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REVIEW

Total pancreatectomy compared with pancreaticoduodenectomy: a systematic review and meta-analysis

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Aim: To assess whether total pancreatectomy (TP) is as feasible, safe, and efficacious as pancreaticoduodenectomy (PD).

Materials and Methods: Major databases, including PubMed, EMBASE, Science Citation Index Expanded, Scopus and the Cochrane Library, were searched for studies comparing TP and PD between January 1943 and June 2018. The meta-analysis only included studies that were conducted after 2000. The primary outcomes were morbidity and mortality. Pooled odds ratios (ORs), weighted mean differences (WMDs) or hazard ratios (HRs) with 95 percent confidence intervals (CIs) were calculated using fixed effects or random effects models. The methodological quality of the included studies was evaluated by the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.

Results: In total, 45 studies were included in this systematic review, and 5 non-randomized comparative studies with 786 patients (TP: 270, PD: 516) were included in the meta-analysis. There were no differences in terms of mortality (OR: 1.44, 95% CI: 0.66–3.16; *P*=0.36), hospital stay (WMD: −0.60, 95% CI: −1.78–0.59; *P*=0.32) and rates of reoperation (OR: 1.12; 95% CI: 0.55–2.31; *P*=0.75) between the two groups. In addition, morbidity was not significantly different between the two groups (OR: 1.41, 95% CI: 1.01–1.97; *P*=0.05); however, the results showed that the TP group tended to have more complications than the PD group. Furthermore, the operation time (WMD: 29.56, 95% CI: 8.23–50.89; *P*=0.007) was longer in the TP group. Blood loss (WMD: 339.96, 95% CI: 117.74–562.18; *P*=0.003) and blood transfusion (OR: 4.86, 95% CI: 1.93–12.29; *P*=0.0008) were more common in the TP group than in the PD group. There were no differences in the long-term survival rates between the two groups.

Conclusion: This systematic review and meta-analysis suggested that TP may not be as feasible and safe as PD. However, TP and PD may have the same efficacy.

Keywords: total pancreatectomy, pancreaticoduodenectomy, morbidity, mortality, meta-analysis

Introduction

Surgical resection plays an essential role in patients with periampullary disease. At present, two surgical methods to treat periampullary disease, total pancreatectomy (TP) and pancreaticoduodenectomy (PD), have been reported. TP was reported for the first time in 1943.[1] At that time, it was performed to avoid pancreaticojejunostomy-associated complications and to attempt to improve the long-term survival for patients with pancreatic cancer.[2–5] However, some studies suggested that TP was

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related to increasing morbidity and mortality.[6–10] Furthermore, the survival of patients with pancreatic cancer was not shown to improve after TP in several studies.[11–13] It is important to note that TP also leads to permanent insufficiency of pancreatic endocrine and exocrine function, impacting long-term quality of life.[14–18] Fortunately, as a result of the appearance of advanced postoperative management in recent decades, including better pancreatic enzyme formulas and insulin therapy, we are able to more effectively manage the endocrine and exocrine consequences of TP.[18,19] Nevertheless, TP was not recommended as routine treatment for patients with pancreatic cancer, especially those with pancreatic ductal adenocarcinoma (PDAC).[20]

Currently, no randomized controlled trials (RCTs) have been reported for comparison between these two approaches. Nevertheless, a large number of retrospective comparative studies have been reported. To address this issue, we conducted the most comprehensive systematic review and meta-analysis to our knowledge to assess the quality of individual studies and to produce the most rigorous analysis evaluating whether TP can be considered to be as feasible, safe, and efficacious as PD.

Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were used as guidelines in the construction of the meta-analysis.[21]

Literature search

We performed a systematic literature search in PubMed, EMBASE, Science Citation Index Expanded, Scopus and the Cochrane Library from January 1943 to June 2018, using combinations of the following terms: "Total pancreatectomy", "Total pancreatic resection", "Pancreatectomy", "Pancreaticoduodenectomy", "Whipple", "Pancreatic head resection", "Duodenopancreatectomy" and "Subtotal pancreatectomy. In addition, the references of all selected articles were screened for any potential eligible studies.

Study selection

Studies were included based on the following criteria: (1) human study; (2) primary outcome was reported; (3) if studies were reported by the same institution, either the study with the larger sample size or the study with the higher quality was included; And (4) meta-analysis only include studies with a study period after 2000.

