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Pancreaticojejunostomy Versus Pancreaticogastrostomy After Pancreaticoduodenectomy: An Up-to-date Meta-analysis of RCTs Applying the ISGPS (2016) Criteria

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Abstract: The goal of our study was to compare the impact of pancreaticogastrostomy (PG) versus pancreaticojejunostomy (PJ) on the incidence of complications after pancreaticoduodenectomy. A systematic search was performed using RevMan 5.3 software. A meta-analysis showed that PG was not superior to PJ in terms of postoperative pancreatic fistula (POPF). In multicenter randomized controlled trials, the incidence of POPF was lower in patients undergoing PG than in those undergoing PJ. However, PG was associated with an increased risk of postoperative intraluminal hemorrhage, but no significant difference was observed between 2-layer PG and PJ. No significant differences were found in the rate of overall delayed gastric emptying, biliary fistula, reoperation, mortality, and morbidity. PG and PJ have similar incidences of POPF, but PG could be slightly superior to PJ in multicenter trials. However, this analysis verifies that PG has a higher rate of postpancreatectomy hemorrhage. Of note, a 2-layer anastomosis could reduce the occurrence of postpancreatectomy hemorrhage.

Key Words: meta-analysis, pancreaticojejunostomy, pancreaticogastrostomy, postoperative pancreatic fistula, randomized control trial

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Pancreaticoduodenectomy (PD) is a complex, high-risk surgical procedure that is indicated primarily for neoplasms. PD may also be needed to manage pancreatic or duodenal trauma and chronic pancreatitis. Although operative mortality in patients undergoing PD has decreased to <5%, the incidence of postoperative morbidity remains high at 35% to 60%.[1–6] Postoperative pancreatic fistula (POPF), with a prevalence of 5% to 30% after PD,[7,8] still represented a clnically relevant problem, which could lead to many other postoperative complications and death.[9] Therefore, the prevention and treatment of POPF is of the utmost importance. Before 2005, POPF was defined in a variety of manners, with >20 different definitions for clinical research exchange and the comparison of difficulties.[10–12] The International Study Group on Pancreatic Fistula (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.[13] In 2016, the ISGPS changed Grade A POPF to "biochemical leak," which did not affect the clinical course.[14]

Pancreaticogastrostomy (PG) and pancreaticojejunostomy (PJ) are 2 widely undertaken surgical reconstruction techniques after PD. PG was first described by Waugh and Clagett[15] in 1946 and has gained popularity in recent years as a result of a possible reduction in the occurrence of POPF. The optimal method of pancreatic-enteric anastomosis is not clear. Some studies comparing PJ with PG showed no difference between these methods.[16–18] However, others showed that fewer postoperative fistulas develop after PG.[19–21] Therefore, we performed an up-to-date meta-analysis of randomized controlled trials (RCTs) to summarize the currently available evidence on PG versus PJ according to the newest 2016 ISGPS criteria.

METHODS

Search Strategy

Two authors independently conducted a comprehensive search of sources including PubMed, Embase, Web of Science, and Cochrane Library Central from August 1, 1990 to August 1, 2017. The English search terms included the following: "pancreaticogastrostomy," "pancreaticgastrostomies," "pancreatogastrostomy," "pancreatogastrostomies," "pancreaticogastricanastomosis," "pancreaticojejunostomy," "pancreaticojejunostomies," "pancreatojejunostomy," "pancreatojejunostomies," "pancreaticojejunal anastomosis," "pancreaticoduodenectomy," "pancreatoduodenectomy," and "Whipple." Only RCTs that reported POPF as the primary endpoint were included. The references of the articles identified after an initial search were also manually reviewed.

Inclusion and Exclusion Criteria

The following inclusion criteria were applied: (1) RCTs comparing the incidence of POPF after PG and PJ; (2) the definition of POPF conformed to the ISGPS (2016) guidelines; and (3) clinical studies using only human subjects.

We excluded studies that (1) were non-RCTs, retrospective studies, review articles, case reports, abstracts, editorials, and letters to the editor; (2) were published by the same author or agency repeatedly; and (3) had insufficient data on outcome measures of POPF.

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All the data used in the study can be obtained from the original articles.

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Outcomes of Interest

The primary outcome measure was POPF. Secondary endpoints included postoperative delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH), biliary fistula, and overall morbidity, mortality, and reoperation rates.

