

Early precut sphincterotomy does not increase the risk of adverse events for patients with difficult biliary access

A systematic review of randomized clinical trials with meta-analysis and trial sequential analysis

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Abstract

Objective: The present study was conducted to investigate whether early precut sphincterotomy (EPS) itself increases the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP), bleeding, and perforation, or improves the overall success rates of biliary cannulation.

Methods: Four electronic databases were searched systematically for randomized controlled trials (RCTs) reporting the incidence of adverse events for difficult biliary access (DBA) between EPS groups and persistent cannulation attempts (PCA). The primary endpoint was the incidence of PEP. Secondary outcomes were the incidence of bleeding and perforation, and the overall success rates of biliary cannulation. The Mantel-Haenszel method was used to pool data on the outcomes into random-effect models. Heterogeneity, sensitivity, and stratified analyses were performed with Review Manager 5.3. Furthermore, we performed trial sequential analysis (TSA) to evaluate the reliability of the primary endpoint and secondary outcomes.

Results: Seven RCTs (999 patients with DBA of 10450, 9.5%) were included. The incidence of PEP was significantly lower in EPS groups than PCA (risk ratio [RR] = 0.57, 95% confidence interval [CI] 0.36, 0.92, $P = .02$). Furthermore, TSA (TSA-adjusted 95% CI 0.30–0.82, $P = .0061$) and subgroup analysis stratified by the fellow involvement in initial cannulation before randomization, technique of precut, and the definition of DBA confirmed this finding. Success rates of overall cannulation (RR = 1.00, $P = .94$), bleeding (RR = 1.22, $P = .58$), and perforation (RR = 1.59, $P = .32$) were similar in both groups; however, the results of TSA could not confirm these findings.

Conclusion: Both the quality and the quantity of evidence supporting, compared with PCA, EPS itself do not increase the risk of PEP for DBA patients. Moreover, subgroup analysis demonstrated that EPS can significantly decrease the risk of PEP when it is performed by qualified staff endoscopists with using needle-knife fistulotomy earlier for patients with DBA.

Abbreviations: CI = confidence interval, DBA = difficult biliary access, EPS = early precut sphincterotomy, ERCP = endoscopic retrograde cholangiopancreatography, NKF = needle-knife fistulotomy, NKP = needle-knife papillotomy, PCA = persistent cannulation attempts, PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis, RCTs = randomized controlled trials, RR = risk ratio, TSA = trial sequential analysis.

Keywords: difficult biliary access, early precut sphincterotomy, ERCP, post-ERCP pancreatitis, systematic review

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1. Introduction

Since first reported in 1968,^[1] endoscopic retrograde cholangiopancreatography (ERCP) has become an invaluable procedure in the diagnosis and management of a variety of pancreaticobiliary disorders. However, about 10% of therapeutic ERCP may be considered difficult biliary access (DBA) in normal anatomy.^[2]

Precut sphincterotomy, which includes needle-knife papillotomy (NKP), septotomy, and needle-knife fistulotomy (NKF), is often performed to facilitate access to the common bile duct of patients with DBA. Furthermore, NKF has been recommended as the preferred technique for precutting by the European Society of Gastrointestinal Endoscopy (moderate quality, strong recommendation)^[3] and the latest International Consensus Panel (evidence level: I-B, recommendation grade:A).^[4]

Some meta-analyses^[5–8] of randomized controlled trials (RCTs) that compared the rates of biliary cannulation and the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) between early precut sphincterotomy (EPS) and persistent cannulation attempts (PCA), but the conclusions made by these meta-analyses^[5–8] are inconsistent which mainly was caused by the limitation of heterogeneity in the

study design that the majority of subjects (509 patients) of 2 RCTs reported by de Weerth et al^[9] and Khabtibian et al^[10] included in these meta-analyses were not subjects with DBA, and the patients in EPS groups accepted precut technique immediately after randomization. Moreover, no stratified analyses were conducted to give more details about the incidence of PEP. In addition, a recent meta-analysis^[11] with subgroup analysis stratified by trainees involvement, found a significant reduction in the incidence of PEP among patients with DBA in EPS groups wherein the procedure was implemented only by qualified biliary endoscopists. It also concluded that the rates of primary biliary cannulation increased in EPS groups. Nevertheless, the latest RCTs proved that EPS can significantly reduce the risk of PEP^[12] and there was no significant difference in the rates of primary biliary cannulation.^[12,13]

The definition of DBA varied widely,^[3,4,12,13] and these meta-analyses described above did not provide a clear idea about how to define the DBA. Furthermore, the latest guidelines for definition of DBA differed widely between the Latest guideline of European Society of Gastrointestinal Endoscopy^[3] (defining DBA as the presence of ≥ 1 of the following: >5 contacts with the papilla while attempting to cannulate; >5 minutes spent attempting to cannulate following visualization of the papilla; >1 unintended pancreatic duct cannulation or opacification) and the International Consensus Panel^[4] (defining DBA as the inability to achieve selective biliary cannulation by the standard ERCP technique within 10 minutes or up to 5 attempts or failure of access to the major papilla).

We, therefore, performed a pooled analysis of studies to investigate whether EPS itself increases the risk of PEP, bleeding, and perforation, or improve, the cannulation success rates for patients with DBA randomized to EPS or PCA. In addition, a trial sequential analysis (TSA) was conducted to ascertain whether the cumulative number of patients met the required sample size.

2. Methods

2.1. Literature research

A comprehensive literature search was performed on January 10, 2017 using PubMed, EMBASE, Web of Science, and ScienceDirect, restricted to articles published only in English. Keywords used were “endoscopic retrograde cholangiopancreatography/ERCP,” “difficult biliary cannulation/access,” “early precut sphincterotomy,” “precut sphincterotomy/papillotomy,” “needle-knife,” “transpancreatic papillary septotomy/sphincterotomy,” and “randomized controlled trial/trials.” The reference lists of any studies meeting the inclusion criteria were viewed manually to identify additional relevant publications.

2.2. Inclusion/exclusion criteria

Published studies were included if they met the following criteria: only patients with DBA consenting to randomization in an interventional design RCT that compare EPS with PCA; patients who required biliary cannulation but without previous sphincterotomy; and studies in which the incidence of PEP, bleeding, and perforation, and the rates of biliary cannulation were reported. The exclusion criteria were: animal studies; review articles, case reports or letters; duplicated publication; non-English articles; and studies in which enrolled patients were younger than 18 years, or patients with coagulopathy or acute pancreatitis.

2.3. Data extraction

Data extraction was conducted independently by 2 investigators (Z.T. and Y.Y.), with the discrepancies resolved by the consensus of these 2 investigators. The following details were recorded: Methods (study design, definition of DBA, enrollment period, year of publication, number of centers involved and their location, technique used in PCA group, timing of PCA, and type of precut techniques); Patients (the total number of patients enrolled in each study and the number of patients with DBA in each management group, indication of ERCP, mean age and sex, the number of salvage precut implemented in PCA groups, inclusion and exclusion criteria of each study; Intervention (fellows involved in the cannulation attempts in patients with DBA before the declaration of DBA, unintended pancreatic duct cannulations/injections, patients with DBA accepted EPS or PCA after randomization, use of pancreatic duct stent and/or nonsteroidal anti-inflammatory drugs; Outcomes (the incidence of PEP, bleeding, perforation, and rates of cannulation). This study did not require ethical approval as all the data used have been published previously, and hence are already in the public domain.