The following types of studies were excluded: abstracts, letters, editorials, expert opinions, case reports, reviews and studies without comparisons.

Data extraction

Each study was evaluated by two independent reviewers for inclusion or exclusion. Disagreements between the reviewers were resolved by consultation with a third reviewer when necessary. Data were collected by two independent researchers using standardized forms. Study characteristics, quality assessment, intraoperative and postoperative outcomes were included. Means were used for meta-analysis unless otherwise mentioned. If the mean was not reported by the author, the means or standard deviations were calculated as medians or ranges, respectively.[22] The following data were extracted from each study: author, year, country, study period, study design, number of patients, age, gender, tumor size, mortality, morbidity, operation time, blood loss, blood transfusion, hospital stay, reoperation and long term survival including 3-year overall survival (3-OS) and 5-year overall survival (5-OS).

Qualitative assessment

The risk of bias in the included non-randomized studies were evaluated using a tool for assessing Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I).[23]

Outcomes of interest and definitions

The primary outcomes were mortality and morbidity. Mortality was defined as the number of deaths during hospitalization or within 30 days after surgery. Morbidity was defined as any complication following surgery up to the day of discharge or within 30 days of discharge.

The secondary outcomes included operation time, blood loss, blood transfusion, reoperation, hospital stay and long-term survival reported in the individual papers. Hospital stay was defined as the length of time from postsurgery to discharge from the hospital. 3-OS was defined as the number of surviving patients three years after surgery. 5-OS was defined as the number of surviving patients five years after surgery. 3-OS and 5-OS were calculated for patients with PDAC.

Statistical analysis

Meta-analysis was performed using Review Manager Version 5.3 software (The Cochrane Collaboration, Oxford, UK). For continuous and categorical variables,

treatment effects were expressed as weighted mean differences (WMDs) and odds ratios (ORs) or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). For survival analysis, the data were extracted from the survival curves by referring to a method reported in a previous study, and HR was used for quantitative analysis.[24] A Chi-square test was used to assess heterogeneity with a $P<0.1$ considered significant. I^2 values were used for the evaluation of statistical heterogeneity: an I^2 value of 50% or more was indicative of the presence of heterogeneity.[25] A fixed effects model was initially used for all outcomes, while a random effects model was used if the test suggested rejection of the assumption of homogeneity.[26] Descriptive methods were used if the data were inappropriate for meta-analysis. Sensitivity analyses were conducted to explore possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall pooled estimate. Funnel plots were constructed to evaluate potential publication bias based on mortality and morbidity.[27]

Results

Results of the literature review

A flow diagram of the study is shown in Figure 1. In total, 45 studies were included in the systematic review that reported the morbidity or mortality for TP (Appendix Table).[5,9,12,13,18,28–66] A total of 15 studies focused on pancreatic cancer,[9,12,13,19,28,29,34,35,43,45–47,49,51,53] 16 studies focused on malignant and benign pancreatic disease,[18,32,36,48,50,52,54–61,63,64] 10 studies reported on PDAC,[30–33,40–42,62,65,66] and 4 studies[37–39,44] focused on