Data Extraction

To ensure the homogeneity of the extracted data, 2 authors independently extracted the original data in the literature onto a standardized form, including the first author, year of publication, type of study, country where the study was conducted, study design, and occurrence of POPF, PPH, DGE, and postoperative complications. If necessary, the author or authors of the study were contacted to obtain study data. Conflicts in data abstraction were resolved by a consensus and by referring to the original article.

Risk of Bias Assessment

The authors independently assessed the quality of the literature in accordance with the Cochrane Collaboration Handbook.[22] The scoring system included the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the result assessment, incomplete data in the results, selective reporting, and other sources of bias.

Study quality was also assessed with the Jadad scale for RCTs.[23] Two reviewers independently assessed the quality of the included studies, and discrepancies were resolved by discussion in plenum. One point was given for each of the 5 criteria the study fulfilled, resulting in a score ranging from 0 to 5. Studies receiving total scores between 0 and 2 were considered to be of poor methodological quality, whereas studies with a total score between 3 and 5 were considered to be of high methodological quality.

Statistical Analysis

All statistical analyses were performed using the Review Manager (RevMan) version 5.3 software (The Cochrane Collaboration, Oxford, UK). Risk ratios (RRs) with a 95% confidence interval (CI) were used to describe dichotomous outcomes. The publication bias was evaluated by a χ^2 test and funnel plots. The heterogeneity among studies was evaluated by a χ^2 test. A 2-tailed p-value of <0.05 was considered statistically significant. We also assessed the potential for publication bias through a visual inspection of funnel plot asymmetry. The meta-analysis was conducted according to the PRISMA statement.

RESULTS

Selected Studies and Characteristics of the Trials

On the basis of our search criteria, we identified 450 papers from the respective search engines, of which 360 duplicate articles were excluded. The remaining 150 studies were retrieved to examine their titles and abstracts, resulting in 9 articles that appeared to meet our selection criteria. Among these articles, 2 were excluded because they were retrospective studies. Finally, 7 RCTs with 1184 participants were included in the meta-analysis.[1,2,24–28] A detailed flowchart of the selection process is shown in Figure 1.

The 1184 patients were randomized to either the PG (n = 603) or PJ (n = 581) groups. Sample sizes ranged from 90 to 329, and the incidence rate of POPF varied from

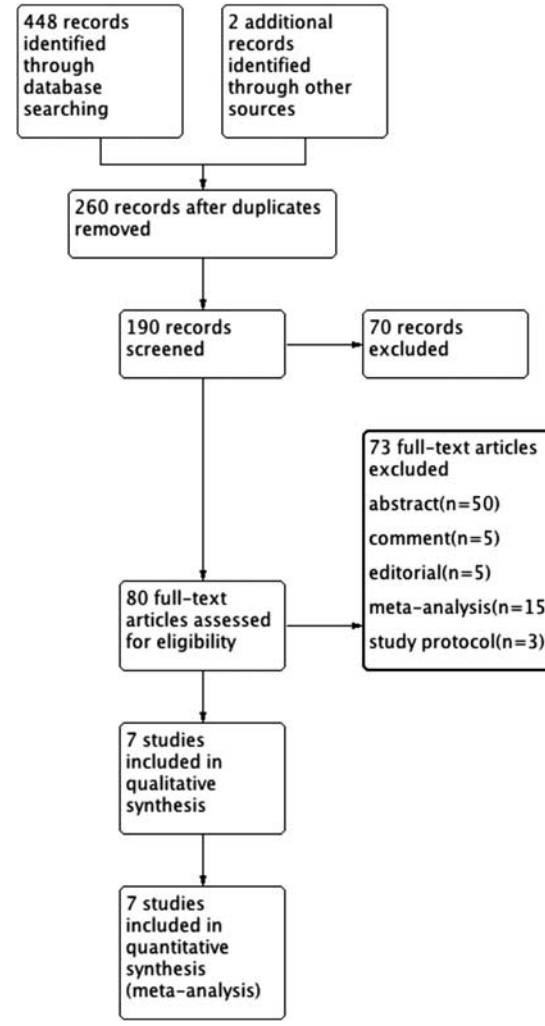

FIGURE 1. Flow diagram of the published articles evaluated for inclusion in this meta-analysis.

11.11% to 21.14%. Three RCTs were multicenter trials, and 4 were single-center trials. All RCTs were published between 2008 and 2016. The indications for a surgical procedure included pancreatic ductal adenocarcinoma, duodenal cancer, ampullary carcinoma, distal bile duct cancer, and others. The texture of the pancreas was described in 6 studies. Six studies reported the prophylactic use of octreotide, and the data were comparable between the 2 intervention groups. The main characteristics of the studies included in this meta-analysis are presented in Table 1. Figure 2 presents an overview of the methodological quality of the studies included in the review.

