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REVIEW ARTICLE

Duct-to-Mucosa Versus Invagination Pancreaticojejunostomy Following Pancreaticoduodenectomy: a Systematic Review and Meta-Analysis

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Abstract
Background Postoperative pancreatic fistula (POPF) is one of the most common complications after pancreaticoduodenectomy (PD). The ideal choice of pancreaticojejunostomy (PJ) anastomosis remains a matter of debate.
Methods A meta-analysis of randomized controlled trials (RCTs) comparing duct-to-mucosa with invagination PJ following PD was performed. Pooled odds ratio (OR) with 95 % confidence intervals (CI) were calculated using fixed-effects or random-effects models.
Results In total, five RCTs involving 654 patients were included. Meta-analysis revealed no significant difference in POPF rate between the duct-to-mucosa and invagination PJ techniques (OR=1.23, 95 % CI=0.78–1.93; P=0.38). Two of five trials applied the POPF definition proposed by the International Study Group of Pancreatic Surgery (ISGPS). Using this definition, the incidence of clinically relevant POPF was lower in patients undergoing invagination PJ than in those undergoing duct-to-mucosa PJ (OR=2.94, 95 % CI=1.31–6.60; P=0.009). There was no significant difference in terms of delayed gastric emptying, intra-abdominal collection, overall morbidity and mortality, reoperation rate, and length of hospital stay between the two groups.
Conclusion Invagination PJ is not superior to duct-to-mucosa PJ in terms of POPF and other complications but appears to reduce clinically relevant POPF. Further well-designed RCTs that use ISGPS definition are still required before strong evidence-based recommendations can be formulated.

Keywords Duct-to-mucosa · Invagination · Pancreaticojejunostomy · Pancreaticoduodenectomy · Pancreatic fistula

Introduction

Pancreaticoduodenectomy (PD) is the standard of care for patients with malignant or benign diseases of the pancreatic head and periampullary region. Following the resectional aspect of PD, three anastomoses are commonly used to reestablish gastrointestinal continuity: a pancreatic-enteric anastomosis, a biliary-enteric anastomosis, and a gastric or duodenal-enteric anastomosis.[1] The pancreatic-enteric anastomosis is, by far, the most problematic, and has been considered the Achilles heel of PD because it is associated with significant measurable risk of leakage or failure of healing, resulting in postoperative pancreatic fistula (POPF).[1,2] POPF then drives the majority of surgical complications associated with PD, including the potential for intra-abdominal collection or abscess, hemorrhage, the occasional need for reoperation, and possible death. Although the mortality rate after PD has decreased to less than 5 % among high-volume centers, the morbidity rate remains high, ranging from 30 to 50 %.[3] Among these, POPF arising from the pancreatic-enteric anastomosis is the most common cause of morbidity, with a frequency ranging from 5 to 40 %.[4] It is associated with increased morbidity (sepsis and hemorrhage) and mortality (20–40 %) and may

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result in prolonged hospitalization and increased hospital costs.[4]

Multiple clinical trials have been published focused on reducing POPF following PD, including the use of prophylactic octreotide,[5,6] the use of sealants,[7] placement of a pancreatic duct stent,[8,9] and reconstruction with pancreaticogastrostomy (PG).[10,11] The safe pancreatic reconstruction after PD continues to be a challenge and the variety of reconstruction is a reflection of the lack of the ideal one.[4]

Pancreaticojejunostomy (PJ) is the preferred reconstruction after PD and there are two widely used methods to accomplish an end-to-side PJ: duct-to-mucosa PJ or invagination PJ.[1] In an early single-institution trial comparing the duct-to-mucosa with invagination PJ techniques, Bassi and colleagues[12] reported a POPF rate of 14 % in 144 patients, with no significant difference between the two techniques. In another experience reported by Chou and colleagues,[13] the POPF rate was 4 % for duct-to-mucosa PJ and 15 % for invagination PJ, and duct-to-mucosa is the preferred pancreatic-enteric anastomosis. However, a dual-institution trial by Berger et al.[2] revealed fewer POPF with invagination (12 %) compared with duct-to-mucosa PJ (24 %) after PD. A more recent randomized study by El Nakeeb and colleagues[14] found that invagination PJ was not associated with a lower rate of POPF, but it was associated with decreased severity of POPF. Thus, whether there is a difference regarding POPF rate between duct-to-mucosa and invagination techniques is unclear and the optimal PJ method remains controversial.

The aim of this systematic review was to meta-analyze the evidence regarding outcomes of PD with duct-to-mucosa or invagination PJ. The POPF rate as well as other postoperative complications between these two techniques were compared.

Materials and Methods

Study Selection

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15] A systematic review of the literature was conducted to identify studies comparing duct-to-mucosa with invagination PJ during PD. Studies were identified by searching MEDLINE, EMBASE, and Cochrane-controlled trial register for studies published between November 1945 (when duct-to-mucosa anastomosis technique during PD was first mentioned[16]) and April 2015. The following search terms were used: "duct-to-mucosa," "invagination," "pancreaticojejunostomy," and "pancreaticoduodenectomy." Our literature search was limited to articles that described the design of randomized controlled trial (RCT). The electronic search was supplemented by a hand search in ClinicalTrials.gov and the Current Controlled Trials registry. Reference lists for all relevant studies, recent editorials, and related review articles were also checked for further eligible studies.

