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Review Article

Minimally invasive pancreatoduodenectomy is as safe and efficacious as open surgery for pancreatic ductal adenocarcinoma: a meta-analysis

Kewei Ji, Gengyuan Hu, Feng Tao, Wei Wang

Department of Gastrointestinal Surgery, Shaoxing People's Hospital, Zhejiang University, Shaoxing 312000, Zhejiang Province, China

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Abstract: Minimally invasive pancreaticoduodenectomy (MIPD) remains to be established as a safe and effective alternative to open pancreaticoduodenectomy (OPD) for pancreatic ductal adenocarcinoma (PDAC). The aim of this meta-analysis was to compare MIPD with OPD for PDAC with regards to perioperative and oncologic outcomes. A literature search, up to April 2018, was performed to identify comparative studies reporting outcomes for both MIPD and OPD for PDAC. Postoperative pancreatic fistula (POPF), morbidity, mortality, operation time, blood loss, transfusion, hospital stay, retrieved lymph nodes, and survival outcomes were compared. Of the seven identified studies, 1,055 underwent LPD and 8,116 underwent OPD. Pooled data showed that MIPD was associated with less morbidity (OR=0.61, 95% CI: 0.37~1.01, *P*=0.05), less blood loss (WMD=-372.96 mL, 95% CI: -507.83~-238.09, *P*<0.01), and shorter hospital stay (WMD=-1.69 days, 95% CI: -3.27~-0.12, *P*=0.04), with comparable POPF (OR=0.90, 95% CI: 0.52~1.56, *P*=0.70) and overall survival (HR=1.04, 95% CI: 0.90~1.20, *P*=0.61), compared to OPD. Operative times were longer in MIPD (WMD=66.95 min, 95% CI: -81.22~215.12, *P*=0.38) and retrieved lymph nodes tended to be more in MIPD (WMD=1.93, 95% CI: -0.35~4.22, *P*=0.10). These differences, however, failed to reach statistical significance. MIPD can be performed as safely and effectively as OPD for PDAC, comparing surgical and oncological outcomes. MIRH is associated with less intraoperative blood loss and postoperative morbidity, serving as a promising alternative to OPD in selected individuals.

Keywords: Minimally invasive, pancreaticoduodenectomy, adenocarcinoma, morbidity, meta-analysis

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy, often characterized by late diagnosis, extensive metastases, and low response to chemotherapy, with a really poor 5-year survival rate of about 6% [1]. Despite the poor availability of therapeutic options, surgical resection represents the only chance for cure in patients with early stage pancreatic adenocarcinoma. Pancreatic surgery is one of the most demanding fields in General Surgery, associated with approximately 30% perioperative mortality [2]. Recently, the centralization of pancreatic surgery to experienced high-volume centers has led to a dramatic reduction of perioperative mortality rates, to approximately 5%, for pancreatoduodenectomies (PD) [3]. Despite progress in patient selection, surgical techniques, and postoperative care, morbidity still occurs in up to 40% and mortality rates are approximately 5% in patients undergoing open PD (OPD) [4].

Minimally invasive surgery has been one of the main directions of surgical development in the twenty-first century. Historically, the first minimally invasive pancreatoduodenectomy (MIPD), a laparoscopic surgery, was performed in 1994. However, MIPD has been limited to tertiary referral centers and highly skilled surgeons due to associated technical demands. In addition, the lack of evidenced-based quality data and great variability among centers in the management of PDAC have led to dramatically slow progress in MIPD for PDAC. Although several meta-analyses comparing MIPD and OPD have been reported, these studies grouped results of MIPD for malignant and benign conditions, hampering specific analyses of minimally invasive man-

agement of PDAC [5, 6]. The present study abstracted data in collected studies and conducted this first meta-analysis of MIPD versus OPD for PDAC. The aim of this study was to evaluate the safety, feasibility, and potential benefits of this minimally invasive approach.

Methods

Search strategy

Systematic searches of PubMed, EMBASE, and Cochrane Library were performed to identify articles published, up to April 2018, comparing outcomes with MIPD versus OPD in the treatment of PDAC. Search terms "minimally invasive", "laparoscopy", "robot", "pancreatectomy", "Whipple", "pancreaticoduodenectomy", "pancreatic ductal adenocarcinoma", and "pancreatic cancer" were utilized. MIPD included both laparoscopic PD (LPD) and robot-assisted PD (RPD). Both free-text and medical subject heading (MeSH) searches were used for keywords. All eligible studies were retrieved and bibliographies were checked for other relevant publications. Only studies written in English were considered for inclusion.

