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Review

Postoperative Pancreatic Fistula: Is Minimally Invasive Surgery Better than Open? A Systematic Review and Meta-analysis

NICCOLO PETRUCCIANI[1], ANNA CROVETTO[1], FRANCESCA DE FELICE[2], MARCO PACE[1], DIEGO GIULITTI[1], MARCO YUSEF[1], GIUSEPPE NIGRI[1], STEFANO VALABREGA[1], RADWAN KASSIR[3], FRANCESCO D'ANGELO[1], TAREK DEBS[4], GIOVANNI RAMACCIATO[1] and PAOLO AURELLO[1]

[1]Department of Medical and Surgical Sciences and Translational Medicine, St Andrea University Hospital, Sapienza University, Rome, Italy;
[2]Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University, Rome, Italy;
[3]Digestive Surgery and Liver Transplantation Unit, Archet 2 Hospital, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France;
[4]Department of Digestive Surgery, CHU Félix Guyon, La Réunion, Saint Denis, France

Abstract. *Background/Aim: Minimally invasive pancreaticoduodenectomy (PD) is gaining popularity. The aim of this study was to compare the incidence of postoperative pancreatic fistula (POPF) after minimally invasive versus open procedures. Materials and Methods: Following the PRISMA statement, literature research was conducted focusing on papers comparing the incidence of POPF after open pancreaticoduodenectomy (OPD) versus minimally invasive pancreaticoduodenectomy (MIPD). Results: Twenty-one papers were included in this meta-analysis, for a total of 4,448 patients. A total of 2,456 patients (55.2%) underwent OPD, while 1,992 (44.8%) underwent MIPD. Age, ASA score III patients, incidence of pancreatic ductal adenocarcinoma and duct diameter were significantly lower in the MIPD group. No statistically significant differences were found between the OPD and MIPD regarding the incidence of major complications (15.6% vs. 17.0%, respectively, p=0.55), mortality (3.7% vs. 2.4%, p=0.81), and POPF rate (14.3% vs. 12.9%, p=0.25). Conclusion: MIPD and OPD had comparable rates of postoperative complications, postoperative mortality, and POPF.*

Correspondence to: Marco Pace, MD, Sapienza University of Rome, Department of Medical and Surgical Sciences and Translational Medicine, St. Andrea Hospital, Via di Grottarossa 1035/1039, 00189 Rome, Italy. Tel: +39 3455874837, e-mail: marco.pace@uniroma1.it

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Surgery represents the main treatment for patients with pancreatic, duodenal, or biliary neoplasms, usually in combination with neoadjuvant and/or adjuvant chemotherapy. Pancreaticoduodenectomy (PD) is one of the main procedures in this setting even if it is associated with a non-negligible rate of postoperative morbidity and mortality (1, 2). Pancreatic fistula is a common and potentially life-threatening postoperative complication, affecting between 13 and 41% of patients (3). The International Study Group of Pancreatic Surgery defined postoperative pancreatic fistula (POPF) as a drain output of any measurable volume of fluid with an amylase level >3 times the upper limit normal serum amylase activity on or after postoperative day, 3 associated with a clinically relevant condition related directly to the POPF. If no clinically relevant symptoms are evidenced, the drain output is defined as biochemical leak, and it has been shown to have no prognostic significance (4).

Even though PD remains one of the most challenging abdominal surgeries, minimally invasive approaches are gaining popularity in the treatment of pancreatic head, duodenal, and biliary diseases. Robotic surgery has played a key role in this sense, as this technology may partially overcome some of the limitations of laparoscopic surgery (5). Data from the NSQIP database has shown a significant improvement in surgical outcomes achieved by mini-invasive techniques, especially in the reduction of pancreatic fistula (6). However, the LEOPARD-2 trial has been prematurely terminated for the higher rate of postoperative complications-related mortality in the laparoscopic group and has raised

Table I. *Risk of bias assessment. H: High risk of bias; L: low risk of bias; U: unclear risk of bias.*

