Original Article

Perioperative and short-term oncological outcomes following laparoscopic versus open pancreaticoduodenectomy after learning curve in the past 10 years: a systematic review and meta-analysis

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Background: To compare perioperative and short-term oncologic outcomes of laparoscopic pancreaticoduodenectomy (LPD) to open pancreaticoduodenectomy (OPD) using data from large-scale retrospective cohorts and randomized controlled trials (RCTs) in the last 10 years.

Methods: A meta-analysis to assess the safety and feasibility of LDP and OPD registered with PROSPERO: (CRD42020218080) was performed according to the PRISMA guidelines. Studies comparing LPD with OPD published between January 2010 and October 2020 were included; only clinical studies reporting more than 30 cases for each operation were included. Two authors performed data extraction and quality assessment independently. The primary endpoint was operative times, blood loss, and 90 days mortality. Secondary endpoints included reoperation, length of hospital stay (LOS), morbidity, Clavien-Dindo ≥3 complications, postoperative pancreatic fistula (POPF), blood transfusion, delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH), and oncologic outcomes (R0-resection, lymph node dissection).

Results: Overall, the final analysis included 15 retrospective cohorts and 3 RCTs comprising 12,495 patients (2,037 and 10,458 patients underwent LPD and OPD). It seems OPD has more lymph nodes harvested but no significant differences [weighted mean difference (WMD): 1.08; 95% confidence interval (CI): 0.02 to 2.14; P=0.05]. Nevertheless, compared with OPD, LPD was associated with a higher R0 resection rate [odds ratio (OR): 1.26; 95% CI: 1.10–1.44; P=0.0008] and longer operative time (WMD: 89.80 min; 95% CI: 63.75–115.84; P<0.00001), patients might benefit from lower rate of wound infection (OR: 0.36; 95% CI: 0.33–0.59; P<0.0001), much less blood loss (WMD: –212.25 mL; 95% CI: –286.15 to –138.14; P<0.00001) and lower blood transfusion rate (OR: 0.58; 95% CI: 0.43–0.77; P=0.0002) and shorter LOS (WMD: –1.63 day; 95% CI: –2.73 to –0.51; P=0.004). No significant differences in 90-day mortality, overall morbidity, Clavien-Dindo ≥3 complications, reoperation, POPF, DGE and PPH between LPD and OPD.

Conclusions: Our study suggests that after learning curve, LPD is a safe and feasible alternative to OPD as it provides similar perioperative and acceptable oncological outcomes when compared with OPD.

Keywords: Pancreatic cancer; laparoscopic pancreaticoduodenectomy (LPD); open pancreaticoduodenectomy (OPD); meta-analysis

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Introduction

Pancreaticoduodenectomy (PD) is a complex procedure which can provide cure or prolonged survival for benign lesion and cancer in periampullary region and pancreatic head. And in resectable patients, it can achieve a 5-year survival rate of 30% (1). Open pancreaticoduodenectomy (OPD) is the classic procedure for pancreatic and periampullary malignancies and some benign diseases. Since Gagner and Pomp first reported laparoscopic pancreaticoduodenectomy (LPD) in 1994 (2), LPD is increasingly used worldwide, but only 285 reported cases have been reported as of 2011 (3). However, during 2010–2020, more and more studies have confirmed the safety and feasibility of LPD and emphasized it is superior to OPD in reducing blood loss, shorter hospital stay, earlier oral intake, less pain, and faster recovery (4-7). However, an analysis of 983 patients found that patients who underwent LPD had higher 30-day mortality compared to those with OPD in low-volume centers (8).

Although LPD has the potential advantages of small trauma, fast recovery and excellent vision, surgeons need a relatively long training time to become technically proficient in this complex procedure. As with all surgical studies, surgeons' experience and performance has a significant impact on outcomes which can be a source of bias. However, the great majority of the studies on LPD and OPD are small sample study and the surgeons remained in the early training phase. Nagakawa *et al.* showed that hepatopancreatobiliary surgeons need more than 30 cases to make LPD become stable (9). In addition, even at high-volume centers, the surgical results during the learning curve are not satisfactory (10,11). According to our search, there are no prospective studies and no meta-analysis was performed specifically to compare the perioperative and short-term oncological outcomes of LPD to OPD from RCTs and large-scale retrospective cohorts in the last 10 years to avoid bias. Hence, we carefully selected some RCTs or large-scale retrospective cohorts to conduct a systematic review and meta-analysis to compare the clinical outcomes of LPD versus OPD after learning curve.

Methods

Materials and methods

This study has been reported in line with the recommendations of the PRISMA guidelines (available at http://dx.doi.org/10.21037/gs-20-916) (12) and registered at PROSPERO with registration number: CRD42020218080. This article is a meta-analysis; therefore, Institutional Review Board approval is not needed for this paper.

Data sources and search strategy

A literature search was performed in October 2020. The primary searched sources were the PubMed, Web of Science, EMBASE, Cochrane Central Register, and ClinicalTrials.gov databases for studies published between January 2010 and October 2020 by two independent investigators (QB Feng, ZC Xin). The following key terms and their combinations were used: laparoscopic, open, conventional, Whipple, and PD. To prevent missing relevant publications, computer search was supplemented with manual searches of the references of publication and reviews.

Inclusion and exclusion criteria

Inclusion criteria were: (I) types of interventions: LPD and OPD; (II) types of studies: randomized controlled trials (RCTs), retrospective studies, cohort studies and case-control studies; (III) large-scale retrospective cohorts (LPD ≥30, OPD ≥30); (IV) primary article published in English;

Exclusion criteria were: (I) non-English studies; (II) insufficient information available in the abstracts; (III) data that were incomplete; (IV) editorials, letters, nonhuman studies, expert opinions, reviews, case reports, and studies without control groups.

Data extraction and quality assessment

Two reviewers (QB Feng, ZC Xin) extracted the data independently using a unified datasheet, and in the

case of any ambiguity, a third observer (B Zhu) was consulted to review the study to reach a consensus. Data extraction include the following items: study and patient characteristics, operative and postoperative outcomes. Study and patient characteristics include first author, country, publication year, research design, sample size, and mean age; the latter included operative time, blood loss, blood transfusion, tumor size, postoperative morbidity and 90-daymortality, LOS, R0 resections, and number of harvested lymph nodes. We adopted the Newcastle-Ottawa Scale (NOS) to assess methodological quality (13). Each study was scored between 0 and 9 according to NOS, a score of ≥6 is considered indicative of high quality. Two reviewers (B Zhu, ZC Xin) assessed the included studies independently.

