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Minimally invasive pancreaticoduodenectomy for periampullary disease: a comprehensive review of literature and meta-analysis of outcomes compared with open surgery

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Abstract

Background: Minimally invasive pancreatoduodenectomy (MIPD) has been gradually attempted. However, whether MIPD is superior, equal or inferior to its conventional open pancreatoduodenectomy (OPD) is not clear.

Methods: Studies published up to May 2017 were searched in PubMed, Embase, Cochrane Library, and Web of Science. Main outcomes were comprehensively reviewed and measured including conversion to open approach, operation time (OP), estimated blood loss (EBL), transfusion, length of hospital stay (LOS), overall complications, postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), post-pancreatectomy hemorrhage (PPH), readmission, reoperation and reasons of preoperative death, number of retrieved lymph nodes (RLN), surgical margins, recurrence, and survival. The software of Review Manage version 5.1 was used for meta-analysis.

Results: One hundred studies were included for systematic review and 26 out of them (totally 3402 cases, 1064 for MIPD, 2338 for OPD) were included for meta-analysis. In the early years, most articles were case reports or non-control case series studies, while in the last 6 years high-volume and comparative researches were increasing gradually. Systematic review revealed conversion rates of MIPD to OPD ranged from 0% to 40%. The mean or median OP of MIPD ranged from 276 to 657 min. The total POPF rates vary between 3.8% and 50% observed in all systematic reviewed studies. Meta-analysis demonstrated MIPD had longer OP (WMD = 99.4 min; 95%CI: 46.0 ~ 152.8, P < 0.01), lower blood loss (WMD = −0.54 ml; 95% CI, −0.88 ~ −0.20 ml; P < 0.01), lower transfusion rate (RR = 0.73, 95%CI: 0.57 ~ 0.94, P = 0.02), shorter LOS (WMD = −3.49 days; 95%CI: -4.83 ~ −2.15, P < 0.01). There was no significant difference in time to oral intake, postoperative complications, POPF, reoperation, readmission, perioperative mortality and number of retrieved lymph nodes.

Conclusion: Our study demonstrates MIPD is technically feasible and safety on the basis of historical studies. MIPD is associated with less blood loss, faster postoperative recovery, shorter length of hospitalization and longer operation time. These findings are waiting for being confirmed with robust prospective comparative studies and randomized clinical trials.

Keywords: Laparoscopy, Robot, Minimally invasive, Pancreaticoduodenectomy, Morbidity, Review, Meta-analysis

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Background

Gagner & Pomp [1] described the first laparoscopic pancreatoduodenectomy (LPD) in 1994. There are two commonly used version of LPD. Laparoscopic-assisted PD (LAPD), also known as hybrid laparoscopic PD (HLPD), is characterized as performing lymphadenectomy and bloc extraction of the specimen under laparoscopy, then requiring an auxiliary incision to finish reconstruction of the digestive tract. If the operation were completely performed intracorporeally, the technique was referred as totally laparoscopic pancreatoduodenectomy (TLPD). Robotic surgery is an emerging technology. If robotic system, usually da Vinci, was used to facilitate procedures of resection or reconstruction, it was referred as RPD. LPD and PPD are collectively known as minimally invasive PD (MIPD). MIPD is technically demanding and postoperative pancreatic fistula or bile leakage can be deadly without secure completion of the complicated pancreatic and biliary anastomoses [2, 3]. Very few institutions have committed to advocating the development of MIPD initially. Nowadays, with recent advances of laparoscopic surgical instruments and the accumulation of operative experience, especially the emerging of robotic system to facilitate the complexity of reconstruction, increasing centers attempted to carry out MIPD for benign and malignant periampullary disease [2, 4]. In fact, during the past six years, there had been a steep increase in the use of MIPD. However, reported series on MIPD were influenced by small sample size, single center experience and selection bias [2]. The majority of them were nonrandomized retrospective trials, while case series and high-quality comparative studies remained limited [2]. Therefore, in the current study, we aimed to perform a comprehensive systematic review of all available studies to improve on these single-institution series as well as a meta-analysis comparing MIPD and conventional open PD (OPD) to evaluate the safety, feasibility, and efficacy of MIPD.

Methods

Systematic literature search

Systematic searches of PubMed, Embase, Cochrane Library, and Web of Science were performed to identify articles published up to May 2017. Strategies included the terms "minimally invasive", "laparoscopic", "laparoscopy", "robot", "robotic", "Da Vinci", "pancreaticoduodenectomy", "Whipple", "PD" and "pancreatic resection" and "pancreatic surgery". The language of the publications was confined to English. References were searched for studies not found through the initial search.

Eligibility criteria

The inclusion criteria for systematic review were prospective or retrospective case series studies assessing surgical outcomes of MIPD, and comparative studies of MIPD and OPD, but case reports were excluded. Abstracts, letters, comments, conference proceedings, reviews were also excluded. Studies included more than 20 cases of MIPD were used for summarizing perioperative the relevant information. Studies included in the meta-analysis fulfilled the following criteria: (1) compared the outcomes of MIPD and OPD; (2) reported on at least one of the outcomes of interest mentioned below; (3) had adequate raw data reported such that we could extract the number or percentage of events for categorical outcomes; (4) continuous variables should both present means and standard deviations (SDs). We did not estimate the means and SDs from medians and ranges or inter-quartile ranges as the method of Hozo et al. [5], because this method may lead to deviation, especially when the sample size is small or the samples exhibit serious skewedness; (5) other kind of pancreatectomy such as enucleation, distal, central or total pancreatectomy; (6) if there was overlap between authors or centers, the higher quality or more recent literature were selected.

Data extraction and quality assessment

First, two investigators (Chen K and Pan Y) independently tabulated the data. A double-check procedure was performed to make sure of the accuracy of the data extracted. Then, a manager inputted the extracted data into a spreadsheet. The measured outcomes of all eligible publications can be divided into four categories: ① Study baseline: author, geographical region, facility, journal, publishing year, study period, sample volume, study subject, indications and surgical procedure; ② Intraoperative effects: conversion to open approach, operation time (OP), estimated blood loss (EBL), transfusion; ③ Postoperative recovery: time to first flatus or restart oral intake, length of hospital stay (LOS), morbidity and mortality [overall complications, postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH), readmission, reoperation and reasons of preoperative death]; ④ Oncologic outcomes: retrieved lymph nodes (RLN), surgical margins, recurrence, and survival. Relied on the complication reporting system of Memorial Sloan-Kettering Cancer Center [6], postoperative complications are categorized into medical complications (pulmonary embolism; nonsurgical infections; respiratory, cardiovascular, or metabolic events; arrhythmia, cerebral vascular accident; and deep venous thrombosis, phlebitis) or surgical complications (pancreatitis, bleeding events, any complication which required reoperation, any anastomotic leakage or stricture, wound complications, intra-abdominal collections, delayed gastric emptying and ileus). The use of intention-to-treat (ITT) analysis was investigated. POPF, DGE, and PPH were diagnosed in

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accordance with the International Study Group for Pancreatic Fistula (ISGPF) criteria [7–9]. Severe POPF was defined as ISGPF grade B/C [7]. Perioperative mortality was defined as deaths from any cause postoperatively. The Newcastle-Ottawa Quality Assessment Scale (NOS) was utilized to evaluate the quality of the researches included. The scale changes from 0 to 9 stars: researches with a score higher than or equal to 6 could be deemed as good methodologically.

Statistical analysis

The risk ratio (RR) was utilized to analyze the dichotomous variables and the weighted mean difference (WMD) was utilized to assess the continuous variables. Based on Der Simonian and Laird approach, the random-effects model was utilized so as to account for clinical heterogeneity due to both sampling variability and other factors such as differences in surgical skill and the numbers of procedures carried out by a surgeon. According to the overall POPF rate, the bias of potential publication was determined by carrying out informal visual inspection of funnel plots. The software of Review Manage version 5.1 (RevMan 5.1) that was downloaded from Cochrane Library was used to conduct data analysis. $P < 0.05$ was deemed as statistically important.

