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Systematic Review

Minimally invasive *versus* open pancreatic surgery: meta-analysis of randomized clinical trials

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Abstract

Background: Widespread implementation of the minimally invasive technique in pancreatic surgery has proven to be challenging. The aim of this study was to compare the perioperative outcomes of minimally invasive (laparoscopic and robotic) pancreatic surgery with open pancreatic surgery using data obtained from RCTs.

Methods: A literature search was done using Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Web of Science; all available RCTs comparing minimally invasive pancreatic surgery and open pancreatic surgery in adults requiring elective distal pancreatectomy or partial pancreatoduodenectomy were included. Outcomes were mortality rate, general and pancreatic surgery specific morbidity rate, and length of hospital stay.

Results: Six RCTs with 984 patients were included; 99.0 per cent (486) of minimally invasive procedures were performed laparoscopically and 1.0 per cent (five) robotically. In minimally invasive pancreatic surgery, length of hospital stay (−1.3 days, −2 to −0.5, $P = 0.001$) and intraoperative blood loss (−137 ml, −182 to −92, $P < 0.001$) were reduced. In the subgroup analysis, reduction in length of hospital stay was only present for minimally invasive distal pancreatectomy (−2 days, −2.3 to −1.7, $P < 0.001$). A minimally invasive approach showed reductions in surgical site infections (OR 0.4, 0.1 to 0.96, $P = 0.040$) and intraoperative blood loss (−131 ml, −173 to −89, $P < 0.001$) with a 75 min longer duration of surgery (42 to 108 min, $P < 0.001$) only in partial pancreatoduodenectomy. No significant differences were found with regards to mortality rate and postoperative complications.

Conclusion: This meta-analysis presents level 1 evidence of reduced length of hospital stay and intraoperative blood loss in minimally invasive pancreatic surgery compared with open pancreatic surgery. Morbidity rate and mortality rate were comparable, but longer duration of surgery in minimally invasive partial pancreatoduodenectomy hints that this technique in partial pancreatoduodenectomy is technically more challenging than in distal pancreatectomy.

Introduction

Beginning with the first laparoscopic appendectomy and cholecystectomy performed in the 1980s, the minimally invasive technique has become increasingly common in abdominal surgery over the past decades. Today, the laparoscopic approach represents the standard of care in many basic surgical procedures[1,2]. Recognizing the advantages of minimally invasive surgery, such as reduced postoperative pain, reduction in length of hospital stay (LOS), and faster return to daily activities, the indications for the laparoscopic approach have extended to increasingly complex procedures. Meanwhile, enhanced recovery after surgery protocols broadly incorporated laparoscopic technique as an essential part in bariatric, colorectal and upper gastrointestinal surgery[3–5] and focus of research has shifted to the implementation of robotic surgery.

However, widespread implementation of the laparoscopic and robotic technique in pancreatic surgery has proven to be more challenging. Despite considerable improvements in operative techniques and perioperative care, the rate of postoperative complications and subsequent impairment in patients' quality of life remain high in open pancreatic surgery. For increased comparability of postoperative results and improved complication monitoring, several attempts to define benchmark outcomes have been made. The benchmark for mortality rate is reported as 2 per cent for partial pancreatoduodenectomy (PD) and less than 1 per cent for distal pancreatectomy (DP) by the Evidence Map of Pancreatic Surgery[6], with an overall complication rate of 53 per cent for PD and 59 per cent for DP. The benefit of a minimally invasive approach in pancreatic surgery remains unclear; however, an increasing amount of high-level evidence in the form of RCTs

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comparing laparoscopic with open pancreatic resection is available.

The aim of this systematic review and meta-analysis was to compare the perioperative outcomes of minimally invasive (laparoscopic and robotic) pancreatic surgery with open pancreatic surgery using data obtained from RCTs only. Furthermore, subgroup analysis of open *versus* minimally invasive PD and DP was performed.

Methods

This systematic review and meta-analysis was conducted according to an *a priori*-developed review protocol predefined by Probst *et al.*[7] and is in line with the PRISMA statement[8]. Study selection, data extraction, and critical appraisal were performed according to Evidence Map of Pancreatic Surgery protocols. A detailed methodological description has been published by Probst *et al.*[6,7].

Systematic literature search

A systematic literature search was done using Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via PubMed), and Web of Science for all RCTs on pancreatic surgery. The detailed search strategy of Probst *et al.*[7] was applied and is displayed in *Table S1*. The last database search was performed on 24 April 2022. No date or language restrictions were applied.

Study selection

RCTs comparing minimally invasive (laparoscopic or robotic) *versus* open pancreatic resection for benign, premalignant, or malignant pancreatic disease that met the following PICOS criteria were considered eligible for inclusion: P (patients) - patients over 18 years of age with benign, premalignant, or malignant disease, who required elective PD or DP; I (intervention) - minimally invasive (laparoscopic or robotic) PD or DP; C (control) - open PD or DP; O (outcome) - predefined outcome parameters as described in the 'Data extraction' section; and S (study design) - RCTs only.

Study selection was performed according to the recommendations of The Cochrane Collaboration[9]. Further, the World Health Organization trial registry[10] was systematically searched for ongoing RCTs and unpublished terminated RCTs, which were regularly incorporated in the analysis as results became available.

Data extraction

The screening of titles, abstracts, and full texts was performed by two independent reviewers. Disagreements were resolved by consensus or a third party. Outcomes of interest were mortality rate, complications greater than or equal to grade III according to Clavien–Dindo classification[11], postoperative pancreatic fistula (POPF)[12], post-pancreatectomy haemorrhage (PPH)[13], delayed gastric emptying (DGE)[14], bile leakage[15], surgical site infection (SSI), reoperations, readmissions, R0 resection, lymph node yield (LNY), and LOS. Safety outcomes were examined 90 days after surgery. Definitions of the International Study Group of Pancreatic Surgery for pancreatic surgery specific complications were applied.

Critical appraisal

The assessment of methodological quality of included trials was done according to The Cochrane Collaboration tool for assessing risk of bias 2.0[9]. In summary, five different domains were assessed for all types of bias that are currently understood: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result.

Each domain was assigned one of three levels of risk of bias ('low-risk', 'some concern', and 'high-risk'), determined by an algorithm based on answers to signalling questions. In conclusion, an overall risk-of-bias assessment was achieved. For assessment of certainty in the body of evidence, the GRADE approach was used[16].

Statistical analysis

Data pooling and statistical analysis were performed using review manager software (Review Manager (RevMan) (computer program), Version 5.4, The Cochrane Collaboration, 2020). All categorical data were analysed using the Mantel–Haenszel model and are presented as odds ratio (OR) and 95 per cent c.i. For all continuous data, the mean difference (MD) and 95 per cent c.i. were calculated using the inverse variance model. Non-normally distributed data were converted to mean and standard deviation (s.d.) according to Hozo *et al.*[17]. Heterogeneity among trials was assessed using the I^2 test and random-effects model was used. All reported *P*-values are two-sided.

Results

Study selection

In a systematic literature search, a total of 32 388 studies were found and screened for eligibility. After title, abstract, and full-text screening, six RCTs were included for further analysis[18–23]. Reasons for exclusion included wrong study type, wrong intervention, and wrong organ investigated. Two studies were excluded due to data duplication[24,25]. The flow chart in *Fig. 1* depicts the process of study selection according to PRISMA[6,7]. An overview of study characteristics is displayed in *Table 1*.

Qualitative analysis—bias

An overview of risk-of-bias assessment according to bias domains and overall assessment is displayed in *Fig. 2*. None of the studies was considered at high overall risk of bias. In three of six studies the overall risk of bias was considered of some concern, whereas three showed a low overall risk of bias. 'Deviations from intended intervention' and 'outcome measurement' represented the main sources of bias and received an assessment of some concern in three out of six studies. In one study[25], the randomization process revealed some concern for bias.

Quantitative analysis

A summary of quantitative outcomes is shown in *Table 2*. A total of 166 patients for DP (80 minimally invasive pancreatic surgery *versus* 86 open pancreatic surgery) in two RCTs and 818 patients for PD (411 minimally invasive pancreatic surgery *versus* 407 open pancreatic surgery) in four RCTs were analysed.

Intraoperative outcomes

Intraoperative blood loss was decreased by 137 ml (−182 to −92, $P < 0.001$, $I^2 = 96$ per cent, GRADE: low) in minimally invasive surgery. Duration of surgery increased in minimally invasive

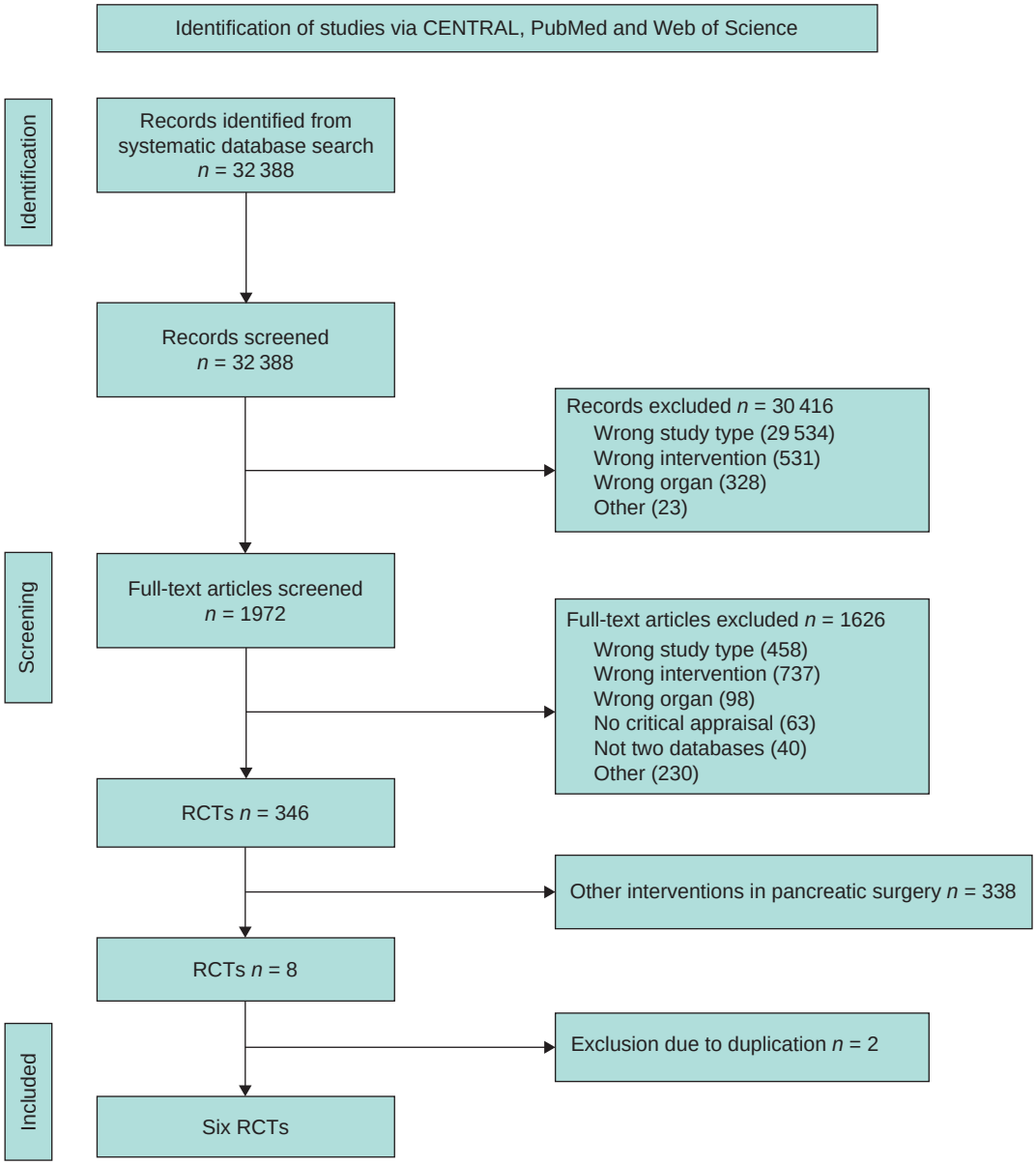


Fig. 1 PRISMA flow chart

pancreatic surgery by 54 min (32 to 76, $P < 0.001$, $I^2 = 98$ per cent, GRADE: low) compared with open pancreatic surgery.

Postoperative outcomes

An overall 90-day mortality rate of 2.6 per cent (13) for minimally invasive pancreatic surgery and 2.4 per cent (12) for open pancreatic surgery without a significant difference between the two groups was reported (OR (95 per cent c.i.) 0.94 (0.34 to 2.56), $P = 0.900$). Neither overall nor pancreatic surgery specific complications differed between the two groups. The incidence of complications of greater than or equal to grade III according to the Clavien–Dindo classification was 32.8 per cent (161) in the minimally invasive group and 26.8 per cent (132) in the open group (OR (95 per cent c.i.) 1.15 (0.55 to 2.39), $P = 0.710$). Overall, readmissions and reoperations were necessary in 9.0 per cent (89; minimally invasive pancreatic surgery 9.4 per cent, 46; and open pancreatic surgery 8.7 per cent, 43) and 5.2 per cent (48; minimally invasive pancreatic surgery 5.4 per cent, 25; and open pancreatic surgery 5.0 per cent, 23) of patients respectively. No significant difference between minimally invasive pancreatic surgery and open pancreatic surgery was seen (OR (95 per cent c.i.) 1.11 (0.70 to 1.77) ($P = 0.660$) and OR (95 per cent c.i.) 0.93 (0.30 to 2.87) ($P = 0.890$) respectively). Meta-analysis showed a reduction in LOS of 1.3 days (−2 to −0.5, $P < 0.001$) in the minimally invasive group compared with the open group.

