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Effect of Antecolic versus Retrocolic Gastroenteric Reconstruction after Pancreaticoduodenectomy on Delayed Gastric Emptying: A Meta-Analysis of Six Randomized Controlled Trials

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Key Words
Pancreaticoduodenectomy · Gastroenteric reconstruction · Delayed gastric emptying · Meta-analysis

Abstract
Background: One of the most frequent complications of pancreaticoduodenectomy (PD) is delayed gastric emptying (DGE). The study aim was to evaluate the impact of the type of gastro/duodenojejunal reconstruction (antecolic vs. retrocolic) after PD on DGE incidence. ***Methods:*** A systematic review was made according to the PRISMA guidelines. Randomized controlled trials (RCTs) comparing antecolic vs. retrocolic reconstruction were included irrespective of the PD techniques. A meta-analysis was then performed. ***Results:*** Six RCTs were included for a total of 588 patients. The overall quality was good. General risk of bias was low. DGE was not statistically significantly different between the antecolic and retrocolic group (OR 0.6, 95% CI 0.31–1.16, p = 0.13). The other main surgery-related complications (pancreatic fistula, hemorrhage, intra-abdominal abscess, bile leak and wound infection) were not dependent on the reconstruction route (OR 0.84, 95% CI 0.41–1.70, p = 0.63). No statistically significant difference in terms of length of hospital stay was found between the 2 groups. There was also no difference of DGE incidence if only pylorus-preserving PD was considered and between the DGE grades A, B or C. ***Conclusion:*** This meta-analysis shows that antecolic reconstruction after PD is not superior to retrocolic reconstruction in terms of DGE.

Introduction

High postoperative morbidity remains a major concern after pancreatic surgery, whereby pancreaticoduodenectomies (PDs) are associated with particular complications such as fistula, bleeding or delayed gastric emptying (DGE) [1–3]. DGE after PD is one of the most frequently described specific complications [4, 5] with reported incidences between 20 and 40% [6–8]. Its occurrence often represents a troublesome postoperative complication for patients and surgeons [9–11]. DGE lengthens the hospital stay, increases costs and may even require enteral or parenteral feeding [12–14]. The precise pathophysiological mechanisms causing DGE are not yet well elucidated but a few hypotheses like vagal disruption, absence of motilin after duodenectomy or pylorospasm secondary to pyloric devascularization after pyloric-preserving PD have been suggested [5, 12, 13]. The prolonged gastroparesis subsequently delays postoperative oral food intake. For many decades, DGE was not uniformly de-

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fined until 2007, when an expert consensus of the International Study Group of Pancreatic Surgery (ISGPS) proposed a severity-graded definition including the need for nasogastric tube or its reinsertion, the presence of nausea/vomiting and the use of prokinetics [5]. Despite this consensual definition, DGE is still not systematically used by all authors in the literature, as shown in the present analysis.

Various studies have attempted to identify risk factors impacting on the incidence of DGE [15–23]. Thereby, the numerous types of surgical resection and reconstruction have been assessed. It has been suggested that the anatomical configuration of the gastroenteric anastomosis could be particularly important for both gastric motility and emptying [12, 24, 25]. Since the available evidence remains conflicting, there is an ongoing debate as to whether an antecolic or retrocolic (through the mesocolon) reconstruction should be favored. Some retrospective studies and randomized controlled trials (RCTs) have shown that the antecolic method is associated with fewer DGE [15, 17, 18, 21, 26], but other studies found no difference [16, 19, 20, 22, 23]. Three specific meta-analyses were performed: two concluding that the antecolic reconstruction was superior [25, 27] and one finding that there was no difference [28]. Our study differs from the 3 above-mentioned meta-analyses in a 3-fold manner: 2 meta-analyses included RCTs and non-RCTs [25, 27], the third one only included 4 RCTs [28] and 1 meta-analysis included 2 RCTs based on the same patient group [27].

The primary aim of the present study was to compare the antecolic with the retrocolic reconstruction after PD in terms of DGE incidence. Additionally, this analysis also assessed if the reconstruction route had any influence on other surgery-related complications.

Materials and Methods

Study Selection and Inclusion Criteria

A systematic review of the current literature was conducted following the PRISMA guidelines [29]. Studies were selected according to inclusion criteria defined a priori. The latter were the following: studies comparing antecolic vs. retrocolic route for PD, RCT design and English language [30, 31]. All types of indication for PD were considered (cancer, benign tumors and benign diseases) as well as any type of PD, that is, classic PD (cPD), pylorus-preserving PD (ppPD) and subtotal stomach-preserving PD (sspPD).

Search Methods

Studies were searched electronically on Medline/PubMed, Ovid, Isis, the Cochrane Library, Google Scholar, Web of Knowledge and Embase. Interval of research spread from January 1, 1990 to March 31, 2015. Only full-text articles published in English were considered.