Results

Search results and baseline characteristics

A systematic review of the literature of peer-reviewed medical journals was performed to identify all studies published up to January 2017 that focused on the use of MIPD. The last search was performed on May 27th, 2017. A total of 528 potential articles published between 1994 and 2017 were initially identified from the literature searches. After the titles, abstracts and full text if necessary were reviewed, papers without according the eligibility criteria were excluded. A total of 144 studies included 37 comparative studies of MIPD and OPD, and the remaining 107 studies focused on therapeutic outcomes for MIPD (including 36 case reports and 8 video reports). The relevant literature was very scarce prior to 2004 ($n = 3$) [1, 10, 11]. After that, the articles about MIPD increased year by year. In the early years, most articles were case reports or non-control case series studies, which mainly came from Western Europe and South Asia countries. However, in the last 6 years high-volume and comparative researches were increasing gradually (Additional file 1). Growing medical centers, especially in USA, Japan and China, reported their trails in performing MIPD, from case report to case series, then to comparative studies. The highest number of publications has been from USA ($n = 54$), followed by Japan ($n = 20$), China ($n = 19$) (Additional file 2). There still had been no prospective randomized studies (RCTs) yet.
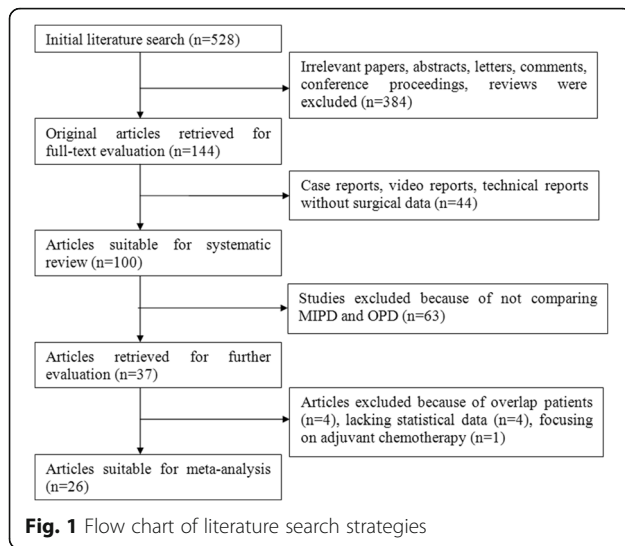
Additional file 3 shows a summary of previously published original articles that without including case reports, video reports or technical reports without surgical data [12–111].

The majority of papers were single center research based on their initial experience with short-term surgical outcomes. Thirteen studies reported mid- or long-term postoperative results [15, 16, 24, 31, 55, 57, 68, 80, 86, 90, 92, 96, 107], and one study concentrated on long-term quality of life (QOL) after surgery [61]. The indications of MIPD were periampullary or pancreatic disease with one exception, which reported three cases of LPD for the treatment of locally advanced gastric cancer [19]. Four studies reported experience of MIPD involving venous resection for locally advanced disease [27, 29, 69, 97]. Five reports have inquired into the learning curve of MIPD [60, 63, 67, 70, 109]. Two studies have investigated the safety and feasibility of MIPD for elderly patients [20, 85], whereas one research have evaluated the influence of obesity on the surgical outcomes of RPD [94]. Five papers had the focus on analyzing the hospital costs of MIPD [50, 71, 84, 88, 108]. Two multi-institution researches have compared the outcomes for MIPD between low-volume hospital and high-volume center [87, 99].

Of these 37 cohort studies, which have compared MIPD and OPD with perioperative outcomes, four studies were excluded from the meta-analysis due to overlap patient cohorts [50, 69, 85, 107]. Another five studies based on the American National Cancer Database (NCDB) and Nationwide Inpatient Sample (NIS) were also excluded because of lacking statistical data or focusing on adjuvant chemotherapy [66, 81, 96, 104, 108]. Besides, there may be potential overlap patients with other included studies from the United States medical centers. Finally, a total of 26 comparative studies were included for quantitative meta-analysis [17, 26, 30, 31, 33–36, 47, 53, 55, 57, 61, 63–65, 68, 70, 71, 74, 83, 84, 88, 92, 106, 110]. A flow chart of the search strategies, which contains reasons of excluded studies, is illustrated in (Fig. 1).

Characteristics and quality of studies for meta-analysis

A total of 3402 patients were included in the analysis with 1064 undergoing MIPD (31.3%) and 2338 undergoing OPD (68.7%). Total sample size for included studies ranged from 16 to 1239, with patient numbers in the MIPD arms ranging from 8 to 211. They represented an international experience (11 USA, 5 China, 2 South Korea, 2 Japan, 2 Canada, 1 UK, 1 Spain, 1 Germany and 1 France). Because MIPD was still much less performed than OPD in many centers, approximately, half of the included studies used case-match comparative analysis [31, 34, 53, 57, 61, 65, 68, 70, 83, 84, 106]. Two multi-

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Fig. 1 Flow chart of literature search strategies

institutional studies were found [65, 110]. Only three studies did not use the ISGPF criteria [30, 57, 61]. Nine studies used an ITT approach [26, 34–36, 53, 55, 63, 65, 68, 70, 88, 92], whereas eight were not [31, 33, 61, 64, 83, 84, 106, 110], and the remaining six were unclear [17, 30, 47, 57, 71, 74]. According to the NOS, sixteen out of the twenty-six observational studies got 6 stars, five articles got 7 stars, three articles got 8 stars and the remaining two got 9 stars. Additional file 4 presents the characteristics and quality assessment based on the NOS of the included studies. Other baseline description of these studies could be found in S3 Table 1.

Technical details and outcomes definitions of the meta-analysis included studies

The number of surgeons who performed robot-assisted surgery was reported in 80.8% of the included studies (21/26). Most of the included studies represented the experience of single surgeon or term (Additional file 5). The majority researches included both patients with benign and malignant disease, whereas five studies only confined to malignant tumors [30, 55, 57, 61, 92]. Although MIPD has been described for all indications, even locally advanced malignant disease invading surrounding organs or portal vein system [29, 69], most studies excluded patients with adenocarcinoma involving the vascular structures or very large tumor [17, 33, 35, 36, 53, 63, 64, 68, 70, 71, 110]. The most commonly reported pancreatic anastomosis procedure were duct-to-mucosa, end-to-side pancreaticojejunostomy (PJ) with or without stents. Some studies also included cases of pancreaticogastrostomy (PG) [26, 30, 65, 106]. The surgical indications and technical details reported by the included studies are shown in Additional file 5.

Intraoperative effects

Additional file 6 summarizes the reports that have evaluated the short-term surgical outcomes of MIPD, which included at least 20 cases. Conversion rates to open surgery vary substantially between 0% and 40%. Adam et al. [66] reported a conversion rate of 30% based on 983 cases of MIPD from the NCDB. The most common cause was bleeding, followed by unclear tumor margin or vein resection. Other reported causes of conversion included severe adhesions, difficult progression, and

Table 1 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				
Operation time (min)	12	518	1054	<0.01, 96%	WMD = 99.4	46.0 ~ 152.8	<0.01
Blood loss (mL)	9	408	845	<0.01, 83%	WMD = −0.54	−0.88 ~ −0.20	<0.01
Transfusion	15	739	1527	0.25, 18%	RR = 0.73	0.57 ~ 0.94	0.02
Time to oral intake (days)	3	172	333	0.02, 73%	WMD = −0.86	−1.90 ~ 0.18	0.11
Hospital stay (days)	11	402	829	<0.01, 76%	WMD = −3.49	−4.83 ~ −2.15	<0.01
Overall complications	24	825	1496	<0.01, 57%	RR = 0.89	0.78 ~ 1.02	0.10
POPF	25	853	1521	0.60, 0%	RR = 0.91	0.78 ~ 1.07	0.25
Severe POPF	21	983	2169	0.80, 0%	RR = 1.04	0.86 ~ 1.27	0.68
DGE	19	720	1349	0.81, 0%	RR = 0.70	0.53 ~ 0.94	0.02
PPH	10	427	839	0.46, 0%	RR = 1.18	0.79 ~ 1.78	0.42
Reoperation	14	449	817	0.49, 0%	RR = 1.02	0.70 ~ 1.49	0.92
Readmission	9	512	1219	0.46, 0%	RR = 1.16	0.96 ~ 1.40	0.13
Mortality	21	972	2158	0.99, 0%	RR = 0.81	0.51 ~ 1.30	0.39
Retrieved lymph nodes	11	421	995	<0.01, 79%	WMD = 1.13	−0.32 ~ 2.59	0.13
R0 rate	21	582	1554	0.13, 27%	RR = 1.06	1.00 ~ 1.12	0.04

