

Antecolic reconstruction is associated with a lower incidence of delayed gastric emptying compared to retrocolic technique after Whipple or pylorus-preserving pancreaticoduodenectomy

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Abstract

Background: The aim of present study is to investigate the relationship between the antecolic (AC) route of gastrojejunostomy (GJ) after pancreaticoduodenectomy (PD) or duodenojejunostomy (DJ) reconstruction after pylorus-preserving pancreaticoduodenectomy (PPPD), and the incidence of delayed gastric emptying (DGE).

Methods: An electronic search of 4 databases to identify all articles comparing AC and retrocolic (RC) reconstruction after PD or PPPD was performed.

Results: Fifteen studies involving 2270 patients were included for final pooled analysis. The overall incidence of DGE was 27.2%. Meta-analysis results showed AC group had lower incidence of DGE (odds ratio, 0.29; 95% confidence interval [CI], 0.16–0.52, $P < .0001$) and shorter hospital length of stay (weight mean difference, -3.29 ; 95% CI, -5.2 to -1.39 , $P = .0007$). Days until to liquid and solid diet in the AC group were also significantly earlier than that in the RC group ($P = .0006$ and $P < .0001$). There was no difference in operative time, incidence of pancreatic fistula and bile leakage, and mortality, respectively.

Conclusions: AC route of GJ after PD or DJ after PPPD is associated with a lower incidence of DGE. However, the preferred route for GJ or DJ reconstruction remains to be investigated in well-powered, randomized, controlled trial.

Abbreviations: AC = antecolic, DGE = delayed gastric emptying, DJ = duodenojejunostomy, GJ = gastrojejunostomy, NGT = nasogastric intubation, PD = pancreaticoduodenectomy, POD = postoperative of days, PPPD = pylorus-preserving pancreaticoduodenectomy, RC = retrocolic, WMD = weighted mean difference.

Keywords: delayed gastric emptying, duodenojejunostomy, gastrojejunostomy, pancreaticoduodenectomy, pylorus-preserving pancreaticoduodenectomy

1. Introduction

Pancreatoduodenectomy (PD) is the standard surgical treatment for pancreatic and other periampullary malignancies.^[1–3] Pylorus-preserving PD (PPPD) is a procedure with equal short- and long-term outcomes compared to the classic PD, which has been demonstrated by several studies.^[4–7] Both PD and PPPD procedures were considered the only possibly curative treatment.

Despite the mortality of such procedures have decreased to less than 5% in high-volume surgical institutions, but postoperative morbidity remains relatively high.^[8] One of the most frequent postoperative complications after PD or PPPD is delayed gastric emptying (DGE), which ranges from 5% to 80% among published studies.^[9–13]

Generally, DGE is not a lethal complication; it is associated with significantly longer hospital stay and higher costs. Several retrospective comparative studies (RSCs), as well as prospective randomized trials (RCTs) comparing antecolic (AC) versus classic retrocolic (RC) reconstruction, has provided controversial results and the influence of the chosen route of reconstruction is still a matter of discussion.^[14–16] Tani et al^[14] suggested that the route of gastrojejunostomy (GJ) after a classic Whipple's resection or a duodenojejunostomy (DJ) after a PPPD might be to help to prevent DGE and further revealed that an AC route leads to lower incidences of DGE, as compared with a RC route. However, a RCT conducted by Eshuis et al^[16] demonstrated that the AC and RC route of GJ reconstruction after PD does not influence the postoperative incidence of DGE.

Currently, 2 systematic reviews and meta-analyses focused on this topic have been published.^[17,18] RC was reported to have higher incidence of DGE than cases associated with AC procedure. However, these previous meta-analyses maybe limited by its small sample sizes; the pooled results of these studies may be unreliable and underpowered for comparison among surgical

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techniques because potential studies and publication biases are more likely to occur. Therefore, we conducted an update analysis that included the largest available database from RCTs and RSCSs to overcome these limitations, and to investigate the relationship between the AC versus RC route of GJ after PD or DJ after PPPD and the incidence of DGE using the meta-analytical method and sensitivity analyses.

2. Materials and methods

2.1. The literature review

This study was performed under a human investigational protocol that was approved and monitored by the Institutional Review Board of The first affiliated hospital of Chongqing Medical University. We adhered to the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement.^[19] An electronic databases search of the Medline Ovid, PubMed, Cochrane Library, and the Controlled Trials Registry was performed, using the following Mesh search headings and their combinations “Pancreaticoduodenectomy,” “Pylorus-preserving pancreaticoduodenectomy,” “Delayed gastric emptying,” “gastrojejunostomy,” “duodenojejunostomy,” articles published in English language as a limit. We gathered all RCTs and RSCSs between 1991 and 2018 and compared the outcomes of AC and RC route of GJ after PD or DJ after PPPD. Retrieval time was ended by December 2017. Title and abstracts of each identified publication were screened, and only publications that reported the clinical outcomes of this analysis were further retrieved.

2.2. Inclusion and exclusion criteria

Inclusion criteria for all eligible studies must have to compare the outcomes of AC to RC reconstruction after PD or PPPD and it reported the postoperative outcome of incidence of DGE or at least one of the measured outcomes that referred as follows: when 2 studies containing overlapping (more than 50%) patients were reported from the same institution or authors, either the one of higher quality or the most recent publication was included in the analysis unless an older publication had more measured outcomes or an RCT publication; and studies with limited information, cases reports, and results that were not published in English language were excluded from this analysis.

2.3. Measured outcomes and definitions

The primary outcome measure was the postoperative incidence of DGE, according to the International Study Group of Pancreatic Surgery (ISGPS) consensus definition,^[20] grade A was defined as nasogastric intubation (NGT) lasting more than 3 postoperative of days (POD) or the inability to tolerate a solid diet by POD 7; grade B was defined as NGT lasting for 8 to 14 days, the need for reinsertion of the NGT after 7 days, or the necessity of prolonged gastric drainage and a delayed return to solid food intake; grade C was defined as NGT lasting more than 14 days, the need for NGT reinsertion after 14 days, or the inability to tolerate a solid diet by POD 21 (Table 1).

The following secondary outcomes were used to compare AC with RC route:

- (1) Operative parameters: operative time (minutes); blood loss (ml), transfusion rate.
- (2) Postoperative outcomes: days until to liquid diet (days); days until to solid diet (days); lengths of hospital stay (days).

Table 1

ISGPS definition of DGE grade.

ISGPS DGE grade	Nasogastric tube needed	Unable to tolerate solid diet by POD
A	4–7 d or reinsertion after POD 3	7
B	8–14 d or reinsertion after POD 7	14
C	>14 d or reinsertion after POD 14	21

DGE=delayed gastric emptying, ISGPS=International Study Group of Pancreatic Surgery, POD=postoperative day.

- (3) Postoperative complications: overall complications, pancreatic leakage; bile leakage; wound infections, intra-abdominal abscess, reoperation, and intra-abdominal hemorrhage.
- (4) Postoperative mortality.