MeSH terms used were 'pancreaticoduodenectomy' AND 'anastomosis' AND 'gastroparesis'. Free-text search was made using 'Whipple operation' OR 'pancreatic resection' AND 'antecolic reconstruction' OR 'retrocolic reconstruction' AND 'delayed gastric emptying' OR 'complications'. The same terms were used for all databases. A cross-reference check of all bibliographies of eligible articles was also performed.

Outcomes of Interest

The primary outcome was the impact of the reconstruction route on the incidence of DGE. ISGPS recommendations were preferentially used to define DGE [5], but other reported definitions were accepted as they resembled ISPGS definitions.

A subgroup analysis was performed regarding the type of PD. It was only possible to perform a subgroup meta-analysis for the ppPD type because there were insufficient data for the 2 other types (2 studies with cPD and 1 with sspPD). Another subgroup analysis was done regarding the grades of DGE defined by the ISGPS (grades A, B and C) [5].

The secondary outcomes were the effects of the reconstruction route on other surgery-specific complications (pancreatic fistula, hemorrhage, intra-abdominal abscess, bile leak and wound infection), length of hospital stay and mortality. Pancreatic fistula and hemorrhage were defined according to the ISGPS consensus [32, 33]. Intra-abdominal abscess was defined as organ or space surgical site infection as described by the Centers for Disease Control and Prevention (CDC) [34]. Bile leak was defined as the presence of bile in the drains. Wound infection was defined as a superficial or deep incisional surgical site infection as described by the CDC [34]. Length of hospital stay started on the day of operation and lasted until the date of hospital discharge. Mortality was defined as postoperative death (Dindo–Clavien grade V) 30 days after the operation or during the hospitalization for the index operation [35].

Data Collection and Analysis

Two independent reviewers (G.-R.J. and I.L.) were involved in the search for eligible studies and in the inclusion process. They worked independently, and then compared and combined their results. Study characteristics were extracted from every report. In case of disagreement, a consensus was made under the supervision of the senior author (P.A.). In case of incomplete or missing data, the corresponding authors were contacted for clarification. Odds ratios (ORs) were used to measure the effect on postoperative complications and mean difference for the length of hospital stay. Incidence of DGE and other complications were expressed in percent, and length of hospital stay was presented as mean and standard deviation.

Quality Assessment and Risk of Bias

The quality of the studies was assessed according to the Oxford quality scoring system, described by Jadad et al. [36].

Risks of bias were assessed according to the Cochrane Collaboration recommendations [37]. They were defined by random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and investigators (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias).