2.4. Definition of outcomes

The primary endpoint of this meta-analysis was the comparison of the incidence of PEP (EPS group vs. PCA group). The second endpoint was comparison of the incidence of the bleeding, perforation, and the rates of cannulation in these 2 groups. We assessed the incidence of PEP and perforation based on the consensus criteria.^[14] The procedure-related bleeding was defined as bleeding that required endoscopic intervention, transfusion, or surgery intervention. And the cannulation success rates were arbitrarily defined as the achievement of biliary cannulation successfully in the first ERCP session after randomization.

2.5. Quality assessment

The quality of RCTs was evaluated using domain-based risk of bias tables as recommended by the Cochrane Collaboration.^[15] Risk of bias was assessed according to the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; other biases. If ≥ 1 domains were judged as being high or unclear, we classified the trial as having a high risk of bias.^[15]

2.6. Statistical analysis

Meta-analysis of aggregate patient data was conducted by combining the risk ratio (RR) of individual studies into a pooled RR using the Mantel-Haenszel method. Intention-to-treat data were extracted from all studies. We used the χ^2 test to evaluate heterogeneity between trials and the I^2 statistic to describe the percentage of variability in effect estimates that are owing to heterogeneity rather than chance.^[16] Forest plots were generated by using standard techniques to summarize the included studies, with horizontal lines representing 95% confidence interval (CI) and the area of each square indicating the RR point estimate. All statistical analyses were carried out with the software Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2014) and TSA (0.9.5.10 Beta).

3. Results

3.1. Search results

The results of the literature search identified 121 articles, and among these, 7 RCTs^[12,13,17-21] (999 patients with DBA of 10450, 9.5%) were eligible for inclusion criteria in the meta-analysis. The number of studies excluded and included of each selective step is shown in Figure 1.

3.2. Characteristics of included studies

Various characteristics of 7 RCTs^[12,13,17-21] included in this meta-analysis are outlined in Table 1. The definition of DBA

varied widely according to cannulation time (failed cannulation after 5–12 minutes), the number of cannulation attempts or the number of pancreatic duct cannulations/ injections (failed cannulation after 3–5 unintended pancreatic duct cannulations/injections), in the RCTs included in the meta-analysis, but 2 studies^[12,19] defined DBA as failed biliary access within 5 minutes of initial biliary cannulation attempts or up to 3 passes of unintended pancreatic duct cannulations; 3 studies^[18,20,21] defined DBA as failed biliary access within 10 minutes of initial biliary cannulation attempts or up to 3 to 5 passes of unintended pancreatic duct cannulations/injections; 1 study^[17] just defined DBA as failed biliary access within 12 minutes of initial biliary

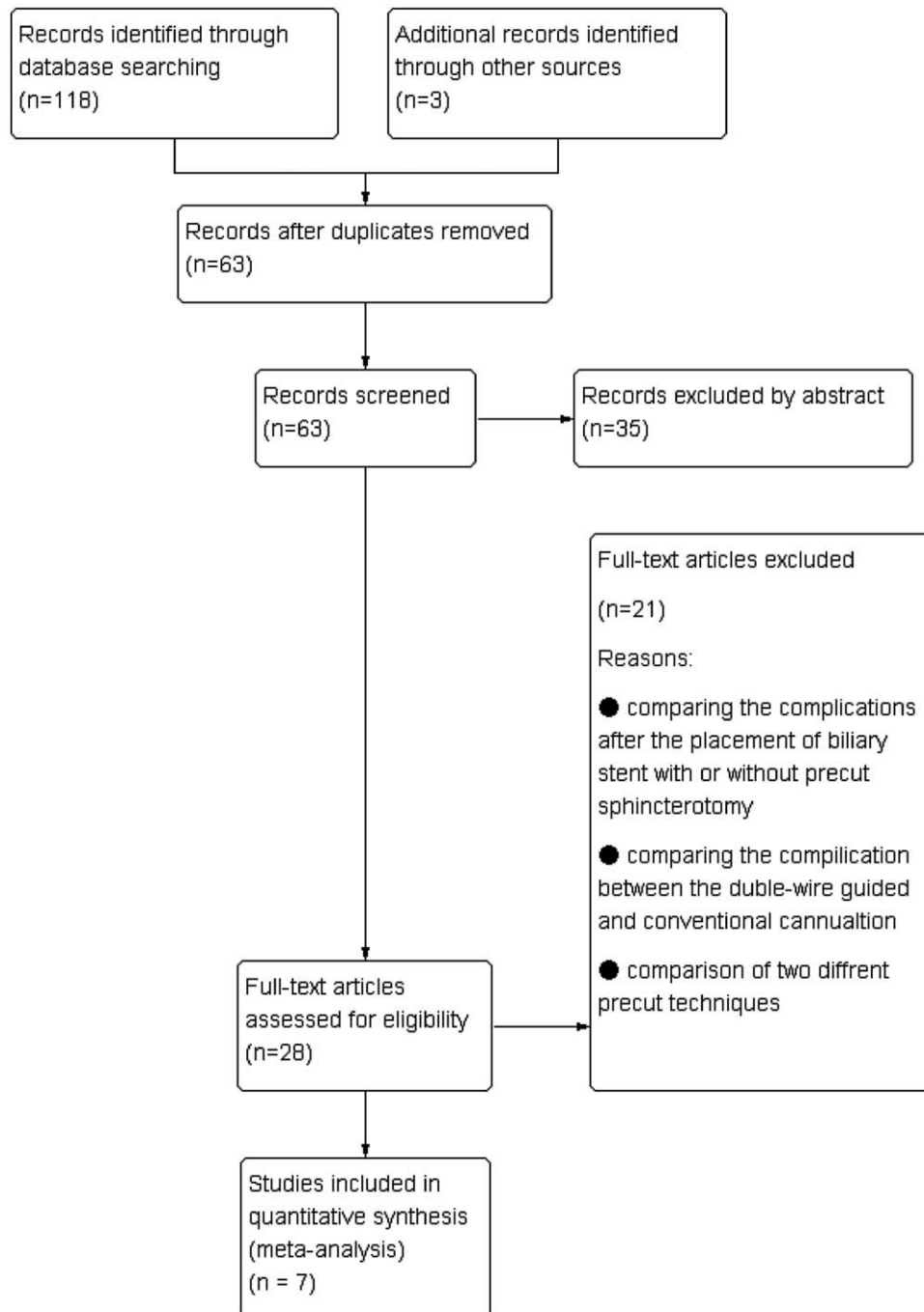


Figure 1. Search Flow Diagram.