A pancreatic fistula was defined as drainage of fluid with an amylase concentration 3 times the upper limit of normal serum as per the ISGPF definition.^[20]

2.4. Data extraction and quality assessment

Two authors (QJQ and LM) examined the studies independently and extracted data according to a predefined criteria. If data were not presented in the articles, the corresponding authors were contacted by email to specifically ask for the missing information. If all required numbers were obtained, the study was included. Any discrepancy between the 2 reviewers was assessed and resolved by panel consensus. The methodological quality of each RCT was evaluated by individual components based on the Cochrane risk of bias tool.^[19] For RSCSs, the quality of these studies was assessed by using the Modified Newcastle–Ottawa Score,^[21] which allocates a maximum of 9 points each to patient selection, the comparability of the 2 groups (AC and RC), and outcome assessment.

2.5. Statistical analysis

This meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines.^[22,23] The statistical software Review Manager version 5.0 (The Cochrane Collaboration, Oxford, United Kingdom) was used to perform all statistical analyses. For the analysis, continuous data with weighted mean differences (WMDs) and corresponding standard deviations were presented as weighted WMDs with 95% confidence intervals (CIs). However, odds ratios (ORs) with 95% CIs as the summary statistics were used to perform statistical analysis for dichotomous variables. Clinical heterogeneity was tested by means of the I^2 value; a value exceeding 50% was considered to represent a significant difference. A random-effects model was used to report the results of heterogeneous data; otherwise, a fixed-effects model was used. Funnel plots were constructed to detect and assess publication bias and any associations between treatment estimates and sample size. Forest plots were constructed, and the value of $P < .05$ was considered to indicate statistical significance.

3. Results

3.1. Study selection

The PRISMA flow chart of literature search strategies is illustrated in Figure 1. Initially, a total of 456 potential articles

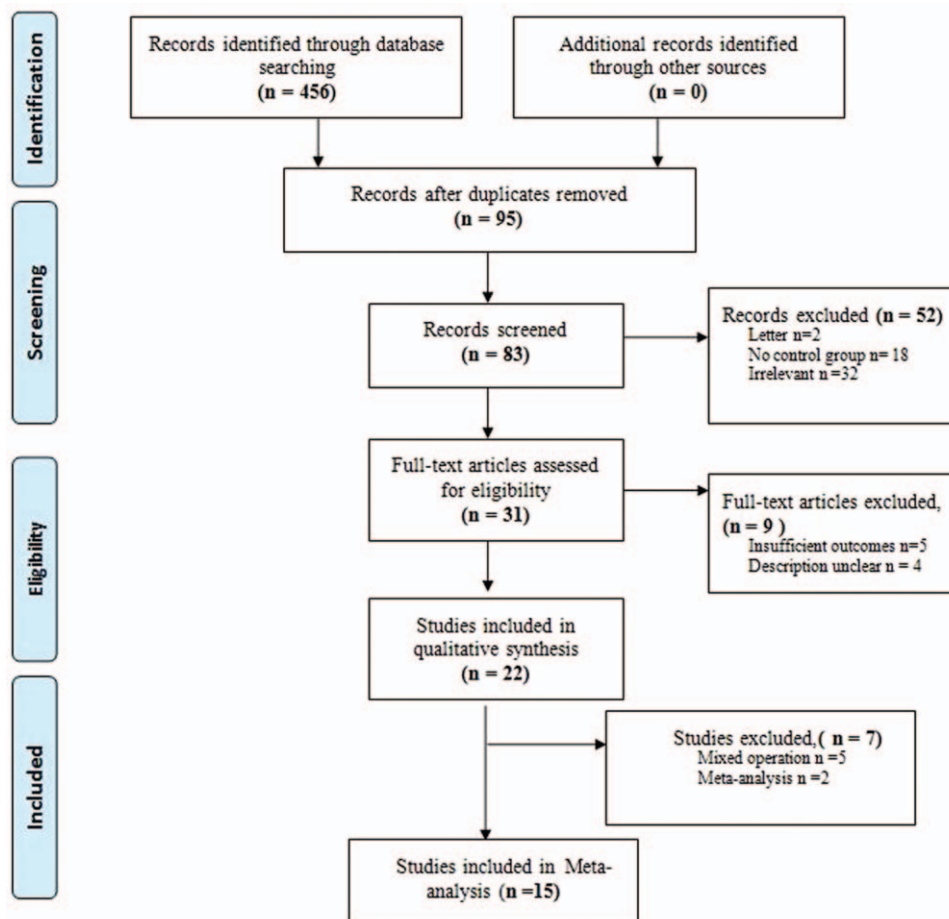


Figure 1. The PRISMA flowchart of literature review. PRISMA = preferred reporting items for systematic reviews and meta-analysis.

published until 2017 were identified from literature searches after screening all titles and abstracts; no other eligible studies were found from other sources. Overall, 31 articles were included for a full-text evaluation. Of these, 7 were excluded for not meeting the inclusion criteria. In addition, 4 authors were contacted for additional information or to correct inaccurate information, and 2 provided data that were incomplete or not extractable from the original report. Subsequently, 22 studies were potentially included in this study. Of these, 5 studies, in which mixed groups of surgeries were reported and from which data could not be extracted separately and 2 meta-analysis studies were excluded. Finally, in total, 15^[14,16,24–36] studies met our inclusion criteria and were retrieved for more detailed evaluation.

3.2. Study characteristics and methodological quality assessment

The baseline characteristics of the 15 included studies and the study design are summarized in Table 2. The sample size of these studies ranged from 30 to 800 patients. Analysis was performed on 2270 patients, of whom 1080 (47.6%) underwent AC route reconstruction and 1190 (52.4%) underwent RC route. The quality assessment of 7 RCTs^[14,16,29,31,32,33,34] is shown in Table 3. The quality

assessment of RSCSs^[24–28,30,35,36] is also presented in Table 2. In general, 6 studies^[24,26,28,30,33,36] were considered to be of high quality by achieving a score of 6.

3.3. Primary outcome measure

Basic demographics and treatment characteristics did not differ among the study populations. The overall observed incidence of DGE in the 2270 analyzed patients was 27.2% (Table 4). There was a significant difference in the overall incidence of DGE between the AC and the RC group (OR = 0.29; 95% CI, 0.16–0.52; $P < .0001$; Fig. 2). However, no significant differences were seen in any grade A ($P = .14$), grade B ($P = .41$), and grade C ($P = .78$) DGE between AC and RC reconstruction by subgroup analysis, respectively.

3.4. Secondary outcome measures

3.4.1. Meta-analysis of operative parameters (Fig. 3). Twelve studies^[14,16,25,27–32,34–36] reported data on operative time that included a total of 1704 patients. The meta-analysis showed that operative time did not differ significantly between the 2 operations (MD = -0.94 ; 95% CI, -9 to 7.11; $P = .82$). Similarly, the estimated blood loss (MD = -46.11 ; 95% CI, -179.18 to 86.97; $P = .5$) and transfusion rate (OR = 0.76; 95% CI, 0.12 to 5.07; $P = .78$) were also not differ significantly,

Table 2
Characteristics of all included studies and quality assessment of retrospective comparative studies (list by publication year).

