Adjuvant steroid treatment following Kasai portoenterostomy and clinical outcomes of biliary atresia patients: an updated meta-analysis

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Meta-analysis

Background: **It is controversial whether adjuvant steroid treatment should be given to biliary atresia (BA) patients following a Kasai portoenterostomy (KPE). This study aimed to quantitatively and systematically evaluate the effect of adjuvant steroid therapy post-KPE in relation to major clinical outcomes of BA patients.**

Methods: **We systematically reviewed the literature in PubMed, Embase, the Cochrane Library, China Knowledge Resource Integrated Database, Wanfang Database, Scholarly and Academic Information Navigator and manually searched for relevant papers published before August, 2015. We extracted data on the effects of steroid treatment following KPE on clinical outcome, including jaundice free rate and native liver survival rate at 6 months, 1 or 2 years after KPE. The weighted overall relative risk (RR) and 95% confidence intervals (CIs) were calculated by using a random-effects model.**

Results: **Eight cohort studies and two randomized controlled trials (RCTs) were identified (n=998). Of them, 6 cohort studies and 2 trials investigated the effect of steroid treatment as compared to non-users or placebo (n=566), and 2 cohort studies compared the effects of high-dose to low-dose steroid treatment (n=432). Steroid usage increased the clearance rates of jaundice at 6 months (pooled RR: 1.32; 95% CI: 0.995-1.76; I^2=72.6%) and 1 year (pooled RR: 1.35; 95% CI: 1.12-1.61; I^2=0.0%), but not 2 years (pooled RR: 0.82; 95% CI: 0.55-1.22; I^2=0.0%) after KPE. There was no solid evidence supporting that steroid treatment would improve native liver survival rate at 6 months (pooled RR: 1.02; 95% CI: 0.90-1.15; I^2=0.0%), 1 year (pooled RR: 1.10; 95% CI: 0.91-1.34; I^2=35.2%) or 2 years (pooled RR: 1.00; 95% CI: 0.73-1.35; I^2=57.4%) after KPE.**

Conclusions: **Adjuvant steroid treatment following KPE may improve short-term (≤1 year) clearance rate of jaundice, but no significant effects on long-term (≥2 years) clearance rate of jaundice and native liver survival rate. Studies on doses and duration of steroids, and long-term follow-up studies are warranted.**

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Key words: **biliary atresia; Kasai portoenterostomy; steroid treatment**

Introduction

Biliary atresia (BA) is a disease with progressive obstruction of biliary tract during the neonatal period. It occurs in between 1 in 5000 and 1 in 19 000 live births.[1] Without surgery, cholestasis progresses rapidly to the end-stage cirrhosis and liver transplantation may become inevitable. Kasai portoenterostomy (KPE) is currently the primary surgery for BA patients to restore bile flow and preserve the native liver.[2]

Adjuvant steroid treatment has been used to assist restoring bile flow after KPE for over 40 years.[3] However, the efficiency of steroid treatment still remains unknown.[1] A systematic review and meta-analysis published in 2011 found no significant effect of steroids over standard therapy on clearance rate of jaundice at 6 months or reduced need for liver transplantation at 1 year after KPE.[4] Another systematic review published in 2014 found that steroid therapy post-KPE did not improve jaundice-free or cholangitis rates.[5] A recent systematic review and meta-analysis published in 2015, including newly published RCT studies,[6,7] reported no improvement in jaundice clearance after steroid use at 6

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months after KPE.[8] However, these reviews did not focus on the effects of treatment with different follow-up period and no definitive conclusion has been made. Therefore, we have incorporated data from all relevant published studies[6,9] to update the evaluation of adjuvant steroid treatment following KPE in patients with BA by focusing on the short-term/mid-term effect of steroid therapy.

Methods

Data sources, search strategy and selection criteria

We searched PubMed, Embase, the Cochrane Library and three major databases in China and Japan including China Knowledge Resource Integrated Database (CNKI), Wanfang Database (Wanfang), and Scholarly and Academic Information Navigator (CiNii) through August 15, 2015, with no language restriction using the following text words or MeSH headings: ("biliary atresia" OR "biliary duct") AND ("Kasai" OR "portoenterostomy") AND ("steroid" OR "corticosteroid").