Oncologic outcomes

Surgical oncologic outcomes did not differ between the two groups. R0 resection was achieved in 91.2 per cent (392) in the minimally invasive pancreatic surgery group and 89.7 per cent (374) in the open pancreatic surgery group (OR (95 per cent c.i.) 1.44 (0.85 to 2.45), $P = 0.180$, $I^2 = 0$ per cent, GRADE: low); no difference in LNY was seen (MD (95 per cent c.i.) 0.0 (−2 to 1), $P = 0.690$, $I^2 = 95$ per cent, GRADE: low). Overall, the mean (s.d.) number of lymph nodes resected was 13 (3) in the minimally

Table 1 Study characteristics

First author	Year published	Country	Design	Primary endpoint	Sample size	Method of analysis	Centre experience	Surgeon experience
DP								
Björnsson	2020	Sweden	RCT	Length of postoperative hospital stay	58	ITT	ns	≥37 lap. DP
de Rooij	2019	Netherlands	RCT	Time to functional recovery	108	ITT	≥20 PDs/year	≥50 advanced MI procedures ≥20 DP (MI or open) ≥5 MI DP
PD								
Palanivelu	2017	India	RCT	Length of hospital stay	64	ITT	≥40 PDs/year	≥25 open PD ≥25 lap. PD
Poves	2018	Spain	RCT	Length of hospital stay	61	ITT	Expert surgeon	Expert surgeon
van Hilst	2019	Netherlands	RCT	Time to functional recovery	99	ITT	≥20 PDs/year (of which ≥10 lap.)	≥50 advanced lap. procedures ≥50 PD (lap. or open) ≥20 lap. PD
Wang	2021	China	RCT	Length of postoperative stay	594	mITT	≥50 PDs/year (of which ≥20 lap.)	≥104 lap. PD ≥104 open PD

DP, distal pancreatectomy; ITT, intention to treat; lap., laparoscopic; PD, partial pancreatoduodenectomy; MI, minimally invasive; mITT, modified intention to treat; ns, not specified.

Fig. 2 Risk-of-bias assessment

invasive pancreatic surgery group and 14 (4) in the open pancreatic surgery group.

Subgroup analysis

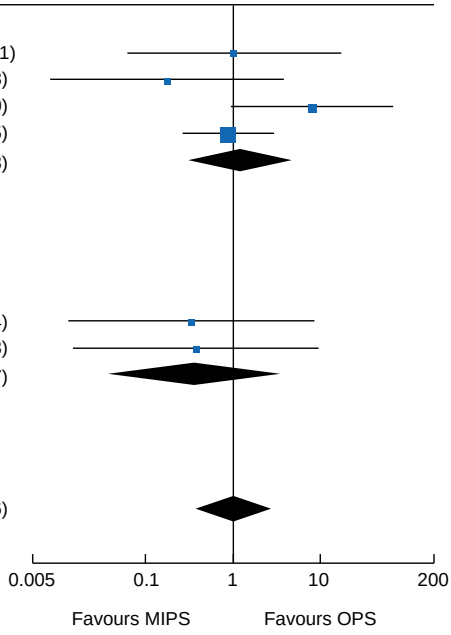
An overview of the main outcomes and procedural subgroup analysis is shown in *Table 3* and *Table 4*. In the subgroup analysis, reduction in LOS was only present in minimally invasive DP (−2 days, −2.3 to −1.7, $P < 0.01$, $I^2 = 0$ per cent, GRADE: low). A minimally invasive approach showed reductions in SSI (OR 0.4 (0.1 to 0.96), $P = 0.04$, $I^2 = 0$ per cent, GRADE: low) and intraoperative blood loss (−131 ml, −173 to −89, $P < 0.01$, $I^2 = 93$ per cent, GRADE: low) only in PD. However, the duration of surgery was about 75 min longer in minimally invasive PD (42 to 108 min, $P < 0.01$, $I^2 = 99$ per cent, GRADE: low), but not in DP. Analysis showed no further significant differences between subgroups with regards to mortality rate, general and pancreatic surgery specific complications, and intraoperative and oncologic outcomes.

Further subgroup analysis was performed stratifying for studies assessed with a low risk of bias and some concern for bias. In *Table 5*, detailed results after risk-of-bias stratification are displayed. A separate analysis of studies with a low risk of bias showed no differences between minimally invasive

Table 2 Quantitative outcomes

90-day mortality rate

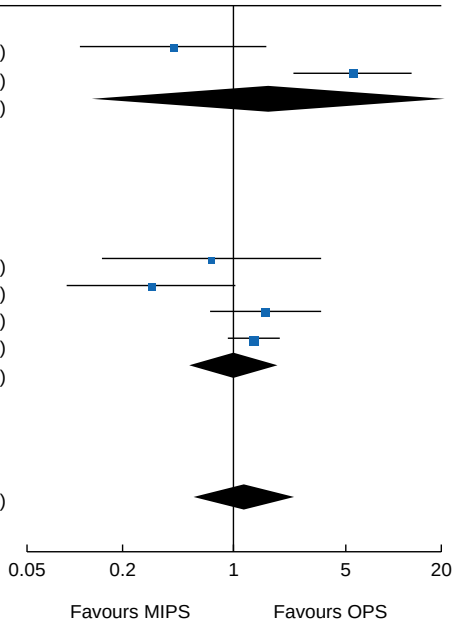
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight %	OR M-H, random, 95% c.i.
Pancreatoduodenectomy						
Palanivelu 2017	1	32	1	32	11.4	1.00 (0.06, 16.71)
Poves 2018	0	32	2	29	9.7	0.17 (0.01, 3.68)
van Hilst, de Rooij 2019	7	50	1	49	18.4	7.81 (0.92, 66.10)
Wang 2021	5	297	6	297	42.8	0.83 (0.25, 2.75)
Subtotal (95% c.i.)		411		407	82.3	1.18 (0.30, 4.63)
Total events	13		10			
Heterogeneity: $\tau^2 = 0.77$; $\chi^2 = 4.94$, 3 d.f., $P = 0.18$; $I^2 = 39\%$						
Test for overall effect: $Z = 0.24$, $P = 0.81$						
Distal pancreatectomy						
Björnsson 2020	0	29	1	29	8.8%	0.32 (0.01, 8.24)
de Rooij 2019	0	51	1	57	8.9%	0.37 (0.01, 9.18)
Subtotal (95% c.i.)		80		86	17.7%	0.34 (0.03, 3.37)
Total events	0		2			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.00$, 1 d.f., $P = 0.96$; $I^2 = 0\%$						
Test for overall effect: Z = 0.92, $P = 0.36$						
Total (95% c.i.)		491		493	100.0%	0.94 (0.34, 2.56)
Total events	13		12			
Heterogeneity: $\tau^2 = 0.24$; $\chi^2 = 5.83$, 5 d.f., $P = 0.32$; $I^2 = 14\%$						
Test for overall effect: $Z = 0.12$, $P = 0.90$						
Test for subgroup differences: $\chi^2 = 0.83$, 1 d.f., $P = 0.36$; $I^2 = 0\%$						



Certainty of evidence: low

Clavien–Dindo ≥grade III

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Distal pancreatectomy						
Björnsson 2020	4	29	8	29	13.5	0.42 (0.11, 1.59)
de Rooij 2019	39	51	21	57	18.5	5.57 (2.40, 12.93)
Subtotal (95% c.i.)		80		86	32.0	1.61 (0.13, 20.37)
Total events	43		29			
Heterogeneity: $\tau^2 = 3.03$; $\chi^2 = 10.36$, 1 d.f., $P = 0.001$; $I^2 = 90\%$						
Test for overall effect: $Z = 0.37$, $P = 0.71$						
Pancreatoduodenectomy						
Palanivelu 2017	3	32	4	32	11.4	0.72 (0.15, 3.53)
Poves 2018	5	32	11	29	14.6	0.30 (0.09, 1.02)
van Hilst, de Rooij 2019	25	50	19	49	18.9	1.58 (0.71, 3.51)
Wang 2021	85	297	69	297	23.0	1.32 (0.92, 1.92)
Subtotal (95% c.i.)		411		407	68.0	1.01 (0.55, 1.86)
Total events	118		103			
Heterogeneity: $\tau^2 = 0.19$; $\chi^2 = 6.06$, 3 d.f., $P = 0.11$; $I^2 = 51\%$						
Test for overall effect: $Z = 0.03$, $P = 0.98$						
Total (95% c.i.)		491		493	100.0	1.15 (0.55, 2.39)
Total events	161		132			
Heterogeneity: $\tau^2 = 0.57$; $\chi^2 = 20.41$, 5 d.f., $P = 0.001$; $I^2 = 75\%$						
Test for overall effect: $Z = 0.37$, $P = 0.71$						
Test for subgroup differences: $\chi^2 = 0.12$, 1 d.f., $P = 0.72$; $I^2 = 0\%$						



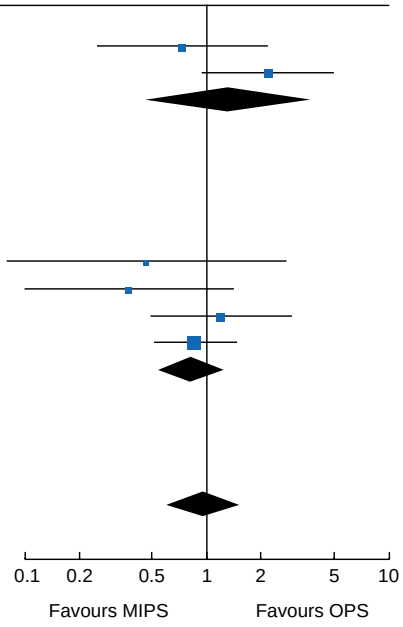
Certainty of evidence: low

(continued)

Table 2 (continued)

Postoperative pancreatic fistula

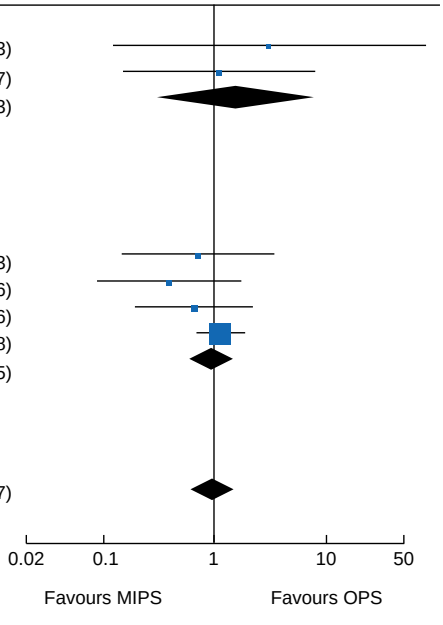
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight %	OR M-H, random, 95% c.i.
Distal pancreatectomy						
Björnsson 2020	9	29	11	29	13.4	0.74 (0.25, 2.18)
de Rooij 2019	20	51	13	57	19.7	2.18 (0.95, 5.04)
Subtotal (95% c.i.)		80		86	33.1	1.34 (0.47, 3.87)
Total events	29		24			
Heterogeneity: $\tau^2 = 0.35$; $\chi^2 = 2.41$, 1 d.f., $P = 0.12$; $I^2 = 59\%$						
Test for overall effect: $Z = 0.55$, $P = 0.58$						
Pancreatoduodenectomy						
Palanivelu 2017	2	32	4	32	5.8	0.47 (0.08, 2.75)
Poves 2018	4	32	8	29	9.7	0.38 (0.10, 1.41)
van Hilst, de Rooij 2019	14	50	12	49	17.9	1.20 (0.49, 2.94)
Wang 2021	29	297	33	297	33.5	0.87 (0.51, 1.47)
Subtotal (95% c.i.)		411		407	66.9	0.83 (0.54, 1.25)
Total events	49		57			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 2.45$, 3 d.f., $P = 0.48$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.9$, $P = 0.37$						
Total (95% c.i.)		491		493	100.0	0.96 (0.61, 1.50)
Total events	78		81			
Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 6.88$, 5 d.f., $P = 0.23$; $I^2 = 27\%$						
Test for overall effect: $Z = 0.18$, $P = 0.85$						
Test for subgroup differences: $\chi^2 = 0.70$, 1 d.f., $P = 0.40$; $I^2 = 0\%$						