Reference, yr	Country	Design	Patient #		Procedure	Quality Score
			AC	RC		
Park 2003 ^[24]	Korea	Retro.	46	104	GJ after PD	*****
Sugiyama 2004 ^[25]	Japan	Retro.	12	18	GJ after PD	****
Hartel 2005 ^[26]	Germany	Retro.	100	100	GJ after PD	*****
Kurosaki 2005 ^[27]	Japan	Retro.	25	19	GJ after PD	*****
Tani 2006 ^[14]	Japan	RCT	20	20	GJ after PD	—
Murakami 2008 ^[28]	Japan	RCT	78	54	GJ after PD	*****
Chijiwa 2009 ^[29]	Japan	RCT	17	18	GJ after PD	—
Nifkarjam 2009 ^[30]	America	Retro.	36	115	DJ after PPPD	*****
Gangavatiker 2011 ^[31]	India	RCT	32	36	DJ after PPPD	—
Kurahara 2012 ^[32]	Japan	RCT	24	22	DJ after PPPD	—
Eshuis 2012 ^[33]	Netherlands	Retro.	77	77	DJ after PPPD	*****
*Eshuis WJ 2014 ^[16]	Netherlands	RCT	121	125	DJ after PPPD	—
Imamura 2014 ^[34]	Japan	RCT	58	58	GJ after PD	—
Tamandl 2014 ^[35]	Australia	RCT	34	26	GJ after PD	—
Sahora 2015 ^[36]	America	Retro.	400	400	DJ after PPPD	*****

AC = antecolic, DJ = duodenojejunostomy, GJ = gastrojejunostomy, PD = pancreaticoduodenectomy, PPPD = pylorus-preserving PD, RC = retrocolic, RCT = randomized controlled trial, Retro = retrospective studies.

*Including another 92 patients in the AC and RC group.

Table 3
Quality assessment of all eligible randomized controlled trials based on the cochrane risk of bias tool.

Reference	Adequate sequence generation	Allocation concealment	Postoperative protocol reported	Incomplete outcome data addressed	Free of selective reporting	Operator bias
Tani et al ^[14]	Yes	Yes	No	Yes	Yes	No
Chijiwa et al ^[29]	Unclear	Yes	Yes	Yes	Yes	Unclear
Gangavatiker et al ^[39]	Yes	Unclear	Yes	Yes	Yes	No
Kurahara et al ^[32]	Yes	Yes	Unclear	Yes	Yes	Yes
Eshuis WJ et al ^[16]	Unclear	Yes	Yes	Yes	Yes	Unclear
Imamura et al ^[34]	Yes	Unclear	Yes	No	Yes	No
Tamandl et al ^[35]	Yes	Yes	Yes	Yes	Yes	Unclear

The level of bias was determined as follows: No = indicating no risk of bias, Unclear = indicating an uncertain risk of bias, Yes = indicating a risk of bias. When articles fulfilled all methodological requirements, entries are given in bold type.

although these findings were associated with significant heterogeneity between the studies ($I^2 = 81\%$ and 89%).

3.4.2. Meta-analysis of postoperative outcomes (Fig. 4). The length of hospital stay was measured in 14 studies^[14,16,24-26,28-36] including 2228 participants, meta-analysis performed for which showed that patients undergoing AC reconstruction were found to have a significantly shorter than those undergoing RC procedure with a difference of 3.29 days (95% CI, -5.2 to -1.39; $P = .0007$). However, there was significant heterogeneity between the 14 studies reporting on this outcome ($HG P < .00001$). The time until to liquid and solid diet were both found to be significantly earlier in the AC group by 1.12 days (95% CI, -1.77 to -0.48; $P = .0006$) and by 0.71 days (95% CI, -0.88 to -0.54; $P < .0001$) when compared with the RC group, respectively.

3.4.3. Meta-analysis of postoperative morbidity. All included studies reported on the overall incidence of postoperative morbidity. The meta-analysis showed that the incidence of overall morbidity was 0.86% lower in the AC group than in the RC group, although this difference was not statistically significant (95% CI, 0.71-1.03; $P = .09$; Fig. 5). Data on

postoperative incidence of pancreatic fistula were available in 13 out of 15 studies.^[14,16,25-31,33-36] Pooled analysis showed a fewer pancreatic fistula rate in the AC group without reaching the level of statistical significance (OR = 0.87; 95% CI, 0.66-1.14; $P = .31$; Fig. 6), as well as the subgroup analysis of ISGPS grade A ($P = .36$), B ($P = .71$), and C ($P = .74$), respectively. Seven studies^[14,16,27,29,31,32,34] reported on the wound infection rate after surgery. Meta-analysis showed there was no significant difference between the AC and RC groups (OR = 0.81; 95% CI, 0.55-1.2; $P = .3$), as were the rates of reoperation (OR = 0.54; 95% CI, 0.28-1.07; $P = .08$). The incidence of bile leakage was measured in 8 studies^[14,16,27,31-35] with 774 participants. Meta-analysis showed there was no significant difference between the AC and RC groups (OR = 1.1; 95% CI, 0.55-2.21; $P = .78$), as were the incidence of intra-abdominal abscess and hemorrhage (OR = 1.72; 95% CI, 0.76-3.88, $P = .19$) from 12 studies^[14,16,25,27-33,35,36] and 6 studies,^[29-31,33-35] respectively.

3.4.4. Meta-analysis of mortality. As related to postoperative mortality, there were only 6 studies^[14,16,25,29,32,33] reporting and

Table 4
Diverse definitions of DGE.

References, yr	Definition of DGE	DGE # (%)	
		AC	RC
Park 2003 ^[24]	(a) NGT ≥300 mL/d left ≥POD 10; (b) NGT reinsertion because of vomiting; (c) failure to tolerate a regular diet after POD 14;	3(6.5)	33 (32.3)
Sugiyama 2004 ^[25]	NGT ≥ POD 10	1 (8.3)	13 (72.2)
Hartel 2005 ^[26]	(a) NGT ≥ POD 10; (b) inability to tolerate a solid diet ≤ POD 14;	5 (5)	24 (24)
Kurosaki2005 ^[27]	(a) NGT ≥ POD 10;; (b) reinsertion of NGT;	1 (4)	4 (21.1)
Tani 2006 ^[14]	(a) aspiration >500 mL/d from NGT left ≥ POD 10; (b) reinsertion of NGT; (c) failure of unlimited oral intake by POD 14;	1 (5)	10 (50)
Murakami 2008 ^[28]	(a) NGT ≥ POD 10; (b) inability to tolerate regular diet ≤ POD 10; (c) vomiting ≥3 consecutive days after POD 5; (d) radiographic passage with water-soluble contrast medium revealing a holdup of the contrast medium in the stomach;	8 (10.3)	44 (81.5)
Chijiwa 2009 ^[29]	(a) NGT ≥ POD 10; (b) reinsertion of NGT; (c) inability to tolerate an appropriate amount solid food ≤ POD 14;	1 (5.9)	4 (22.2)
Nifkarjam 2009 ^[30]	(a) inability to return to a standard diet by POD 7 (b) reinsertion of NGT	0 (0)	20 (17.4)
Gangavatiker 2011 ^[31]	ISGPS definition	11 (34.4)	10 (27.8)
Kurahara 2012 ^[32]	ISGPS definition	5 (20.8)	11 (50)
Eshuis 2012 ^[33]	ISGPS definition	40 (51.9)	45 (58.4)
*Eshuis WJ 2014 ^[16]	ISGPS definition	74 (61.2)	75 (60)
Imamura 2014 ^[34]	ISGPS definition	7 (12.1)	12 (20.7)
Tamandl 2014 ^[35]	(a) NGT ≥ POD 10; (b) emesis after NGT removal; (c) NGT reinsertion; (d) failure to progress with the diet; (e) use of prokinetics after POD 10;	4 (11.1)	6 (23.1)
Sahora 2015 ^[36]	ISGPS definition	59 (14.8)	84 (21)

AC=antecolic, DGE=delayed gastric emptying, ISGPS=International Study Group of Pancreatic Surgery, NGT=nasogastric intubation, POD=postoperative of days, RC=retrocolic.