Table 1**Characteristics of included studies.**

Author (year)	Study period	Country	Study design	Definition of difficult biliary cannulation	Precut technique	Technique used in PCA group	No. of difficult cannulation/ total enrollment	Fellow involved	Center involved	Timing of early precut	Timing of PCA post-randomization	Salvage precut in PCA group	Use of PEP prophylactic drugs or PD stents
Tang et al (2005) ^[17]	Sep 1985–Nov 1998	Canada	RCT	>12 min (7 min by fellow and 5 min by endoscopist)	NKP	Non-wire-guided sphincterotome	62/642 (9.7%)	Yes	Single	Precut immediately	15 min of biliary cannulation attempts AR	3/30 (10.0%)	No
Zhou et al (2006) ^[18]	Oct 2004–Feb 2006	China	RCT	>10 min OR >3 PD cannulation	NKP or NKF	Both wire- and non-wire-guided sphincterotome	91/948 (9.6%)	No	Single	Precut immediately	Not available	0/48 (0.0%)	-
Gennamo et al (2009) ^[19]	May 2004–Mar 2006	Italy	RCT	>5 min OR >3 PD cannulation	NKP	Wire-guided sphincterotome	146/1078 (13.5%)	No	Single	Precut immediately	20 min of biliary cannulation attempts AR	32/110 (29.1%)	No
Manes et al (2009) ^[20]	Jan 2007–Dec 2007	Italy	RCT	>10 min OR >5 PD injection	NKF	Both wire- and non-wire-guided sphincterotome	158/1654 (9.6%)	No	Multi center	Precut immediately	10 min of biliary cannulation attempts AR	50/74 (67.6%)	No
Swan et al (2013) ^[21]	Jul 2007–Dec 2009	Australia	RCT	>10 min OR >10 Attempts OR >4 PD cannulation	NKP	Wire-guided sphincterotome	73/690 (10.1%)	yes	Single	Precut immediately	10 min of biliary cannulation attempts AR	22/34 (64.7%)	PD stent was placed if PD have been cannulated at least twice before randomization (38/73, 52%)
Zagalsky et al (2016) ^[13]	Nov 2011–Dec 2013	Argentina	RCT	8 min OR >3 PD Cannulation	NKP	Wire-guided sphincterotome	101/1498 (6.7%)	No	Single	Precut immediately	Not available	0/51 (0.0%)	All patients in PCA group accepted PD stents placement (51/51, 100%)
Mariani et al (2016) ^[12]	Jan 2012–Dec 2013	Italy	RCT	>5 min OR >3 MPD cannulation	NKF	Wire-guided sphincterotome	375/3940 (9.5%)	No	Multicenter	Precut immediately	10 min of biliary cannulation attempts OR 3 additional MPD cannulation	135/190 (71.1%)	No

AR = after randomization; MPD = main pancreatic duct; NKF = needle-knife fistulotomy; NKP = needle-knife papillotomy; PCA = persistent cannulation attempts; PD = pancreatic duct; RCT = randomized controlled trial.

Table 2**Baseline characteristics and number of ERCP-related complications.**

Author (year)	Study group and number of each group	Mean age, y	Male/female	No. cannulation success	No. pancreatitis	No. bleeding	No. perforation
Tang et al (2005) ^[17]	Early precut (32)	64.6±13.3	15/17	31	2	1	0
	Persistent attempts (30)	67.2±12.7	14/16	28	2	0	0
Zhou et al (2006) ^[18]	Early precut (43)	62.7±11.5	26/17	39	1	1	0
	Persistent attempts (48)	64.3±10.6	29/19	36	2	0	0
Cennamo et al (2009) ^[19]	Early precut (36)	68 (38–84)	16/20	33	1	1	1
	Persistent attempts (110)	71 (34–88)	51/59	104	6	1	0
Manes et al (2009) ^[20]	Early precut (77)	66 (29–94)	50 /27	63	2	5	4
	Persistent attempts (74)	65 (26–95)	48 /26	66	11	2	2
Swan et al (2013) ^[21]	Early precut (39)	59±17.6	11/28	34	8	1	0
	Persistent attempts (34)	57±17.2	11/23	29	6	2	0
Zagalsky et al (2016) ^[13]	Early precut (50)	52±15.1	16/34	49	2	1	1
	Persistent attempts (51)	49±16.68	36/15	49	2	0	0
Mariani et al (2016) ^[12]	Early precut (185)	70.4±14.2	88/97	168	10	4	3
	Persistent attempts (190)	68.2±16.0	77/113	176	23	7	4

ERCP = endoscopic retrograde cholangiopancreatography.

cannulation attempts, and 1 study^[13] defined DBA as failed biliary access within 8 minutes of initial biliary cannulation attempts or up to 3 passes of unintended pancreatic duct cannulation. Furthermore, 1 study^[18] used NKF or NKP, 2^[12,20] used NKF, and remaining studies used NKP. In addition, 2 studies^[17,21] reported endoscopic trainees involved in the initial cannulation before randomization of patients with DBA during ERCP.

ERCP-related complications and the number of biliary cannulation success rates are summarized in Table 2. Except for 1 study reported by Zhou et al,^[18] which did not describe the definition of adverse events of ERCP and the inclusion and exclusion criteria, all studies^[12,13,17,19–21] defined adverse events of PEP according to published consensus criteria.^[14] In one study^[21] included in the analysis of PEP, a pancreatic duct stent was placed before randomization if the pancreatic duct had been cannulated at least twice, whereas there was no statistically significant difference in the use of pancreatic duct stent in both groups (15/34 [44%] in the PCA group vs. 23/39 [59%] in the EPS, $P < .01$). Another study^[13] in which a pancreatic stent was placed after randomization, but only in the PCA group. Furthermore, study reported by Zhou et al^[18] did not give details of whether PEP prophylaxis was used in PCA group or in EPS. No other RCTs included used PEP prophylaxis such as pancreatic stents, gabexate mesylate, somatostatin, indomethacin, or other nonsteroidal anti-inflammatory drugs.

For patients with DBA, the indications for ERCP varied, but the major indication for ERCP in included studies was choledocholithiasis (559/999, 56%). Data on patients with suspected biliary sphincter of Oddi dysfunction (25/999, 3%) and with a history of pancreatitis (31/999, 4%) were reported in four studies,^[12,13,20,21] and other 4four studies,^[12,17–19] respectively. All studies excluded patients who had a previous sphincterotomy and active pancreatitis.

3.3. Primary endpoint: the incidence of PEP in EPS groups versus PCA

The incidence of PEP for patients with DBA was 8% (78/999) among 7 studies.^[12,13,17–21] The RR and 95% CI for each study and the summary RR are shown in Figure 2A. The overall

summary estimated RR was 0.57 (95% CI 0.36, 0.92, $P = .02$). Heterogeneity testing revealed that $I^2 = 0\%$ and the P for heterogeneity was 0.44, using a random-effect model.