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injury. We summarized the causes for conversion in the meta-analysis included studies in Additional file 7. The mean or median OP ranged from 276 to 657 min observed in all systematic review studies. The majority of the researches considered applicable for the meta-analysis revealed a longer OP for MIPD than for OPD. Twelve studies reported OP with mean and SDs, the pooled-data showed a statistically significant longer OP for MIPD (WMD = 99.4 min; 95%CI: 46.0 ~ 152.8, $P <$ 0.01) (Fig. 2). Another thirteen studies reported OP with median and range, seven of which revealed a significant long OP in MIPD compared to OPD in their individual research. Two studies reported shorter OP in MIPD, but in these series, OP for OPD appeared to be longer than that usually reported [26, 65] (Additional file 8). The mean or median intraoperative EBL ranged from 65 to 842 ml and the recorded numerical data ranged from 30 to 8500 mL in all reviewed studies (Additional file 6). The meta-analysis showed the EBL was significantly lower in the MIPD compared with the OPD group (WMD = −0.54 ml; 95% CI, −0.88 ~ −0.20 ml; $P <$ 0.01) (Fig. 3). Another thirteen studies reported EBL with median and range, the majority of which revealed a significant less EBL in MIPD compared to OPD in their individual research (Additional file 8). Transfusion rates were reported in two reviewed studies with a range from 0% to 32%. And the quantitative meta-analysis revealed that MIPD group have a lower transfusion rate than OPD group (RR = 0.73, 95%CI: 0.57 ~ 0.94, $P = 0.02$) (Fig. 4). The intraoperative effect outcomes of the quantitative meta-analysis are summarized in Table 1.

Postoperative recovery

Only two studies reported the length of ICU stay, and the pooled-data showed a shorter length of ICU stay after MIPD than OPD (WMD = −2.08 days; 95% CI: -2.88 ~ −1.29, $P <$ 0.01). Two studies reported the times

of analgesic injection to evaluate the postoperative pain, and the pooled-data showed less analgesic use of MIPD than OPD (WMD = −3.72; 95% CI: -6.05 ~ −1.40, $P <$ 0.01). Besides, Wang et al. [64] reported less total 7-day analgesic usage in MIPD, but the difference was not significant ($P = 0.08$). Tan et al. [84] reported less visual analogue score (VAS) on postoperative day 4 in the LPD group ($P = 0.01$). Other two studies only revealed analgesic usage tended to favor the MIPD group but was not statistically significant [53, 71]. Zhou et al. [30] reported early time to begin walk ($P <$ 0.01) and Chen et al. [68] reported early time to off-bed activities (P < 0.01) and bowel movement (P < 0.01) after RPD, whereas Tan et al. [84] reported early time to return of bowel sounds ($P <$ 0.01) after LPD. As for quantitative meta-analysis, only three studies with data available reported the postoperative time to restart oral intake. Analysis of the pooled data revealed early time to oral intake in MIPD group, but the difference did not reach statistically significant (WMD = −0.86 days; 95%CI: -1.90 ~ 0.18, $P = 0.11$). Forty-nine of systematic reviewed studies reported on mean or median length of hospital stay, which ranged from 6 to 25 days, respectively, and the recorded length ranged from 3 to 118 days (Additional file 6). Eleven studies with mean and SDs considered suitable for the meta-analysis which indicated a shorter hospital stay in the MIPD group than OPD group (WMD = −3.49 days; 95%CI: -4.83 ~ −2.15, P < 0.01) (Fig. 5). All postoperative outcomes the quantitative meta-analysis are also summarized in Table 1.

Morbidity and mortality

The majority of the included studies reported on adverse events with a range of 18.2%-87.5% for MIPD and 8.0%–92.9% for OPD. According to the results of the meta-analysis, though the incidence of postoperative complications tended to favor the MIPD group, but there was
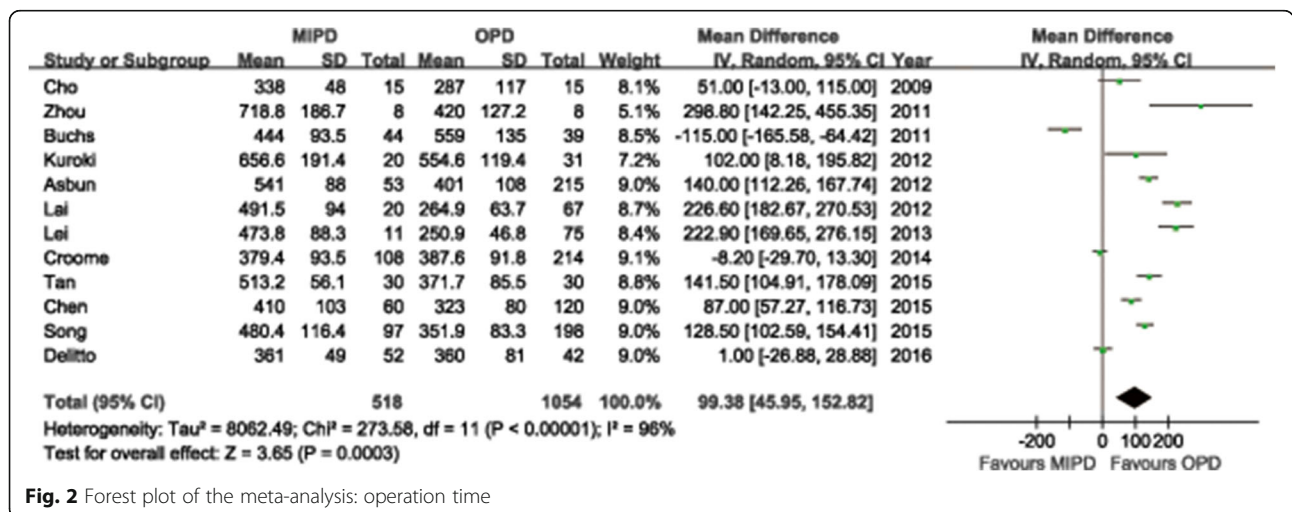

Fig. 2 Forest plot of the meta-analysis: operation time

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Study or Subgroup	MIPD Mean	SD	Total	OPD Mean	SD	Total	Weight	Std. Mean Difference IV. Random, 95% CI	Year
Cho	445	384	15	552	336	15	8.9%	-0.29 [-1.01, 0.43]	2009
Buchs	387	334	44	827	439	39	11.7%	-1.13 [-1.59, -0.66]	2011
Zhou	153.8	43.4	8	210	53.2	8	6.0%	-1.09 [-2.17, -0.02]	2011
Kuroki	376.6	291.4	20	1,509.5	1,000.2	31	9.9%	-1.39 [-2.02, -0.76]	2012
Asbun	195	136	53	1,032	1,151	215	13.3%	-0.81 [-1.12, -0.50]	2012
Lei	1,106	52.7	11	1,103	56.1	75	9.8%	0.05 [-0.58, 0.69]	2013
Croome	492.4	519.3	108	866.7	733.7	214	14.0%	-0.56 [-0.79, -0.32]	2014
Song	592	376	97	555	462	198	13.9%	0.08 [-0.16, 0.33]	2015
Delitto	260	1,296	52	518	2,916	50	12.5%	-0.11 [-0.50, 0.27]	2016
Total (95% CI)			408			845	100.0%	-0.54 [-0.88, -0.20]	