Inclusion and Exclusion Criteria

Two reviewers (J.H. and Z.H.) identified and screened the search findings for potentially eligible RCTs that compared duct-to-mucosa with invagination PJ after PD. For inclusion in the meta-analysis, a study had to fulfill the following criteria: an English language article published in a peer-reviewed journal, with the report describing at least one of the outcomes mentioned below. The following were excluded: abstracts, letters, editorials, case reports, expert opinions, and reviews without original data.

Outcomes of Interest

The primary outcome measure was POPF rate. For studies published after 2005 when the definition of POPF by the International Study Group of Pancreatic Surgery (ISGPS)[3] was formulated, clinically relevant POPF (grades B and C) was also recorded. Secondary outcome measures included delayed gastric emptying (DGE), intra-abdominal collection, overall morbidity and mortality, reoperation rate, and length of hospital stay.

Data Collection

The following data were extracted: first author, year of study period, country where the study was conducted, number of patients in each arm, study population characteristics, operation details, postoperative somatostatin analogs use, histopathology, and outcomes of interest mentioned earlier. Data were extracted independently onto a standardized collection form by two reviewers (J.H. and Z.H.) and cross-checked. Inconsistencies were resolved through discussion with a third reviewer (Z.S.) until consensus was reached.

Evaluation of Quality and Levels of Evidence

The methodological quality of included RCTs was assessed based on the Cochrane Handbook for Systematic Reviews of Interventions.[17] Each RCT was assessed according to the following seven criteria: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias. In addition, trials were rated for levels of evidence according to the Oxford Centre for Evidence-Based Medicine in the UK.[18]

Statistical Analysis

Data analyses were performed using Review Manager 5.3 software (The Cochrane Collaboration 2012, The Nordic Cochrane Centre, Copenhagen, Denmark). Heterogeneity among trials was assessed by the Cochrane Q statistic ($P<0.10$ was considered representative of statistically significant heterogeneity) and the I^2 statistic ($I^2>50$ % was considered to represent significant heterogeneity).[19] Initially, a fixed-effects model was used to synthesize all data. However, if there was evidence of heterogeneity among the included studies, random-effects model as described by DerSimonian and Laird was used.[20] Results of all meta-analyses are presented as odds ratios (ORs) with 95 % confidence intervals (CIs). Subgroup analysis stratified by pancreatic texture on POPF was performed if possible. Sensitivity analysis was performed to evaluate the stability of the results. Each study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled effect estimate. Funnel plots were used to evaluate potential publication bias, based on the primary outcome POPF.

Results

Literature Search

A flow diagram of our literature search is shown in Fig. 1. Initially, through the electronic database search, we found 162 citations: 114 from MEDLINE, 26 from EMBASE, and 22 from Cochrane Library. The searches in ClinicalTrials.gov and the Current Controlled Trials registry yielded four more records. Examinations of reference lists for all relevant papers, recent editorials, and related review articles did not yield any further studies for evaluation. We identified 134 citations after excluding duplicates. Of these citations, we excluded 128 after screening the titles and abstracts. After further screening of the six full-text articles, one study was excluded because it was a non-English study. The remaining five RCTs[2,12–14,21] were included in qualitative analysis and final meta-analysis.

Study Characteristics

The characteristics of each RCT are presented in Tables 1 and 2. Our meta-analysis included 654 patients (368 males and 286 females) who underwent PD from five different countries; of these, 325 received duct-to-mucosa PJ, and 329 received invagination PJ; 60.6 % of the patients in the duct-to-mucosa group (197/325) received pylorus-preserving PD, which was comparable with the invagination group (60.5 %; 199/329). The mean ages were 62 years old in the duct-to-mucosa group and 61 years old in the invagination group. Mean operative times were 367 min in the duct-to-mucosa group and 345 min in the invagination group. The quality assessment of the included RCTs is shown in Fig. 2. The level of evidence was 2b for all included studies, according to the Oxford Centre for Evidence-based Medicine.

Primary Outcomes

Postoperative Pancreatic Fistula

All the included studies reported POPF rate. The POPF rates were 14.5 % (47/325) in the duct-to-mucosa group and 12.2 % (40/329) in the invagination group. Meta-analysis revealed that there was no significant difference in POPF rate between

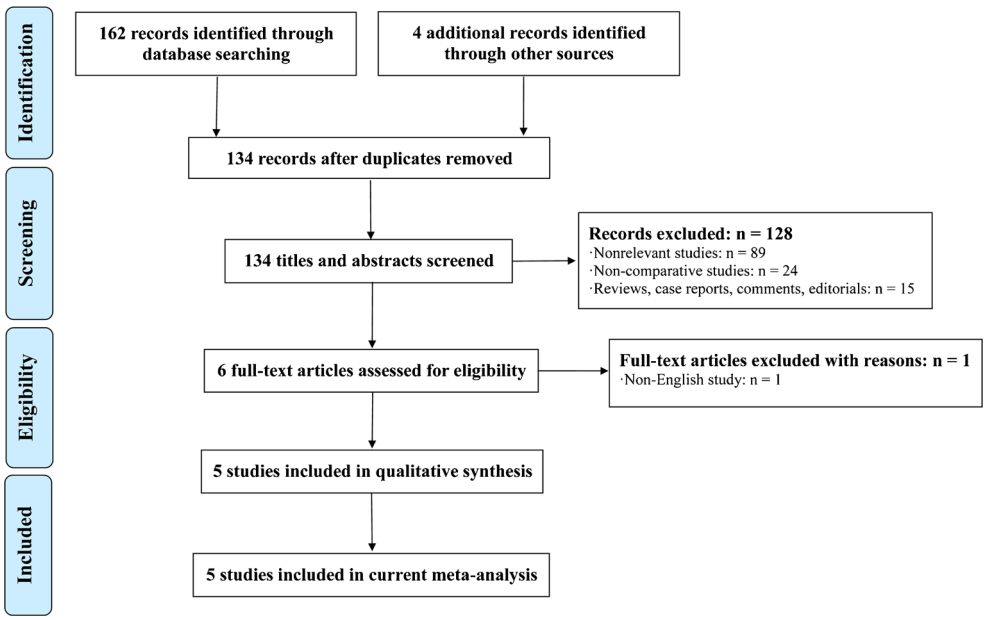


Fig. 1 PRISMA flow diagram of study identification, inclusion, and exclusion

Table 1 Characteristics of included studies comparing duct-to-mucosa with invagination pancreaticojejunostomy

