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Laparoscopic *versus* open pancreatoduodenectomy: a meta-analysis of randomized controlled trials

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Author´s contributions: DZL, ZLY, CXC, YFZ and JCH contributed to study concept and design, acquisition, analysis, interpretation of the data and drafting of the manuscript. JCH and WPC contributed to data collection and manuscript review. DZL and CXC contributed to study concept and design, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. JCH and ZYF supervised the study. All authors read and approved the final manuscript.

**Dezheng Lin, Zhaoliang Yu and Xiaochuan Chen contributed equally to this study.*

Institutional review board statement: This study was approved by the Institutional Review Board (IRB) of The Sixth Affiliated Hospital of Sun Yat-sen University.

Informed consent statement: This is a meta-analysis study and we petition for a waiver of the informed consent.

ABSTRACT

Introduction: the evidence with regard to the benefit of laparoscopic surgery for pancreatoduodenectomy is conflicting. The aim of this meta-analysis was to compare the short-term outcomes in patients undergoing laparoscopic or open pancreatoduodenectomy via randomized controlled trial studies.

Methods: PubMed, Embase and Cochrane Library databases were searched for studies addressing laparoscopic *versus* open pancreatoduodenectomy up to February 2019. Only randomized controlled trial studies were included.

Results: three randomized controlled trial studies were identified, which included a total of 224 patients. Statistically significant differences were found with regard to estimated blood loss in favor of laparoscopic pancreatoduodenectomy (WMD, -150.9 ml; 95% CI, -167.61 to -134.18; $p < 0.001$) but with longer operative time (WMD, 97.66 min; 95% CI, 21.28 to 174.05; $p = 0.01$). No significant differences were found for severe postoperative complications (defined as Clavien-Dindo grade ≥ III complications), complication-related mortality within 90 days, blood transfusion requirements, length of hospital stay, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, surgical site infection, readmission rate, reoperation rate, harvested lymph nodes and R0 resection rate.

Conclusions: the perioperative safety of laparoscopic pancreatoduodenectomy, which may have an advantage of lower estimated blood loss, is comparable to that of open pancreatoduodenectomy. Currently, a small volume of cases may be an important reason that affects the evaluation between laparoscopic and open pancreatoduodenectomy. Further evaluation of laparoscopic pancreatoduodenectomy will require large randomized control trials.

Keywords: Laparoscopic pancreatoduodenectomy. Periampullary tumors. Meta-analysis.

INTRODUCTION

Pancreatoduodenectomy (or Whipple procedure) is one of the most complex procedures in general surgery and is mostly used for premalignant and malignant periampullary lesions (1). Gagner and Pomp firstly described laparoscopic pancreatoduodenectomy (LPD) in 1994 (2), which has been an alternative procedure to open pancreatoduodenectomy (OPD) in the last decade (3). Recently, several observational studies from high-volume centers showed the potential benefits of LPD compared with OPD, such as reduced delayed gastric emptying and a shorter hospital stay (4,5). On the other hand, LPD seems to be associated with an increased operative time, higher rates of postoperative mortality and rising readmission rates in low-volume centers (5-7). It is unclear whether LPD could offer a safe alternative to OPD and patients could achieve benefits from LPD. With the increasing worldwide interest in LPD, evidence on the evaluation of the safety and surgical outcomes of LPD is warranted (8).

Correa-Gallego et al. firstly reported a meta-analysis on LPD *versus* OPD with six observational studies in 2013 (9). As high-volume and comparative studies have increased in the last decade, some meta-analyses have reported on LPD and OPD (4,10-12). Although these studies had found some meaningful results, all of them were based on retrospective studies. Without adequate random sequence generation and blinding, the risk of bias might increase. As a result, the quality of the evidence pooled from these retrospective trials must be judged as low. Therefore, a meta-analysis based on well-designed randomized controlled trial (RCT) study is urgently needed.