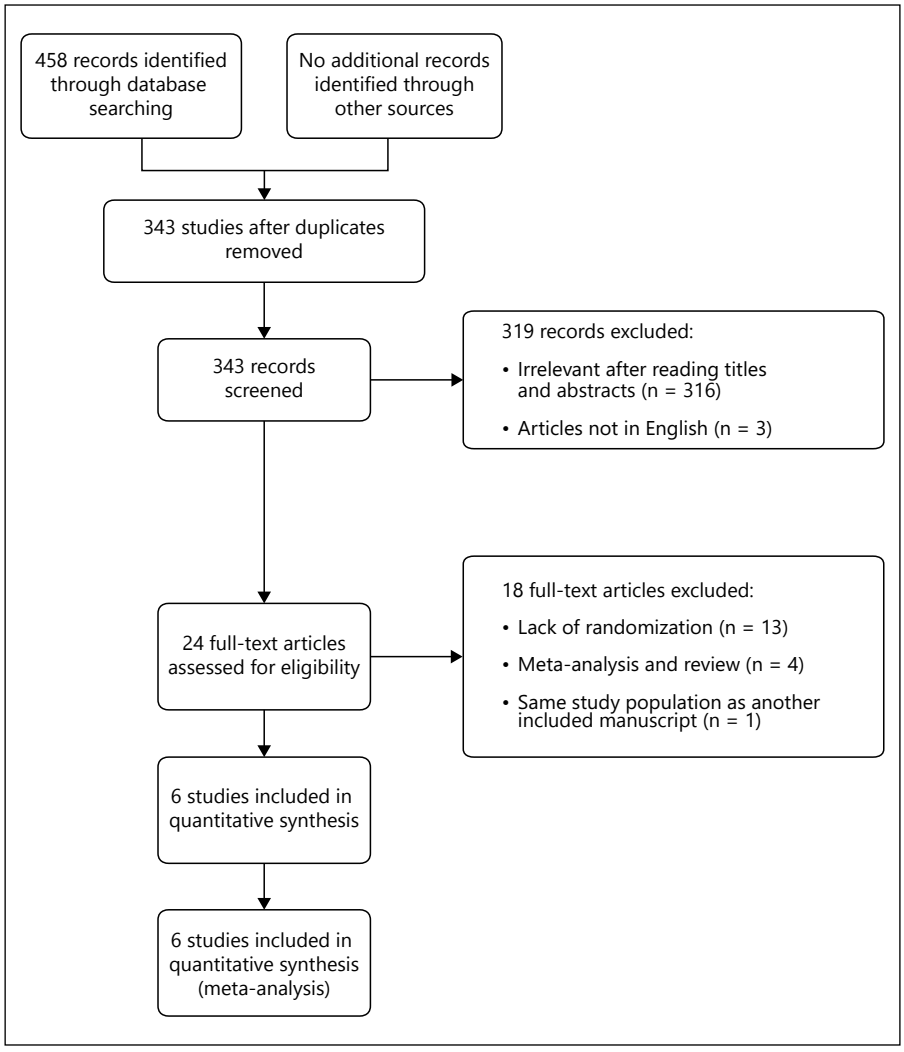

Fig. 1. PRISMA flow chart diagram.

Statistical Analysis

Heterogeneity was assessed in terms of clinical heterogeneity, methodological diversity and statistical heterogeneity. A chi-square test was used to test the presence of statistical heterogeneity. Quantification of the heterogeneity (inconsistency across the studies) was measured by the I^2 value (comprising the chi-square value and the degree of freedom), defining the percentage of variability due to heterogeneity rather than chance. In case of important heterogeneity ($I^2 > 40\%$), further exploration was made, and subgroup analysis was performed if appropriate.

Meta-analyses were performed according to the Cochrane Collaboration recommendations [37]. The Mantel–Haenszel method was used for dichotomous variables and inverse variance method for continuous variables. The random effect model was used to calculate the forest plots considering the between-study heterogeneity. An overall effect $Z \geq 1.96$ (related to a p value ≤ 0.05) was considered statistically significant. The meta-analysis format was based on Review Manager 5.3© for Mac OS X developed by The Nordic Cochrane Centre for the Cochrane Collaboration (2014). A statistician was asked advice for this meta-analysis.

Results

A flow chart summarizes the different steps of the systematic review according to the PRISMA guidelines (fig. 1). A total of 343 studies were primarily found after duplicate removal. After exclusion of irrelevant reports and selection of English articles, 24 full-text articles were considered for inclusion [12, 15–23, 25–28, 38–47].

Included Studies

Six RCTs were finally selected for inclusion in the meta-analysis (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000441480) [16, 18–22]. These RCTs included a total of 588 patients (296 in the antecolic group and 292 in the retrocolic group).

Eshuis et al. [16] published a series of 121 patients with antecolic reconstruction versus 125 patients with retrocolic reconstruction (cPD and ppPD) in 2014 (Jadad score: 5). Patients were recruited among 10 centers in the Netherlands with an annual caseload of ≥10 PDs. The included patients were older than 18 years and had an indication for PD (cancer or benign disease). The primary outcome was DGE incidence and secondary outcomes were morbidity, mortality and length of hospital stay.

Gangavatiker et al. [19] compared the antecolic (35 patients) versus the retrocolic (37 patients) reconstruction in a RCT published in 2011 (Jadad score: 3). The study was performed in a high-volume center in India. All patients <70 years who were selected for a PD were included, and cPD and ppPD were performed. The primary outcome was the incidence of DGE. Secondary outcomes were not precisely described. As the study started before the publication of the DGE definition by the ISGPS, the consensus definition was retrospectively applied.

Imamura et al. [22] conducted a RCT (Jadad score: 3) published in 2013 that compared 60 patients undergoing antecolic duodenojejunostomy with 60 patients undergoing retrocolic duodenojejunostomy. Only patients who underwent ppPD were included. The study was realized in a high-volume center in Japan. All the etiologies were included. The primary end point was the incidence of DGE.

Kurahara et al. [18] performed a RCT in 2011 comparing the antecolic route with the retrocolic route after sspPD among patients with different benign tumors and cancers (Jadad score 3). Twenty-two patients were randomized in the retrocolic group and 24 patients in the antecolic group. The primary outcome was the incidence of DGE. The study was performed in a Japanese University Hospital.

The study by Tamandl et al. [20] published in 2014 and performed in a single high-volume center in Austria compared 36 patients with antecolic reconstruction with 28 patients with retrocolic reconstruction after ppPD (Jadad score: 1). Eligible patients were adults between 18 and 90 years undergoing a PD for benign tumor or cancer. The primary end point was the incidence of DGE.

Tani et al. [21] published a RCT in 2006 comparing 20 patients with antecolic reconstruction with 20 patients with retrocolic reconstruction after ppPD (Jadad score 3). Included patients had periampullary and bile duct lesions with an indication to PD. The study was performed in a high-volume hospital in Japan. The primary end point was DGE incidence.

