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Original Article

No increase in delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy: a meta-analysis of RCTs

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Abstract: Background: The aim of the current meta-analysis was to evaluate the efficacy and safety of pylorus-preserving pancreaticoduodenectomy (PPPD) and pylorus-resecting pancreaticoduodenectomy (PRPD) in cases of periampullary and pancreatic carcinoma, providing updated evidence to clarify which method might be more effective. Methods: A systematic search of literature databases (Cochrane Library, PubMed, Web of Science, and EMBASE) was performed to identify eligible randomized controlled trials (RCTs). Risk of bias summaries, assessing risk of bias, were utilized to evaluate the quality of included studies. Outcome measures for comparisons of PPPD and PRPD for periampullary and pancreatic carcinomas were survival, mortality, morbidity (including overall morbidity, DGE, pancreatic fistulas, wound infections, postoperative bleeding, biliary leakage, and ascites), and operation-related events (hospital stays, operating time, intraoperative blood loss, and reoperation). Results: Eleven randomized controlled trials (RCTs), including 930 patients, were identified and included in the present analysis. Of these RCTs, PRPD was described as conventional pancreatoduodenectomy (CPD) in 8 cases and PRPD was described as subtotal stomach-preserving pancreatoduodenectomy (SSPPD) in 3 cases. No significant differences were found in mortality, postoperative morbidity (overall morbidity, pancreatic fistula, wound infection, postoperative bleeding, biliary leakage, and ascites), operation-related events (hospital stays, operating time, intraoperative blood loss, and reoperation), survival, and hospital stays between the two groups. There was a lower rate of DGE with PRPD than with PPPD (RR=1.73, P=0.04, 95% CI, 1.03-2.92). Further subgroup analysis revealed a comparably lower DGE rate in CPD and SSPPD groups than in the PPPD group. However, operating times for PPPDs were shorter than those for PRPDs (WMD=33.99 minutes, P=0.008, 95% CI, 8.73-59.25). Moreover, there was less estimated intraoperative blood loss (MD=240 mL, P=0.03, 95% CI, 20-460). Conclusion: The current study found that the rate of DGE in the PRPD group was lower than that in the PPPD group. PPPD was comparable with PRPD, according to subgroup analysis of DGE, but obvious advantages in operating times and intraoperative blood loss were found in PPPD. Results suggest that PPPD may be a better treatment for periampullary and pancreatic carcinomas. However, due to limited available data, present conclusions should be confirmed by future high-quality RCTs of complex surgical interventions.

Keywords: Pancreaticoduodenectomy, pylorus, periampullary carcinoma, pancreatic carcinoma, meta-analysis

Introduction

Pancreatic carcinoma is an aggressive malignancy, resulting in a poor prognosis. This is reflected by a 5-year survival <6% and a median survival of <6 months [1, 2]. At present, surgical resection is the best method of treatment for periampullary and pancreatic carcinomas. However, high rates of postoperative complications remain significant causes of mortality and significantly prolonged hospitalizations [3].

Pancreatoduodenectomy (PD) is the standard treatment for benign and malignant tumors of the pancreatic head and chronic pancreatitis in this region [4]. Pylorus-resecting PD (PRPD), conventional PD with resection of the distal stomach, modified in the 1970 s by Traverso and Longmire, introduced preservation of the pylorus [5]. Several randomized controlled trials (RCTs), along with associated meta-analyses, have shown that PRPD and pylorus-preserving pancreaticoduodenectomy (PPPD) are equally