Statistical analysis

Review Manager 5.3 software was used to analysis data. The odds ratio (OR) and weighted mean difference (WMD) with the 95% confidence interval (CI) were used to compare dichotomous and continuous variables, respectively. We adopted the method described by Hozo *et al.* to calculate the standard deviation which was reported as median and range value (14). Funnel plot was used to assess potential publication bias. Statistical heterogeneity quantified using with the I^2 index. A study with an I^2 less than 50% was considered indicative of low or moderate heterogeneity, and the fixed effect mode (FEM) was then applied to pool the results. A study with an I^2>50% was considered a high heterogeneity and the random effect model (REM) was adopted.

Results

Search results and characteristics of the eligible studies

The literature search yielded 534 relevant English publications from the various electronic databases, of which 15 retrospective cohort studies and 3 RCTs (5,7,11,15-29) comparing LPD and OPD in a total of 12,495 patients (2,037 and 10,458 underwent LPD and OPD, respectively) were included for further analysis. A flow chart of our analysis protocol is shown in *Figure 1*. The major features and qualities of these 18 studies are listed in *Table 1*, while the assessment of risk of bias in individual studies made with the Cochrane risk of bias tool is presented as a summary in *Figure 2*. All results of this meta-analysis are presented in *Table 2*.

Operative outcomes

Operative time

Sixteen studies (5,7,11,15-18,20,22-29) with a total of 2,566 patients (953 who underwent LPD and 1,613 patients who underwent OPD) reported operative times. The pooled data revealed that LPD was associated with a longer operative time (WMD: 89.80 min; 95% CI: 63.75–115.84; P<0.00001). The analysis found statistically significant heterogeneity (I^2=96%); thus, a random effects model was adopted (*Figure 3A*).

Blood loss

Estimated blood loss was assessed in 11 studies (5,7,15,17,18,20,22,25-27,29). The pooled data further showed that LPD was associated with a less blood loss (WMD: −212.25 mL; 95% CI: −286.15 to −138.14; P<0.00001). Heterogeneity was high (I^2=94%) (*Figure 3B*).

Blood transfusion

Blood transfusion rate data was available in 8 studies (16,18,20,22,23,27-29). The meta-analysis suggested a higher rate of blood transfusion in the OPD group (OR: 0.58; 95% CI: 0.43 to 0.77; P=0.0002). Heterogeneity was not significant (I^2=0%) (*Figure 3C*).

Postoperative outcomes

Length of stay

All studies (5,7,11,15-29) with a total of 14,565 patients (2,037 who underwent LPD and 10,518 who underwent OPD) investigated the LOS. The meta-analysis suggested a shorter LOS in the LPD group (MD: –1.62; 95% CI: –2.73 to –0.51; P=0.004) (*Figure 4A*).

Overall complication rates

Twelve studies (5,17,18,20,22-29) that encompassed 1,801 patients (695 who underwent LPD and 1,106 who underwent OPD) recorded the postoperative complications, and the present analysis revealed no significant difference between the two groups (OR: 0.86; 95% CI: 0.70 to 1.06; P=0.15). The heterogeneity was low (I^2=35%) and analyzed in FEM (*Figure 4B*).

Clavien-Dindo grade ≥III

Ten studies (7,16-18,20,22,24,26,27,29) with a total of 1,408

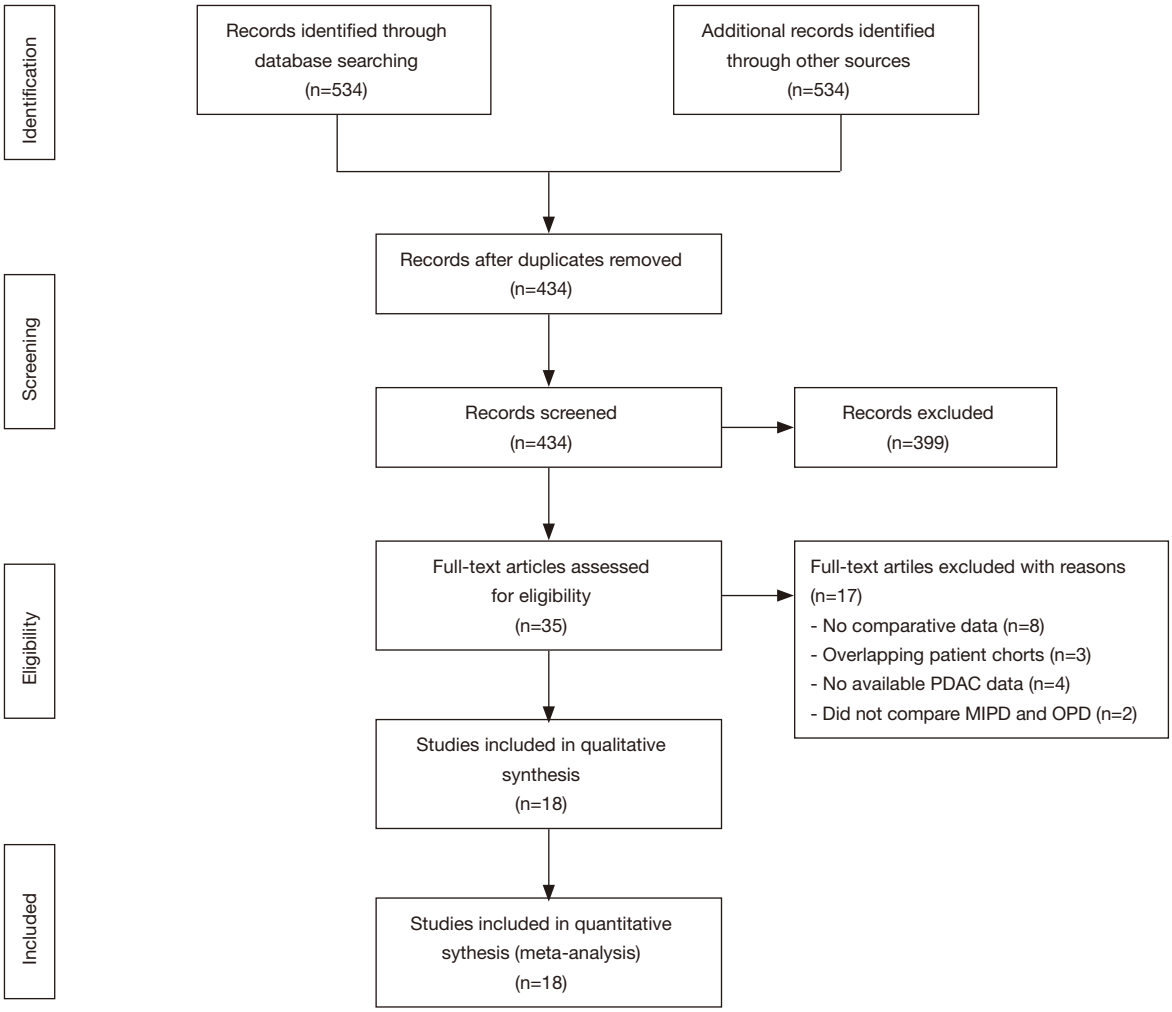


Figure 1 Flow chart of study identification and selection.