Excluded Studies

Eighteen studies did not meet the inclusion criteria and were excluded from the analysis (fig. 1). Among these 18 studies, 13 were not randomized [15, 17, 26, 38–47] and 4 consisted of review or meta-analysis [12, 25, 27, 28]. The RCT by Chijiiwa et al. [23] published in 2009 was excluded as it included the same patients as the study published later in 2014 by the same group [22].

Missing Data

Two studies had no subdivision of DGE described in their manuscript [20, 21]. As the data were not available from the authors, these studies were not included in the subgroup analysis [20, 21]. Figures were missing for DGE after ppPD in 3 studies including cPD and ppPD [16, 18, 19]. Information from one study [16] was collected via the authors; the 2 other articles were not included in the ppPD subgroup meta-analysis [18, 19]. Three studies described the length of hospital stay as median and not as mean [16, 20, 22]. For 2 studies, the mean was obtained from the authors [16, 22]. The other study [20] was not included in the analysis, as the range was not available to estimate the mean from the median and the sample size [48].

Quality Assessment and Risk of Bias

Risks of bias in individual studies are summarized in the online supplementary table 1. Global risk of bias was found to be low. In 5 out of 6 RCTs, blinding of participants and blinding of outcome assessment were not specified (unclear risk of performance and detection bias). Figure 2 shows the risk of bias graph. No other source of bias was found.

The Jadad scores are summarized in table 1.

Meta-Analysis Results

Results and forest plots of the primary and secondary outcomes are presented in figure 3. The incidence of DGE was similar between the 2 groups (6 RCTs, 588 patients, OR 0.60, 95% CI 0.31–1.16, Z = 1.52, p = 0.13). Heterogeneity of the included studies was moderate (I^2 = 56%).

No statistically significant differences were found between the antecolic and retrocolic reconstruction concerning the incidence of pancreatic fistula (OR 0.98, 95% CI 0.65–1.47, Z = 0.12, p = 0.90, I^2 = 0%), intra-abdominal abscess (OR 0.94, 95% CI 0.53–1.65, Z = 0.22, p = 0.83, I^2 = 7%), bile leak (OR 0.87, 95% CI 0.36–2.09, Z = 0.30, p = 0.76, I^2 = 0%) and postoperative mor-

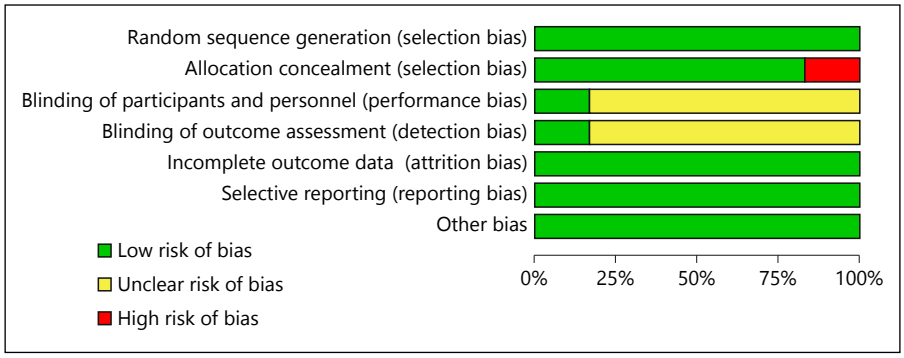

Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Table 1. Summary of all Jadad scores for every study

Study	Jadad score
Eshuis et al. [16], 2014	5
Gangavatiker et al. [19], 2011	3
Imamura et al. [22], 2014	3
Kurahara et al. [18], 2011	3
Tamandl et al. [20], 2014	1
Tani et al. [21], 2006	3

tality (OR 0.82, 95% CI 0.34–1.96, Z = 0.46, p = 0.65, I^2 = 0%). These items were reported in all 6 RCTs. Hemorrhage data were reported in 5 studies, and no hemorrhage case appeared in the remaining study (data obtained after contacting the author). The meta-analysis showed no statistically significant difference (OR 0.72, 95% CI 0.34–1.49, Z = 0.89, p = 0.37, I^2 = 0%). Global meta-analysis of overall surgery-related complications except DGE (pancreatic fistula, hemorrhage, abscess, bile leak and wound infection) showed no statistically significant difference (OR 0.84, 95% CI 0.41–1.70, Z = 0.49, p = 0.63, I^2 = 69%). Data on mean length of hospital stay were reported in 3 studies and 2 authors provided additional data to us. No statistically significant difference was found between the 2 groups (mean difference –0.96, 95% CI –4.66 to 2.75, Z = 0.51, p = 0.61, I^2 = 58%).

