoperative blood transfusion. Fixed effects model: I-V overall, random effects model: D + L overall. SMD, standardized mean difference; CI, confidence interval; I-V, Inverse-Variance; D + L, DerSimonian and Laird; ICU, intensive care unit.

group was older, the difference was statistically significant (SMD =0.68; 95% CI: 0.52, 0.84; P<0.001] (I^2=28.2%, P=0.185); The "non-Asia" subgroup Kasai group was older, and the difference was statistically significant (SMD =0.64; 95% CI: 0.31, 0.98; P<0.001) (I^2=87.6%, P<0.001) (*Figure 5A*).

In the "Cases since 2000" subgroup, there was no significant difference in operation time between the two groups (P=0.241) (I^2=28.5%, P=0.211). In the "Other" subgroup, there was no significant difference in operation time between the two groups (P=0.069) (I^2=92.4%, P<0.001) (*Figure 5B*).

The studies included in the "Cases since 2000" subgroup coincided with the studies included in the "Asia" subgroup, and both showed no significant difference in ICU length of stay between the two groups (P=0.528) (I^2=78.9%, P=0.003) (*Figure 5C*). The studies included in the "Other" subgroup

Table 2 The meta-analysis of postoperative indicators

Postoperative indicators	Number of studies	Test of heterogeneity		Model of effect	OR (95% CI)	P value
		I^2	P value			
Infection	8	6.0%	0.384	Fixed	1.63 (0.97, 2.74)	0.066
Reoperation	11	20.4%	0.255	Fixed	0.92 (0.66, 1.29)	0.636
Retransplantation	8	0.0%	0.522	Fixed	1.12 (0.53, 2.38)	0.769
Hepatic artery complications	14	0.0%	0.900	Fixed	0.92 (0.62, 1.36)	0.659
Hepatic vein complications	3	0.0%	0.571	Fixed	2.76 (0.67, 11.34)	0.160
Portal vein complications	13	0.0%	0.849	Fixed	1.27 (0.93, 1.73)	0.130
Biliary complications	15	31.4%	0.124	Fixed	1.41 (1.05, 1.89)	0.024*
Rejection	7	26.0%	0.230	Fixed	1.22 (0.93, 1.58)	0.146
Lymphatic fistula	3	11.6%	0.323	Fixed	0.82 (0.63, 1.08)	0.167
Bleeding	7	0.0%	0.954	Fixed	1.36 (0.69, 2.68)	0.376
Intestinal perforation	12	7.4%	0.373	Fixed	1.96 (1.20, 3.18)	0.007**
Intestinal obstruction	5	0.0%	0.441	Fixed	0.73 (0.45, 1.19)	0.210

*, P<0.05; **, P<0.01. OR, odds ratio; CI, confidence interval.

coincided with those in the "non-Asia" subgroup, both of which showed no statistically significant difference in the length of ICU stay between the two groups (P=0.977) (I^2=0.0%, P=0.991) (*Figure 5D*).

The intraoperative blood transfusion could not be analyzed by subgroup analysis because there was only one group under the two grouping methods.

Discussion

BA is a severe cholestatic disease involving intrahepatic and extrahepatic bile ducts, which can rapidly develop into cirrhosis if surgical treatment is not performed in time. Among them, the pros and cons of Kasai procedure and liver transplantation for BA have been controversial. The advantages and disadvantages of the two surgical methods in the treatment of BA are shown in *Table 4* (37,38). Of the 26 studies included in this study, 15 studies were more supportive of the Kasai procedure as the first step in the treatment of BA, five studies were more supportive of direct liver transplantation, and six studies had relatively neutral views.

Explanations of findings

The meta-analysis of the present study confirmed that Kasai procedure can prolong the age at the time of liver transplantation in children with BA, increase body weight, and reduce PELD scores. A lower PELD score predicts lower mortality while waiting for transplantation (39). These results indicate that Kasai procedure can not only reduce the potential surgical risk caused by younger age, but also improve preoperative status.

The results showed that the heterogeneity could be well eliminated when the age at surgery was analyzed in the "Asia" group (I^2=28.2%), and the results were not affected and were still being statistically significant. Therefore, we believe that the inference of "the age at surgery of children in the Kasai group is older" is more convincing when applied to the Asian population.

Intestinal adhesion after Kasai procedure will increase the difficulty of liver transplantation. Our preliminary results also showed that children in the Kasai group had longer operation time and more blood loss during transplantation. However, there was no significant difference in intraoperative blood transfusion and hospital stay between the two groups, and the length of ICU stay was even shorter in the Kasai group. Further analysis showed that there was no significant difference in the operation time between the two groups in the "Cases since 2000" subgroup (I^2=28.5%), and there was no significant difference in the length of ICU stay between the two groups in the "Other" subgroup and the "non-