In Figure 2B with stratification by trainee involvement in initial biliary cannulation attempts, the pooled RR for PEP of 2 studies^[17,21] with fellow involvement (subgroup 2.1.1) was 1.11 (95% CI 0.47, 2.60, $P = .81$), heterogeneity testing revealed that $I^2 = 0\%$ and the P for heterogeneity was .84. In subgroup 2.1.2 including 4 studies without fellow involvement, the pooled RR was and 0.43 (95% CI 0.24, 0.75, $P = .003$), heterogeneity testing revealed that I^2 was 0% and the P for heterogeneity was 0.68, using random-effect model.

In Figure 2C, with subgroup analysis stratified by the precut technique, the pooled estimated RR for PEP of 2 studies^[12,20] (subgroup 3.1.1) in which needle-knife fistulotomy was performed was 0.35 (95% CI 0.16, 0.79, $P = .01$); heterogeneity testing revealed that $I^2 = 0\%$ and the P for heterogeneity was .26. The pooled RR of PEP among 4 studies^[13,17,19,21] (subgroup 3.1.2) in which needle-knife papillotomy was performed was 1.00 (95% CI 0.48, 2.07, $P = 1.00$); heterogeneity testing revealed that $I^2 = 0\%$ and the P for heterogeneity was .92.

In Figure 2D, with subgroup analysis stratified by the definition of DBA, the pooled RR for PEP of 2 studies^[12,19] (subgroup 4.1.1) that defined DBA as biliary access failed within 5 minutes of initial biliary cannulation attempts or >3 passes of unintended pancreatic duct cannulations was 0.45 (95% CI 0.23, 0.89, $P = .02$); heterogeneity testing revealed that $I^2 = 0\%$ and the P for heterogeneity was .91; and among 5 studies^[13,17,18,20,21] (subgroup 4.1.2) that defined the DBA as failed biliary access >8 minutes of initial biliary cannulation attempts or 3 to 5 passes of unintended pancreatic duct cannulations/injections was 0.68 (95% CI 0.31, 1.49), $P = .33$, and heterogeneity testing revealed that $I^2 = 20\%$ and the P for heterogeneity was .29.

3.4. Secondary Outcomes: the incidence of bleeding and perforation, and the success rates of overall biliary cannulation

All included studies^[12,13,17–21] provided the data on overall biliary cannulation success rates, and the incidence of bleeding and perforation, but no statistically significant

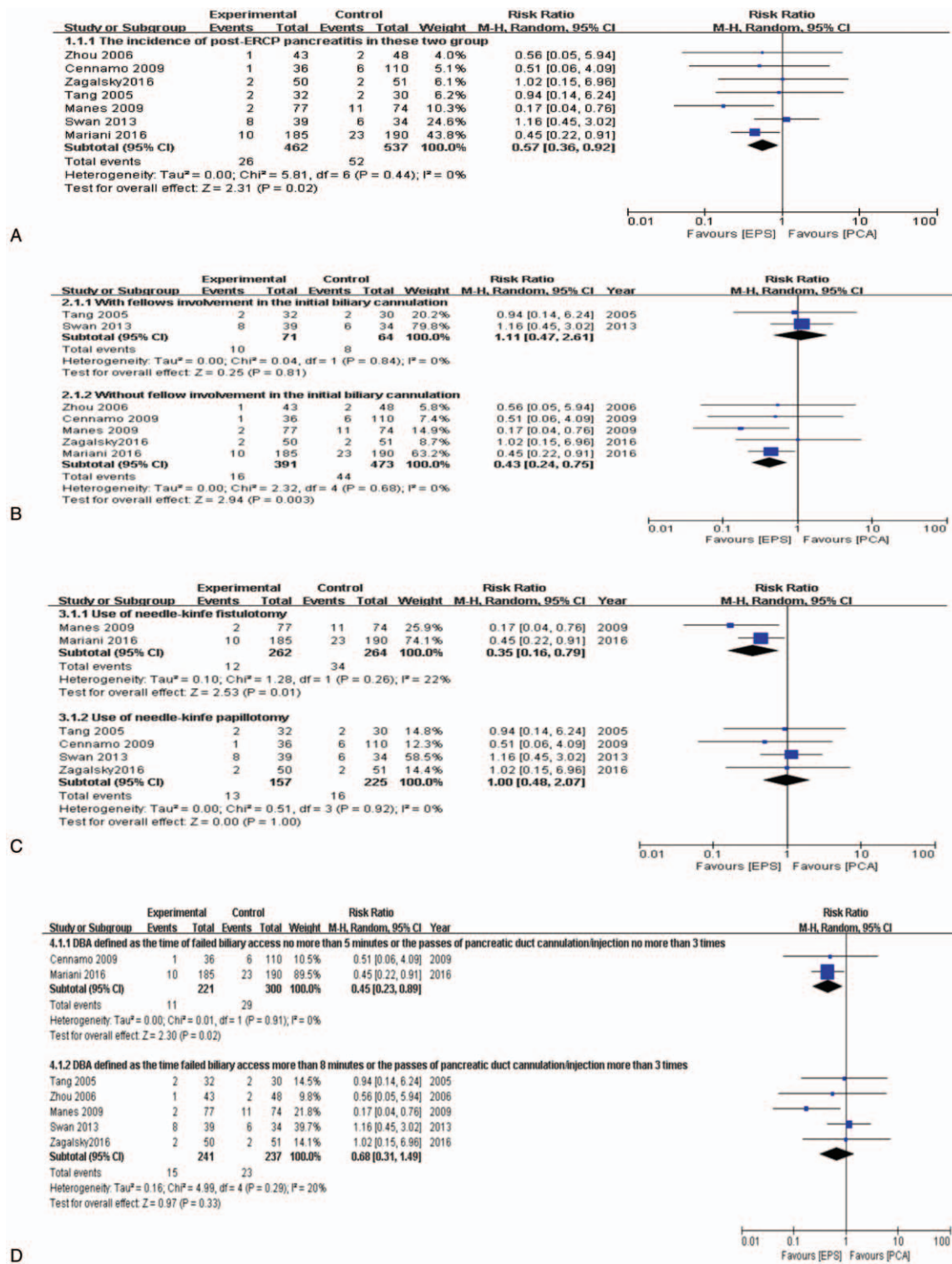


Figure 2. Forest plot for the incidence of PEP (A); stratification by trainee involvement initial cannulation before randomization (B); stratification by the technique of precut used in EPS group (C); stratification by the definition of DBA (D). CI = confidence interval, DBA = difficult biliary access, EPS = early precut sphincterotomy, PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis.

difference was found between 2 groups (Fig. 3). The pooled RRs were 1.22 (95% CI 0.60, 2.49, P = .58), 1.59 (95% CI 0.63, 4.02, P = .32), and 1.00 (95% CI 0.96, 1.04, P = .94), respectively.

The summary of results was provided in Table 3.