Hence, this meta-analysis was performed to evaluate the short-term outcomes of LPD *versus* OPD. Main outcomes and secondary outcomes (intraoperative, postoperative and oncological outcomes) were measured using meta-analytical methods.

METHODS

Search and selection strategies

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The Spanish Journal of Gastroenterology

This meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analysis and Meta-analysis guidelines (13,14). PubMed, Embase and the Cochrane library were searched up to February 2019. The search terms were [Title/Abstract]: "laparoscopy", "laparoscopic", "pancreaticoduodenectomy", "pancreatoduodenectomy". If multiple reports describing the same population were published, the newest report was used. The literature search was performed independently by two reviewers (DZL and ZLY). All inconsistent results were resolved by discussion with a third reviewer (JCH).

Inclusion and exclusion criteria

Only RCT studies reporting laparoscopic *versus* open pancreatoduodenectomy were included, regardless whether the lesions were benign, premalignant or malignant conditions. All the included studies had at least one of the relevant outcomes mentioned below. Editorials, letters, conference abstracts, review articles, case reports and animal experimental studies were excluded.

Outcomes of measures

Main outcomes

Severe postoperative complications (defined as Clavien-Dindo grade ≥ III complications) and complication-related mortality within 90 days.

Secondary outcomes

Intraoperative outcomes: operative time, estimated blood loss (EBL) and blood transfusion requirements.

Postoperative outcomes: length of hospital stay, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, surgical site infection, readmission rate and reoperation rate.

Oncologic outcomes: harvested lymph nodes and R0 resection rate.

Data extraction and statistical analyses

Statistical analyses were performed using the RevMan 5.3 software (Cochrane

Collaboration, Oxford, UK). The weighted mean differences (WMDs) were calculated for continuous variables. Risk ratios (RRs) were calculated for dichotomous variables. A *p* value < 0.05 was considered to be statistically significant. For continuous data with the median and range values, the means and standard deviations were calculated using the formula described by Hozo et al. (15). The Q test (also known as Chi-squared test) and I^2 statistic were used to evaluate the heterogeneity among studies. A Cochrane Q statistical p < 0.10 and/or I^2 > 50% was taken to indicate significant heterogeneity (16). A random effect model was used in this meta-analysis.

RESULTS

The PRISMA flow chart is shown in figure 1 and 1,557 citations were retrieved from the search strategy. Three RCTs (17-19) from three different counties were included in the analysis, with a total of 224 patients (114 patients in LPD group, 110 patients in OPD group). The characteristics of eligible studies are shown in table 1.

Main outcomes

Severe postoperative complications (defined as Clavien-Dindo grade ≥ III complications)

All three studies documented severe postoperative complications, which were defined as Clavien-Dindo grade ≥ III complications. There was a significant heterogeneity among the studies (I^2 = 60%, p = 0.08). A random effect model was adopted and the RR was 0.80 (95% CI, 0.36-1.79, p = 0.59) (Fig. 2A), indicating no significant difference in severe postoperative complications between the two groups.

Complication-related mortality within 90 days

Data from the three studies reported complication-related mortality. There was no significant heterogeneity among the studies (I^2 = 37%, p = 0.20). No statistically significant difference was noted between the two groups using a random effect model, (RR 1.22; 95% CI, 0.19-8.02, p = 0.84) (Fig. 2B).

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The Spanish Journal of Gastroenterology

Secondary outcomes

All three studies addressed operative time and these data suggested that there was no significant heterogeneity among the studies (I^2 = 98%, p < 0.001). The pooled data showed that operative time was significantly longer in the LPD group compared to the OPD group (WMD, 97.66 min; 95% CI, 21.28 to 174.05; p = 0.01) (Fig. 3A). Only two studies reported EBL. No significant heterogeneity was observed among the studies (I^2 = 0%, p < 0.001). The EBL was lower in the LPD group than in the OPD group (WMD, -150.9 ml; 95% CI, -167.61 to -134.18; p < 0.001) (Fig. 3B).