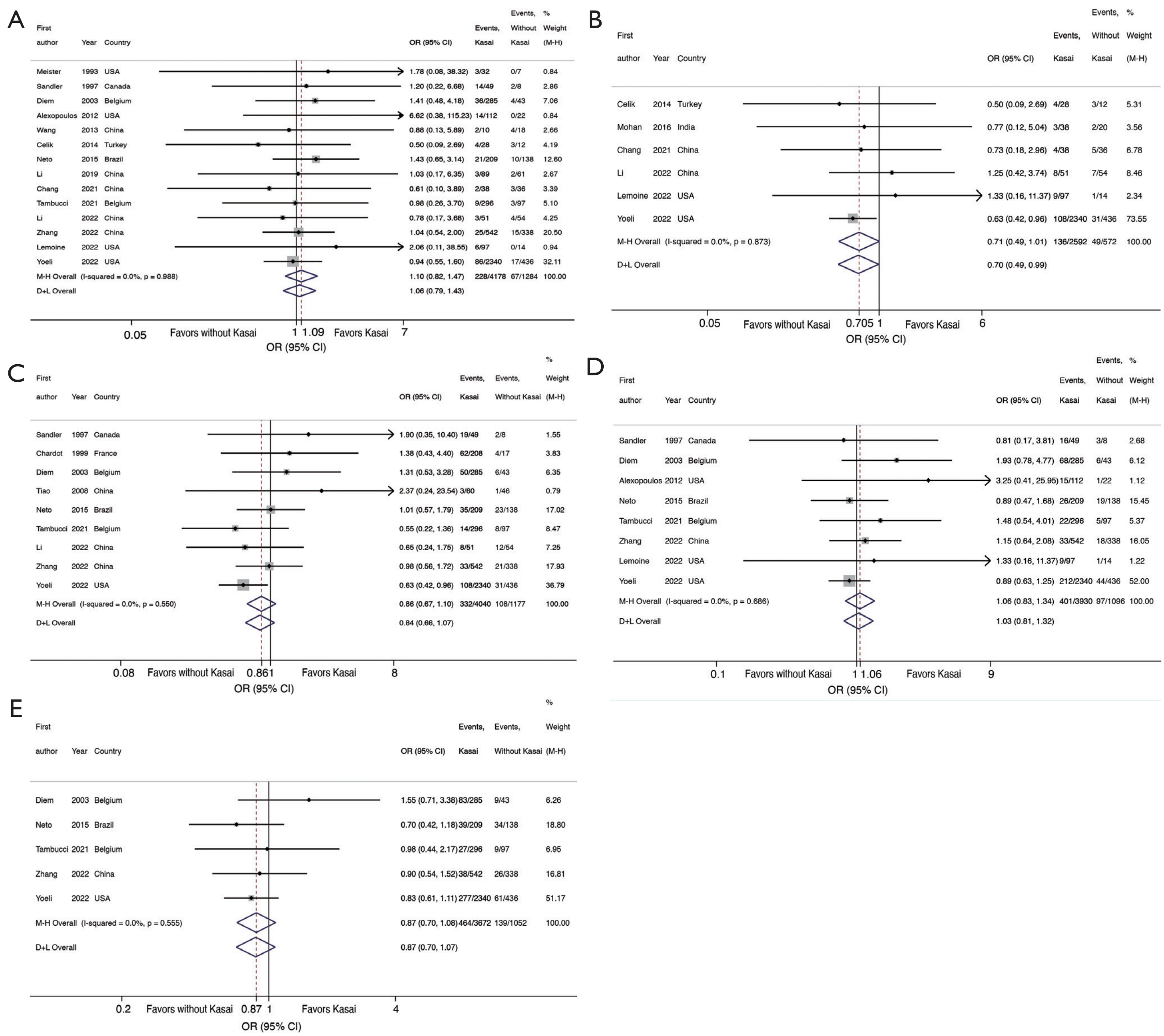

Figure 4 Forest plot of the meta-analysis of survival information. (A) 1-year survival rate. (B) 3-year survival rate. (C) 5-year survival rate. (D) 1-year graft survival rate. (E) 5-year graft survival rate. Fixed effects model: M-H overall, random effects model: D + L overall. OR, odds ratio; CI, confidence interval; M-H, Mantel-Haenszel; D + L, DerSimonian and Laird.

significant. Although the prognosis of early failure was not better than that of the primary transplantation group, current technical means cannot predict BA children with early failure. However, the timing of the Kasai procedure can affect the survival rate of the autologous liver. Yang *et al.* (40) showed that the prognosis was good when the age of surgery was about 60 days. When the age of surgery was more than 90 days, the survival time of autologous liver shortened with the increase of the age of surgery, and the probability of early failure also increased.