Reference	Country	Year of study	Design	No. of patients (M/F)		Age, mean (range or SD), year		Surgeon
				D-to-M	Inv	D-to-M	Inv	
Berger et al.[2]	USA	2006–2008	RCT	97 (45:42)	100 (54:46)	68 (32–84)	68 (41–90)	8
Bassi et al.[12]	Italy	1999–2001	RCT	72 (40:32)	72 (46:26)	62 (10)	61 (12)	>1
Langrehr et al.[21]	Germany	1999–2000	RCT	56 (34:22)	57 (32:25)	59 (28–86)	60 (35–79)	>1
Chou et al.[13]	Taiwan	1984–1996	RCT	47 (23:24)	46 (27:19)	60 (11)	56 (12)	5
El Nakeeb et al.[14]	Egypt	2011–2013	RCT	53 (34:19)	54 (33:21)	54 (12–73)	54 (20–75)	>1

RCT randomized controlled trial, *Retro* retrospective, *M/F* male/female ratio, *D-to-M* duct-to-mucosa, *Inv* invagination, *SD* standard deviation, *NA* not available

the two groups (OR=1.23, 95 % CI=0.78–1.93; P=0.38) (Fig. 3a). No statistically significant heterogeneity among studies was observed (Q statistic=7.25, P=0.12; I^2=45 %). Two studies[2,14] including 304 patients used the definition and grading system for POPF defined by ISGPS. Meta-analysis showed that 15.3 % of patients in the duct-to-mucosa group and 5.8 % in the invagination group developed clinically relevant POPF and invagination PJ technique was associated a statistically significant reduction in clinically relevant POPF rate (OR=2.94, 95 % CI=1.31–6.60; P=0.009) (Fig. 3b).

Secondary Outcomes

Delayed Gastric Emptying

There was heterogeneity in the definitions of postoperative DGE among studies. In most studies, DGE was defined as gastric stasis requiring nasogastric intubation for more than 7 days, more or less associated with vomiting and reinsertion of a nasogastric tube after failure of postoperative feeding. Four of the five studies reported postoperative DGE rates.[12–14,21] The DGE rates were 6.6 % (15/228) in the duct-to-mucosa group and 4.8 % (11/229) in the invagination group. Meta-analysis showed no significant difference in the DGE rate between the two groups (OR=1.40, 95 % CI=0.63–3.11; P=0.41) (Fig. 4a).

Intra-Abdominal Collection

Postoperative intra-abdominal collection was reported in four RCTs.[12–14,21] There was no significant difference regarding intra-abdominal collection between groups (OR=1.30, 95 % CI=0.69–2.43; P=0.42), with the incidence of 11.4 % (26/228) in the duct-to-mucosa group and 9.2 % (21/229) in the invagination group (Fig. 4b).

Overall Morbidity

Overall morbidity included intra-abdominal and medical complications. All the studies reported postoperative morbidity

Table 2 Intraoperative data of the duct-to-mucosa and invagination groups

Reference		Pylorus preservation	Operative time (min)[a]	Estimated blood loss (ml)[a]	Stents	Pancreatic texture (S/H)	Somatostatin analogs use	Pathology (B/M)
Berger et al.[2]	D-to-M	84	379 (203–698)	500 (100–2000)	Intraoperative temporary[b]	50/47	No	21/76
	Inv	88	347 (204–704)	450 (100–10,000)		51/49	No	34/66
Bassi et al.[12]	D-to-M	62	379 (63)	NA	Yes	72/0	Yes	18/54
	Inv	65	379 (68)	NA	No	72/0	Yes	23/49
Langrehr et al.[21]	D-to-M	43	346 (225–550)	560 (0–2000)	Yes	NA	52 used	18/38
	Inv	39	356 (240–540)	656 (0–2000)	Yes	NA	54 used	14/43
Chou et al.[13]	D-to-M	8	390 (112)	884 (826)	NA	NA	NA	0/47
	Inv	7	326 (78)	1130 (920)	NA	NA	NA	0/46
El Nakeeb et al.[14]	D-to-M	0	330 (180–480)	500 (100–3000)	Intraoperative temporary[b]	25/28	NA	NA
	Inv	0	300 (240–540)	500 (50–2600)		27/27	NA	NA

D-to-M duct-to-mucosa, *Inv* invagination, *NA* data not available, *S/H* soft/hard, *B/M* benign/malignant

[a] Values are expressed as median (range) or mean (standard deviation)

[b] The pancreatic duct stent was inserted during the anastomosis to allow an easy and accurate suture placement, ensure an adequate pancreatic duct exposure, and protect the opposite wall from inadvertently held by needles