No significant differences were found in blood transfusion requirements, length of hospital stay (p = 0.45), postoperative pancreatic fistula (p = 0.45), postpancreatectomy hemorrhage (p = 0.20), bile leakage (p = 0.97), delayed gastric emptying (p = 0.76), surgical site infection (p = 0.05), readmission rate (p = 0.89), reoperation rate (p = 0.79), harvested lymph nodes (p = 0.54) and R0 resection rate (p = 0.32) (Table 2).

Quality assessment and risk of bias analysis

The outcomes of quality assessment and risk of bias are shown in figure 4. In general, the three RCTs included were of a moderate quality with a low risk of bias.

DISCUSSION

A total of three RCTs with up to 224 patients (114 patients in LPD group, 110 patients in OPD group) were included in this meta-analysis. Our results showed that the LPD group had a longer operative time and lower EBL compared to the OPD group. There were no significant differences in the other clinical outcomes including severe postoperative complications and complication-related mortality within 90 days. We hope these data will help to illustrate the safety and feasibility of LPD and promote its application in treating periampullary tumors.

At present, the optimal surgical treatment for periampullary tumors is yet to be achieved. The traditional OPD surgery has been performed for a long time (20), but this procedure is still considered to date as the gold standard of surgical treatment. With the development of surgical technology and the increased efforts, LPD has become increasingly popular and has been shown to improve the PD, thereby obtaining a better prognosis (21). However, there are still some controversies with regard to the safety, feasibility and clinical benefits of LPD. To our knowledge, some meta-analyses compared the LPD with OPD, demonstrating that LPD might benefit from lower intraoperative blood loss, reduced delayed gastric emptying and a shorter hospital stay (4,22,23). However, this might be associated with increased operative time, high postoperative mortality and higher readmission rate (5,7,24). Many studies focused on this comparison but none were based on RCT. Moreover, retrospective studies have no adequate random sequence generation and blinding, which may increase the risk of bias. Therefore, the quality of the evidence pooled from these observational trials is often judged as low.

In the last two years, three RCTs compared LPD with OPD: the PLOT trial (17), the PADULAP trial (18) and the LEOPARD-2 trial (19). These three RCTs all showed that LPD was associated with a longer operative time, while the results from the PLOT and PADULAP trials supported that LPD was superior to OPD in terms of the length of hospital stay. However, these RCTs compared LPD with OPD and they included a small number of patients. In this study, all RCTs about LPD *versus* OPD were included in order to reduce the influence on statistical significance caused by the small number of patients. In this meta-analysis, we found that LPD was safe, and comparable to OPD with regard to the main outcomes and secondary outcomes. Our result also showed that the LPD group had a lower rate of surgical site infection compared to the OPD group, although it is not statistically significant ($p = 0.05$). This is consistent with that in minimally invasive procedures, indicating that LPD may reduce surgery-related infections, which may be one explanation for the shorter length of hospital stay in the LPD group.

Currently, one of the leading topics for LPD is the quality of excision. Our results indicated that there were no differences in harvested lymph nodes and the R0 resection rate between both groups, suggesting that the oncologic outcomes of LPD were not inferior to OPD. However, LPD is a relatively novel technique with complex procedures and requires a long learning time (25). Thus, leading to fewer studies that assess the long-term observation between LPD and OPD. The Conrad study reported that LPD was not inferior to OPD with respect to long-term outcomes for adenocarcinoma among 87 patients (26). The Stauffer study found that long-term survival was similar for one-, two-, three-, four- and five-year survival for OPD (n = 193) and LPD (n = 58) (27). At present, all these reports about long-term outcomes are based on retrospective studies. As current RCTs have not reported long-term outcomes, it is impossible to compare the superiority of the techniques in this meta-analysis. Moreover, it still requires more time for long-term follow up in RCTs.