Subgroup Meta-Analysis (fig. 4)

Three and 4 studies provided adequate information regarding the incidence of DGE after antecolic vs. retrocolic reconstruction in case of ppPD, and the grades of DGE (A, B and C), respectively. For the DGE incidence after ppPD, one author provided further information. No statistically significant difference was found between the 2 types of reconstruction in case of ppPD (OR 0.57, 95% CI 0.23–1.43, Z = 1.19, p = 0.23, I^2 = 64%) and for the different grades of DGE (OR 1.00, 95% CI 0.70–1.42, Z = 0.00, p = 1.00, I^2 = 0%).

Discussion

This meta-analysis was performed to assess the different techniques of gastro/duodenoenteric reconstruction after pancreatic head resection. The results of this study demonstrated that an antecolic reconstruction is not associated with a significantly lower incidence of DGE compared to retrocolic reconstruction, irrespective of the type of resection (cPD, ppPD and sspPD). Incidences of pancreatic fistula, hemorrhage, intra-abdominal abscess, bile leak, wound infection, length of hospital stay and postoperative mortality were also not significantly different.

The results of previously published papers that have addressed the issue of the best type of reconstruction showed conflicting evidence. Moreover, unlike this present meta-analysis, all these reviews included only a part of the available published series, particularly the 3 largest RCTs by Imamura et al. [22], Tamandl et al. [20] and Eshuis et al. [16] recently published. Su et al. [25] performed a meta-analysis based on 2 RCTs and 3 non-RCTs, and their results were in favor of an antecolic reconstruction. Another meta-analysis published by Cao et al. [28] found that antecolic reconstruction after PD did not offer any advantage in terms of DGE compared to retrocolic reconstruction. This meta-analysis included 4 RCTs involving 189 patients. However, the 3 largest RCTs were not included as they were published later [16, 20, 22]. A recent meta-analysis by Bell et al. [27] showed that DGE after ppPD was less frequent after antecolic reconstruction when RCTs (5) and non-RCTs (3) were included but that there was no difference between antecolic and retrocolic reconstructions when only the 5 RCTs were included. Of