Author (Ref.)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Ding *et al*. (25)	H	H	H	H	L	U
Lee *et al*. (16)	H	H	H	U	U	L
Shyr *et al*. (14)	H	H	U	U	L	L
Cai *et al*. (29)	H	H	H	H	L	U
Choi *et al*. (17)	H	H	H	H	L	U
Marino *et al*. (27)	H	H	H	H	L	U
Van Hilst *et al*. (7)	L	L	L	U	L	L
Deichmann *et al*. (18)	H	H	H	H	U	U
Kim *et al*. (15)	H	H	H	H	U	U
Lee *et al*. (19)	H	H	H	H	U	U
Napoli *et al*. (31)	H	H	H	H	L	U
Poves *et al*. (12)	L	U	U	U	L	U
Wang *et al*. (26)	H	H	H	H	L	U
Palanivelu *et al*. (13)	L	U	U	U	L	L
Delitto *et al*. (21)	H	H	H	H	U	U
Tan *et al*. (22)	H	H	H	H	L	U
Dokmak *et al*. (30)	H	H	H	H	L	U
Song *et al*. (28)	H	H	H	H	U	U
Mendoza *et al*. (20)	H	H	H	H	U	U
Bao *et al*. (23)	H	H	H	H	U	U
Asbun *et al*. (24)	H	H	H	H	U	U

concerns about the safety of the procedure (7). Furthermore, minimally invasive PD seems to remain a procedure mostly performed in highly specialized centers by experienced hepato-bilio-pancreatic surgeons. The reluctance in adopting minimally invasive PD is mostly related to the concern of higher rates of POPF, due to the perception that pancreatic anastomosis is more technically demanding, and risky, if performed by laparoscopic or robotic surgery.

The aim of this meta-analysis was to assess the incidence of POPF after open pancreaticoduodenectomy (OPD) *versus* minimally invasive pancreaticoduodenectomy (MIPD), including both laparoscopic and robotic procedures.

Materials and Methods

Study selection. A systematic literature search was performed using PubMed, Embase, and Cochrane library databases to identify all studies published up to and including June 2021 that compared POPF rate following OPD *versus* that following MIPD. The PRISMA statement criteria (8) were followed.

The search was conducted using the following search algorithm: [(laparoscop* OR minimally invasive OR robotic OR Vinci) AND (pancreatoduodenectomy OR pancreaticoduodenectomy OR Whipple OR pancreatic surgery OR pancreatic head resection) AND (pancreatic fistula OR pancreatic leak OR pancreatic leakage)]. The research was restricted to English language articles dealing with human patients. The “related articles” function was used to broaden the search, and all abstracts, studies, and citations scanned were reviewed.

Data extraction. Potentially relevant articles were examined by two independent investigators (AC, NP) who extracted the following data: first author; year of publication; study design; number of subjects; patient characteristics; indications for surgery; surgical technique; intraoperative outcomes; postoperative outcomes.

Inclusion criteria. To be included in this meta-analysis, papers had to 1) compare POPF rate in patients who underwent MIPD (robotic or laparoscopic) with that in those who underwent OPD; 2) assess POPF following the ISGPS definition (4); 3) contain a previously unreported patient group (if patient material was reported more than once by the same institution, the most informative and recent article was included in the analysis). Both retrospective and prospective studies were included. Risk of bias was calculated using Cochrane "Risk of Bias Assessment Tool" 6th edition (9) (Table I). For studies prior to 2016 using the former definition of POPF only patients with grade B-C POPFs were included.

Exclusion criteria. The following articles were not considered: 1) studies in which the outcomes of interests (specified later) were not reported or impossible to calculate for both OPD and MIPD; 2) series including less than 10 patients.

Outcomes of interest. All the studies were abstracted for the following relevant data: patient baseline characteristics [age, sex, BMI, ASA (American Society of Anesthesiologists) score (10)], type of procedure (OPD or MIPD, type of anastomosis), intra-operative data (pancreatic duct diameter, pancreas texture, intraoperative blood loss, operative time), postoperative outcomes (rate and type of complications, POPF, mortality, length of stay). The main outcome was the rate of POPF,