3.5. Quality assessment and publication bias

All studies included were RCTs, but no trials were judged to be of low risk of bias in all 6 domains (Fig. 4). The main reasons for high risk of bias were in adequate of allocation concealment, blinding of participants and personnel, or blinding of outcome

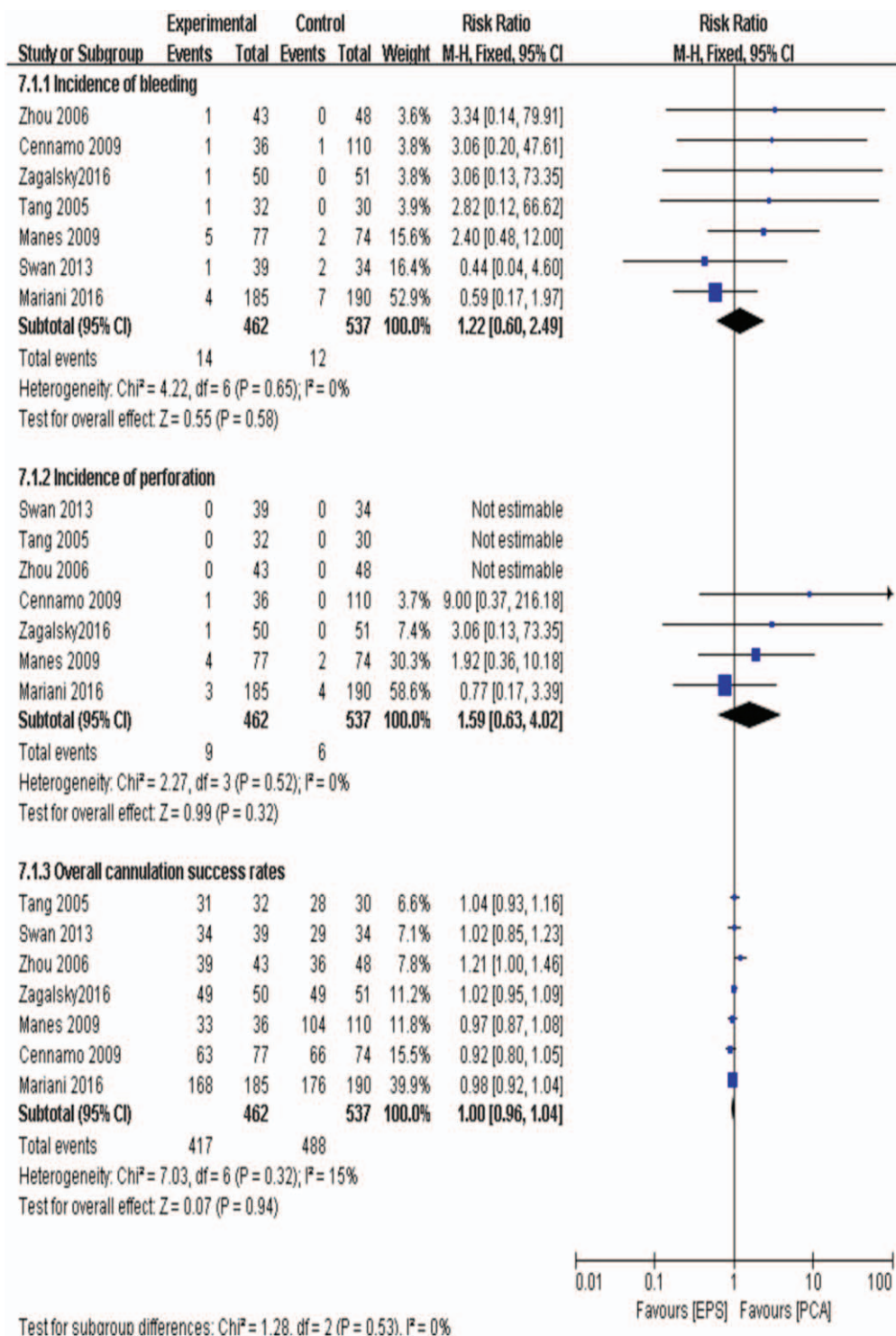


Figure 3. Forest plot for success rates of cannulation, the incidence of bleeding, and perforation.

assessment. Although all studies were conducted with a randomized controlled design, only 1^[21] was blinding of participants and personnel (performance bias). All studies had adequate generation of allocation sequence; concealment allocation was reported in only 4 studies. Furthermore, 3 studies^[12,20,21] had a blinding outcome assessment, and 2 studies^[12,21] were terminated by the researchers after interim

analysis. Visual inspection of the funnel plots revealed no obvious asymmetry to suggest publication bias (Fig. 5).

3.6. TSA

As Figure 6A showed, TSA showed that the required information size (required number of DBA patients) for the incidence of PEP

Table 3
Summary of results.

Outcomes	Studies (participants)	Risk ratio (95% CI)	Test for heterogeneity			
			<i>P</i> *	<i>I</i> †		
Incidence of post-ERCP pancreatitis	Primary endpoint					
	Figure 2A	Overall results	7 (999)	0.57 (0.36, 0.92)	.44	0%
	Supplementary Figure 1	Overall results	5 (825)	0.42 (0.24, 0.75)	.70	0%
	Supplementary Figure 2	Overall results	4 (734)	0.42 (0.23, 0.75)	.54	0%
	Figure 2B	Subgroup 2.1.1	2 (135)	1.11 (0.47, 2.60)	.84	0%
		Subgroup 2.1.2	5 (864)	0.43 (0.24, 0.75)	.68	0%
	Figure 2C	Subgroup 3.1.1	2 (526)	0.35 (0.16, 0.79)	.26	22%
		Subgroup 3.1.2	4 (382)	1.00 (0.48, 2.07)	.92	0%
	Figure 2D	Subgroup 4.1.1	2 (521)	0.45 (0.23, 0.89)	.91	0%
		Subgroup 4.1.2	5 (478)	0.68 (0.31, 1.49)	.29	20%
Incidence of bleeding	Figure 3	Subgroup 7.1.1	7 (999)	1.22 (0.60, 2.49)	.65	0%
Incidence of perforation	Figure 3	Subgroup 7.1.2	7 (999)	1.59 (0.63, 4.02)	.52	0%
Overall cannulation success rates	Figure 3	Subgroup 7.1.3	7 (999)	1.00 (0.96, 1.04)	.32	15%

CI = confidence interval, ERCP = endoscopic retrograde cholangiopancreatography.

* *P* value of χ^2 test for heterogeneity.

† *I* test for heterogeneity.

was 599. The cumulative *z* curve crossed the conventional boundary for benefit ($P < .05$) and the trial sequential monitoring boundary for benefit ($P < .05$). However, as Figure 6B–D showed, *z* curves for the incidence of bleeding and perforation, and the success rates of overall biliary cannulation showed no intersection with the conventional boundary for benefit ($P = .05$). The cumulative number of DBA patients failed to meet the required information size. The required number of patients for the incidence of bleeding and perforation, and the success rates of overall biliary cannulation were 3995, 6086, and 8124, respectively, which indicated that the false-negative results are possible. Therefore, further studies are needed to validate these conclusions.