To be included, studies should meet the following criteria: 1) original studies; 2) either cohort study or clinical trial; 3) examined the effect of adjuvant steroid treatment after KPE on the jaundice free rate and/or native liver survival rate of BA patients; 4) reported the relative risks (RRs) and the corresponding confidence intervals (CIs) of jaundice free rate and/or native liver survival rate or such information could be derived.

One investigator (ZZM) did an initial screening based on the key words, and then two authors (ZZM, XPC) independently reviewed the selected abstracts to decide which studies should be included in the meta-analysis.

Data extraction

Two authors (ZZM, XPC) independently extracted the relevant data based on a pre-designed standard form. The categories of extracted data included author, year of publication, country of studies, study design, study populations, age and bilirubin level before KPE, steroid treatment regimen, other adjuvant therapies, jaundice free rate and native liver survival rate in the experimental and control groups.

Data analysis

We used STATA (Version 13.0, STATA Corp, College Station, Texas, U.S.) for all the analyses and graphics. A two-sided *P*-value ≤0.05 was considered statistically significant, if not otherwise specified.

The primary analysis was a comparison of relative risks (RRs) of jaundice-free rates or native liver survival rates between steroid users and non-users/placebo, or high-dose and low-dose users, at different follow-up times (i.e. 6-month, 1-year, and 2-year). RRs and 95% CIs were retrieved from each study directly or estimated based on the information provided. We consistently used random-effects model rather than fixed-effect model in the main analysis to allow for variation of effects across studies. We measured the degree of heterogeneity across studies using I^2 statistic, and 50% and 75% were used as the cutoffs for defining low, moderate, and high degrees of heterogeneity. We tested the statistical significance of heterogeneity with Cochran's Q test (α=0.10). We assessed the publication bias using Egger's regression asymmetry test (if the numbers of pooling ≥3) or Begg's rank correlation test (if the numbers of pooling <3) with setting the alpha level at 0.10.

In the sensitivity analyses, we first excluded data from the two studies that compared high-dose steroid with low-dose steroid users. Second, we evaluated if an individual study substantially affects the pooled results by removing a single study at each time from the analysis. Third, we assessed if using fixed-effects models would generate different results.

Results

We initially identified 121 potentially relevant articles. Eighty-seven were excluded sequentially because of the following reasons: 1) animal studies or laboratory researches (*n*=4); 2) not original studies (e.g., reviews, meta-analyses, or abstracts) (*n*=39); 3) exposure not steroid use (*n*=36); or 4) duplicated publications (*n*=8). Of the 34 remaining articles, 24 were further excluded from full-text review because of: 1) no control group (*n*=9); 2) included patients without KPE (*n*=1); or 3) information on RR and 95% CI not available (*n*=14) (Figure 1). Therefore, 10 original studies were included in the meta-analysis.

The final dataset included 998 patients. Of the original studies, 8 were cohort studies (*n*=690) and two RCTs (*n*=308).[6,7,9-16] Four studies were from Asia

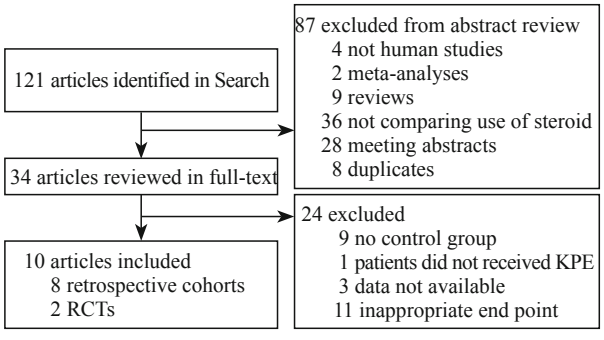

Fig. 1. Flow chart of study screening and selection. KPE: Kasai portoenterostomy; RCT: randomized clinical trial.