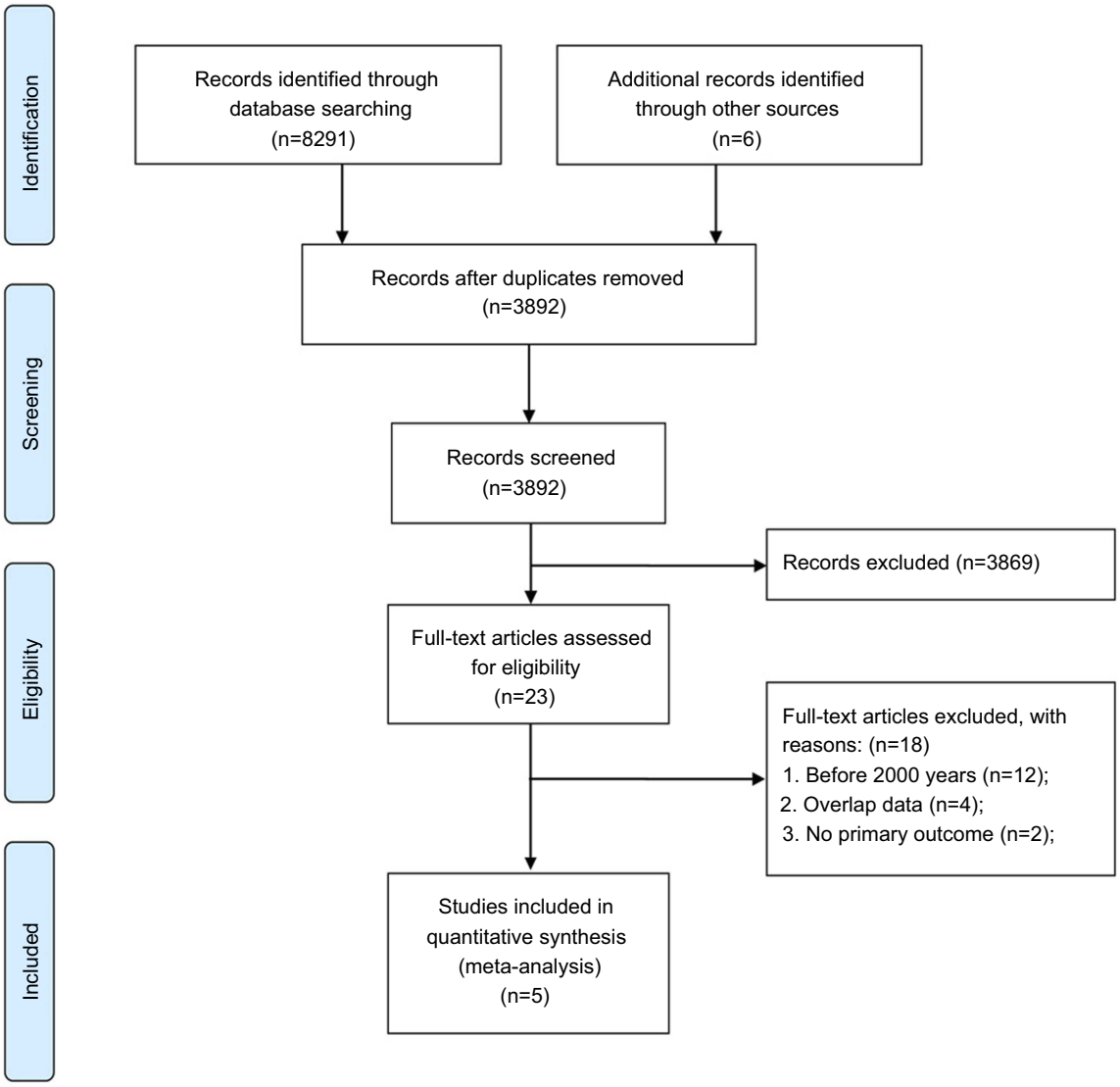

Figure 1 Study selection flow chart according to PRISMA statement.

benign disease. In studies focusing on pancreatic cancer, the morbidity of TP ranged from 36.2% to 75.0% and mortality ranged from 4.0% to 26.9%. 3-OS ranged from 4.5% to 36.6%, and 5-OS ranged from 4.5% to 18.5% in studies reporting on pancreatic cancer. In studies focusing on PDAC, the morbidity from TP ranged from 27.0% to 53.0%, and mortality ranged from 0% to 26.0%. 3-OS ranged from 9% to 38.0%, and 5-OS ranged from 2.3% to 18.8%.

A total of 23 comparative studies were included,[9,18,19,30–32,34,36,39,42,43,45,46,48–50,53,58–60,62,64,65] however, two studies[9,19] came from Johns Hopkins Hospital. One study was excluded because it included less relevant outcomes.[9] Two studies both came from Columbia University.[32,34] One study was excluded because it included less relevant outcomes.[32] Moreover, one study was based on the National Surgical Quality Improvement Project database,[58] and another study was based on the Nationwide Inpatient Sample database;[50] both were excluded because of overlap with other studies. Two studies were excluded because of the absence of a primary outcome.[49,53] Twelve studies were excluded because of the study duration before 2000.[19,30,31,34,36,39,42,43,45,46,48,59] Finally, 5 studies were included in the meta-analysis.[18,60,62,64,65] The study characteristics are shown in Table 1. In total, 786 patients were included, of whom 270 patients were in the TP group, and 516 patients were in the PD group. These studies came from Germany,[18] Australia,[60] Japan,[62] Italy,[64] and China.[65] A total of three studies were retrospective comparative studies,[60,62,65] and two studies[18,64] were prospective comparative studies. Three studies used matched design.[18,64,65]

Study characteristics

The intraoperative and postoperative outcomes are shown in Table 2. The results of the meta-analysis are shown in Figures 2 and 3.