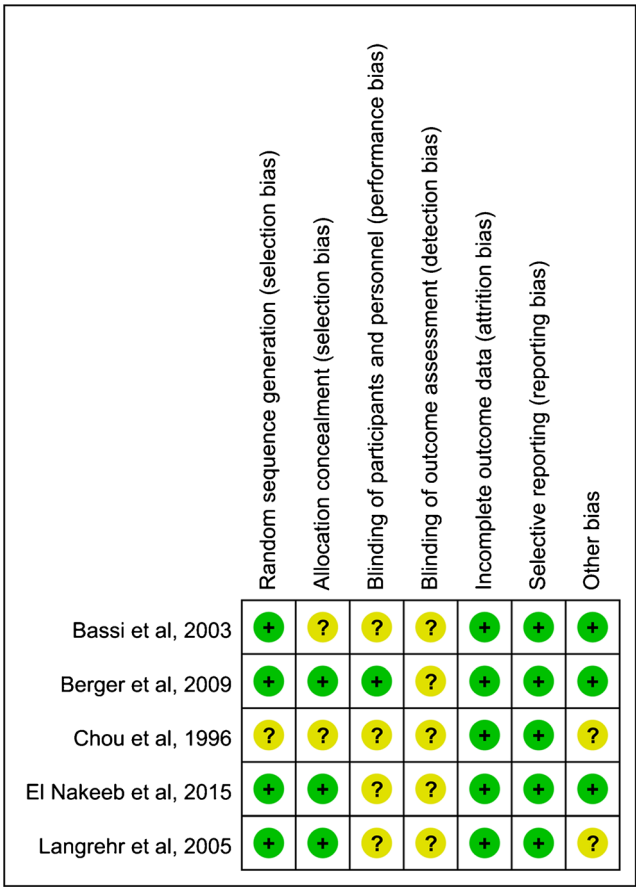


Fig. 2 Quality assessment of the included RCTs using the Cochrane Handbook for Systematic Reviews of Interventions. *Green circle* indicates low risk of bias, while *yellow circle* indicates risk unable to assessed

rates. The overall morbidity rates were 51.1 % (166/325) in the duct-to-mucosa group and 48.9 % (161/329) in the invagination group. Meta-analysis using a fixed-effects model revealed no significant difference between the duct-to-mucosa and invagination techniques (OR=1.10, 95 % CI=0.80–1.50; P=0.56) (Fig. 4c). Analysis of major complications (grades III to V) according to the Clavien-Dindo Classification of Surgical Complications System also revealed no significant difference between the two techniques (OR=1.42, 95 % CI=0.44–4.52; P=0.55). Although some degree of heterogeneity was present (Q statistic=6.19, P=0.05; I^2=68 %), use of the random-effects model did not change the result.

Overall Mortality

All the included studies reported postoperative mortality rates and the reasons for deaths. The overall mortality rates were 2.8 % (9/325) in the duct-to-mucosa group and 2.4 % (8/329) in the invagination group. Meta-analysis showed no significant difference in overall mortality rate between the two groups (OR=1.12, 95 % CI=0.44–2.83; P=0.81) (Fig. 4d).

Reoperation

Reoperations were often remedial measures for life-threatening complications, such as grade C POPF and severe hemorrhage. The reoperation rates were 7.1 % (23/325) in the duct-to-mucosa group and 5.2 % (17/329) in the invagination group, and there was no significant difference in this event (OR=1.42, 95 % CI=0.74–2.74; P=0.29) (Fig. 4e).

