

# Selection of pancreaticojejunostomy technique after pancreaticoduodenectomy: duct-to-mucosa anastomosis is not better than invagination anastomosis

# A meta-analysis

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# Abstract

**Background:** One of the most clinically significant current discussions is the optimal pancreaticojejunostomy (PJ) technique for pancreaticoduodenectomy (PD). We performed a meta-analysis to compare duct-to-mucosa and invagination techniques for pancreatic anastomosis after PD.

**Methods:** A systematic search of PubMed, Embase, Web of Science, the Cochrane Central Library, and ClinicalTrials.gov up to June 1, 2018 was performed. Randomized controlled trials (RCTs) comparing duct-to-mucosa versus invagination PJ were included. Statistical analysis was performed using RevMan 5.3 software.

**Results:** Eight RCTs involving 1099 patients were included in the meta-analysis. The rate of postoperative pancreatic fistula (POPF) was not significantly different between the duct-to-mucosa PJ (110/547, 20.10%) and invagination PJ (98/552, 17.75%) groups in all 8 studies (risk ratio, 1.13; 95% Cl, 0.89–1.44; P=.31). The subgroup analysis using the International Study Group on Pancreatic Fistula criteria showed no significant difference in POPF between duct-to-mucosa PJ (97/372, 26.08%) and invagination PJ (78/377, 20.68%). No significant difference in clinically relevant POPF (CR-POPF) was found between the 2 groups (55/372 vs 40/377, P=.38). Additionally, no significant differences in delayed gastric emptying, post-pancreatectomy hemorrhage, reoperation, operation time, or length of stay were found between the 2 groups. The overall morbidity and mortality rates were not significantly different between the 2 groups.

**Conclusion:** The duct-to-mucosa technique seems no better than the invagination technique for pancreatic anastomosis after PD in terms of POPF, CR-POPF, and other main complications. Further studies on this topic are therefore recommended.

**Abbreviations:** DGE = delayed gastric emptying, ISGPF = international study group on pancreatic fistula, LOS = length of stay, MD = mean difference, PD = pancreaticoduodenectomy, PG = pancreaticogastrostomy, PJ = pancreaticojejunostomy, POD = postoperative day, POPF = postoperative pancreatic fistula, PPH = post-pancreatectomy hemorrhage, RCT = randomized controlled trial.

Keywords: duct-to-mucosa, invagination, meta-analysis, pancreatoduodenectomy, systematic review

# 1. Introduction

Pancreaticoduodenectomy (PD) is a complex, high-risk standard surgical procedure that is indicated primarily for periampullary

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Availability of data and materials: As this is a systematic review and metaanalysis, all included studies and the related results in our paper are listed in the reference and manuscript.

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Received: 26 July 2018 / Accepted: 7 September 2018 http://dx.doi.org/10.1097/MD.000000000012621 diseases. Central to the entire discipline of PD are postoperative mortality and morbidity. Although operative mortality in patients undergoing PD has decreased, the incidence of postoperative morbidity remains high at 40% to 50%.[1-6] Postoperative pancreatic fistula (POPF) is the most common complication, with rates ranging from 5% to 30% in previous studies.<sup>[7,8]</sup> Many methods have been described to decrease the risk of POPF, including the use of medications (prophylactic octreotide,<sup>[9,10]</sup> sealants<sup>[11]</sup>), prophylactic pancreatic stenting,<sup>[12]</sup> and improvements in pancreatic reconstruction techniques.<sup>[1,2]</sup> The most commonly used pancreatic reconstruction techniques are pancreaticogastrostomy (PG) and pancreaticojejunostomy (PJ). Several methods of PJ currently exist, the 2 most common of which are duct-to-mucosa PJ and invagination PJ. In the past few decades, many studies have assessed the safety and efficacy of these 2 methods.<sup>[13–15]</sup> A major advantage of duct-to-mucosa PJ is that it allows drainage of the main duct into the intestine. Many previous studies have shown a lower incidence of pancreatic fistula after duct-to-mucosa PJ than invagination PJ.<sup>[16-</sup> <sup>19]</sup> Therefore, duct-to-mucosa PJ is one of the most widely used PJ

methods. Theoretically, however, duct-to-mucosa PJ cannot provide drainage of minor ducts and may require higher-level technology. A previous study demonstrated that invagination PJ could reduce the rate of POPF.<sup>[20]</sup> However, a recent randomized controlled trial

(RCT) showed that invagination PJ was not associated with a lower rate of POPF but was instead associated with a decreased severity of POPF.<sup>[15]</sup> One of the most clinically significant current discussions is the optimal PJ technique for PD. Increasingly more RCTs have been performed or are ongoing. The aim of this study was to compare the clinical outcomes of duct-to-mucosa PJ and invagination PJ.

# 2. Materials and methods

# 2.1. Search strategy

Two researchers (TL and YXL) independently conducted a comprehensive and systematic search of PubMed, Embase, Web of Science, the Cochrane Central Library, and ClinicalTrials.gov up to June 2018. English search terms included but were not limited to the following: pancreatoduodenectomy, PD, PJ, duct-to-mucosa, and invagination. The search was limited initially to publications of RCTs. The references of the articles identified after the initial search were also manually reviewed. This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

#### 2.2. Inclusion and exclusion criteria

The following inclusion criteria were applied: the RCT must have compared the clinical outcomes between duct-to-mucosa PJ and invagination PJ after PD. The participants must have had a clinical diagnosis of POPF. The study must have provided adequate data on the clinical outcomes.

We excluded studies that were non-RCTs, retrospective studies, review articles, case reports, abstract, editorials, and letters to the editor; were repeatedly published by the same author or agency; and had insufficient data on outcome measures.

# 2.3. Clinical outcomes of interest

The primary outcomes were the incidence of POPF and clinically relevant POPF (CR-POPF) after PD. The other outcomes were delayed gastric emptying (DGE), post-pancreatectomy hemorrhage (PPH), reoperation, morbidity, mortality, operation time, and length of stay (LOS).

# 2.4. Data extraction

Two reviewers (YXC and BW) independently extracted the following original data from the literature and entered it onto a standardized form: first author, year of publication, study period, and country where the study took place; sample size, types of PJ, texture and diameter of the pancreas, and definition of POPF. If necessary, the author or authors of the study were contacted to obtain the necessary data. Conflicts in data abstraction were resolved by consensus and by referring to the original article.

# 2.5. Quality assessment

The authors independently assessed the quality of the literature in accordance with the Cochrane Collaboration Handbook.<sup>[21]</sup> The scoring system included the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the results assessment, incomplete data of the results, selective reporting, and other sources of bias.

# 2.6. Statistical analysis

All included data were assessed using Review Manager (RevMan) version 5.3 software (Cochrane Informatics and

Knowledge Management Department, Copenhagen, Kongeriget Danmark). The risk ratio (RR) and 95% confidence interval (CI) were used for dichotomous outcomes. Publication bias was evaluated by the chi-squared test and funnel plots. Heterogeneity among studies was evaluated by the chi-squared test. A two-tailed P value of <.05 was considered statistically significant.

#### 2.7. Ethics statement

This study was a secondary analysis regarding human subject data published in the public domain; thus, no ethical approval was required.

#### 3. Results

#### 3.1. Selected studies and characteristics of the trials

Based on our search criteria, we yielded a total of 487 papers from the respective search engines, of which 320 duplicate articles were excluded. The remaining 159 studies were retrieved for assessment of their titles and abstracts, leaving 8 articles that met the inclusion criteria. Finally, 8 RCTs involving 1099 participants were included in the meta-analysis.<sup>[13–15,20,22–25]</sup> A detailed flowchart of the selection process is depicted in Fig. 1.



Figure 1. Flow diagram of the published articles evaluated for inclusion in this meta-analysis.

Table 1

Characteristics of	f the incl	uded studies.	ı.							
			A	ge	Samp	ole	Texture of panci	reas (soft/hard)	Diameter of p	ancreatic duct
Author year	Country	Study period	D-to-M	I	D-to-M	I	D-to-M	I	D-to-M	I
Bai et al 2016	China	2012-2015	62±10	64±11	64	68	5/13	4/17	3±2.3	3±2.7
Bassi et al 2003	Italy	1999–2001	$62 \pm 10$	$61 \pm 12$	72	72	72	72	NA	NA
Berger et al 2009	USA	2006-2008	68 (32-84)	68 (41-90)	97	100	47/50	49/51	4 (1-10)	4 (1-12)
Chou et al 1996	China	1986–1994	$60 \pm 11$	$56 \pm 12$	47	46	NA	NA	NA	NA
El Nakeeb et al 2015	Egypt	2011-2013	54 (12–73)	54 (20-75)	53	54	28/25	27/27	30/23	25/29
Langrehr et al 2005	Germany	1999–2000	59 (28-86)	60 (35-79)	56	57	NA	NA	NA	NA
Senda et al 2018	Japan	2011-2015	66 (36-84)	68 (22-81)	61	59	31/30	30/29	27/44	21/38
Singh et al 2017	India	2009–2015	53.4±12.1	$51.5 \pm 14.2$	97	96	42/55	48/48	4.3±2.1	$4.1 \pm 1.5$

D-to-M = duct-to-mucosa PJ, I = invagination PJ, NA = no available

The 1099 patients were divided into the duct-to-mucosa PJ group (n = 547) and invagination group (n = 552). The sample sizes ranged from 92 to 197, and the incidence rate of POPF varied from 3.5% to 32.0%. Of these studies, 5 trials<sup>[15,20,22,24,25]</sup> provided POPF data using the definition established by the International Study Group on Pancreatic Fistula (ISGPF), and 3 studies<sup>[13,14,23]</sup> used different definitions of POPF. Data regarding the pancreatic texture were provided in 6 studies, <sup>[13,15,22,24,25]</sup> and the diameter of the pancreatic duct was provided in 5 studies.<sup>[15,20,22,24,25]</sup>Table 1 shows the main characteristics of the studies included in this metaanalysis, and Table 2 shows the definitions of POPF used in the studies. Figure 2 presents an consensus risk-of bias assessment of the included studies.

# 3.2. POPF

All 8 trials involving 1099 participants were pooled to compare the incidence of POPF after PD. There were no significant differences between the duct-to-mucosa PJ group (20.1%) and invagination PJ group (17.75%) (RR, 1.13; 95% CI, 0.89-1.44; P=.31) (Fig. 3A). Five studies involving 661 samples using the ISGPF definition showed that there were no significant differences between the duct-to-mucosa group and invagination group (RR, 1.26; 95% CI, 0.97–1.63; P=.08) (Fig. 3A).

# 3.3. CR-POPF

Five trials provided data regarding CR-POPF in accordance with the ISGPF criteria. The pooled data demonstrated no statistically

Table 2								
Definition of POPF.								
Author/year	Definition of POPF							
Bai et al 2016	ISGPF							
Bassi et al 2003	Output >30 mL/24 h; rich in amylase content for at least 7 days from postoperative day 4, confirmed by fistulography							
Berger et al 2009	ISGPF							
Chou et al 1996	Persistent drainage of ≥50 mL amylse-rich fluid a day for >2 wks							
El Nakeeb et al 2015	ISGPF							
Langrehr et al 2005	Drainage fluid with elevated amylase and lipase levels from POD 5 on >1000 U/L and beyond POD 10, clinical symptoms (pain, fever, etc.)							
Senda et al 2018	ISGPF							
Singh et al 2017	ISGPF							

ISGPF=International Study Group on Pancreatic Fistula, POD=postoperative day, POPF= postoperative pancreatic fistula.

significant difference between the duct-to-mucosa PJ and invagination PJ groups (RR, 1.14; 95% CI, 0.65–3.04; P=.38) (Fig. 3B).

# 3.4. DGE

We calculated the pooled estimates using a random-effects model  $(I^2 = 0\%)$ . Data regarding DGE were provided in 7 studies with



Figure 2. Consensus risk-of-bias assessment of the included studies. Green, low risk; yellow, unclear; red, high risk.

Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Fixed, 95% Cl           All ALL         Bai et al. 2016         18         64         21         68         11.6 %         0.91 [0.54, 1.55]           Bassi et al. 2016         18         64         21         68         11.6 %         0.91 [0.54, 1.55]           Berger et al. 2009         23         97         12         100         6.8%         0.98 [1.04, 3.75]           Langrehr et al. 2005         2         56         2         57         1.13         1.02 [0.15, 6.98]           Senda et al. 2018         21         61         15         59         8.7%         1.33 [0.78, 2.36]           Subtotal (95% CD)         547         752         55         5.7%         1.13 [0.89, 1.44]           Total events         110         98         113 [0.89, 1.44]         98           Heterogeneity: Ch <sup>2</sup> = 8.12, df = 7 (P = 0.32); l <sup>2</sup> = 100         6.8%         1.98 [1.04, 3.75]           El Nakeeb et al. 2018         18         64         2.1         68         1.68 [0.63, 1.28]           Singh et al.2017         24         97         12         100         10         10         10		Experim	nental	Cont	rol		<b>Risk Ratio</b>	Risk Ratio
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Basi et al. 2003 5 72 11 72 6.3% 0.82 [0.36, 1.85] Berger et al. 2009 23 97 12 100 6.8% 1.98 [1.04, 3.75] El Nakeeb et al. 2015 11 53 8 54 4.5% 1.40 [0.61, 3.21] Langerhe et al. 2015 2 56 2 57 1.13 [0.40, 0.78, 2.36] Singh et al. 2017 24 97 22 96 12.6% 1.08 [0.55, 1.79] Subtoal (95% Ct) 5 77 2 20 96 12.6% 1.08 [0.55, 1.79] Subtoal (95% Ct) 5 77 78 Heterogeneity: Ch <sup>2</sup> = 8.12, df = 7 (P = 0.32); l <sup>2</sup> = 14% Test for overall effect: 2 = 1.02 (P = 0.31) L1.2 ISCPF El Nakeeb et al. 2015 11 53 8 54 4.5% 1.40 [0.61, 3.21] L1.2 ISCPF El Nakeeb et al. 2015 11 53 8 54 4.5% 1.40 [0.61, 3.21] L1.2 ISCPF El Nakeeb et al. 2015 11 53 8 54 4.5% 1.40 [0.61, 3.21] L1.2 ISCPF El Nakeeb et al. 2015 11 53 8 54 4.5% 1.40 [0.61, 3.21] Total events 97 78 Heterogeneity: Ch <sup>2</sup> = 3.83, df = 4 (P = 0.43); l <sup>2</sup> = 0% A Experimental Control 77 78 Heterogeneity: Ch <sup>2</sup> = 1.22, df = 12 (P = 0.43); l <sup>2</sup> = 0% A Experimental Control 78 Stubtoal (95% Ct) 919 929 100.0% 1.19 [1.00, 1.42] Total events 97 78 Heterogeneity: Ch <sup>2</sup> = 2.1.23, df = 12 (P = 0.43); l <sup>2</sup> = 0% A Experimental Control 81 Study or Subgroup Events Total 4.9% 0.18 [0.04, 0.76] Bai et al. 2015 2 64 12 68 14.9% 0.18 [0.04, 0.76] Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Bai et al. 2018 14 61 6 16 59 22.4% 2.28 [0.39, 5.74] Singh et al.2017 16 97 13 96 25.6% 11.22 [0.62, 3.39] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: 2 = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: 2 = 0.48; CH <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: 2 = 0.48; CH <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: 2 = 0.87 (P = 0.38) Total events 55 40 Het	Bai et al. 2016	18	64	21	68	11.6%	0.91 [0 54 1 55]	
$ \begin{array}{c} \mbox{regree rel al 2009} & 23 & 97 & 12 & 100 & 6.8\% & 1.98 [1.04, 3.75] \\ \mbox{chue et al.} 2015 & 11 & 53 & 8 & 54 & 4.5\% & 1.04 [0.61, 3.21] \\ \mbox{Langerber et al.} 2015 & 11 & 53 & 8 & 54 & 4.5\% & 1.04 [0.61, 3.21] \\ \mbox{Langerber et al.} 2018 & 21 & 61 & 15 & 59 & 8.7\% & 1.35 [0.78, 2.36] \\ \mbox{Subtoal (95% CO)} & 547 & 552 & 557 & 1.13 [0.65, 1.79] \\ \mbox{Subtoal (95% CO)} & 547 & 552 & 557 & 1.13 [0.65, 1.78] \\ \mbox{Late constraints} & 110 & 98 \\ \mbox{Heterogeneity: Chi^2 = 8.12, df = 7 (P = 0.32)} \\ \mbox{L12 ISCPF} \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Bai et al.} 2016 & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \mbox{Subotal (95\% CI)} & 372 & 377 & 44.3\% & 1.26 [0.97, 1.63] \\ \mbox{Total events} & 207 & 176 \\ \mbox{Heterogeneity: Chi^2 = 2.1.32 (P = 0.0.3)} \\ \mbox{Total events} & 207 & 176 \\ \mbox{Heterogeneity: Chi^2 = 2.1.32 (P = 0.0.5), 1^2 = 0\% \\ \mbox{A} & \mbox{Experimental} Favours [control] \\ \mbox{Fist for overall effect: Z = 1.92 (P = 0.0.2); 1^2 = 66\% \\ \mbox{Subotal (95\% CI)} & \ 372 & 377 & 100.0\% & 1.41 [0.65, 3.04] \\ \mbox{Total events} & 55 & 40 \\ \mbox{Heterogeneity: Tau^2 = 0.48 (Chi^2 = 11.87, df = 4 (P = 0.02); 1^2 = 66\% \\ \mbox{Subotal (95\% CI)} & \ 372 & 377 & 100.0\% & 1.41 [0.65, 3.04] \\ T$	Bassi et al. 2003	9	72	11	72	6.3%	0.82 [0.36, 1.85]	
Chou et al. 1996 2 2 47 7 46 4.0% 0.28 [0.06, 1.28] El Nakeeb et al. 2015 11 53 8 54 4.5% 1.40 [0.61, 3.21] Langerher tal. 2005 2 56 2 57 1.13 [0.02 (0.15, 6.98] Senda et al. 2017 24 97 22 96 [2.6% 1.08 [0.06, 1.35] Subtotal (95% CI) 547 552 55.7% 1.13 [0.08, 1.44] Total events 10 98 Heterogeneity: Ch <sup>2</sup> = 8.12, df = 7 (P = 0.32); l <sup>2</sup> = 14% Test for overall effect: Z = 1.02 (P = 0.31) 1.12 ISGPF Bai et al. 2016 18 64 21 68 11.6% 0.91 [0.54, 1.55] Bai et al. 2015 11 53 8 54 4.5% 1.40 [0.61, 3.21] 1.12 ISGPF Bai et al. 2015 11 53 8 54 4.5% 1.40 [0.65, 1.79] Subtotal (95% CI) 372 377 44.3% 1.26 [0.97, 1.63] Total events 97 78 Heterogeneity: Ch <sup>2</sup> = 1.21, df = 2 (P = 0.43); l <sup>2</sup> = 0% A Experimental Control Events Total Weight M-H, Random, 95% CI A Experimental Control Events Total Weight M-H, Random, 95% CI A Experimental Control Events Total Weight M-H, Random, 95% CI A Experimental Control Events Total Events Total Weight M-H, Random, 95% CI A Experimental Control Events Total Events Total Weight M-H, Random, 95% CI A Experimental Control Events Total Events Total Weight M-H, Random, 95% CI A Experimental Control Events Total Events Total Weight M-H, Random, 95% CI A Experimental Control Events Total Events Total Weight M-H, Random, 95% CI A Experimental Control Events Total Events Total Weight M-H, Random, 95% CI A Experimental Control Events Total Events Total Weight M-H, Random, 95% CI A Experimental Events Total Events Total Events Total Weight M-H, Random, 95% CI Bai et al. 2015 6 53 2 54 13.9% 3.06 [0.65, 1.447] Bai et al. 2016 14 61 6 59 22.2% 2.26 [0.93, 5.44] Favours [experimental Favours [control] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 1.187, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 1.187, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 1.187, df = 4 (P = 0.02); l <sup>2</sup> = 66% T	Berger et al. 2009	23	97	12	100	6.8%	1 98 [1 04 3 75]	
Ell Nakeeb et al. 2015 11 53 8 54 4.5% 1.40 [0.61, 3.23] Langerh et al. 2015 2 56 2 57 1.1% 1.02 [0.15, 6.98] Singh et al. 2018 21 61 15 59 8.7% 1.35 [0.78, 2.36] Singh et al. 2017 24 97 22 96 12.6% 1.08 [0.05, 1.79] Subtoral (95% C) 547 7552 55.7% 1.13 [0.89, 1.44] Heterogeneity: Ch <sup>2</sup> = 3.24, 67 ( $P = 0.32$ ); $P = 14\%$ Total events 10 98 Heterogeneity: Ch <sup>2</sup> = 3.24, 67 ( $P = 0.32$ ); $P = 14\%$ Total events 207 176 Heterogeneity: Ch <sup>2</sup> = 3.24, 67 4( $P = 0.32$ ); $P = 1\%$ Total events 207 176 Heterogeneity: Ch <sup>2</sup> = 1.21, 2d = 12 ( $P = 0.44$ ); $P = 0.\%$ Total events 207 176 Heterogeneity: Ch <sup>2</sup> = 1.21, 2d = 12 ( $P = 0.44$ ); $P = 1\%$ Total events 207 176 Heterogeneity: Ch <sup>2</sup> = 1.21, 2d = 12 ( $P = 0.44$ ); $P = 1\%$ Total events 207 176 Heterogeneity: Ch <sup>2</sup> = 3.84, df = 4 ( $P = 0.32$ ); $P = 1\%$ Total events 207 176 Heterogeneity: Ch <sup>2</sup> = 3.84, df = 4 ( $P = 0.34$ ), df = 1 ( $P = 0.56$ ), $P = 0\%$ A Experimental Control Risk Ratio Study or Subgroup Differences: Ch <sup>2</sup> = 0.34, df = 1 ( $P = 0.56$ ), $P = 0\%$ A Experimental Control Risk Ratio Study or Subgroup Differences: Ch <sup>2</sup> = 0.37 ( $P = 0.63$ ) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; (Ch <sup>2</sup> = 11.87, df = 4 ( $P = 0.02$ ); $P^2 = 66\%$ Test for overall effect: 2 = 0.87 ( $P = 0.38$ ) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; (Ch <sup>2</sup> = 11.87, df = 4 ( $P = 0.02$ ); $P^2 = 66\%$ Test for overall effect: 2 = 0.87 ( $P = 0.38$ ) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; (Ch <sup>2</sup> = 11.87, df = 4 ( $P = 0.02$ ); $P^2 = 66\%$ Test for overall effect: 2 = 0.87 ( $P = 0.38$ ) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; (Ch <sup>2</sup> = 11.87, df = 4 ( $P = 0.02$ ); $P^2 = 66\%$ Test for overall effect: 2 = 0.87 ( $P = 0.38$ ) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; (Ch <sup>2</sup> = 11.87, df = 4 ( $P = 0.02$ ); $P^2 = 66\%$ Test for overall effect: 2 = 0.87 ( $P = 0.38$ ) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; (Ch <sup>2</sup> = 11.87, df = 4 ( $P = 0.02$ ); $P^2 = 66\%$ Test for overall effect: 2 = 0.87 ( $P = 0.38$ ) Total events 55 40 Heterogeneity	Chou et al 1996	23	47	7	46	4 0%	0.28 [0.06, 1.28]	
Largerber et al. 2005 2 56 2 57 1.78 1.05 [0.15, 6.98] Senda et al. 2018 21 61 15 59 8.7% 1.35 [0.76, 2.36] Singh et al. 2017 24 97 22 96 1.26% 1.08 [0.65, 1.79] Subtoral (95% C1) 547 552 55.7% 1.13 [0.89, 1.44] Total events 110 98 Heterogeneity: Ch <sup>2</sup> = 8.12, df = 7 ( $P = 0.32$ ); $P^2 = 14\%$ Test for overall effect: Z = 1.02 ( $P = 0.33$ ); $P^2 = 14\%$ Test for overall effect: Z = 1.02 ( $P = 0.33$ ); $P^2 = 14\%$ Test for overall effect: Z = 1.02 ( $P = 0.33$ ); $P^2 = 16\%$ A Experimental Control Risk Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% C1 1.21 SGPF Bai et al. 2016 2 64 12 ( $P = 0.44$ ); $P^2 = 0\%$ A Experimental Control Risk Ratio Study or Subgroup IFferences: Ch <sup>2</sup> = 0.34, df = 1 ( $P = 0.56$ ), $P^2 = 0\%$ A Experimental Control Risk Ratio Study or Subgroup IFferences: Ch <sup>2</sup> = 0.34, df = 1 ( $P = 0.56$ ), $P^2 = 0\%$ A Experimental Control Risk Ratio Study or Subgroup IFferences: Ch <sup>2</sup> = 0.34, df = 1 ( $P = 0.56$ ), $P^2 = 0\%$ A Experimental Control Risk Ratio Study or Subgroup 17 97 7 100 23.2% 2.50 (1.09, 5.77] Et Naceb et al. 2015 2 64 12 6 14.9% 0.18 (0.04, 0.76] Berger et al. 2018 14 61 6 59 2.2.4% 2.26 (1.93, 5.48] Singh et al.2017 16 97 13 96 62.5.6% 1.22 (0.52, 3.59] Studtoral (95% C1) 372 377 100.0% 1.41 [0.65, 3.04] Total events Total Events Total Weight M-H, Random, 95% C1 1.21 ISGPF Bai et al. 2018 14 61 6 59 2.2.4% 2.2.60 (1.93, 5.48] Singh et al.2018 14 61 6 59 2.2.4% 2.2.60 (1.93, 5.48] Singh et al.2018 14 61 6 59 2.2.4% 2.2.60 (1.93, 5.48] Singh et al.2018 14 61 6 59 2.2.4% 2.2.60 (1.93, 5.48] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 1.1.87, df = 4 ( $P = 0.02$ ); $P^2 = 66\%$ Test for overall effect: Z = 0.87 ( $P = 0.38$ ) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 1.1.87, df = 4 ( $P = 0.02$ ); $P^2 = 66\%$ Test for overall effect: Z = 0.87 ( $P = 0.38$ ) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 1.1.87, df = 4 ( $P = 0.02$ ); $P^2 = 66\%$ Test for overall effect: Z = 0.87 ( $P = 0.38$ ) Total ev	Fl Nakeeb et al. 2015	11	53	8	54	4.5%	1 40 [0 61 3 21]	
$ \begin{array}{c} \mbox{Label{Labe}Label{Labe}Label{Labe}Label{Label{Labe}Label{Labe}Label{Labe}Label{Labe}Label{Labe}Label{Labe}Label{Labe}Label{Labe}Label{Labe}Label{Labe}Labe}Label{Labe}Label{Labe}Labe}Label{Labe}Labe}Label{Labe}Labe}Label{Labe}Labe}Label{Labe}Labe}Label{Labe}Labe}Labe}Label{Labe}Labe}Labe}Labe}Labe}Label{Labe}Labe}Labe}Labe}Labe}Labe}Labe}Labe}$	Langrehr et al. 2015	2	56	2	57	1.1%	1 02 [0 15 6 98]	
Singh et al. 2019 24 97 22 96 12.6% 1.08 $[0.05, 1.73]$ Subtotal (95% C) 547 552 55.7% 1.13 $[0.89, 1.44]$ Total events 10 98 Heterogeneity: Ch <sup>2</sup> = 8.12, df = 7 (P = 0.32); l <sup>2</sup> = 14% Test for overall effect: 2 = 1.02 (P = 0.31) 1.12 ISCPF Bai et al. 2016 18 64 21 68 11.6% 0.91 $[0.54, 1.55]$ Berger et al. 2016 18 64 21 68 11.6% 0.91 $[0.54, 1.55]$ Berger et al. 2017 24 97 22 96 12.6% 1.08 $[0.65, 1.79]$ Subtotal (95% C) 372 377 44.3% 1.26 $[0.97, 1.63]$ Total events 97 78 Heterogeneity: Ch <sup>2</sup> = 3.83, df = 4 (P = 0.43); l <sup>2</sup> = 0% A Experimental Control Risk Ratio Study or Subgroup Ifferences: Ch <sup>2</sup> = 0.34, df = 1 (P = 0.56), l <sup>2</sup> = 0% A Experimental Control Risk Ratio Study or Subgroup 17 97 7 100 23.2% 2.26 $[0.93, 5.48]$ Singh et al.2015 2 64 12 68 14.9% 0.18 $[0.06, 1.77]$ El Nakeeb et al. 2015 2 64 12 68 14.9% 0.18 $[0.06, 5, 3.04]$ Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.387 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.487 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Ch <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.487 (P = 0.38) Total events 55 Hot philabel	Senda et al 2018	21	61	15	59	8 7%	1 35 [0 78 2 36]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Singh et al 2017	24	97	22	96	12.6%	1 08 [0 65 1 79]	
Total events 110 98 Heterogeneity: $Ch^2 = 8.12, df = 7 (P = 0.32); l^2 = 14\%$ Test for overall effect: Z = 1.02 (P = 0.32); l^2 = 14\% Test for overall effect: Z = 1.02 (P = 0.32); l^2 = 14\% Bai et al. 2016 18 64 21 68 11.6% 0.91 [0.54, 1.55] Berger et al. 2009 23 97 12 100 6.8% 1.98 [1.04, 3.75] El Nakeeb et al. 2015 11 53 8 54 4.5% 1.40 [0.61, 3.21] Senda et al.2018 21 61 15 59 8.7% 1.35 [0.78, 2.36] Subtotal (95% CI) 372 377 44.3% 1.26 [0.97, 1.63] Total events 97 78 Heterogeneity: $Ch^2 = 3.83, df = 4 (P = 0.43); l^2 = 0\%$ Total events 207 176 Heterogeneity: $Ch^2 = 12.12, df = 12 (P = 0.44); l^2 = 1\%$ Total events 207 176 Heterogeneity: $Ch^2 = 12.12, df = 12 (P = 0.44); l^2 = 1\%$ Total events 207 176 Heterogeneity: $Ch^2 = 12.12, df = 12 (P = 0.44); l^2 = 1\%$ Total events 207 176 Heterogeneity: $Ch^2 = 12.12, df = 12 (P = 0.44); l^2 = 1\%$ Total events 207 176 Heterogeneity: $Ch^2 = 12.12, df = 12 (P = 0.44); l^2 = 1\%$ Total events 207 176 Heterogeneity: $Ch^2 = 12.12, df = 12 (P = 0.44); l^2 = 1\%$ Total events 207 176 Heterogeneity: $Ch^2 = 12.12, df = 12 (P = 0.34), df = 1 (P = 0.56), l^2 = 0\%$ A Experimental Control Risk Ratio Study or Subgroup differences: $Ch^2 = 0.34, df = 1 (P = 0.56), l^2 = 0\%$ Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Berger et al. 2009 17 97 7 100 23.2% 2.50 [1.09, 5.77] El Nakeeb et al. 2017 16 97 13 96 25.6% 1.22 [0.62, 2.39] Subtotal (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chl <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chl <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chl <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38] Test for subgroup differences: Not applicable	Subtotal (95% CI)	27	547	~~	552	55.7%	1.13 [0.89, 1.44]	<b></b>