Certainty of evidence: moderate

Post-pancreatectomy haemorrhage

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Distal pancreatectomy						
Björnsson 2020	1	29	0	29	1.6	3.11 (0.12, 79.43)
de Rooij 2019	2	51	2	57	4.3	1.12 (0.15, 8.27)
Subtotal (95% c.i.)		80		86	5.9	1.49 (0.27, 8.13)
Total events	3		2			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.28$, 1 d.f., $P = 0.60$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.46$, $P = 0.65$						
Pancreatoduodenectomy						
Palanivelu 2017	3	32	4	32	6.8	0.72 (0.15, 3.53)
Poves 2018	3	32	6	29	7.7	0.40 (0.09, 1.76)
van Hilst, de Rooij 2019	5	50	7	49	11.4	0.67 (0.20, 2.26)
Wang 2021	37	297	33	297	68.3	1.14 (0.69, 1.88)
Subtotal (95% c.i.)		411		407	94.1	0.95 (0.62, 1.45)
Total events	48		50			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.26$, 3 d.f., $P = 0.52$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.25$, $P = 0.80$						
Total (95% c.i.)		491		493	100.0	0.97 (0.64, 1.47)
Total events	51		52			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.79$, 5 d.f., $P = 0.73$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.13$, $P = 0.90$						
Test for subgroup differences: $\chi^2 = 0.25$, 1 d.f., $P = 0.62$; $I^2 = 0\%$						



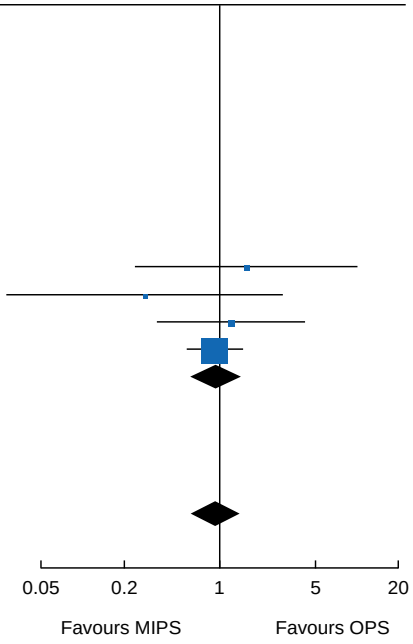
Certainty of evidence: moderate

(continued)

Table 2 (continued)

Bile leakage

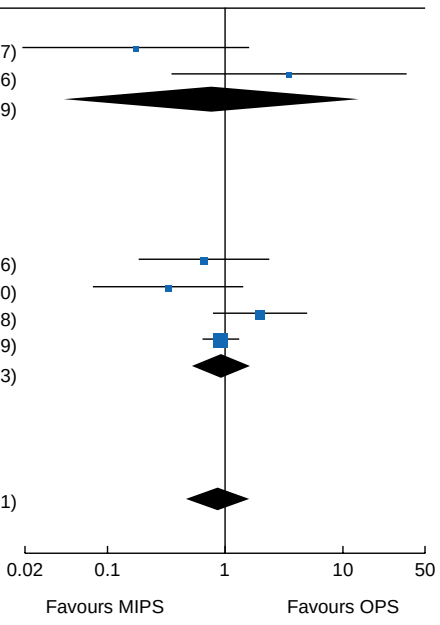
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Distal pancreatectomy						
Björnsson 2020	0	0	0	0		Not estimable
de Rooij 2019	0	0	0	0		Not estimable
Subtotal (95% c.i.)		0		0		Not estimable
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Pancreatoduodenectomy						
Palanivelu 2017	3	32	2	32	5.1	1.55 (0.24, 9.97)
Poves 2018	1	32	3	29	3.3	0.28 (0.03, 2.85)
van Hilst, de Rooij 2019	6	50	5	49	11.2	1.20 (0.34, 4.22)
Wang 2021	39	297	42	297	80.4	0.92 (0.57, 1.47)
Subtotal (95% c.i.)		411		407	100.0	0.93 (0.61, 1.42)
Total events	49		52			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.48$, 3 d.f., $P = 0.69$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.32$, $P = 0.75$						
Total (95% c.i.)		411		407	100.0	0.93 (0.61, 1.42)
Total events	49		52			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.48$, 3 d.f., $P = 0.69$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.32$, $P = 0.75$						
Test for subgroup differences: Not applicable						



Certainty of evidence: moderate

Delayed gastric emptying

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Distal pancreatectomy						
Björnsson 2020	1	29	5	29	6.2	0.17 (0.02, 1.57)
de Rooij 2019	3	51	1	57	5.8	3.50 (0.35, 34.76)
Subtotal (95% c.i.)		80		86	12.1	0.76 (0.04, 14.69)
Total events	4		6			
Heterogeneity: $\tau^2 = 3.23$; $\chi^2 = 3.44$, 1 d.f., $P = 0.06$; $I^2 = 71\%$						
Test for overall effect: $Z = 0.18$, $I^2 = 0.86$						
Pancreatoduodenectomy						
Palanivelu 2017	5	32	7	32	14.8	0.66 (0.19, 2.36)
Poves 2018	3	32	7	29	12.1	0.33 (0.08, 1.40)
van Hilst, de Rooij 2019	17	50	10	49	22.0	2.01 (0.81, 4.98)
Wang 2021	90	297	96	297	39.1	0.91 (0.64, 1.29)
Subtotal (95% c.i.)		411		407	87.9	0.93 (0.53, 1.63)
Total events	115		120			
Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 5.04$, 3 d.f., $P = 0.17$; $I^2 = 40\%$						
Test for overall effect: $Z = 0.27$, $P = 0.79$						
Total (95% c.i.)		491		493	100.0	0.89 (0.49, 1.61)
Total events	119		126			
Heterogeneity: $\tau^2 = 0.20$; $\chi^2 = 8.56$, 5 d.f., $P = 0.13$; $I^2 = 42\%$						
Test for overall effect: $Z = 0.39$, $P = 0.70$						
Test for subgroup differences: $\chi^2 = 0.02$, 1 d.f., $P = 0.90$; $I^2 = 0\%$						



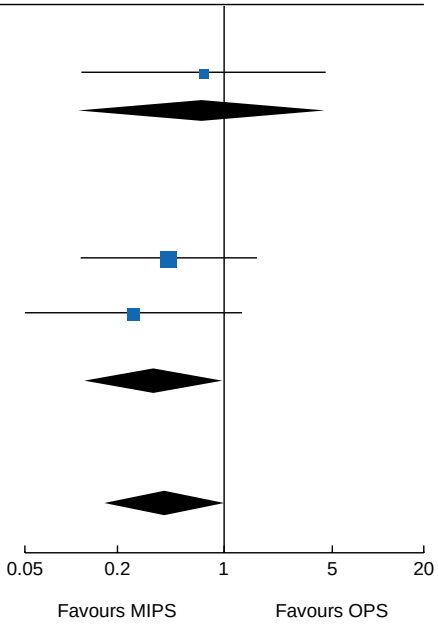
Certainty of evidence: low

(continued)

Table 2 (continued)

Surgical site infection

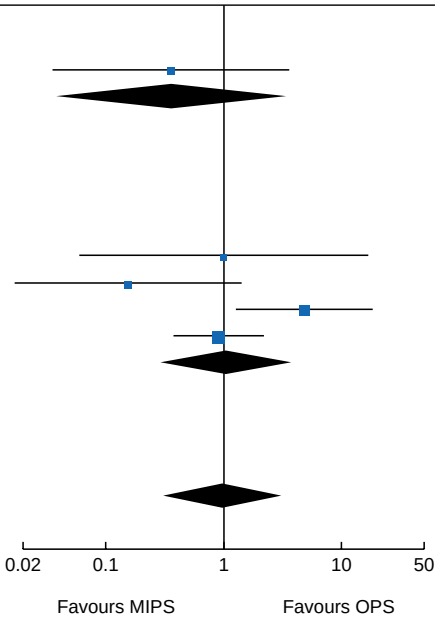
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Distal pancreatectomy						
Björnsson 2020	0	0	0	0		Not estimable
de Rooij 2019	2	51	3	57	23.8	0.73 (0.12, 4.58)
Subtotal (95% c.i.)		51		57	23.8	0.73 (0.12, 4.58)
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: $Z = 0.33$, $P = 0.74$						
Pancreatoduodenectomy						
Palanivelu 2017	4	32	8	32	45.9	0.43 (0.11, 1.60)
Poves 2018	0	0	0	0		Not estimable
van Hilst, de Rooij 2019	2	50	7	49	30.2	0.25 (0.05, 1.27)
Wang 2021	0	0	0	0		Not estimable
Subtotal (95% c.i.)		82		81	76.2	0.35 (0.12, 0.96)
Total events	6		15			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.26$, 1 d.f., $P = 0.61$; $I^2 = 0\%$						
Test for overall effect: $Z = 2.03$, $P = 0.04$						
Total (95% c.i.)		133		138	100.0	0.41 (0.17, 1.01)
Total events	8		18			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.75$, 2 d.f., $P = 0.69$; $I^2 = 0\%$						
Test for overall effect: $Z = 1.93$, $P = 0.05$						
Test for subgroup differences: $\chi^2 = 0.50$, 1 d.f., $P = 0.48$; $I^2 = 0\%$						



Certainty of evidence: low

Reoperation

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Distal pancreatectomy						
Björnsson 2020	0	0	0	0		Not estimable
de Rooij 2019	1	51	3	57	15.1	0.36 [0.04, 3.58]
Subtotal (95% c.i.)		51		57	15.1	0.36 [0.04, 3.58]
Total events	1		3			
Heterogeneity: Not applicable						
Test for overall effect: $Z = 0.87$, $P = 0.38$						
Pancreatoduodenectomy						
Palanivelu 2017	1	32	1	32	11.5	1.00 (0.06, 16.71)
Poves 2018	1	32	5	29	15.8	0.15 (0.02, 1.41)
van Hilst, de Rooij 2019	12	50	3	49	25.6	4.84 (1.27, 18.42)
Wang 2021	10	297	11	297	32.1	0.91 (0.38, 2.17)
Subtotal (95% c.i.)		411		407	84.9	1.08 (0.29, 3.97)
Total events	24		20			
Heterogeneity: $\tau^2 = 1.02$; $\chi^2 = 7.89$, 3 d.f., $P = 0.05$; $I^2 = 62\%$						
Test for overall effect: $Z = 0.11$, $P = 0.91$						
Total (95% c.i.)		462		464	100.0	0.93 (0.30, 2.87)
Total events	25		23			
Heterogeneity: $\tau^2 = 0.84$; $\chi^2 = 8.84$, 4 d.f., $P = 0.07$; $I^2 = 55\%$						
Test for overall effect: $Z = 0.13$, $P = 0.89$						
Test for subgroup differences: $\chi^2 = 0.66$, 1 d.f., $I^2 = 0.42$, $I^2 = 0\%$						



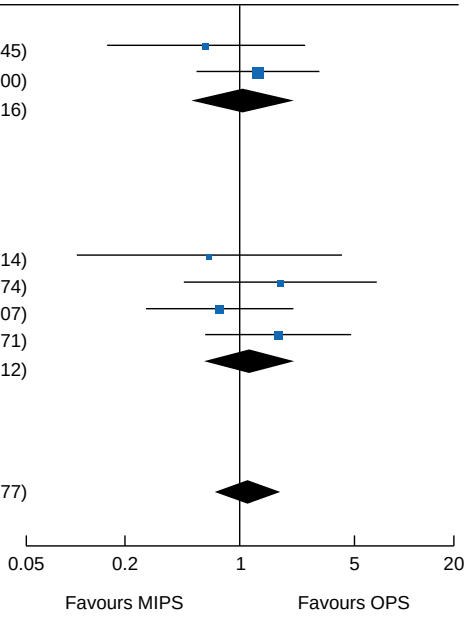
Certainty of evidence: low

(continued)

Table 2 (continued)

Readmission

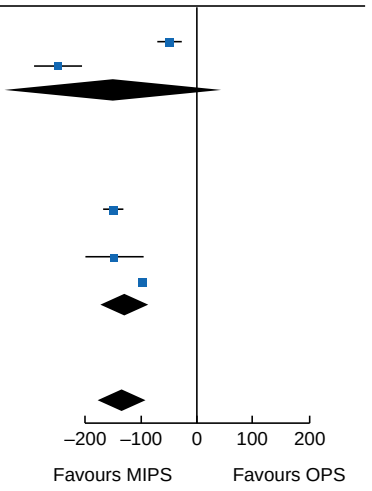
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Distal pancreatectomy						
Björnsson 2020	4	29	6	29	11.2	0.61 (0.15, 2.45)
de Rooij 2019	15	51	14	57	29.7	1.28 (0.55, 3.00)
Subtotal (95% c.i.)		80		86	40.9	1.05 (0.51, 2.16)
Total events	19		20			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.78$, 1 d.f., $P < 0.38$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.12$, $P = 0.90$						
Pancreatoduodenectomy						
Palanivelu 2017	2	32	3	32	6.2	0.64 (0.10, 4.14)
Poves 2018	7	32	4	29	11.9	1.75 (0.45, 6.74)
van Hilst, de Rooij 2019	8	50	10	49	20.5	0.74 (0.27, 2.07)
Wang 2021	10	297	6	297	20.5	1.69 (0.61, 4.71)
Subtotal (95% c.i.)		411		407	59.1	1.16 (0.63, 2.12)
Total events	27		23			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.98$, 3 d.f., $P < 0.58$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.47$, $P = 0.64$						
Total (95% c.i.)		491		493	100.0	1.11 (0.70, 1.77)
Total events	46		43			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.81$, 5 d.f., $P < 0.73$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.44$, $P = 0.66$						
Test for subgroup differences: $\tau^2 = 0.04$, 1 d.f., $P = 0.83$; $I^2 = 0\%$						