With regard to complication-related mortality in this meta-analysis, there were six deaths in the LPD group (mortality ranged from 0% to 10%). One patient died from septic shock as there were multiple spontaneous perforations involving the small bowel in the PLOT trial (17). Five patients died in the LEOPARD-2 trial (19): one died from bowel ischemia due to intraoperative vascular damage, two died from post-pancreatectomy hemorrhage and one died from grade C pancreatic fistula. However, the pooled data demonstrated that there were no statistically significant differences between the LPD and OPD groups, which is similar to the results in the meta-analyses reported by de Rooij T (4) and Chen (11). Recently, a retrospective multicenter analysis of 1,029 patients in China (28) showed that there was a total of 61 (5.93%) deaths within 90 days, which is also in line with the mortality rate (5.26%) in this meta-analysis.

There are several limitations in this meta-analysis that must be taken into account. The main limitation is that only limited numbers of RCTs and patients were included, which will affect the adequate power of this study. Secondly, there may be a publication bias as all the included studies were published in English and these data were not from high-volume centers. Finally, it is known that the most important value of the minimally invasive technique is the possibility of achieving a better long-term oncological outcome. However, there were no data about overall survival and disease-free survival in this meta-analysis, which needs more time for long-term observations.

CONCLUSIONS

The perioperative safety of LPD, which may have an advantage of lower EBL, is comparable to that of OPD. Currently, a small number of cases may be an important factor that affected the comparison between LPD and OPD. Further evaluation of LPD requires large scale RCTs.

ACKNOWLEDGMENTS

Dezhen Lin, Zhaoliang Yu and Xiaochuan Chen contributed equally to this study and should be considered as co-first author. We thank National Key Clinical Discipline for supporting this project.

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ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Table 1. Characteristics of studies included in this meta-analysis

Study	Country	Period (y)	Setting	Sample size	Gender (n, M: F)		BMI (kg/m2)	ASA (I /II/III)	
				LPD/OPD	LPD	OPD	LPD/OPD	LPD	OPD
Palanivelu 2017	India	2013-2015	Single center	32/32	22/10	18/14	20.4 ± 0.6/20.9 ± 0.7	11/18/3	13/17/2
Poves 2018	Spain	2013-2017	Single center	32/29	13/19	20/9	24 (16-33)/26 (17-43)	1/18/13	1/13/15
Van Hilst 2019	Netherlands	2013-2017	Multicenter	50/49	20/30	25/24	25 ± 3/26 ± 4	5/32/13	7/26/16

LPD: laparoscopic pancreatoduodenectomy; OPD: open pancreatoduodenectomy; BMI: body mass index.

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The Spanish Journal of Gastroenterology

Table 2. Results of the meta-analysis comparison of LPD and LS

Outcomes	Studies	Patients		WMD/RR	p value	Study heterogeneity	
		LPD	OPD	(95% CI)		I^2, %	p value
Intraoperative outcomes							
Blood transfusion requirements	2	64	61	0.75 (0.39, 1.43)	0.38	5	0.31
Postoperative outcomes							
LOS	3	114	110	-2.26 (-8.08, 3.55)	0.45	77	0.01
POPF	3	114	110	0.87 (0.60, 1.26)	0.45	0	0.59
PPH	3	114	110	0.62 (0.31, 1.27)	0.20	0	0.84
Bile leakage	3	114	110	1.02 (0.43, 2.41)	0.97	0	0.49
DGE	3	114	110	0.84 (0.37, 2.07)	0.76	58	0.09
Surgical site infection	2	82	81	0.41 (0.17, 1.00)	0.05	0	0.54
Readmission rate	3	114	110	0.96 (0.51, 1.79)	0.89	0	0.56
Reoperation rate	3	114	110	0.81 (0.18, 3.714)	0.79	45	0.16
Oncologic outcomes							
Harvested lymph nodes	3	114	110	-0.78 (-3.24, 1.69)	0.54	95	< 0.01
R0 resection rate	3	114	110	1.05 (0.95, 1.15)	0.32	0	0.71

LOS: length of hospital stay; POPF: postoperative pancreatic fistula; PPH: post-pancreatectomy hemorrhage; DGE: delayed gastric emptying (DGE); WMD: weighted mean difference; RR: risk ratio; CI: confidence interval.