Total (95% C) 919 929 100.0% 1.19 [1.00, 1.42] Total (95% C) 919 929 100.0% 1.19 [1.00, 1.42] Total (95% C) 917 71 00 05.6% 1.28 [0.04, 0.76] Study or Subgroup differences: $Ch^2 = 0.34$ ; $f^2 = 1.87$ , $df = 4 (P = 0.56)$ , $l^2 = 0\%$ A Exprimental Control Risk Ratio Study or Subgroup 17 97 7 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: $Tat^2 = 0.48$ ; $Ch^2 = 11.87$ , $df = 4 (P = 0.02)$ ; $l^2 = 66\%$ Total (95% C) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: $Tat^2 = 0.48$ ; $Ch^2 = 11.87$ , $df = 4 (P = 0.02)$ ; $l^2 = 66\%$ Total (95% C) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: $Tat^2 = 0.48$ ; $Ch^2 = 11.87$ , $df = 4 (P = 0.02)$ ; $l^2 = 66\%$ Total (95% C) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: $Tat^2 = 0.48$ ; $Ch^2 = 11.87$ , $df = 4 (P = 0.02)$ ; $l^2 = 66\%$ Total (95% C) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: $Tat^2 = 0.48$ ; $Ch^2 = 11.87$ , $df = 4 (P = 0.02)$ ; $l^2 = 66\%$ Test for overall effect: $z = 0.87 (P = 0.38)$ Total events 55 40 Heterogeneity: $Tat^2 = 0.48$ ; $Ch^2 = 11.87$ , $df = 4 (P = 0.02)$ ; $l^2 = 66\%$ Test for overall effect: $z = 0.87 (P = 0.38)$ Total events 55 40 Heterogeneity: Tat $u^2 = 0.48$ ; $Ch^2 = 11.87$ , $df = 4 (P = 0.02)$ ; $l^2 = 66\%$ Test for overall effect: $z = 0.87 (P = 0.38)$ Total events 55 40 Heterogeneity: Tat $u^2 = 0.48$ ; $Ch^2 = 11.87$ , $df = 4 (P = 0.02)$ ; $l^2 = 66\%$ Test for overall effect: $z = 0.87 (P = 0.38)$	Total events	110		98				
$\begin{array}{c} \text{Retrogeneity. Chi = 0.12, (i = 7, 0 = 0.22, (i = 1.456) \\ \text{Test for overall effect: $Z = 1.02, (P = 0.31) \\ \hline \textbf{1.12 ISCPF} \\ \text{Bai et al. 2016} & 18 & 64 & 21 & 68 & 11.6\% & 0.91 [0.54, 1.55] \\ \text{Berger et al. 2009} & 23 & 97 & 12 & 100 & 6.8\% & 1.98 [1.04, 3.75] \\ \text{El Nakeeb et al. 2015} & 11 & 53 & 8 & 54 & 4.5\% & 1.40 [0.61, 3.21] \\ \text{Senda et al. 2018} & 21 & 61 & 15 & 59 & 8.7\% & 1.35 [0.78, 2.36] \\ \text{Singh et al. 2017} & 24 & 97 & 22 & 96 & 12.6\% & 1.08 [0.65, 1.79] \\ \text{Subtotal (95\% CI)} & 372 & 377 & 44.3\% & 1.26 [0.97, 1.63] \\ \text{Total events} & 97 & 78 \\ \text{Heterogeneity: Chi^{2} = 3.83, df = 4 (P = 0.44); l^{2} = 0\% \\ \text{Test for overall effect: $Z = 1.92, (P = 0.04); l^{2} = 0\% \\ \text{Test for overall effect: $Z = 1.92, (P = 0.44); l^{2} = 1\% \\ \text{Test for overall effect: $Z = 1.92, (P = 0.44); l^{2} = 1\% \\ \text{Test for overall effect: $Z = 1.92, (P = 0.04); l^{2} = 1\% \\ \text{Test for overall effect: $Z = 1.92, (P = 0.04); l^{2} = 1\% \\ \text{Test for overall effect: $Z = 1.92, (P = 0.04); l^{2} = 1\% \\ \text{Test for overall effect: $Z = 1.92, (P = 0.04); l^{2} = 1\% \\ \text{Test for overall effect: $Z = 1.92, (P = 0.05), l^{2} = 0\% \\ \text{A} \\ \begin{array}{c} \text{Experimental for overall effect: $Z = 1.92, (P = 0.04); l^{2} = 1\% \\ \text{Test for overall effect: $Z = 1.92, (P = 0.05), l^{2} = 0\% \\ \text{A} \\ \begin{array}{c} \text{Experimental for overall effect: $Z = 0.34, df = 1 (P = 0.56), l^{2} = 0\% \\ \text{Favours [experimental] Favours [control] \\ \text{Favours [experimental] Favours [control] \\ \text{Events Total Weight M-H, Random, 95\% CI \\ \hline \text{Heterogeneity: Chi^{2} = 0.48; Chi^{2} = 11.87, df = 4 (P = 0.02); l^{2} = 66\% \\ \text{Test for overall effect: $Z = 0.87, (P = 0.38) \\ \hline \text{Total events} & 55 & 40 \\ \text{Heterogeneity: Tau^{2} = 0.48; Chi^{2} = 11.87, df = 4 (P = 0.02); l^{2} = 66\% \\ \text{Test for overall effect: $Z = 0.87, (P = 0.38) \\ \hline \text{Total events} & 55 & 40 \\ \text{Heterogeneity: Tau^{2} = 0.48; Chi^{2} = 11.87, df = 4 (P = 0.02); l^{2} = 66\% \\ \text{Test for subgroup differences: Not applicable \\ \hline \text{Out} & 0.1 & 10 \\ \hline \text{Out} & 0.1 & 10 \\ \hline Favours [exper$	Heterogeneity: Chi <sup>2</sup> -	8 12 df -	7 (P -	0 32) 12	- 14%			
I.1.2 ISGPF         Bai et al. 2016       18       64       21       68       1.6%       0.91 [0.54, 1.55]         Bai et al. 2010       18       64       21       68       1.98 [1.04, 3.75]         El Nakeeb et al. 2015       11       53       8       54       4.5%       1.40 [0.61, 3.21]         Singh et al.2017       24       97       22       96       12.6%       1.08 [0.65, 1.79]         Subtotal (95% Cl)       372       377       78       1.19 [1.00, 1.42]         Total events       97       78         Heterogeneity: Chi <sup>2</sup> = 1.73 ( $P = 0.43$ ); $i^2 = 0\%$ 76         Test for overall effect: Z = 1.73 ( $P = 0.08$ )       700       1.19 [1.00, 1.42]         Total events       207       176         Heterogeneity: Chi <sup>2</sup> = 12.12, df = 12 ( $P = 0.43$ ); $i^2 = 0\%$ 8       8       1.00       1.19 [1.00, 1.42]         Test for overall effect: Z = 1.73 ( $P = 0.03$ , $df = 1$ ( $P = 0.56$ ), $i^2 = 0\%$ 8       8       8       1.00       1.00       1.00         Favours [control]       Risk Ratio       Risk Ratio       8       1.00       8       1.00       1.00       1.00         Study or Subgroup       Events       Total Events       0.18 [0.0	Test for overall effect:	7 - 1.02	P - 0 3	1)	- 14/0			
1.1.2 ISGPF         Bai et al. 2016       18       64       21       68       11.6%       0.91       [0.54, 1.55]         Berger et al. 2009       23       97       12       100       6.8%       1.98       [1.04, 3.75]         El Nakeeb et al. 2015       11       53       8       54       4.5%       1.40       [0.61, 3.21]         Senda et al.2017       24       97       22       96       12.6%       1.08       [0.65, 1.79]         Subtotal (95% CI)       372       377       44.3%       1.26       [0.97, 1.63]         Total events       97       78         Heterogeneity: Chi <sup>2</sup> = 3.83, df = 4 (P = 0.43); l <sup>2</sup> = 0%       76         Test for overall effect: Z = 1.73 (P = 0.08)       77       78         Total events       207       176         Heterogeneity: Chi <sup>2</sup> = 1.2, 2(P = 0.44); l <sup>2</sup> = 1%       74       92.9       100.0%       1.19 [1.00, 1.42]         Total events       207       176       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       Experimental       Control       Risk Ratio       M-H, Random, 95% CI       M-H, Random, 95% CI         L2.1 ISCF       10       10       10       10	rest for overall effect.	2 - 1.02 (	r = 0.5	1)				
Bai et al. 2016 Bai et al. 2009 El Nakeeb et al. 2015 Study or Subgroup Study or Subgroup Study or Subgroup Catal (95% CI) Total (95%	1.1.2 ISGPF							
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Bai et al. 2016	18	64	21	68	11.6%	0.91 [0.54, 1.55]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Berger et al. 2009	23	97	12	100	6.8%	1 98 [1 04 3 75]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	El Nakeeb et al. 2015	11	53	8	54	4 5%	1 40 [0 61 3 21]	
Sing et al. 2010 24 97 22 96 12.6 (0.65, 1.79) Subtotal (95% CI) 372 377 44.3% 1.26 [0.97, 1.63] Total events 97 78 Heterogeneity: Chi <sup>2</sup> = 3.83, df = 4 (P = 0.43); l <sup>2</sup> = 0% Test for overall effect: Z = 1.73 (P = 0.08) Total events 207 176 Heterogeneity: Chi <sup>2</sup> = 1.212, df = 12 (P = 0.44); l <sup>2</sup> = 1% Test for overall effect: Z = 1.92 (P = 0.44); l <sup>2</sup> = 1% Test for subgroup differences: Chi <sup>2</sup> = 0.34, df = 1 (P = 0.56), l <sup>2</sup> = 0% A Experimental Control Risk Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI 1.2.1 ISGPF Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Berger et al. 2019 6 53 2 54 13.9% 3.06 [0.65, 1.447] El Nakee be tal. 2015 6 53 2 54 13.9% 3.06 [0.65, 1.447] Subtotal (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for oxerall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for oxerall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for oxerall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for oxerall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for oxerall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Test for oxerall effect: Z = 0.87 (P = 0.38) Test for oxerall effect: Z = 0.87 (P = 0.38) Test for oxerall effect: Z = 0.87 (P = 0.38) Test for oxerall effect: Z = 0.87 (P = 0.38) Test for oxerall effect: Z = 0.87 (P = 0.38) Test for oxerall effect: Z = 0.87 (P = 0.38) Test for oxerall effect: Z = 0	Senda et al 2018	21	61	15	59	8 7%	1 35 [0 78 2 36]	
Subtotal (95% CI) 372 377 44.3% 1.26 [0.97, 1.63] Total events 97 78 Heterogeneity: Chi <sup>2</sup> = 3.83, df = 4 (P = 0.43); l <sup>2</sup> = 0% Total (95% CI) 919 929 100.0% 1.19 [1.00, 1.42] Total events 207 176 Heterogeneity: Chi <sup>2</sup> = 12.12, df = 12 (P = 0.44); l <sup>2</sup> = 1% Test for overall effect: Z = 1.92 (P = 0.05) Test for subgroup differences: Chi <sup>2</sup> = 0.34, df = 1 (P = 0.56), l <sup>2</sup> = 0% A Experimental Control Risk Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI 1.2.1 ISGPF Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Berger et al. 2009 17 97 7 100 23.2% 2.50 [1.09, 5.77] El Nakeeb et al. 2015 6 53 2 54 13.9% 3.06 [0.65, 1.4.47] Senda et al.2018 14 61 6 59 22.4% 2.26 [0.93, 5.48] Subtotal (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Test for overall effect: Z = 0.87 (P = 0.38) Total (95% CI) 57 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total (95% CI) 57 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall	Singh et al 2017	24	97	22	96	12.6%	1.08 [0.65, 1.70]	
Total events       97       78         Heterogeneity: Chi <sup>2</sup> = 3.83, df = 4 (P = 0.43); l <sup>2</sup> = 0%         Total events       207       176         Heterogeneity: Chi <sup>2</sup> = 12.12, df = 12 (P = 0.44); l <sup>2</sup> = 1%       0.01       0.1       100         Test for overall effect: Z = 1.92 (P = 0.44); l <sup>2</sup> = 1%       0.01       0.1       100       100         A       Experimental       Control       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total Events       Total Events       0.18 [0.04, 0.76]       M-H, Random, 95% Cl         L1.1 ISCPF       Events       Total Events       2.5 4 13.9%       3.06 [0.65, 14.47]       M-H, Random, 95% Cl         Singh et al. 2016       2       64       12       68       14.9%       0.18 [0.04, 0.76]         Berger et al. 2015       6       53       2       54       13.9%       3.06 [0.65, 14.47]         Singh et al. 2017       16       97       13       96       25.6%       1.22 [0.62, 2.39]         Subtotal (95% Cl)       372       377       100.0%       1.41 [0.65, 3.04]         Total events       55       40       -0.02); l <sup>2</sup> = 66%       1.41 [0.65, 3.04]         Total events       55       40 <td>Subtotal (95% CI)</td> <td>27</td> <td>372</td> <td>22</td> <td>377</td> <td>44.3%</td> <td>1.26 [0.97, 1.63]</td> <td></td>	Subtotal (95% CI)	27	372	22	377	44.3%	1.26 [0.97, 1.63]	
Total events $f_{1} = 1, 3, 3, df = 4 (P = 0, 43); l^{2} = 0\%$ Test for overall effect: $Z = 1.73 (P = 0.08)$ Total (95% CI) 919 929 100.0% 1.19 [1.00, 1.42] Total events 207 176 Heterogeneity: Chi <sup>2</sup> = 12.12, df = 12 (P = 0.43); l <sup>2</sup> = 1% Test for overall effect: $Z = 1.92 (P = 0.05)$ Test for subgroup differences: Chi <sup>2</sup> = 0.34, df = 1 (P = 0.56), l <sup>2</sup> = 0% A Experimental Control Risk Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI 1.2.1 ISGPF Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Berger et al. 2009 17 97 7 100 23.2% 2.50 [1.09, 5.77] El Nakeeb et al. 2015 6 53 2 54 13.9% 3.06 [0.65, 14.47] Senda et al.2017 16 97 13 96 25.6% 1.22 [0.62, 2.39] Subtotal (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: $Z = 0.87 (P = 0.38)$ Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: $Z = 0.87 (P = 0.38)$ Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: $Z = 0.87 (P = 0.38)$ Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: $Z = 0.87 (P = 0.38)$ Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: $Z = 0.87 (P = 0.38)$ Total (95% CI) 372 377 100.0% 1.41 [0.65, 3.04] Test for overall effect: $Z = 0.87 (P = 0.38)$ Test for overall effect: $Z = 0.87 (P = 0.38)$ Test for overall effect: $Z = 0.87 (P = 0.38)$ Test for overall effect: $Z = 0.87 (P = 0.38)$ Test for overall effect: $Z = 0.87 (P = 0.38)$ Test for overall effect: $Z = 0.87 (P = 0.38)$ Test for overall effect:	Total events	07	572	78	5	111370	1120 [0151] 1105]	
Test for overall effect: $Z = 1.73$ (P = 0.05) Total (95% Cl) 919 929 100.0% 1.19 [1.00, 1.42] Total events 207 176 Heterogeneity: Chi <sup>2</sup> = 12.12, df = 12 (P = 0.44); l <sup>2</sup> = 1% Test for overall effect: $Z = 1.92$ (P = 0.05) Test for subgroup differences: Chi <sup>2</sup> = 0.34, df = 1 (P = 0.56), l <sup>2</sup> = 0% A Experimental Control Risk Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl 1.2.1 ISGPF Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Berger et al. 2009 17 97 7 100 23.2% 2.50 [1.09, 5.77] El Nakeeb et al. 2015 6 53 2 54 13.9% 3.06 [0.65, 14.47] Events Total Events Total Section 2.2.6 (0.93, 5.48] Singh et al.2017 16 97 13 96 25.6% 1.22 [0.62, 2.39] Subtotal (95% Cl) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total (95% Cl) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total (95% Cl) 372 377 100.0% 1.41 [0.65, 3.04] Total vents 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total vents 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total vents 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total vents 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Test for overall effect: Z = 0.87 (P = 0.38) Test for subgroup differences: Not applicable	Heterogeneity: Chi <sup>2</sup> -	3 83 df -	A (P -	0 43) 12	- 0%			
Total (95% Cl)       919       929       100.0%       1.19 [1.00, 1.42]         Total events       207       176         Heterogeneity: Chi <sup>2</sup> = 12.12, df = 12 ( $P = 0.44$ ); l <sup>2</sup> = 1%       0.01       0.1       1       10       100         Fest for overall effect: Z = 1.92 ( $P = 0.44$ ); l <sup>2</sup> = 1%       0.01       0.1       1       10       100         Fest for subgroup differences: Chi <sup>2</sup> = 0.34, df = 1 ( $P = 0.56$ ), l <sup>2</sup> = 0%       Risk Ratio       Risk Ratio       Risk Ratio         A       Experimental       Control       Risk Ratio       M-H, Random, 95% Cl       M-H, Random, 95% Cl         1.2.1 ISCPF       Bai et al. 2016       2       64       12       68       14.9%       0.18 [0.04, 0.76]         Berger et al. 2009       17       97       7       100       23.2%       2.50 [1.09, 5.77]         El Nakeeb et al. 2015       6       53       2       54       13.9%       3.06 [0.65, 14.47]         Senda et al.2018       14       61       6       59       2.4%       2.26 [0.93, 5.48]         Singh et al.2017       16       97       13       96       25.6%       1.22 [0.62, 2.39]         Subtotal (95% Cl)       372       377       100.0%       1.41 [0.65, 3.04]	Test for overall effect:	7 - 173	P - 0.0	8)	- 070			