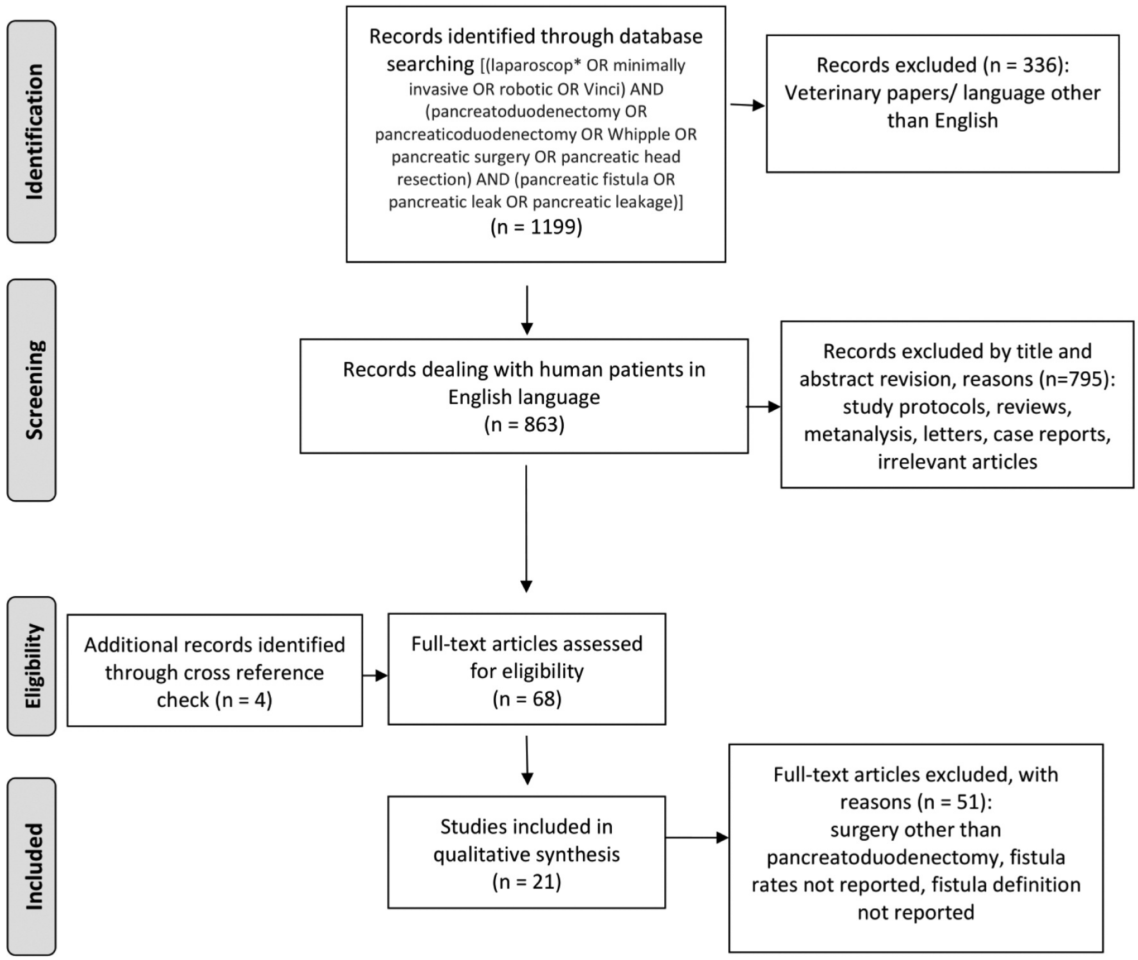

Figure 1. *PRISMA flow chart of selection process to identify studies eligible for pooling.*

defined according to the ISGPS. Secondary outcomes were: postoperative mortality, postoperative overall complications, defined also according to the Clavien-Dindo classification (11) operative time, blood loss, length of hospital stay.

Statistical analysis. Statistical analysis was carried out in line with the principles reported in the PRISMA statement (8). 18 RevMan software version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) was used to perform the meta-analysis. Variables were pooled only if evaluated by three or more studies. For dichotomous variables, odds ratios (ORs) were used as summary measures of efficacy, corresponding to the odds of an event occurring in the mini-invasive group compared to the open group. For continuous variables, only data reported as mean±standard deviation were included. An odd ratio more than 1 indicates the probability of an outcome to more likely occur in the mini-invasive group and is considered statistically significant when $p<0.05$ and when the 95% confidence interval (CI) does not include the value 1. The Mantel Haenszel method was used to combine the ORs for outcomes of interest. A random effect model, which is more robust in terms of anticipated heterogeneity, was used. The random effect-weighted mean difference (MD) between groups was used as the summary statistic for continuous variables; 95% confidence intervals were reported. Statistical heterogeneity was evaluated using the I 2 statistics. I 2 values of 0 to 25%, 26 to 50%, and >51% were indicative of homogeneity, moderate heterogeneity, and high heterogeneity, respectively. All statistical data were considered significant if $p<0.05$.