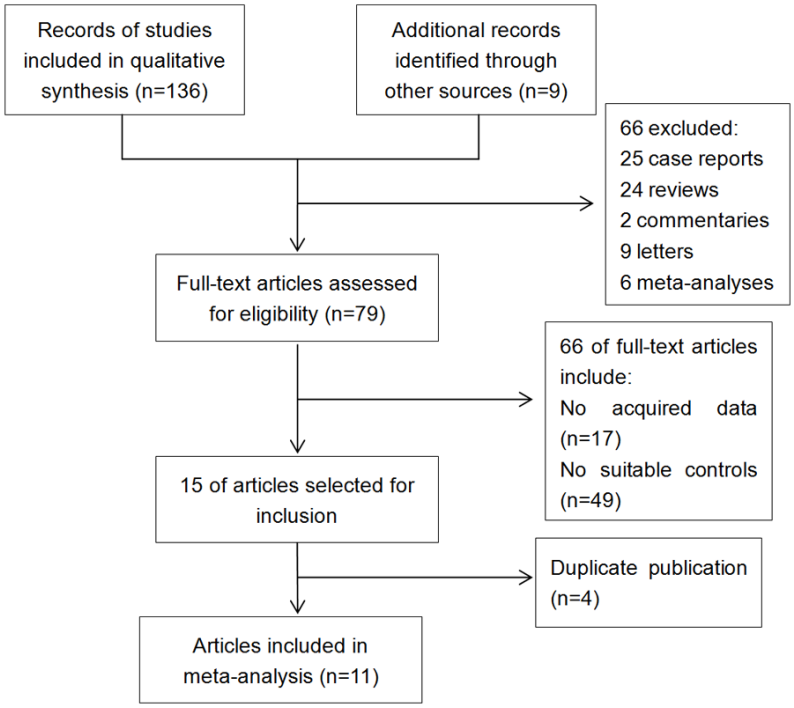

Figure 1. Flow diagram of the selection and screening process for eligible studies.

effective in terms of morbidity, mortality, quality of life (QOL), and survival. However, times of operation and degrees of blood loss were significantly lower for PPPD than for PRPD [6-8]. However, PPPD has been associated with a higher incidence of DGE, with rates ranging from 33% to 44%, compared with PRPD [9]. Recently published randomized controlled trials (RCTs) have revealed that pylorus resections during PD did not reduce incidence or severity of DGE [10]. However, comments concerning DGE remain controversial.

The aim of the current meta-analysis was to evaluate the efficacy and safety of PPPD and PRPD in cases of periampullary and pancreatic carcinomas, providing updated evidence to clarify which procedure might be more effective.

Methods and materials

Systematic literature search

A systematic literature search was performed using Cochrane Library, PubMed, Web of Science, and EMBASE databases, aiming to identify relevant articles published before October 1, 2017. No date or specific language limits were applied. MeSH headings and keywords, including Whipple operation, pylorus, pancreaticoduodenectomy, pylorus-preserving, and pancreatic/periampullary tumor, were used to identify as many articles as possible. The search strategy also included text terms, such as Whipple procedure, standard pancreaticoduodenectomy, classic duodenopancreatectomy, duodenopancreatectomy, and pylorus preserving pancreaticoduodenectomy, to identify relevant information. Boolean operators (AND, OR, NOT) were used to combine or exclude search terms. The search was limited, initially, to publications concerning human RCTs. References of included studies and related publications were screened. Results were handled manually for eligible trials. Investigators and experts in the field of pancreatic surgery were contacted to ensure that all relevant studies were identified.

Selection and exclusion criteria

This study included all human RCTs in which the relative effects of pancreatic or periampullary cancer, in patients undergoing PPPD or PRPD, were evaluated. Only RCTs reporting quantitative data for at least one of the following outcomes were selected for data extraction: survival, mortality, morbidity (including overall morbidity, DGE, pancreatic fistulas, wound infections, postoperative bleeding, biliary leakage, and ascites), and operation-related events (hospital stays, operating time, intraoperative blood loss, and reoperation). The following were excluded: a) Papers lacking a control group; b) Studies of an original paper published, such as conference abstracts and letters to the editor; and c) Duplicate publications. The search of related studies (inclusion or exclusion) was carried out by two authors (WTL and XYL). In cases of uncertainty or disagreements, a third author was consulted (CY).

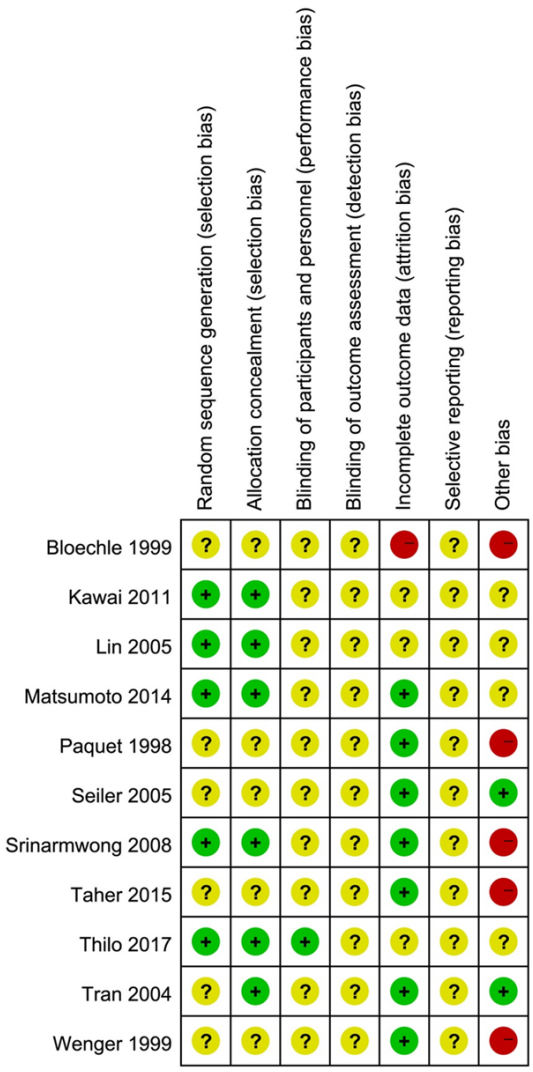

Figure 2. Risk of bias summary.