Heterogeneity: Tau² = 0.20; Chi² = 48.06, df = 8 (P < 0.00001); I² = 83%
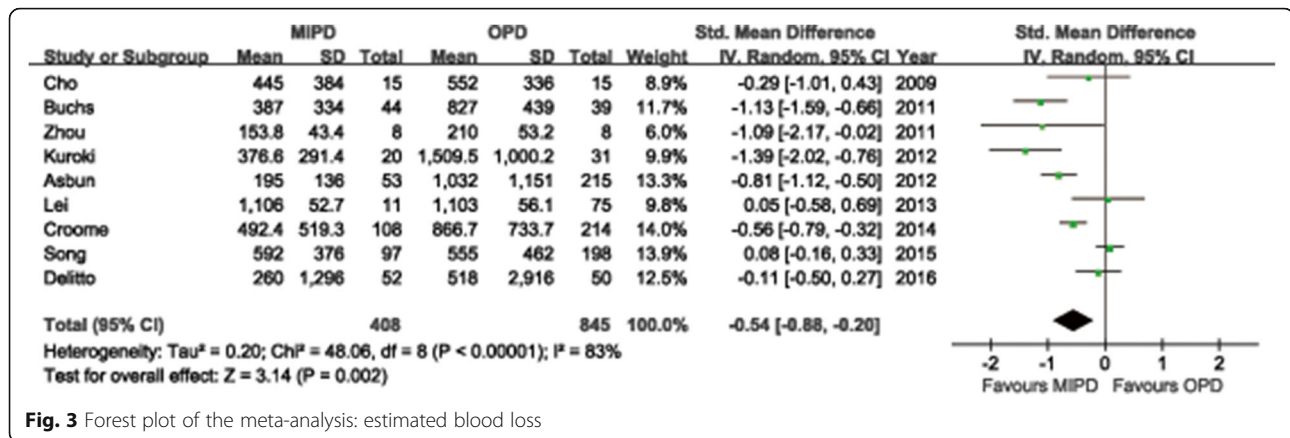Test for overall effect: Z = 3.14 (P = 0.002)

Fig. 3 Forest plot of the meta-analysis: estimated blood loss

not statistically significant difference (RR = 0.89, 95%CI: 0.78 ~ 1.02, P = 0.10). We summarized the specific postoperative surgical and medical complications based on all reviewed researched in Table 2 and Table 3. The most common surgical complication was POPF, followed by DGE, PPH, fluid collection or abscess, wound infection, bile leakage, ileus, et al. And the most common medical complication was respiratory complications, especially pulmonary infection, followed by cardiovascular complications and renal complications. The total POPF rates vary substantially between 3.8% and 50% observed in all systematic reviewed studies (Additional file 6). As to quantitative meta-analysis, no significant difference was found in pooled data of the meta-analysis between the MIPD group and OPD group in regard to the rate of overall POPF (RR = 0.91, 95%CI: 0.78 ~ 1.07, P = 0.25) (Fig. 6), as was the severe POPF rates (RR = 1.04, 95%CI:

0.86 ~ 1.27, P = 0.68), which was defined as grade B and above according to the ISGPF. The meta-analysis also did not find any statistically significant differences between groups regarding other complications, such as DGE and PPH. Fourteen studies reported reoperation cases, and there was no significant difference in reoperation rate (RR = 1.02, 95%CI: 0.70 ~ 1.49, P = 0.92). The specific reoperation reasons observed in the meta-analysis included studies are summarized in Additional file 9. Nine studies reported readmission cases, and there was also no significant difference in readmission rate (RR = 1.16, 95%CI: 0.96 ~ 1.40, P = 0.13). The overall perioperative mortality rates range from 0%–6.9% in all systematic reviewed studies (Additional file 6). As for quantitative analysis of perioperative mortality, the meta-analysis of cohorts demonstrated no significant difference between the two groups (RR = 0.81, 95%CI: 0.51
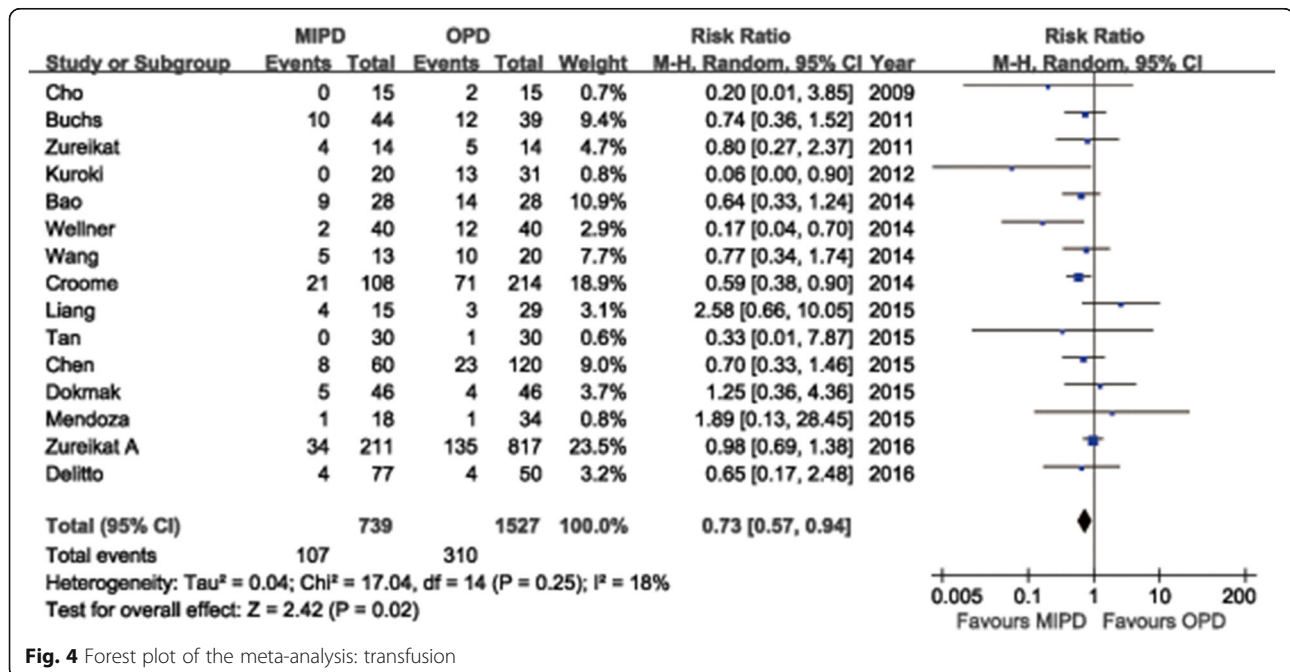

Study or Subgroup	MIPD Events	Total	OPD Events	Total	Weight	Risk Ratio M-H. Random, 95% CI	Year
Cho	0	15	2	15	0.7%	0.20 [0.01, 3.85]	2009
Buchs	10	44	12	39	9.4%	0.74 [0.36, 1.52]	2011
Zureikat	4	14	5	14	4.7%	0.80 [0.27, 2.37]	2011
Kuroki	0	20	13	31	0.8%	0.06 [0.00, 0.90]	2012
Bao	9	28	14	28	10.9%	0.64 [0.33, 1.24]	2014
Wellner	2	40	12	40	2.9%	0.17 [0.04, 0.70]	2014
Wang	5	13	10	20	7.7%	0.77 [0.34, 1.74]	2014
Croome	21	108	71	214	18.9%	0.59 [0.38, 0.90]	2014
Liang	4	15	3	29	3.1%	2.58 [0.66, 10.05]	2015
Tan	0	30	1	30	0.6%	0.33 [0.01, 7.87]	2015
Chen	8	60	23	120	9.0%	0.70 [0.33, 1.46]	2015
Dokmak	5	46	4	46	3.7%	1.25 [0.36, 4.36]	2015
Mendoza	1	18	1	34	0.8%	1.89 [0.13, 28.45]	2015
Zureikat A	34	211	135	817	23.5%	0.98 [0.69, 1.38]	2016
Delitto	4	77	4	50	3.2%	0.65 [0.17, 2.48]	2016
Total (95% CI)		739		1527	100.0%	0.73 [0.57, 0.94]	
Total events	107		310				

Heterogeneity: Tau² = 0.04; Chi² = 17.04, df = 14 (P = 0.25); I² = 18%
Test for overall effect: Z = 2.42 (P = 0.02)