Results

Included studies. Extended paper revision led to the final inclusion of 21 studies, for a total of 4,448 patients (Figure 1). This meta-analysis includes three randomized trials (7, 12, 13) and two prospective studies (14, 15). In the remaining papers, data were retrieved in a retrospective fashion: we included 9 retrospective reviews (16-24); 7 case-control matched analysis (25-31): of those, four performed a propensity score analysis (25, 26, 28, 29). The articles by Girgis *et al*. (32), Zureikat *et al*. (33) and McMillan *et al*. (34) were excluded due to patients overlapping. Studies' characteristics are reported in Table II.

Table II. *Studies characteristics.*

Author	Year	Study design	MI technique	OPD (n)	MIPD (n)	Conversion rate %
Ding *et al*. (25)	2021	Propensity Score Matching (data analyzed after matching)	Laparoscopic	112	112	Excluded
Lee *et al*. (16)	2021	Retrospective review	Laparoscopic	305	274	Excluded
Shyr *et al*. (14)	2020	Prospective study	Robotic	172	304	Excluded
Cai *et al*. (29)	2019	Propensity Score Matching (data analyzed before matching)	Robotic	405	460	4.1
Choi *et al*. (17)	2019	Retrospective review	Laparoscopic	34	27	Excluded
Marino *et al*. (27)	2019	Case-control matched analysis	Robotic	35	35	8.6
Van Hilst *et al*. (7)	2019	Randomized trial	Laparoscopic	49	50	20
Deichmann *et al*. (18)	2018	Retrospective review	Laparoscopic with open reconstruction	60	60	Na
Kim *et al*. (15)	2018	Prospective study	Hybrid tecnique: laparoscopic resection, robotic reconstruction	186	51	Na
Lee *et al*. (19)	2018	Retrospective review	Laparoscopic; open pancreaticogastrostomy	31	31	Na
Napoli (31)	2018	Propensity Score Matching (data analyzed before matching)	Robotic	227	82	1.2
Poves *et al*. (12)	2018	Randomized trial	Laparoscopic; 1 hand-assisted	29	32	25
Wang *et al*. (26)	2018	Propensity Score Matching (data analyzed before matching)	Robotic	178	118	10
Palanivelu *et al*. (13)	2017	Randomized trial	Laparoscopic	32	32	3.1
Delitto *et al*. (21)	2016	Retrospective review	Laparoscopic	50	52	12.3
Tan *et al*. (22)	2015	Retrospective review	Laparoscopic	30	30	6.2
Dokmak *et al*. (30)	2015	Case-control matched analysis	Laparoscopic; 1 hand-assisted	46	46	6.5
Song *et al*. (28)	2015	Case-control matched analysis (data analyzed before matching)	Laparoscopic	198	97	Na
Mendoza *et al*. (20)	2015	Retrospective review	Laparoscopic with open reconstruction	34	18	Na
Bao *et al*. (23)	2014	Retrospective review	Hybrid tecnique: laparoscopic resection, robotic reconstruction	28	28	14.3
Asbun *et al*. (24)	2012	Retrospective review	Laparoscopic	215	53	14.5

MI: Mini-invasive; OPD: Open pancreatoduodenectomy; MIPD: mini-invasive pancreatoduodenectomy; na: not assessed.

Patient characteristics. Overall, males represented 53.4% of the total population, without any statistically significant difference between the OPD and MIPD groups ($p=0.10$) (Figure 2A). The MIPD group had a significantly lower mean age in comparison to the OPD group (mean difference 1.72; $p<0.05$) (Figure 2B). No statistically significant differences were found between the OPD and MIPD groups regarding mean BMI ($p=0.6$). Rates of ASA I and II patients were similar between the OPD and MIPD groups (ASA I: 11.3% *vs*. 17.3%, $p=0.24$; ASA II: 47.7% *vs*. 54.3% $p=0.18$), whereas more ASA III patients underwent open pancreaticoduodenectomy (38.8% *vs*. 28.3%, $p<0.05$) (Figure 2C). Patients' characteristics are shown in Table III. Pancreatic adenocarcinoma was the indication for surgery in 38.1% of patients. The rate of pancreatic head cancer was significantly higher in the OPD group (42.0% *vs*. 33.1% $p<0.05$) (Figure 3). Eleven papers reported the rate of neoadjuvant treatment in patients undergoing PD, which was comparable in the two groups (14.9% *vs*. 12.2%, $p=0.19$).