* Including another 92 patients in the AC and RC group.

suggesting that there was no significant difference between the 2 groups by pooled analysis (OR, 0.84; 95% CI, 0.35–2.01; *P* = .69; Fig. 7).

3.5. Sensitivity analysis

The sensitivity analysis included the following:

- (1) 7 RCTs;
- (2) 8 RSCSs;
- (3) 13 studies of high quality (7 RCTs and 6 RSCSs with quality score of 6 or more using the modified Newcastle–Ottawa scale);
- (4) AC versus RC route of GJ after PD procedure;
- (5) AC versus RC route of DJ after PPPD procedure;
- (6) 9 studies with more than 30 patients in each group; and
- (7) 6 studies with DGE was defined as ISGPS consensus definition.

The results from sensitivity analysis were summarized in Table 5. The forest plots of DGE by sensitivity analysis were illustrated in Figure S1–7, <http://links.lww.com/MD/D196>.

3.6. RCTs

When only RCTs^[14,16,29,31,32,33,34] were analyzed, DGE rate was still significantly fewer in the AC group by 0.71% (95% CI, 0.50–1.01; *P* = .05). Hospital stay and days until to liquid diet

became not significantly between the AC and RC group. The rest of the outcomes were consistent with the overall analysis, including operative time (*P* = .84), blood loss (*P* = .29), overall complications (*P* = .30), incidence of pancreatic fistula (*P* = .76), bile leakage (*P* = .97), and mortality (*P* = .32). There was generally a reduction in the degree of heterogeneity.

3.7. RSCSs

Eight RSCSs^[24–28,30,35,36] compared the perioperative parameters between the AC and RC groups. Incidence of DGE remained significantly fewer in the AC group by 0.35% (95% CI, 0.27–0.46; *P* < .00001). The other variables remained similar to the original AC versus RC analysis. Heterogeneity was once again reduced.

3.8. High-quality studies (scores of >6 and RCTs)

The outcomes showed similar results as the original analysis. The heterogeneity was once again reduced.

3.9. Sample size (studies with more than 30 patients in each group)

There were 9 studies^[16,24,26,28,30,31,33,34,36] with more than 30 patients in each AC and RC group. Operative time

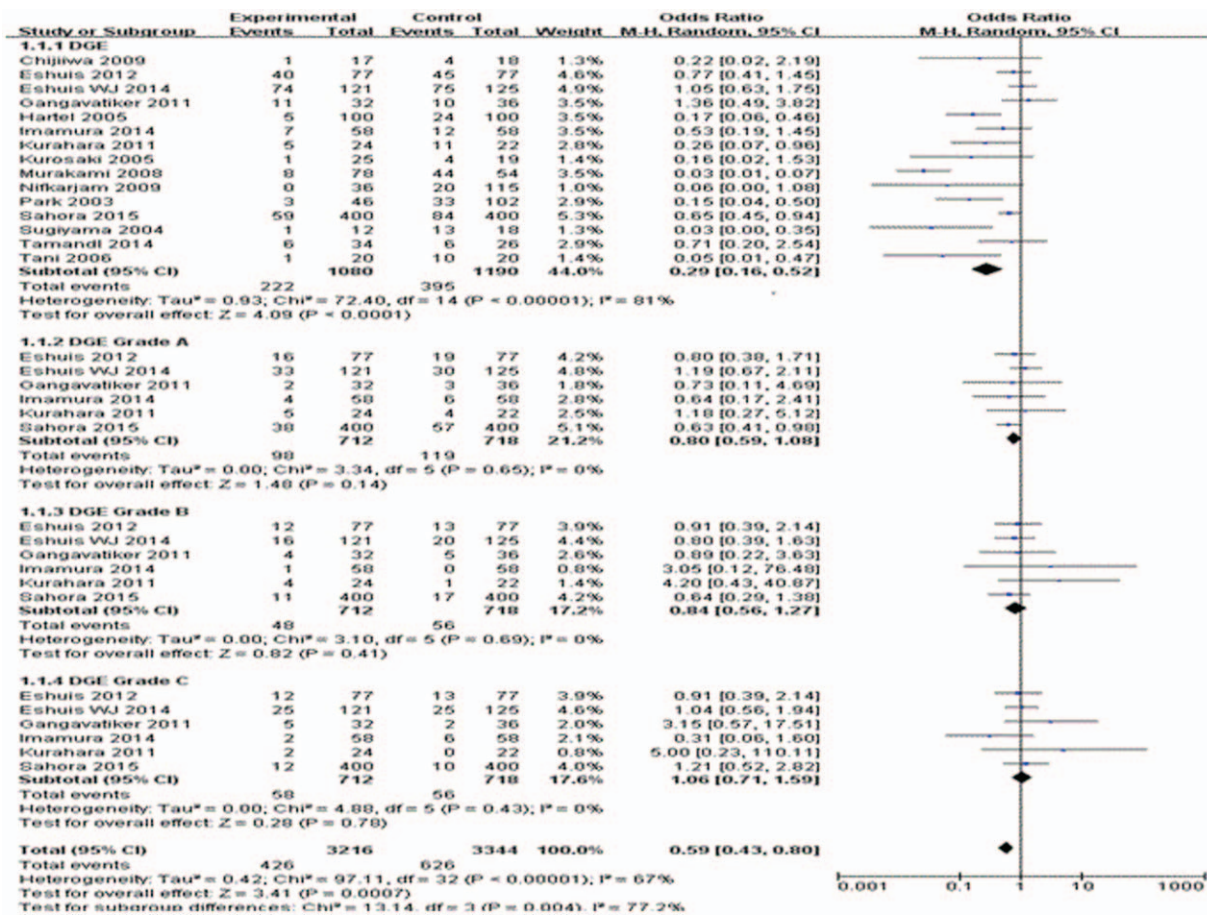


Figure 2. Meta-analysis of delayed gastric emptying and subgroup analysis of Grade A, B, and C.

became significantly shorter in the AC group than RC group (MD = -22.48 minutes; 95% CI, -30.63 to -8.93 minutes; $P = .001$). The remaining results were similar to the original analysis, and heterogeneity was once again reduced.

3.10. AC versus RC route of GJ after PD procedure

There were 6 studies^[16,30-33,36] comparing AC with RC route of GJ after PD procedure. Hospital stay became no significant (MD = 1.32 days; 95% CI, -2.7 to 0.06 days; $P = .06$), whereas operative time became significantly shorter in the AC group than RC group (MD = 32.92 minutes; 95% CI, -47.93 to -17.92 minutes; $P < .00001$). The remaining results were similar to the original analysis, and heterogeneity was once again reduced.

3.11. AC versus RC route of DJ after PPPD procedure

There were 9 studies^[14,24-29,34,35] comparing AC with RC route of DJ after PPPD procedure. Operative time and estimated blood loss became significantly lower in the AC group than RC group ($P = .01$ and $P = .02$), respectively. The remaining results were similar to the original analysis, and heterogeneity was once again reduced.