patients (567 who underwent LPD and 841 who underwent OPD) reported the Clavien-Dindo classifications of complications according to Dindo *et al.* (30). No significant differences in Clavien-Dindo grade ≥ III were observed between these two groups (OR: 1.02; 95% CI: 0.78 to 1.35; P=0.87). The heterogeneity was low (I^2=0%) and analyzed in FEM (*Figure 4C*).

90-day mortality

Pooling the data from seven studies (15,17,19,23-25,29) that included 9,341 patients (1,191 who underwent LPD and 8,150 who underwent OPD) assessed the 90-day mortality. The pooled data showed no significant difference between the LPD group and OPD group (OR: 0.95; 95% CI: 0.71 to 1.27; P=0.74), with low heterogeneity (I^2=0%) in FEM (*Figure 4D*).

Post pancreatectomy hemorrhage

Pooling the data of eight studies (7,11,15,17,19,20,22-24,26,28,29) that included 1,299 patients (450 who underwent LPD and 849 who underwent OPD) assessed postpancreatectomy hemorrhage (PPH), the present analysis revealed no significant difference between the LPD and OPD groups (WMD: 1.00; 95% CI: 0.63 to 1.61; P=0.99), with a low heterogeneity (I^2=0%) in the FEM (*Figure 5A*).

Wound infection

Six studies (15,20,22,26,27,29) with a total of 989 patients (328 who underwent LPD and 661 who underwent OPD)

Table 1 Characteristics of included studies

Author, year	Country	Study type	Study interval	Samples		Age (mean ± SD, year)		Sex (M/F)		BMI (mean ± SD, year)	
				LPD	OPD	LPD	OPD	LPD	OPD	LPD	OPD
Asbun 2012 (12)	USA	RS	2005–2011	53	215	62.9±14.14	67.3±11.53	29/24	95/120	27.64±7.16	26.6±5.08
Mesleh 2013 (13)	USA	RS	2009–2012	75	48	NR	NR	43/32	23/25	NR	NR
Croome 2014 (7)	USA	RS	2008–2013	108	214	66.6±9.6	65.4±10.9	51/57	131/83	27.4±5.4	27.2±5.3
Croome 2014 (14)	USA	RS	2007–2013	31	58	69.5±9.0	63.6±11.3	17/14	33/25	26.1±4.7	26.2±4.8
Dokmak 2015 (15)	France	RS	2011–2014	46	46	60 [27–85]	63 [47–81]	26/20	28/18	22.6 [17–30]	26.4 [19–42]
Song 2015 (5)	South Korea	RS, PSM	2007–2012	93	93	49.6±13.4	50.1±13	47/46	47/46	22.8±2.7	23.1±2.5
Tan 2015 (16)	China	RS	2009–2014	30	30	59.3±9.3	59.9±10.4	18/12	23/7	NR	NR
Kantor 2016 (17)	USA	RS	2010–2013	828	7,325	65.9±10.7	65.7±10.4	NR	NR	NR	NR
Stauffer 2016 (18)	USA	RS	1995–2014	58	193	69.9 [40.6–84.8]	68.9 [33.3–86.9]	32/26	96/97	25.9 [17.7–49.7]	25.6 [15.0–46.2]
Chapman 2017 (19)	USA	RS	2010–2013	248	1,520	79.6±3.5	79.5±3.4	132/116	721/799	NR	NR
Palanivelu 2017 (20)	India	RCT	2013–2015	32	32	57.8±2.0	58.6±2.1	18/14	22/10	24.9±0.7	22.4±0.6
Kuesters 2018 (21)	Germany	RS	2010–2016	62	278	71	68	31/31	137/141	24.7 [15–39]	24.7 [16–46]
Poves 2018 (22)	Spain	RCT	2013–2017	32	29	69 [34–86]	70 [36–83]	13/17	20/9	24 [16–33]	26 [17–43]
Han 2019 (23)	Korea	RS, PSM	2012–2017	87	87	65.1±8.8	63.6± 9.5	49/38	53/34	23.52±2.74	23.32±3.08
Hilst 2019 (24)	Netherland	RCT	2016–2017	50	49	67 [59–76]	66 [61–73]	30/20	24/25	25±3	26±4
Nakeeb 2020 (25)	Egypt	RS	2013–2018	37	74	54 [33–62]	53 [17–63]	22/15	40/34	NR	NR
Yoo 2020 (26)	Korea	RS, PSM	2011–2017	69	69	62.8±10.1	63.2±8.6	34/35	38/31	23.1±2.7	23.5±3.3
Huang 2020 (27)	China	RS, PSM	2016–2019	98	98	57.47±13.0	59.09±11.5	54/44	56/42	24.5±3.12	25.1±2.26

RS, retrospective study; PSM, propensity score-matched analysis; LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; M/F, male/female; SD, standard deviation; BMI, body mass index; NR, not reported.