Surgical procedures. On the total group of 4,448 patients, 2,456 patients (55.2%) underwent OPD, while 1,992 (44.8%) underwent MIPD, either robotically (1,078, 54.1%) or laparoscopically (914, 45.9%). Kim *et al*. (15) and Bao *et al*. (23) reported a hybrid technique, in which the resection phase was performed laparoscopically and the anastomoses were fashioned robotically. Deichmann *et al*. (18) and Mendoza *et al*. (20) reported performing the reconstructive phase of their MIPD through a mini-laparotomy; in the paper by Lee *et al*. (19) the pancreaticogastric anastomosis was

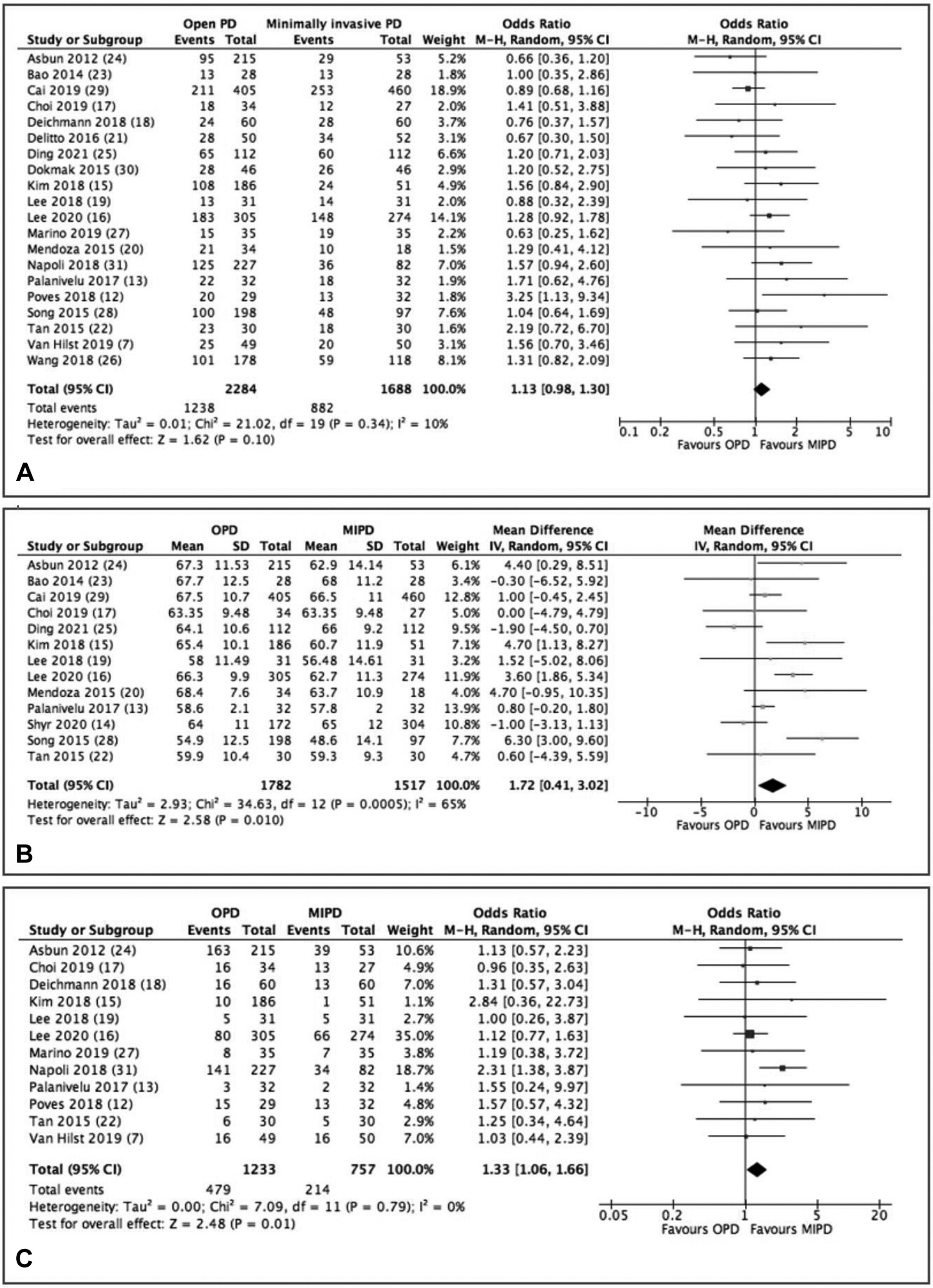

Figure 2. *Forest plot for comparison of the rate of patients' characteristics between patients undergoing open (OPD) or minimally invasive pancreaticoduodenectomy (MIPD). (A) Male sex, (B) sex, (C) ASA score.*