3.7. Sensitivity analysis

As described in characteristics of included studies, in one study reported by Swan et al,^[21] pancreatic duct stent was placed if pancreatic duct had been cannulated at least twice before randomization, even though there was no significant difference ($P < .01$) in the use of pancreatic duct stents between these 2

groups. Furthermore, in another study reported by Zagalsky et al,^[13] pancreatic stent was placed after randomization, but only in the PCA group. To minimize this confounding factor, we excluded these 2 studies, the pooled RR was 0.42 (95% CI 0.24, 0.75, $P = .003$), and the heterogeneity testing revealed that $I^2 = 0\%$ and the *P* for heterogeneity was .70, as shown in Supplementary Figure 1, <http://links.lww.com/MD/C455>. In addition, we excluded a study^[18] reported by Zhou et al, as there was no details of using PEP prophylaxis as represented in Supplementary Figure 2, <http://links.lww.com/MD/C455>; the pooled RR was 0.42 (95% CI 0.23–0.75) and the heterogeneity testing revealed that I^2 was 0%, and *P* for heterogeneity was .54. In summary, we get a more authentic result and the significant result of pooled analysis of the incidence of PEP did not vary by excluding these studies.

4. Discussion

Although diclofenac or indomethacin rectally administered before or closely after ERCP is inexpensive and safe and is recommended in every patient^[22] (without renal failure)

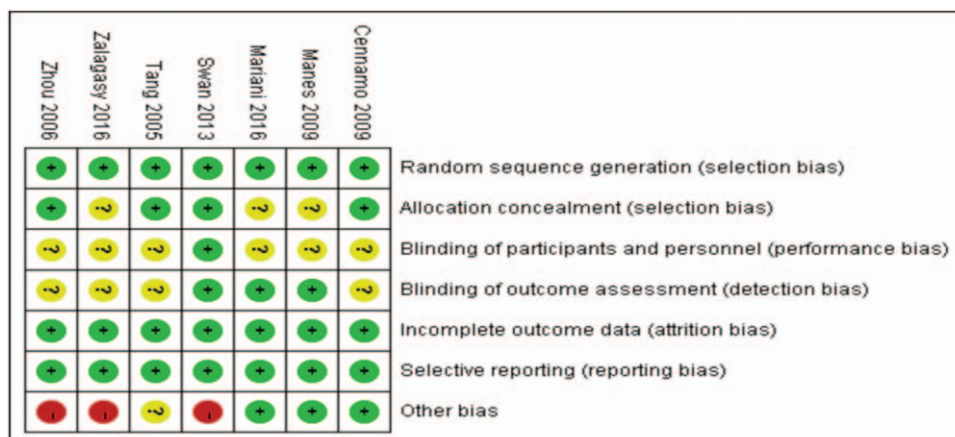


Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

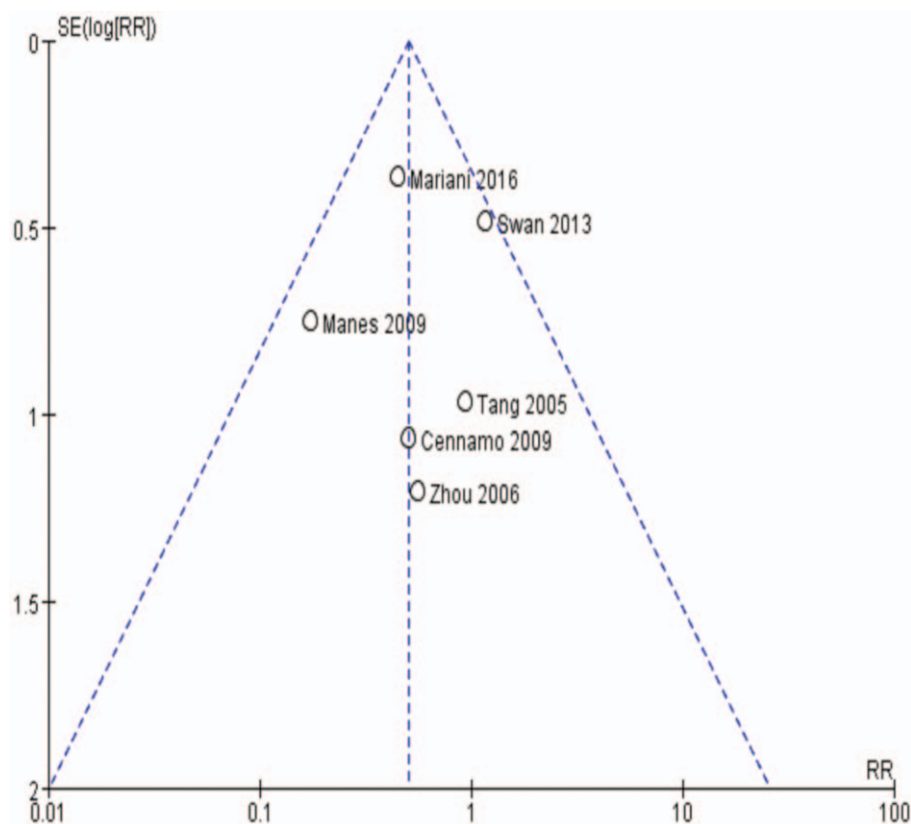


Figure 5. Funnel plot for the pooled analysis of PEP. PEP=post-endoscopic retrograde cholangiopancreatography pancreatitis.

undergoing ERCP, no trials included in this meta-analysis utilized the use of rectal nonsteroidal anti-inflammatory drugs. Furthermore, pancreatic stenting in patients with DBA has also been shown to reduce the incidence of PEP,^[23] but in our meta-analysis, we performed a sensitivity analysis in the pooled analysis of the incidence of PEP by excluding 2 studies^[13,21] in which pancreatic stenting was performed in PCA groups or EPS. And the significant result ($RR = 0.42$, $P = .003$) of pooled analysis did not vary by excluding these 2 studies. Importantly, this result was confirmed in the subgroup analyses (Fig. 2B–D) and in the TSA (Fig. 6A.)

In the subgroup analysis of fellow involvement in the initial biliary cannulation before randomization (Fig. 2B), for patients with DBA, the risk of PEP was significantly decreased ($RR = 0.43$, $P = .003$) in the EPS group wherein the procedure of ERCP was fulfilled only by the staff endoscopists (subgroup 2.1.2). On the contrary, no significant difference was found in subgroup 2.1.1 wherein trainees were involved in the initial biliary cannulation in patients with DBA. The finding implies that when trainees are involved in the initial cannulation in patients with DBA, there seems no difference in terms of the rates of PEP whether the staff endoscopist uses PCA or EPS when he/ she takes over the scope after the DBA is declared. However, for the staff endoscopist, in case of encountering patients suspected with DBA, there is a significant reduction in the risk of PEP when EPS is used compared with using PCA, and in subjects with the risk factors of PEP (patient related), the initial cannulation attempts should be performed only by qualified endoscopists.