Primary Outcome

All 7 studies compared the 2 anastomotic techniques with regard to the POPF rate (RR, 0.61; 95% CI, 0.34-1.09; $P = 0.09$) (Fig. 3). The rate of POPF in the 3 multicenter studies was lower in the PG group (RR, 0.45; 95% CI, 0.21-0.98; $P = 0.04$) (Fig. 4A), but no significant difference was found in single-center studies (RR, 0.87; 95% CI, 0.35-2.17; $P = 0.76$) (Fig. 4B). The incidence of POPF after 2-layer PG was not significantly different from that of PJ (RR, 0.8; 95%

TABLE 1. Characteristics of Studies Included in the Systematic Review

	N (PG/PJ)	Setting	Peroids (Country)	Age [Mean (SD) or Median (IQR)] (y)		Sex (M/F)		Technique	Jadad Score
				PG	PJ	PG	PJ		
El Nakeeb et al[24]	45/45	Single center	2011-2013 (Egypt)	58	54	23/22	27/18	PG: 2-layers end-to-side, posterior gastrostomy PJ: 2-layer end-to-side	4
Fernández-Cruz et al[25]	53/55	Single center	2005-2007 (Spain)	63 ± 13	63 ± 14	29/24	38/17	PG: end-to-side duct-to-mucosa PJ: End-to-side duct mucosa	4
Figueras et al[1]	65/58	Multiple centers	2008-2012 (Spain)	67	65.5	44/21	37/21	PG: 2-layers invaginated posterior PJ: Duct-to-mucosa	4
Grendar et al[26]	48/50	Single center	2006-2012 (Canada)	63.6 ± 13.1	68.1 ± 10.7	20/28	29/21	PG: 2-layers end-to-side, posterior gastrostomy PJ: 2-layers end-to-side duct-to-mucosa	3
Keck et al[27]	171/149	Multiple centers	2011-2012 (Germany)	68	66	95/67	93/56	PG: Invagatination PJ: Duct-to-mucosa	5
Topal et al[2]	162/167	Multiple centers	2009-2013 (Belgium)	67	66.1	100/62	91/76	PG: End-to-side telescoped PJ: End-to-side telescoped	4
Wellner et al[28]	59/57	Single center	2006-2011 (Germany)	67	64	27/32	29/28	PG: Invagination PJ: Duct-to-mucosa	3

PG indicates pancreaticogastrostomy; PJ, pancreaticojejunostomy.

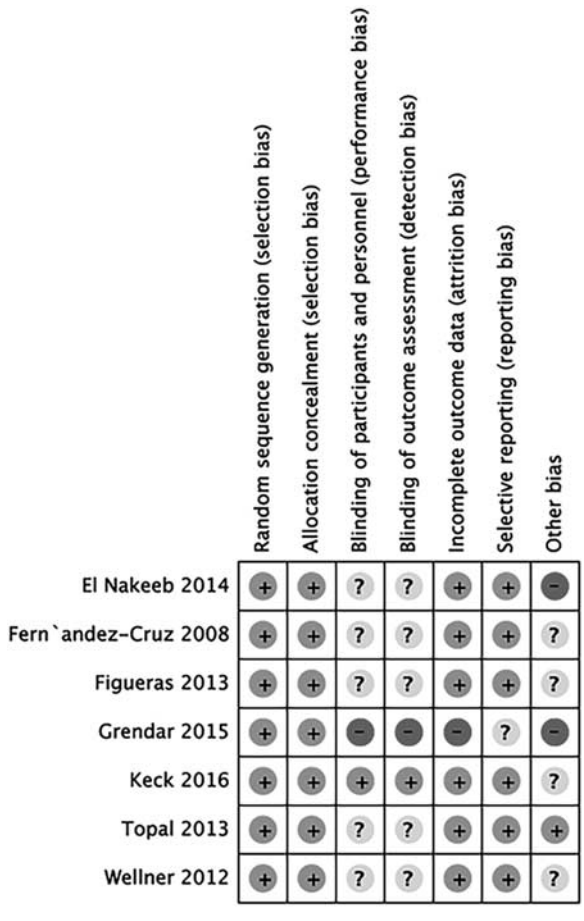

FIGURE 2. Consensus risk of bias assessment of the included studies.