Total (95% Cl)       919       929       100.0%       1.19 [1.00, 1.42]         Total events       207       176         Heterogeneity: Chi <sup>2</sup> = 12.12, df = 12 (P = 0.44); l <sup>2</sup> = 1%       0.01       0.1       10         Test for overall effect: Z = 1.92 (P = 0.44); l <sup>2</sup> = 0.35)       Favours [experimental] Favours [control]       Favours [experimental] Favours [control]         A       Experimental       Control       Risk Ratio       M-H, Random, 95% Cl         1.2.1 ISCPF       Events       Total       Events       Total       State (0.4, 0.76]         Berger et al. 2009       17       97       7       100       23.2%       2.50 [1.09, 5.77]         El Nakeeb et al. 2015       6       53       2       54       13.9%       3.06 [0.65, 14.47]         Senda et al. 2018       14       61       6       59       22.4%       2.26 [0.93, 5.48]         Singh et al.2017       16       97       13       96       2.56%       1.22 [0.62, 2.39]         Subtotal (95% Cl)       372       377       100.0%       1.41 [0.65, 3.04]       0.01       0.1         Total events       55       40       4 (P = 0.02); l <sup>2</sup> = 66%       0.01       0.1       10       100         Favours [experimenta	rest for overall effect.	2 = 1.75 (	F = 0.0	0)				
Total events       207       176         Heterogeneity: Chi <sup>2</sup> = 12.12, df = 12 (P = 0.44); l <sup>2</sup> = 1%       0.01       0.1       1       10       100         Test for overall effect: Z = 1.92 (P = 0.05)       Total Events       Control       Risk Ratio       Risk Ratio       Risk Ratio         A       Experimental       Control       Risk Ratio       Risk Ratio       Risk Ratio         12.1 ISCPF       Events       Total Events       Total Events       Total Veight       M-H, Random, 95% Cl         Bai et al. 2016       2       64       12       68       14.9%       0.18 [0.04, 0.76]         Berger et al. 2009       17       97       7       100       23.2%       2.50 [1.09, 5.77]         El Nakeeb et al. 2017       16       97       13       96       25.6%       1.22 [0.62, 2.39]         Subtotal (95% Cl)       372       377       100.0%       1.41 [0.65, 3.04]         Total events       55       40         Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%       1.41 [0.65, 3.04]         Total (95% Cl)       372       377       100.0%       1.41 [0.65, 3.04]         Total events       55       40       4 (P = 0.02); l <sup>2</sup> = 66%       1.41 [0.65, 3.04] </td <td>Total (95% CI)</td> <td></td> <td>919</td> <td></td> <td>929</td> <td>100.0%</td> <td>1.19 [1.00, 1.42]</td> <td>•</td>	Total (95% CI)		919		929	100.0%	1.19 [1.00, 1.42]	•
Heterogeneity: $Chi^2 = 12.12$ , $df = 12$ (P = 0.44); $l^2 = 1\%$ Test for overall effect: $Z = 1.92$ (P = 0.05)         Test for overall effect: $Z = 1.92$ (P = 0.44); $l^2 = 0.56$ , $l^2 = 0.56$ Risk Ratio       Risk Ratio         A       Experimental       Control       Risk Ratio         Subgroup       Events       Total Events       Total Events       Total Events       Total Events       Total Version (0.1 1 1 0 0)         Subgroup       Risk Ratio         Mark Astain (0.01 0.1 1 0 0)         Total 2018       Control       Risk Ratio         Subtoal (95% CI)       Sign et al. 2017       16 97 13 96 25.66 12.22 [0.62, 2.39]         Subtoal (95% CI)       377 100.0%       1.41 [0.65, 3.04]         Total (95% CI)       377 377 377 100.0%       1.41 [0.65, 3.04]         Total (95% CI)       377 377 377 100.0%	Total events	207		176				
Test for overall effect: $Z = 1.92$ (P = 0.05)       100         Test for overall effect: $Z = 1.92$ (P = 0.05)       Favours [control]         Test for subgroup differences: Chi <sup>2</sup> = 0.34, df = 1 (P = 0.56), l <sup>2</sup> = 0%       A         A       Experimental       Control       Risk Ratio         Study or Subgroup       Events       Total       Events       Total       Weight       M-H, Random, 95% CI         1.2.1 ISGPF       Bai et al. 2016       2       64       12       68       14.9%       0.18 [0.04, 0.76]         Berger et al. 2009       17       97       7       100       23.2%       2.50 [1.09, 5.77]         El Nakee et al. 2015       6       53       2       54       13.9%       3.06 [0.65, 14.47]         Senda et al.2017       16       97       13       96       25.6%       1.22 [0.62, 2.39]         Subtotal (95% CI)       372       377       100.0%       1.41 [0.65, 3.04]         Total events       55       40         Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%         Test for overall effect: Z = 0.87 (P = 0.38)       300       1.41 [0.65, 3.04]         Test for overall effect:: Z = 0.87 (P = 0.38)       10       0.01       0.1       10         Favo	Heterogeneity: $Chi^2 = $	12.12, df :	= 12 (P	= 0.44);	$ ^2 = 1\%$	6		
Test for subgroup differences: $Chi^2 = 0.34$ , df = 1 (P = 0.56), l <sup>2</sup> = 0%         A       Experimental       Control       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total       Events       Total       Weight       M-H, Random, 95% CI         1.2.1 ISGPF       Bai et al. 2016       2       64       12       68       14.9%       0.18 [0.04, 0.76]       M-H, Random, 95% CI         Senda et al. 2015       6       53       2       54       13.9%       3.06 [0.65, 14.47]       Image: Chi and the state of the	Test for overall effect:	Z = 1.92 (	P = 0.0	5)				0.01 0.1 1 10 100
A         Experimental         Control         Risk Ratio         Risk Ratio           1.2.1         ISGPF         Events         Total         Events         Total         Weight         M-H, Random, 95% Cl         M-H, Random, 95% Cl           1.2.1         ISGPF         Bai et al. 2016         2         64         12         68         14.9%         0.18<[0.04, 0.76]	Test for subgroup diffe	erences: C	$hi^2 = 0.$	34, df =	1 (P =	0.56), l <sup>2</sup> =	= 0%	Favours [experimental] Favours [control]
Experimental         Control         Risk Ratio         Risk Ratio           Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% CI           1.2.1 ISGPF         Bai et al. 2016         2         64         12         68         14.9%         0.18 [0.04, 0.76]           Berger et al. 2009         17         97         7         100         23.2%         2.50 [1.09, 5.77]           El Nakeeb et al. 2015         6         53         2         54         13.9%         3.06 [0.65, 14.47]           Senda et al.2018         14         61         6         59         22.4%         2.26 [0.93, 5.48]           Singh et al.2017         16         97         13         96         25.6%         1.22 [0.62, 2.39]           Subtotal (95% CI)         372         377         100.0%         1.41 [0.65, 3.04]         1.41 [0.65, 3.04]           Total events         55         40         4         4 (P = 0.02); I <sup>2</sup> = 66%         4.41 [0.65, 3.04]         4.41 [0.65, 3.04]           Total events         55         40         4.41 [0.65, 3.04]         4.41 [0.65, 3.04]         4.41 [0.65, 3.04]         4.41 [0.65, 3.04]         4.41 [0.65, 3.04]         4.41 [0.65, 3.04]         4.41 [	A		0.000		6.90		1.00106000000000	100000000000000000000000000000000000000
Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% Cl         M-H, Random, 95% Cl           1.2.1 ISCPF         Bai et al. 2016         2         64         12         68         14.9%         0.18 [0.04, 0.76]           Berger et al. 2009         17         97         7         100         23.2%         2.50 [1.09, 5.77]         100           El Nakeeb et al. 2015         6         53         2         54         13.9%         3.06 [0.65, 14.47]           Senda et al.2017         16         97         13         96         25.6%         1.22 [0.62, 2.39]         1.41 [0.65, 3.04]           Singh et al.2017         16         97         13         96         25.6%         1.22 [0.62, 2.39]         1.41 [0.65, 3.04]           Total events         55         40         4(P = 0.02); l <sup>2</sup> = 66%         1.41 [0.65, 3.04]         1.41 [0.65, 3.04]           Total events         55         40         4(P = 0.02); l <sup>2</sup> = 66%         1.41 [0.65, 3.04]         1.41 [0.65, 3.04]           Total events         55         40         4(P = 0.02); l <sup>2</sup> = 66%         1.41 [0.65, 3.04]         1.41 [0.61, 1 1 10         100           Test for overall effect: Z = 0.87 (P = 0.38)         55		Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
1.2.1 ISCPF         Bai et al. 2016       2       64       12       68       14.9%       0.18       [0.04, 0.76]         Berger et al. 2009       17       97       7       100       23.2%       2.50       [1.09, 5.77]         El Nakeeb et al. 2015       6       53       2       54       13.9%       3.06       [0.65, 14.47]         Senda et al.2018       14       61       6       59       22.4%       2.26       [0.93, 5.48]         Singh et al.2017       16       97       13       96       25.6%       1.22       [0.62, 2.39]         Subtotal (95% CI)       372       377       100.0%       1.41       [0.65, 3.04]         Total events       55       40         Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%         Test for overall effect: Z = 0.87 (P = 0.38)         Total events       55       40         Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%         Test for overall effect: Z = 0.87 (P = 0.38)         Test for subgroup differences: Not applicable         Destine to subgroup differences: Not applicable	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bai et al. 2016 2 64 12 68 14.9% 0.18 [0.04, 0.76] Berger et al. 2009 17 97 7 100 23.2% 2.50 [1.09, 5.77] El Nakeeb et al. 2015 6 53 2 54 13.9% 3.06 [0.65, 14.47] Senda et al. 2018 14 61 6 59 22.4% 2.26 [0.93, 5.48] Singh et al. 2017 16 97 13 96 25.6% 1.22 [0.62, 2.39] Subtotal (95% Cl) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: $Z = 0.87$ (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: $Z = 0.87$ (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: $Z = 0.87$ (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: $Z = 0.87$ (P = 0.38) Test for subgroup differences: Not applicable	1.2.1 ISGPF							
Berger et al. 2009 17 97 7 100 23.2% 2.50 [1.09, 5.77] El Nakeeb et al. 2015 6 53 2 54 13.9% 3.06 [0.65, 14.47] Senda et al. 2018 14 61 6 59 22.4% 2.26 [0.93, 5.48] Singh et al. 2017 16 97 13 96 25.6% 1.22 [0.62, 2.39] Subtotal (95% Cl) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Test for subgroup differences: Not applicable	Bai et al. 2016	2	64	12	68	14.9%	0.18 [0.04, 0.76]	
El Nakeeb et al. 2015 6 53 2 54 13.9% $3.06 [0.65, 14.47]$ Senda et al. 2018 14 61 6 59 22.4% 2.26 [0.93, 5.48] Singh et al. 2017 16 97 13 96 25.6% 1.22 [0.62, 2.39] Subtotal (95% Cl) 372 377 100.0% 1.41 [0.65, 3.04] Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Test for subgroup differences: Not applicable	Berger et al. 2009	17	97	7	100	23.2%	2.50 [1.09, 5.77]	
Senda et al. 2018 14 61 6 59 22.4% 2.26 $[0.93, 5.48]$ Singh et al. 2017 16 97 13 96 25.6% 1.22 $[0.62, 2.39]$ Subtotal (95% CI) 372 377 100.0% 1.41 $[0.65, 3.04]$ Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Test for subgroup differences: Not applicable	El Nakeeb et al. 2015	6	53	2	54	13.9%	3.06 [0.65, 14.47]	
Singh et al.20171697139625.6%1.22[0.62, 2.39]Subtotal (95% CI) $372$ $377$ 100.0%1.41[0.65, 3.04]Total events $55$ $40$ Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%Total (95% CI) $372$ $377$ 100.0%Total events $55$ $40$ Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%Total events $55$ $40$ Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%Test for overall effect: Z = 0.87 (P = 0.38)Test for subgroup differences: Not applicableFavours [experimental]Favours [control]	Senda et al.2018	14	61	6	59	22.4%	2.26 [0.93, 5.48]	
Subtotal (95% Cl) $372$ $377$ $100.0\%$ $1.41$ [0.65, $3.04$ ]         Total events $55$ $40$ Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%         Total (95% Cl) $372$ $377$ $100.0\%$ $1.41$ [0.65, $3.04$ ]         Total (95% Cl) $372$ $377$ $100.0\%$ $1.41$ [0.65, $3.04$ ]         Total events $55$ $40$ Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%         Test for overall effect: Z = 0.87 (P = 0.38)         Test for subgroup differences: Not applicable         Favours [experimental]         Favours [control]	Singh et al.2017	16	97	13	96	25.6%	1.22 [0.62, 2.39]	
Total events       55       40         Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%       Image: Chi = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%         Total (95% Cl)       372       377       100.0%       1.41 [0.65, 3.04]         Total events       55       40         Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%       1.41 [0.65, 3.04]         Total events       55       40         Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%       1.41 [0.65, 3.04]         Test for overall effect: Z = 0.87 (P = 0.38)       1.41 [0.65, 3.04]         Test for subgroup differences: Not applicable       100         Favours [experimental]       Favours [control]	Subtotal (95% CI)	2017	372	1.02	377	100.0%	1.41 [0.65, 3.04]	
Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Total events 55 40 Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% Test for overall effect: Z = 0.87 (P = 0.38) Test for subgroup differences: Not applicable Test for subgroup differences: Not applicable	Total events	55		40		-		
Test for overall effect: $Z = 0.87$ (P = 0.38)         Total (95% Cl)       372       377       100.0%       1.41 [0.65, 3.04]         Total events       55       40         Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66%       0.01       0.1       1       10         Test for overall effect: Z = 0.87 (P = 0.38)       Test for subgroup differences: Not applicable       Favours [experimental]       Favours [control]	Heterogeneity: $Tau^2 = 0$	0.48; Chi <sup>2</sup>	= 11.87	, df = 4	(P=0.)	$(02); 1^2 = 6$	56%	
Total (95% Cl)       372       377       100.0%       1.41 [0.65, 3.04]         Total events       55       40         Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 11.87, df = 4 (P = 0.02); l <sup>2</sup> = 66% $0.01$ $0.1$ $1$ $100$ Test for overall effect: Z = 0.87 (P = 0.38)       Test for subgroup differences: Not applicable $Favours [experimental]$ Favours [control]	Test for overall effect: 2	Z = 0.87 (F)	P = 0.38	()				
Total events5540Heterogeneity: Tau² = 0.48; Chi² = 11.87, df = 4 (P = 0.02); l² = 66% $0.01$ $0.1$ $1$ Test for overall effect: Z = 0.87 (P = 0.38)Favours [experimental]Favours [control]Test for subgroup differences: Not applicableFavours [experimental]Favours [control]	Total (95% CI)		372		377	100.0%	1.41 [0.65, 3.04]	
Heterogeneity: $Tau^2 = 0.48$ ; $Chi^2 = 11.87$ , $df = 4$ (P = 0.02); $l^2 = 66\%$ Test for overall effect: Z = 0.87 (P = 0.38) Test for subgroup differences: Not applicable Favours [experimental] Favours [control]	Total events	55		40				
Test for overall effect: Z = 0.87 (P = 0.38)       0.01       0.1       1       100         Test for subgroup differences: Not applicable       Favours [experimental]       Favours [control]	Heterogeneity: $Tau^2 = 0$	0.48: Chi <sup>2</sup>	= 11.87	7. $df = 4$	(P = 0.0)	(02): $I^2 = 6$	56%	transfer the second
Test for subgroup differences: Not applicable	Test for overall effect: 2	Z = 0.87 (F	P = 0.38	()	1012456	20041020202	5.894g (	
	Test for subgroup diffe	rences: No	ot applic	able				ravours (experimental) Favours (control)
B	B			10000				