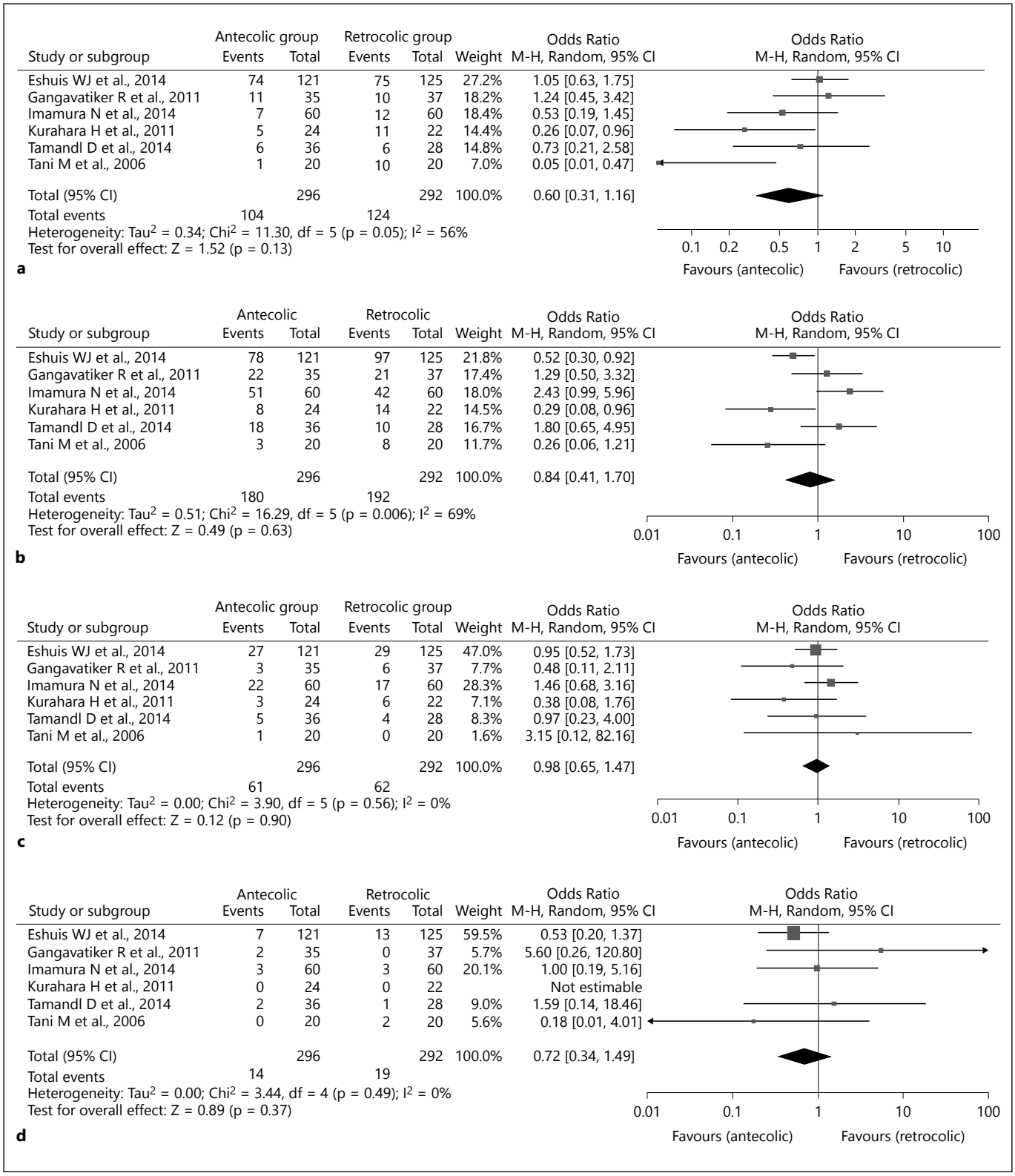

Fig. 3. Forest plots of primary and secondary outcomes. **a** Incidence of DGE; **b** main surgery-related complications except DGE (pancreatic fistula, hemorrhage, abscess, bile leak and wound infection); **c** pancreatic fistula; **d** hemorrhage.

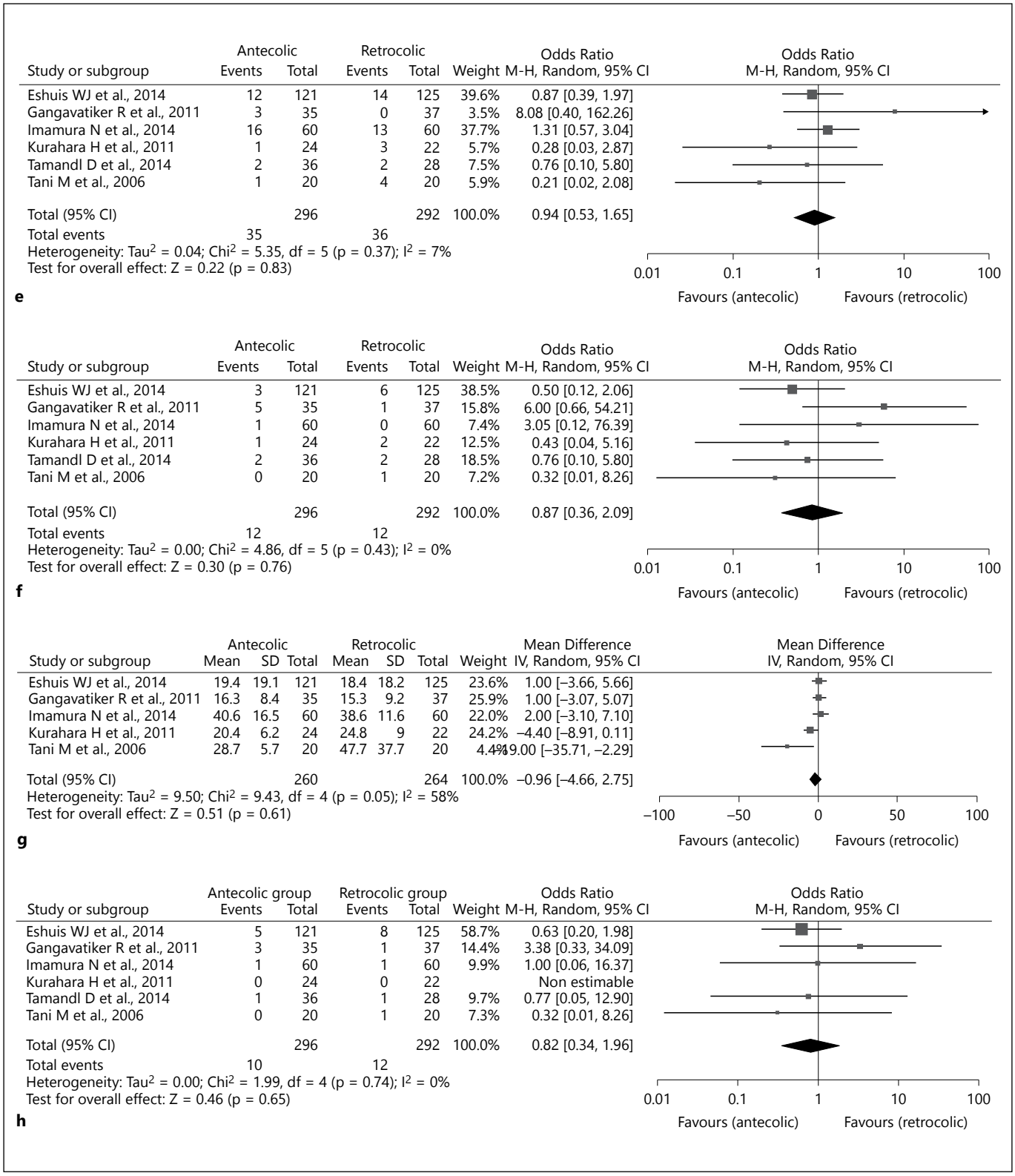

Fig. 3. Forest plots of primary and secondary outcomes. **e** Intra-abdominal abscess; **f** bile leak; **g** length of hospital stay; **h** hospital mortality.