Eligibility criteria

Included studies were comparative peer-reviewed studies of MIPD versus RPD for patients with PDAC in which the full text of the article was available, including objective evaluations of at least one of the perioperative outcome measures mentioned below. Studies including malignant lesions other than PDAC were excluded. If there was overlap between authors or centers, the higher quality or more recent study was selected.

Methodological quality appraisal

Quality of non-randomized studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS), examining the following three factors: patient selection, comparability of the study groups, and assessment of outcomes. Maximum scores in the selection, comparability, and outcome categories were four, two, and three, respectively. Summation of the scores of these three categories was used to assess the quality of retrieved studies. Studies with a score higher than or equal to 6 were deemed as sound, methodologically.

Data extraction

Information was carefully extracted from all eligible studies by two of the authors (Ji KW and Hu GY), according to the inclusion criteria listed above. The following information was collected from each study: author, region, operative time, intraoperative blood loss, length of hospital stays, morbidity, mortality, tumor size, margin distance, and long-term oncologic outcomes. Clavien-Dindo classification for postoperative morbidity and intent-to-treat (ITT) analysis were investigated [7]. POPF was confirmed according to the International Study Group for Pancreatic Fistula (ISGPF) criteria [8]. Clinically significant POPF was defined as ISGPF grade B/C [8].

Statistical analysis

This study was performed in accordance with recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement using Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Dichotomous variables were analyzed using estimation of odds ratios (OR) with a 95% confidence interval (95% CI). Continuous variables were analyzed using weighted mean difference (WMD) with a 95% CI. If the study provided medians and ranges instead of means and standard deviations (SDs), the means and SDs were estimated, as described by Hozo et al. Statistical heterogeneity, indicating between-study variance, was evaluated according to the Higgins I^2 statistic. I^2 values of less than 25%, 25-50%, and more than 50% indicate low, moderate, and high heterogeneity, respectively. To account for clinical heterogeneity, which refers to diversity in a sense that is relevant for clinical situations, a random effects model was used based on DerSimonian and Laird's method. Publication bias was qualitatively evaluated using funnel plots. A value of $P<0.05$ indicates statistical significance.

Results

Studies selected

The initial literature search yielded 622 studies reporting on MIPD versus OPD for PDAC. No disclosure of results from any prospective, ran-

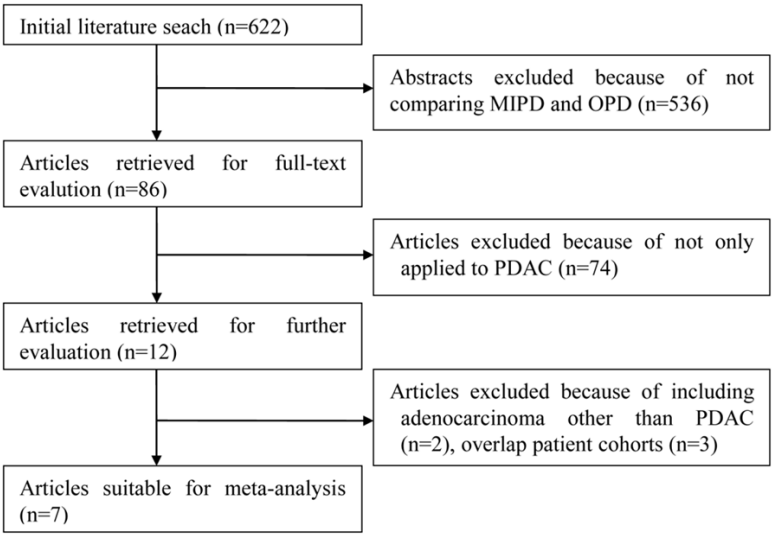

Figure 1. Flow chart of literature search strategy.

domized, and controlled trial was identified. Of these, 12 articles were selected based on their titles and abstracts. A full examination of the text was performed. Five papers were excluded when the full text was read, due to including adenocarcinoma rather than PDAC [9, 10] and overlapping patient cohorts [11-13]. This left a total of seven comparative observational studies [14-20]. **Figure 1** illustrates the selection process.