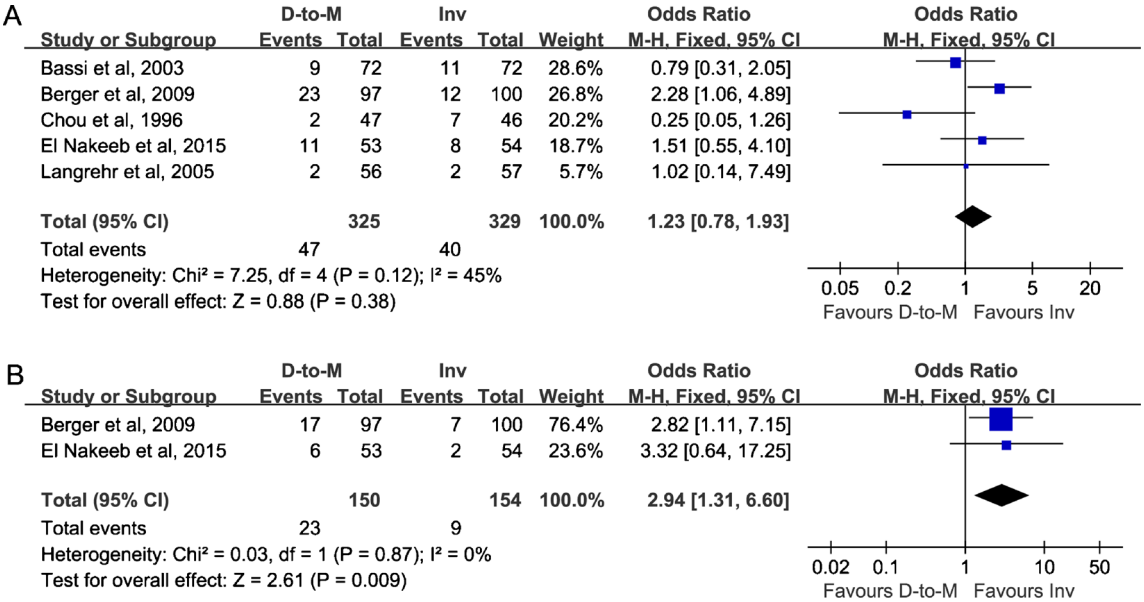
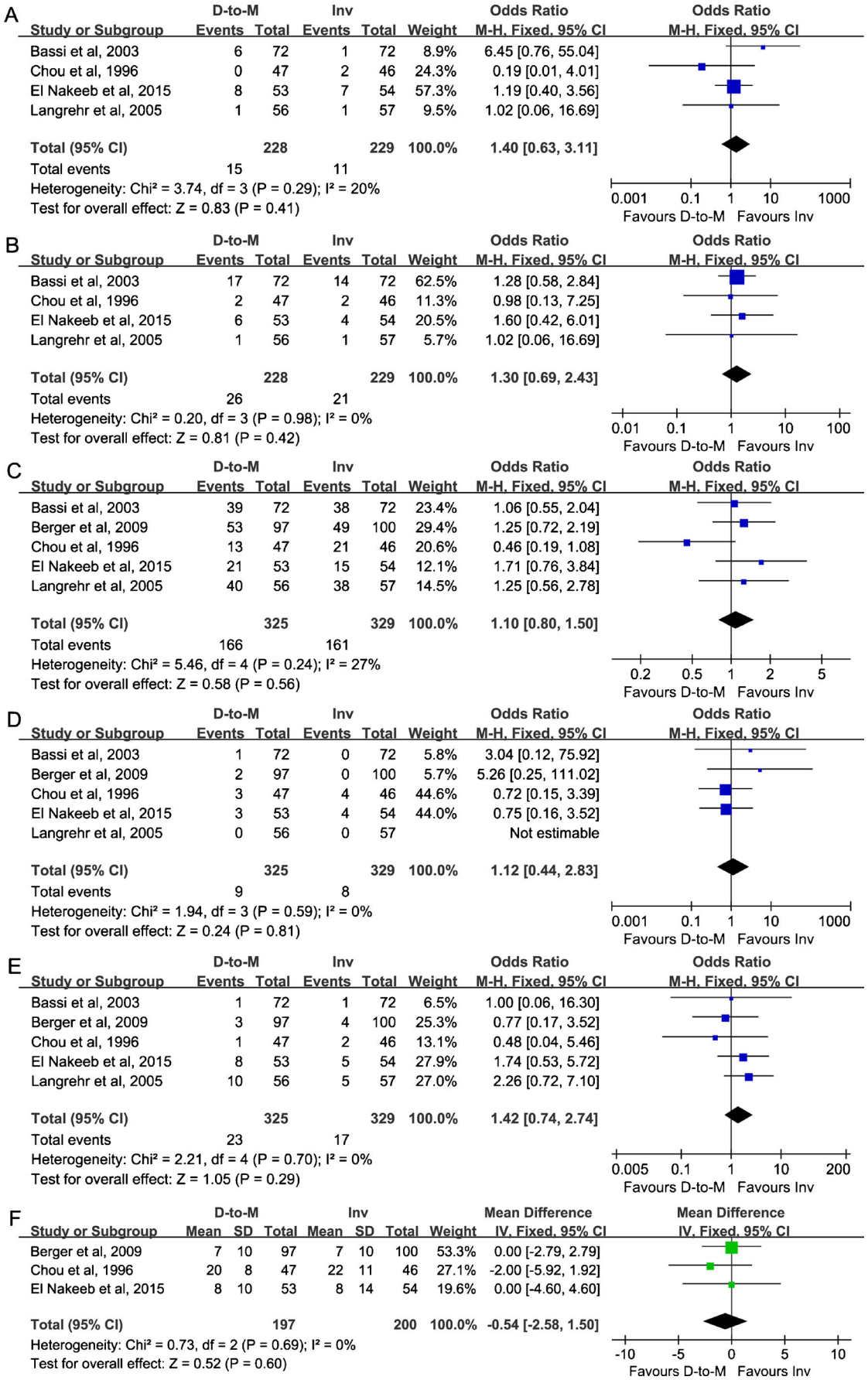


Fig. 3 Meta-analysis for aggregated data in RCTs comparing effect of duct-to-mucosa PJ and invagination PJ on POPF (**a**) and clinically relevant POPF (**b**) in patients undergoing PD. D-to-M, duct-to-mucosa; Inv, invagination; M-H, Mantel-Haenszel method; CI, confidence interval