Fig. 4 Forest plot of the meta-analysis: transfusion

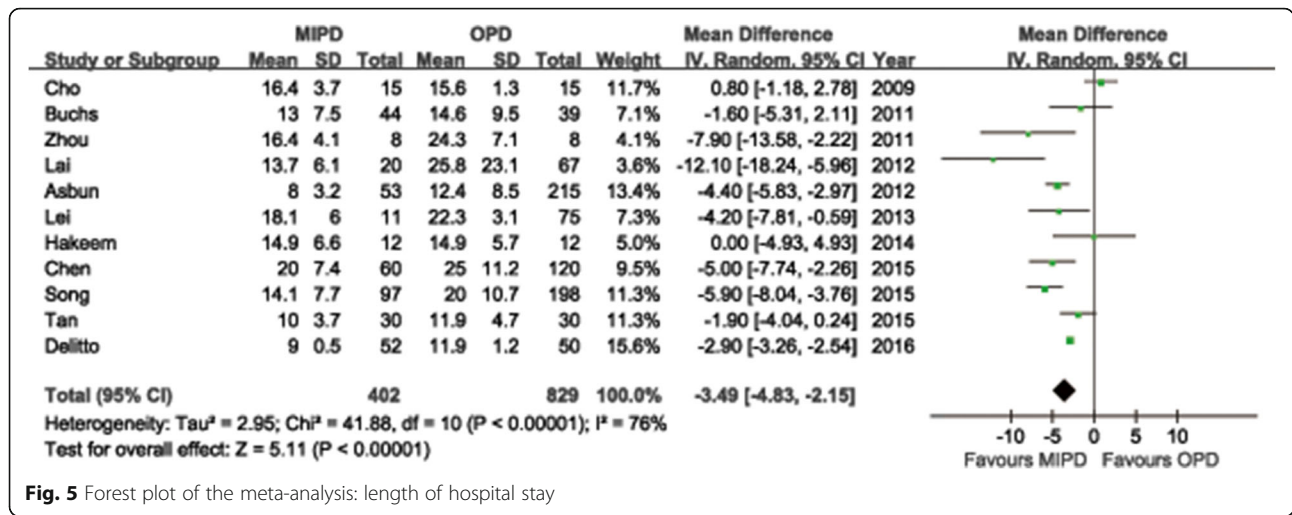Chen et al. BMC Gastroenterology (2017) 17:120

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Fig. 5 Forest plot of the meta-analysis: length of hospital stay

~ 1.30, P = 0.39). The specific death reasons in the meta-analysis studies are summarized in Additional file 10. The grade C POPFs were primary causes of postoperative reoperation and death. The morbidity and mortality outcomes of the quantitative meta-analysis are also summarized in Table 1.

Oncologic outcomes and long-term survival

The mean or median number of retrieved lymph nodes ranged from 6 to 32 observed in systematic review studies (Additional file 6). For meta-analysis, all studies reported tumor histology in both MIPD and OPD groups. The difference in the mean number of retrieved lymph nodes was not significant in the pooled data with a tendency of more in MIPD group than in OPD group (WMD = 1.13; 95%CI: -0.32 ~ 2.59, P = 0.13) (Fig. 7). As for margin status, only malignant cases were considered, thus twenty-one studies reported margin status. On

pooling the results, the negative margins (R0) rate was higher in MIPD group than that in OPD group (RR = 1.06, 95%CI: 1.00 ~ 1.12, P = 0.04). Survival status is the most critical outcome for evaluating surgical interventions in oncological therapy. However, limited long-term survival outcomes are available from this review. We summarized the information available about long-term survival outcomes in Table 4. Only three studies reported the cancer recurrence, and the difference between MIPD group and OPD group was not significant (RR = 0.78, 95%CI: 0.61 ~ 1.01, P = 0.06). Five studies reported comparable survival time or rate between two groups [55, 57, 68, 83, 92]. However, the meta-analysis of survival rate cannot be done due to limited data.

Publication bias

As showed in Fig. 8, the funnel plot for studies reporting the RRs of POPF was used to detect the publication bias. All the plots standing for the studies fall within the 95% CI axis and distributed symmetrically. This result suggested the publication bias was minimal and acceptable.

Table 2 Surgical complications of MIPD in reviewed studied (list by constituent ratio)

Complications	Total events (n = 1003)
POPF	372 (37.1%)
DGE	255 (25.4%)
PPH	141 (14.1%)
Fluid collection/abscess	84 (8.4%)
Wound complications	60 (6.0%)
Bile leakage	56 (5.6%)
Ileus	17 (1.7%)
Chyle leakage	5 (0.5%)
Gastrointestinal anastomotic leakage	4 (0.4%)
Peptic ulcer	3 (0.3%)
Other	6 (0.6%)

Other complications included colitis (n = 1), colon perforation (n = 1), bowel ischemia (n = 1), PV thrombus (n = 1), dumping syndrome (n = 1), trocar site bleeding (n = 1)

Table 3 Medical complications of MIPD in reviewed studied (list by constituent ratio)

Complications	Total events (n = 199)
Respiratory	98 (49.2%)
Cardiovascular	69 (34.7%)
Renal	18 (9.0%)
Deep venous thrombosis	10 (5.0%)
Other	4 (2.0%)