Table III. *Patient characteristics.*

Author	Age (mean/median)		Male sex %		BMI (mean/median)		PDAC		PDAC %		Neoadj		Neoadj %	
	O	MI	O	MI	O	MI	O	MI	O	MI	O	MI	O	MI
Ding *et al*. (25)	64.1	66.0	58.0	53.6	22.1	22.9	65	65	58.0	58.0	na	na	na	na
Lee *et al*. (16)	66.3	62.7	60.0	54.0	23.4	23.9	141	58	46.2	21.2	na	na	43.0	7.0
Shyr *et al*. (14)	64	66	53.5	53.3	23.0	24.0	85	101	49.4	33.2	na	na	na	na
Cai *et al*. (29)	67.5	66.5	52.1	55.0	27.2	27.8	231	226	57.0	49.1	162	157	40.0	34.1
Choi *et al*. (17)	63.35	63.35	52.9	44.4	22.94	23.2	34	27	100.0	100.0	0	0	0.0	0.0
Marino *et al*. (27)	62.3	60.4	42.9	54.3	23.5	23.8	13	16	37.1	45.7	4	6	11.4	17.1
Van Hilst *et al*. (7)	66	67	51.0	40.0	26	25	15	14	30.6	28.0	na	na	na	na
Deichmann *et al*. (18)	63	65.5	40.0	46.7	24	24.5	13	12	21.7	20.0	na	na	na	na
Kim *et al*. (15)	65.4	60.7	58.1	47.1	24	22.7	70	4	37.6	7.8	13	0	7.0	0.0
Lee *et al*. (19)	58	56.48	41.9	45.2	23.85	24	0	0	0.0	0.0	0	0	0.0	0.0
Napoli *et al*. (31)	67.4	61.6	55.1	43.9	24.8	23.5	95	23	41.9	28.0	na	na	na	na
Poves *et al*. (12)	70	69	69.0	40.6	26	24	21	15	72.4	46.9	na	na	na	na
Wang *et al*. (26)	na	na	56.7	50.0	na	na	74	29	41.6	24.6	na	na	na	na
Palanivelu *et al*. (13)	58.6	57.8	68.8	56.3	22.4	24.9	na	na	na	na	0	0	0.0	0.0
Delitto *et al*. (21)	68.6	65.3	56.0	65.4	25.5	26.3	22	28	44.0	53.8	3	3	6.0	5.8
Tan *et al*. (22)	59.9	59.3	76.7	60.0	na	na	0	0	0.0	0.0	0	0	0.0	0.0
Dokmak *et al*. (30)	63	60	60.9	56.5	26.4	22.6	14	15	30.4	32.6	na	na	na	na
Song *et al*. (28)	54.9	48.6	50.5	49.5	23.9	22.7	na	na	0	0	0	0	0.0	0.0
Mendoza *et al*. (20)	68.4	63.7	61.8	55.6	21.9	22.7	30	12	88.2	66.7	na	na	na	na
Bao *et al*. (23)	67.7	68	46.4	46.4	24	26	13	10	46.4	35.7	0	0	0.0	0.0
Asbun *et al*. (24)	67.3	62.9	44.2	54.7	26.6	27.64	100	22	46.5	41.5	na	na	na	na

BMI: Body mass index; PDAC: pancreatic ductal adenocarcinoma; Neoadj: neoadjuvant therapy; O: open; MI: mini-invasive; na: not assessed.

fashioned through a mini-laparotomy. Poves *et al*. (12) and Dokmak *et al*. (30) reported the need of hand-assistance in one patient each. A pancreaticojejunostomy was performed in 97.1% of cases. Characteristics of the surgical procedures are reported in Table II.