A
D-to-M Inv Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Bassi et al, 2003 6 72 1 72 8.9% 6.45 [0.76, 55.04]
Chou et al, 1996 0 47 2 46 24.3% 0.19 [0.01, 4.01]
El Nakeeb et al, 2015 8 53 7 54 57.3% 1.19 [0.40, 3.56]
Langrehr et al, 2005 1 56 1 57 9.5% 1.02 [0.06, 16.69]
Total (95% CI) 228 229 100.0% 1.40 [0.63, 3.11]
Total events 15 11
Heterogeneity: Chi² = 3.74, df = 3 (P = 0.29); I² = 20%
Test for overall effect: Z = 0.83 (P = 0.41)
0.001 0.1 1 10 1000
Favours D-to-M Favours Inv
B
D-to-M Inv Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Bassi et al, 2003 17 72 14 72 62.5% 1.28 [0.58, 2.84]
Chou et al, 1996 2 47 2 46 11.3% 0.98 [0.13, 7.25]
El Nakeeb et al, 2015 6 53 4 54 20.5% 1.60 [0.42, 6.01]
Langrehr et al, 2005 1 56 1 57 5.7% 1.02 [0.06, 16.69]
Total (95% CI) 228 229 100.0% 1.30 [0.69, 2.43]
Total events 26 21
Heterogeneity: Chi² = 0.20, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)
0.01 0.1 1 10 100
Favours D-to-M Favours Inv
C
D-to-M Inv Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Bassi et al, 2003 39 72 38 72 23.4% 1.06 [0.55, 2.04]
Berger et al, 2009 53 97 49 100 29.4% 1.25 [0.72, 2.19]
Chou et al, 1996 13 47 21 46 20.6% 0.46 [0.19, 1.08]
El Nakeeb et al, 2015 21 53 15 54 12.1% 1.71 [0.76, 3.84]
Langrehr et al, 2005 40 56 38 57 14.5% 1.25 [0.56, 2.78]
Total (95% CI) 325 329 100.0% 1.10 [0.80, 1.50]
Total events 166 161
Heterogeneity: Chi² = 5.46, df = 4 (P = 0.24); I² = 27%
Test for overall effect: Z = 0.58 (P = 0.56)
0.2 0.5 1 2 5
Favours D-to-M Favours Inv
D
D-to-M Inv Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Bassi et al, 2003 1 72 0 72 5.8% 3.04 [0.12, 75.92]
Berger et al, 2009 2 97 0 100 5.7% 5.26 [0.25, 111.02]
Chou et al, 1996 3 47 4 46 44.6% 0.72 [0.15, 3.39]
El Nakeeb et al, 2015 3 53 4 54 44.0% 0.75 [0.16, 3.52]
Langrehr et al, 2005 0 56 0 57 Not estimable
Total (95% CI) 325 329 100.0% 1.12 [0.44, 2.83]
Total events 9 8
Heterogeneity: Chi² = 1.94, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
0.001 0.1 1 10 1000
Favours D-to-M Favours Inv
E
D-to-M Inv Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Bassi et al, 2003 1 72 1 72 6.5% 1.00 [0.06, 16.30]
Berger et al, 2009 3 97 4 100 25.3% 0.77 [0.17, 3.52]
Chou et al, 1996 1 47 2 46 13.1% 0.48 [0.04, 5.46]
El Nakeeb et al, 2015 8 53 5 54 27.9% 1.74 [0.53, 5.72]
Langrehr et al, 2005 10 56 5 57 27.0% 2.26 [0.72, 7.10]
Total (95% CI) 325 329 100.0% 1.42 [0.74, 2.74]
Total events 23 17
Heterogeneity: Chi² = 2.21, df = 4 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)
0.005 0.1 1 10 200
Favours D-to-M Favours Inv
F
D-to-M Inv Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI
Berger et al, 2009 7 10 97 7 10 100 53.3% 0.00 [-2.79, 2.79]
Chou et al, 1996 20 8 47 22 11 46 27.1% -2.00 [-5.92, 1.92]
El Nakeeb et al, 2015 8 10 53 8 14 54 19.6% 0.00 [-4.60, 4.60]
Total (95% CI) 197 200 100.0% -0.54 [-2.58, 1.50]
Heterogeneity: Chi² = 0.73, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.60)
-10 -5 0 5 10
Favours D-to-M Favours Inv

◀ **Fig. 4** Meta-analysis for aggregated data in RCTs comparing effect of duct-to-mucosa PJ and invagination PJ on DGE (**a**), intra-abdominal collection (**b**), overall morbidity (**c**), overall mortality (**d**), reoperation (**e**), and length of hospital stay (**f**) in patients undergoing PD. D-to-M, duct-to-mucosa; Inv, invagination; M-H, Mantel-Haenszel method; CI, confidence interval; IV, Inverse Variance method; SD standard deviation

Length of Hospital Stay

Length of hospital stay was reported in all five studies with data in three studies[2,13,14] being able to quantitative analyzed. The results did not show any statistically significant difference in length of hospital stay between the duct-to-mucosa and invagination groups (WMD=−0.54 days, 95 % CI=−2.58 to 1.50; P=0.60) (Fig. 4f). No evidence of statistically significant heterogeneity among studies was observed (Q statistic=0.73, P=0.69; I^2=0 %).

Subgroup and Sensitivity Analysis

Considering that POPF rate is directly related to pancreatic texture, we performed a subgroup analysis for patients with soft texture of the pancreatic remnant. A total of 245 patients in two studies[2,12] were reported to have soft pancreas. Meta-analysis revealed no statistically significant difference regarding POPF rate between the duct-to-mucosa and invagination PJ groups (Fig. 5). The OR was 1.45 (95 % CI=0.45–4.69; P=0.54), as assessed using the Mantel-Haenszel method and the random-effects model, with some evidence of heterogeneity between studies (Q statistic=3.15, P=0.08), with a corresponding I^2 statistic of 68 %.

For each outcome, sensitivity analysis was conducted by deleting each study to examine the stability of the results. Our analysis revealed that the influence of each individual data set to the pooled results was not significant, indicating that our meta-analysis was stable.

Publication Bias

The funnel plot based on the incidence of POPF is shown in Fig. 6. The shape of the funnel plot did not reveal asymmetry and no study lay outside the limits of the 95 % CI, indicating no obvious publication bias.

Discussion

The results of this meta-analysis of five RCTs suggest that POPF was not statistically different between duct-to-mucosa PJ and invagination PJ techniques. However, invagination PJ is associated with significantly lower rate of clinically relevant POPF (grades B and C according to ISGPS definition). In an analysis of secondary outcomes, there was no significant difference in terms of the incidence of DGE and intra-abdominal collection, overall morbidity and mortality, reoperation rate, and length of hospital stay between the two groups.