Quality of studies

The methodological quality of the included studies was evaluated by ROBINS-I (Table 3). Based on ROBINS-I, three studies were graded as low-risk,[18,64,65] and two studies[62,64] were graded as moderate-risk.

Results of meta-analysis

Primary outcome

Mortality was reported in five studies. There were no differences between the TP group and the PD group (OR: 1.44, 95%CI: 0.66–3.16; P=0.36). In total, five studies showed that there was no significant difference in morbidity (OR: 1.41, 95%CI: 1.01–1.97; P=0.05), and the results showed that the TP group tended to have more complications than the PD group.

Secondary outcomes

A longer operation time (WMD: 29.56, 95%CI: 8.23–50.89; P=0.007) and more blood loss (WMD: 339.96, 95%CI: 117.74–562.18; P=0.003) were found in the TP group than in the PD group. Blood transfusion (OR: 3.37, 95%CI: 1.25–9.12; P=0.02) in the TP group was also significantly more commom than in the PD group. However, there were no differences in hospital stay (WMD: −0.60, 95%CI: −1.78–0.59; P=0.32) and reoperation (OR: 1.12; 95%CI: 0.55–2.31; P=0.75) between the groups. There were also no differences between the

Table 1 Characteristics of the studies

Author	Year	Country	Study Period	Design	Disease	No. of patients		Age		Sex(M/F)		Tumor size(cm)	
						TP	PD	TP	PD	TP	PD	TP	PD
Muller[15]	2007	Germany	2001–2006	Pro	MB	87	87	63.8 ±10.9	63.5 ±9.3	40/47	40/47	NR	NR
Nikfarjam[59]	2014	Australia	2005–2012	Retro	MB	15	150	73±6.2	67 ±11.5	9/7	89/61	NR	NR
Satoi[61]	2015	Italy	2011–2015	Pro	PDAC	45	45	66±8	67±4.7	21/24	21/24	3.2 ±2.3	3.1 ±0.7
Casadei[63]	2016	Japan	2001–2011	Retro	MB	73	184	70±7.7	67±13	32/41	76/108	NR	NR
Xiong[65]	2017	China	2009–2015	Retro	PDAC	50	50	57 ±10.2	57.5 ±10.3	32/18	30/20	3.3 ±1.3	3.3 ±1.1

Abbreviations: TP, total pancreatectomy; PD, pancreaticoduodenectomy; Retro, rRetrospective; Pro, prospective; PDAC, pancreatic ductal adenocarcinoma; MB, malignant and benign pancreatic diseases; NR, not report.

Table 2 Intraoperative and postoperative outcomes of the studies include in system review

Author	Mortality (%)		Morbidity (%)		Operation time(min)		Blood loss(ml)		Blood transfusion(n)		Hospital stay(d)		Reoperation (n)	
	TP	PD	TP	PD	TP	PD	TP	PD	TP	PD	TP	PD	TP	PD
Muller[15]	6.9	3.5	35.6	26.4	385 ±72.6	359 ±88.9	1000 ±740.7	500 ±333.3	NR	NR	11 ±5.9	12±3	NR	NR
Nikfarjam[59]	6.7	2.0	86.7	57.3	630 ±98	420 ±768	600 ±300	350±400	11	28	17 ±22.3	19±6	0	11
Satoi[61]	0.0	0.0	31.1	40.0	526 ±104.2	530 ±106.5	1872 ±931.7	1205 ±1061.3	36	19	NR	NR	NR	NR
Casadei[63]	4.1	4.9	32.9	23.9	380 ±50.8	335 ±90	NR	NR	NR	NR	16 ±13.7	16 ±29.2	65	162
Xiong[65]	6.0	4.0	52.0	48.0	415 ±22.2	395 ±25.9	600 ±444.4	500 ±268.5	28	18	18.7 ±6.8	18 ±6.3	4	2

Abbreviations: TP, total pancreatectomy; PD, pancreaticoduodenectomy; NR, not report.