3.12. ISGPS DGE definition

Six studies^[16,31-34,36] reported the overall incidence of DGE according to the ISGPS definition. Incidence of DGE remained

significantly fewer in the AC group by 0.73% (95% CI, 0.56-0.97; $P = .03$). Operative time became significantly shorter in the AC group than RC group (MD = -33.75 minutes; 95% CI, -48.76 to -18.74 minutes; $P < .00001$). The remaining results were similar to the original analysis, and heterogeneity was once again reduced.

3.13. Publication bias

The funnel plot of this study based on postoperative incidence of DGE is shown in Figure 8. All studies except 2 lay inside the limits of the 95% CIs and distributed more evenly about the vertical, showing no evidence of publication bias.

4. Discussion

4.1. Research frontiers and summary of the study

Since the first report of PPPD was published in 1978,^[37] there has been a boom in the number of PPPD being performed during the past few years. Several studies have shown that PPPD had a higher incidence of DGE versus the standard PD.^[38-40] At the same time, other studies have revealed no difference in the incidence of DGE after PPPD or PD.^[41-43] Regardless of the type of PD, DGE is still a frustrating complication following PD or PPPD and is seen in a significant proportion of patients leading to prolonged hospital stay, decreased patient comfort, increased morbidity,

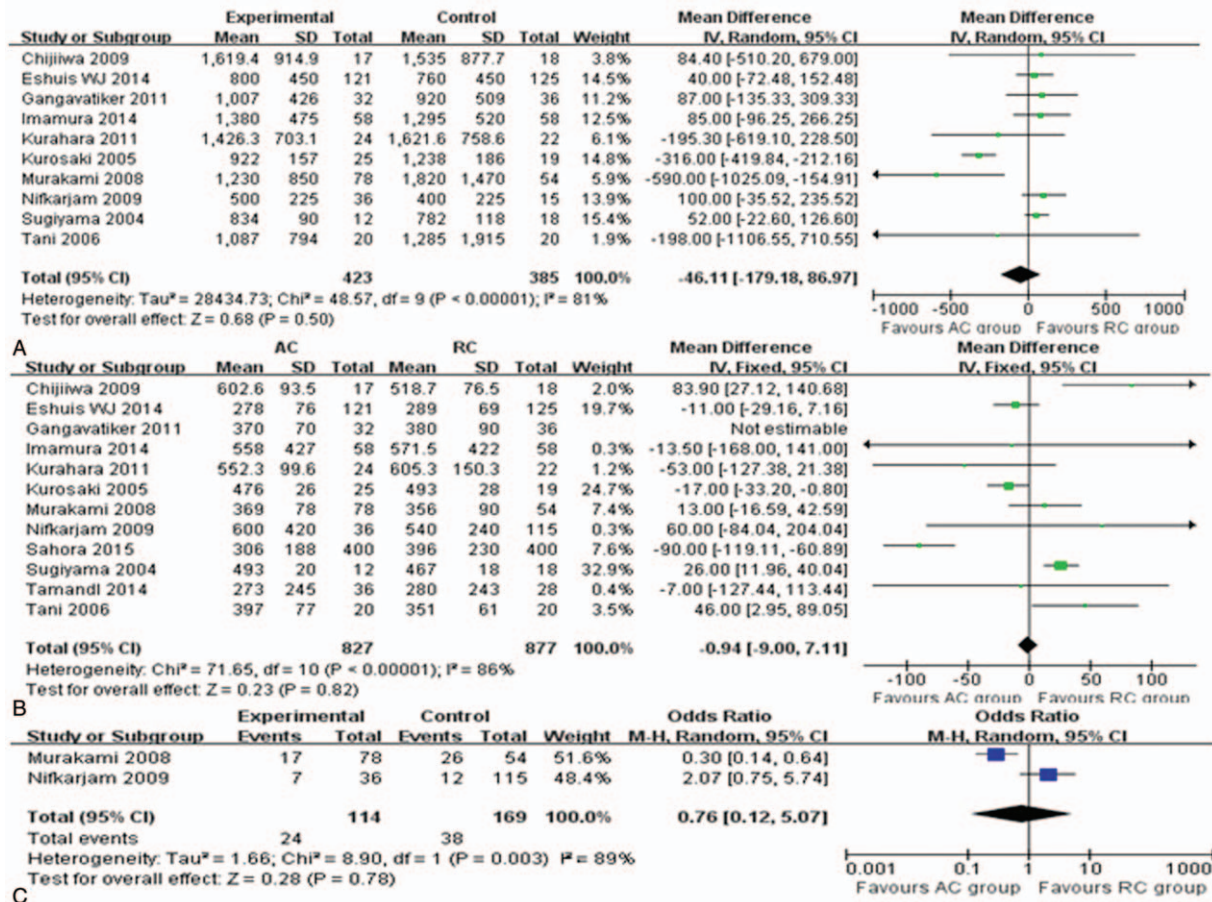


Figure 3. Meta-analysis of operative parameters: (A) operative time, (B) blood loss, (C) transfusion rate.

and medical costs.^[42,43] Many interventions have been tried in an attempt to reduce the high incidence of DGE. One of the most commonly advocated techniques is to perform an AC route of GJ/DJ instead of a RC reconstruction.^[16-18] Murakami et al^[28] showed that AC reconstruction was better than RC reconstruction in terms of DGE. Another 2 randomized studies also found a significant benefit in favor of AC reconstruction following PPPD.^[14,29] However, the influence of the chosen route of reconstruction is still controversial. Therefore, the aim of this study was to compare the incidence of DGE and other parameters between AC and RC route of reconstruction after PD or PPPD using meta-analytical techniques. AC reconstruction was associated with a lower incidence of DGE, shorter hospital stay, and faster recovery to regular diet compared to that in RC group. No statistically significant differences were found between the 2 groups regarding operative time, incidence of pancreatic and bile leakage, and postoperative mortality. These results are similar to majority of the previous published studies.^[14,17,18,28,29] Due to the included number of RCTs was too small to make confirm conclusion, we performed several sensitivity analyses including all the RCTs and the high-quality nonrandomized trials and so on, which greatly increase the credibility of the results without necessarily compromising the quality of the study. Results from sensitivity analysis of high-quality and large trials are in accordance with original analysis, which suggesting the reliability of our results.

4.2. DGE consensus definition and its influencing factors

The reported incidence of DGE after surgical procedure varies between 6% to 81.5% from the available literature database.^[9-13,16,28,44] The lack of a uniform definition of DGE is largely responsible for the diversity. Some authors have defined DGE as requiring NGT decompression for more than 7 or 10 days postoperatively.^[45-47] Others have defined DGE as the inability to tolerate a normal diet after the POD 10 or POD 14,^[48,49] or a liquid diet after the 7th postoperative day.^[14,50] It seems that to establish an internationally accepted uniform definition of DGE is imminent, therefore, a consensus definitions for DGE and other major pancreas-specific complications was proposed by the ISGPS in 2007,^[51] which defined the DGE was based on whether there is a need for nasogastric tube placement (and if so, for how long), how soon after the operation the patient is able to tolerate solid oral intake, and whether prokinetic therapy is administered.^[19,52] Welsch et al^[13] evaluated the ISGPS definition of DGE after PD in a high-volume center and revealed that the ISGPS DGE definition is feasible and applicable in patients with an uneventful postoperative course.