Certainty of evidence: low

Blood loss

Study or subgroup	MIPS Mean	MIPS SD	MIPS Total	OPS Mean	OPS SD	OPS Total	Weight (%)	Mean difference IV, random, 95% c.i.
Distal pancreatectomy								
Björnsson 2020	50	31.25	29	100	50	29	21.0	–50.00 (–71.46, –28.54)
de Rooij 2019	150	75	51	400	143.75	57	18.5	–250.00 (–292.62, –207.38)
Subtotal (95% c.i.)			80			86	39.5	–149.12 (–345.11, 46.87)
Heterogeneity: $\tau^2 = 19703.65$; $\chi^2 = 67.49$, 1 d.f., $P < 0.00001$; $I^2 = 99\%$								
Test for overall effect: $Z = 1.49$, $P = 0.14$								
Pancreatoduodenectomy								
Palanivelu 2017	250	22	32	401	46	32	21.4	–151.00 (–168.67, –133.33)
Poves 2018	0	0	0	0	0	0		Not estimable
van Hilst, de Rooij 2019	300	59.5	50	450	175	49	17.1	–150.00 (–201.70, –98.30)
Wang 2021	200	50	297	300	38.33	297	22.0	–100.00 (–107.17, –92.83)
Subtotal (95% c.i.)			379			378	60.5	–131.02 (–173.29, –88.75)
Heterogeneity: $\tau^2 = 1188.67$; $\chi^2 = 30.08$, 2 d.f., $P < 0.00001$; $I^2 = 93\%$								
Test for overall effect: $Z = 6.08$, $P < 0.00001$								
Total (95% c.i.)			459			464	100.0	–136.64 (–181.77, –91.51)
Heterogeneity: $\tau^2 = 2398.96$; $\chi^2 = 100.41$, 4 d.f., $P < 0.00001$; $I^2 = 96\%$								
Test for overall effect: $Z = 5.93$, $P = 0.00001$								
Test for subgroup differences: $\tau^2 = 0.03$, 1 d.f., $P = 0.86$; $I^2 = 0\%$								



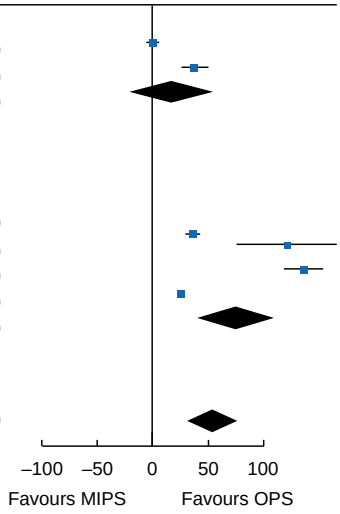
Certainty of evidence: low

(continued)

Table 2 (continued)

Duration of surgery

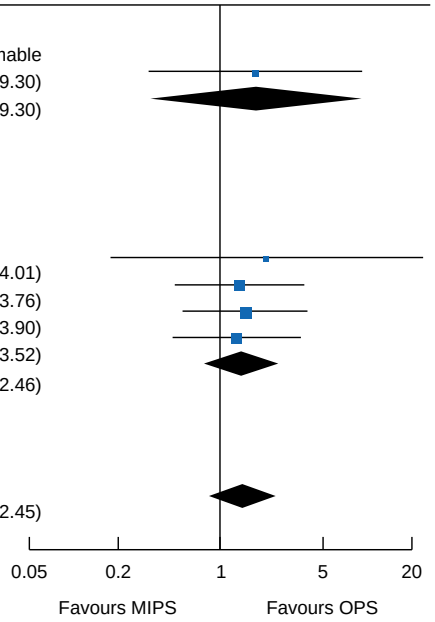
Study or subgroup	MIPS Mean	MIPS SD	MIPS Total	OPS Mean	OPS SD	OPS Total	Weight (%)	Mean difference IV, random, 95% c.i.
Distal pancreatectomy								
Björnsson 2020	120	8.75	29	120	11.5	29	18.4	0.00 (–5.26, 5.26)
de Rooij 2019	217	35.5	51	179	25.5	57	17.6	38.00 (26.22, 49.78)
Subtotal (95% c.i.)			80			86	36.0	18.62 (–18.61, 55.85)
Heterogeneity: τ^2 = 700.34; χ^2 = 33.33, 1 d.f., P < 0.00001; I^2 = 97%								
Test for overall effect: Z = 0.98, P = 0.33								
Pancreatoduodenectomy								
Palanivelu 2017	359	14	32	320	13	32	18.3	39.00 (32.38, 45.62)
Poves 2018	486	107.5	32	265	67.5	29	10.6	121.00 (76.38, 165.62)
van Hilst, de Rooij 2019	410	57.25	50	274	26.25	49	16.6	136.00 (118.51, 153.49)
Wang 2021	325	18.33	297	300	18.17	297	18.5	25.00 (22.06, 27.94)
Subtotal (95% c.i.)			411			407	64.0	75.40 (42.48, 108.32)
Heterogeneity: τ^2 = 1008.14; χ^2 = 175.35, 3 d.f., P < 0.00001; I^2 = 98%								
Test for overall effect: Z = 4.49, P < 0.00001								
Total (95% c.i.)			491			493	100.0	53.93 (31.68, 76.18)
Heterogeneity: τ^2 = 694.79; χ^2 = 281.08, 5 d.f., P < 0 .00001; I^2 = 98%								
Test for overall effect: Z = 4.75, P < 0.00001								
Test for subgroup differences: χ^2 = 5.01, 1 d.f., P = 0.03; I^2 = 80.1%								



Certainty of evidence: low

R0 resection

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Distal pancreatectomy						
Björnsson 2020	4	6	0	0		Not estimable
de Rooij 2019	7	13	4	10	10.1	1.75 (0.33, 9.30)
Subtotal (95% c.i.)		19		10	10.1	1.75 (0.33, 9.30)
Total events	11		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66, P = 0.51						
Pancreatoduodenectomy						
Palanivelu 2017	31	32	30	32	4.7	2.07 (0.18, 24.01)
Poves 2018	19	32	15	29	27.4	1.36 (0.49, 3.76)
van Hilst, de Rooij 2019	41	50	37	49	29.8	1.48 (0.56, 3.90)
Wang 2021	290	297	288	297	28.1	1.29 (0.48, 3.52)
Subtotal (95% c.i.)		411		407	89.9	1.41 (0.80, 2.46)
Total events	381		370			
Heterogeneity: τ^2 = 0.00; χ^2 = 0.13, 3 d.f., P = 0.99; I^2 = 0%						
Test for overall effect: Z = 1.20, P = 0.23						
Total (95% c.i.)		430		417	100.0	1.44 (0.85, 2.45)
Total events	392		374			
Heterogeneity: τ^2 = 0.00; χ^2 = 0.19, 4 d.f., P = 1.00; I^2 = 0%						
Test for overall effect: Z = 1.35, P = 0.18						
Test for subgroup differences: χ^2 = 0.06, 1 d.f., P = 0.81; I^2 = 0%						



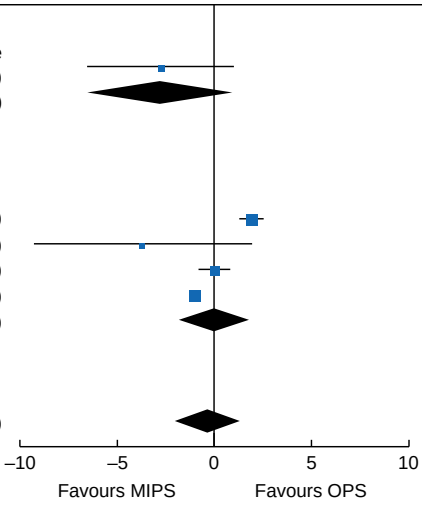
Certainty of evidence: low

(continued)

Table 2 (continued)

Lymph node yield

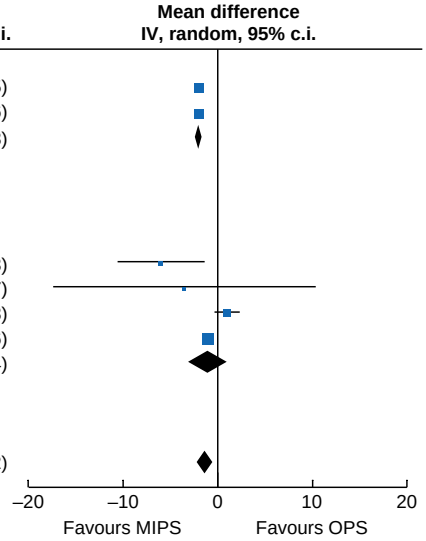
Study or subgroup	MIPS Mean	MIPS SD	MIPS Total	OPS Mean	OPS SD	OPS Total	Weight (%)	Mean difference IV, random, 95% c.i.
Distal pancreatectomy								
Björnsson 2020	0	0	0	0	0	0		Not estimable
de Rooij 2019	11.5	4.05	13	14.25	4.93	10	11.8	–2.75 (–6.52, 1.02)
Subtotal (95% c.i.)			13			10	11.8	–2.75 (–6.52, 1.02)
Heterogeneity: Not applicable								
Test for overall effect: $Z = 1.43$, $P = 0.15$								
Pancreatoduodenectomy								
Palanivelu 2017	18.9	1	32	17	1.4	32	27.1	1.90 (1.30, 2.50)
Poves 2018	17.25	6.25	24	21	13	25	6.8	–3.75 (–9.43, 1.93)
van Hilst, de Rooij 2019	11	1.75	50	11	2.25	49	26.4	0.00 (–0.80, 0.80)
Wang 2021	12	1.67	297	13	1.5	297	27.9	–1.00 (–1.26, –0.74)
Subtotal (95% c.i.)			403			403	88.2	–0.02 (–1.85, –1.80)
Heterogeneity: $\tau^2 = 2.72$; $\chi^2 = 79.77$, 3 d.f., $P < 0.00001$; $I^2 = 96\%$								
Test for overall effect: $Z = 0.03$, $P = 0.98$								
Total (95% c.i.)			416			413	100.0	–0.34 (–2.05, 1.36)
Heterogeneity: $\tau^2 = 2.69$; $\chi^2 = 81.13$, 4 d.f., $P < 0.00001$; $I^2 = 95\%$								
Test for overall effect: $Z = 0.40$, $P = 0.69$								
Test for subgroup differences: $\chi^2 = 1.63$, 1 d.f., $P = 0.20$; $I^2 = 38.7\%$								



Certainty of evidence: low

Length of hospital stay

Study or subgroup	MIPS Mean	MIPS SD	MIPS Total	OPS Mean	OPS SD	OPS Total	Weight (%)	Mean difference IV, random, 95% c.i.
Distal pancreatectomy								
Björnsson 2020	6	0.75	29	8	1	29	26.1	–2.00 (–2.45, –1.55)
de Rooij 2019	6	0.75	51	8	1.5	57	26.2	–2.00 (–2.44, –1.56)
Subtotal (95% c.i.)			80			86	52.3	–2.00 (–2.32, –1.68)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.00$, 1 d.f., $P = 1.00$; $I^2 = 0\%$								
Test for overall effect: $Z = 12.39$, $P < 0.00001$								
Pancreatoduodenectomy								
Palanivelu 2017	7	11.75	32	13	6	32	2.9	–6.00 (–10.57, –1.43)
Poves 2018	13.5	12.25	32	17	36	29	0.3	–3.50 (–17.27, 10.27)
van Hilst, de Rooij 2019	11	3.25	50	10	3.25	49	16.7	1.00 (–0.28, 2,28)
Wang 2021	15	1.67	297	16	1.33	297	27.7	–1.00 (–1.24, –0.76)
Subtotal (95% c.i.)			411			407	47.7	–0.94 (–2.93, 1.04)
Heterogeneity: $\tau^2 = 2.21$; $\chi^2 = 13.89$, 3 d.f., $P = 0.003$; $I^2 = 78\%$								
Test for overall effect: Z = 0.93, $P = 0.35$								
Total (95% c.i.)			491			493	100.0	–1.34 (–2.16, –0.52)
Heterogeneity: $\tau^2 = 0.61$; $\chi^2 = 41.14$, 5 d.f., $P < 0.00001$; $I^2 = 88\%$								
Test for overall effect: $Z = 3.22$, $P = 0.001$								
Test for subgroup differences: $\chi^2 = 1.06$, 1 d.f., $P = 0.30$; $I^2 = 6.0\%$								



Certainty of evidence: low

MIPS, minimally invasive pancreatic surgery; OPS, open pancreatic surgery; OR, odds ratio.

pancreatic surgery and open pancreatic surgery regarding general and pancreatic surgery specific morbidity rate, as well as oncologic outcomes. Reduction in blood loss in minimally invasive pancreatic surgery compared with open pancreatic surgery could be confirmed in low-risk studies by a mean of −165 ml (−262 to −69, $P < 0.001$, $I^2 = 96$ per cent, GRADE: low), with longer operative time by a mean of 66 min (14 to 117, $P = 0.010$, GRADE: low). The reduction in LOS previously reported in the minimally invasive group compared with the open group could not be confirmed in the low-risk subgroup (−0.9 days, −1.9 to 0.2, $P = 0.100$, $I^2 = 92$ per cent, GRADE: low).