CI, 0.22-3.18; $P = 0.80$) (Fig. 4C). No statistically significant differences were observed in the incidence rates of POPF in 4 of 7 RCTs, and the incidence after single-layer PG was not significantly different from that of PJ (RR, 0.53; 95% CI, 0.27-1.02; $P = 0.06$) (Fig. 4D). The meta-analysis of 7 studies also showed no significant difference in the rate of POPF in the PG group versus the duct-to-mucosa or telescope PJ group (RR, 0.63; 95% CI, 0.33-2.18; $P = 0.15$ vs. RR, 0.74; 95% CI, 0.15-3.79; $P = 0.72$) (Figs. 5E, F).

Secondary Outcomes

PPH

Six RCTs reported the overall PPH incidence (81/555 vs. 48/523) in the PG and PJ groups, respectively. A meta-analysis of the 6 studies, using a fixed-effect model, demonstrated that PJ was significantly superior to PG (RR, 1.65; 95% CI, 1.13-2.42, $P = 0.01$) (Fig. 5A). Three RCTs that reported the overall PPH incidence were multicenter trials. A meta-analysis of these 3 studies demonstrated that PJ was significantly superior to PG (RR, 1.80; 95% CI, 1.19-2.72; $P = 0.005$) (Fig. 5B). Four RCTs reported the overall PPH incidence in single centers. A meta-analysis of these 4 studies showed that PJ was not significantly superior to PG (RR, 1.09; 95% CI, 0.44-2.67; $P = 0.85$) (Fig. 5C). Two RCTs reported the overall PPH incidence after 2-layer PG. A meta-analysis of these 2 studies demonstrated that PJ was not significantly superior to PG (RR, 1.89; 95% CI, 0.79-4.48; $P = 0.15$) (Fig. 5D). Four RCTs reported the overall PPH incidence after single-layer PG. A meta-analysis of these 4 studies demonstrated that PJ was significantly superior to PG (RR, 1.69; 95% CI, 1.10-2.59; $P = 0.02$) (Fig. 5D).

DGE

Six RCTs reported the overall DGE incidence (13/555 vs. 116/531) in the PG and PJ groups. A meta-analysis of these 6 studies demonstrated that PG was not significantly superior to PJ (RR, 1.10; 95% CI, 0.82-1.48; $P = 0.50$) (Fig. 6A).

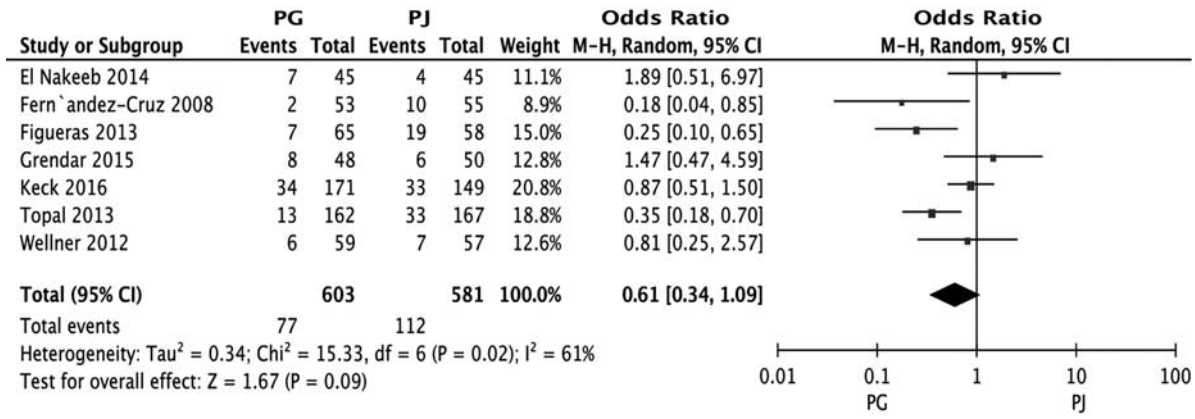

FIGURE 3. Forest plot of the meta-analysis comparing PG and PJ with regard to the incidence of POPF. CI indicates confidence interval; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; POPF, postoperative pancreatic fistula.

Bile Fistula

Three RCTs reported the bile fistula incidence (9/269 vs. 10/249) in the PG and PJ groups. A meta-analysis of 6 studies demonstrated that PG was not significantly superior to PJ (RR, 0.85; 95% CI, 0.34-2.11; $P = 0.73$) (Fig. 6B).

Mortality

Seven RCTs reported mortality rates (24/603 vs. 24/581) in the PG and PJ groups. A meta-analysis of these 7 studies demonstrated that PG was not significantly superior to PJ (RR, 0.84; 95% CI, 0.53-1.68; $P = 0.84$) (Fig. 6C).