Although the ISGPS grading system for DGE is clearly measurable, it does not explain why DGE has occurred. Several studies have focused on its possible cause and pharmacologic strategies to reduce the high incidence of DGE have been published so far. Sato et al^[53] and other researches^[54-56] revealed that DGE have a correlation of intra-abdominal complications

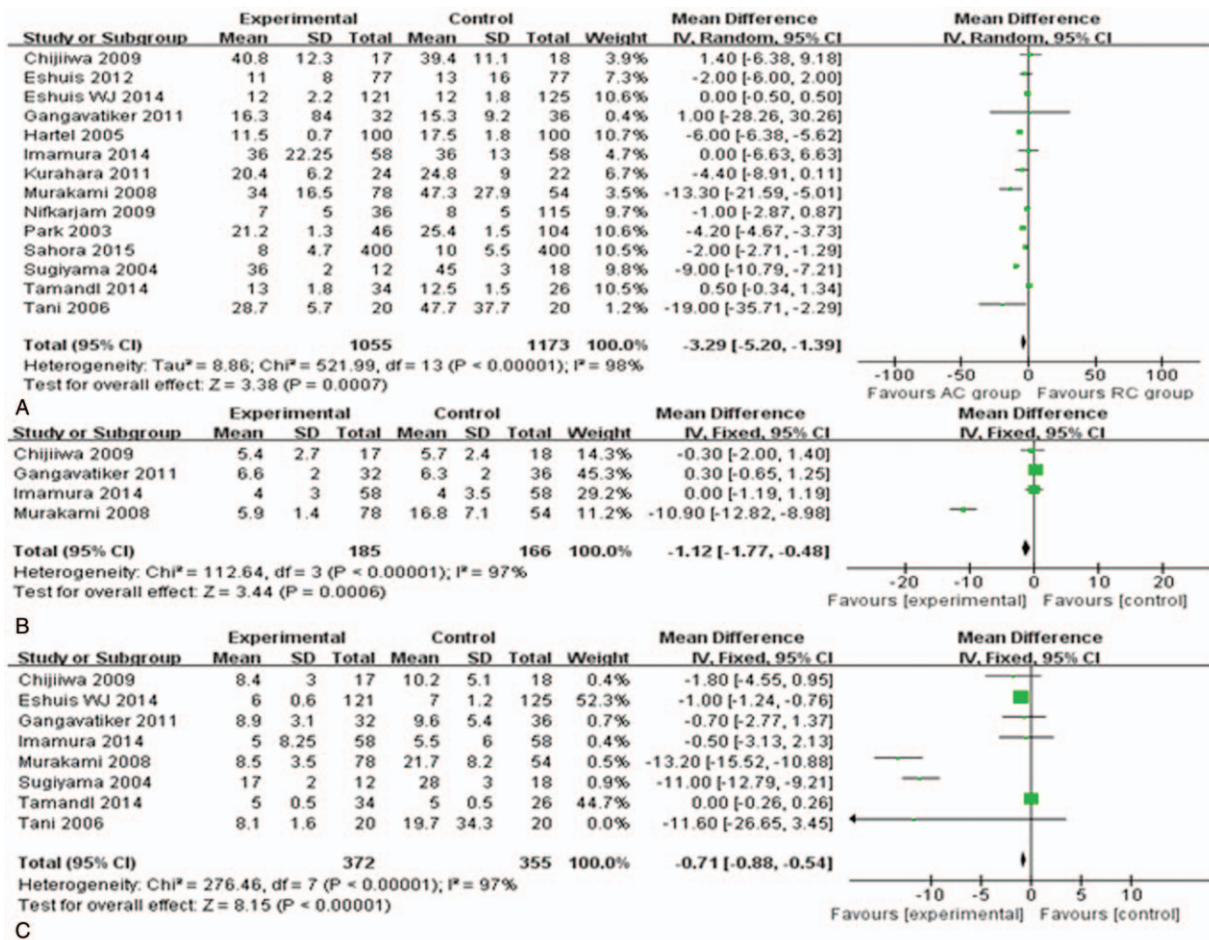


Figure 4. Meta-analysis of postoperative parameters: (A) hospital stay, (B) days until to liquid diet, (C) days until to solid diet.

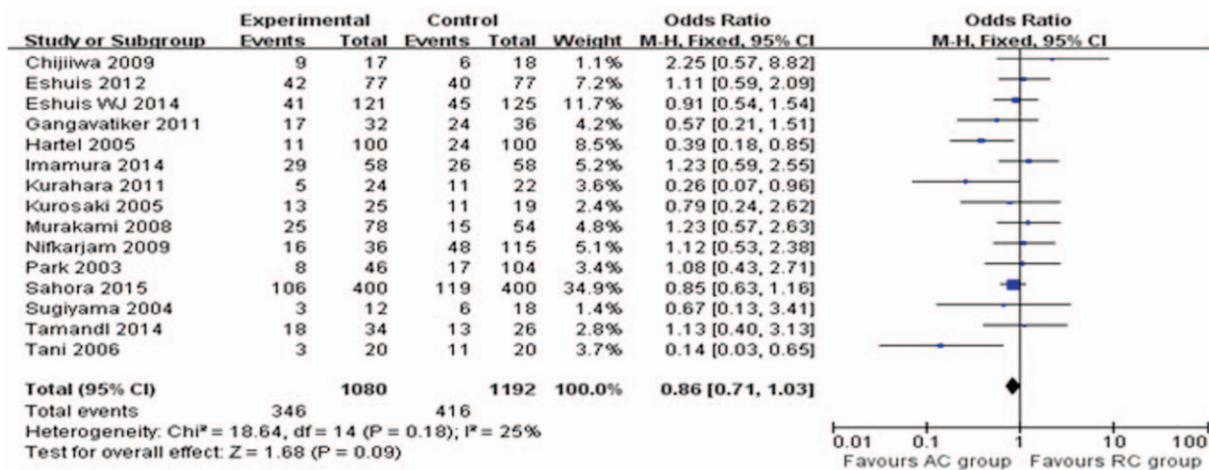


Figure 5. Meta-analysis of overall morbidity.

such as anastomotic leak or abscess. Gastric dysrhythmias, disruption of gastroduodenal neural connections, ischemia of the pylorus muscle, and ligation of the right gastric artery were all related to DGE, respectively.^[57-59] In addition, preoperative

diabetes mellitus condition, cholangitis, previous abdominal surgery as well as retromesenteric route of jejunal reconstruction were significantly associated with a higher incidence of DGE.^[25] Park et al^[24] found that the incidence of DGE was 31.7% in the