Strengths and limitations

The strengths of this study are as follows: (I) a total of 26 studies were included in the meta-analysis, which makes the results highly convincing. (II) Indicators from each study were collected as comprehensively as possible during data extraction. (III) To find the source of heterogeneity,

Table 3 Publication bias

Indicators	Number of studies	P value for Egger's test
Preoperative indicators		
Age at surgery	17	0.215
Weight at surgery	13	0.125
PELD score	14	0.003**
Perioperative indicators		
Operation time	12	0.411
Intraoperative blood loss	7	0.114
Intraoperative blood transfusion	4	0.779
Length of hospital stay	9	0.162
Length of ICU stay	6	0.817
Postoperative complications		
Infection	8	0.154
Reoperation	11	0.939
Retransplantation	8	0.686
Hepatic artery complications	14	0.353
Hepatic vein complications	3	0.659
Portal vein complications	13	0.434
Biliary complications	15	0.310
Rejection	7	0.650
Lymphatic fistula	3	0.449
Bleeding	7	0.083
Intestinal perforation	12	0.210
Intestinal obstruction	5	0.794
Survival		
1-year survival rate	14	0.509
3-year survival rate	6	0.311
5-year survival rate	9	0.091
1-year graft survival rate	8	0.084
5-year graft survival rate	5	0.297

**, P<0.01. PELD, pediatric end-stage liver disease; ICU, intensive care unit.

Asia" subgroup (I^2=0.0%). This may indicate that with the gradual development of Kasai procedure, it does not affect the operation time and postoperative recovery of liver transplantation, but the increase of intraoperative blood loss is inevitable.

The incidence of biliary complications and intestinal perforation was higher in children who had undergone the Kasai procedure, which may be due to the easy injury of the intestinal tract and bile duct when the anastomosis between the hepatic hilum and jejunum was separated during liver transplantation. However, there were no significant differences in other postoperative indicators (including infection, reoperation, retransplantation, hepatic artery complications, portal vein complications, hepatic vein complications, rejection, bleeding, lymphatic fistula, and intestinal obstruction) and prognostic survival (including 1-/3-/5-year patient survival rate and 1-/5-year graft survival rate) between the two groups. This may be due to the advancement of surgical techniques and postoperative management, so that biliary complications (biliary fistula and biliary stricture) and intestinal perforation can be timely and effectively prevented and controlled, without affecting the survival of patients and grafts.

In addition, four studies subdivided the Kasai group of patients into two groups: early failure (patients who eventually received a transplant within the first year after Kasai) and late failure (patients who required a transplant after the first year) (20,23,34,35). Alexopoulos *et al.* (20) showed that patients with early failure had a higher risk of infection than those with late failure and non-Kasai. Neto *et al.* (23) showed that the late failure group had the highest patient survival and graft survival, while the early failure group had no significant difference in patient survival and graft survival compared with the non-Kasai group. Yoeli *et al.* (34) showed that outcomes in the early failure group were not significantly different from those in the non-Kasai group, whereas the waiting list and graft survival were higher in the late failure group. Liu *et al.* (35) showed that the survival difference in the early (<1 year), middle (1–5 years), and late (>5 years) failed groups and no Kasai group was not