Morbidity

Four RCTs reported morbidity rates (158/308 vs. 161/317) in the PG and PJ groups. A meta-analysis of 4 studies demonstrated that PG was not significantly superior to PJ (RR, 1.00, 95% CI, 0.57-1.72, $P = 1.00$) (Fig. 6D).

Reoperation

Five RCTs reported reoperation rates (46/490 vs. 52/473) in the PG and PJ groups. A meta-analysis of 5 studies demonstrated that PG was not significantly superior to PJ (RR, 0.81; 95% CI, 0.53-1.24, $P = 0.34$) (Fig. 6E).

DISSCUSSION

The results of this meta-analysis show that PG and PJ are comparable anastomotic techniques following PD. Previous studies have suggested that PG is superior to PJ. Three RCTs,[10,11,29] 2 from high-volume centers and 1 multicenter trial,[10,11] found no differences in terms of reconstruction techniques. Some differences are present in these studies, largely because of the lack of a uniform definition of POPF. Compared with previous meta-analyses on the same topic, our study included RCTs on the basis of the newest definition of POPF by the ISGPS, which increased its statistical strength. Of note, our analysis showed no significant difference in terms of POPF after PG compared with PJ. Most previous studies that have compared PG with PJ with regard to POPF were single-center trials. The strengths of single-center RCTs might be insufficient compared with multicenter RCTs. Subgroup analysis showed that the incidence of POPF in the PG group was lower than that of the PJ group in multicenter trials, but no significant difference was found in the single-center trials. Therefore, PG is slightly superior to PJ in terms of POPF occurrence. Some potential advantages of PG include that the presence of gastric acid can effectively inhibit the activation of pancreatic enzymes,[2] the tension between the stomach and the pancreatic stump is minimized, and the abundant stomach wall vascularization decreases the chance of anastomotic ischemia.[19] The occurrence of POPF after pancreatic surgery is related to the normal texture of the pancreas and the diameter of the pancreatic duct.[30–32] Some studies included a description of the pancreatic texture.[33,34] The texture of the pancreas and the diameter of the pancreatic ducts were different among the 7 included studies. These differences might have affected the outcome. Therefore, subgroup analysis of risk factors of different types of pancreatic fistula is necessary.

The surgical reconstruction techniques of PG include single-layer or double-layer PG with or without anterior gastrotomy. Few studies have examined the effect of different PG reconstruction techniques on POPF occurrence. This study demonstrated no difference in the incidence of POPF between 2-layer and single-layer techniques. Similar results were obtained in another study.[16] Two predominant methods of PJ reconstruction exist: duct-to-mucosa anastomosis and invagination of the pancreatic remnant. No conclusive evidence to favor 1 method over the other exists. The subgroup analysis of the duct-to-mucosa and telescope techniques showed no difference between PG and PJ. These studies may indicate that specific surgical approaches in PG and PJ have little impact on POPF occurrence. The choice is determined by surgeon preference and the familiarity with different surgical approaches. However, it remains debatable which is the better reconstruction method after PD. However, the details of specific surgical methods were varied in these studies, and this conclusion remains to be further studied.

Another complication after PD is PPH. In the previous RCTs, the incidence of PPH was significantly higher in the PG group than in the PJ group.[1,28,29] One potential reason is the abundant blood supply. A similar conclusion is also shown in the present study.[35] The different PG anastomotic techniques include the single-layer or double-layer technique. For this reason, we have provided a subgroup analysis. In the 2-layer subgroup, the incidence of PPH in the PG group was similar to that of the PJ group. However, the rate of PPH was higher in the single-layer PG subgroup. A possible explanation is that double-layer anastomosis reduces the incidence of gastrointestinal tract bleeding after