The best pancreatic anastomosis technique after PD is still debated. PJ is the commonly preferred method of reconstruction after PD, although recent evidence showed that PG is associated with significantly lower pancreatic and biliary fistula rates and a shorter length of hospital stay than PJ.[22] The two widely performed PJ techniques, duct-to-mucosa and invagination, were always debatable in terms of reducing POPF rate. In duct-to-mucosa PJ, mucosa-to-mucosa sutures are beneficial for anastomosis healing, and support by the jejunal serosa also protects the pancreatic remnant. However, dead space may exist between the pancreatic stump and jejunal wall, resulting in retention of pancreatic juice from the accessory or tiny pancreatic ducts.[4] In addition, if the Wirsung's duct is in small diameter, duct-to-mucosa PJ is difficult and prone to obstruction. In contrast, invagination PJ is easier to perform, and theoretically, all the pancreatic juice is drained into the jejunum.[14] In our meta-analysis, duct-to-mucosa PJ showed no better than invagination PJ regarding POPF rate, in fact, POPF rate (grades B and C) was higher in patients who underwent duct-to-mucosa PJ as compared with invagination (15.3 versus 5.8 %; P=0.009) when ISGPS definition was applied (Table 3). ISGPS definition of POPF was proposed in 2005 and it allows accurate comparison of different surgical experiences.[3] By the ISGPS grading system, grade A fistula has no clinical impact and requires little change in management, while grade B and C fistulas are ones in which a major deviation from the clinical pathway occurs.[2] Although only two included studies (one by Berger et al. in 2009[2] and the other by El Nakeeb et al. in 2015[14]) reported POPF by using the ISGPS grading system, it is not difficult to see that there is a tendency that invagination PJ was associated with lower POPF rate.

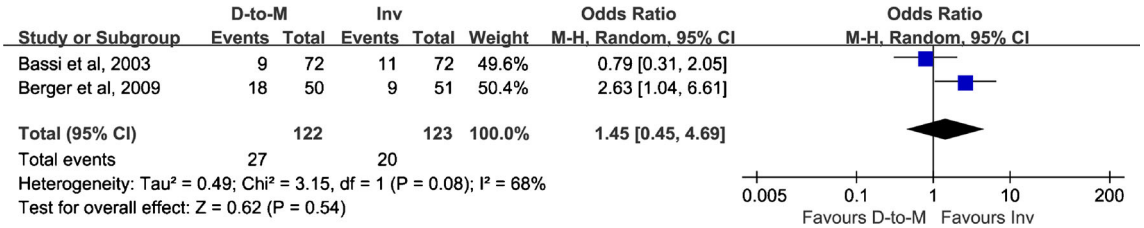


Fig. 5 Meta-analysis for aggregated data in RCTs comparing effect of duct-to-mucosa PJ and invagination PJ on POPF in patients with soft texture of the pancreatic remnant. D-to-M, duct-to-mucosa; Inv, invagination; M-H, Mantel-Haenszel method; CI, confidence interval

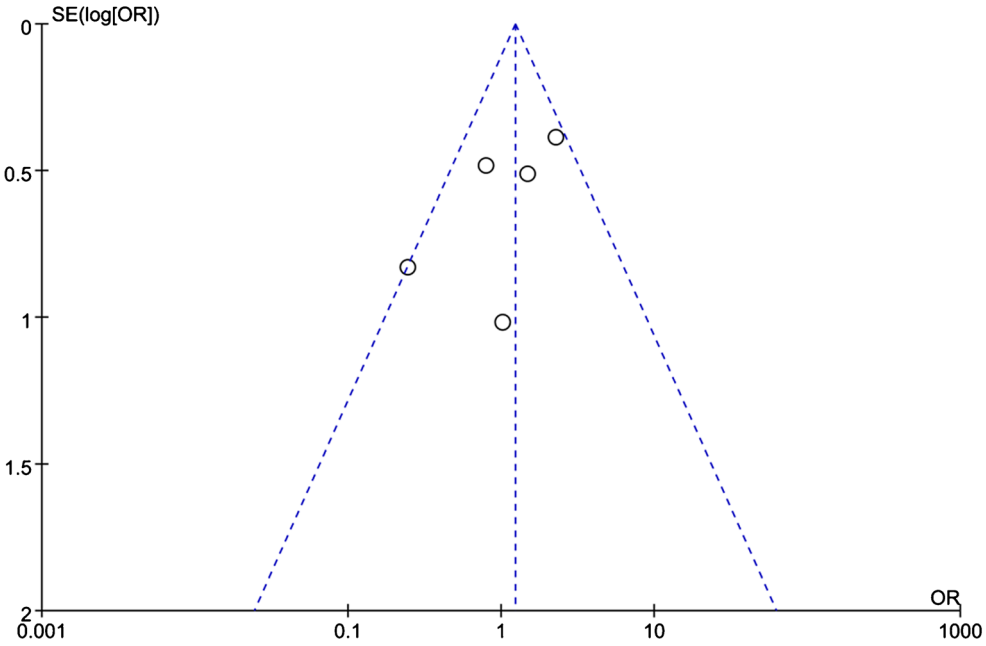


Fig. 6 Funnel plots of postoperative pancreatic fistula in included RCTs. The plot revealed no publication bias. OR, odds ratio; SE(log[OR]), standard error of the natural logarithm of the odds ratio

In addition to duct-to-mucosa and invagination PJ techniques, binding PJ was proposed by Peng et al. in 2004.[23] It was reported that the POPF rate was 0 % using binding PJ anastomosis in their own RCT.[24] However, in the European population, binding PJ did not reduce POPF rate (18.8 %).[25] This discrepancy may be due to the difficulty in controlling the binding tension because too tight binding may cause necrosis, resulting in severe POPF, while too loose binding may not impede pancreatic juice leakage. Besides, the jejunal mucosa is destroyed by carbolic acid in binding PJ anastomosis, which may lead to decreased vascularization at the site of the anastomosis. Furthermore, since binding PJ was originally performed in an end-to-end manner, it may not be successful when the jejunum is too small or the pancreatic stump is too large to invaginate the pancreatic stump into the jejunum. Thus, the binding PJ technique may still need some modifications and is therefore not within the scope of this review. Further well-designed RCTs are required before definitive conclusions can be drawn.