Respiratory: included pulmonary infection, pneumonias, pleural effusion, pulmonary embolism, pulmonary edema, atelectasis, lung failure, ARDS; Cardiovascular: included heart failure, myocardial infarction, arrhythmia, hypotension, acute coronary syndrome; Renal: included renal failure, urinary infection, urinary retention, renal insufficiency; other complications included thrombocytopenia (n = 1), anemia (n = 1), hepatic insufficiency (n = 2)
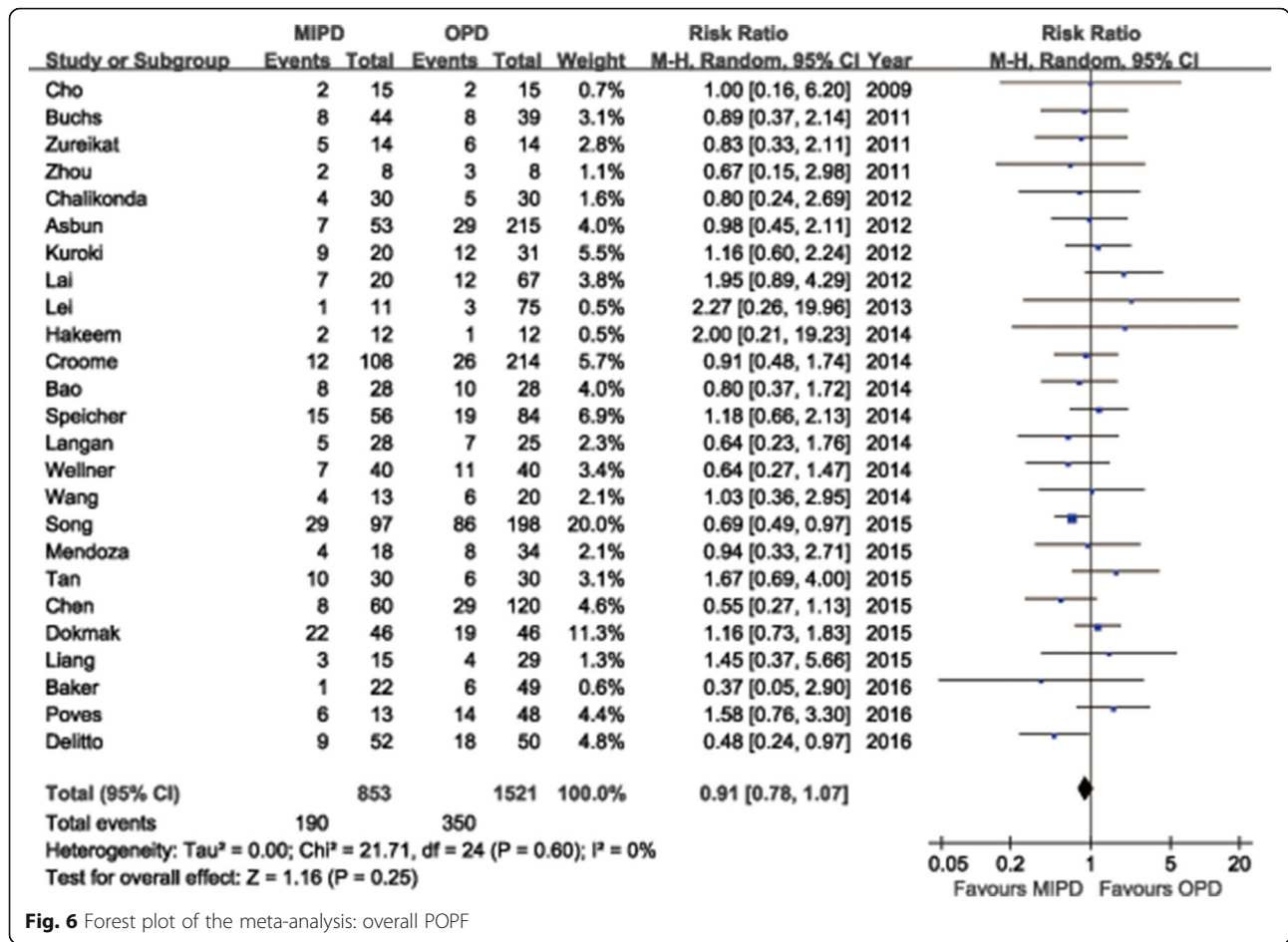
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Study or Subgroup	MIPD Events	Total	OPD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Cho	2	15	2	15	0.7%	1.00 [0.16, 6.20]	2009
Buchs	8	44	8	39	3.1%	0.89 [0.37, 2.14]	2011
Zureikat	5	14	6	14	2.8%	0.83 [0.33, 2.11]	2011
Zhou	2	8	3	8	1.1%	0.67 [0.15, 2.98]	2011
Chalikonda	4	30	5	30	1.6%	0.80 [0.24, 2.69]	2012
Asbun	7	53	29	215	4.0%	0.98 [0.45, 2.11]	2012
Kuroki	9	20	12	31	5.5%	1.16 [0.60, 2.24]	2012
Lai	7	20	12	67	3.8%	1.95 [0.89, 4.29]	2012
Lei	1	11	3	75	0.5%	2.27 [0.26, 19.96]	2013
Hakeem	2	12	1	12	0.5%	2.00 [0.21, 19.23]	2014
Croome	12	108	26	214	5.7%	0.91 [0.48, 1.74]	2014
Bao	8	28	10	28	4.0%	0.80 [0.37, 1.72]	2014
Speicher	15	56	19	84	6.9%	1.18 [0.66, 2.13]	2014
Langan	5	28	7	25	2.3%	0.64 [0.23, 1.76]	2014
Wellner	7	40	11	40	3.4%	0.64 [0.27, 1.47]	2014
Wang	4	13	6	20	2.1%	1.03 [0.36, 2.95]	2014
Song	29	97	86	198	20.0%	0.69 [0.49, 0.97]	2015
Mendoza	4	18	8	34	2.1%	0.94 [0.33, 2.71]	2015
Tan	10	30	6	30	3.1%	1.67 [0.69, 4.00]	2015
Chen	8	60	29	120	4.6%	0.55 [0.27, 1.13]	2015
Dokmak	22	46	19	46	11.3%	1.16 [0.73, 1.83]	2015
Liang	3	15	4	29	1.3%	1.45 [0.37, 5.66]	2015
Baker	1	22	6	49	0.6%	0.37 [0.05, 2.90]	2016
Poves	6	13	14	48	4.4%	1.58 [0.76, 3.30]	2016
Delitto	9	52	18	50	4.8%	0.48 [0.24, 0.97]	2016
Total (95% CI)		853		1521	100.0%	0.91 [0.78, 1.07]	
Total events	190		350				

Heterogeneity: Tau² = 0.00; Chi² = 21.71, df = 24 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.25)

Fig. 6 Forest plot of the meta-analysis: overall POPF

Discussion

It is well-known that PD is one of the most complicated abdominal surgeries, and the completion of dissection of the porta hepatis, extensive lymphadenectomy and uncinate process detachment intracorporeally is technically high-demanding. This inevitably leads to the traditional view that minimally invasive surgical approaches are relatively contraindicated in the setting of PD. With the accumulation of minimally invasive surgical experience, more surgeons introduced MIPD and some of them
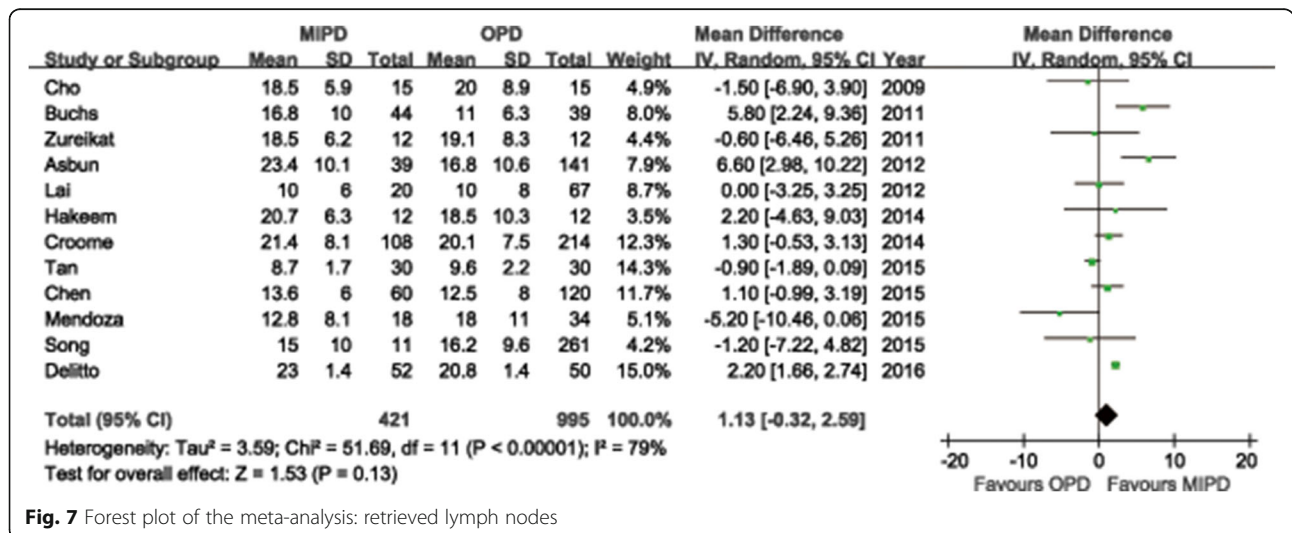

Study or Subgroup	MIPD Mean	SD	Total	OPD Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Cho	18.5	5.9	15	20	8.9	15	4.9%	-1.50 [-6.90, 3.90]	2009
Buchs	16.8	10	44	11	6.3	39	8.0%	5.80 [2.24, 9.36]	2011
Zureikat	18.5	6.2	12	19.1	8.3	12	4.4%	-0.60 [-6.46, 5.26]	2011
Asbun	23.4	10.1	39	16.8	10.6	141	7.9%	6.60 [2.98, 10.22]	2012
Lai	10	6	20	10	8	67	8.7%	0.00 [-3.25, 3.25]	2012
Hakeem	20.7	6.3	12	18.5	10.3	12	3.5%	2.20 [-4.63, 9.03]	2014
Croome	21.4	8.1	108	20.1	7.5	214	12.3%	1.30 [-0.53, 3.13]	2014
Tan	8.7	1.7	30	9.6	2.2	30	14.3%	-0.90 [-1.89, 0.09]	2015
Chen	13.6	6	60	12.5	8	120	11.7%	1.10 [-0.99, 3.19]	2015
Mendoza	12.8	8.1	18	18	11	34	5.1%	-5.20 [-10.46, 0.06]	2015
Song	15	10	11	16.2	9.6	261	4.2%	-1.20 [-7.22, 4.82]	2015
Delitto	23	1.4	52	20.8	1.4	50	15.0%	2.20 [1.66, 2.74]	2016
Total (95% CI)			421			995	100.0%	1.13 [-0.32, 2.59]	