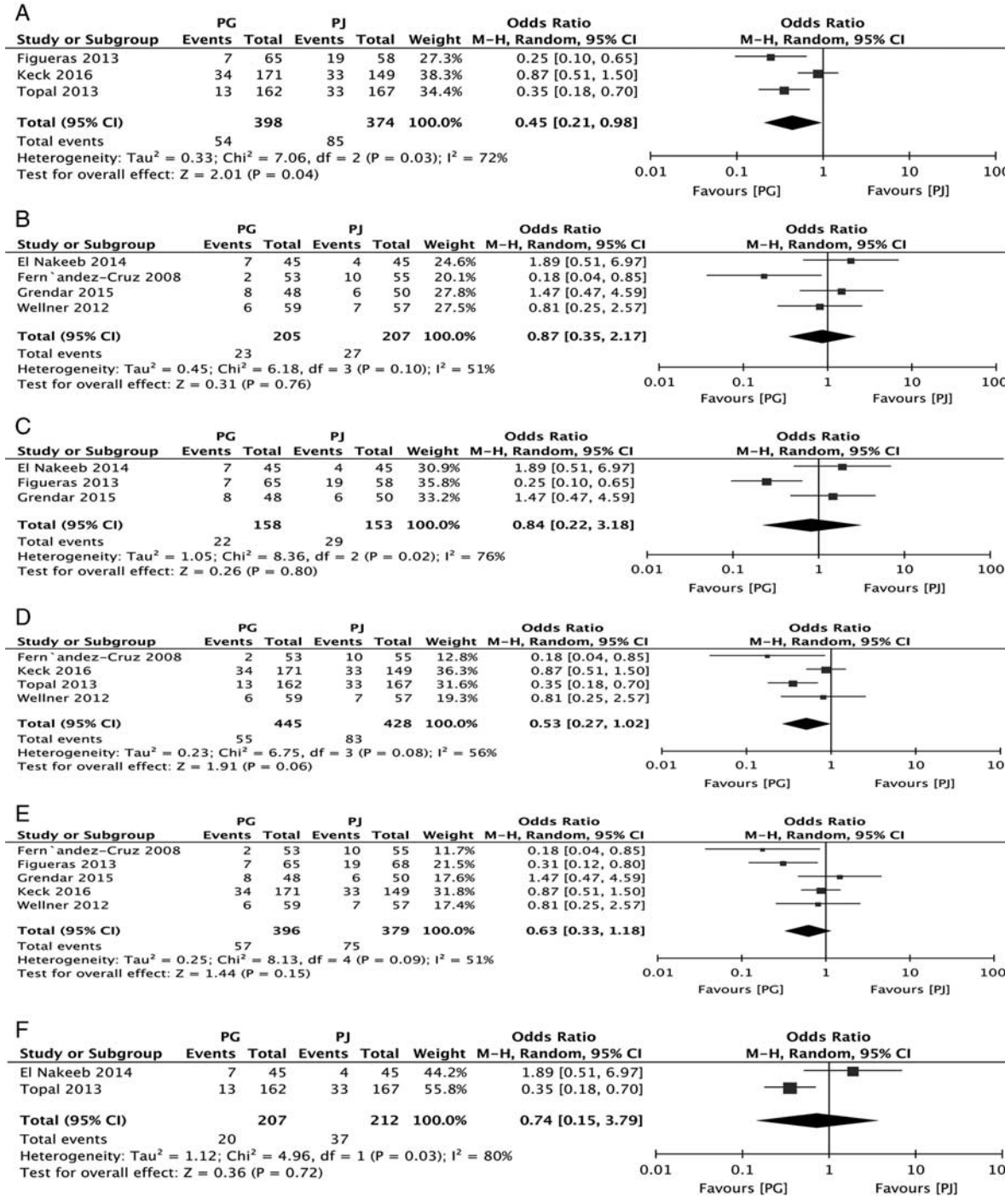

FIGURE 4. Forest plot of the subgroup meta-analysis of the incidence of POPF according to the type of center (A and B); based on the type of PG (C and D); based on the type of PJ (E and F). CI indicates confidence interval; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; POPF, postoperative pancreatic fistula.

PG. PPH includes gastrointestinal bleeding and intraperitoneal hemorrhage. Among the 7 included RCTs, some studies did not distinguish between gastrointestinal bleeding and intraperitoneal hemorrhage. Further study on bleeding due to different causes is needed.

No differences were observed in DGE after PD between the 2 anastomosis groups. High heterogeneity was found between studies because of the lack of a standard definition of DGE among the studies. As previously described, some factors such as old age, early enteral nutrition and resection techniques, including PD and pylorus preserving pancreatoduodenectomy (PPPD), are the major risk factors of DGE after PD. Therefore, more RCTs on this subject are needed. No differences were observed between groups in the incidence of other site-related