Table. Characteristics of the studies included in the meta-analysis

Sources	Country	Study design	Sample size	Group	Age at KPE (d)	Bilirubin at KPE (μmol/L)	Steroid regimen	Other adjuvant therapies
Meyers et al, 2003	United States	Cohort	28	No: 14 Yes: 14	No: 51.3±16.8 Yes: 57.0±27.1	NA	IV MP (taper of 10, 8, 6, 5, 4, 3, 2 mg/kg/d), oral PND 2 mg/kg/d for 8-12 wk	Antibiotics, UDCA
Escobar et al, 2006	United States	Cohort	43	No: 22 Yes: 21	42.7±16.8	138.5±66.7	Most use is IV PND & Dex from 20 mg/kg/d to 2 mg/kg/d with tapers lasting 2 to 6 wk	Antibiotics, UDCA, phenobarbital fat-soluble vitamin
Wang et al, 2006	China	Cohort	52	Low: 25 High: 27	Low: 65.28±3.09 High: 69.00±3.84	Low: 190±42 High: 168±48	Low: IV Dex 1 mg/kg/d for 3 d with tapers lasting 1 wk High: IV MP 4 mg/kg/d for 3 d, oral PND 4 mg/kg/d qod with tapers lasting 18-30 wk	Antibiotics, UDCA Fat-soluble vitamin
Davenport et al, 2007	United Kingdom	RCT	71	No: 37 Yes: 34	No: 54 (45-70) Yes: 60 (50-71)	No: 158 (125-183) Yes: 132 (112-166)	Oral PND 2 mg/kg/d from D7-D21 and 1 mg/kg/d from D22-D28	Antibiotics, phenobarbital, fat-soluble vitamin, MCT
Vejchapipat et al, 2007	Thailand	Cohort	53	No: 20 Yes: 33	No: 98.3±38.0 Yes: 84.7±25.7	No: 176.1±49.6 Yes: 189.8±44.5	PND 4 mg/kg/d for 3 d began on the D7 postoperatively, then at alternate d for 1-3 mon	Antibiotics, UDCA, fat-soluble vitamin
Chung et al, 2008	Hong Kong	Cohort	30	No: 17 Yes: 13	No: 62.5±16.5 Yes: 69.7±12.3	No: 160.2±18.3 Yes: 146.2±14.2	Oral PND 4 mg/kg/d for 2 wk on D7 postoperatively, then 2 mg/kg/d for 2 weeks, followed by 1 mg/kg/d for the last 2 wk	NA
Petersen et al, 2008	Germany	Cohort	49	No: 29 Yes: 20	No: 57±22 Yes: 63±32	No: 165±60 Yes: 175±67	IV MP 10 mg/kg/d for 5 d, then oral MP 1 mg/kg/d for 3 wk	Antibiotics, UDCA, fat-soluble vitamin, MCT
Davenport et al, 2013	United Kingdom	Cohort	152	No: 90 Low: 18 High: 44	No: 50(41-61) Low: 54(42-60) High: 46(39-55)	No: 144 (122-200) Low: 143 (112-177) High: 141 (103-182)	Low: oral PND 2 mg/kg/d for 2 wk from D7 postoperatively, followed by 1 mg/kg/d from D22-D28 High: oral PND 5 mg/kg/d D5-D9, with tapers D10-D30, then hydrocortisone 2.5 mg/kg/d bid D30-D32; 2.5 mg/kg/d qd D33-D35,	MCT, antibiotics, cholestyramine, phenobarbital Fat-soluble vitamin
Dong et al, 2015	China	Cohort	380	Low: 127 High: 253	NA	NA	Low: PND 4 mg/kg/d initially which was tapered to 2 mg/kg/d 1-2 wk High: IV PND4 mg/kg/d with tapers lasting 1 wk, then 8 to 12 weeks of oral PND 4 mg/kg/d qod and was tapered until patients became jaundice-free	Antibiotics, UDCA
Bezerra et al, 2014	United States	RCT	140	No: 70 Yes: 70	No: 69±25.2 Yes: 69±27.9	No: 7.9±2.8 Yes: 7.5±2.6	IV MP 4 mg/kg/d for 2 wk and oral PND 2 mg/kg/d for 2 wk followed by a tapering protocol for PND for 9 wk	NA

IV: intravenous; MP: methylprednisolone; PND: prednisone; Dex: dexamethasone; MCT: medium-chain triglyceride; UDCA: ursodeoxycholic acid; RCT: randomized controlled trial; KPE: Kasai portoenterostomy; NA: not available; qd: once a day; qod: every other day.