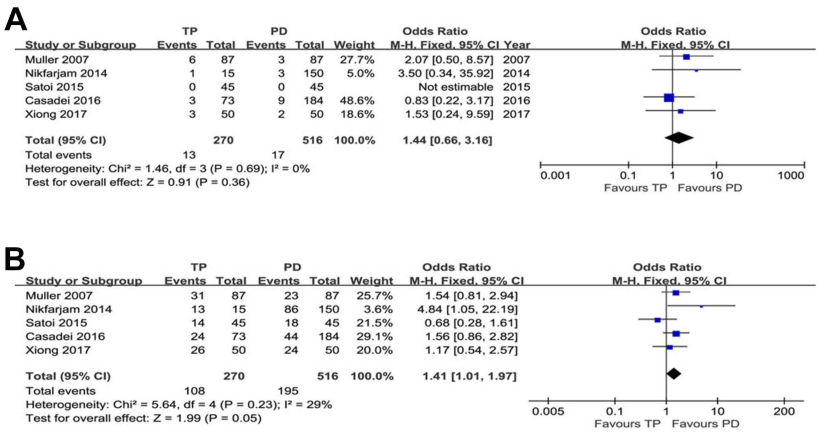

Figure 2 The forest plot of primary outcomes. (**A**) Mortality; (**B**) Morbidity.

two groups in terms of 3-OS (HR: 1.26, 95%CI: 0.86–1.85; *P*=0.24) and 5-OS (HR: 1.30, 95%CI: 0.90–1.88; *P*=0.16).

Sensitivity analysis

Sensitivity analysis was performed for outcomes with high heterogeneity. TP had a longer operation time in the fixed effects model (WMD: 25.39, 95%CI: 17.67–33.12; *P*<0.00001) and random effects model (WMD: 29.56, 95%CI: 8.23–50.89; *P*=0.007) than that of PD. For blood loss, the same result was found in the fixed (WMD: 280.24, 95%CI: 190.91–369.56; *P*<0.00001) and random (WMD: 339.96, 95%CI:00 117.74–562.18; *P*=0.003) effects model. There was no significant difference in blood transfusion between the fixed effects model (OR: 4.20, 95%CI: 2.46–7.18; *P*<0.00001) and random effects model (OR: 3.37, 95%CI: 1.25–9.12; *P*=0.02).

Publication bias

The funnel plots based on mortality and morbidity are shown in Figure 4. No study laid outside the limits of the 95%CI; therefore, there was no evidence of publication bias.

Discussion

This study summarizes the evidence to date that suggest that TP may not be as feasible and safe as PD. We found that the TP group had a longer operation time, more blood loss, and more frequent blood transfusion than the PD group. However, TP and PD may have the same efficacy because of no significant difference in overall survival.

The difference in morbidity in TP among studies from the past compared to studies in the present was vast. The lowest morbidity (17.5%) was reported by Balcom, and the highest morbidity (86.7%) was reported by