Study characteristics and quality

A total of 9,171 patients were included in this analysis, with 1,055 undergoing LPD (11.5%) and 8,116 undergoing OPD (88.5%). Most studies were single-center retrospective studies. Only one multi-institutional study was found [19]. **Table 1** lists the characteristics of included studies and details of enrolled participants. Quality assessment using the NOS showed that included studies were methodologically adequate. Five studies received 8 stars, while the remaining one received 6 stars (**Table 2**).

Results of the meta-analysis

Safety of MIPD for PDAC: All eligible parameters were pooled for the meta-analysis. Results are listed in **Table 3**. The present analysis showed no statistically significant differences in operative times between the two groups (WMD=66.95 min, 95% CI: -81.22~215.12, *P*=0.38) (**Figure 2A**). Intraoperative blood loss was significantly lower in the MIPD group, compared with the OPD group (WMD= -372.96 Ml, 95% CI: -507.83 ~-238.09, *P*<0.01) (**Figure 2B**). MIPD was also associated with a lower transfusion rate (OR=0.45, 95% CI: 0.29 ~0.68, *P*<0.01). Regarding postoperative effects, a reduced overall morbidity rate was observed in the MIPD group (OR=0.61, 95% CI: 0.37~1.01, *P*=0.05) (**Figure 2C**). In addition, pooled data indicated reduced major complication rates in the MIPD group (OR=0.54, 95% CI: 0.31~0.94, *P*=0.03). This study further analyzed specific complications, finding no statistical differences in incidence of POPF (OR=0.90, 95% CI: 0.52~1.56, *P*=0.70) (**Figure 2D**), clinically significant POPF (OR=0.92, 95% CI: 0.50~1.69, *P*=0.78), DGE (OR=0.74, 95% CI: 0.28~1.96, *P*=0.55), and PPH (OR=1.39, 95% CI: 0.67~ 2.89, *P*=0.38). The unplanned readmission rate was lower in the MIPD group, compared to the OPD group, but did not reach statistical significance (OR=0.77, 95% CI: 0.58~1.01, *P*=0.06). Pooling data revealed a comparable mortality rate between groups (OR=0.91, 95% CI: 0.66~1.25, *P*=0.54). However, pooled data showed a reduced length of hospital stay in the MIPD group (WMD=-1.69 days, 95% CI: -3.27~ -0.12, *P*=0.04) (**Figure 2E**).

Efficacy of MIPD for PDAC

For oncologic clearance, mean tumor size was shorter in the MIPD group than the OPD group (WMD=-0.23, 95% CI: -0.45~0.01, *P*=0.04). Pooling data showed that the mean number of retrieved lymph nodes was higher in MIPD but did not reach statistical significance (WMD =1.93, 95% CI: -0.35~4.22, *P*=0.10) (**Figure 3A**). Pooling data also showed a higher R0 rate in MIPD than OPD, with marginal differences (OR=1.16, 95% CI: 0.99~1.36, *P*=0.06) (**Figure 3B**). In addition, the present meta-analysis indicated comparable recurrence rates (OR=0.68, 95% CI: 0.44~1.07, *P*=0.09) (**Figure 3C**) and 5-year overall survival rates (HR=1.04, 95% CI: 0.90~1.20, *P*=0.61) (**Figure 3D**).

Table 1. Summary of studies included in the meta-analysis

Author	Region	Design	Year	Study Period	Sample size		Age		Sex (male)		Conversion n (%)	ITT	ISGPF	Clavien-Dindo	Mortality
					MIPD	OPD	MIPD	OPD	MIPD	OPD					
Croome	USA	OCS (P, S)	2014	2008-2013	108	214	66.6 ± 9.6	65.4 ± 10.9	51 (47.2%)	131 (61.2%)	7 (6.5)	Yes	Yes	Yes	30 d
Chen	China	OCS (P, S)	2015	2010-2013	19	38	NR	NR	NR	NR	1 (5.3)	Yes	Yes	Yes	NR
Song	Korea	OCS (R, S)	2015	2007-2012	11	261	68.1 ± 7	61.8 ± 10.5	NR	NR	NR	No	Yes	Yes	30 d
Dokmak	France	OCS (P, S)	2015	2011-2014	15	14	NR	NR	NR	NR	NR	Yes	Yes	Yes	90 d
Boggi	Italy	OCS (P, S)	2016	2008-2014	16	11	NR	NR	NR	NR	NR	Yes	Yes	Yes	90 d
Stauffer	USA	OCS (P, S)	2017	1995-2014	58	193	69.9 (40.6-84.8)	68.9 (33.3-86.9)	32 (55.2%)	96 (49.7%)	14 (24.1)	Yes	Yes	Yes	90 d
Kantor	USA	OCS (R, M)	2017	2010-2013	828	7385	65.9 ± 10.7	65.7 ± 10.4	NR	NR	E	NR	NR	NR	90 d