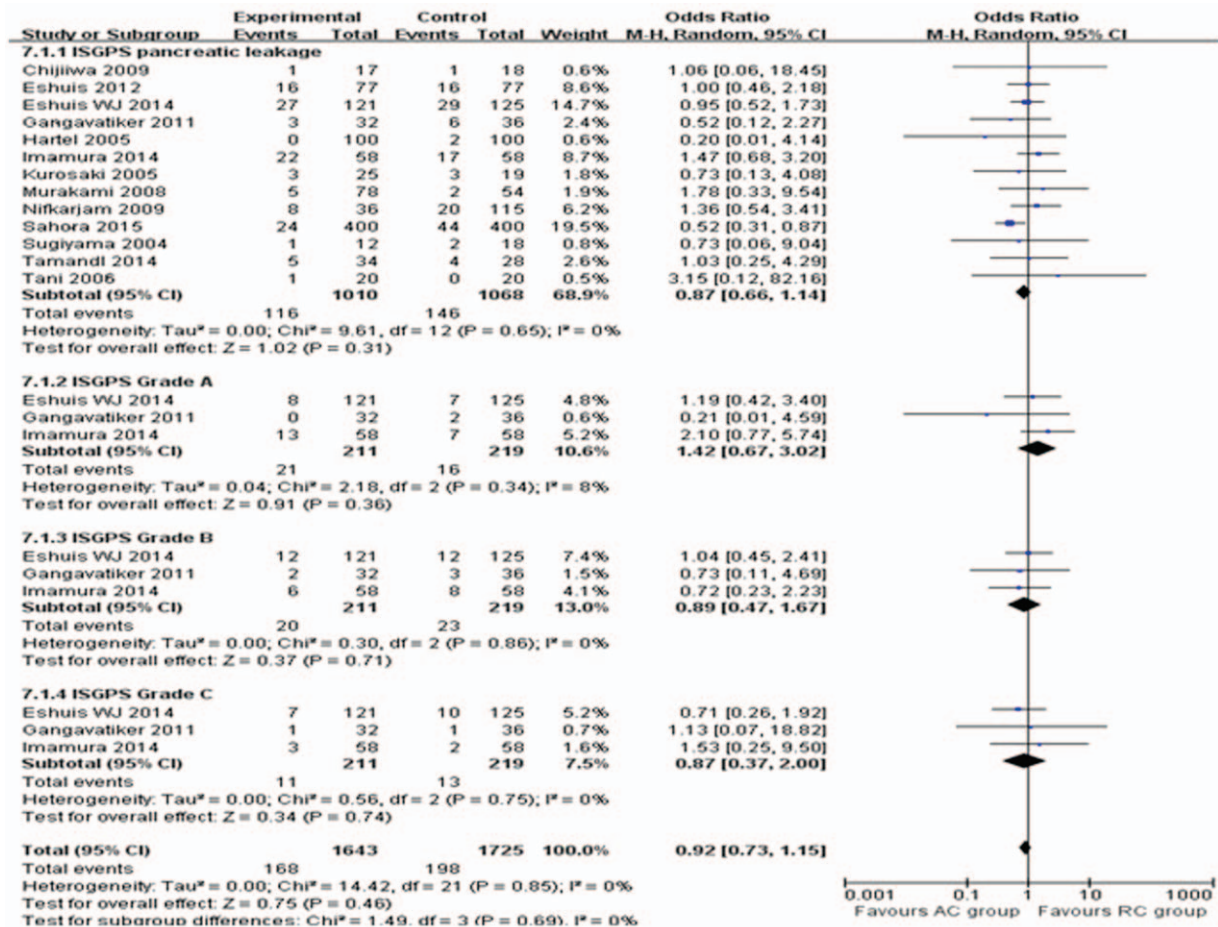


Figure 6. Meta-analysis of pancreatic fistula and subgroup analysis of Grade A, B, and C.

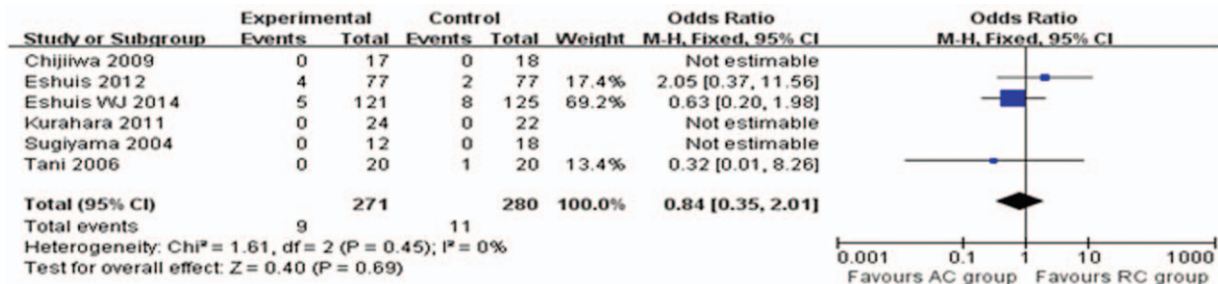


Figure 7. Meta-analysis of mortality.

RC group, but only 6.5% in the AC group. Similar results were found by Sugiyama et al,^[25] which reported that DGE occurred in 8% patients (8%) in the AC group, but in 72% patients in the RC group. Hartel et al^[26] reported an incidence of 5% with the AC route and 24% with the RC route. Meta-analysis of these studies has suggested that the incidence of DGE is lower with the AC route than with the RC route. In the future, to research the exact mechanism of DGE will become more and more urgent and important.

4.3. Limitations and recommendations

This systematic review and meta-analysis still have several limitations that must be taken into account. First, the majority of our included studies were comparative studies, although there is evidence that estimates derived from high-quality nonrandomized comparative studies may be similar to those derived from randomized studies. Second, the strength and limitations of meta-analytic techniques have been a source of considerable debate. Third, despite a relatively large number of patients were included

Table 5
Sensitivity analysis comparing AC versus RC group.