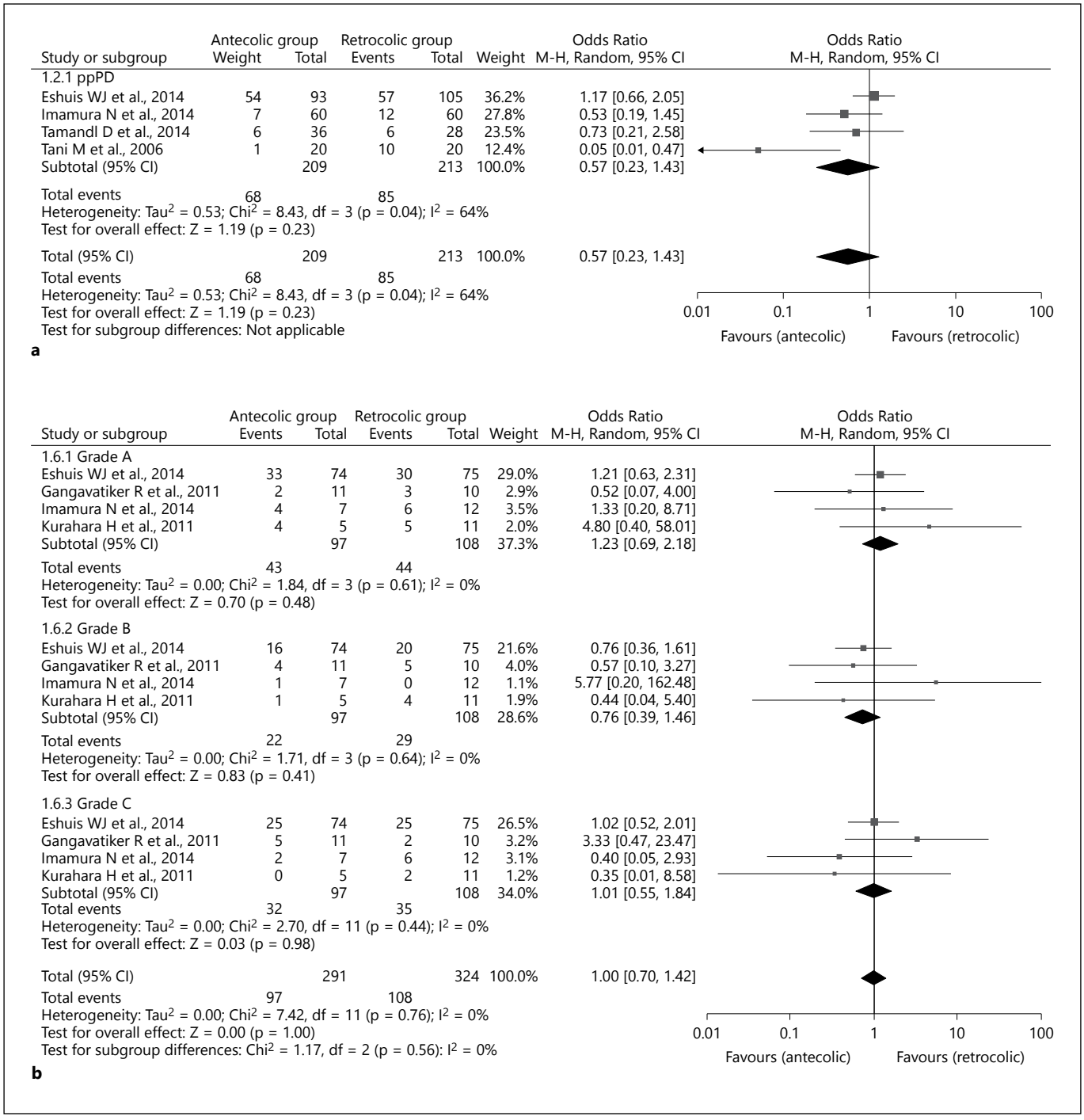

Fig. 4. Forest plots of subgroup analyses. **a** Incidence of DGE for ppPD; **b** incidence of DGE grades A, B and C.

note, this meta-analysis included 2 RCTs from the same author group that were derived from the same patient cohort [22, 23]. Finally, Qu et al. [12] published a general systematic review and meta-analysis of the risk factors of DGE after PD. They showed that preoperative diabetes, pancreatic fistulas and postoperative complications were predictive risk factors for DGE. Moreover, antecolic reconstruction and preoperative biliary drainage were associated with a lower DGE incidence. They included 7 studies (2 RCTs and 5 non-RCTs) with a total of 871 pa-

tients. DGE among antecolic reconstruction patients appeared in 10% compared to 22% in the retrocolic group (OR 0.17, 95% CI 0.07–0.41, $p < 0.001$). In addition, including RCTs as well as non-RCTs in a meta-analysis can bring important intrinsic selection bias due to inclusion of retrospective studies.