OCS, observational clinical study; P, prospectively collected data; R, retrospectively collected data; M, multi-centers; S single center; MIPD: minimally invasive pancreaticoduodenectomy; OPD: open pancreaticoduodenectomy; ITT: intention-to-treat analysis; ISGPF: international study group of pancreatic fistula; E, exclude; NR, not reported.

Table 2. Quality assessment based on the NOS

Author	Selection (Out of 4)				Comparability (Out of 2)	Outcomes (Out of 3)			Total (Out of 9)
	①	②	③	④		⑤	⑥	⑦	
Croome	*	*	*	*	**	*		*	8
Chen	*	*	*	*	**	*		*	8
Song	*	*	*	*	**	*		*	8
Dokmak	*	*	*	*	**	*			7
Boggi	*	*	*	*	**	*		*	8
Stauffer	*	*	*	*	**	*		*	8
Kantor	*	*	*	*	**	*		*	8

① Representativeness of exposed cohort; ② Selection of nonexposed cohort; ③ Ascertainment of exposure; ④ Outcome not present at the start of the study; ⑤ Assessment of outcomes; ⑥ Length of follow-up; ⑦ Adequacy of follow-up.

Table 3. Results of the meta-analysis

Outcomes	No. of studies	Sample size		Heterogeneity (P, I^2)	Overall effect size	95% CI of overall effect	P
		MIPD	OPD				
Operative time (min)	2	166	407	<0.001, 98%	WMD=66.95	-81.22~215.12	0.38
Blood loss (mL)	2	166	407	0.94, 0%	WMD=-372.96	-507.83~-238.09	<0.01
Transfusion	2	166	407	0.65, 0%	OR=0.45	0.29~0.68	<0.01
Morbidity	3	181	421	0.21, 36%	OR=0.61	0.37~1.01	0.05
Major complications	2	166	407	0.32, 1%	OR=0.54	0.31~0.94	0.03
POPF	3	181	421	0.90, 0%	OR=0.90	0.52~1.56	0.70
Significant POPF	2	166	407	0.95, 0%	OR=0.92	0.50~1.69	0.78
DGE	2	166	407	0.07, 69%	OR=0.74	0.28~1.96	0.55
PPH	2	166	407	0.68, 0%	OR=1.39	0.67~2.89	0.38
Readmission	2	886	7578	0.31, 3%	OR=0.77	0.58~1.01	0.06
Mortality	3	994	7792	0.78, 0%	OR=0.91	0.66~1.25	0.54
Hospital stay (days)	4	1009	7806	0.29, 21%	WMD=-1.69	-3.27~-0.12	0.04
Tumor size (cm)	6	227	731	0.19, 33%	WMD=-0.23	-0.45~-0.01	0.04
Retrieved lymph nodes	6	1040	8102	0.002, 73%	WMD=1.93	-0.35~4.22	0.10
R0 rate	7	1055	8116	0.69, 0%	OR=1.16	0.99~1.36	0.06
Recurrence	2	124	225	0.68, 0%	OR=0.68	0.44~1.07	0.09
5 y-overall survival	4	1013	7830	0.25, 27%	HR=1.04	0.90~1.20	0.61

Publication bias

Visual inspection of the funnel plot revealed symmetry, indicating no serious publication bias (**Figure 4**).