(40%),[9,12,14,15] 3 from the United States (30%),[6,10,11] and 3 from Europe (30%) (Table).[7,13,16] Eight studies investigated the effect of steroid treatment as compared to placebo,[6,7,10,11,13-16] and two studies compared the effects of high-dose to low-dose steroids.[9,12] There were no significant differences in age and bilirubin levels at KPE between patients received adjuvant high-dose steroid treatment and patients received low-dose or no steroids.

In the original studies, steroids were mainly methylprednisolone or prednisone or combined with other steroids such as dexamethasone. Other adjuvant therapies patients received include antibiotics, choleretic agents (e.g., ursodeoxycholic acid, cholestyramine), medium-chain triglyceride and fat-soluble vitamins.

Steroid treatment and jaundice free rate

Fig. 2 shows the results of the pooled associations between steroid treatment and jaundice free rate at different follow-up times following KPE. A marginal significant association between steroid treatment and jaundice free rate was found at 6 months after KPE (RR: 1.32; 95% CI: 0.995-1.76). There was a moderate heterogeneity across 9 studies included (I^2=72.6%, P<0.01). A significant association was found at 1 year of follow-up after KPE (RR: 1.35; 95% CI: 1.12-1.61) based on available data from 3 studies without heterogeneity (I^2=0.0%, P=0.91). However, the observed association disappeared at 2 years of follow-up (RR: 0.82; 95% CI: 0.55-1.22) based on available data from 2 studies. No heterogeneity was found between these 2 studies (I^2=0.0%, P=0.82). Publication bias was not evident using Egger's test or Begg's test (P>0.10 for all three pooled analyses).

Steroid treatment and native liver survival rate

Fig. 3 presents the results of the combined association between steroid treatment and native liver survival rate. According to the available data, no significant association was found between steroid treatment and native liver survival rate at any follow-up times after KPE [RR: 1.02; 95% CI: 0.95-1.15 for 6-month follow-up; RR: 1.10; 95% CI: 0.91-1.34 for 1 year; and RR: 1.00; 95% CI: 0.73-1.35 for 2-year]. Heterogeneity did not exist in the studies for the analysis at 6-month follow-up (I^2=0.0%, P=0.74) and 1-year (I^2=35.2%, P=0.19), but existed at 2-year follow-up after KPE (I^2=57.4%, P=0.052). Egger's test or Begg's test did not suggest publication bias for any of these three pooled analyses.

Sensitivity analysis

We excluded two studies that compared high-dose to low-dose steroid treatment from the pooled analyses,