Data extraction and quality assessment

Only RCTs reporting quantitative data on long term survival, postoperative mortality, morbidity, and operation-related events were selected for data extraction. Two authors (WTL and XYL), independently, extracted data from the trials, comparing and analyzing results. Any discrepancies between the authors were resolved by consensus. All data were evaluated for internal consistency and disagreements were resolved via a discussion with a third author (CY). The modified Jadad score was used to evaluate the quality of included trials [11]. Two independent reviewers (Youfeng Zhu and Haiyan Yin) assessed bias of the included studies, according to methods described in the Cochrane Handbook for Systematic Reviews of Interventions [12]. The following parameters were assessed: random sequence generation, blinding of participants and personnel, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. According to the Cochrane Handbook, other sources of bias included a risk of bias related to the specific trial design used or early termination of the study due to an extreme baseline imbalance in selected patients.

Statistical analysis

Eleven studies were included for data extraction. Cochrane Collaboration's Review Manager Software 5.3 (RevMan 5.3) was used to perform the meta-analysis. Risk ratios (RR) and 95% confidence intervals (CI) were calculated to describe results. I^2 and *P*-values were used to explore heterogeneity. If I^2<50% or *P*<0.10, the RRs were pooled using a fixed-effects model. Otherwise, a random-effects model was considered. *P*-values less than 0.05 indicate significance. Continuous data reported as medians and ranges were converted to means and standard deviation, using the method of Hozo [13]. For continuous outcomes, data was pooled using the mean difference (MD). Long-term survival rates were generated by extracting events and calculating logarithmic hazard ratios (6 standard error), using corresponding *p*-values (log-rank test) [14]. A funnel plot (**Figure 10**) displays present results and publication bias.

Results

Characteristics of selected studies

Results of the literature search are depicted in **Figure 1**. The initial search strategy yielded a total of 145 potentially relevant clinical studies. First, reviews, case reports, commentaries, letters, and meta-analyses were excluded. Second, articles in which the effects between PRPD and PPPD were not directly compared or with no data were also excluded. Of the 15 studies left, 4 articles [15-18] were excluded because of duplicate publication. Therefore, 11 RCTs [6, 7, 10, 19-26] were available for the current analysis. Random sequence generation, blinding of participants and personnel, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective out-

Table 1. Characteristics of included trials

Study	Year	Country	Intervention	n	Age: range (years)	Sex ratio (M/F)
Paquet [26] et al.	1998	German	PPPD	17	NA	NA
			CPD	23	NA	NA
Bloechle [25] et al.	1999	German	PPPD	23	69: (47-76)	14/9
			CPD	21	67: (43-78)	13/8
Wenger [22] et al.	1999	German	PPPD	24	61.2: (54-68.4)	12/12
			CPD	24	61.6: (52.7-70.5)	12/12
Lin [23] et al.	2005	Taiwan, China	PPPD	14	64.5: (48-77)	10/4
			CPD	19	66.7: (46-84)	13/6
Seiler [7] et al.	2005	Switzerland	PPPD	64	65.4: (26-83)	36/28
			CPD	66	65.4: (33-86)	33/33
Tran [6] et al.	2004	Netherlands	PPPD	87	64: (43-78)	50/37
			CPD	83	62: (27-78)	58/25
Srinarmwong [24] et al.	2008	Thailand	PPPD	14	61.8: (51-74)	10/4
			CPD	13	63.3: (52-72)	8/5
Kawai [20] et al.	2011	Japan	PPPD	64	68: (59-77)	33/31
			SSPPD	66	67: (58-76)	38/28
Matsumoto [19] et al.	2014	Japan	PPPD	50	66: (56-76)	29/21
			SSPPD	50	67: (58-76)	35/15
Taher [21] et al.	2015	Bangladesh	PPPD	12	50.3: (39.7-60.9)	NA
			CPD	8	44: (33.1-54.9)	NA
Hackert [10] et al.	2017	German	PPPD	95	62.9: (51.8-74.0)	55/40
			SSPPD	93	63.8: (52.3-75.3)	49/44

NA: non-acquired data.

come reporting are listed in **Figure 2**. This meta-analysis fully complied with the PRISMA statement for systematic reviews and meta-analyses.