Heterogeneity: Tau² = 3.59; Chi² = 51.69, df = 11 (P < 0.00001); I² = 79%
Test for overall effect: Z = 1.53 (P = 0.13)

Fig. 7 Forest plot of the meta-analysis: retrieved lymph nodes

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Table 4 Summary of Recurrence and Long-term Survivals

Author	Group	Malignant case	Follow-up (month)	Recurrence	Survival (time: month; rate: %)
Zureikat [31]	MIPD	12	9.5(4–21)	1	NR
Croome [55]	MIPD	108	16.5	44	MOS: 25.3 m
	OPD	214	15.1	113	MOS: 21.8 m
Hakeem [57]	MIPD	12	46.8(13.0–73.7)	2	1, 3, 5y–DFS: 100; 92, 83, 5y–OS: 100, 83, 83
	OPD	12	56.0(1.0–97.4)	2	1, 3, 5y–DFS: 100; 92, 75, 5y–OS: 75, 58, 50
Song [83]	MIPD	11	NR	NR	5y–OS: 53.6
	OPD	222	NR	NR	5y–OS: 28.8
Chen [68]	MIPD	19	22 ± 10	NR	MDFS: 14.0 m; MOS: 23.0 m
	OPD	39	21 ± 8	NR	MDFS: 13.0 m; MOS: 22.0 m
Delitto [92]	MIPD	52	NR	NR	MOS: 27.9 m; MOS: 20.7 m*
	OPD	50	NR	NR	MOS: 23.5 m; MOS: 21.1 m*
Palanivelu [15]	MIPD	49	36.5	NR	MOS: 49 m; 5y–OS: 30.4
Pugliese [16]	MIPD	11	32(12–45)	7	MDFS: 11 m; MOS: 18 m
Senthilnathan [80]	MIPD	130	24	NR	MOS: 33 m; 5y–OS:29.4
Wang [86]	MIPD	16	18(8–48)	10	MDFS: m16; MOS: 19 m
Coratti [90]	MIPD	41	15.8(2–47)	12	MOS: 40 m; 1, 2, 3y–OS: 81, 69, 55
Kantor [96]	MIPD	828	18	NR	MOS: 20.7 m
	OPD	7385		NR	MOS: 20.9 m
Stauffer [107]	MIPD	58	19.6 ± 17.4	NR	MOS: 18.5 m; 1, 2, 3, 4, 5y–OS: 66.5, 43.3, 43.3, 38.5, 32.1
	OPD	193	24.5 ± 27.4	NR	MOS: 20.3 m; 1, 2, 3, 4, 5y–OS: 67.5, 40.2, 24.3, 17.1, 15.3

Follow-up time were shown as median (range) or median only; DFS: disease-free survival rate; OS: overall survival rate; MDFS: median disease-free survival time; MOS: median overall survival time; y: year; *special for PDAC; NR: not report

even adapted it as a conventional procedure. Our systematic review also revealed a trend of steeply increasing surgeons performing MIPD around the world. By reviewing some overlapped studies from the same centers, we found surgeons were improving their surgical techniques in MIPD, from benign disease to malignances, from patients with good condition to those with

bad condition. Speicher et al. reported their train projects for surgeons in adaption of LPD [63]. These all suggested MIPD was not a trick specially played by the talents but can be adapted by more surgeons with fully training and practices.

The conversion rate to OPD appears to be higher when comparing to other minimally invasive gastroenterological
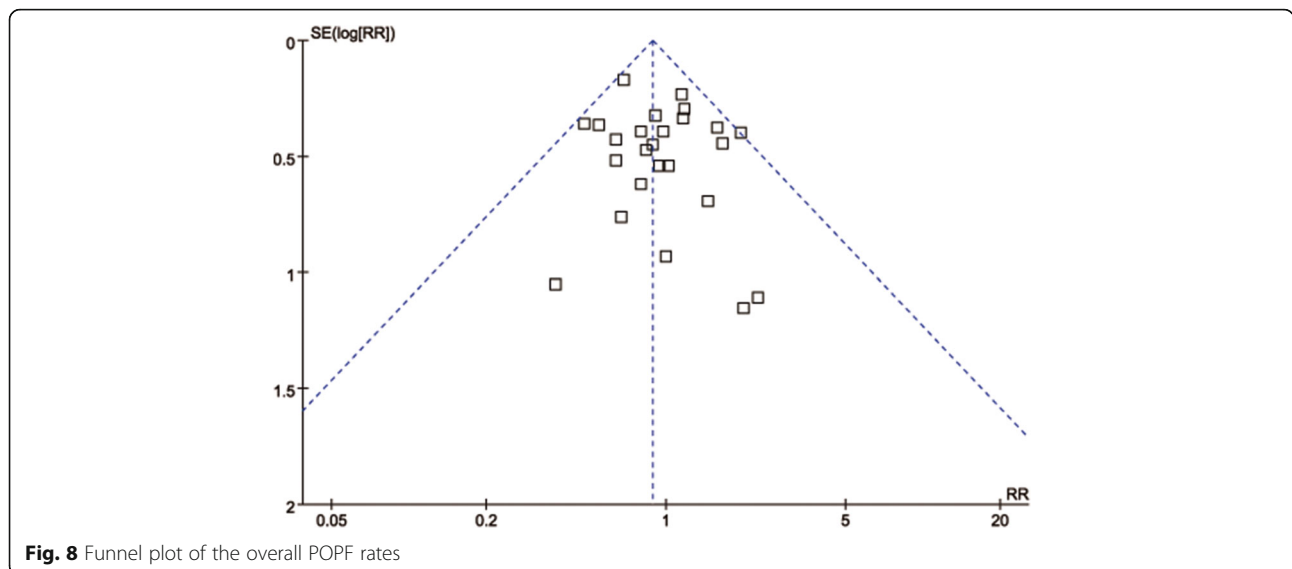
Fig. 8 Funnel plot of the overall POPF rates

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surgery. Reasons attributed to conversion including larger tumors, pancreatic adenocarcinoma or chronic pancreatitis, adhesions to vascular structures, uncontrollable bleeding et al. [65]. The reported rates based this comprehensive review for conversion to open approach range from 0% to 40%. Such substantial difference in conversion rates reported was mainly attributed to the learning curve of the surgeon in obtaining proficiency and the discrepancy in patient selection. Furthermore, the liberalization of intraoperative decision to convert varies from individual to individual. Wellner et al. argued that the minimally invasive approach should not be pursued at the cost of major increase in technical difficulties or operation time [65], leading their decision to conversion more liberalized. Some excellent surgeons argued that MIPD could performed for all indications, even locally advanced malignant disease invading surrounding organs or portal vein system [27, 29, 69, 97]. However, they also admitted that major venous resection intracorporeally was only feasible in selected patients and advocated that extensive experience with complex laparoscopic pancreatic resection and reconstruction should prior to attempt such procedure.

In our pooled analysis, the mean OP during MIPD was significantly longer than that during OPD. In spite of the considerable heterogeneity, the prolonged OP in MIPD was shown in the majority researches included. In addition to the complicated resection phase, the lengthy gastroenterological, pancreatic and biliary anastomoses are especially technically demanding and time-consuming. Given the fact that the majority studies included in the meta-analysis reported on their initial experience, OP could be expected to decrease or even close to OPD when more experience is gained. For these approaches it will take a surgeon several years to overcome the learning curve and achieve high- quality outcomes [67].

A hybrid or laparoscopic assisted approach, in which the anastomoses are performed via a small laparotomy, might facilitate MIPD and be useful to accumulate experience [64, 65]. Some publications advised that minimally invasive procedures can be safely performed when using a hybrid method before starting with totally intracorporeal surgery. Performing MIPD using hybrid method in initial series helped to safely shift to totally intracorporeal method [31, 63]. Nevertheless, intracorporeally anastomosis, especially for PJ, should base on progressive practice. Practice on the simulator then to animal models for simple suture under laparoscopy, and finally to intracorporeal gastrointestinal anastomosis can effectively shorten the learning curve. Some researcher did the resection laparoscopically, then introduced robot to promote the reconstruction, which was so-called robotic and laparoscopic hybrid PD, demonstrating favorite outcomes [24, 59].