Ongoing trials

A total of 12 ongoing RCTs comparing minimally invasive with open PD and eight ongoing RCTs comparing minimally invasive with open DP were found in a systematic search in the World Health Organization trial registry. An overview of trials and their expected termination is shown in *Table 6*.

Discussion

The present systematic review and meta-analysis of all currently available RCTs comparing minimally invasive (laparoscopic and robotic) and open pancreatic surgery showed no significant difference between the minimally invasive and open approaches regarding 90-day mortality rate, as well as general and pancreatic surgery specific morbidity rate. However, overall reductions in intraoperative blood loss and LOS using the minimally invasive approach were seen. On the other hand, a longer duration of surgery was reported for minimally invasive

Table 3 Subgroup analysis of categorical outcomes

Outcomes	PD				DP				Overall			
	n	MIPS	OPS	OR (95% c.i.)	*n*	MIPS	OPS	OR (95% c.i.)	*n*	MIPS	OPS	OR (95% c.i.)
Mortality rate	818	13 (3.2)	10 (2.5)	1.18 (0.30 to 4.63)	166	0 (0)	2 (2.3)	0.34 (0.03 to 3.37)	984	13 (2.6)	12 (2.4)	0.94 (0.34 to 2.56)
Clavien–Dindo ≥grade III	818	118 (28.7)	103 (25.3)	1.01 (0.55 to 1.86)	166	43 (53.8)	29 (33.7)	1.61 (0.13 to 20.37)	984	161 (32.8)	132 (26.8)	1.15 (0.55 to 2.39)
POPF	818	49 (11.9)	57 (14.0)	0.83 (0.54 to 1.25)	166	29 (36.3)	24 (27.9)	1.34 (0.47 to 3.87)	984	78 (15.9)	81 (16.4)	0.96 (0.61 to 1.50)
PPH	818	48 (11.7)	50 (12.3)	0.95 (0.62 to 1.45)	166	3 (3.8)	2 (2.3)	1.49 (0.27 to 8.13)	984	51 (10.4)	52 (10.5)	0.97 (0.64 to 1.47)
DGE	818	115 (27.9)	120 (29.5)	0.93 (0.53 to 1.63)	166	4 (5.0)	6 (7.0)	0.76 (0.04 to 14.69)	984	119 (24.2)	126 (25.6)	0.89 (0.49 to 1.61)
Bile leakage	818	49 (11.9)	52 (12.8)	0.93 (0.61 to 1.42)	ns	ns	ns	ns	818	49 (11.9)	52 (12.8)	0.93 (0.61 to 1.42)
SSI	163	6 (7.3)	15 (18.5)	0.35 (0.12 to 0.96)	108	2 (3.9)	3 (5.3)	0.73 (0.12 to 4.58)	271	8 (6)	18 (13.0)	0.41 (0.17 to 1.01)
Readmission	818	27 (6.6)	23 (5.7)	1.16 (0.63 to 2.12)	166	19 (23.8)	20 (23.3)	1.05 (0.51 to 2.16)	984	46 (9.4)	43 (8.7)	1.11 (0.70 to 1.77)
Reoperation	818	24 (5.8)	20 (4.9)	1.08 (0.29 to 3.97)	108	1 (2.0)	3 (5.3)	0.36 (0.04 to 3.58)	926	25 (5.4)	23 (5.0)	0.93 (0.30 to 2.87)
R0 resection	818	381 (92.7)	370 (90.9)	1.41 (0.80 to 2.46)	29	11 (57.9)	4 (40.0)	1.75 (0.33 to 9.30)	847	392 (91.2)	374 (89.7)	1.44 (0.85 to 2.45)

Values are *n* (%) unless otherwise indicated. PD, partial pancreatoduodenectomy; DP, distal pancreatectomy; MIPS, minimally invasive pancreatic surgery; OPS, open pancreatic surgery; OR, odds ratio; POPF, postoperative pancreatic fistula; PPH, post-pancreatectomy haemorrhage; DGE, delayed gastric emptying; SSI, surgical site infection; ns, not specified.

Table 4 Subgroup analysis of continuous outcomes

Outcomes	PD			DP			Overall		
	n	MD (95% c.i.)	*P*	*n*	MD (95% c.i.)	*P*	*n*	MD (95% c.i.)	*P*
Duration of surgery (min)	818	75 (42 to 108)	<0.001	166	19 (−19 to 56)	0.330	984	54 (32 to 76)	<0.001
Blood loss (ml)	757	−131 (−173 to −89)	<0.001	166	−149 (−345 to 47)	0.140	923	−137 (−182 to −92)	<0.001
LNY (*n*)	806	0.0 (−2.0 to 2.0)	0.980	23	−3 (−7 to 1)	0.150	829	0.0 (−2 to 1)	0.20
LOS (days)	818	−0.9 (−2.9 to 1.0)	0.610	166	−2.0 (−2.3 to −1.7)	<0.001	984	−1.3 (−2.0 to −0.5)	<0.001

PD, partial pancreatoduodenectomy; DP, distal pancreatectomy; MD, mean difference; LNY, lymph node yield; LOS, length of hospital stay.

pancreatic surgery. Taking the subgroup analysis into account, decreased intraoperative blood loss, reduction in SSI, and longer duration of surgery were only present in PD. Similarly, reduction in LOS was reported only in DP, not PD. Apart from reduced LOS using the minimally invasive approach, these results were confirmed in a subgroup of studies with a low risk of bias.

None of the studies was considered to be at high overall risk of bias. Some concern for bias was present in the domains 'deviations from intended intervention' and 'outcome measurement' in half of the studies. In the other half of the studies, the overall risk of bias was considered low. After critical appraisal, the certainty of evidence of outcomes was only low to moderate.

In the past, safety concerns, especially regarding minimally invasive PD, have been expressed in line with the results of early observational studies[26,27]. The highly complex surgical technique and consecutive long learning curves were regarded as presumable reasons[28]. On the other hand, higher mortality rate in minimally invasive PD was considered the result of a surmountable learning curve with supposedly comparable safety outcomes after its completion[29]. Meanwhile, centre volume and surgeon experience remain crucial for favourable postoperative safety and efficacy outcomes in high-risk and pancreatic surgery[30–33]. In a study performed by Sharpe *et al.*[29] reporting data from a nationwide database in the USA comparing laparoscopic with open pancreatoduodenectomy, a more than two-fold increased risk of mortality rate was found for the laparoscopic approach compared with the open approach in centres performing fewer than ten laparoscopic PDs/2 years. In larger-volume centres (greater than or equal to ten laparoscopic PDs/2 years) no difference in 30-day mortality rate between the laparoscopic and open approaches was reported[29]. All studies in this meta-analysis subjectively reported high levels of surgeon experience in pancreatic and minimally invasive surgery. The minimal number of laparoscopic DPs required was 37[18] and five[19]. In PD, at least 25[20], 20[22] and 104[23] minimally invasive procedures per participating surgeon were required before the start of the study. Further, several authors described standardized training programmes as eligibility criteria[34,35]. A centre volume of at least 20–50 PDs annually was reported, with a minimum of 10–20 being done laparoscopically.

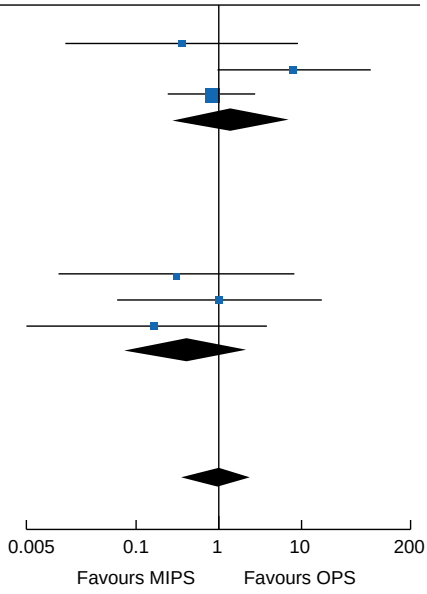
Whereas the importance of centre and surgeon volume is already undebated in successful open pancreatic surgery, its role in minimally invasive surgery appears to be at least as essential in achieving acceptable postoperative results[29]. Further, data on the standardized assessment of a learning curve are still missing. An attempt to define median learning curves for minimally invasive pancreatic surgery was recently done in a systematic review by Fung *et al.*,[36] reporting a median learning curve in DP of 17 (10–30) and 23.5 (7–40) cases for laparoscopic and robotic procedures respectively. The median learning curve for PD was reported to have been achieved at 30 (4–60) cases for the laparoscopic approach and 36.5 (20–80) cases for the robotic approach[36]. Comparing surgeon experience reported in the included studies with extrapolated learning curves from the literature[28,36], it becomes evident that not all surgeons reached sufficient expertise in minimally invasive pancreatic surgery before the start of the investigation. Nevertheless, postoperative mortality rate and morbidity rate between minimally invasive and open pancreatic surgery seem to be comparable. Taking surrogate outcomes into account, a minimally invasive approach even seems to be beneficial compared with open surgery, with regard to intraoperative blood loss, SSI, and LOS. A word of caution is necessary with regards to intraoperative blood loss, as inconsistency between different evaluation methods has been reported in pancreatic surgery[37].

However, data on compelling benefits of a minimally invasive approach known from other fields of surgery, such as in general,

Table 5 Subgroup analysis of risk-of-bias stratification

90-day mortality rate

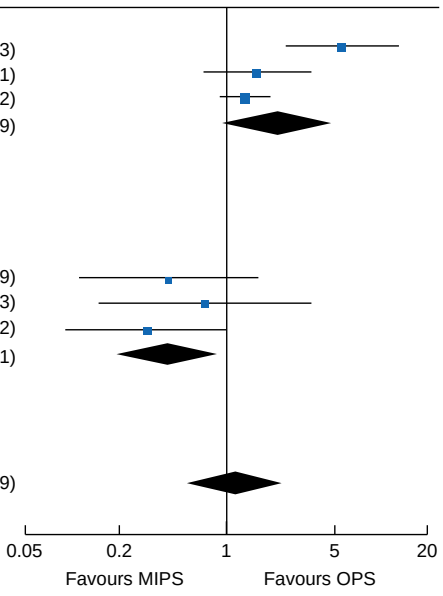
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	0	51	1	57	8.9	0.37 (0.01, 9.18)
van Hilst, de Rooij 2019	7	50	1	49	18.4	7.81 (0.92, 66.10)
Wang 2021	5	297	6	297	42.8	0.83 (0.25, 2.75)
Subtotal (95% c.i.)		398		403	70.1	1.45 (0.28, 7.58)
Total events	12		8			
Heterogeneity: $\tau^2 = 1.07$; $\chi^2 = 3.96$, 5 d.f., $P = 0.14$; $I^2 = 50\,\%$						
Test for overall effect: $Z = 0.44$, $P = 0.66$						
Some concern for bias						
Björnsson 2020	0	29	1	29	8.8	0.32 (0.01, 8.24)
Palanivelu 2017	1	32	1	32	11.4	1.00 (0.06, 16.71)
Poves 2018	0	32	2	29	9.7	0.17 (0.01, 3.68)
Subtotal (95% c.i.)		93		90	29.9	0.41 (0.07, 2.33)
Total events	1		4			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.73$, 2 d.f., $P = 0.69$; $I^2 = 0\,\%$						
Test for overall effect: $Z = 1.01$, $P = 0.31$						
Total (95% c.i.)		491		493	100.0	0.94 (0.34, 2.56)
Total events	13		12			
Heterogeneity: $\tau^2 = 0.24$; $\chi^2 = 5.83$, 1 d.f., $P = 0.32$; $I^2 = 14\,\%$						
Test for overall effect: $Z = 0.12$, $P = 0.90$						
Test for subgroup differences: $\chi^2 = 1.07$, 1 d.f., $P = 0.30$; $I^2 = 6.6\,\%$						



Certainty of evidence: low

Clavien–Dindo ≥3 grade III

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight %	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	39	51	21	57	18.5	5.57 (2.40, 12.93)
van Hilst, de Rooij 2019	25	50	19	49	18.9	1.58 (0.71, 3.51)
Wang 2021	85	297	69	297	23.0	1.32 (0.92, 1.92)
Subtotal (95% c.i.)		398		403	60.4	2.14 (0.94, 4.89)
Total events	149		109			
Heterogeneity: $\tau^2 = 0.41$; $\chi^2 = 9.41$, 2 d.f., $P = 0.009$; $I^2 = 79\,\%$						
Test for overall effect: $Z = 1.81$, $P = 0.07$						
Some concern for bias						
Björnsson 2020	4	29	8	29	13.5	0.42 (0.11, 1.59)
Palanivelu 2017	3	32	4	32	11.4	0.72 (0.15, 3.53)
Poves 2018	5	32	11	29	14.6	0.30 (0.09, 1.02)
Subtotal (95% c.i.)		93		90	39.6	0.42 (0.19, 0.91)
Total events	12		23			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.73$, 2 d.f., $P = 0.69$; $I^2 = 0\,\%$						
Test for overall effect: $Z = 2.18$, $P = 0.03$						
Total (95% c.i.)		491		493	100.0	1.15 (0.55, 2.39)
Total events	161		132			
Heterogeneity: $\tau^2 = 0.57$; $\chi^2 = 20.41$, 5 d.f., $P = 0.001$; $I^2 = 75\,\%$						
Test for overall effect: $Z = 0.37$, $P = 0.71$						
Test for subgroup differences: $\chi^2 = 7.92$, 1 d.f., $P = 0.005$; $I^2 = 87.4\,\%$						