Figure 3. Forest plot of the meta-analysis comparing duct-to-mucosa PJ and invagination PJ with respect to (A) POPF, (B) CR-POPF, (C) DGE, (D) PPH, and (E) reoperation. CR-POPF = clinically relevant POPF, DGE = delayed gastric emptying, PJ = pancreaticojejunostomy, POPF = postoperative pancreatic fistula, PPH = post-pancreatectomy hemorrhage.

60 of 450 patients in the duct-to-mucosa PJ group and 48 of 452 in the invagination PJ group. There was no significant difference between the 2 groups (RR, 1.24; 95% CI, 0.88–1.76; P=.22) (Fig. 3C). In accordance with the ISGPF criteria, no significant difference was shown in the meta-analysis (RR, 1.22; 95% CI, 0.85–1.75; P=.27) (Fig. 3C).

# 3.5. PPH

In a comparison of the incidence of PPH, we found that 5 studies reported the clinical outcome of interest. The incidence of PPH in the duct-to-mucosa and invagination PJ groups is presented in Fig. 3D. This meta-analysis demonstrated no significant difference between the 2 PJ techniques (RR, 0.94; 95% CI, 0.44–2.00; P=.87) (Fig. 3D). After stratifying the patients according to the definition of PPH, duct-to-mucosa PJ was not superior to invagination PJ (RR, 1.01; 95% CI, 0.45–2.26; P=.98) (Fig. 3D).