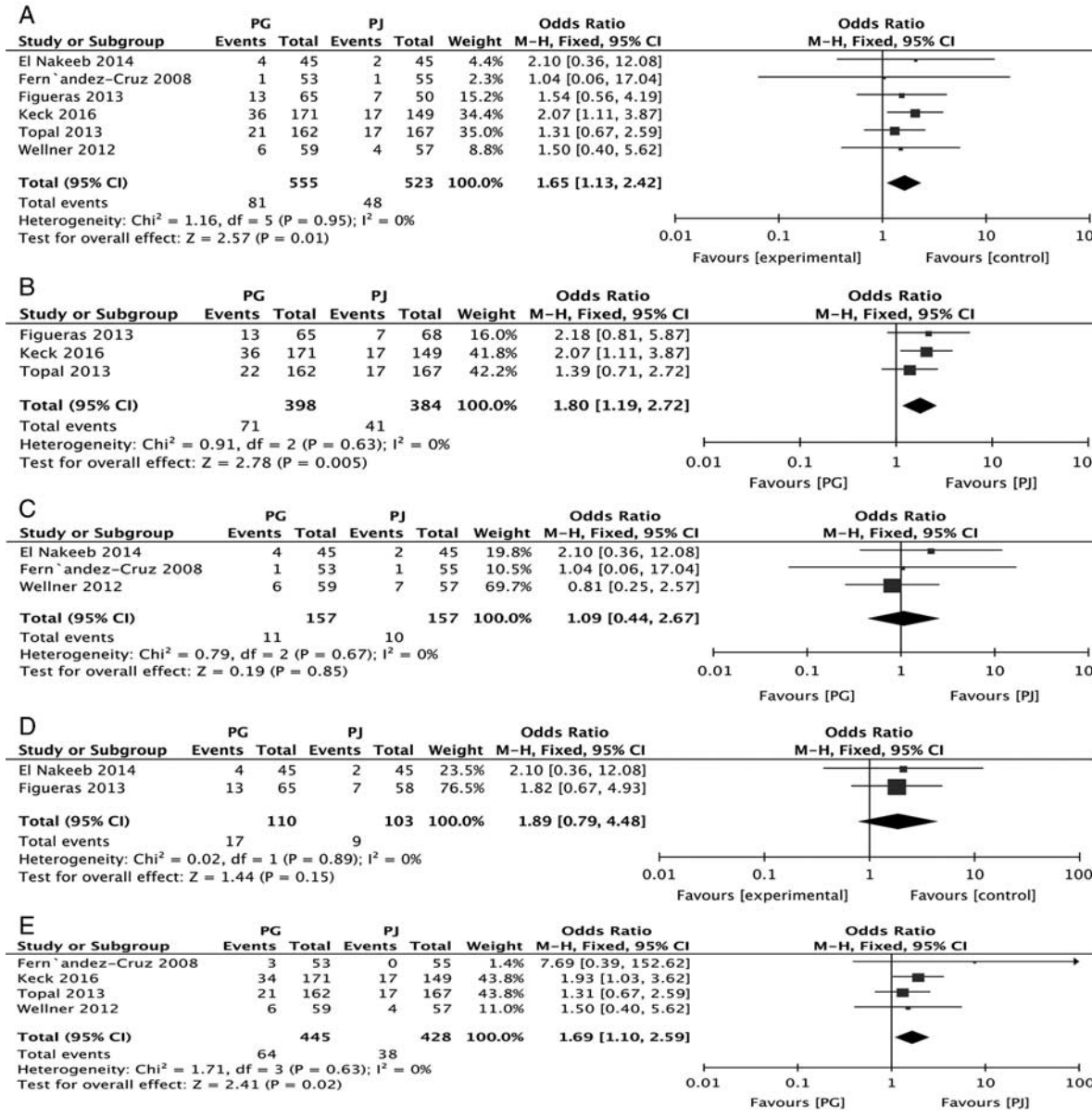

FIGURE 5. Forest plot of the subgroup meta-analysis of the incidence of PPH (A); according to type of center (B and C); according to the type of PG (D and E). CI indicates confidence interval; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; PPH, postpancreatectomy hemorrhage.

complications such as enteric or biliary fistula, mortality, morbidity, and reoperation, although these factors were only reported in a few studies.

Some limitations should be considered with regard to this review. First, the details of the surgical technique, such as the use of pancreatic stents and different types of sutures, are highly heterogeneous. In addition, because it was not possible to perform subgroup analyses according to pancreatic duct size, pancreatic texture or pancreatic pathology, it is unclear whether the potential advantages of PG are applicable to all subgroups of patients. Third, the use of prophylactic somatostatin or somatostatin analogs may also contribute to reducing the risk of POPF.