In the subgroup analysis by the technique precut (Fig. 2C), for patients with DBA, compared with PCA, the risk of PEP was

significantly decreased in the EPS group (subgroup 3.1.1) wherein NKF was performed ($RR = 0.35$, $P = .01$). However, no significant difference was found in terms of the incidence of PEP between PCA group and EPS group where NKP was performed by operators. Furthermore, comparing the incidence of PEP in the EPS groups wherein NKF was performed and wherein NKP was performed, we found a stronger trend of the incidence of PEP (12/150, 8.0%) in EPS group wherein NKP was performed compared with wherein the NKF was performed (12/262, 4.6%). Differences in severity of papillary trauma caused by these 2 types of precuts may account for this difference. The finding implies that there is no significant difference in the rates of PEP for patients with DBA whether the staff endoscopist uses NKP or PCA. On the contrary, if the staff endoscopist encounters the DBA, there is a significant reduction in the rates of PEP when NKF is performed compared with PCA.

In the pooled analysis the incidence of PEP with subgroup analyses stratified by the definition of DBA (Fig. 2D). When the DBA was defined as the time of biliary cannulation no more than 5 minutes or the passes of pancreatic duct cannulation/injection no more than 3 times, the risk of PEP in EPS group was significantly lower than that of PCA ($RR = 0.45$, $P = .02$). However, when DBA was defined as the time of initial biliary cannulation >8 minutes or >3 passes of unintended pancreatic duct cannulations, there was no statistically significant difference in terms of the risk of PEP for patients with DBA in these 2 groups ($RR = 0.54$, $P = .08$). This finding indirectly strengthens the hypotheses^[23–26] that mechanical damage to papilla and to the pancreatic sphincter owing to prolonged cannulation attempts or damage owing to contrast injections/unintended pancreatic duct cannulations results in PEP.

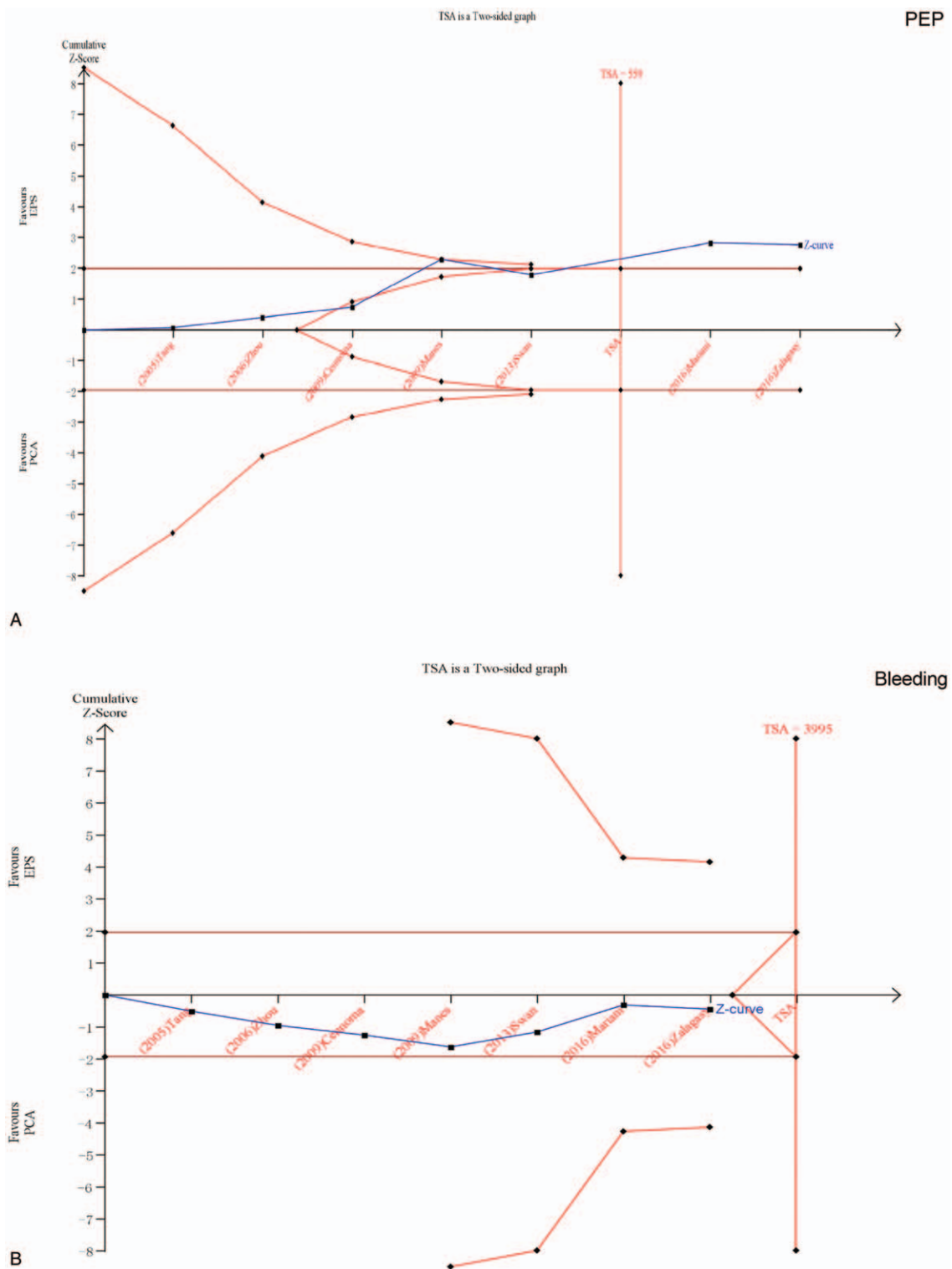


Figure 6. Trial sequential analysis of included trials investigating the incidence of PEP, bleeding, and perforation, and the overall success rates of biliary cannulation of EPS and PCA for DBA patients. (A) The incidence of PEP. (B) The incidence of bleeding. (C) The incidence of perforation. (D) The overall success rates of biliary cannulation. DBA=difficult biliary access, EPS=early precut sphincterotomy, PCA=persistent cannulation attempts, PEP=post-endoscopic retrograde cholangiopancreatography pancreatitis, TSA=trial sequential analysis.

No statistically significant difference was found in the pooled analysis of the incidence of bleeding (RR=1.22, $P=.58$) and perforation (RR=1.59, $P=.32$), and the biliary cannulation success rates (RR=1.00, $P=.94$). Although there is a tendency

for higher rates of bleeding (RR=1.22, $P=.58$) and perforation (RR=1.59, $P=.32$) in EPS groups compared with PCA, the incidence of these complications was low and comparable to the data reported in the literatures.^[27,28] Furthermore, in the TSA of