Intraoperative EBL is an important index to judge the safety in operation, which was shown in the pooled data to be lower in MIPD, so was the need for transfusions. The need for transfusion arises due to excessive blood loss and the two outcomes are therefore correlated. The EBL is subjective and tended to bias, whereas transfusion is an objective outcome. However, the definition of blood loss and criteria for blood transfusion were not explicitly reported in any of the included studies. Besides, there were serious skewedness in EBL between studies (recorded numerical data ranged from 50 to 1800 mL in review studies), with significant heterogeneity mainly due to different methods of EBL. Therefore, the results should be interpreted prudently and need further study to confirm.

The substantial risk of perioperative mortality and morbidity remains a major concern to limit the development of MIPD. Although surgical safety had been improved gradually mainly related to centralization, the conventional OPD was still associated with postoperative morbidity rates of 23% to 66% and mortality rates of 3% to 5% even in high-volume centers [112–114]. The range of overall morbidity and mortality rate of MIPD observed from the series analyzed were 18.2% to 87.5% and 0% to 6.9%, respectively, which is comparable to the OPD literature. And the quantitative meta-analysis also demonstrated no significant differences with regard to perioperative mortality and morbidity between two groups. POPFs remain one of the most threatening complications after PD, with rates ranging from 4% to 33% in series from expert centers [115]. The reviewed series in this study also revealed a comparable POPFs range of 3.8% to 50%. Our quantitative meta-analysis demonstrated the comparable complication rates of POPF, especially the severe POPF, DGE and PPH in the MIPD versus the OPD group, and the low heterogeneity encourages us to believe that MIPD could be as safe as OPD. PD involved in multiple systems and would cause more medical complications than other operations. It was observed from the reviewed studies that respiratory complications were the most commonly medical complications, mainly pulmonary infection, followed by cardiovascular ones. Less pain and faster recovery obtained from minimally invasive approach bring about mild inflammatory reaction, which may contribute to the maintaining of normal pulmonary function [116]. It was also reported that more intraoperative blood loss and transfusion could increase respiratory complication risks [117]. In our study, MIPD had significantly less blood loss and transfusion, which helped to reduce respiratory complications. Therefore, MIPD may be more suitable to patients with severe impaired pulmonary function [118]. It was conceivable that mortality was similar between groups due to the similar complication and

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reoperation rates. Summary for causes of reoperation and death based on the reviewed studies revealed that the common causes were abdominal hemorrhage, abscess, and sepsis mainly due to grade C POPF. These outcomes turned out to be equivalent between MIPD and OPD in our meta-analysis. Likewise, Gagner et al. argued that a pancreatic fistula from a failed pancreatic anastomosis can portend serious complications, including bleeding, sepsis, and death [119]. The two-layer, end-to-side, duct-to-mucosa PJ was the most commonly used pancreatic anastomosis approach. In order to reduce PF, various modified techniques have been reported, such as so-called "pancreas-hanging maneuver" [23], linear stapler pancreatic stump closure [37], "double jejunal loop reconstruction" [48], "barbed suture PJ" [56], "dunking PJ using mattress sutures" [54], "intussuscepting PJ" [58], "two transpancreatic sutures with buttresses" [98], "purse-string suture without pancreatic parenchymal stitches" [95], "laparoscopic-adapted Blumgart PJ" [106], "imbedding PJ" [111], et al. or even intracorporeal PG [73]. Although the authors reported favorable results, the exact value of these techniques remains unclear and needs further studies to confirm.

As for postoperative recovery, the pooled data demonstrates mixed outcomes with less time spent in ICU and less usage of analgesic in MIPD group than OPD group, while only moderate earlier time to oral intake in the MIPD group without significant difference, indicating MIPD likely enhanced the recovery of intestinal function. Reduced use of analgesic drugs, shortened time of abdominal cavity exposure, and earlier postoperative activities are considered to be the main reasons for earlier gastrointestinal recovery from MIPD.

As the removal of a sufficient amount of lymph nodes can enhance the accuracy of staging and regional disease control, appropriate lymphadenectomy is one of the most crucial steps in radical pancreatic surgery. The mean or median number of retrieved lymph nodes ranged from 6 to 32 observed in systematic review studies and the quantitative meta-analysis showed no significant difference between MIPD and OPD groups. It is well-documented that only about 20% eligibility rate for surgery among patients with pancreatic cancer when diagnosed. It has also been suggested that even patients who are eligible for surgery preoperatively cannot be offered potentially curative resection mainly due to vascular invasion [120, 121]. Because few reports have compared long-term survival outcomes with other methods, a meta-analysis of long-term oncologic results comparing MIPD versus OPD could not be done due to limited data. Because of most surgeons performed their initial minimally invasive Whipple procedures in patients with resectable small ampullary, distal bile duct or duodenal adenocarcinoma, and the prognosis of periampullary tumors with different pathological types is very different. Therefore, the oncological efficiency of MIPD should ideally be assessed in a randomized controlled trial.

Our researches have some limitations as below: (1) No RCTs were included: All the evidence was derived from observational studies with either concurrent or historical controls, and the use of some historical control groups that may be inadequately matched to the intervention group and because of poor or selective outcome reporting. (2) Selection bias: Most hospitals are still in the learning curve now and during that phase only the most ideal patients are selected. (3) Clinical heterogeneity: The variety of postoperative management, discharge criteria and application of fast track protocol et al. will lead to clinical heterogeneity and a sequence of biases. (4) Lacking long-term outcomes: large studies on the long-term outcomes, such as oncological efficiency, especially for long-term survival and quality of life (QOL) are scarce.

Conclusions

Our systematic review and meta-analysis demonstrates that MIPD is technically feasible and safety, especially in experienced hands. MIPD alleviates surgical traumas and enhanced postoperative recovery. Account for the inherent limitations of our study, our findings should also be interpreted with cautions. Robust prospective comparative studies and randomized clinical trials are awaited to bring more high quality evidences.

Additional files

Additional file 1: Number of original publications concerning MIPD by year according to the study design (abstracts, letters, comments, reviews were not included). (TIFF 56 kb)

Additional file 2: Number of total publications concerning MIPD by year according to the place of origin (the majority North American studies came from USA; other regions included Turkey and Brazil). (TIFF 67 kb)

Additional file 3: Published articles of MIPD. (DOCX 52 kb)

Additional file 4: Baseline and quality assessment based on the NOS for meta-analysis included studies. (DOCX 30 kb)

Additional file 5: Summary of indications and laparoscopic technical details in the meta-analysis included studies. (DOCX 26 kb)

Additional file 6: Summary of perioperative outcomes in reviewed studies with more than twenty cases of MIPD. (DOCX 37 kb)

Additional file 7: Summary of reasons for conversion. (DOCX 22 kb)

Additional file 8: Summary of perioperative outcomes in studies without quantitative data presenting mean and standard deviation. (DOCX 24 kb)

Additional file 9: Summary of the specific reoperation reasons. (DOCX 22 kb)

Additional file 10: Summary of the specific perioperative death reasons. (DOCX 23 kb)

Abbreviations

CI: Confidence interval; DGE: Delayed gastric emptying; EBL: Estimated blood loss; ISGPF: International Study Group for Pancreatic Fistula; ITT: Intention-to-treat; LOS: Length of hospital stay; LPD: Laparoscopic pancreatoduodenectomy; MIPD: Minimally invasive pancreatoduodenectomy;

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NOS: Newcastle-Ottawa Quality Assessment Scale; OP: Operation time; OPD: Open pancreatoduodenectomy; PD: Pancreatoduodenectomy; PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy; POPF: Postoperative pancreatic fistula; PPH: Post-pancreatectomy hemorrhage; QOL: Quality of life; RCT: Prospective randomized studies; RLN: Retrieved lymph nodes; RPD: Robotic pancreatoduodenectomy; RR: Risk ratio; SD: Standard deviation; WMD: Weighted mean difference

Authors' contributions
KC and YP designed the study; XLL, GYJ and DW collected literatures and conducted the analysis of pooled data; HM helped to draft the manuscript; KC and YP wrote the manuscript; XJC proofread and revised the manuscript. All authors have approved the version to be published.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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