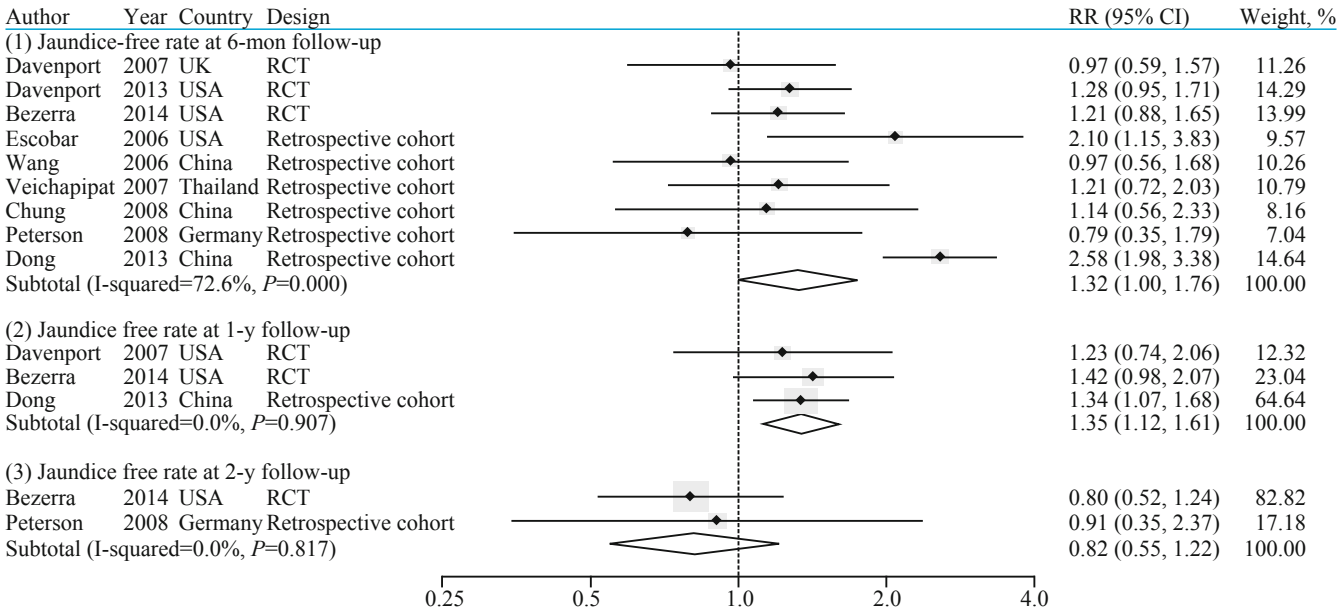

Fig. 2. Relative risk (RRs) and 95% confidence intervals (CIs) of jaundice free rate of biliary atresia patients at 6-month, 1-year and 2-year after Kasai portoenterostomy (KPE) comparing steroid users to non-users/placebo, or high-dose to low-dose or no steroids. The overall association is estimated by a random-effects model. The dots indicate the point estimates and the horizontal lines represent 95% CIs; the size of the shaded square is proportional to the weight of each study. RCT: randomized clinical trial.

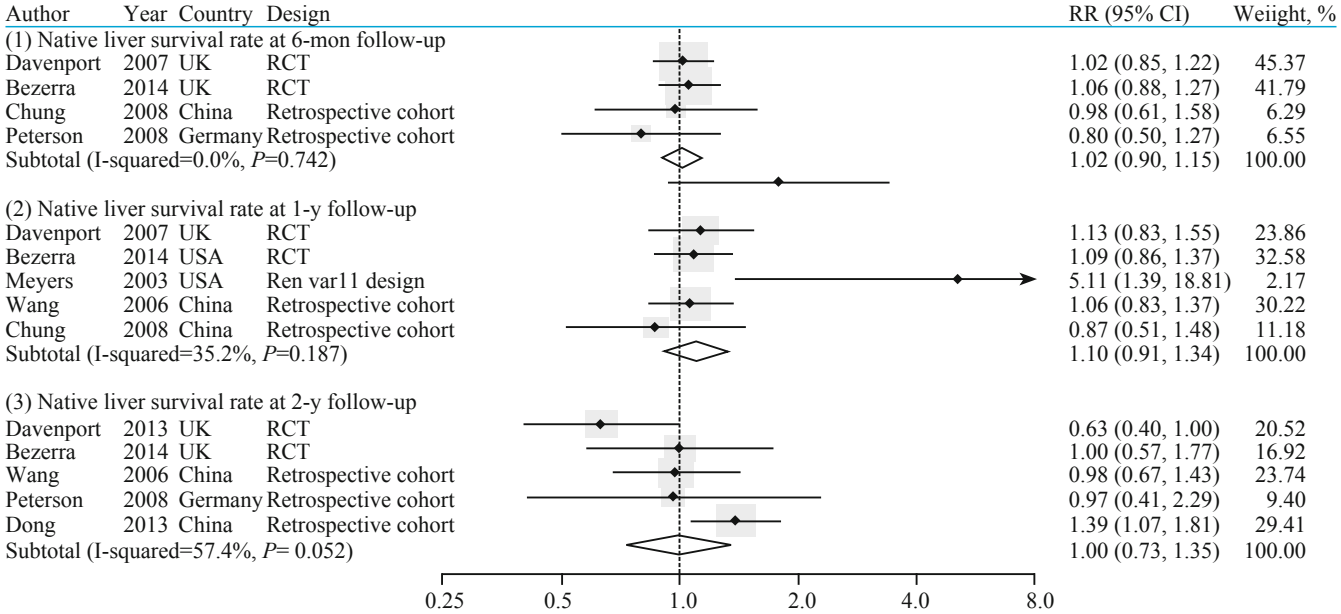

Fig. 3. Relative risk (RRs) and 95% confidence intervals (CIs) of native liver rate of biliary atresia patients at 6-month, 1-year and 2-year after Kasai portoenterostomy (KPE) comparing steroid users to non-users/placebo, or high-dose to low-dose or no steroids. The overall estimate is from a random-effects model; the dots indicate the point estimates and the horizontal lines represent 95% CIs; the size of the shaded square is proportional to the weight of each study. RCT: randomized clinical trial.