It is interesting to assess the potential reasons of the influence on DGE of the reconstruction route. Antecolic reconstructions seem to be advantageous due to the following considerations. First, the risk of mechanical outflow obstruction caused by a tight transmesocolic window can be avoided, and this reconstruction route would not impair gastric motility [18]. Second, reconstructing a passage anterior to the transverse colon allows separation of the anastomosis from the pancreas, therefore creating a protective anatomical barrier in case of pancreatic leak [12, 18, 21, 24, 49]. Third, it has been hypothesized that the antecolic reconstruction could avoid important angulation and venous stasis of the alimentary limb and reduce the postoperative edema [26, 40, 47].

On the contrary, some authors promoted the use of a retrocolic reconstruction [12, 19, 25]. They argued that this type of reconstruction has less tension and is therefore less prone to anastomotic dehiscence. Moreover, a retrocolic anastomosis could be less risky in case of cancer recurrence, because it usually appears superior to the mesocolon.

While these explanations are feasible, it must be noted that a robust scientific background is still lacking. The previous explanations appear more intuitive than based on rigorous scientific evidences. The findings of the present study favor that the reconstruction technique does not play a crucial role on the incidence of DGE. Mechanisms of DGE are likely to be due to complex multifactorial etiologies and cannot be related to only one simple aspect like the reconstruction route.

As mentioned above, some authors showed that DGE was also associated with other specific postoperative complications (e.g., pancreatic fistula, intra-abdominal abscess) [12, 18, 21, 24, 49]. Therefore, DGE incidence in the antecolic or retrocolic groups, with or without such complications would also have been very interesting to know. Unfortunately, only one RCT [16] mentioned that 26% of patients without complications had primary DGE in the antecolic group versus 31% in the retrocolic group ($p = 0.72$). No data were available in the 6 included RCTs regarding specific complications (pancreatic fistula or abscess) and DGE incidence in both groups (antecolic and retrocolic).

Prokinetic drugs have occasionally been used to prevent DGE. Some studies have shown the benefit of erythromycin [50, 51] or metoclopramide [52] in reducing the incidence of DGE by stimulating the gastric motility (counterbalancing the tachygastria and gastric dysrhythmia). Indeed, the prokinetics stimulate firstly the antrum, and then the contraction waves propagate to the small intestine. In the 6 included RCTs [16, 18–22], prokinetic drugs were not used on a routine basis, so this parameter does not affect the analysis. Moreover, the perioperative management of the nasogastric tube was not uniform in the included studies, which can bring some heterogeneity.

Quality of the Evidence, Strengths, and Potential Biases in the Review Process

The body of evidence is strong enough to allow a robust conclusion, as only RCTs were included in the present meta-analysis (6 RCTs, 588 patients). Jadad scores of the included RCTs were ≥3 in 5 studies, which proves that the overall quality of the included studies is good and reliable [36]. One study randomized the patients according to their date of birth [20], which represented a key methodological limitation. Five studies did not clearly mention blinding of participants and investigators, and the blinding of outcome assessment leading to unclear risks of performance and detection biases [18–22]. Overall study result consistency was judged good.

Clinical heterogeneity was low as participants, outcome measures and interventions were similar across all studies. Measure of the primary outcome (incidence of DGE) was defined according to the ISGPS definition, except for 2 older studies as the consensus definition was not published at that time [19, 21]. The limitation of using the ISGPS definition is that it does not exclude patients with severe complications who cannot get oral feeding for a prolonged time (e.g., mechanical ventilation in the ICU, grade C pancreatic fistula). Inclusion of such patients can be misleading and can falsely increase the DGE rate. Unfortunately, this was impossible to discern in the included trials. This global meta-analysis included all types of PD techniques as several articles proved that pylorus preservation did not influence DGE incidence [6, 43, 53–61]. Interventions consisted of cPD (2 studies including cPD and ppPD), ppPD (3 studies), and sspPD (1 study), which can bring some heterogeneity. Only 5 studies out of the 6 RCTs provided data on mean length of hospital stay (one provided only median length of hospital stay) and 4 studies provided the grades of DGE, which can be a source of bias of this meta-analysis.

Conclusions

This meta-analysis shows that antecolic reconstruction is not superior to retrocolic reconstruction in terms of DGE. As other specific complications were also not influenced, the type of reconstruction does not seem to play a major role on the postoperative outcomes after PD.

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Disclosure Statement

None.

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