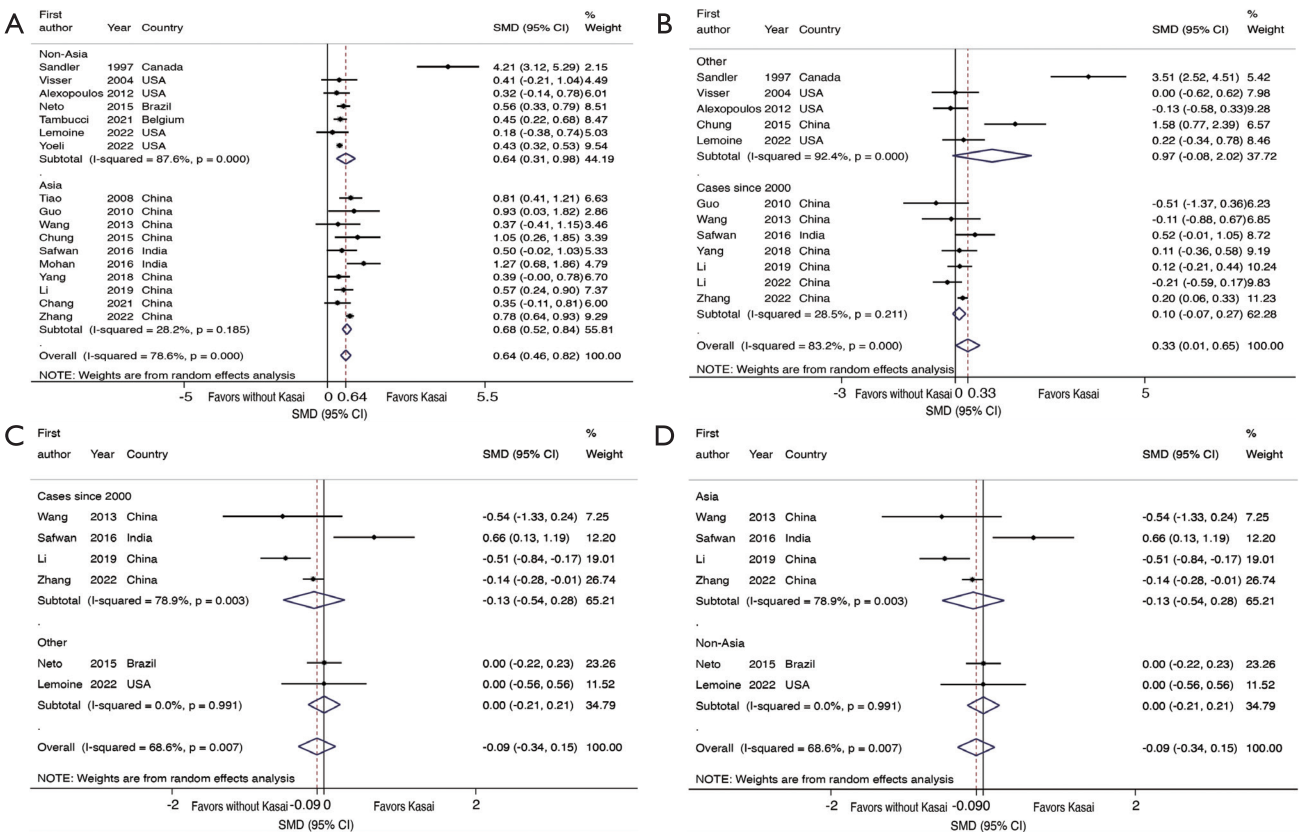

Figure 5 Subgroup analysis. (A) Age at surgery was analyzed according to the subgroups of region. (B) The operation time was analyzed according to the subgroups of case time. (C) The length of ICU stay was divided into subgroups according to patient time. (D) The length of ICU stay was analyzed according to the subgroups of region. SMD, standardized mean difference; CI, confidence interval; ICU, intensive care unit.

subgroup analysis and sensitivity analysis were conducted. The limitations of this study include: (I) all studies are retrospective and lack of data from prospective studies. (II) The disease of some patients with BA progressed too fast and the liver was in the decompensated stage, so they can only choose liver transplantation, which was an inevitable selection bias. (III) Confounding by unknown or no measurable factors cannot be completely ruled out, and any inherent limitations in the included studies could have biased our results.

Conclusions

For children with BA undergoing liver transplantation, although previous Kasai procedure may increase the risk of intraoperative bleeding, biliary complications, and intestinal perforation, it does not affect the main clinical outcomes and can even delay the timing of liver transplantation and improve the preoperative status of children. In this sense, the failed Kasai procedure is also of some significance. It has been shown that 20–40% of patients can achieve long-term native liver survival

Table 4 Comparison of the advantages and disadvantages of Kasai procedure and liver transplantation

Surgical methods	Advantages	Disadvantages
Kasai procedure	(I) It can prolong the survival time of native liver to a certain extent, and even some patients can survive for a long time without liver transplantation	(I) The long-term survival is not satisfactory, which may be hit by the second operation
	(II) Improve the preoperative status of liver transplant recipients	(II) Cause abdominal adhesion and scar formation, which will increase the difficulty of liver transplantation and the complications after transplantation
	(III) Relieve the tension of insufficient donor liver	(III) Maybe affect the growth and development of patients in childhood and adolescence, leading to malnutrition and growth and development disorders
	(IV) Liver transplantation can be postponed to a better age when the basic conditions of BA patients such as body weight, hepatic vessel diameter, and upper abdominal cavity volume are better (37)	
	(V) The Roux-en-Y anastomosis established in the Kasai procedure can be used for liver transplantation, which helps save time	
	(VI) The abdominal adhesions were mostly membranous, and the separation was not very difficult	
Liver transplantation	(I) Low cost (some countries will provide social support)	(I) Losing the chance of native liver survival
	(II) High survival rate	(II) Young age will inevitably increase the difficulty of surgery and the probability of postoperative complications
		(III) The long-term use of immunosuppressants also increases the probability of infection and cancer
		(IV) If the number of grafts is not proportional to the supply, survival can be affected
		(V) In some countries, liver transplantation is more expensive than Kasai procedure (38)

BA, biliary atresia.

(≥10 years) after Kasai procedure (35). Therefore, in the treatment of BA children, when there is no obvious contraindication to Kasai procedure, the sequential treatment of Kasai procedure-liver transplantation should be supported first.

Acknowledgments

Funding: We acknowledge the Tianjin Science and Technology Program (No. 21ZXGWSY00070) and the Tianjin Applied Basic Research Project (No. 22JCZDJC00290) for the support of the research.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-504/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-504/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-504/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Liu S, Yang Q, Ji Q, Wang Z, Sun R, Zhan J. Effect of Kasai procedure on liver transplantation in children with biliary atresia: a systematic review and updated meta-analysis. Transl Pediatr 2024;13(1):10-25. doi: 10.21037/tp-23-504

Supplementary

Table S1 Newcastle-Ottawa quality assessment scale for included studies

First author year country	Selection	Comparability	Outcome	Total
Millis 1988 USA	4	1	2	7
Wood 1990 USA	3	2	1	6
Meister 1993 USA	4	2	3	9
Sandler 1997 Canada	4	2	2	8
Chardot 1999 France	3	2	2	7
Diem 2003 Belgium	4	2	2	8
Visser 2004 USA	4	2	2	8
Cowles 2008 USA	4	1	1	6
Tiao 2008 China	4	1	1	6
Guo 2010 China	3	2	2	7
Alexopoulos 2012 USA	4	1	3	8
Wang 2013 China	4	2	3	9
Celik 2014 Turkey	4	2	1	7
Neto 2015 Brazil	4	1	2	7
Chung 2015 China	4	1	2	7
Safwan 2016 India	4	1	2	7
Mohan 2016 India	4	1	1	6
Yang 2018 China	4	2	2	8
Li 2019 China	4	2	3	9
Chang 2021 China	4	1	3	8
Tambucci 2021 Belgium	4	1	2	7
Li 2022 China	4	1	2	7
Zhang 2022 China	4	1	2	7
Lemoine 2022 USA	4	2	3	9
Yoeli 2022 USA	4	1	2	7
Liu 2022 China	4	1	2	7