our results were not appreciably changed. Also, the findings were generally consistent when replacing random-effects model with fixed-effects model. In addition, omitting 1 study each time and the pooled RRs were not substantially influenced (data not shown).

Discussion

Accumulated evidence generated from this meta-analysis suggests that adjuvant steroid therapy following KPE may significantly improve postoperative clearance of jaundice for about a year, but may not

favorably affect native liver survival rate up to two years of follow-up.

Early successful clearance of jaundice, e.g., jaundice-free in the first 3 months after KPE,[17-20] has been recognized as an important predictor of good clinical outcome. The beneficial effect of adjuvant steroid therapy following KPE on jaundice in the first year of postoperation was observed in the present meta-analysis. Of note, the short-term improvement on clearance of jaundice did not improve ultimate clinical outcomes (indicators for later liver transplantation) up to 2 years of follow-up. One possible postulation is that most studies included only provided short-term/mid-term follow-up, which might not reflect long-term outcome. In addition, the successful clearance of jaundice at 3 months after KPE, a predictor of good clinical outcome, was only available in one study and not sufficient for further analysis.[15] Furthermore, the absence of cholangitis after KPE leads to a good clinical outcome.[20,21] A previous meta-analysis evaluated the effect of adjuvant steroid therapy on postoperative cholangitis rate, and found no significant improvement.[5] Since then, only one published study has investigated the impact of steroids on postoperative cholangitis rate.[12] Thus, we did not include cholangitis rate as a major clinical outcome in the present meta-analysis. Moreover, one study reported that adjuvant steroid treatment resulted in 3.5 days shorter hospital stay.[22] Unfortrunately, there were not enough studies for us to pool the results in the present meta-analysis.

Our meta-analysis adds substantial amount of additional information to the literature. Besides the updated literature, we included both clearance of jaundice and native liver survival rate as two major clinical outcomes in our study, which are of great clinical significance. Although the most recently published meta-analysis has reported that moderate-high steroid regimens improved jaundice clearance,[8] it did not analyze the effect of steroid treatment on improving native liver survival rate. In addition, the previously published meta-analyses of steroid treatment post-PKE included studies with limited sample sizes. Since the prevalence of BA is relatively high in eastern countries, we did comprehensive literature search from different databases including publications in English, Chinese and Japanese to find additional studies with the updated results. The relatively large sample size and diversity of the study populations may make our findings more generalizable. Of note, no evidence of publication bias was noted in the present meta-analysis. Moreover, the clinical outcomes of interest in the present meta-analysis were accessed at different period following PKE, which were not systematically evaluated in the previously published meta-analyses. This additional information generated from the present meta-analysis is of great significance of clinical practice.

However, some limitations of the present meta-analysis need to be discussed. First, a moderate heterogeneity was found when analyzing the relation between steroid use and jaundice free rate, which may result from variations in sample size, patient characteristics of each cohort, operation skills, postoperative therapy, etc. For example, patients receive KPE at a later age are more likely to have poor liver function and severe liver fibrosis, which lead to worse clinical outcomes.[23-26] However, our comparison of age and bilirubin level at KPE did not indicate clear heterogeneity across studies. Also, a variety of other adjuvant medicines was used across the studies to improve bile drainages and liver function, including different choleretic agents and nutritional supplements. However, previous studies found no significant benefits of these adjuvant medicines in improving clinical outcomes.[27-30] In addition, different prophylactic antibiotics were used to prevent cholangitis after KPE, but there is controversy about the value of any published antibiotic regimen. The data collected from the studies included in the present meta-analysis were not enough for us to conduct a stratified analysis to evaluate the effect of other adjuvant therapies. Nevertheless, further studies are needed to better understand the other adjuvant therapies. Furthermore, considering the heterogeneity across studies, a random-effects model was used instead of a fixed-effects model in the analyses to more accurately capture the overall association.