Characteristics of included trials are listed in **Table 1**. Publication years of these RCTs ranged from 1998 to 2017. Of these 11 RCTs, 8 RCTs described PRPD as CPD [6, 7, 21-26], while 3 RCTs described PRPD as SSPPD [10, 19, 20]. A total of 930 patients, including 464 in the PPPD group and 466 in the PRPD group, were identified and included for analysis.

Clinical outcomes

Mortality and morbidity: In the included 11 trials, there were 10 RCTs [6, 7, 10, 19-21, 23-26] reporting the mortality of a total of 882 patients. No heterogeneity was identified among these studies concerning mortality (**Figure 3**, P=0.85, I^2=0%). Based on a fixed-effects model, the Mantel-Haenszel pooled relative RR for PPPD versus PRPD was 0.73 (95% CI, 0.37-1.43) (**Figure 3**). Therefore, there were no significant differences in mortality.

Based on a fixed-effects model, no significant differences in risks of overall morbidity, pancreatic fistula, wound infections, postoperative bleeding, biliary leakage, and ascites were found between PRPD and PPPD groups. However, confidence intervals for these outcomes were relatively wide (**Figure 3**). Based on the high substantial heterogeneity present in DGE (I^2=67%, P=0.001), a random-effects model was adopted for analysis. Results indicated a lower DGE rate in the PRPD group (**Figure 4**, RR=1.73, P=0.04, 95% CI, 1.03-2.92).

Survival

There were 5 RCTs reporting survival analysis [6, 7, 23, 24, 26]. Heterogeneity between these studies was low (I^2=14%). Based on a fixed-effects model, the Inverse Variance pooled relative HR for PPPD versus PRPD was 0.82 (95% CI, 0.63-1.06; P=0.13). Meta-analysis revealed no differences in survival between PPPD and PRPD groups (**Figure 5**).