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Table S2 Data summary information on indications for transplantation in children from each study

First author year country	Indications for liver transplantation
Millis 1988 USA	Not mentioned
Wood 1990 USA	Not mentioned
Meister 1993 USA	Not mentioned
Sandler 1997 Canada	Not mentioned
Chardot 1999 France	Liver failure (n=191)
Diem 2003 Belgium	Early liver failure (n=252)
	Digestive hemorrhage (n=26)
	Late liver failure (n=38)
	Recurrent cholangitis (n=12)
Visser 2004 USA	Failure to thrive (n=19)
	Inadequate drainage (n=16)
	Coagulopathy (n=12)
	Recurrent cholangitis (n=6)
	Portal hypertension (n=5)
	Gastrointestinal bleeding (n=4)
	Ascites (n=2)
	Portal vein thrombosis (n=1)
	Intractable pruritis (n=1)
Cowles 2008 USA	Not mentioned
Tiao 2008 China	Not mentioned
Guo 2010 China	Not mentioned
Alexopoulos 2012 USA	Not mentioned
Wang 2013 China	Not mentioned
Celik 2014 Turkey	Not mentioned
Neto 2015 Brazil	Not mentioned
Chung 2015 China	Portal hypertension (n=60)
Safwan 2016 India	Not mentioned
Mohan 2016 India	Not mentioned
Yang 2018 China	Not mentioned
Li 2019 China	Not mentioned
Chang 2021 China	Not mentioned
Tambucci 2021 Belgium	Not mentioned
Li 2022 China	Not mentioned
Zhang 2022 China	Not mentioned
Lemoine 2022 USA	Cholangitis (n=31; KPE[†] =31; pLT[‡] =0)
	Infections (other than cholangitis) (n=47; KPE[†] =41; pLT[‡] =6)
	Gastrointestinal bleeding (n=22; KPE[†] =20; pLT[‡] =2)
	Ascites or spontaneous bacterial peritonitis (n=30; KPE[†] =25; pLT[‡] =5)
	Malnutrition (n=28; KP[†] =24; pLT[‡] =4)
Yoeli 2022 USA	Not mentioned
Liu 2022 China	Jaundice (n=127; N-KP[§] =43; P-KP[¶] =84)
	Cholangitis (n=62; N-KP[§] =0; P-KP[¶] =62)
	GEV bleeding (n=30; N-KP[§] =1; P-KP[¶] =29)
	Severe hypersplenism (n=12; N-KP[§] =1; P-KP[¶] =11)
	Growth retardation (n=60; N-KP[§] =15; P-KP[¶] =45)
	Massive ascites (n=3; N-KP[§] =0; P-KP[¶] =3)
	Liver failure (n=32; N-KP[§] =14; P-KP[¶] =18)

[†], KPE = Kasai portoenterostomy; [‡], pLT = primary liver transplantation; [§], N-KP = non-Kasai procedure; [¶], P-KP = post Kasai procedure.