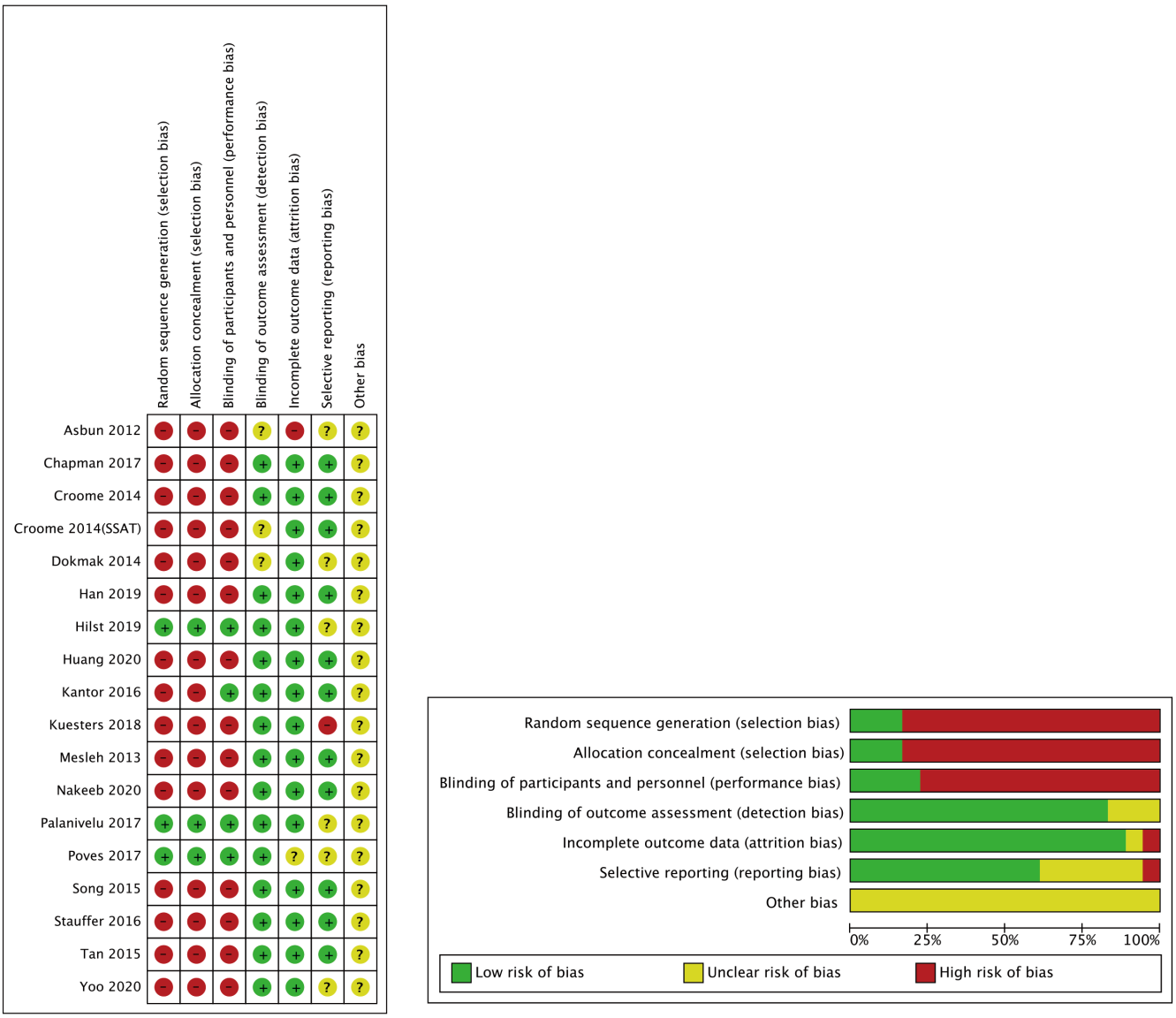


Figure 2 Quality assessment of included studies. Overall (left) and study-level risk of bias (right), using Cochrane's risk of bias assessment tool. Studies were deemed to be at high, low or unclear risk of bias based on adequacy of sequence generation, allocation concealment, blinding, method of addressing incomplete data, selective reporting, and other biases. The review authors' judgments about each risk of bias item are presented as percentages across all included studies, and for each included study.

reported the wound infection rate, and the pooled data revealed a significant lower wound infection rate in LPD group (OR: 0.36; 95% CI: 0.22 to 0.59; P<0.0001), with no heterogeneity (I^2=0%) in FEM (*Figure 5B*).

Postoperative pancreatic fistula (POPF)

POPF incidence rates were described for 2,234 patients in 15 studies (5,7,11,15-18,20,22,24-29). No significant differences in POPF rates were observed between these two groups (OR: 0.98; 95% CI: 0.78 to 1.23; P=0.88), with a low heterogeneity (I^2=24%) in FEM (*Figure 5C*).

Delayed gastric emptying (DGE)

Fourteen studies (5,7,11,15,16,18,20,22,24-29) with a total of 2,145 patients (868 who underwent LPD and 1,277 who underwent OPD) reported DGE rate, and the result of

Table 2 Summary results of the meta-analyses

Outcomes of interest	Studies, n	LPD	OPD	WMD/OR (95% CI)	P value	Heterogeneity			
						χ^2	df	I^2, %	P value
Operative outcomes									
Operative time (min)	16	953	1,613	89.8 (63.75, 115.84)	<0.001	395.73	15	96	<0.001
Blood loss (mL)	11	693	1,085	–212.25 (–286.12, –138.34)	<0.001	139.59	9	94	<0.001
Blood transfusion	8	510	1,004	0.58 (0.43, 0.77)	<0.001	5.27	7	0	0.63
Postoperative outcomes									
Length of stay (day)	18	2,037	10,518	–1.62 (–2.73, –0.51)	0.004	92.90	17	82	<0.001
Overall complication rates	12	695	1,106	0.86 (0.70, 1.06)	0.15	16.95	11	35	0.11
Clavien-Dindo grade ≥ III	10	567	841	1.02 (0.78, 1.35)	0.87	20.93	9	57	0.01
90-days mortality	7	1,191	8,150	0.95 (0.71, 1.27)	0.74	3.65	6	0	0.72
Postpancreatectomy hemorrhage	8	450	849	1.00 (0.63, 1.61)	0.99	4.36	7	0	0.74
Wound infection	6	328	661	0.36 (0.22, 0.59)	<0.001	3.3	5	0	0.65
Postoperative pancreatic fistula	15	899	1,335	0.98 (0.78, 1.23)	0.88	18.53	14	24	0.18
Delayed gastric emptying	14	868	1,277	–0.01 (–0.05, 0.03)	0.74	26.2	13	50	0.02
Reoperation	10	598	1,117	0.96 (0.63, 1.46)	0.84	11.83	9	24	0.22
Short-term oncological outcomes									
R0 resection rate	14	1,793	10,301	1.26 (1.10, 1.44)	<0.001	13.04	13	0	0.44
Lymph nodes harvested	12	1,451	8,650	1.08 (0.02, 2.14)	0.05	77.61	11	86	<0.001

LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; WMD, weighted mean difference; OR, odds ratio; CI, confidence interval.

meta-analysis indicated no significant differences between the LPD and OPD groups (OR: –0.01; 95% CI: –0.05 to 0.03; P=0.70), with a moderate heterogeneity (I^2=50%) in REM (*Figure 5D*).

Reoperation

Ten studies (15,16,18,20,23-27,29) with a total of 1,715 patients (598 who underwent LPD and 1,117 who underwent OPD) reported the incidence of reoperation, and the pooled data revealed no significant difference between the two groups (OR: 0.96; 95% CI: 0.63 to 1.46; P=0.84), with low heterogeneity (I^2=24%) in FEM (*Figure 5E*).