#### 3.6. Reoperation

All 8 studies reported the rates of reoperation. No significant difference was found between the 2 groups (RR, 1.15; 95% CI, 0.67–0.1.97; P < .62) (Fig. 3E). Similar results were obtained in the ISGPF analysis (RR, 0.95; 95% CI, 0.47–1.92; P = .89) (Fig. 3E).

#### 3.7. Operation time

Data on the operation time were reported in all trials. However, there was no significant difference between the 2 groups in the metaanalysis (mean difference [MD], 22.45; 95% CI,- 7.14–52.04;

	Experim	ental	Contr	ol		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.3.1 ALL							
Bai et al. 2016	3	64	6	68	6.3%	0.53 [0.14, 2.04]	
Bassi et al. 2003	6	72	1	72	1.1%	6.00 [0.74, 48.59]	2
Chou et al.1996	0	47	2	46	2.7%	0.20 [0.01, 3.97]	· · · · · · · · · · · · · · · · · · ·
El Nakeeb et al. 2015	8	53	7	54	7.5%	1.16 [0.45, 2.98]	
Langrehr et al. 2005	1	56	1	57	1.1%	1.02 [0.07, 15.88]	
Senda et al.2018	13	61	9	59	9.9%	1.40 [0.65, 3.02]	
Singh et al.2017	29	97	22	96	23.9%	1.30 [0.81, 2.10]	
Subtotal (95% CI)		450		452	52.4%	1.24 [0.88, 1.75]	•
Total events	60		48				3 ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) (
Heterogeneity: $Chi^2 = $	5.33, df =	6(P = 0)	$(.50); 1^2 =$	• 0%			
Test for overall effect:	Z = 1.25 (	P = 0.21	l)				
1.3.2 ISGPF							
Bai et al. 2016	3	64	6	68	6.3%	0.53 [0.14, 2.04]	
El Nakeeb et al. 2015	8	53	7	54	7.5%	1.16 [0.45, 2.98]	
Senda et al.2018	13	61	9	59	9.9%	1.40 [0.65, 3.02]	
Singh et al.2017	29	97	22	96	23.9%	1.30 [0.81, 2.10]	
Subtotal (95% CI)		275		277	47.6%	1.20 [0.84, 1.71]	•
Total events	53		44			ALCONTRACTOR OF ALL AND ALCON	
Heterogeneity: $Chi^2 = 1$	1.69 df =	3(P = 0)	$(64) \cdot 1^2 =$	: 0%			
Test for overall effect:	Z = 1.00 (	P = 0.32	2)	070			
Total (95% CI)		725		729	100.0%	1.22 [0.95, 1.56]	•
Total events	113	0.755	92		1.		•
Heterogeneity: Chi <sup>2</sup> - 3	7 01 df -	10 (P -	0 72) 12	- 0%			
Test for overall offect:	7 - 150 (	P = 0.11	0.72), 1	- 070			0.01 0.1 i 10 100
Test for subgroup diffe	2 = 1.39 (	- 0.11	17 46 1	10	0.001 12	001	Favours [experimental] Favours [control]
					1 XU1 1		
Test for subgroup unit	erences: Cr	$n^{-} = 0.0$	$j_{2}, a_{1} = j_{2}$	L(P = 0)	$(.89), 1^{-} =$	: 0%	
	Fxperim	ental	Contr		).89), 1* =	Risk Ratio	Risk Ratio
C Study or Subaroup	Experim Events	ental Total	Contr Events	ol Total	).89), 1* =	Risk Ratio	Risk Ratio M-H. Fixed, 95% Cl
Study or Subgroup	Experim Events	ental Total	Contr Events	ol Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.4.1 ALL	Experim Events	ental Total	Contr Events	ol Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.4.1 ALL Bai et al. 2016	Experim Events	ental Total 64	Contr Events	ol Total	Weight 15.7%	Risk Ratio M-H, Fixed, 95% CI 0.53 [0.10, 2.80]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.4.1 ALL Bai et al. 2016 El Nakeeb et al. 2015	Experim Events	ental Total 64 53	Contr Events 4 2	ol Total 68 54	Weight 15.7% 8.0%	Risk Ratio M-H, Fixed, 95% CI 0.53 [0.10, 2.80] 1.53 [0.27, 8.78]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.4.1 ALL Bai et al. 2016 El Nakeeb et al. 2015 Langrehr et al. 2005	Experim Events 2 3 1	ental Total 64 53 56	Contr Events 4 2 2	ol Total 68 54 57	Weight 15.7% 8.0%	Risk Ratio M-H, Fixed, 95% CI 0.53 [0.10, 2.80] 1.53 [0.27, 8.78] 0.51 [0.05, 5.45]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.4.1 ALL Bai et al. 2016 El Nakeeb et al. 2015 Langrehr et al. 2005 Senda et al.2018	Experim Events 2 3 1	ental Total 64 53 56 61	Contr Events 4 2 0	ol Total 68 54 57 59	Weight 15.7% 8.0% 2.1%	Risk Ratio M-H, Fixed, 95% CI 0.53 [0.10, 2.80] 1.53 [0.27, 8.78] 0.51 [0.05, 5.45] 2.90 [0.12, 69.87]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.4.1 ALL Bai et al. 2016 El Nakeeb et al. 2015 Langrehr et al. 2005 Senda et al.2018 Singh et al.2017 Subtotal (95% CI)	Experim Events 2 3 1 1 5	ental Total 64 53 56 61 97 331	Contr Events 4 2 0 5	68 54 57 59 96	Weight 15.7% 8.0% 2.1% 20.3%	Risk Ratio M-H, Fixed, 95% CI 0.53 [0.10, 2.80] 1.53 [0.27, 8.78] 0.51 [0.05, 5.45] 2.90 [0.12, 69.87] 0.99 [0.30, 3.31]	Risk Ratio M-H, Fixed, 95% CI
Study or Subgroup 1.4.1 ALL Bai et al. 2016 El Nakeeb et al. 2015 Langrehr et al. 2005 Senda et al.2018 Singh et al.2017 Subtotal (95% CI)	Experim Events 2 3 1 1 5	ental Total 64 53 56 61 97 <b>331</b>	Contr Events 4 2 0 5	68 54 57 59 96 <b>33</b> 4	Weight 15.7% 8.0% 2.1% 20.3% 54.0%	Risk Ratio M-H, Fixed, 95% CI 0.53 [0.10, 2.80] 1.53 [0.27, 8.78] 0.51 [0.05, 5.45] 2.90 [0.12, 69.87] 0.99 [0.30, 3.31] 0.94 [0.44, 2.00]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.4.1 ALL Bai et al. 2016 El Nakeeb et al. 2015 Langrehr et al. 2005 Senda et al.2018 Singh et al.2017 Subtotal (95% Cl) Total events	Experim Events 2 3 1 1 5	eental Total 64 53 56 61 97 331	Contr Events 4 2 0 5 13	68 54 57 59 96 334	Weight 15.7% 8.0% 2.1% 20.3% 54.0%	Risk Ratio M-H, Fixed, 95% CI 0.53 [0.10, 2.80] 1.53 [0.27, 8.78] 0.51 [0.05, 5.45] 2.90 [0.12, 69.87] 0.99 [0.30, 3.31] 0.94 [0.44, 2.00]	Risk Ratio M-H, Fixed, 95% Cl
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Study or Subgroup unite 1.4.1 ALL Bai et al. 2016 El Nakeeb et al. 2015 Langrehr et al. 2005 Senda et al.2018 Singh et al.2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 1 1.4.2 ISCPE	Experim Events 2 3 1 1 5 12 1.50, df = Z = 0.17 (f	eental Total 64 53 56 61 97 331 4 (P = C P = 0.87	Z, or = 1           Contr           Events           4           2           0           5           13           ).83); 1 <sup>2</sup> = 7)	ol Total 68 54 57 59 96 334 • 0%	Weight 15.7% 8.0% 2.1% 20.3% 54.0%	Risk Ratio M-H, Fixed, 95% CI 0.53 [0.10, 2.80] 1.53 [0.27, 8.78] 0.51 [0.05, 5.45] 2.90 [0.12, 69.87] 0.99 [0.30, 3.31] 0.94 [0.44, 2.00]	Risk Ratio M-H, Fixed, 95% Cl
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P=.14). The meta-analysis of studies performed in accordance with the ISGPF criteria demonstrated no significant difference between the 2 groups (MD, 26.30; 95% CI, -19.55-72.15; P=.26) (Fig. 4A).

# 3.8. LOS

Six studies involving 842 patients (419 in the duct-to-mucosa PJ group and 423 in the invagination PJ group) were pooled to compare the LOS. There was no significant difference between

the 2 groups (MD, -0.17; 95% CI, -2.56-2.23; P=.89). Among studies using the ISGPF definition, no significant difference was found between the 2 groups (MD, 0.37; 95% CI, -2.54-3.28; P=.80) (Fig. 4B).

## 3.9. Morbidity

All trials provided data regarding morbidity. The meta-analysis demonstrated no significant difference between the 2 groups (RR,



1.06; 95% CI, 0.95–1.19; P=.31) (Fig. 4D). Analysis of morbidity according to the ISGPF criteria revealed no significant difference between the 2 techniques (RR, 1.12; 95% CI, 0.97–1.29; P=.12) (Fig. 4D).

#### 3.10. Mortality

The analysis of mortality was performed using a random-effects model ( $I^2=0\%$ ). All studies provided data on mortality rates among 1099 patients. The meta-analysis demonstrated no significant difference between the 2 groups (RR, 0.94; 95% CI, 0.47–1.89; P=.86) (Fig. 4E). Analysis according to the ISGPF criteria did not change the result (RR, 0.92; 95% CI, 0.40–2.13; P=.85) (Fig. 4E).

#### 4. Discussion

The optimal reconstruction technique for PJ after PD remains controversial. In the present study, duct-to-mucosa PJ did not seem to be superior to invagination PJ in terms of POPF and CR-POPF. No significant differences in DGE, PPH, or the main clinical outcomes were found between the 2 groups.

The most effective pancreatic construction technique has been debated in many studies.<sup>[2,26,27]</sup> Two major techniques performed universally are PG and PJ. Although many studies have compared PG with PJ, the best way to reconstruct the pancreas has not been determined.<sup>[28–30]</sup> PJ is the most commonly used method to restore the pancreatic anastomosis, and its main advantage is that it is more physiological. The surgical techniques of PJ are duct-to-mucosa, invagination, and binding PJ. Binding PJ was proposed in 2002 by Peng et al.<sup>[31]</sup> Some studies have

proposed that binding PJ may reduce the incidence of POPF.<sup>[27,32]</sup> In the European population, however, binding PJ did not reduce the incidence of POPF.<sup>[33]</sup> Few clinical studies have been performed to evaluate binding PJ, and the technique may still need some modifications. Therefore, assessment of this technique is not within the scope of the present study.

As mentioned above, the 2 most widely used PJ methods are duct-to-mucosa PJ and invagination PJ. A primary concern of PD is POPF. POPF can lead to intra-abdominal abscess formation, DGE, PPH, and increased morbidity. The occurrence of POPF is multifactorial, and studies have shown that it may be related to obesity, the pancreatic texture, the pancreatic duct diameter, and pancreas reconstruction.<sup>[34-38]</sup> Previously published studies of the effect of pancreatic reconstruction on POPF are not consistent. The main advantage of duct-to-mucosa PJ is that it assures drainage of the main duct into the intestine. Previous studies involving animals and humans suggest that duct-tomucosa PJ is associated with a lower incidence of POPF than is invagination PJ.<sup>[17-19,39]</sup> In the present meta-analysis, 7 studies demonstrated that invagination PJ was associated with a lower incidence of POPF. However, minor ducts and a soft pancreas make duct-to-mucosa PJ difficult. In contrast to duct-to-mucosa PJ, invagination PJ allows for easier reconstruction and has advantages in patients with a soft pancreas. Some studies, including an RCT, demonstrated that invagination PJ was associated with a lower incidence of POPF. Nevertheless, the conclusions of previous relevant research regarding the effects of duct-to-mucosa PJ and invagination PJ on the development of POPF remain controversial.<sup>[40–42]</sup> A major strength of the present study is the inclusion of 2 recent RCTs. Nonetheless, the results of previous studies are conflicted.