Intraoperative variables. Soft pancreatic parenchyma was found more frequently in patients undergoing MIPD (45.9% *vs*. 65.0%, $p<0.05$) (Figure 4). Duct diameter was analyzed as a continuous variable, showing a significant smaller duct diameter in the MIPD group ($p<0.05$). Mean operative time was significantly shorter in the OPD group (mean difference 55.9, $p<0.05$) (shown in Figure 5A). Mean estimated blood loss was lower in the MIPD group (mean difference 247.5, $p<0.05$) (Figure 5B). Overall conversion rate was 7.3%. Four papers (14, 16, 17, 25) excluded from their analyses patients whose procedure was converted. Five studies (15, 18-20, 28) did not report their conversion rate. All the papers that reported their conversion rate, except the one by Asbun *et al*. (24), treated the data as to an intention-to-treat analysis. Asbun *et al*. (24), on the other hand, included the converted procedures (n=9) in the OPD cohort.

Postoperative outcomes. No statistically significant differences were found between the OPD and MIPD regarding postoperative outcomes and the incidence of POPF. Length of stay was comparable between the OPD and MIPD groups ($p=0.25$). Overall, clinically relevant morbidity (Clavien-Dindo, CD ≥3) was 16.2%; overall mortality was 3.1%. There was no significant difference between OPD and MIPD regarding the incidence of major complications (CD ≥3) (15.6% *vs*. 17.0%, $p=0.55$) (Figure 6A), or mortality (3.7% *vs*. 2.4%, $p=0.81$) (Figure 7). Overall POPF rate, as described by the 2016 ISGPS criteria, or grade B/C POPF, as described by the previous ISGPS criteria, was 13.7%. No statistically significant difference in clinically relevant POPF and grade C POPF incidence was found between the OPD and MIPD groups (CR-POPF 14.3% *vs*. 12.9%, $p=0.25$: C-POPF 2.8% *vs*. 4.4%, $p=0.11$) (Figure 6B-C). No further analysis was conducted on ISGPS former grade A fistula or, as it is defined now, biochemical leak, as literature suggest it has no relevance on outcomes (35). Intraoperative and postoperative outcomes are furtherly described in Table IV.

Discussion

Minimally invasive surgery has probably represented the main evolution of abdominal surgery in the last decades. When compared to open procedures, minimally invasive

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Asbun 2012 (24)	100	215	22	53	7.8%	1.23 [0.67, 2.25]
Bao 2014 (23)	13	28	10	28	4.3%	1.56 [0.53, 4.56]
Cai 2019 (29)	231	405	226	460	11.2%	1.37 [1.05, 1.80]
Choi 2019 (17)	34	34	27	27		Not estimable
Deichmann 2018 (18)	13	60	12	60	5.5%	1.11 [0.46, 2.67]
Delitto 2016 (21)	22	50	28	52	6.2%	0.67 [0.31, 1.47]
Dokmak 2015 (30)	14	46	15	46	5.5%	0.90 [0.38, 2.18]
Kim 2018 (15)	70	186	4	51	4.3%	7.09 [2.45, 20.53]
Lee 2018 (19)	0	31	0	31		Not estimable
Lee 2020 (16)	141	305	58	274	10.3%	3.20 [2.22, 4.62]
Marino 2019 (27)	13	35	16	35	5.0%	0.70 [0.27, 1.82]
Mendoza 2015 (20)	30	34	12	18	2.8%	3.75 [0.90, 15.69]
Napoli 2018 (31)	95	227	23	82	8.4%	1.85 [1.07, 3.20]
Poves 2018 (12)	21	29	15	32	4.3%	2.98 [1.02, 8.67]
Shyr 2020 (14)	85	172	101	304	10.1%	1.96 [1.34, 2.88]
Song 2015 (28)	0	198	0	97		Not estimable
Tan 2015 (22)	0	30	0	30		Not estimable
Van Hilst 2019 (7)	15	49	14	50	5.6%	1.13 [0.48, 2.70]
Wang 2018 (26)	74	178	29	118	8.7%	2.18 [1.31, 3.65]
Total (95% CI)		**2312**		**1848**	**100.0%**	**1.67 [1.27, 2.19]**
Total events	971		612			

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 38.13$, df = 14 (P = 0.0005); $I^2 = 63\%$
Test for overall effect: Z = 3.67 (P = 0.0002)