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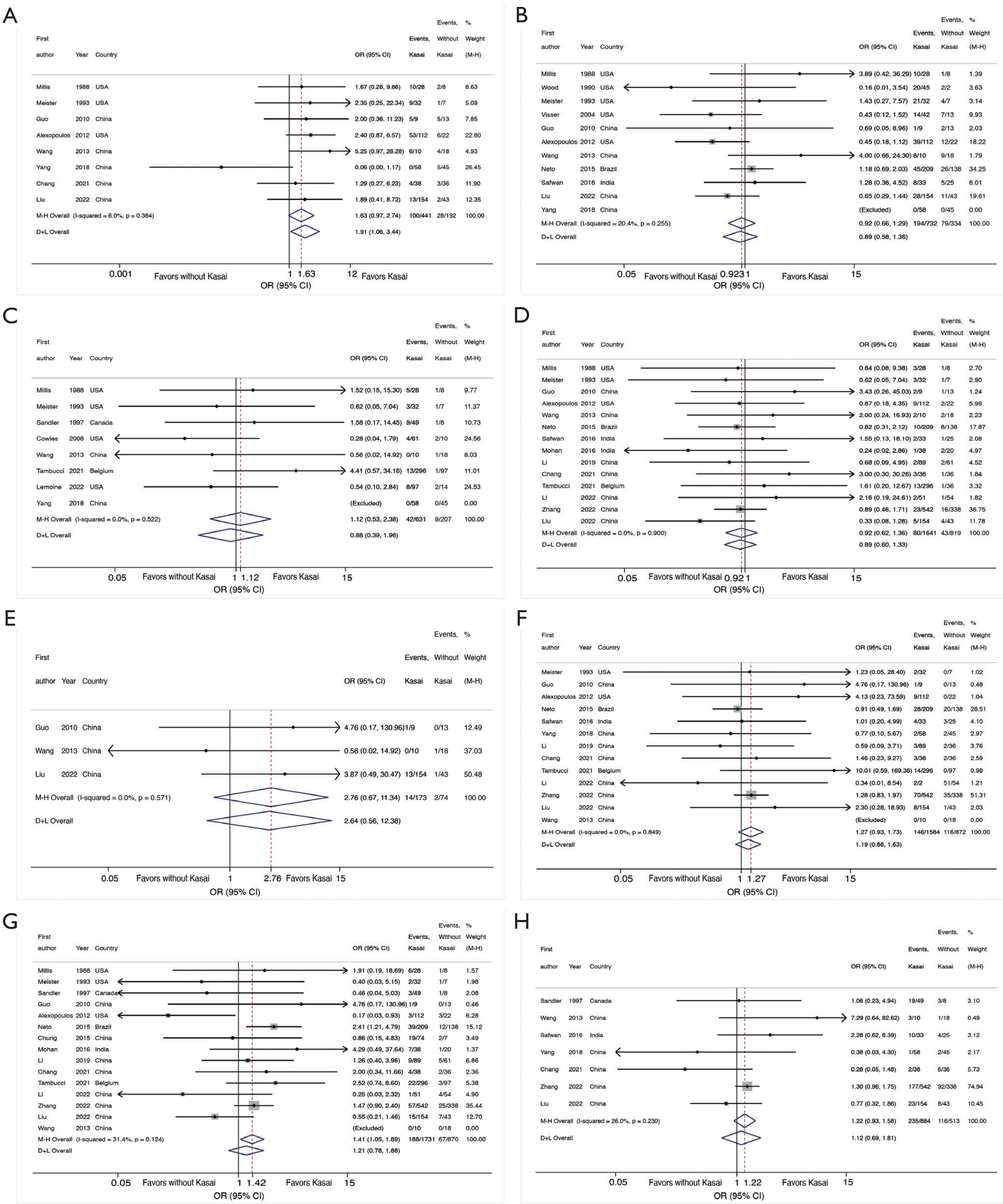

Figure S1 Forest plot of the meta-analysis of postoperative indicators. (A) Infection. (B) Reoperation. (C) Retransplantation. (D) Hepatic artery complications. (E) Hepatic vein complications. (F) Portal vein complications. (G) Biliary complications. (H) Rejection. Fixed effects model: M-H overall, random effects model: D + L overall. M-H, Mantel-Haenszel; D + L, DerSimonian and Laird; OR, odds ratio; CI, confidence interval.

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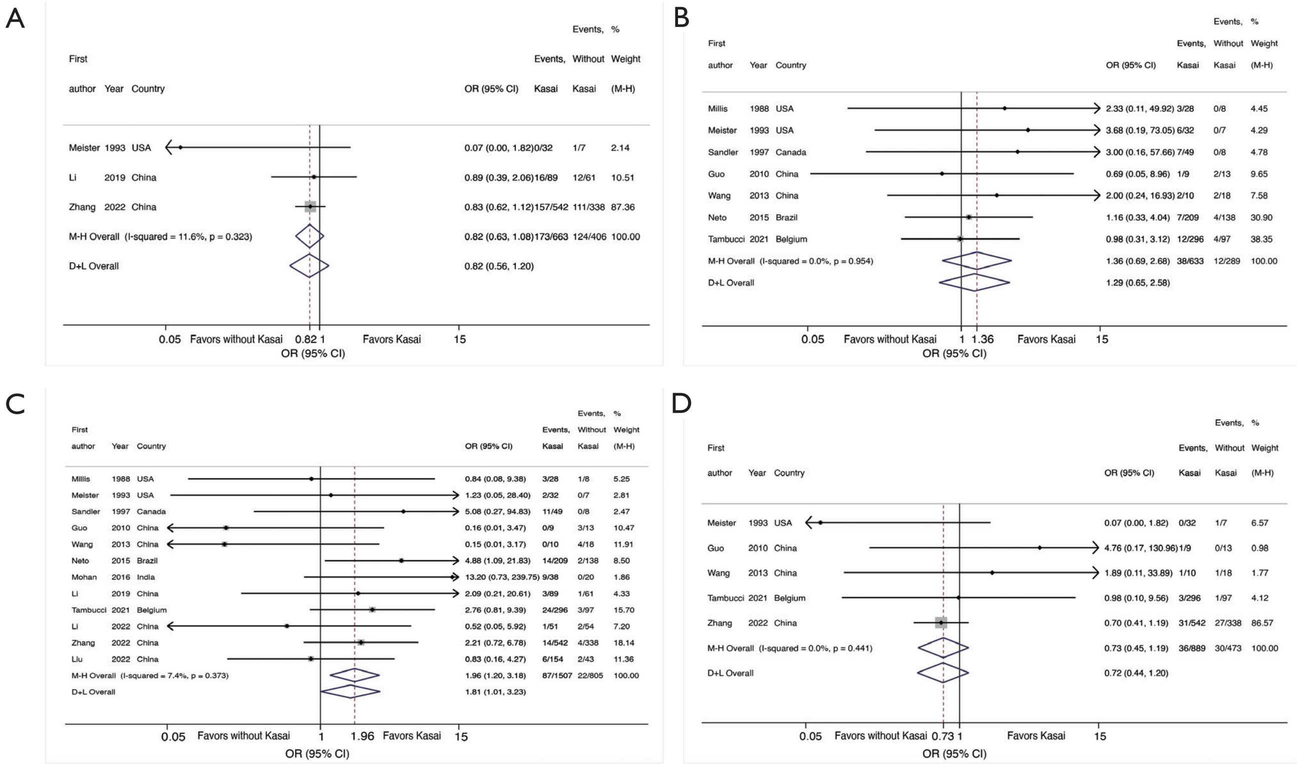