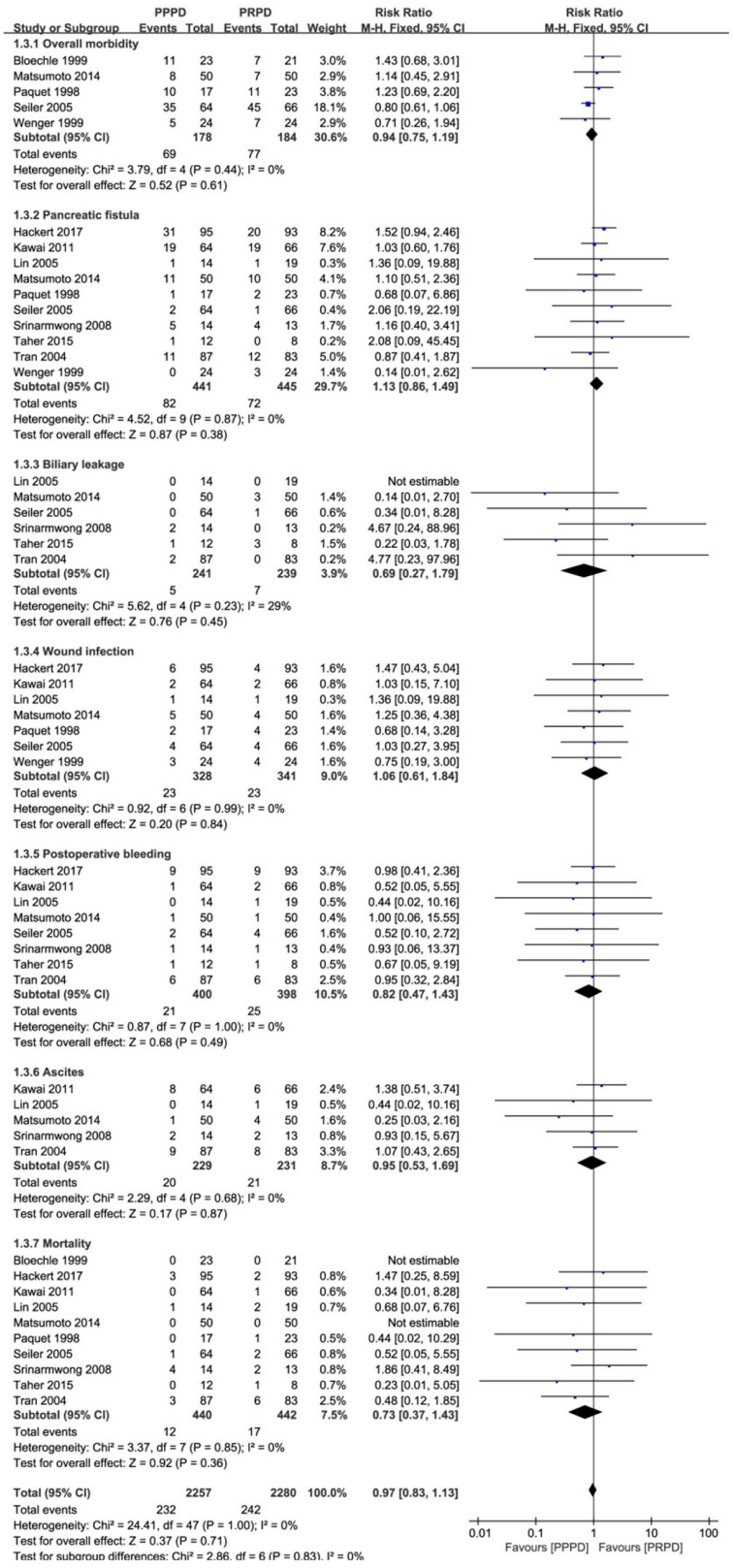

Figure 3. Forest plot of mortality and morbidity: Forest plot of risk ratio (RR) for morbidity including the rates of overall morbidity, pancreatic fistula, wound infection, postoperative bleeding, biliary leakage, and ascites, based on a fixed-effects model.

Operation-related events

The current study calculated the MD for operating times, intraoperative blood loss, and hospital stays from these RCTs. In the included 8 RCTs that reported operating times, operating times for PPPDs were shorter than those for PRPDs, with an MD of 33.99 minutes (**Figure 6**, P=0.008, 95% CI, 8.73-59.25). Similarly, there was less estimated intraoperative blood loss (**Figure 7**, MD=240 mL, P=0.03, 95% CI, 20-460). No differences were found in hospital stays between PPPD and PRPD groups, with an MD of 0.78 days (**Figure 8**, P=0.32, 95% CI, 0.77-2.32).

There were 5 RCTs [6, 7, 10, 20, 21] that reported reoperations. No heterogeneity was identified among these studies concerning reoperations (**Figure 8**, P=0.72, I^2=0%). Based on a random-effects model, the Mantel-Haenszel pooled relative RR for PPPD versus PRPD was 0.99 (95% CI, 0.61-1.59). (**Figure 9**). Therefore, there were no significant differences in reoperations.

Discussion

Pancreaticoduodenectomy (PD) is a standard procedure performed to achieve complete removal of peri-pancreatic head malignancies with surrounding tissues. However, pancreatic carcinoma is one of the most fatal malignant tumors, with poor prognosis. With the development of perioperative management and operative techniques in recent years, postoperative 30-day mortality after PPPD and PRPD has decreased to <4%, but morbidity remains high [10]. De-

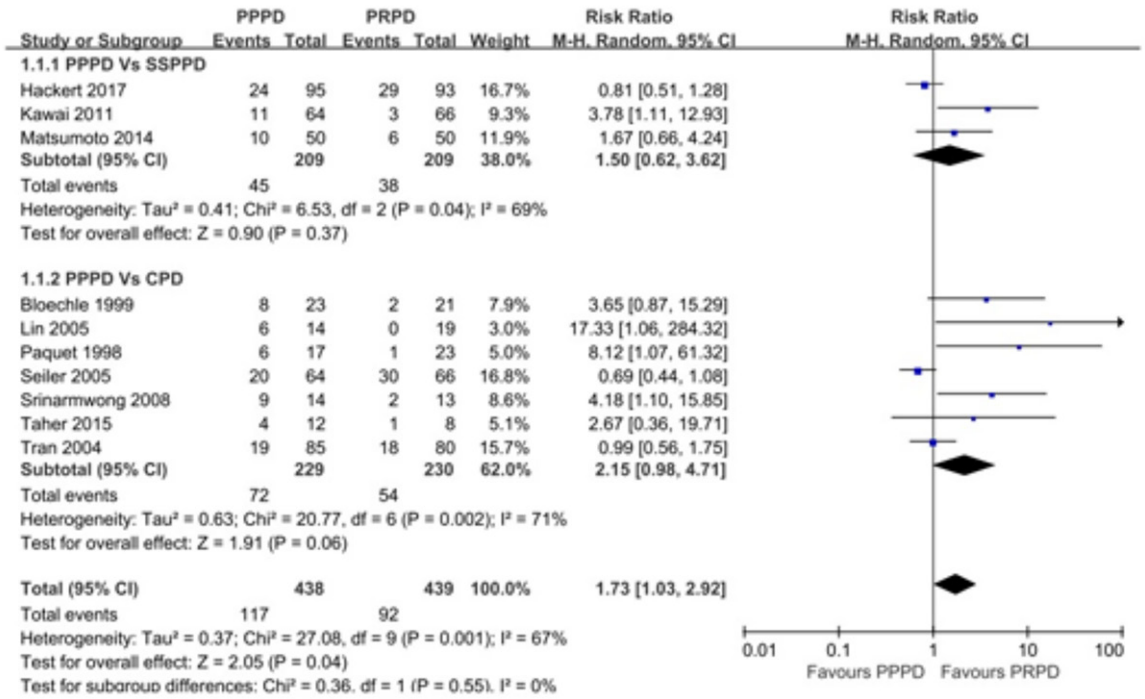

Figure 4. Forest plot of risk ratio (RR) for DGE rate of the subgroup of PRPD (CPD versus PPPD and SSPPD versus PPPD, respectively), based on a random-effects model.