Discussion

Laparoscopic abdominal surgery has experienced rapid development in recent years [21-24]. However, the laparoscopic approach for pancreatic adenocarcinoma is highly demanding and challenging for every experienced surgeon. The progress of this operation has been slow due to huge technical demands and great reconstructive difficulties. With recent advancements in laparoscopic experience, techniques, and instruments, reports of laparoscopic surgery for pancreatic-head and periampullary malignancies have increased. However, it remains controversial and under-reported whether laparoscopic surgery should be applied to efficiently and safely treat pancreatic adenocarcinoma, a lethal gastrointestinal malignancy. This meta-analysis selected and summarized available literature comparing the short- and long-term outcomes of LPD and OPD for PDAC. Pooled data revealed that LPD for PDAC showed significant reductions in intraoperative blood loss, postoperative morbidity, major complications, and length of hospital stay. No statistically significant differences were identified between the two groups regarding operative

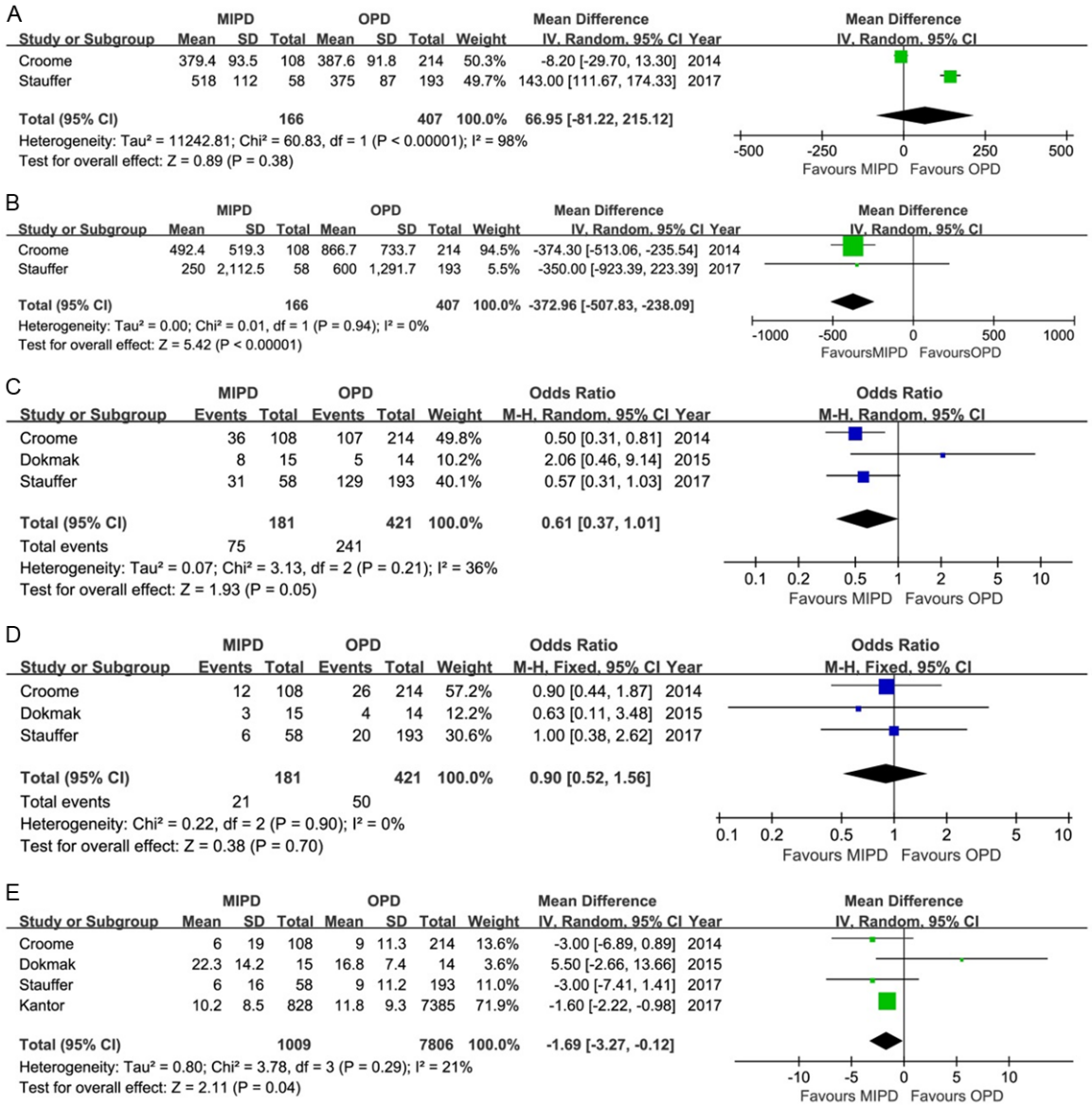

Figure 2. Forest plot of the meta-analysis: (A) Operative time, (B) Blood loss, (C) Overall morbidity, (D) POPF, (E) Length of hospital stay.

time, mortality, and specific complications, such as POPF, DGE, and PPH. LPD also exhibited advantages in terms of retrieved lymph nodes and margin clearance. In addition, pooling results indicated comparable recurrence and 5 year-overall survival rates between the two groups.