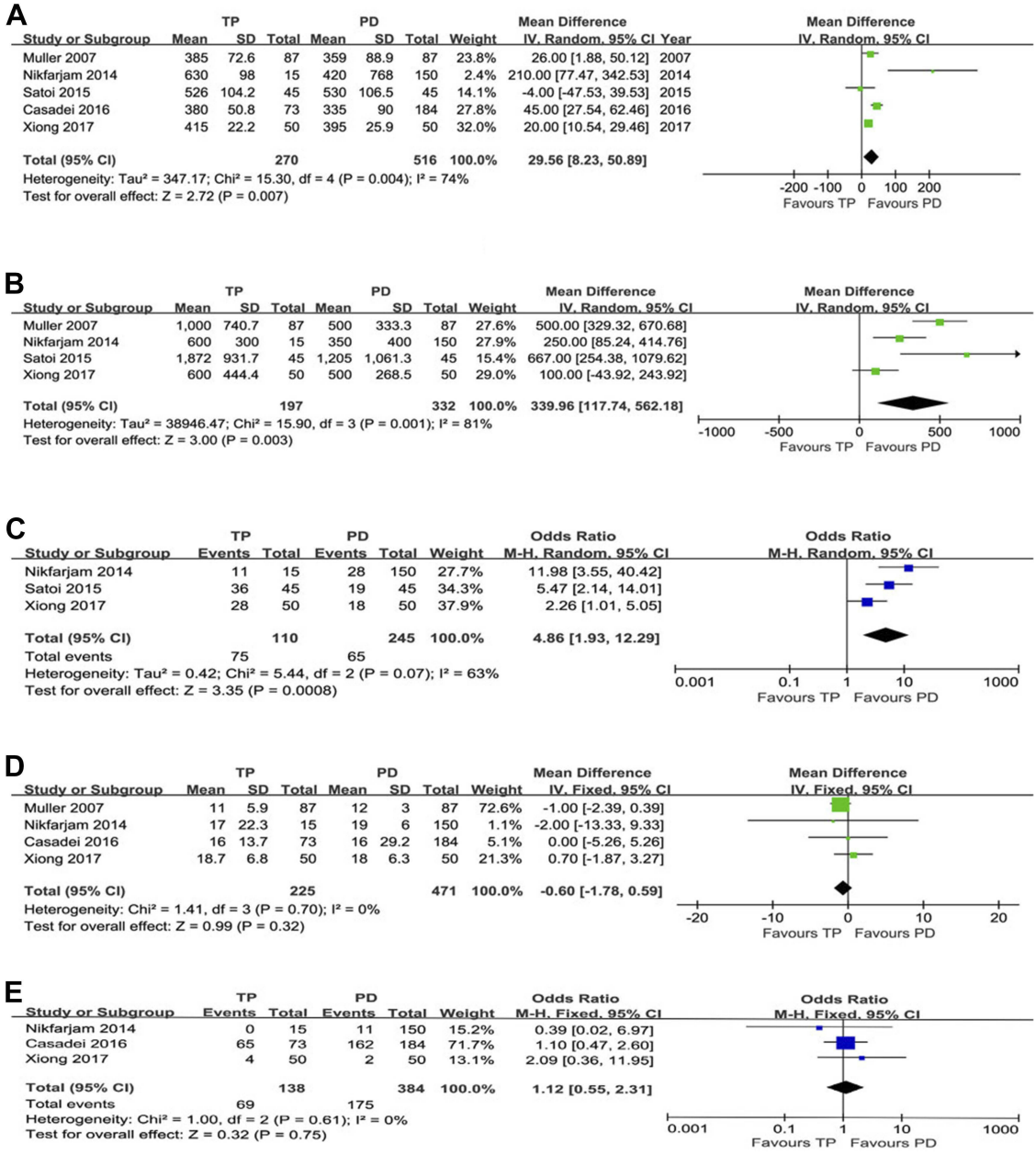

Figure 3 The forest plot of secondary outcomes. (**A**) Operation time; (**B**) Blood loss; (**C**) Blood transfusion; (**D**) Hospital stay; (**E**) Reoperation.

Nikfarjam.[48,60] Many studies suggested that more extended surgery led to higher morbidity, even in high-volume centers.[13,19,60] Similar results were found in the present study. As mentioned previously, the improvement of operative techniques and postoperative management have dramatically decreased the morbidity associated with TP.[62,64] Therefore, it can be inferred that morbidity was closely related to the skill of the surgeon and postoperative management. In this meta-analysis, most studies came from high-volume centers. This ensured that there were consistent skills of the surgeons and good postoperative management. Therefore, even if its mortality and morbidity have dramatically decreased in recent decades, TP remains an extended surgical procedure.

In the past, the mortality associated with TP was more than 20%.[28,31,32] With the improvement of operative techniques and postoperative management, the mortality of the TP has dramatically decreased.[62,64,65] However, higher mortality from TP was found in several studies.[19,42,46,58] Several studies have suggested that there is no difference between the TP and PD groups.[18,64] Muller reported that TP should no longer be generally avoided, because the mortality rate after elective TP was not significantly different from that associated with PD.[18] Casadei also

Table 3 Quality of studies

ROBINS-I	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Muller[15]	L	L	L	L	L	L	L	L
Nikfarjam[59]	M	L	L	M	L	L	M	M
Satoi[61]	L	L	L	L	L	L	L	L
Casadei[63]	M	L	L	M	L	L	L	M
Xiong[65]	L	L	L	L	L	L	L	L

Abbreviations: ROBINS-I, Risk of bias in nonrandomized studies of interventions; S, Serious; M, Moderate; L, Lower.

showed that postoperative mortality was similar between TP and PD.[64] In this study, the mortality in TP seems to not to be different from that of PD, but for TP it never reaches the level (<2–3%) accepted for PD in high volume center. The results of the present study were consistent with the results that have been published in most of the studies for several decades.