termination of which procedure is better, PPPD or PRPD, remains controversial.

Delayed gastric emptying is one of the most common postoperative complications after PD. However, the exact pathological mechanisms of DGE after PD remain unclear and may be multifactorial [27]. First, DGE may occur due to mechanical problems, such as transient torsion or angulations of the anastomotic intestine, which can be improved by various types of intestinal reconstruction [28]. Position of duodenojejunostomy, as an antecolic or retrocolic route, may also be a cause of DGE [29]. Tani et al. reported that PPPD with antecolic duodenojejunostomy is a safer operation [30]. There are several RCTs reporting that antecolic reconstruction after PPPD does not decrease incidence of DGE [31-33]. However, Khan et al. reported that delayed gastric emptying rates in flange gastrojejunostomy (FL-GE) and non-FL-GE were 9% and 23%, respectively (P=0.012). However, the flange technique has been associated with a marked reduction in incidence of DGE after PD [34]. Therefore, the flange technique should be widely used in clinical for DGE prevention after PD. Second, postoperative gastroparesis may cause transient interruption of gastric output, leading to DGE [35]. Postoperative DGE can be treated conservatively. Intravenous erythromycin is the only pharmacologic intervention to reduce incidence of DGE after PPPD [36]. However, the motilin agonist is not widely used prophylactically, because of restricted hospital formularies and a lack of its availability, intravenously. Moreover, preservation of right gastric arteries and vagus nerves, during surgery, has been associated with decreased incidence of DGE [37]. Otherwise, higher BMI, indigestion, and intraabdominal major complications are known significant risk factors for DGE [10].

Differences between CPD and SSPPD include the stomach resection margin. The SSPPD stomach was divided 3 cm above the pylorus ring at the pyloric region of the stomach. The pylorus ring was resected with the preservation of more than 95% of the stomach [10, 19, 20]. Although SSPPD has the advantage of preserving innervation and vascularity to the prepyloric area, compared with CPD, differences between CPD and SSPPD remain controversial. In addition, Oida et al. reported that morbidity rates for PPPD and SSPPD were similar but DGE rates were higher in the PPPD group [38].

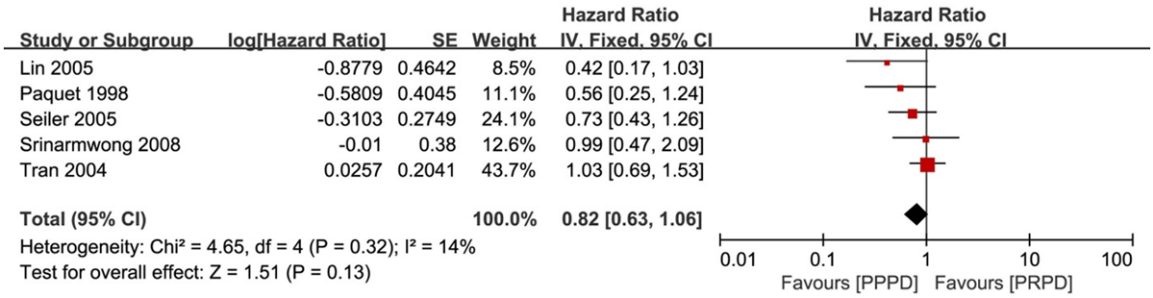

Figure 5. Forest plot of hazard ratio (HR) for survival based on a fixed-effects model.