Figure S2 Forest plot of the meta-analysis of postoperative indicators. (A) Lymphatic fistula. (B) Bleeding. (C) Intestinal perforation. (D) Intestinal obstruction. Fixed effects model: M-H overall, random effects model: D + L overall. M-H, Mantel-Haenszel; D + L, DerSimonian and Laird; OR, odds ratio; CI, confidence interval.

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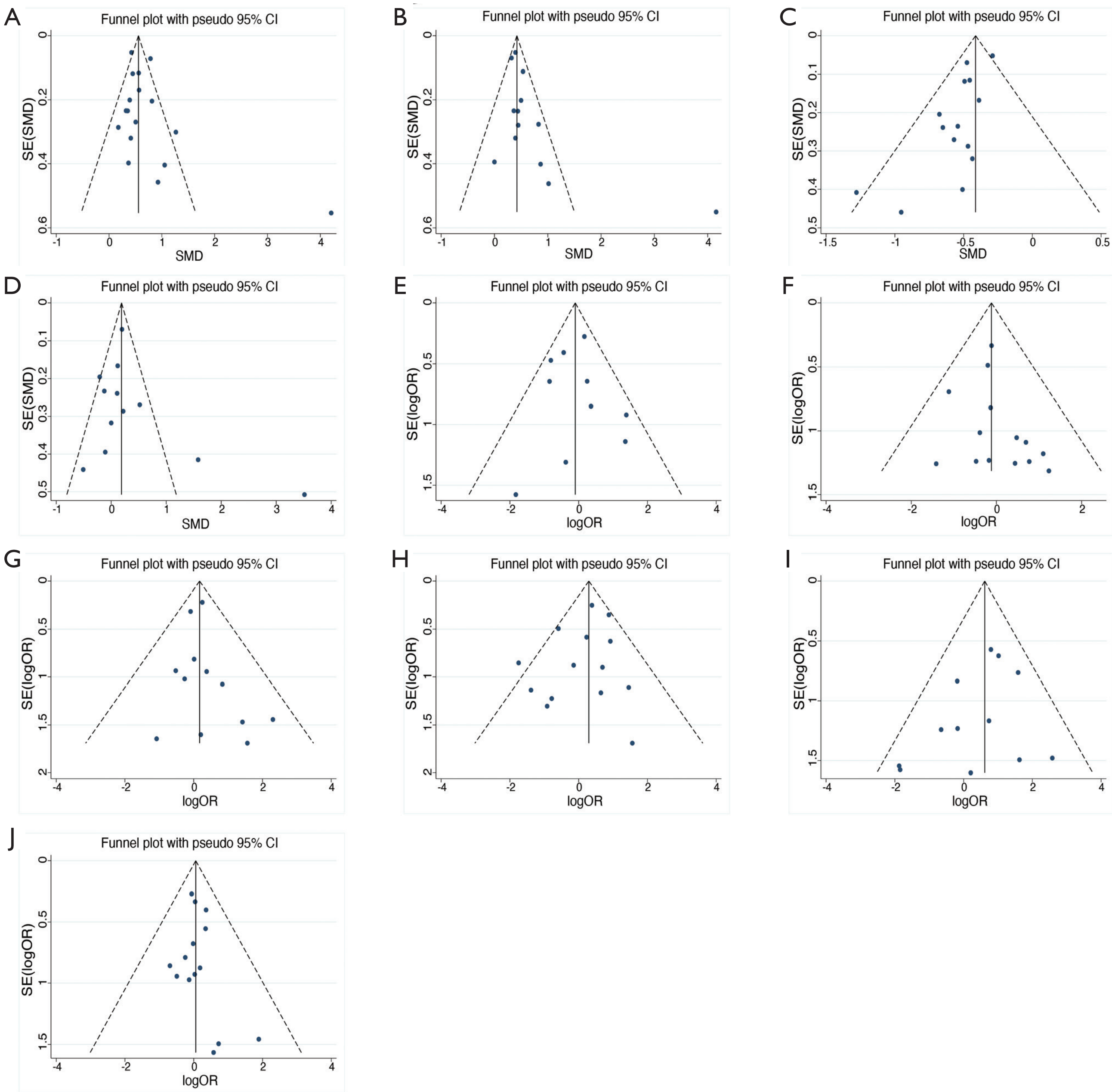

Figure S3 Plot of funnel. (A) Age at surgery. (B) Weight at surgery. (C) PELD score. (D) Operation time. (E) Reoperation. (F) Hepatic artery complications. (G) Portal vein complications. (H) Biliary complications. (I) Intestinal perforation. (J) 1-year survival rate. SE, standard error; SMD, standardized mean difference; CI, confidence interval; PELD, pediatric end-stage liver disease; OR, odds ratio.