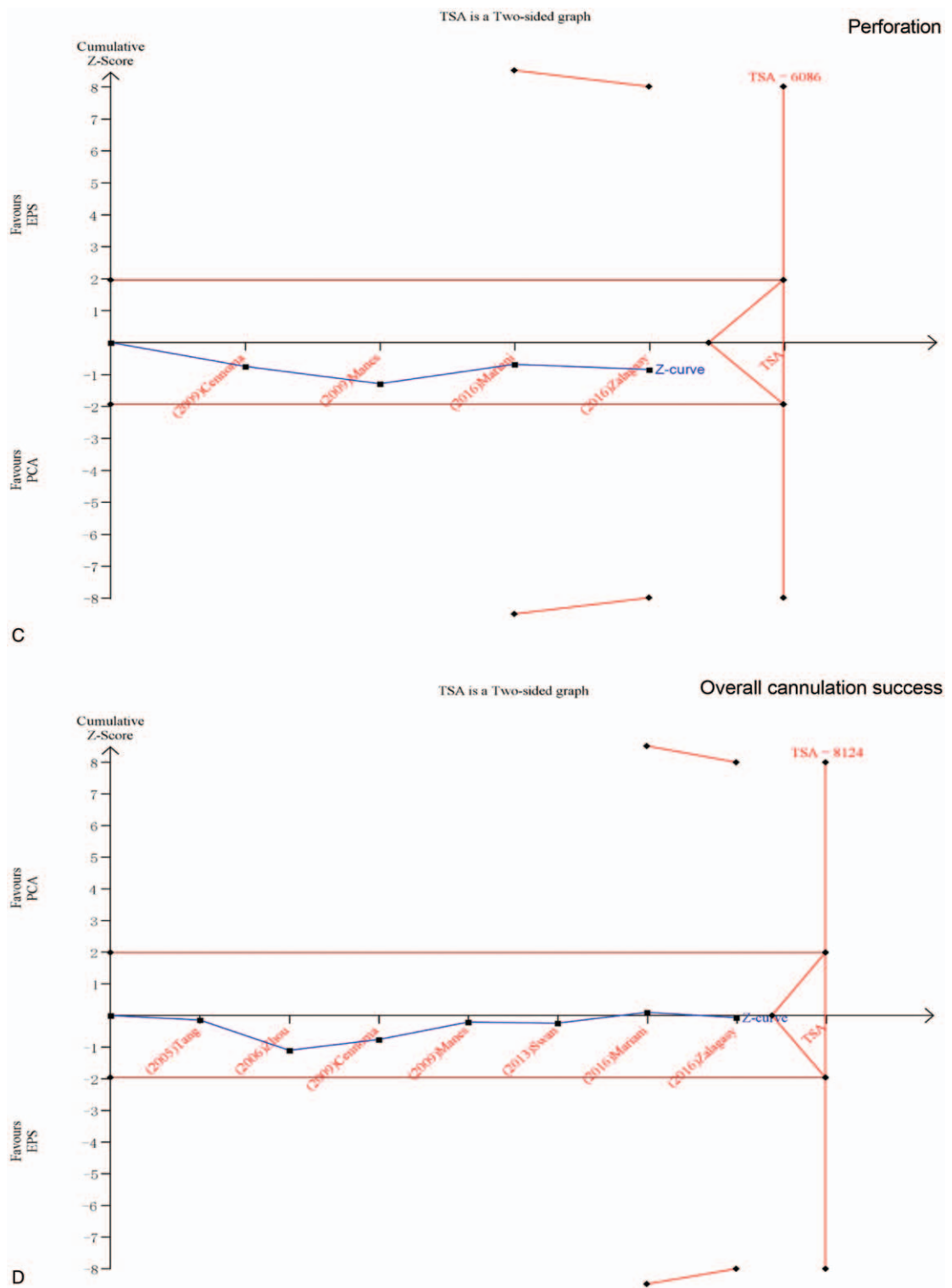


Figure 6. (Continued).

the incidence of bleeding and perforation, and the success rates of overall biliary cannulation, none of the z curves intersected with the conventional boundary for benefit ($z = \pm 1.96, P = .05$), and the cumulative number of DBA patients failed to meet the required information size, which indicates that false-negatives were possible. Further studies are needed to validate these findings.

As we know, precut sphincterotomy is employed as a salvage technique in case of encountering DBA after multiple attempts at conventional cannulation in routine clinical practice. The conclusions of previous meta-analyses^[5-8,11] focused on investigating whether EPS itself increase the risk of adverse events for patients with DBA were not consistent (3 studies^[5,8,11] concluded that EPS can reduce the risk of PEP, and another 2^[6,7] concluded

that EPS does not increase the risk of PEP compared with PCA), which can be accounted for the heterogeneity among studies included in these meta-analyses. To reduce the heterogeneity among studies (varied definition of DBA, type of precut, and fellows' involvement in initial cannulation attempts before declaration of DBA) included in the meta-analysis, we conducted a subgroup analysis and sensitivity analysis on the analysis of the risk of PEP between EPS group and PCA. By comparing the EPS after failed conventional cannulation with a reduced other risk factors among studies included in this meta-analysis, we made a more reliable conclusions.

Our meta-analysis has several limitations. First, the definition of DBA and the indication of ERCP for patients with DBA varied among RCTs included in this meta-analysis. Second, the salvage precut sphincterotomy (242/438, 55.3%) had been implemented in PCA groups in eventually 5 of 7 RCTs.^[12,17,19–21] Finally, 2 types of precut techniques were used across the studies, and it was reported that NKF had a lower risk of PEP than NKP.^[29] These confounding factors may introduce a bias that cannot be neglected.

The strength of this current meta-analysis is the inclusion of only RCTs, which represents the highest level of evidence for evaluating the efficacy of preventive interventions.^[30] Stratification by the fellow involvement, definition of DBA, and technique of precut were performed in pooled analysis of the risk of PEP to minimize the confounding factors in each group. The stable results of sensitivity analysis made the primary endpoints of present meta-analysis more credible. In addition, we conducted the TSA to assess the reliability and conclusiveness of the endpoints.

Seven RCTs^[12,13,17–21] included in this meta-analysis offered adequate information of randomization. Although 4^[17–19,21] offered the details of allocation concealment, the allocation concealment in the remaining studies^[12,13,20] was unclear, which would yield selection bias and performance bias. In study reported by Zhou et al,^[18] NKP was always applied when stricture of papillary orifice and failure of standard cannulation were encountered, and the fistulotomy technique with needle knife was always indicated when stricture of the papillary orifice inflammatory or tumorous, stone impacting on the papillary orifice, significant eminence of the ampulla, and the failure of normal cannulation were encountered, so this would lead to high performance bias more or less.

5. Conclusions

This systematic review using meta-analysis and TSA has demonstrated that the quality and quantity of evidence supporting, compared with PCA, EPS itself does not increase the risk of PEP for DBA patients. Nevertheless, EPS can significantly decrease the risk of PEP when it is performed by qualified staff endoscopists using needle-knife fistulotomy earlier for patients with DBA. EPS cannot improve the success rates of overall biliary cannulation for DBA patients. There is a high trend of risk of bleeding and perforation in EPS group, but it is not significant.

Author contributions

Z.T.—study concept and design; collection and extraction of data, statistical analysis and interpretation of data, and drafting of the manuscript; critical revision of the manuscript for important intellectual content; final approval of the version to be published;

Y.Y. and Z.Y.—collection and extraction of data, analysis and interpretation of data, and final approval of the version to be published.

W.M. and X.L.—study supervision and funding acquisition, critical revision of the manuscript for significant intellectual content, final approval of the version to be published.

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