Short-term oncological outcomes

R0 resection rate

In total, fourteen studies including 12,094 patients (1,793 who underwent LPD and who underwent OPD) provided data regarding the R0 resection rate (7,15,17,19-29). We found that LPD was associated with a higher R0 resection rate (OR: 1.26; 95% CI: 1.10 to 1.44; P=0.0008), with low heterogeneity (I^2=0%) as shown in the FEM (*Figure 6A*).

Lymph node dissection

Twelve studies (7,11,15,17,19,20,22-24,26,28,29) that included 10,101 patients (1,451 who underwent LPD and 8,650 who underwent OPD) assessed the number of lymph node dissection, the result of meta-analysis showed no statistically significant difference between the LPD and OPD groups (WMD: 1.08; 95% CI: 0.02 to 2.14; P=0.05), with a high heterogeneity (I^2=86%) in the REM (*Figure 6B*).

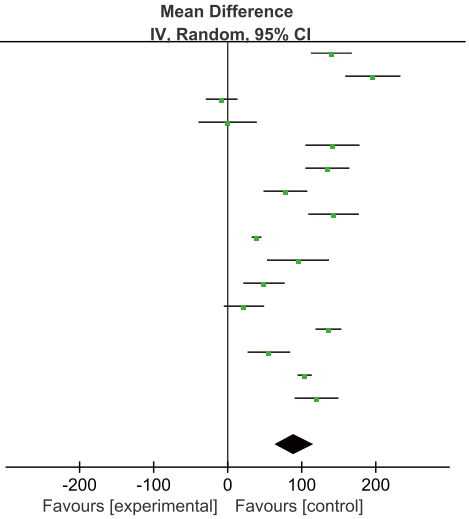
Publication bias

Begg's funnel plot were drawn for each outcome and used to assess publication bias. As shown in the funnel plot of POPF (*Figure 7*), and all studies lie inside the 95% CIs

A

Study or Subgroup	LPD Mean	LPD SD	LPD Total	OPD Mean	OPD SD	OPD Total	Weight	Mean Difference IV, Random, 95% CI	Year
Asbun 2012	541	88	53	401	108	215	6.3%	140.00 [112.26, 167.74]	2012
Mesleh 2013	551	67	75	355	120.5	48	6.0%	196.00 [158.69, 233.31]	2013
Croome 2014	379.4	93.5	108	387.6	91.8	214	6.5%	-8.20 [-29.70, 13.30]	2014
Kris 2014	465	86	31	465	98	58	5.9%	0.00 [-39.40, 39.40]	2014
Tan 2015	513.17	56.13	30	371.67	85.53	30	6.0%	141.50 [104.89, 178.11]	2015
Song 2015	482.5	117.6	93	347.9	87.2	93	6.2%	134.60 [104.85, 164.35]	2015
Dokmak 2015	342	75	46	264	70	46	6.2%	78.00 [48.35, 107.65]	2015
Stauffer 2016	518	112	58	375	130.5	193	6.1%	143.00 [108.80, 177.20]	2016
Palanivelu 2017	359	14	32	320	13	32	6.7%	39.00 [32.38, 45.62]	2017
Poves 2018	460	84.75	24	365	67.5	29	5.8%	95.00 [53.13, 136.87]	2018
Kuesters 2018	477	97.75	62	428	117.25	278	6.3%	49.00 [21.04, 76.96]	2018
Han 2019	470.4	73.6	87	448.4	107.1	87	6.3%	22.00 [-5.31, 49.31]	2019
Hilst 2019	410	57.25	50	274	26.25	49	6.6%	136.00 [118.51, 153.49]	2019
Yoo 2020	400.2	91.2	69	344.6	80.9	69	6.3%	55.60 [26.83, 84.37]	2020
Huang 2020	432	40.75	98	328	26.75	98	6.7%	104.00 [94.35, 113.65]	2020
Nakeeb 2020	420	75	37	300	75	74	6.2%	120.00 [90.40, 149.60]	2020
Total (95% CI)			**953**			**1613**	**100.0%**	**89.80 [63.75, 115.84]**	

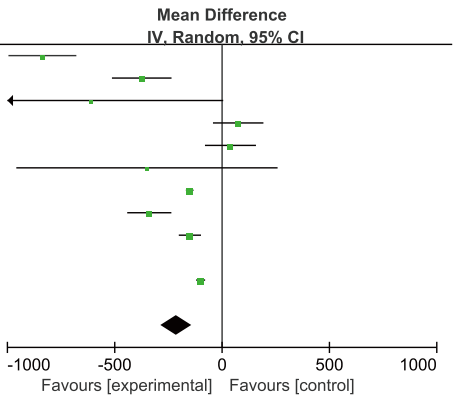
Heterogeneity: Tau² = 2604.83; Chi² = 395.73, df = 15 (P < 0.00001); I² = 96%
Test for overall effect: Z = 6.76 (P < 0.00001)



B

Study or Subgroup	LPD Mean	LPD SD	LPD Total	OPD Mean	OPD SD	OPD Total	Weight	Mean Difference IV, Random, 95% CI	Year
Asbun 2012	195	136	53	1,032	1,151	215	9.0%	-837.00 [-995.15, -678.85]	2012
Croome 2014	492.4	519.3	108	866.7	733.7	214	9.9%	-374.30 [-513.06, -235.54]	2014
Kris 2014	841.8	994.8	31	1,452.1	1,966.7	58	1.3%	-610.30 [-1225.78, 5.18]	2014
Dokmak 2015	368	287.5	46	293	287.5	46	11.0%	75.00 [-42.50, 192.50]	2015
Song 2015	609	375	93	570	448	93	11.0%	39.00 [-79.74, 157.74]	2015
Stauffer 2016	250	2,112.5	58	600	1,937.5	193	1.3%	-350.00 [-958.51, 258.51]	2016
Palanivelu 2017	250	22	32	401	46	32	15.2%	-151.00 [-168.67, -133.33]	2017
Han 2019	246.7	187.8	87	585.8	452	87	11.8%	-339.10 [-441.95, -236.25]	2019
Hilst 2019	300	59.5	50	450	175	49	14.2%	-150.00 [-201.70, -98.30]	2019
Nakeeb 2020	250	362.5	37	450	362.5	0		Not estimable	2020
Huang 2020	200	75	98	300	75	98	15.1%	-100.00 [-121.00, -79.00]	2020
Total (95% CI)			**693**			**1085**	**100.0%**	**-212.25 [-286.15, -138.34]**	