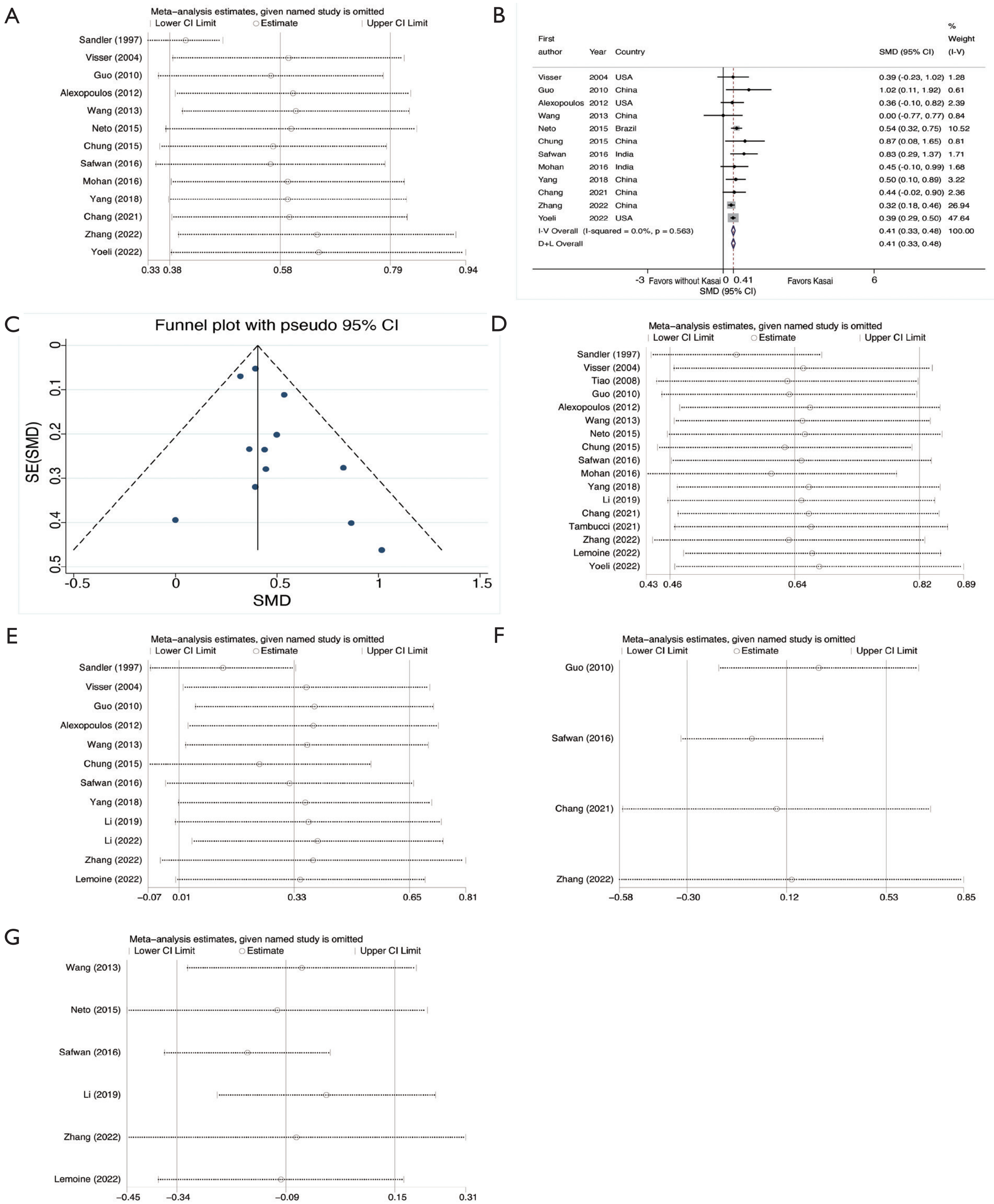

Figure S4 Sensitivity analysis. (A) Sensitivity analysis of weight at surgery. (B) Forest plot of meta-analysis of surgical weight after excluding one study. (C) Funnel plot of meta-analysis of surgical weight after excluding one study. (D) Sensitivity analysis of age at surgery. (E) Sensitivity analysis of operation time. (F) Sensitivity analysis of intraoperative blood transfusion. (G) Sensitivity analysis of length of ICU stay. Fixed effects model: I-V overall, random effects model: D + L overall. I-V, Inverse-Variance; D + L, DerSimonian and Laird; SMD, standardized mean difference; CI, confidence interval; SE, standard error; ICU, intensive care unit.

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