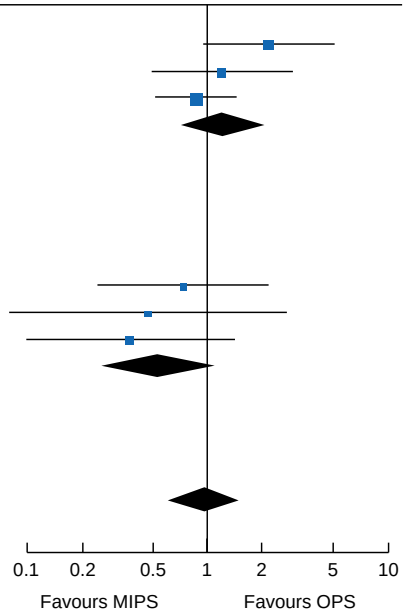
Certainty of evidence: low

(continued)

Table 5 (continued)

Postoperative pancreatic fistula

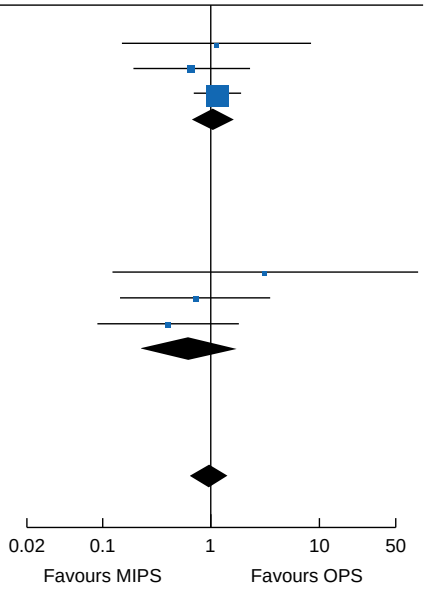
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	20	51	13	57	19.7	2.18 (0.95, 5.04)
van Hilst, de Rooij 2019	14	50	12	49	17.9	1.20 (0.49, 2.94)
Wang 2021	29	297	33	297	33.5	0.87 (0.51, 1.47)
Subtotal (95% c.i.)		398		403	71.1	1.22 (0.70, 2.12)
Total events	63		58			
Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 3.38$, 2 d.f., $P = 0.18$; $I^2 = 41\%$						
Test for overall effect: $Z = 0.71$, $P = 0.48$						
Some concern for bias						
Björnsson 2020	9	29	11	29	13.5	0.74 (0.25, 2.18)
Palanivelu 2017	2	32	4	32	5.8	0.47 (0.08, 2.75)
Poves 2018	4	32	8	29	9.7	0.38 (0.10, 1.41)
Subtotal (95% c.i.)		93		90	28.9	0.54 (0.25, 1.16)
Total events	15		23			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.63$, 2 d.f., $P = 0.73$; $I^2 = 0\%$						
Test for overall effect: $Z = 1.58$, $P = 0.12$						
Total (95% c.i.)		491		493	100.0	0.96 (0.61, 1.50)
Total events	78		81			
Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 6.88$, 5 d.f., $P = 0.23$; $I^2 = 27\%$						
Test for overall effect: $Z = 0.18$, $P = 0.85$						
Test for subgroup differences: $\chi^2 = 2.87$, 1 d.f., $P = 0.09$; $I^2 = 65.1\%$						



Certainty of evidence: moderate

Post-pancreatectomy haemorrhage

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	2	51	2	57	4.3	1.12 (0.15, 8.27)
van Hilst, de Rooij 2019	5	50	7	49	11.4	0.67 (0.20, 2.26)
Wang 2021	37	297	33	297	68.3	1.14 (0.69, 1.88)
Subtotal (95% c.i.)		398		403	83.9	1.06 (0.67, 1.66)
Total events	44		42			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.63$, 2 d.f., $P = 0.73$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.24$, $P = 0.81$						
Some concern for bias						
Björnsson 2020	1	29	0	29	1.6	3.11 (0.12, 79.43)
Palanivelu 2017	3	32	4	32	6.8	0.72 (0.15, 3.53)
Poves 2018	3	32	6	29	7.7	0.40 (0.09, 1.76)
Subtotal (95% c.i.)		93		90	16.1	0.63 (0.22, 1.76)
Total events	7		10			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.33$, 2 d.f., $P = 0.51$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.88$, $P = 0.38$						
Total (95% c.i.)		491		493	100.0	0.97 (0.64, 1.47)
Total events	51		52			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.79$, 5 d.f., $P = 0.73$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.13$, $P = 0.90$						
Test for subgroup differences: $\chi^2 = 0.82$, 1 d.f., $P = 0.36$; $I^2 = 0\%$						



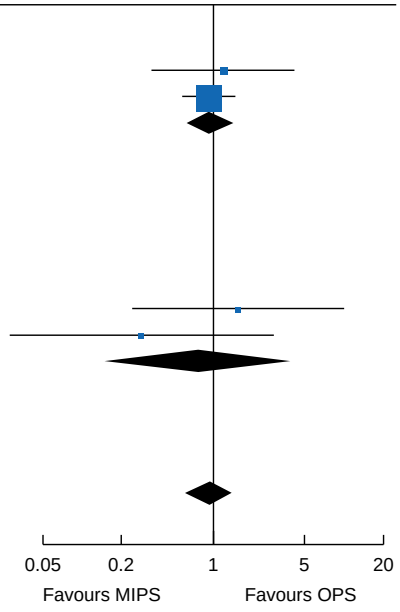
Certainty of evidence: moderate

(continued)

Table 5 (continued)

Bile leakage

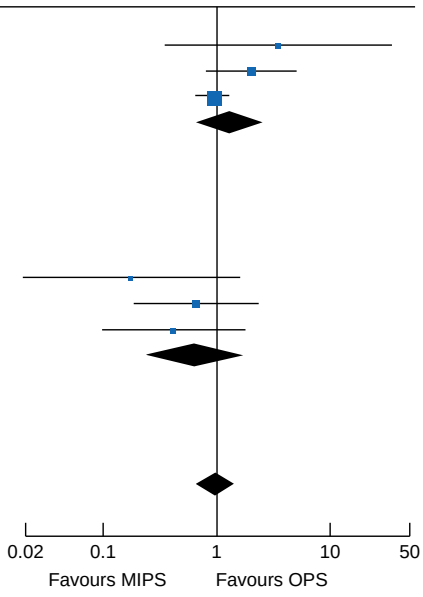
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	0	0	0	0		Not estimable
van Hilst, de Rooij 2019	6	50	5	49	11.2	1.20 (0.34, 4.22)
Wang 2021	39	297	42	297	80.4	0.92 (0.57, 1.47)
Subtotal (95% c.i.)		347		346	91.6	0.95 (0.61, 1.47)
Total events	45		47			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.15$, 1 d.f., $P = 0.70$; $I^2 = 0\,\%$						
Test for overall effect: $Z = 0.24$, $P = 0.81$						
Some concern for bias						
Björnsson 2020	0	0	0	0		Not estimable
Palanivelu 2017	3	32	2	32	5.1	1.55 (0.24, 9.97)
Poves 2018	1	32	3	29	3.3	0.28 (0.03, 2.85)
Subtotal (95% c.i.)		64		61	8.4	0.76 (0.15, 4.00)
Total events	4		5			
Heterogeneity: $\tau^2 = 0.32$; $\chi^2 = 1.28$, 1 d.f., $P = 0.26$; $I^2 = 22\,\%$						
Test for overall effect: $Z = 0.32$, $P = 0.75$						
Total (95% c.i.)		411		407	100.0	0.93 (0.61, 1.42)
Total events	49		52			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.48$, 3 d.f., $P = 0.69$; $I^2 = 0\,\%$						
Test for overall effect: Z = 0.32, $P = 0.75$						
Test for subgroup differences: $\chi^2 = 0.06$, 1 d.f., $P = 0.80$; $I^2 = 0\,\%$						



Certainty of evidence: moderate

Delayed gastric emptying

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	3	51	1	57	5.8	3.50 (0.35, 34.76)
van Hilst, de Rooij 2019	17	50	10	49	22.0	2.01 (0.81, 4.98)
Wang 2021	90	297	96	297	39.1	0.91 (0.64, 1.29)
Subtotal (95% c.i.)		398		403	66.9	1.31 (0.65, 2.61)
Total events	110		107			
Heterogeneity: $\tau^2 = 0.18$; $\chi^2 = 3.66$, 2 d.f., $P = 0.16$; $I^2 = 45\,\%$						
Test for overall effect: $Z = 0.76$, $P = 0.45$						
Some concern for bias						
Björnsson 2020	1	29	5	29	6.2	0.17 (0.02, 1.57)
Palanivelu 2017	5	32	7	32	14.8	0.66 (0.19, 2.36)
Poves 2018	3	32	7	29	12.1	0.33 (0.08, 1.40)
Subtotal (95% c.i.)		93		90	33.1	0.41 (0.17, 1.00)
Total events	9		19			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.24$, 2 d.f., $P = 0.54$; $I^2 = 0\,\%$						
Test for overall effect: $Z = 1.97$, $P = 0.05$						
Total (95% c.i.)		491		493	100.0	0.89 (0.49, 1.61)
Total events	119		126			
Heterogeneity: $\tau^2 = 0.20$; $\chi^2 = 8.56$, 5 d.f., $P = 0.13$; $I^2 = 42\,\%$						
Test for overall effect: $Z = 0.39$, $P = 0.70$						
Test for subgroup differences: $\chi^2 = 4.06$, 1 d.f., $P = 0.04$, $I^2 = 75.4\,\%$						



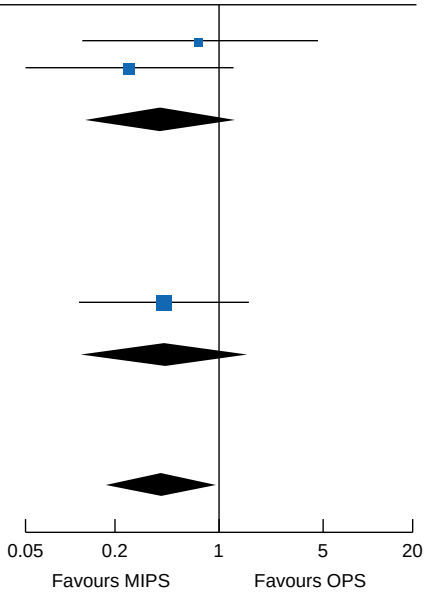
Certainty of evidence: low

(continued)

Table 5 (continued)

Surgical site infection

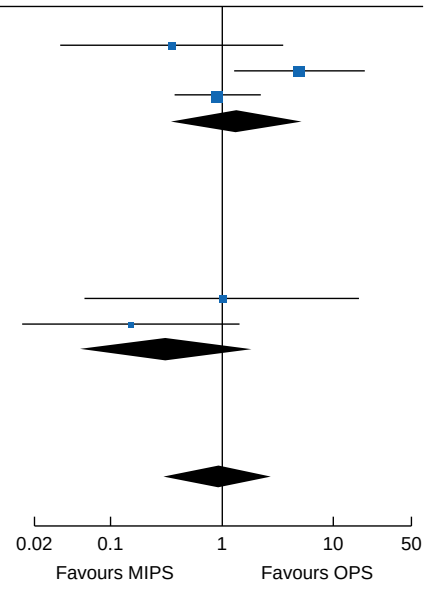
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	2	51	3	57	23.8	0.73 (0.12, 4.58)
van Hilst, de Rooij 2019	2	50	7	49	30.2	0.25 (0.05, 1.27)
Wang 2021	0	0	0	0		Not estimable
Subtotal (95% c.i.)		101		106	54.1	0.40 (0.12, 1.36)
Total events	4		10			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.75$, 1 d.f., $P = 0.39$; $I^2 = 0\,\%$						
Test for overall effect: $Z = 1.47$, $P = 0.14$						
Some concern for bias						
Björnsson 2020	0	0	0	0		Not estimable
Palanivelu 2017	4	32	8	32	45.9	0.43 (0.11, 1.60)
Poves 2018	0	0	0	0		Not estimable
Subtotal (95% c.i.)		32		32	45.9	0.43 (0.11, 1.60)
Total events	4		8			
Heterogeneity: not applicable						
Test for overall effect: $Z = 1.26$, $P = 0.21$						
Total (95% c.i.)		133		138	100.0	0.41 (0.17, 1.01)
Total events	8		18			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.75$, 2 d.f., $P = 0.69$; $I^2 = 0\,\%$						
Test for overall effect: $Z = 1.93$, $P = 0.05$						
Test for subgroup differences: $\chi^2 = 0.00$, 1 d.f., $P = 0.94$; $I^2 = 0\,\%$						