Heterogeneity: Tau² = 9284.37; Chi² = 139.59, df = 9 (P < 0.00001); I² = 94%
Test for overall effect: Z = 5.63 (P < 0.00001)



C

Study or Subgroup	LPD Events	LPD Total	OPD Events	OPD Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Croome 2014	21	108	71	214	29.7%	0.49 [0.28, 0.85]	2014
Dokmak 2015	5	46	4	46	2.8%	1.28 [0.32, 5.11]	2015
Stauffer 2016	15	58	90	193	23.8%	0.40 [0.21, 0.77]	2016
Palanivelu 2017	3	32	7	32	4.9%	0.37 [0.09, 1.58]	2017
Kuesters 2018	9	62	65	278	15.7%	0.56 [0.26, 1.19]	2018
Yoo 2020	9	69	10	69	6.7%	0.89 [0.34, 2.33]	2020
Nakeeb 2020	11	37	26	74	9.4%	0.78 [0.33, 1.83]	2020
Huang 2020	9	98	10	98	7.0%	0.89 [0.35, 2.30]	2020
Total (95% CI)		**510**		**1004**	**100.0%**	**0.58 [0.43, 0.77]**	
Total events	82		283				

Heterogeneity: Chi² = 5.27, df = 7 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.78 (P = 0.0002)

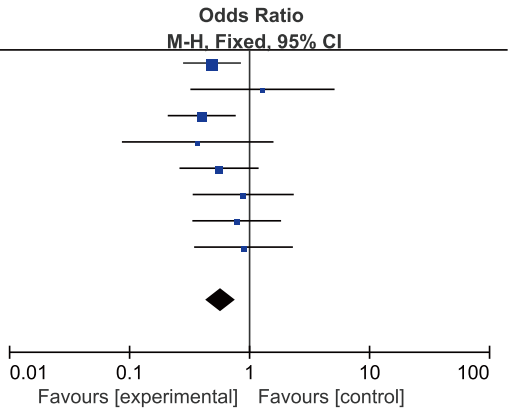


Figure 3 Forest plot of comparison of LPD versus OPD for operative outcomes. (A) Forest plot for operative time; (B) forest plot for operative time; (C) forest plot for operative time. LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

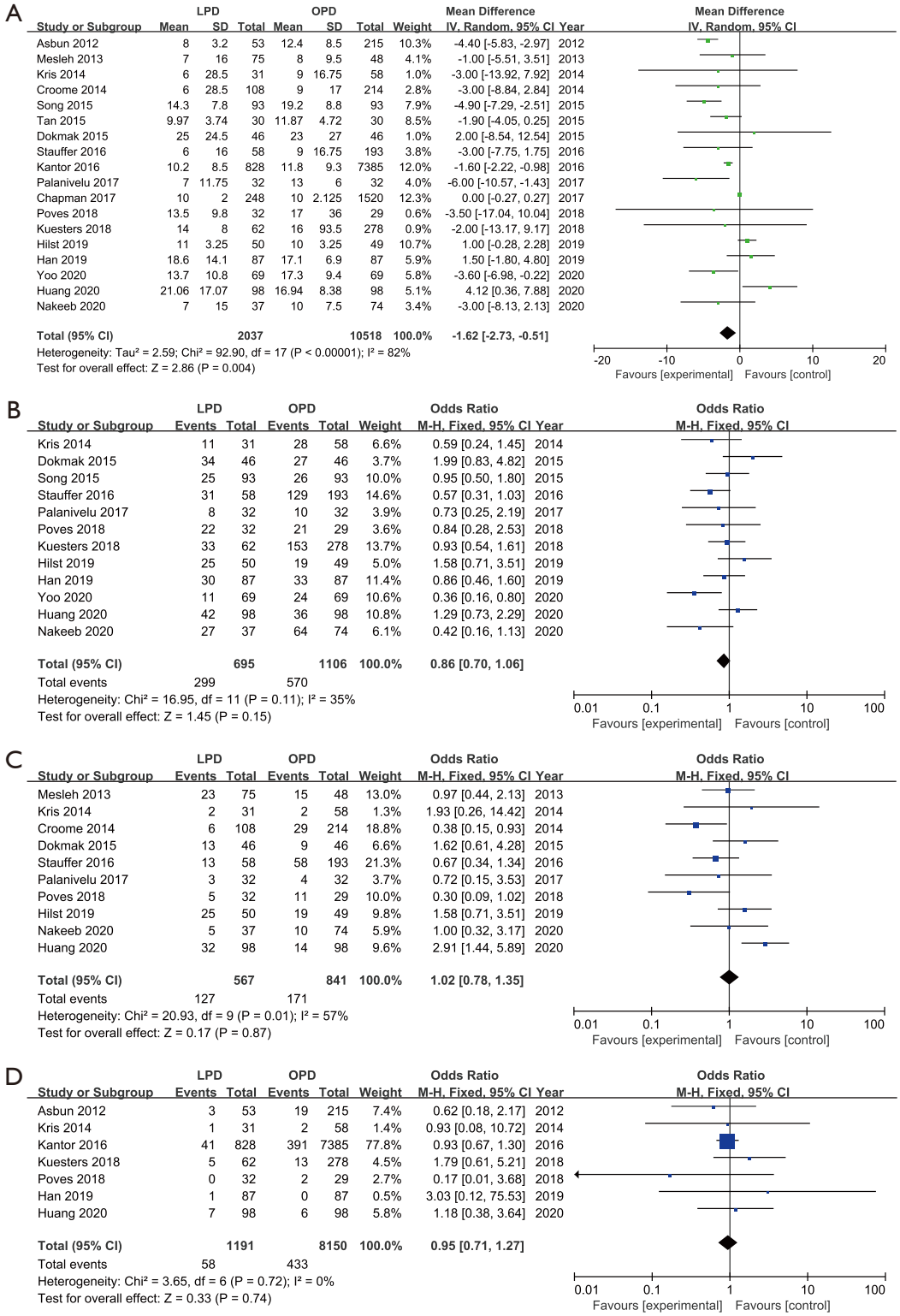


Figure 4 Forest plot of comparison of LPD versus OPD for Postoperative outcomes. (A) Forest plot for length of stay; (B) forest plot for overall complication rates; (C) forest plot for Cliavien-Dindo grade ≥ III; (D) forest plot for 90-day mortality. LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