Second, the studies included in the present meta-analysis used different steroid regimens with various doses and durations. Unfortunately, there were insufficient data for stratified analysis based on dosage. Nevertheless, it is noteworthy that the effect of steroids in reducing the need for liver transplantation later in life seemed to be consistent across the individual studies. In addition, three studies compared the effects of high-dose to low-dose steroid treatment, no evidence has shown that high-dose steroid treatment has any advantage over low-dose treatment.[7,9,12] It can be reasonably speculated that the combination of different postoperative steroid regimens may function synergistically. Moreover, the duration of post-KPE steroids therapy still remains controversial. The debate focused on the timing of initial steroids therapy and tapering strategies. Of note, two introductory strategies had been described in the studies included: some studies used oral intake of steroids on restarting enteral feedings,[7,9-11,14,15] while others advocated IV steroids at the first day after KPE.[6,12,13,16] Since the initial steroids dosage and tapering strategy were not consistent across included studies, we were not able to conduct a stratified

analysis. Nevertheless, further research is warranted.

Another limitation is that the definition of native liver survival rate was inconsistent across included studies. Only two studies provided a clear definition of native liver survival with jaundice free status.[6,10] In future studies, the native liver survival rates should be strictly defined as the status with normal bilirubin level. Finally, in the present meta-analysis, we combined observational studies with RCTs because of the limited studies. Regardless, our findings were not appreciably modified by the study design (cohort studies vs. RCTs).

The failure to achieve jaundice-free state is a major complication of KPE, which indicates poor bile flow and clinical outcome.[19] Several pathological changes have been suggested to play important roles in the pathogenesis of the disease, and inflammation is considered as a key factor. Therefore, steroids have been used post-KPE for many years because of its anti-inflammatory and immunomodulatory properties.[3] Specifically, 1) Postoperative inflammatory closure of transected microscopic ducts was thought to be the major cause of jaundice after KPE. Steroids can impede the access of inflammatory cells to an inflammatory site to reduce inflammation;[31] 2) Abnormal inflammation-related cytokines may play a role in injures of intrahepatic bile ducts and liver fibrosis.[32,33] In addition, the elevation of inflammatory adhesion molecules and cytokines are detected and persisted even after successful KPE.[34] Steroids may ameliorate abnormal autoimmunity and tame the progress of bile ductules closure,[35] and 3) Liver fibrosis is common among the patients with BA ,which is caused by the obstruction of biliary ducts.[36] Steroids can increase canalicular electrolyte exchange by the induction of Na-K ATPase and stimulate bile flow.[37] Consequently, steroid therapy could reduce cholestasis and improve liver function. Although our results did not provide a clear pattern of supporting application of steroid therapy after KPE, the future studies can investigate the personalized usage of different dose and duration of steroid therapy.

Adverse effects associated with steroid use were not commonly reported in the primary studies, including fluid retention, increased appetite and gastrointestinal bleeding.[7,12,14] In addition, a RCT showed no statistically significant difference in adverse events between the steroids and placebo groups.[6] Therefore, the potential adverse effects did not limit the use of adjuvant steroids.

In conclusion, we found that adjuvant steroid therapy after KPE improved the clearance of jaundice up to one year. To date, no solid evidence supports longer-term beneficial effect of steroid use on the clearance of jaundice. In addition, adjuvant steroid therapy did not significantly improve the native liver survival rate or reduce the need for liver transplantation later in life. Future studies should focus on long-term effect of steroid use and the optimal dose of steroids.

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Ethical approval: All analyses were based on previous published studies, hence no ethical approval was required.

Competing interest: None of the authors had any conflicts of interest to disclose.

Contributors: CW and HK: study concept and design; ZMZ and XPC: literature search, study selection, and data extraction; XPC: statistical analysis; XPC and ZMZ: table and figure preparation; ZMZ, XPC and HK: the original manuscript drafting. All the authors completely consented with all the data in the study, critically reviewed the manuscript for important intellectual content and approved the final manuscript. All authors had the primary responsibility for the final manuscript.

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