In recent studies, the Fistula Risk Score, a 10-point scale that relies on weighted influence of four variables (small pancreatic duct size, soft pancreatic texture, high-risk pathology, and excessive blood loss) has been proposed and validated.[26,27] Some retrospective studies showed that the

Table 3 Summary of the results on the efficacy of duct-to-mucosa versus invagination pancreaticojejunostomy following pancreaticoduodenectomy

	No. of studies	No. of patients	Odds ratio	*P* value	*P* for heterogeneity	I^2 (%)
Primary outcomes						
Pancreatic fistula	5	654	1.23 (0.78–1.93)	0.38	0.12	45
Clinically relevant POPF	2	304	2.94 (1.31–6.60)	0.009*	0.87	0
Secondary outcomes						
Delayed gastric emptying	4	457	1.40 (0.63–3.11)	0.41	0.29	20
Intra-abdominal collection	4	457	1.30 (0.69–2.43)	0.42	0.98	0
Overall morbidity	5	654	1.10 (0.80–1.50)	0.56	0.24	27
Major complications[a]	3	397	1.42 (0.44–4.52)	0.55	0.05	68
Overall mortality	5	654	1.12 (0.44–2.83)	0.81	0.59	0
Reoperation	5	654	1.42 (0.74–2.74)	0.29	0.70	0
Length of stay	3	397	−0.54 (−2.58–1.50)	0.60	0.69	0

Values in parentheses are 95 % confidence intervals

POPF postoperative pancreatic fistula

*Statistically significant

[a] Defined as Clavien-Dindo grade III to V

duct-to-mucosa PJ was associated with a lower rate of POPF in the low-risk patients with dilated pancreatic duct or hard pancreas, whereas the invagination PJ technique was safer in the high-risk patients with small pancreatic duct or soft pancreas.[28,29] However, in our current meta-analysis, the advantage was not found in patients with soft pancreatic stump. Significant heterogeneity was present probably due to relatively subjective classification of pancreatic texture. None of the included studies assessed the diameter of the pancreatic duct, surgical pathology, or blood loss for POPF. As these factors represent important risk factors for POPF and increased Fistula Risk Scores correlated well with clinically relevant POPF development, further RCTs evaluating POPF should also use Fistula Risk Score as a predictive tool for clinically relevant POPF development.

In our study, the DGE rates were similar between duct-to-mucosa and invagination PJ groups. In most patients, DGE is not a life-threatening complication after PD, but it can cause discomfort, increase the duration of postoperative hospitalization, increase hospital costs, and decrease quality of life postoperatively. A consensus definition of DGE has been proposed by ISGPS since 2007.[30] The ISGPS classification and grading system correlates well with the clinical course of DGE and is feasible for patient management.[31] However, none of the included studies used this definition, mainly because most studies were published earlier than the proposed definition.

The present study showed that the mortality and morbidity rates were 2.6 and 50 %, respectively, which was consistent with other studies. The incidence of complications after PD remains high and clinically relevant POPF remains the most cause of morbidity, resulting in intra-abdominal collection, postoperative hemorrhage, the occasional need for reoperation, and possible death. Besides, Qu et al.[32] reported that POPF is a clinical risk factor predictive for DGE (OR=2.66, 95 % CI=1.65–4.28; $P<0.0001$). Thus, it is clear that once the incidence of POPF decreased to some extent, the incidence of overall morbidity will be under-controlled.

The current meta-analysis has some strengths. First, meta-analysis is an important tool to highlight trends that may not be apparent in a single study. Pooling of independent but similar studies increases precision, and therefore increases the confidence level of the findings. Second, the results did not change considerably after sensitivity analysis was performed, indicating our results to be stable. Third, no publication bias was detected, which indicates that the pooled results may be unbiased. However, there are also some limitations in our meta-analysis that should be acknowledged. First, only the study by Berger et al.[2] performed sample power analysis while others not. Second, the invagination PJ technique was slightly different in a single layer or double layers among studies. Third, the inclusion of pylorus-preserving PD and the use of stent intraoperatively and somatostatin analogs postoperatively also differed among studies. Finally, the definition of POPF varied among studies, and the ISGPS definition was used in only two of the five included studies. The significance in clinically relevant POPF between duct-to-mucosa and invagination PJ was based on a small sample of 304 patients. The methodological heterogeneity among included studies as described above may lead to different complications and therefore, the results should be interpreted with caution. Further RCTs addressing the above limitations are required before strong evidence-based recommendations can be formulated.

Conclusion

In conclusion, results of our study showed comparable POPF rates between duct-to-mucosa and invagination PJ techniques. Invagination PJ appears to reduce clinically relevant POPF. No significant difference was found in terms of the incidence of DGE and intra-abdominal collection, overall morbidity and mortality, reoperation rate, and length of hospital stay between the two anastomosis techniques. There is a need for well-designed RCTs that use ISGPS definition comparing duct-to-mucosa and invagination PJ to accumulate more evidence of high quality.

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