Longer operating time is a continuing worry for surgeons. A recent study from the American College of Surgeons NSQIP demonstrated that longer operative times were independently associated with worse perioperative outcomes after pancreatic resection [25]. Almost all of the previous meta-analyses for various pancreatic-head and periampullary diseases demonstrated prolonged operating times in MIPD [5, 26, 27], despite significant heterogeneity. Conversely, present pooled outcomes revealed comparable operative times between the MIPD group and OPD group. Kendrick and Cusati reported the initial duration of MIPD to be approximately 8 hours, which improved to 5 hours after approximately 50 cases [28]. The learning curve for MIPD is long and achieving proficiency is paramount. Panelists recommended using narrow inclusion criteria early in the experience with MIPD. When the laparosco-

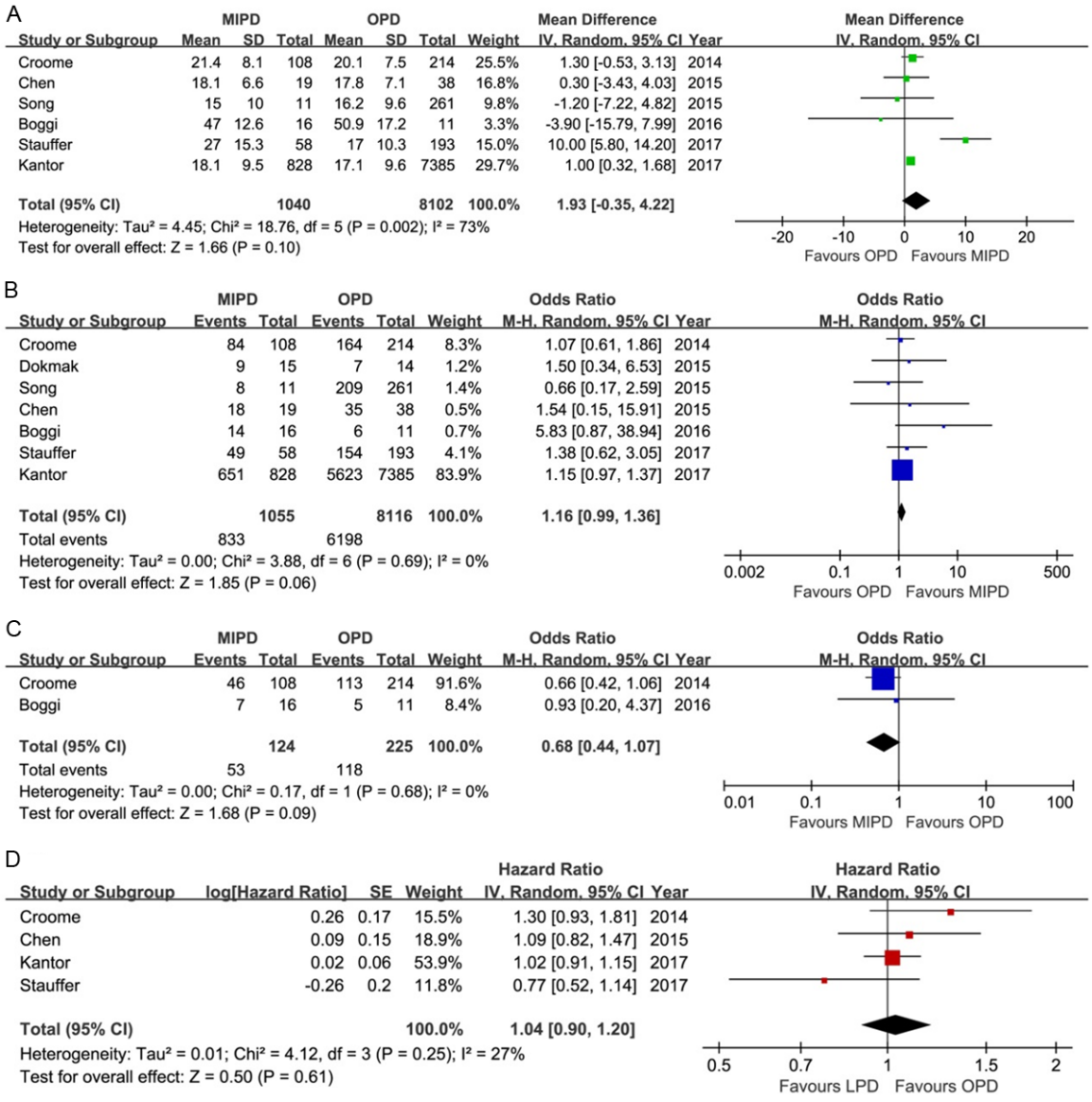

Figure 3. Forest plot of the meta-analysis: (A) Number of retrieved lymph nodes, (B) R0 rate, (C) Recurrence, (D) 5-year overall survival rate.