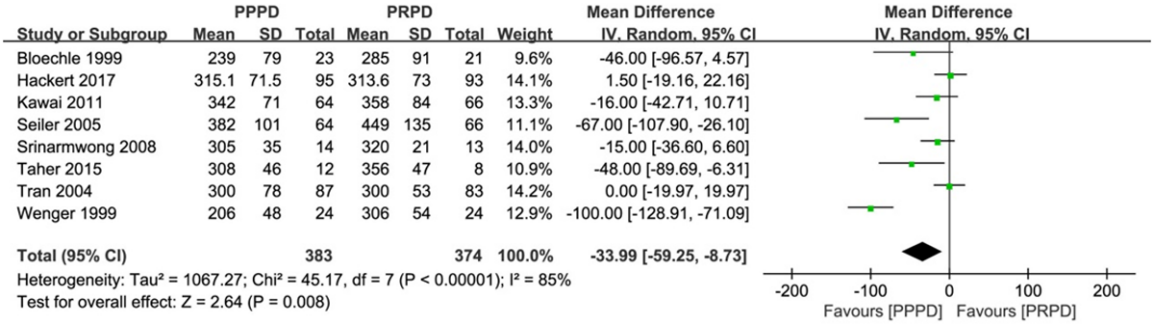

Figure 6. Forest plot of mean difference (MD) for operating times based on a random-effects model.

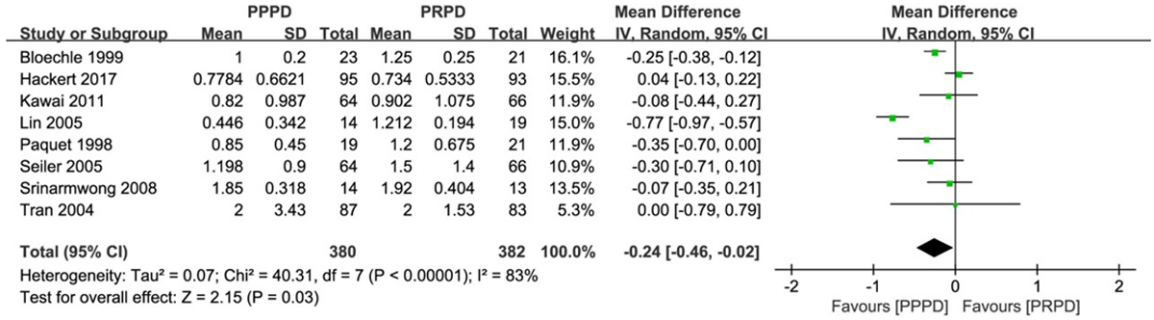

Figure 7. Forest plot of mean difference (MD) for intraoperative blood loss based on a random-effects model.

However, a recently published report on RCTs showed that pylorus resection during PD did not reduce incidence or severity of DGE, compared with PPPD [10], differing from a previous RCT and meta-analysis report on pancreatic head and periampullary carcinomas [20, 39, 40]. However, a retrospective study revealed little significance in preservation of the pyloric ring without vagal innervation but showed better perioperative and long-term outcomes in SSPPD, suggesting that SSPPD is more suitable as a standard procedure for patients with pancreatic head cancer [41]. As a result, the current study initiated subgroup analysis to compare differences in DGE rates between PPPD and CPD or between PPPD and SSPPD. Primary results revealed higher DGE rates in the PPPD group than in the PRPD group (RR=1.73, P=0.04, 95% CI, 1.03-2.92). However, further subgroup analysis indicated no significant differences in DGE rates (P=0.55) between CPD and SSPPD groups, based on a random-effects model, but there was high heterogenicity (I^2=67%). Subgroup analysis results also revealed comparable DGE rates between the PRPD [(CPD group (RR=2.15, P=0.06, 95% CI, 0.98-4.71), SSPPD (RR=1.50, P=0.37, 95% CI, 0.62-3.62)], and PPPD groups, suggesting that differences between primary and subgroup analysis results were not contradictory.

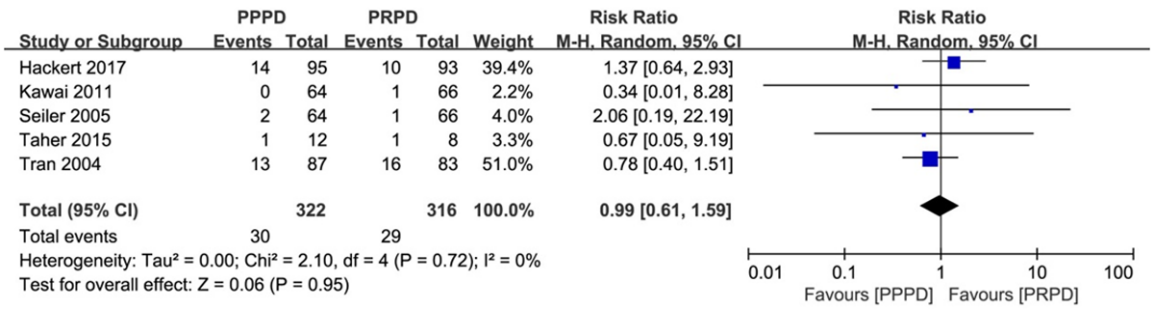

Figure 8. Forest plot of risk ratio (RR) for reoperation based on a random-effects model.