Because TP is a more extensive operation, it is possible that the TP group had more vascular resection than the PD group.[65] Therefore, longer operation times and more blood loss are not surprising. The skill and proficiency of surgeons might also be important factors for intraoperative outcomes. With more advanced technology and more skillful surgeons in the modern era, the number of patients who require blood transfusion should be less than that of previous eras.

Early studies generated a large controversy regarding the long-term survival between the two surgical procedures for patients with PDAC. The TP group with higher 5-OS than the PD group (14% vs 0%).[9] In contrast, two studies reported that 5-OS was higher in the PD group than in the TP group.[45,46] Nevertheless, several studies suggested that long-term survival after TP was comparable to that of PD. A large sample study reported similar 5-OS between the two groups (TP-18.5% vs PD-18.9%).[19] An additional matched-pairs analysis between the TP and PD groups was carried out only for patients with PDAC, revealing similar perioperative outcomes and OS associated with the two surgical procedures.[62] Furthermore, one matched study showed that similar survival of TP and PD in patients with PDAC.[65] The present study also confirmed that TP and PD were similar in overall survival for patients with PDAC. A study from Satio reported worse OS and disease-free survival (DFS) in the TP group than in the PD group.[62] However, using a matched analysis provided similar surgical and pathological outcomes, leading to similar OS between TP and PD matched groups.[62] This suggested that long-term survival might be closely related to surgical and pathological outcomes. Therefore, TP for PDAC does not affect survival.

There are several limitations to this study: first, all included studies had non-randomized designs; second, there was significant variability in some outcomes, including the definition of morbidity and follow-up time; third, we observed some heterogeneity in certain outcome measures. This might be explained by the differences in surgical techniques, the retrospective nature of the studies, and

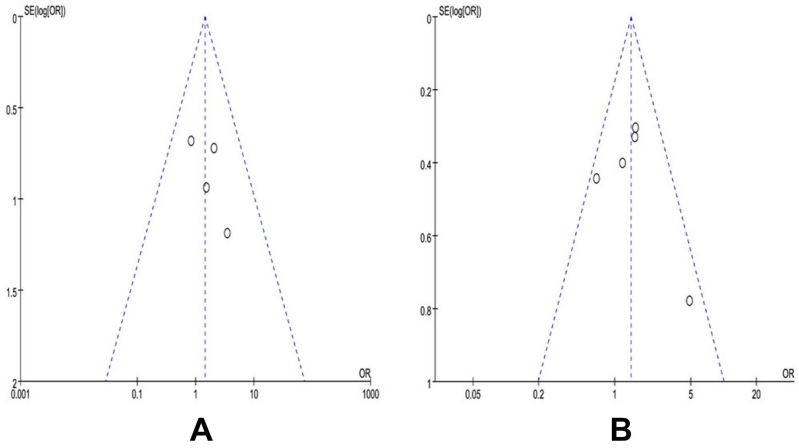

Figure 4 Funnel plot to investigate publication bias. **(A)** Mortality; (**B**) Morbidity.

the limited blinded outcome assessment in some of the trials. Therefore, future high-quality prospective studies are needed to confirm these results.

Conclusion

It seems reasonable to suggest that TP may not be considered to be as feasible and safe as PD. However, TP and PD may have the same efficacy. Nevertheless, there is an evident need for a well-designed study comparing TP and PD with respect to quality of life and long-term survival outcomes.

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Author contributions

Du-Jiang Yang, Jun-Jie Xiong and Wei-Ming Hu designed the study. Du-Jiang Yang and Jun-Jie Xiong performed the study and wrote the paper. Du-Jiang Yang and Xue-Ting Liu assessed the studies included in this review and collected the data. Jiao Li and Kanagarathna Mudiyanselage Dhanushka Layanthi Siriwardena analysed the data. Wei-Ming Hu reviewed the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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