	Exp	erimenta	I	(	Control			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.6.1 ALL							10.001	and the test of the second second		
Bai et al. 2016	340	105	64	360	101	68	7.5%	-20.00 [-55.19, 15.19]		
Bassi et al. 2003	379	63	72	379	68	72	8.4%	0.00 [-21.41, 21.41]		
Berger et al. 2009	379	142	97	247	144	100	7.2%	132.00 [92.06, 171.94]		-
Chou et al.1996	390	112	47	326	78	46	7.3%	64.00 [24.84, 103.16]		
El Nakeeb et al. 2015	330	86.6	53	300	86.6	54	7.7%	30.00 [-2.82, 62.82]		
Langrehr et al. 2005	346	92.8	56	356	86.6	57	7.7%	-10.00 [-43.11, 23.11]		
Senda et al.2018	427	102.85	61	457	111.87	59	7.3%	-30.00 [-68.48, 8.48]		
Singh et al.2017 Subtotal (95% CI)	372	70	97 547	350	68	96 552	8.5% 61.7%	22.00 [2.53, 41.47] 22.45 [-7.14, 52.04]		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	1542.55 Z = 1.49	P = 0.1	53.18, 4)	df = 7 (	P < 0.00	0001); l <sup>i</sup>	<sup>2</sup> = 87%			
1.6.2 ISGPF										
Bai et al. 2016	340	105	64	360	101	68	7 5%	-20 00 [-55 19 15 19]		
Berger et al. 2009	379	142	97	247	144	100	7.2%	132.00 [92.06, 171.94]		-
El Nakeeb et al. 2015	330	86.6	53	300	86.6	54	7.7%	30.00 [-2.82, 62.82]		
Senda et al.2018	427	102.85	61	457	111.87	59	7.3%	-30.00 [-68.48, 8.48]		
Singh et al.2017	372	70	97	350	68	96	8.5%	22.00 [2.53, 41,47]		
Subtotal (95% CI)			372			377	38.3%	26.30 [-19.55, 72.15]		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	2440.52 Z = 1.12	$2; Chi^2 = 4$ 2 (P = 0.2)	41.82, 6)	df = 4 (	P < 0.00	0001); l <sup>i</sup>	<sup>2</sup> = 90%			
Total (95% CI)			919			929	100.0%	23.87 [0.18, 47.56]		
Heterogeneity: $Tau^2 =$	1613.56	$Chi^2 = 0$	95.46.	df = 12	(P < 0.0	00001):	$l^2 = 87\%$		F	
Test for overall effect: Test for subgroup diffe	Z = 1.92 erences:	7 (P = 0.0) Chi <sup>2</sup> = 0.	5) 02, df	= 1 (P =	= 0.89),	$l^2 = 0\%$	4.0503030		-100 -50 0 50 Favours [experimental] Favours [control]	100
A	27	1990 - 1997 1997 - 1997								
19 or 19 or 19 of 19	Ex	periment	tal		Control			Mean Difference	Mean Difference	
Study or Subgroup	Mear	1 SD	Total	Mean	SD	Total	Weight	IV Bandom OF% CI	IV. Random, 95% CI	
	Mean	1 30	Total	Wiean	50		ireigin	IV, Kandom, 95% CI	it, italiaolii, 55% ci	
1.7.1 ALL	mean	1 30	Total	Mean	50		ireight	IV, Kandom, 95% CI		
1 <b>.7.1 ALL</b> Bai et al. 2016	1	3 7	64	15	12	68	11.7%	-2.00 [-5.33, 1.33]		
<b>1.7.1 ALL</b> Bai et al. 2016 Berger et al. 2009	1	3 7 7 15	64 97	15 7	12 27	68 100	11.7% 5.8%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08]		
<b>1.7.1 ALL</b> Bai et al. 2016 Berger et al. 2009 Chou et al.1996	1	3 7 7 15 0 8	64 97 47	15 7 22	12 27 11	68 100 46	11.7% 5.8% 10.0%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015	1	3 7 7 15 0 8 3 10	64 97 47 53	15 7 22 8	12 27 11 14	68 100 46 54	11.7% 5.8% 10.0% 8.4%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2018	1 20 4	3 7 7 15 0 8 3 10 0 20.91	64 97 47 53 61	15 7 22 8 31	12 27 11 14 14.74	68 100 46 54 59	11.7% 5.8% 10.0% 8.4% 5.3%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2018 Singh et al.2017	1 20 40 14.1	3 7 7 15 0 8 3 10 0 20.91 9 10	64 97 47 53 61 97	15 7 22 8 31 16	12 27 11 14 14.74 8.8	68 100 46 54 59 96	11.7% 5.8% 10.0% 8.4% 5.3% 13.8%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2018 Singh et al.2017 Subtotal (95% CI)	1 20 4 14.5	3 7 7 15 0 8 8 10 0 20.91 9 10	64 97 47 53 61 97 <b>419</b>	15 7 22 8 31 16	12 27 11 14 14.74 8.8	68 100 46 54 59 96 <b>423</b>	11.7% 5.8% 10.0% 8.4% 5.3% 13.8% <b>55.0%</b>	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2018 Singh et al.2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect	1 20 44 14.5 = 4.19; ( : Z = 0.1	$\begin{array}{cccc} 3 & 7 \\ 7 & 15 \\ 0 & 8 \\ 8 & 10 \\ 0 & 20.91 \\ 9 & 10 \\ Chi^2 = 9.9 \\ 14 (P = 0.9) \\ 0 & 10 \\$	64 97 47 53 61 97 <b>419</b> 90, df 89)	15 7 22 8 31 16 = 5 (P =	12 27 11 14 14.74 8.8 = 0.08);	$ \begin{array}{r} 68\\100\\46\\54\\59\\96\\423\\1^2=50\end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 13.8% <b>55.0%</b>	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2018 Singh et al.2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISCPF	11 20 44 14.5 = 4.19; ( : Z = 0.5	$\begin{array}{ccc} 3 & 7 \\ 7 & 15 \\ 0 & 8 \\ 8 & 10 \\ 0 & 20.91 \\ 9 & 10 \\ \text{Chi}^2 = 9.9 \\ 14 (P = 0) \end{array}$	64 97 47 53 61 97 <b>419</b> 90, df 89)	15 7 22 8 31 16 = 5 (P =	12 27 11 14 14.74 8.8 = 0.08);	68 100 46 54 59 96 423 $ ^2 = 50$	11.7% 5.8% 10.0% 8.4% 5.3% 13.8% 55.0%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2018 Singh et al.2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISGPF Bai et al. 2016	11 20 44 14.5 = 4.19; ( : Z = 0.:	$\begin{array}{c} 3 & 7 \\ 7 & 15 \\ 0 & 8 \\ 8 & 10 \\ 0 & 20.91 \\ 9 & 10 \\ 0 & 20.91 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ $	64 97 47 53 61 97 <b>419</b> 90, df 89)	15 7 22 8 31 16 = 5 (P =	12 27 11 14 14.74 8.8 = 0.08);	$ \begin{array}{r} 68\\100\\46\\54\\59\\96\\423\\1^2=50\end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 13.8% 55.0%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2017 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISCPF Bai et al. 2016 Berger et al. 2009	11 20 44 14.9; C : Z = 0.1	$\begin{array}{cccc} 3 & 7 \\ 7 & 15 \\ 0 & 8 \\ 3 & 10 \\ 0 & 20.91 \\ 9 & 10 \\ \hline Chi^2 = 9.5 \\ 14 (P = 0 \\ 3 & 7 \\ 7 & 15 \\ \end{array}$	64 97 47 53 61 97 <b>419</b> 90, df 89) 64	15 7 22 8 31 16 = 5 (P =	12 27 11 14 14.74 8.8 = 0.08); 12 27	$ \begin{array}{r} 68\\100\\46\\54\\59\\96\\423\\1^2=50\\68\\100\end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 13.8% 55.0%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISGPF Bai et al. 2016 Berger et al. 2019 El Nakeeb et al. 2019	11 20 44 14.19; ( : Z = 0 11	$\begin{array}{cccc} 3 & 7 \\ 7 & 15 \\ 0 & 8 \\ 8 & 10 \\ 0 & 20.91 \\ 9 & 10 \\ Chi^2 = 9.5 \\ 14 (P = 0) \\ 3 & 7 \\ 15 \\ 8 & 10 \\ \end{array}$	64 97 47 53 61 97 <b>419</b> 90, df .89) 64 97 53	15 7 22 8 31 16 = 5 (P =	12 27 11 14 14.74 8.8 = 0.08); 12 27 14	$ \begin{array}{r} 68\\100\\46\\54\\59\\96\\423\\1^2=50\\68\\100\\54\end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 13.8% 55.0%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2018 Singh et al.2017 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISGPF Bai et al. 2016 Berger et al. 2009 El Nakeeb et al. 2018	11 20 44 14.1 2 = 4.19; ( 2 = 0.1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	64 97 47 53 61 97 <b>419</b> 90, df 89) 64 97 53	15 7 22 8 31 16 = 5 (P = 15 7 8 31	12 27 11 14 14.74 8.8 = 0.08); 12 27 14	$ \begin{array}{r} 68\\100\\46\\54\\99\\423\\1^2=50\\68\\100\\54\\59\end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 55.0% %	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2017 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISCPF Bai et al. 2016 Berger et al. 2009 El Nakeeb et al. 2018 Senda et al.2018	1 20 44 14.5 = 4.19; ( : Z = 0.: 11	$\begin{array}{cccc} 3 & 7 \\ 7 & 15 \\ 0 & 8 \\ 3 & 10 \\ 0 & 20.91 \\ 9 & 10 \\ 0 & 20.91 \\ 9 & 10 \\ 0 & 20.91 \\ 3 & 7 \\ 7 & 15 \\ 8 & 10 \\ 0 & 20.91 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 20.91 \\ 0 & 10 \\ 0 & 1$	64 97 47 53 61 97 <b>419</b> 90, df 89) 64 97 53 61 97	15 7 22 8 31 16 = 5 (P = 15 7 8 31	12 27 11 14 14.74 8.8 = 0.08); 12 27 14 14.74 8 8	$ \begin{array}{r} 68\\100\\46\\54\\99\\423\\1^2=50\\1^2=50\\68\\100\\54\\59\\96\end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 13.8% 55.0% %	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23] -2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] 9.10 [-3.76, 1.56]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2017 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISGPF Bai et al. 2016 Berger et al. 2009 El Nakeeb et al. 2015 Senda et al.2018 Singh et al.2017 Subtotal (95% Cl)	1 2 4 14.1 = 4.19; ( : Z = 0.: 1 1 4 4 14.5	$\begin{array}{c} 30 \\ 7 \\ 7 \\ 15 \\ 0 \\ 8 \\ 10 \\ 0 \\ 20.91 \\ 9 \\ 10 \\ 10 \\ 20.91 \\ 9 \\ 10 \\ 10 \\ 20.91 \\ 9 \\ 10 \\ 10 \\ 20.91 \\ 9 \\ 10 \end{array}$	64 97 47 53 61 97 <b>419</b> 90, df 89) 64 97 53 61 97 <b>372</b>	15 7 22 8 31 16 = 5 (P = 15 7 8 31 16	12 27 11 14 14.74 8.8 = 0.08); 12 27 14 14.74 8.8	$ \begin{array}{r} 68\\100\\46\\54\\99\\423\\1^2=50\\68\\100\\54\\59\\96\\377\end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 55.0% % 11.7% 5.8% 8.4% 5.3% 13.8% 45.0%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23] -2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] 9.00 [2.54, 15.46] 0.37 [-2.54, 3.28]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2017 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISGPF Bai et al. 2016 Berger et al. 2009 El Nakeeb et al. 2015 Senda et al.2017 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for overall effect	11 22 44 14.5 2 = 4.19; ( 2 = 0.1 2 = 0.1 11 14.5 2 = 5.94; ( 2 = 0.2 2 = 0.2	$\begin{array}{c} 3 \\ 7 \\ 7 \\ 15 \\ 0 \\ 8 \\ 10 \\ 0 \\ 20.91 \\ 9 \\ 10 \\ 10 \\ 20.91 \\ 9 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 20.91 \\ 10 \\ 10 \\ 20.91 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ $	64 97 47 53 61 97 <b>419</b> 90, df 889) 64 97 53 61 97 372 372 34, df 880)	15 7 22 8 31 16 = 5 (P = 15 7 8 31 16 = 4 (P =	12 27 11 14 14.74 8.8 = 0.08); 12 27 14 14.74 8.8 = 0.05);	$ \begin{array}{r} 68\\100\\46\\54\\996\\423\\l^2=50\\l^2=50\\68\\100\\54\\89\\96\\377\\l^2=57\end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 55.0% % 11.7% 5.8% 8.4% 5.3% 13.8% 45.0%	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -0.17 [-2.56, 2.23] -2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] 0.37 [-2.54, 3.28]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISGPF Bai et al. 2016 Berger et al. 2009 El Nakeeb et al. 2015 Senda et al.2018 Singh et al.2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect Total (95% CI)	11 22 44 14.5 = 4.19; ( : Z = 0.1 11 44 14.5 = 5.94; ( : Z = 0.7	$\begin{array}{c} 30 \\ \hline 1 \\ 1 \\$	644 97 47 53 61 97 <b>419</b> 900, df 889) 644 97 53 61 97 <b>372</b> 84, df 880) <b>791</b>	15 7 22 8 31 16 = 5 (P = 15 7 8 31 16 = 4 (P =	12 27 11 14 14.74 8.8 = 0.08); 12 27 14 14.74 8.8 = 0.05);	$ \begin{array}{r} 68\\100\\46\\59\\96\\423\\1^2=50\\68\\100\\54\\99\\6\\377\\1^2=57\\800\end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 13.8% 55.0% % 11.7% 5.8% 8.4% 5.3% 45.0% %	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] -0.17 [-2.56, 2.23] -2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] 0.37 [-2.54, 3.28] -0.01 [-1.74, 1.72]		
1.7.1 ALL Bai et al. 2016 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Senda et al.2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect 1.7.2 ISGPF Bai et al. 2016 Berger et al. 2009 El Nakeeb et al. 2015 Senda et al.2018 Singh et al.2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect	1: 22 4 14.1 2 2 2 4 14.1 2 2 2 4 14.1 2 2 2 4 14.1 2 2 4 14.1 3 4 14.1 5 .94; ( 2 2 4 1 4 .1 5 .2 2 1 2 4 .1 9; ( 2 2 5 .2 1 .2 1 .2 1 .2 1 .2 1 .2 1 .2	$\begin{array}{c} 30 \\ \hline & 30 \\ $	644 97 47 53 61 97 <b>419</b> 900, df 889) 64 97 <b>53</b> 61 97 <b>372</b> 849, df 880) <b>791</b> 2.29, df 999) 0.00	$\frac{15}{7}$ $\frac{15}{7}$ $\frac{22}{22}$ $\frac{8}{15}$ $\frac{16}{7}$ $\frac{15}{7}$ $\frac{7}{8}$ $\frac{311}{16}$ $\frac{1}{6}$ $\frac{1}{6}$ $\frac{1}{7}$ $\frac{1}$	12 $27$ $11$ $14$ $14.74$ $8.8$ $= 0.08);$ $12$ $27$ $14$ $14.74$ $8.8$ $= 0.05);$ $P = 0.04$ $P = 0.04$	$ \begin{array}{c} 68\\ 100\\ 46\\ 54\\ 59\\ 96\\ 423\\ l^2 = 50\\ 100\\ 54\\ 59\\ 96\\ 377\\ l^2 = 57\\ 800\\ 4); l^2 = \\ 0, l^2 = 0 \end{array} $	11.7% 5.8% 10.0% 8.4% 5.3% 13.8% 55.0% % 11.7% 5.8% 8.4% 5.3% 13.8% 45.0% %	-2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] -2.00 [-5.92, 1.92] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -0.17 [-2.56, 2.23] -2.00 [-5.33, 1.33] 0.00 [-6.08, 6.08] 0.00 [-4.60, 4.60] 9.00 [2.54, 15.46] -1.10 [-3.76, 1.56] 0.37 [-2.54, 3.28] -0.01 [-1.74, 1.72]	-100 -50 0 50 Favours [experimental] Favours [control]	100