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The Spanish Journal of Gastroenterology

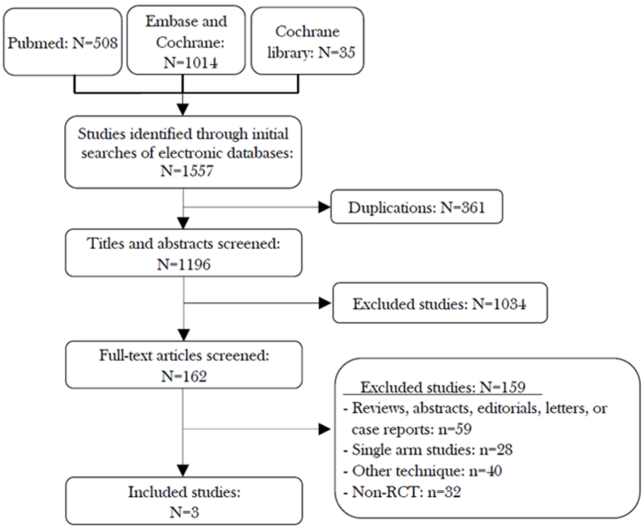

Fig. 1. Flow diagram of trial identification, screening, inclusion and exclusion criteria.

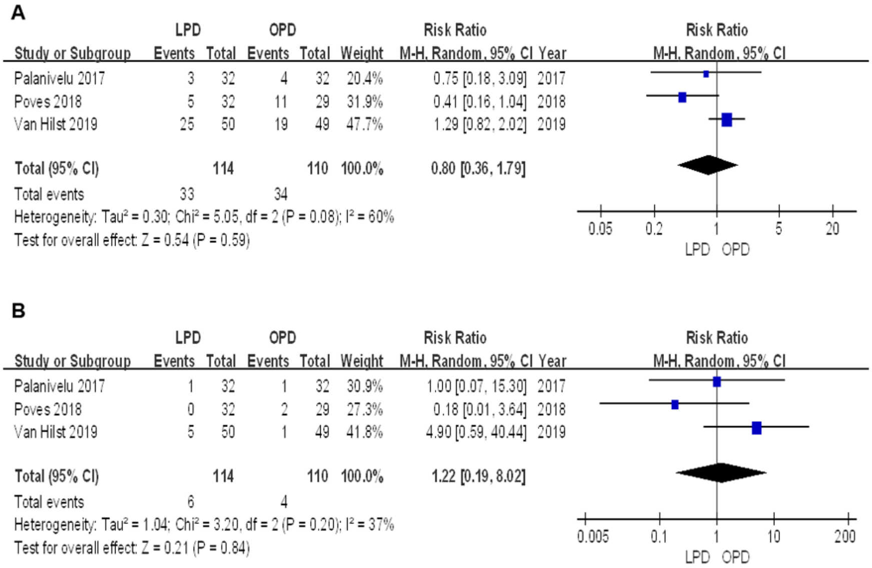

Fig. 2. Forest plots of the main outcomes did not show significant differences between LPD and OPD. A. Severe postoperative complications (defined as Clavien-Dindo grade ≥I II complications) comparing LPD *versus* OPD. B. Complication-related mortality within 90 days, comparing LPD *versus* OPD. LPD: laparoscopic pancreatoduodenectomy; OPD: open pancreatoduodenectomy.