Certainty of evidence: low

Reoperation

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	1	51	3	57	15.1	0.36 (0.04, 3.58)
van Hilst, de Rooij 2019	12	50	3	49	25.6	4.84 (1.27, 18.42)
Wang 2021	10	297	11	297	32.1	0.91 (0.38, 2.17)
Subtotal (95% c.i.)		398		403	72.8	1.34 (0.35, 5.19)
Total events	23		17			
Heterogeneity: $\tau^2 = 0.89$; $\chi^2 = 5.61$, 2 d.f., $P = 0.06$; $I^2 = 64\,\%$						
Test for overall effect: Z = 0.43, $P = 0.67$						
Some concern for bias						
Björnsson 2020	0	0	0	0		Not estimable
Palanivelu 2017	1	32	1	32	11.5	1.00 (0.06, 16.71)
Poves 2018	1	32	5	29	15.8	0.15 (0.02, 1.41)
Subtotal (95% c.i.)		64		61	27.2	0.32 (0.05, 1.91)
Total events	2		6			
Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 1.05$, 1 d.f., $P = 0.31$; $I^2 = 5\,\%$						
Test for overall effect: $Z = 1.25$, $P = 0.21$						
Total (95% c.i.)		462		464	100.0	0.93 (0.30, 2.87)
Total events	25		23			
Heterogeneity: $\tau^2 = 0.84$; $\chi^2 = 8.84$, 4 d.f., $P = 0.07$; $I^2 = 55\,\%$						
Test for overall effect: $Z = 0.13$, $P = 0.89$						
Test for subgroup differences: $\chi^2 = 1.58$, 1 d.f., $P = 0.21$; $I^2 = 36.8\,\%$						



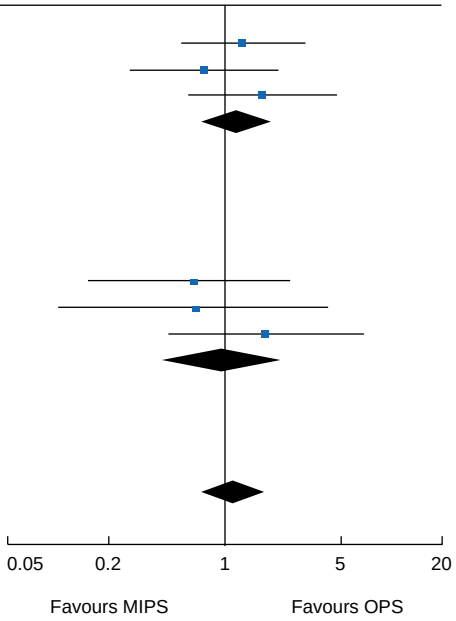
Certainty of evidence: low

(continued)

Table 5 (continued)

Readmission

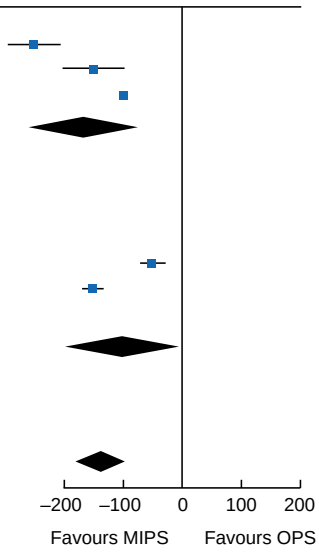
Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	15	51	14	57	29.7	1.28 (0.55, 3.00)
van Hilst, de Rooij 2019	8	50	10	49	20.5	0.74 (0.27, 2.07)
Wang 2021	10	297	6	297	20.5	1.69 (0.61, 4.71)
Subtotal 95% c.i.		398		403	70.7	1.19 (0.68, 2.06)
Total events	33		30			
Heterogeneity: τ^2 = 0.00, χ^2 = 1.29, 2 d.f., P < 0.53; I^2 = 0%						
Test for overall effect: Z = 0.60, P = 0.55						
Some concern for bias						
Björnsson 2020	4	29	6	29	11.2	0.61 (0.15, 2.45)
Palanivelu 2017	2	32	3	32	6.2	0.64 (0.10, 4.14)
Poves 2018	7	32	4	29	11.9	1.75 (0.45, 6.74)
Subtotal 95% c.i.		93		90	29.3	0.95 (0.40, 2.23)
Total events	13		13			
Heterogeneity: τ^2 = 0.00, χ^2 = 1.34, 2 d.f., P = 0.51; I^2 = 0%						
Test for overall effect: Z = 0.12, P = 0.90						
Total 95% c.i.		491		493	100.0	1.11 (0.70, 1.77)
Total events	46		43			
Heterogeneity: τ^2 = 0.00, χ^2 = 2.81, 5 d.f., P < 0.73; I^2 = 0%						
Test for overall effect: Z = 0.44, P = 0.66						
Test for subgroup differences: χ^2 = 0.18, 1 d.f., P = 0.67; I^2 = 0%						



Certainty of evidence: low

Blood loss

Study or subgroup	MIPS Mean	MIPS SD	MIPS Total	OPS Mean	OPS SD	OPS Total	Weight (%)	Mean difference IV, random, 95% c.i.
Low risk of bias								
de Rooij 2019	150	75	51	400	143.75	57	18.5	–250.00 (–292.62, –207.38)
van Hilst, de Rooij 2019	300	59.5	50	450	175	49	17.1	–150.00 (–201.70, –98.30)
Wang 2021	200	50	297	300	38.33	297	22.0	–100.00 (–107.17, –92.83)
Subtotal 95% c.i.			398			403	57.6	–165.37 (–261.85, –68.88)
Heterogeneity: τ^2 = 6887.57; χ^2 = 49.25, 2 d.f., P < 0.00001; I^2 = 96%								
Test for overall effect: Z = 3.36, P = 0.0008								
Some concern for bias								
Björnsson 2020	50	31.25	29	100	50	29	21.0	–50.00 (–71.46, –28.54)
Palanivelu 2017	250	22	32	401	46	32	21.4	–151.00 (–168.67, –133.33)
Poves 2018	0	0	0	0	0	0		Not estimable
Subtotal 95% c.i.			61			61	42.4	–100.69 (–199.67, –1.71)
Heterogeneity: τ^2 = 4.999.93; χ^2 = 50.72, 1 d.f., P < 0.00001; I^2 = 98%								
Test for overall effect: Z = 1.99, P = 0.05								
Total 95% c.i.			459			464	100.0	–136.64 (–181.77, –91.51)
Heterogeneity: τ^2 = 2398.96; χ^2 = 100.41, 4 d.f., P < 0.00001; I^2 = 96%								
Test for overall effect: Z = 5.93, P = 0.00001								
Test for subgroup differences: χ^2 = 0.84, 1 d.f., P = 0.36; I^2 = 0%								



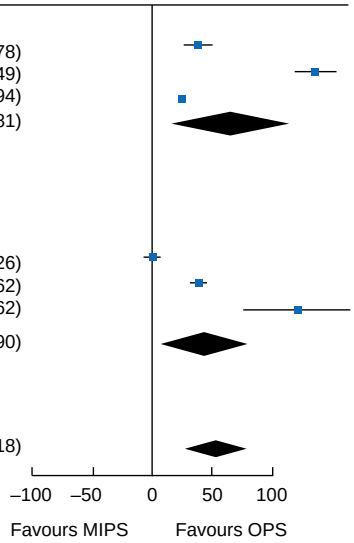
Certainty of evidence: low

(continued)

Table 5 (continued)

Duration of surgery

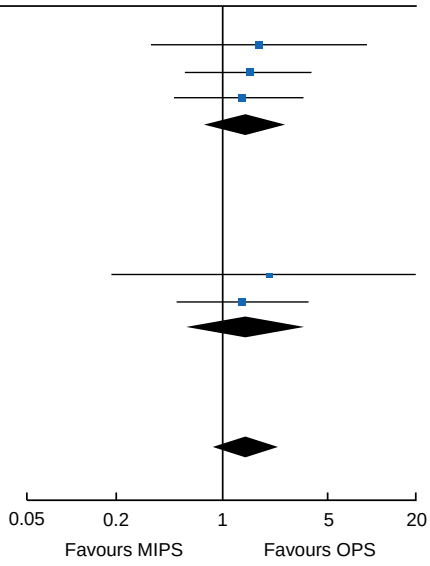
Study or subgroup	MIPS Mean	MIPS SD	MIPS Total	OPS Mean	OPS SD	OPS Total	Weight (%)	Mean difference IV, random, 95% c.i.
Low risk of bias								
de Rooij 2019	217	35.5	51	179	25.5	57	17.6	–38.00 (26.22, 49.78)
van Hilst, de Rooij 2019	410	57.25	50	274	26.25	49	16.6	136.00 (118.51, 153.49)
Wang 2021	325	18.33	297	300	18.17	297	18.5	25.00 (22.06, 27.94)
Subtotal (95% c.i.)			398			403	52.8	65.62 (14.42, 116.81)
Heterogeneity: $\tau^2 = 2007.8$; $\chi^2 = 153.11$, 2 d.f., $P < 0.00001$; $I^2 = 99\%$								
Test for overall effect: $Z = 2.51$, $P = 0.01$								
Some concern for bias								
Björnsson 2020	120	8.75	29	120	11.5	29	18.4	0.00 (–5.26, 5.26)
Palanivelu 2017	359	14	32	320	13	32	18.3	39.00 (32.38, 45.62)
Poves 2018	486	107.5	32	365	67.5	29	10.6	121.00 (76.38, 165.62)
Subtotal (95% c.i.)			93			90	47.2	44.23 (7.56, 80.90)
Heterogeneity: $\tau^2 = 916.65$; $\chi^2 = 103.21$, 2 d.f., $P < 0.00001$; $I^2 = 98\%$								
Test for overall effect: $Z = 2.36$, $P = 0.02$								
Total (95% c.i.)			491			493	100.0	53.93 (31.68, 76.18)
Heterogeneity: $\tau^2 = 694.79$; $\chi^2 = 281.08$, 5 d.f., $P < 0.00001$; $I^2 = 98\%$								
Test for overall effect: $Z = 4.75$, $P = 0.00001$								
Test for subgroup differences: $\chi^2 = 0.44$, 1 d.f., $P = 0.51$; $I^2 = 0\%$								



Certainty of evidence: low

R0 resection

Study or subgroup	MIPS Events	MIPS Total	OPS Events	OPS Total	Weight (%)	OR M-H, random, 95% c.i.
Low risk of bias						
de Rooij 2019	7	13	4	10	10.1	1.75 (0.33, 9.30)
van Hilst, de Rooij 2019	41	50	37	49	29.8	1.48 (0.56, 3.90)
Wang 2021	290	297	288	297	28.1	1.29 (0.48, 3.52)
Subtotal (95% c.i.)		360		356	68.0	1.43 (0.75, 2.73)
Total events	338		329			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.10$, 2 d.f., $P = 0.95$; $I^2 = 0\%$						
Test for overall effect: $Z = 1.10$, $P = 0.27$						
Some concern for bias						
Björnsson 2020	4	6	0	0		Not estimable
Palanivelu 2017	31	32	30	32	4.7	2.07 (0.18, 24.01)
Poves 2018	19	32	15	29	27.4	1.36 (0.49, 3.76)
Subtotal (95% c.i.)		70		61	32.0	1.45 (0.57, 3.70)
Total events	54		45			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.09$, 1 d.f., $P = 0.76$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.78$, $P = 0.44$						
Total (95% c.i.)		430		417	100.0	1.44 (0.85, 2.45)
Total events	392		374			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.19$, 4 d.f., $P = 1.00$; $I^2 = 0\%$						
Test for overall effect: $Z = 1.35$, $P = 0.18$						
Test for subgroup differences: $\chi^2 = 0.00$, 1 d.f., $P = 0.99$; $I^2 = 0\%$						



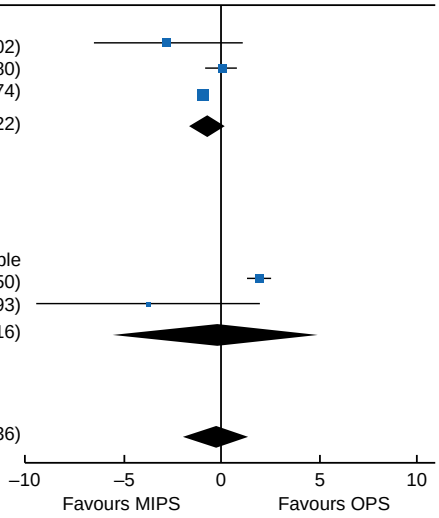
Certainty of evidence: low

(continued)

Table 5 (continued)