pist builds experience and team confidence, the criteria can be expanded to malignancies like PDAC [29]. Results of comparable operative times were partly because of a lack of sample size (only the studies by Croome et al. [14] and Stauffer et al. [20]. However, the main reason was the excellent laparoscopic experience of the two professional pancreatic institutions (Mayo Clinic, Rochester, USA and Mayo Clinic, Jacksonville, USA [30]. Chen et al. indicated that complex gastrointestinal reconstruction was extremely time-consuming. They recommended before conducting MIPs, surgeons should perform intracorporeal pancreaticojejunostomy in laparoscopic central pancreatectomy, for benign and low-grade pancreatic tumors, and perform hepaticojejunostomy and gastrojejunostomy obtained from laparoscopic choledochotomy and totally laparoscopic distal gastrectomy, respectively [5]. MIPD reduces intraoperative blood loss since surgeons may clearly identify tiny blood vessels near pancreatic parenchyma and common bile duct, along with the more detailed operation of ligation hemostasis with the help of local amplified surgical field. The application of energy-dividing devices, such as the Harmonic Scalpel and Ligasure, also contribute to the reduction in blood loss.

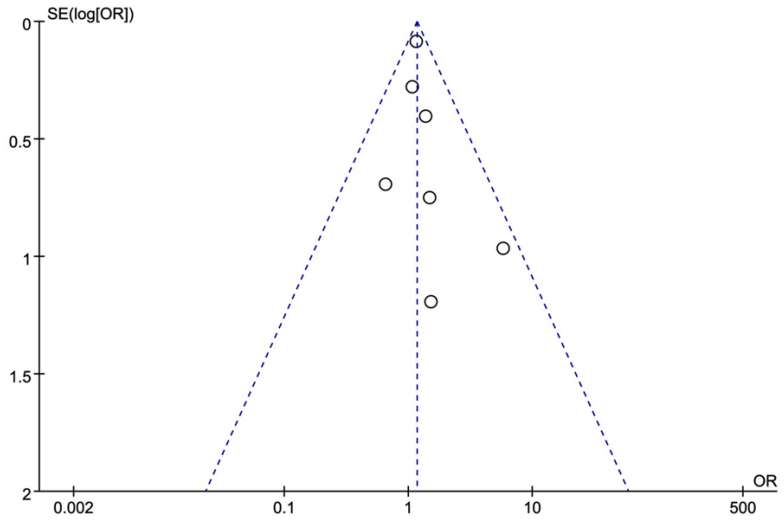

Figure 4. Funnel plots of the R0 rate.