Outcome of interest	Studies (n)	Patients (n)	OR/WMD	95% CI	P-values	Heterogeneity test	
						HG χ^2	P-values
RCTs							
DGE	7	611	0.71	0.50 to 1.01	.05	12.80	.05
Operative time	7	611	1.64	-13.84 to 17.72	.84	16.13	.0006
Blood loss	6	551	46.09	-38.64 to 130.81	.29	1.86	.87
Hospital stay	7	611	-0.04	-1.05 to 1.97	.94	0.46	.13
Days to liquid diet	3	229	0.10	-0.58 to 0.79	.76	0.41	.81
Days to solid diet	6	665	-0.55	-0.72 to -0.37	<.00001	34.68	<.00001
Overall morbidity	7	611	0.76	0.45 to 1.28	.30	12.40	.05
Pancreatic fistula	6	567	1.06	0.70 to 1.61	.76	2.16	.83
Intra-abdominal abscess	7	611	1.00	0.61 to 1.63	.99	5.75	.45
Bile leakage	6	576	0.99	0.45 to 2.16	.97	5.10	.40
Mortality	4	367	0.58	0.20 to 1.70	.32	0.15	.70
RSCSs							
DGE	8	1659	0.35	0.27 to 0.46	<.00001	52.29	<.00001
Operative time	5	1157	-1.90	-11.33 to 7.52	.69	55.37	<.00001
Blood loss	4	257	-53.09	-107.95 to 1.78	.06	43.0	<.00001
Hospital stay	7	1617	-4.51	-6.24 to -2.78	<.00001	147.59	<.00001
Days to solid diet	2	162	-11.82	-13.24 to -10.40	<.00001	2.16	.04
Overall morbidity	8	1659	0.73	0.51 to 1.04	.08	12.77	.08
Pancreatic fistula	7	1611	0.73	0.51 to 1.05	.09	5.88	.44
Intra-abdominal abscess	5	1179	0.88	0.56 to 1.38	.58	4.11	.39
Bile leakage	2	198	1.67	0.36 to 7.79	.52	2.01	.16
Mortality	2	184	2.05	0.37 to 11.56	.41	3.26	.42
HQ Studies							
DGE	13	2198	0.47	0.38 to 0.57	<.00001	85.91	<.00001
Operative time	10	1630	-12.47	-24.83 to -0.11	.05	50.39	<.00001
Blood loss	8	734	43.95	-26.93 to 114.83	.22	10.67	.15
Hospital stay	13	2198	-2.66	-4.63 to -0.70	.008	484.43	<.00001
Days to liquid diet	4	351	-1.12	-1.77 to -0.48	.0006	112.64	<.00001
Days to solid diet	7	697	-0.62	-0.79 to 0.44	<.00001	148.24	<.00001
Overall morbidity	13	2198	0.75	0.55 to 1.02	.01	25.26	.05
Pancreatic fistula	11	2004	0.86	0.65 to 1.14	.29	9.55	.48
Intra-abdominal abscess	10	1716	0.94	0.67 to 1.31	.70	9.88	.36
Bile leakage	7	730	1.21	0.59 to 2.48	.61	6.74	.35
Mortality	5	521	0.84	0.35 to 2.01	.69	1.61	.45
Sample size (≥ 30 in each group)							
DGE	9	2017	0.49	0.39 to 0.61	<.00001	59.56	<.00001
Operative time	6	1445	-22.48	-30.63 to -8.93	.001	28.99	<.00001
Blood loss	5	613	51.93	-20.73 to 124.58	.16	9.11	.06
Hospital stay	9	2017	-2.93	-5.12 to -0.74	.0009	390.94	<.00001
Days to solid diet	4	562	-1.11	-1.35 to -0.88	<.00001	105.43	<.00001
Days to liquid diet	3	316	-1.26	-1.95 to -0.57	.0001	111.58	<.00001
Overall morbidity	9	2017	0.78	0.58 to 1.05	.11	14.82	.06
Pancreatic fistula	8	1867	0.84	0.64 to 1.12	.24	8.86	.26
Intra-abdominal abscess	6	1535	1.0	0.70 to 1.43	.99	6.77	.24
Bile leakage	4	584	1.69	0.71 to 4.03	.24	5.02	.17
AC versus RC after PD							
DGE	6	1465	0.71	0.56 to 0.92	.008	9.08	.11
Operative time	5	1243	-32.92	-47.93 to -17.92	<.00001	22.25	<.00001
Blood loss	4	411	58.25	-20.98 to 137.49	.15	1.90	.59
Hospital stay	6	1465	-1.32	-2.70 to 0.06	.06	23.44	.0003
Days to solid diet	2	314	1.0	-1.23 to -0.76	<.00001	0.08	.78
Overall morbidity	6	1465	0.86	0.69 to 1.08	.20	5.06	.41
Pancreatic fistula	5	1419	0.76	0.56 to 1.05	.10	4.93	.29
Intra-abdominal abscess	6	1465	0.90	0.61 to 1.33	.60	7.18	.21
Bile leakage	4	514	1.35	0.59 to 3.13	.48	5.62	.13
Mortality	3	446	0.92	0.36 to 2.31	.85	1.25	.26
AC versus RC after PPPD							
DGE	9	805	0.15	0.10 to 0.23	<.00001	26.01	.0001
Operative time	7	461	11.99	2.45 to 21.53	.01	24.89	.0004
Blood loss	6	397	-65.64	-122.23 to -9.04	.02	40.44	<.00001

(continued)

Table 5
(continued).

Outcome of interest	Studies (n)	Patients (n)	OR/WMD	95% CI	P-values	Heterogeneity test	
						HG χ^2	P-values
Hospital stay	8	763	-4.62	-7.02 to -2.23	.0002	231.58	<.00001
Days to liquid diet	3	283	-2.30	-3.17 to -1.44	<.00001	96.93	<.00001
Days to solid diet	6	413	-0.39	-0.64 to -0.14	.002	264.22	<.00001
Overall morbidity	9	805	0.68	0.40 to 1.14	.14	18.57	.02
Pancreatic fistula	8	659	1.19	0.70 to 2.03	.52	2.71	.91
Intra-abdominal abscess	6	325	1.03	0.57 to 1.86	.92	2.55	.77
Bile leakage	4	260	0.69	0.19 to 2.45	.56	1.44	.70
ISGPS DGE Definition							
DGE	6	1530	0.75	0.55 to 1.02	.03	6.52	.26
Operative time	5	1208	-33.75	-48.76 to -18.74	<.00001	20.70	.00001
Blood loss	4	476	47.47	-38.51 to -133.45	.28	1.56	.67
Hospital stay	6	1530	-1.36	-2.95 to 0.22	.09	23.40	.0003
Days to liquid diet	2	184	0.18	-0.56 to 0.93	.03	0.15	.70
Days to solid diet	3	430	-0.99	-1.23 to -0.76	<.00001	0.22	.90
Overall morbidity	6	1530	0.87	0.70 to 1.09	.22	5.51	.36
Pancreatic fistula	5	1384	0.83	0.56 to 1.25	.37	6.10	.19
Intra-abdominal abscess	6	1530	0.89	0.62 to 1.29	.54	4.59	.47
Bile leakage	5	630	1.44	0.64 to 3.22	.38	5.91	.21

AC=antecolic, CI=confidence interval, DGE=delayed gastric emptying, HG=heterogeneity between studies, HQ=high quality, OR=odds ratio, PD=pancreaticoduodenectomy, PPPD=pylorus-preserving PD, RC=retrocolic, RCTs=randomized controlled trials, RSCSs=retrospective comparative studies, WMD=weighted mean difference.

in present study, but the sample size was still too small to allow firm conclusions. In future, it is necessary to conduct randomized trials using standardized unbiased methods and well-matched controls.

5. Conclusion

This is the very first and largest meta-analysis including RCTs and RSCSs comparing the incidence of DGE and other perioperative outcomes between AC and RC route of GJ after PD or DJ after PPPD. In this meta-analysis, AC route of GJ or DJ reconstruction shows a significantly lower incidence of DGE compared to the RC technique. Further prospective controlled studies are needed for a more comprehensive study between the 2 procedures in future.

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Writing – original draft: Jian Qiu, Ming Li.
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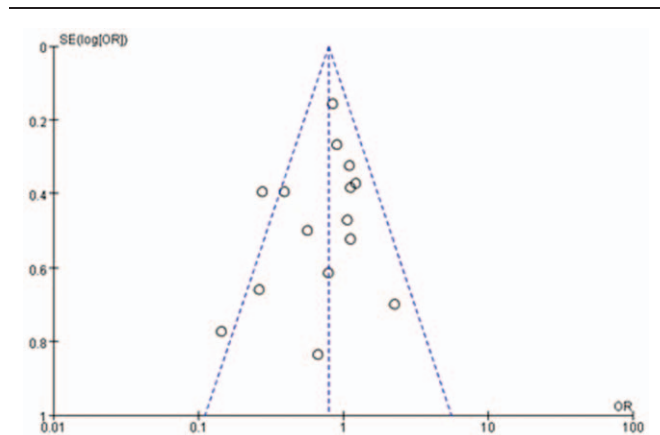


Figure 8. Funnel plot of the incidence of delayed gastric emptying in included studies, showing no publication bias. OR = odds ratio, SE = standard error.

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