Figure 4. Forest plot of the meta-analysis comparing duct-to-mucosa PJ and invagination PJ with respect to the (A) operation time, (B) LOS, (C) morbidity, and (D) mortality. LOS = length of stay, PJ = pancreaticojejunostomy.

In previous studies, a major source of heterogeneity was the difference in the definition of pancreatic fistula. Before 2005, the definition of POPF was variable among individual studies. The ISGPF organized experts from well-known European, Japanese, Australian, North American, and South American centers in 2005 to establish the definition and classification system of pancreatic fistula.<sup>[43]</sup> However, this only included 5 RCTs that applied the definition of POPF established by the ISGPF. In the ISGPF system, Grade B/C POPF is defined as clinically relevant POPF and requires more positive clinical intervention. In the ISGPF criteria, Grade A POPF has no impact on the clinical process. The meta-analysis of 5 RCTs showed no significant difference between duct-to-mucosa and invagination PJ in terms of CR-POPF. However, previous studies have provided conflict-

ing results for this outcome. A meta-analysis involving 5 RCTs showed that invagination PJ appears to reduce CR-POPF rates.<sup>[42]</sup> However, the original study included in this study did not adopt a unified definition of POPF. Similar to our study, the study conducted by Kilambi and Singh<sup>[40]</sup> showed that duct-to-mucosa PJ does not appear to be better than invagination PJ. Our study's strength lies in incorporating the latest and most comprehensive RCTs. The study reported by Han et al<sup>[44]</sup> was excluded because it was published in Chinese and did not provide enough data. A recent trial published by Bai et al<sup>[15]</sup> demonstrated that duct-to-mucosa PJ seems to be better than invagination PJ. One of the factors that affects the development of POPF is the pancreatic texture. An RCT of patients with a soft pancreas conducted by Senda et al<sup>[24]</sup> showed that invagination PJ was

	Experime	ntal	Contr	ol		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.8.1 ALL							
Bai et al. 2016	30	64	38	68	8.0%	0.84 [0.60, 1.17]	
Bassi et al. 2003	39	72	38	72	8.3%	1.03 [0.76, 1.39]	
Berger et al. 2009	53	97	49	100	10.5%	1.12 [0.85, 1.46]	-
Chou et al.1996	13	47	21	46	4.6%	0.61 [0.35, 1.06]	
El Nakeeb et al. 2015	21	53	15	54	3.2%	1.43 [0.83, 2.46]	
Langrenr et al. 2005	40	56	38	57	8.2%	1.07 [0.84, 1.37]	
Senda et al.2018	43	07	28	59	0.2%	1.49 [1.09, 2.03]	
Subtotal (95% CI)	54	547	52	552	60.6%	1.06 [0.95, 1.19]	•
Total events	293		279				
Heterogeneity: $Chi^2 = 1$	11.54, df =	7 (P =	0.12); I <sup>2</sup>	= 39%			
Test for overall effect:	Z = 1.01 (P)	= 0.31	.)				
1.8.2 ISGPF							
Bai et al. 2016	30	64	38	68	8.0%	0.84 [0.60, 1.17]	-
Berger et al. 2009	53	97	49	100	10.5%	1.12 [0.85, 1.46]	+
El Nakeeb et al. 2015	21	53	15	54	3.2%	1.43 [0.83, 2.46]	
Senda et al.2018	43	61	28	59	6.2%	1.49 [1.09, 2.03]	
Singh et al.2017	54	97	52	96	11.4%	1.03 [0.80, 1.33]	+
Subtotal (95% CI)		372		377	39.4%	1.12 [0.97, 1.29]	*
Total events	201		182				
Heterogeneity: $Chi^2 = 3$	7.15, df = 4	$(\mathbf{P}=0)$	$(.13); I^2 =$	= 44%			
Test for overall effect:	Z = 1.56 (P)	= 0.12	2)				
Total (95% CI)		919		929	100.0%	1.08 [0.99, 1.18]	•
Total events	494		461				
Heterogeneity: $Chi^2 = 1$	18.89, df =	12 (P =	= 0.09); 1	$^{2} = 369$	%		
Test for overall effect:	Z = 1.77 (P)	= 0.08	3)				Eavours [experimental] Eavours [control]
Test for subgroup diffe	erences: Chi	$^{2} = 0.3$	4, df = 1	L(P = 0)	$(.56), 1^2 =$	0%	Turous texperimental Turous teorniol
C							
	Evasima	mtal	Conte	-1		Dick Datio	Pick Patio
Study or Subgroup	Experime Events	ntal Total	Contr Events	ol Total	Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup	Experime Events	ntal Total	Contr Events	ol Total	Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.9.1 ALL Bai et al. 2016	Experime Events	ntal Total 64	Contr Events	ol Total 68	Weight 5.5%	Risk Ratio M-H, Fixed, 95% Cl 0.35 [0.01, 8.53]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.9.1 ALL Bai et al. 2016 Bassi et al. 2003	Experime Events 0 1	ntal Total 64 72	Contr Events	ol Total 68 72	Weight 5.5% 1.9%	Risk Ratio M-H, Fixed, 95% Cl 0.35 [0.01, 8.53] 3.00 [0.12, 72.44]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.9.1 ALL Bai et al. 2016 Bassi et al. 2003 Berger et al. 2009	Experime Events 0 1 2	ntal Total 64 72 97	Contr Events	ol Total 68 72 100	Weight 5.5% 1.9% 1.9%	Risk Ratio M-H, Fixed, 95% Cl 0.35 [0.01, 8.53] 3.00 [0.12, 72.44] 5.15 [0.25, 105.98]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.9.1 ALL Bai et al. 2016 Bassi et al. 2003 Berger et al. 2009 Chou et al.1996	Experime Events 0 1 2 3	ntal Total 64 72 97 47	Contr Events 1 0 0 4	ol Total 68 72 100 46	Weight 5.5% 1.9% 1.9% 15.3%	Risk Ratio M-H, Fixed, 95% Cl 0.35 [0.01, 8.53] 3.00 [0.12, 72.44] 5.15 [0.25, 105.98] 0.73 [0.17, 3.10]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.9.1 ALL Bai et al. 2016 Bassi et al. 2003 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015	Experime Events 0 1 2 3 3 3	ntal Total 64 72 97 47 53	Contr Events	ol Total 68 72 100 46 54	Weight 5.5% 1.9% 1.9% 15.3% 15.0%	Risk Ratio M-H, Fixed, 95% Cl 0.35 [0.01, 8.53] 3.00 [0.12, 72.44] 5.15 [0.25, 105.98] 0.73 [0.17, 3.10] 0.76 [0.18, 3.25]	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.9.1 ALL Bai et al. 2016 Bassi et al. 2003 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Langrehr et al. 2005	Experime Events 0 1 2 3 3 3 0	ntal Total 64 72 97 47 53 56	Contr Events	ol Total 68 72 100 46 54 57	Weight 5.5% 1.9% 1.9% 15.3% 15.0%	Risk Ratio M-H, Fixed, 95% Cl 0.35 [0.01, 8.53] 3.00 [0.12, 72.44] 5.15 [0.25, 105.98] 0.73 [0.17, 3.10] 0.76 [0.18, 3.25] Not estimable	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.9.1 ALL Bai et al. 2016 Bassi et al. 2003 Berger et al. 2009 Chou et al.1996 El Nakeeb et al. 2015 Langrehr et al. 2005 Senda et al.2018	Experime Events 0 1 2 3 3 0 0 0	ntal Total 64 72 97 47 53 56 61	Contr Events 1 0 0 4 4 0 0 0	ol Total 68 72 100 46 54 57 59	Weight 5.5% 1.9% 1.9% 15.3% 15.0%	Risk Ratio M-H, Fixed, 95% Cl 0.35 [0.01, 8.53] 3.00 [0.12, 72.44] 5.15 [0.25, 105.98] 0.73 [0.17, 3.10] 0.76 [0.18, 3.25] Not estimable Not estimable	Risk Ratio M-H, Fixed, 95% Cl
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Figure 4. (Continued).

associated with lower rates of POPF and CR-POPF. Retrospective studies have shown that invagination PJ is more suitable for patients with soft pancreatic tissue and a smaller pancreatic duct diameter.<sup>[45,46]</sup> According to a position statement by the ISGPF, no specific technique can reduce the incidence of POPF and CR- POPF.<sup>[47]</sup> Future studies on this topic are therefore recommended.

DGE, which is usually not life-threatening, can increase patient discomfort, LOS, and medical costs. As with POPF, the definition of DGE varies among studies. POPF can increase the incidence of DGE. The DGE rates in the studies of the present meta-analysis ranged from 1.7% to 26.4%, and the rates between the 2 groups were similar. PPH is one consequence of CR-POPF; however, the definition of PPH varies among previous studies. The  $I^2$  test of the RCTs in the present analysis showed no heterogeneity ( $I^2=0$ ) among all studies and among studies using the ISGPF definition. Severe complications including severe POPF, bleeding, and abscess formation may require reoperation. The incidence of reoperation is an indicator for evaluating the safety of the PJ method. No significant difference in the reoperation rate was found in our meta-analysis. The overall rates of morbidity and mortality also vary among different studies. Similar to previous RCTs and meta-analyses,<sup>[48,49]</sup> the morbidity and mortality rates were not significantly differences between the 2 groups.

The indications for PD in the included trials were heterogeneous. The most common indication was malignant disease. Few studies to date have focused on the long-term effects of tumors and the differences in residual pancreatic function between the 2 anastomotic methods. Studies have shown that catheter-tomucosal anastomosis may cause catheter obstruction, leading to insufficient pancreatic function.

This meta-analysis had 2 main limitations. First, the details of the duct-to-mucosa and invagination techniques were variable among previous studies. Second, the usefulness of external stents and somatostatin and the patients' clinical characteristics showed heterogeneity. Give these limitations, further RCTs on this topic are required.

#### 5. Conclusion

Our study showed that duct-to-mucosa PJ is comparable with invagination PJ in terms of POPF, CR-POPF, and other main outcomes. Considering the above-mentioned limitations, highquality RCTs are necessary in the future.

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#### Author contributions

Conception and design of the study: Yunxiao Lyu. Studies selection: Ting Li and Yunxiao Lyu. Data extraction: Yunxiao Cheng and Bin Wang. Statistical analyses: Yunxiao Lyu and Sicong Zhao. Wrote the paper: Ting Li. The paper was revised and approved by Yunxiao Lyu.

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