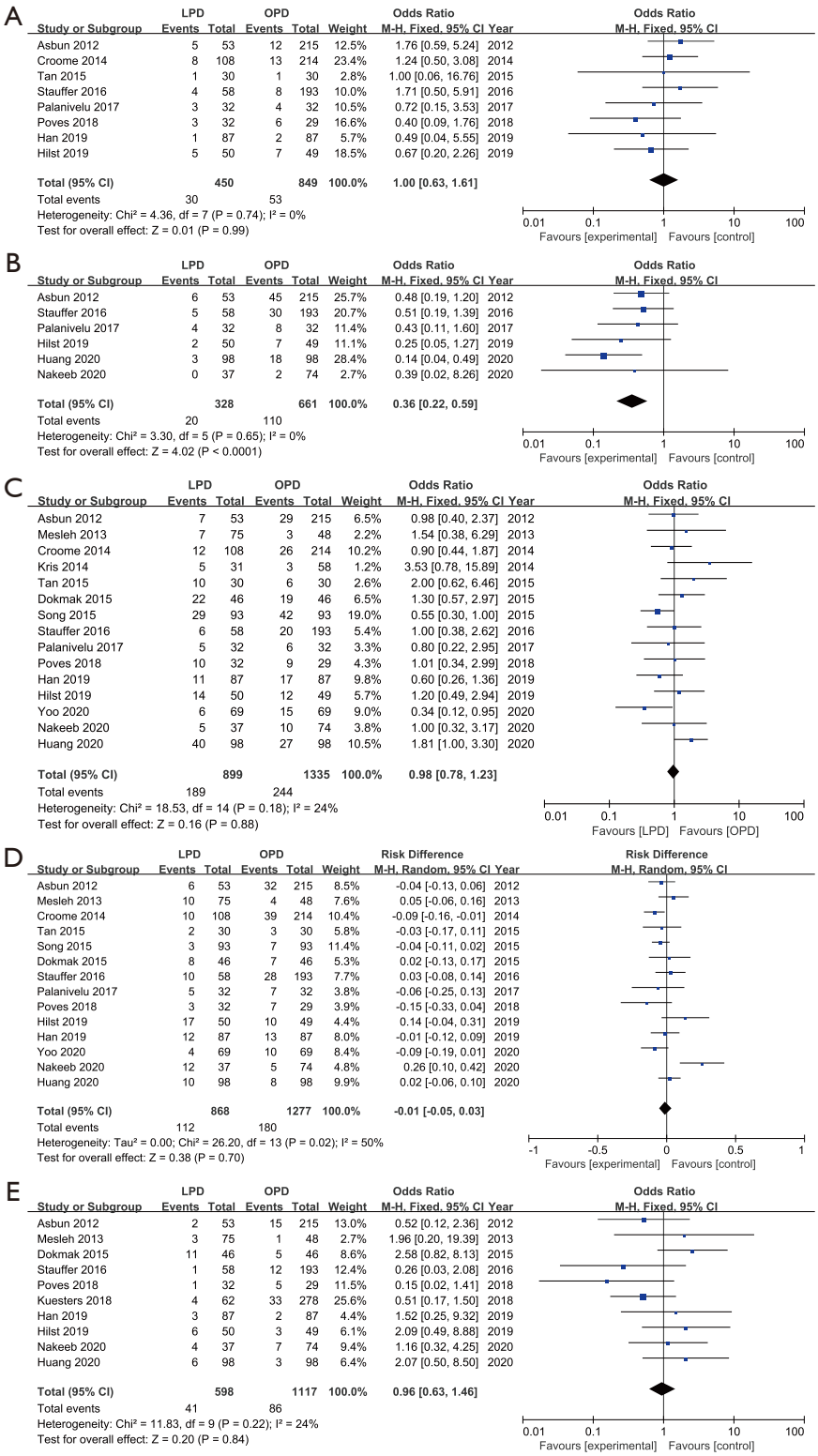


Figure 5 Forest plot of comparison of LPD versus OPD for overall complication rates. (A) Forest plot for postpancreatectomy hemorrhage; (B) forest plot for wound infection; (C) forest plot for postoperative pancreatic fistula; (D) forest plot for delayed gastric emptying; (E) forest plot for reoperation. LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