Lymph node yield

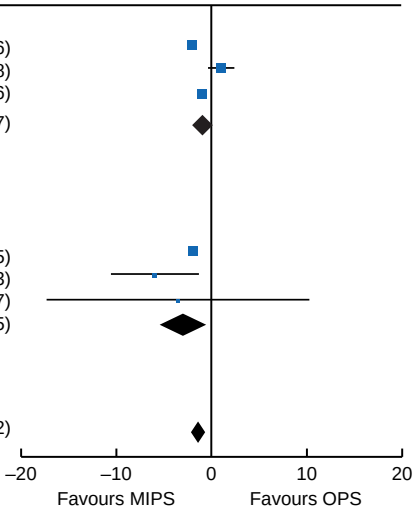
Study or subgroup	MIPS Mean	MIPS SD	MIPS Total	OPS Mean	OPS SD	OPS Total	Weight (%)	Mean difference IV, random, 95% c.i.
Low risk of bias								
de Rooij 2019	11.5	4.05	13	14.25	4.93	10	11.8	–2.75 (–6.52, 1.02)
van Hilst, de Rooij 2019	11	1.75	50	11	2.25	49	26.4	0.00 (–0.80, 0.80)
Wang 2021	12	1.67	297	13	1.5	297	27.9	–1.00 (–1.26, –0.74)
Subtotal (95% c.i.)			360			356	66.1	–0.69 (–1.61, 0.22)
Heterogeneity: $\tau^2 = 0.38$; $\chi^2 = 6.43$, 2 d.f., $P = 0.04$; $I^2 = 69\%$								
Test for overall effect: $Z = 1.48$, $P = 0.14$								
Some concern for bias								
Björnsson 2020	0	0	0	0	0	0		Not estimable
Palanivelu 2017	18.9	1	32	17	1.4	32	27.1	1.90 (1.30, 2.50)
Poves 2018	17.25	6.25	24	21	13	25	6.8	–3.75 (–9.43, 1.93)
Subtotal (95% c.i.)			56			57	33.9	–0.19 (–5.54, 5.16)
Heterogeneity: $\tau^2 = 11.72$; $\chi^2 = 3.76$, 1 d.f., $P = 0.05$; $I^2 = 73\%$								
Test for overall effect: $Z = 0.07$, $P = 0.94$								
Total (95% c.i.)			416			413	100.0	–0.34 (–2.05, 1.36)
Heterogeneity: $\tau^2 = 2.69$; $\chi^2 = 81.13$, 4 d.f., $P < 0.00001$; $I^2 = 95\%$								
Test for overall effect: $Z = 0.40$, $P = 0.69$								
Test for subgroup differences: $\chi^2 = 0.03$; 1 d.f., $P = 0.86$; $I^2 = 0\%$								



Certainty of evidence: low

Length of hospital stay

Study or subgroup	MIPS Mean	MIPS SD	MIPS Total	OPS Mean	OPS SD	OPS Total	Weight (%)	Mean difference IV, random, 95% c.i.
Low risk of bias								
de Rooij 2019	6	0.75	51	8	1.5	57	26.2	–2.00 (–2.44, –1.56)
van Hilst, de Rooij 2019	11	3.25	50	10	3.25	49	16.7	1.00 (–0.28, 2.28)
Wang 2021	15	1.67	297	16	1.33	297	27.7	–1.00 (–1.24, –0.76)
Subtotal (95% c.i.)			398			403	70.7	–0.87 (–1.92, 0.17)
Heterogeneity: $\tau^2 = 0.72$; $\chi^2 = 26.56$, 2 d.f., $P < 0.00001$; $I^2 = 92\%$								
Test for overall effect: $Z = 1.64$, $P = 0.10$								
Some concern for bias								
Björnsson 2020	6	0.75	29	8	1	29	26.1	–2.00 (–2.45, –1.55)
Palanivelu 2017	7	11.75	32	13	6	32	2.9	–6.00 (–10.57, –1.43)
Poves 2018	13.5	12.25	32	17	36	29	0.3	–3.50 (–17.27, 10.27)
Subtotal (95% c.i.)			93			90	29.3	–2.97 (–5.58, –0.35)
Heterogeneity: $\tau^2 = 2.36$; $\chi^2 = 2.96$, 2 d.f., $P = 0.23$; $I^2 = 32\%$								
Test for overall effect: $Z = 2.22$, $P = 0.03$								
Total (95% c.i.)			491			493	100.0	–1.34 (–2.16, –0.52)
Heterogeneity: $\tau^2 = 0.61$; $\chi^2 = 41.14$, 5 d.f., $P < 0.00001$; $I^2 = 88\%$								
Test for overall effect: $Z = 3.22$, $P = 0.001$								
Test for subgroup differences: $\chi^2 = 2.12$; 1 d.f., $P < 0.15$; $I^2 = 52.8\%$								



Certainty of evidence: low

MIPS, minimally invasive pancreatic surgery; OPS, open pancreatic surgery; OR, odds ratio.

bariatric, and lower and upper gastrointestinal surgery, are still missing in pancreatic surgery. Meanwhile, the question of safe implementation of the minimally invasive technique in pancreatic surgery remains a matter of debate. Müller *et al.*[28] suggested a stepwise introduction of different pancreatic resections according to the procedural complexity and standardized reporting of learning curves to reduce learning curve-related bias. Adequate assessment of baseline surgeon experience and skill level, and standardized reporting of learning curves within a three-phase model (competency, proficiency, and mastery) was suggested. Meanwhile, adequate case selection with regards to favourable anatomical (low BMI) and disease specific (no vessel involvement) features in a first learning phase under supervision to reach competency level seems of paramount importance. With increasing experience, proficiency and mastery levels are reached and more complex procedures may be introduced with the goal to achieve benchmark outcomes[28,38]. Furthermore, several initiatives for collaborative research on safe implementation of the minimally invasive technique in pancreatic surgery, such as the European Consortium of Minimally Invasive Pancreatic Surgery (E-MIPS), have emerged[39,40]. Additionally, efforts to provide international evidence-based guidelines for minimally invasive pancreatic resections and the implementation of the minimally invasive approach to obtain optimal patient outcomes and safety have been made[41].

Additionally, in comparison with benchmark criteria in open pancreatic surgery defined by Sánchez-Velázquez *et al.*[42] and Probst *et al.*[6], postoperative safety outcomes from the current

Table 6 Ongoing RCTs and unpublished terminated RCTs

Identifier	Title	Expected end of trial
Partial pancreatoduodenectomy		
NCT03785743	Comparing laparoscopic and open surgery for pancreatic carcinoma	1 March 2026
NCT04171440	Comparison of perioperative outcomes between minimally invasive and open pancreaticoduodenectomy	1 July 2024
ChiCTR1900024788	Robotic pancreaticoduodenectomy (RPD) *versus* open pancreaticoduodenectomy (OPD) in the long-term oncologic outcomes (LR301PD1): a randomized controlled trial	1 September 2021
NCT03870698	Comparison of functional recovery between laparoscopic and open pancreaticoduodenectomy	1 July 2021
NCT03747588	The comparison of laparoscopic and open pancreaticoduodenectomy for pancreatic cancer (LOPA)	30 December 2020
NCT03138213	Comparing total laparoscopic *versus* open pancreaticoduodenectomy	1 September 2020
NCT03722732	Comparison of blood loss in laparoscopic *versus* open pancreaticoduodenectomy in patients with periampullary carcinoma	1 December 2019
DRKS00020407	Evaluation of robotic *versus* open partial pancreaticoduodenectomy of a randomized controlled trial (EUROPA)	Not reported
NCT04400357	Robotic *versus* open pancreaticoduodenectomy for pancreatic and periampullary tumours (PORTAL)	Not reported
ChiCTR1900028686	A prospective randomized controlled trial for the effects of laparoscopic and non-laparoscopic surgery on pancreas islet function	Not reported
ChiCTR2000038932	Robotic *versus* open pancreatoduodenectomy for pancreatic or periampullary tumours: a multicentre, patient-blinded, randomized controlled trial	Not reported
Distal pancreatectomy		
NCT03957135	Laparoscopic *versus* open distal pancreatectomy for pancreatic cancer: a multicentre randomized controlled trial	30 November 2025
NCT04483726	Distal pancreatectomy, minimally invasive or open, for malignancy (DIPLOMA)	9 July 2025
ISRCTN44897265	Distal pancreatectomy, minimally invasive or open, for malignancy	1 May 2024
KCT0004176	Multicentre prospective randomized controlled clinical trial for comparison between laparoscopic and open distal pancreatectomy for ductal adenocarcinoma of the pancreatic body and tail	30 November 2023
NCT03792932	Laparoscopic *versus* open pancreatectomy for body and tail pancreatic cancer	31 January 2022
ChiCTR1900024648	A randomized controlled study for the short-term oncologic outcomes of robot-assisted radical and open anterograde modular pancreaticosplenectomy	30 November 2020
DRKS00014011	Distal pancreatectomy of a randomized controlled trial to compare open *versus* laparoscopic resection (DISPACT 2-TRIAL)	Not reported
ChiCTR2000038933	Robotic *versus* open radical antegrade modular pancreatosplenectomy for pancreatic cancer of the body and tail: a multicentre, randomized controlled trial	Not reported

meta-analysis appear within benchmark cut-offs. Recently published analyses further report benchmark criteria for minimally invasive and open DP[38,43,44]. Benchmark cut-off values for mortality rate in PD were set at less than or equal to 1.6 per cent and 2 per cent by Sánchez-Velázquez *et al.*[42] and Probst *et al.*[6] respectively. In DP, Probst *et al.*[6] reported a benchmark cut-off of 1 per cent. A slightly elevated overall 90-day mortality rate in minimally invasive PD (3.2 per cent), as well as in the open procedure (2.5 per cent), was found in the current study. On the other hand, reduced mortality rate compared with the benchmark cut-off was reported in minimally invasive DP (0 per cent), though without a significant difference compared with open DP in the current study. The discrepancy can most likely be explained by insufficient surgeon and centre experience, as described above. Interestingly, when examining only the two studies with completed learning curves before study start[18,23], postoperative safety outcomes even undercut benchmark cut-offs. Furthermore, 90-day mortality rate cannot be directly compared with in-hospital mortality rate, as presented by Sánchez-Velázquez *et al.*[42] Other general and pancreatic surgery specific morbidity rate outcomes met the predefined benchmark cut-offs. In the current study, a POPF incidence of 11.9 per cent was seen in minimally invasive PD. The benchmark cut-off is defined as less than or equal to 19 per cent by Sánchez-Velázquez *et al.*[42] and 14 per cent by Probst *et al.*[6] In DP, an elevated POPF incidence of 36.3 per cent compared with the benchmark outcome (less than or equal to 8.3 per cent to less than or equal to 32 per cent) without a significant difference compared with open DP was reported. Björnsson *et al.*[18] postulated that this difference derives from the multicentre nature of the study with the inclusion of low-volume centres. de Rooij *et al*[19]. included a subgroup of patients with prolonged percutaneous drainage due to biochemical leakage, leading to an increased POPF incidence.

Focusing on data comparing different minimally invasive techniques (laparoscopic *versus* robotic), superior results in terms of spleen preservation rate, conversion rate, blood loss, and LOS, at the price of higher economic burden, have been reported in DP[45–48]. However, no RCTs on this topic are available and high-quality data are still missing. Data are even more scarce on robotic *versus* laparoscopic PD. In low-quality evidence no difference in clinically relevant outcomes has been seen so far[49–51]. Even though no definite conclusion can be drawn from low-quality evidence, robotic surgery might represent a valid alternative minimally invasive approach to laparoscopy in DP in experienced hands. However, head-to-head comparison in RCTs is required in the future to further address this question.

The current study has some limitations. First, data from only two RCTs with a small sample size in DP were available. Additionally, not all outcomes were investigated in all the studies, leading to a further decrease in reported events for certain outcome parameters (SSI and oncologic outcomes). Inconsistent definitions of R0 resection in the different RCTs further limit a conclusive statement on oncologic outcome

parameters. Moreover, the high grade of heterogeneity between the RCTs needs to be considered when interpreting the results. As minimally invasive data of the current meta-analysis mainly related to the laparoscopic approach (99 per cent, 491), possible benefits resulting from robotic surgery are not displayed.

In summary, data from the current meta-analysis support the assumption that a minimally invasive (laparoscopic and robotic) approach in pancreatic surgery seems feasible and safe. Even though high-quality data after surgeons have surmounted the learning curve are still missing, one might expect superior postoperative outcomes in minimally invasive pancreatic surgery compared with open pancreatic surgery, like in other fields of surgery. However, a tailored approach regarding surgical technique might represent the preferred strategy in the future. Whereas for procedures of high complexity, including multi-visceral resections and vascular reconstructions, the open approach may appear favourable, low-risk patients might benefit from the advantages of minimally invasive surgery in less complex cases. The spectrum of the minimally invasive approach is increasing and, as evidence from mainly retrospective analyses suggests, robotic surgery with its benefits compared with laparoscopy may play a fundamental role in pancreatic resections in the future, tackling the technical issues brought forward in early laparoscopic experience in pancreatic surgery. Furthermore, despite comparable oncologic outcomes between minimally invasive pancreatic surgery and open pancreatic surgery, such as R0 resection and LNY, the minimally invasive technique might be able to improve the oncologic big picture in the future. When projecting improved recovery after surgery on patients undergoing pancreatic procedures for malignant disease, more patients might be able to benefit from adjuvant therapy. Nevertheless, the certainty of evidence remains low to moderate and more RCTs after the learning curve are needed to clarify the role of a minimally invasive approach in pancreatic surgery.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The data that support the findings of this study are openly available in CENTRAL, MEDLINE, and Web of Science.

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