An important concern regarding any new surgical approach is patient safety. In the present analysis, overall complication rates were lower for LPD than for OPD, despite moderate heterogeneity among included studies (I^2=36%). In addition, pooled data indicated reduced major morbidity in the LPD group. Like institutional comparative trials, present data showed no differences in operative mortality. Three studies utilizing the National Cancer Database suggested increased mortality for LPD in low-volume hospitals [11, 12, 31]. However, an association of low-volume and mortality has also been shown for OPD. A high-demand surgery, LPD as a first exposure to advanced laparoscopic surgery is ill-advised. Surgeons should have both formal pancreas training and advanced laparoscopic training. An important aspect of a well-structured LPD training program is deliberate training in and out of the operative setting. The possible reasons of lower overall complications in MIPD are explained below: ① Intraoperative high-solution images helped to meticulously separate and protect pancreatic parenchyma; ② MIPD had less influence on the peripheral organs and peritoneum leading to less seroperitoneum; ③ PD involves multiple systems and ma cause more medical complications than other operations, while MIPD reduces pulmonary complications due to mild postoperative pain and earlier ambulation [32]; ④ Shorter wounds and possibly less ascites associated with MIPD might contribute to this lower incidence of wound infection; and ⑤ Alleviation of gastric dysrhythmias, ameliorative pyloric or antral ischemia, and mitigant pylorospasm could help to reduce delayed gastric emptying [33]. Unfortunately, due to limited studies and samples, the meta-analysis of specific complications failed to find significant differences. Thus, more research is necessary to further investigate postoperative complications of MIPD in the treatment of PDAC.

The roles of MIPD in the setting of malignancy are currently under evaluation. Thus, quality data is limited. n aggressive malignancy, PDAC has a high recurrence rate of about 50% in both minimally invasive and open surgery. Present analysis showed no differences between the two approaches. PDAC has significantly more aggressive inherent tumor biology, with a large series on PDAC in pancreatic head, with reported 5-year survival rates of only 20% [34, 35]. The present meta-analysis found that the HR of 5-year overall survival rates was comparable between MIPD and OPD. Despite demonstrating comparable outcomes, compared to OPD, the short-term assessment and lack of other data to validate these findings should prompt further study. Most published studies have instead focused on the surrogates of an oncologic resection, namely lymph node retrieval and margin status. Major hope for cure in aggressive PDAC is approached only with R0 resection [36]. Pooled results showed that MIPD has been associated with a tendency of lower positive margin rates and more retrieved lymph nodes, which may partly benefit from the meticulous operation under laparoscopy. Appropriate lymphadenectomy is crucial because elimination of a sufficient quantity of lymphadens could help to strengthen the staging accuracy and regional tumor control. In addition, curative R0 resection has been referred to as the most important factor, deemed the only chance to survive PDAC [37]. The prognostic validity of margin status may be primarily confined to pancreatic head cancers rather than neoplasms in the body or tail [38]. Elaborate manipulation and better visualization of critical anatomy could explain present outcomes. However, present results

also indicated a shorter tumor size in the MIPD group. Some researches may include MIPD cases of small and easily resectable tumors that would be partial to MIPD. The benefit of MIPD for margin status and lymph nodes harvesting cannot be confirmed. The short-term assessment and lack of comparable tumor size to validate these findings should prompt further study.

This systematic review and meta-analysis of MIDP versus ODP for PDAC represents the most comprehensive collection of evidence available within this field. However, present results should still be taken with caution due to several limitations. No randomized controlled trials (RCTs) were included and levels of clinical evidence were low. Selection bias necessarily consisted in surgeon or patient decisions on operation and adjuvant therapy. Moreover, various bias was a real concern because hardly any of the included studies employed standardized appraisals for end points. In addition, it should be noted that these studies were conducted in the best centers with MIPD experience, worldwide. Studies showed that specialization in pancreatic surgery results in both better short- and long-term survival [39]. Obtained conclusions might not be feasible in less specialized centers.

Conclusion

The present meta-analysis demonstrated that, compared to OPD, MIPD achieves short-term advantages within blood loss, postoperative morbidity, and hospitalization for pancreatic-head and periampullary malignancies. Moreover, both procedures have comparable long-term survival outcomes. Perhaps it is time to consider changing the standard procedure of cancer treatment in the pancreatic head and ampulla from an open to laparoscopic procedure in selected patients.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

PDAC, pancreatic duct adenocarcinoma; PD, pancreaticoduodenectomy; MIPD, minimally invasive pancreaticoduodenectomy; LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; RPD, robotic pancreaticoduodenectomy; ISGPF, International Study Group for Pancreatic Fistula; RCT, randomized controlled trial; NOS, Newcastle-Ottawa Quality Assessment Scale; OR, odds ratio; WMD, weighted mean difference; SD, standard de-viation; HR: hazard ratio; CI, confidence intervals; SE, standard error.

Address correspondence to: Wei Wang, Department of Gastrointestinal Surgery, Shaoxing People's Hospital, Zhejiang University, Shaoxing 312000, Zhejiang Province, China. E-mail: wangwei197511@163.com

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