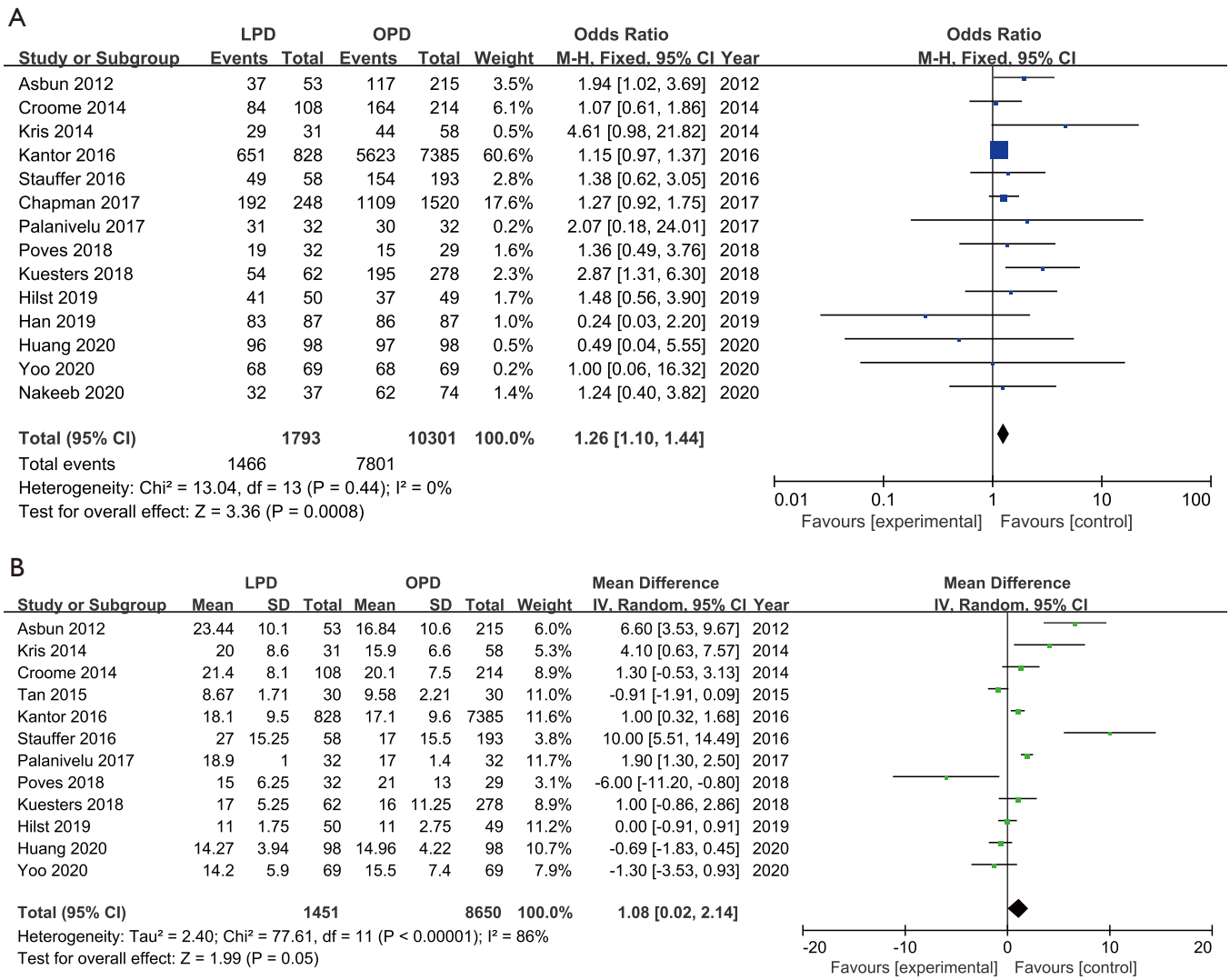


Figure 6 Forest plot of comparison of LPD versus OPD for short-term oncological outcomes. (A) Forest plot for R0 resection rate; (B) forest plot for lymph node dissection. LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

indicated no publication bias.

Discussion

Laparoscopic pancreatoduodenectomy (LPD) is one of the most difficult operations in general surgery due to its complicated operation process and high requirements for surgeons. It is considered as the "Everest" of abdominal endoscopic surgery. After more than 20 years of accumulation and development, and with the improvement of science and technology and the improvement of surgical facilities and equipment, LPD has been widely carried out in large medical centers at home and abroad. Previous clinical studies have preliminarily shown that LPD can achieve the same safety and effectiveness as OPD, and has certain advantages in postoperative recovery time. Because of the limited number of RCTs, it is still difficult to assess the feasibility and oncologic outcomes of LPD. As surgical technique is an important bias factor, assessing the role of the surgeons' learning curve and their impact on the results is of particular importance. Three RCTs and fifteen large-scale retrospective cohorts consisting of 12,495 patients were included in this study to compare the perioperative outcomes and oncologic outcomes and of LPD with OPD

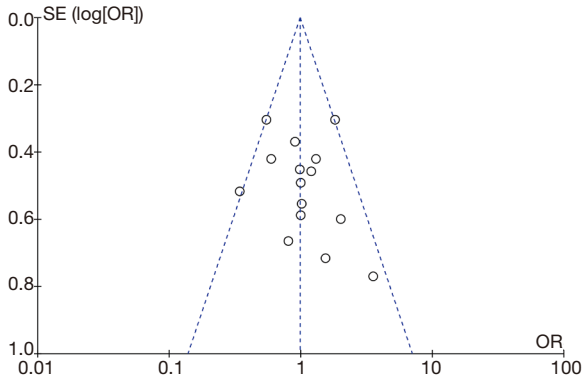


Figure 7 Funnel plots for postoperative pancreatic fistula.

after learning curve.

The results of our meta-analysis shows LPD has a shorter LOS, lower wound infection rate , less blood loss but a longer operative time than OPD, which was similar with the study of Nickel *et al.* (31). The main factors that lead to the longer operation time of LPD are that the technique is in the stage of accumulation and development, the technique is not skilled enough, and the team cooperation is not close enough. Additionally, owing to longer dissection and reconstruction LPD has longer operative time.

Negative margin and the number of lymph node dissection are two important malignancy prognosis factors in PD. Pooled data from this meta-analysis revealed that LPD has a higher R0 rate than OPD. We think that this may be explained by patients with early stage or even benign diseases were chosen to perform LPD. From the perspective of tumor radical effect, the results of this study show that the two surgical methods have the same effect in the number of lymph node dissection, suggesting that LPD and OPD have the same tumor radical effect, which is basically consistent with the results of most existing clinical studies (5,32). Even though the number of lymph node dissection between LPD and OPD were similar, there was a tendency that the OPD group has more lymph nodes harvested which was consistent with the study of Sharpe *et al.* (33). This may be caused by LPD cases are early stage cases with no obvious blood vessels and no invasion of surrounding organs, the sample size may not be enough and there is a possibility of selection deviation.

There are many complications of LPD, including pancreatic fistula, postoperative bleeding, gastric emptying disorder, wound infection, wound dehiscence, pneumonia, respiratory failure, urinary tract infection, stroke, renal failure, cardiac arrest, myocardial infarction, thromboembolic events, septic shock, sepsis, reoperation, etc. The most important of them are pancreatic fistula, postoperative bleeding and gastric emptying disorder.

There was no significant difference in the 90-day mortality, overall complication rates, POPF, and the incidence of severe complications (Clavien Dindo 3/4 grade complications) between the two groups, indicating that the safety of the two groups was similar. POPF was considered the most common and difficult complication after PD, which could cause DGE, hemorrhage, intra-abdominal abscess, sepsis, and influence the postoperative mortality (34,35). At present, most studies have confirmed that the incidence of pancreatic fistula in LPD and OPD is similar, and the difference is not statistically significant. Postoperative bleeding may come from anastomotic stoma, blood vessels, pancreatic stump, stress ulcer, etc.

However, there are still some limitations in this study. First, the main limitation is that there were only 3 RCTs, which may have contributed to biased data. Even though 3 RCTs were included in this meta-analysis, the quality of evidence remained moderate. Furthermore, selection criteria could strongly influence the outcomes. What's more, the follow-up time was too short, some outcomes not being assessed, such as recurrence and survival (disease-free and overall) and long-term complications of LPD needs to be evaluated.

In summary, the present meta-analysis revealed that LPD is a safe alternative to OPD as it is associated with significant reductions in blood loss, blood transfusion, LOS, and the incidence of wound infection. This study suggests that LPD is a technically and oncologically safe and feasible approach for hepatopancreatobiliary surgeons after learning curve and LPD should be a preferable choice as LPD achieved similar postoperative outcomes and superior oncological outcomes compared with OPD. Compared with the 100-year history of OPD, there is still a long way to go. We recommend that LPD should be conducted in experienced centers with specialist surgeons. Future large-scale prospective comparative studies and randomized clinical trials are expected to provide more convincing results for evaluation to further evaluate the safety and efficacy of LPD after learning curve.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs-20-916). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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