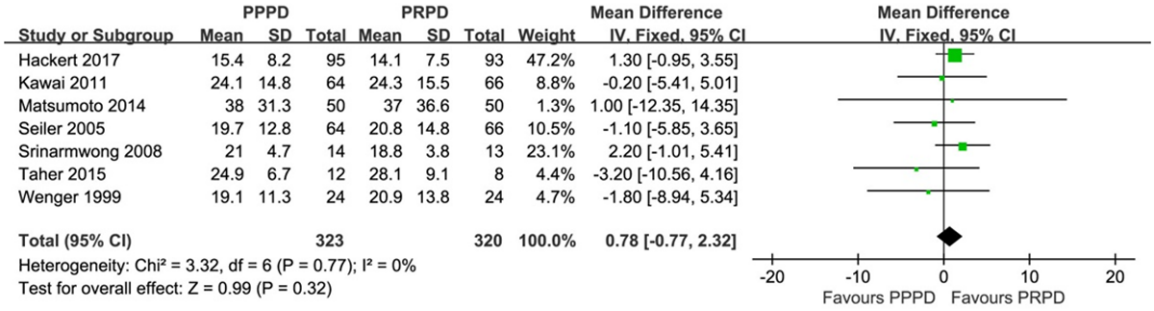

Figure 9. Forest plot of mean difference (MD) for hospital stay based on a random-effects model.

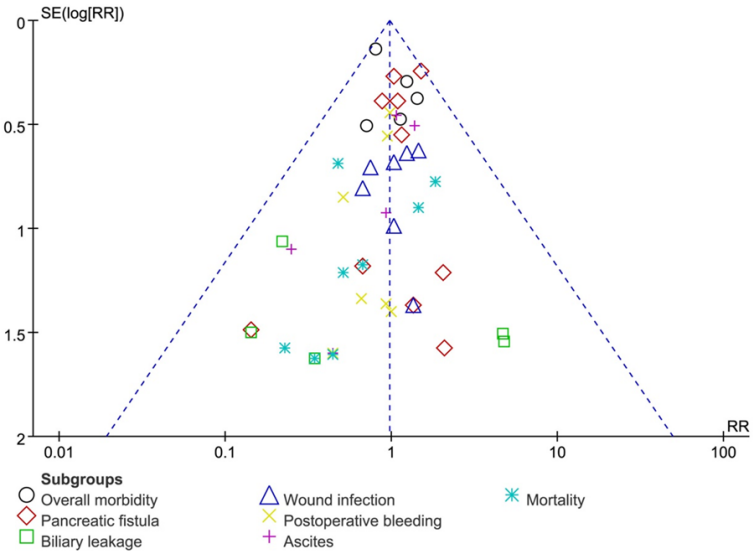

Figure 10. Funnel plot of overall morbidity, pancreatic fistula, wound infection, postoperative bleeding, biliary leakage, mortality, and ascites.

Further evaluations of RCTs, however, are necessary. The current meta-analysis indicated no differences in mortality, other morbidity, survival, reoperation, and hospital stays between the two procedures. However, the PPPD procedure provided a significant benefit in terms of intra-operative blood loss and operating times, compared with PRPD. Therefore, PPPD may be the better procedure for pancreatic head and periampullary carcinomas.

There were limitations to the present study. First, the was bias in the heterogenicity of surgical procedures. In 8 papers, PRPD was described as CPD [6, 7, 21-26], while the other 3 papers described it as SSPPD [10, 19, 20]. However, subgroup analysis revealed no differences in DGE rates between CPD and SSPPD. Thus, future studies should focus on subgroup analysis. Second, the heterogeneous definitions of DGE and pancreatic fistula may have contributed to potential bias of results. Most studies described the standardized definition of DGE, with 3 grades of severity based on International Study Group of Pancreatic Surgery (ISGPS) [42]. However, Tran et al. defined DGE as gastric stasis, requiring

nasogastric intubation for 10 days or more or the inability to tolerate a regular diet on the 14th postoperative day [6]. This difference may affected present conclusions. Third, there were other limiting factors, including unpublished studies, possible publication bias, and adjuvant treatment.

Conclusion

PPPD is comparable with PRPD in survival, mortality, hospital stays, reoperation, and postoperative morbidity. The current study indicated no significant differences in DGE, according to subgroup analysis, between PRPD and PPPD groups. PPPD has obvious advantages in operating times and intraoperative blood loss. Therefore, results suggest that the PPPD procedure may be the better treatment for periampullary and pancreatic carcinomas. However, due to limited available data, present conclusions should be confirmed by future high-quality RCTs of complex surgical interventions.

Disclosure of conflict of interest

None.

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