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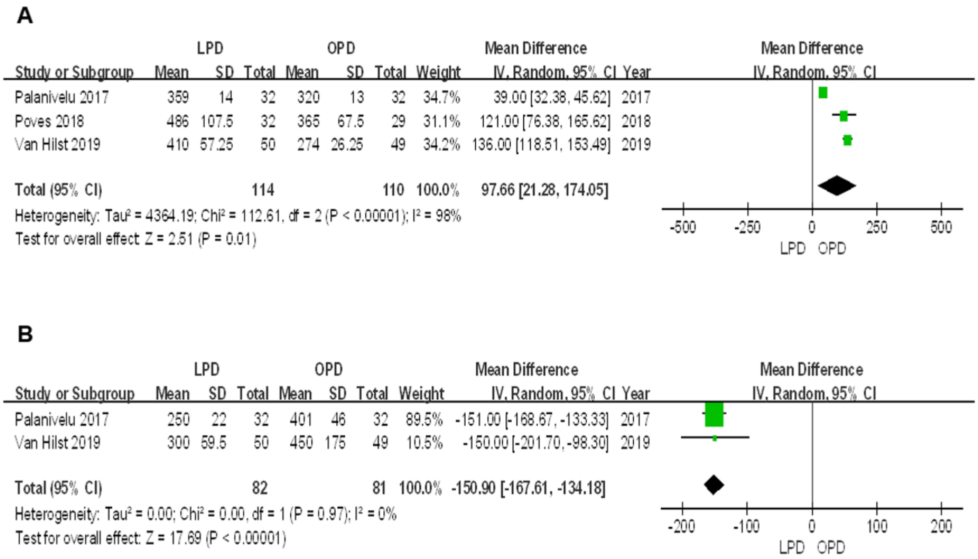

Fig. 3. LPD had a significantly longer operative time and lower EBL. A. Operative time comparing LPD *versus* OPD. B. EBL comparing LPD *versus* OPD. LPD: laparoscopic pancreatoduodenectomy; OPD: open pancreatoduodenectomy; EBL: Estimated blood loss.

REVISTA ESPAÑOLA DE
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The Spanish Journal of Gastroenterology

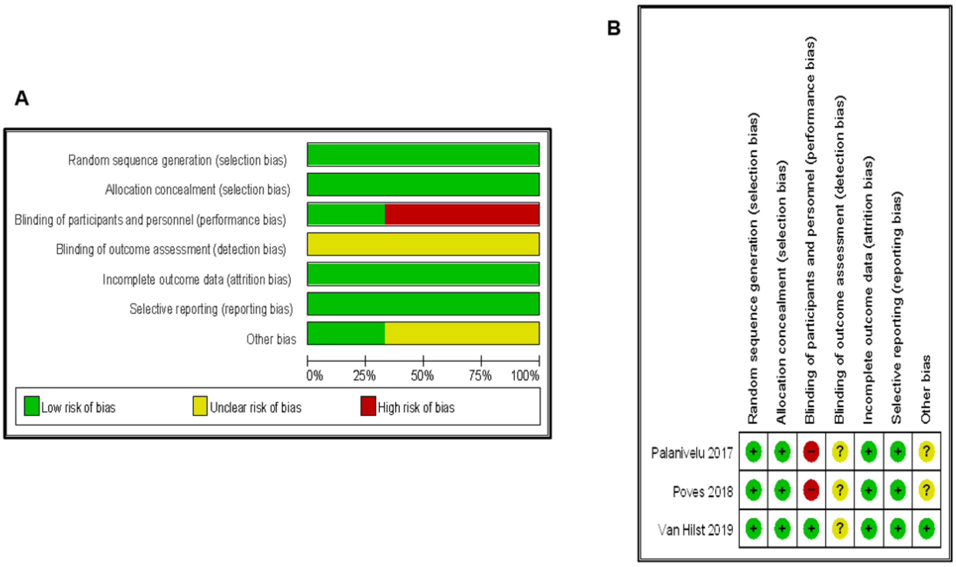

Fig. 4. Summary of quality assessment and the risk of bias in this meta-analysis. A. Risk of bias graph. B. Risk of bias summary.