CONCLUSIONS

In summary, the findings of the present meta-analysis of randomized controlled studies demonstrate that PG and PJ exhibit similar incidences of POPF, but PG could be slightly superior to PJ. However, this study confirms that PG has a higher rate of PPH than PJ. Of note, 2-layer anastomosis could reduce the occurrence of PPH. Although this evidence was obtained from up-to-date randomized trials, PG cannot be considered superior to PJ in the incidence of DGE, bile fistula overall morbidity, reoperations, and mortality. Given the limitations of the current study, more large-scale, high-quality RCTs are required.

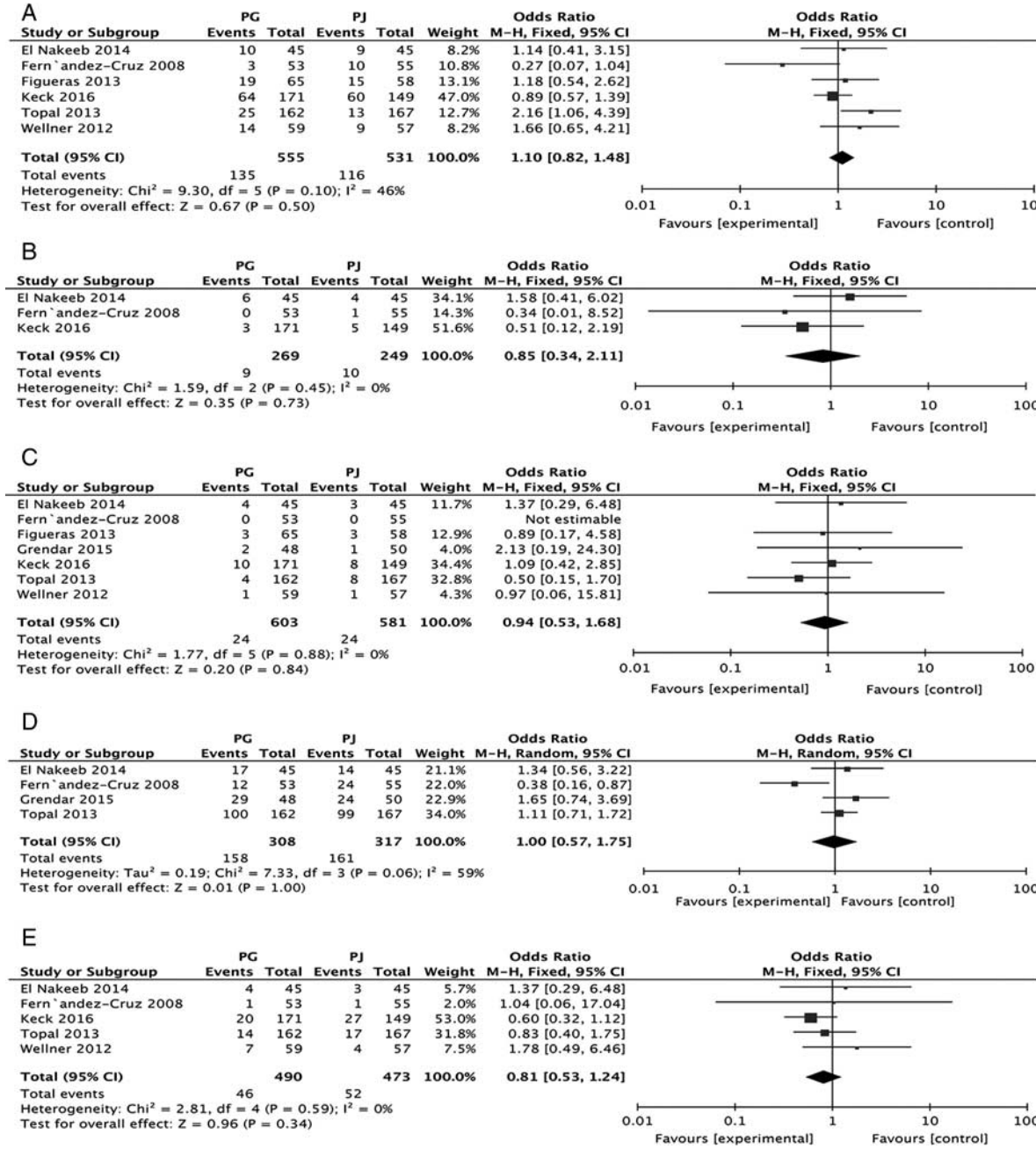

FIGURE 6. Forest plot of the subgroup meta-analysis of the incidence of DGE (A); bile fistula (B); mortality (C); morbidity (D) and reoperation (E). CI indicates confidence interval; DGE, delayed gastric emptying; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy.

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