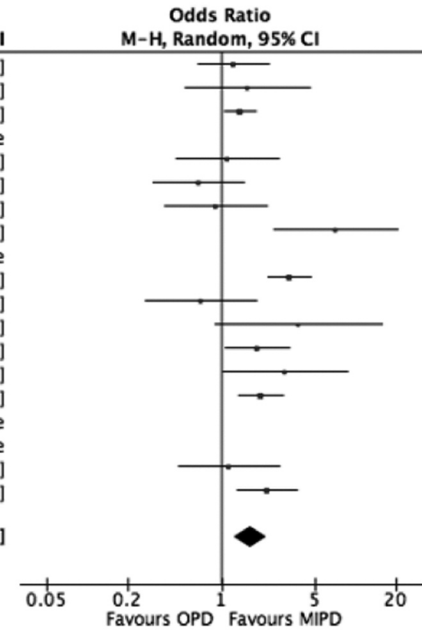

Figure 3. *Forest plot for comparison of the rate of histological diagnosis of pancreatic ductal carcinoma in patients undergoing open (OPD) or minimally invasive pancreaticoduodenectomy (MIPD).*

Study or Subgroup	OPD Events	OPD Total	MIPD Events	MIPD Total	Weight	Odds Ratio M-H, Random, 95% CI
Asbun 2012 (24)	15	215	4	53	4.7%	0.92 [0.29, 2.89]
Bao 2014 (23)	6	28	6	28	4.1%	1.00 [0.28, 3.58]
Cai 2019 (29)	64	405	31	460	9.1%	2.60 [1.65, 4.08]
Choi 2019 (17)	4	34	2	27	2.6%	1.67 [0.28, 9.87]
Deichmann 2018 (18)	12	60	5	60	4.9%	2.75 [0.90, 8.37]
Delitto 2016 (21)	15	50	6	52	5.2%	3.29 [1.16, 9.33]
Ding 2021 (25)	15	112	31	112	7.4%	0.40 [0.20, 0.80]
Dokmak 2015 (30)	15	46	20	46	6.3%	0.63 [0.27, 1.47]
Kim 2018 (15)	19	186	3	51	4.2%	1.82 [0.52, 6.41]
Lee 2018 (19)	1	31	4	31	1.8%	0.23 [0.02, 2.14]
Lee 2020 (16)	54	305	42	274	9.2%	1.19 [0.76, 1.85]
Marino 2019 (27)	4	35	3	35	3.1%	1.38 [0.28, 6.66]
Mendoza 2015 (20)	9	34	2	18	2.9%	2.88 [0.55, 15.08]
Napoli 2018 (31)	34	227	19	82	7.8%	0.58 [0.31, 1.10]
Palanivelu 2017 (13)	4	32	2	32	2.6%	2.14 [0.36, 12.63]
Poves 2018 (12)	8	29	4	32	3.9%	2.67 [0.71, 10.05]
Song 2015 (28)	15	198	6	97	5.6%	1.24 [0.47, 3.31]
Tan 2015 (22)	3	30	1	30	1.7%	3.22 [0.32, 32.89]
Van Hilst 2019 (7)	12	49	14	50	6.0%	0.83 [0.34, 2.05]
Wang 2018 (26)	17	178	13	118	6.9%	0.85 [0.40, 1.83]
Total (95% CI)		**2284**		**1688**	**100.0%**	**1.21 [0.87, 1.68]**
Total events	326		218			

Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 41.91$, df = 19 (P = 0.002); $I^2 = 55\%$
Test for overall effect: Z = 1.14 (P = 0.25)

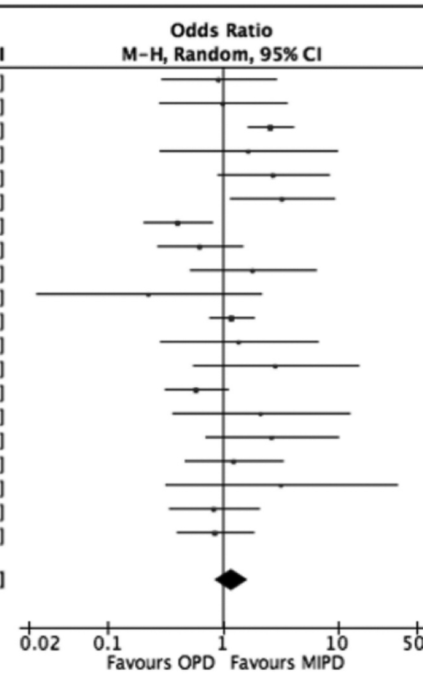

Figure 4. *Forest plot for comparison of the rate of soft pancreatic texture in patients undergoing open (OPD) or minimally invasive pancreaticoduodenectomy (MIPD).*

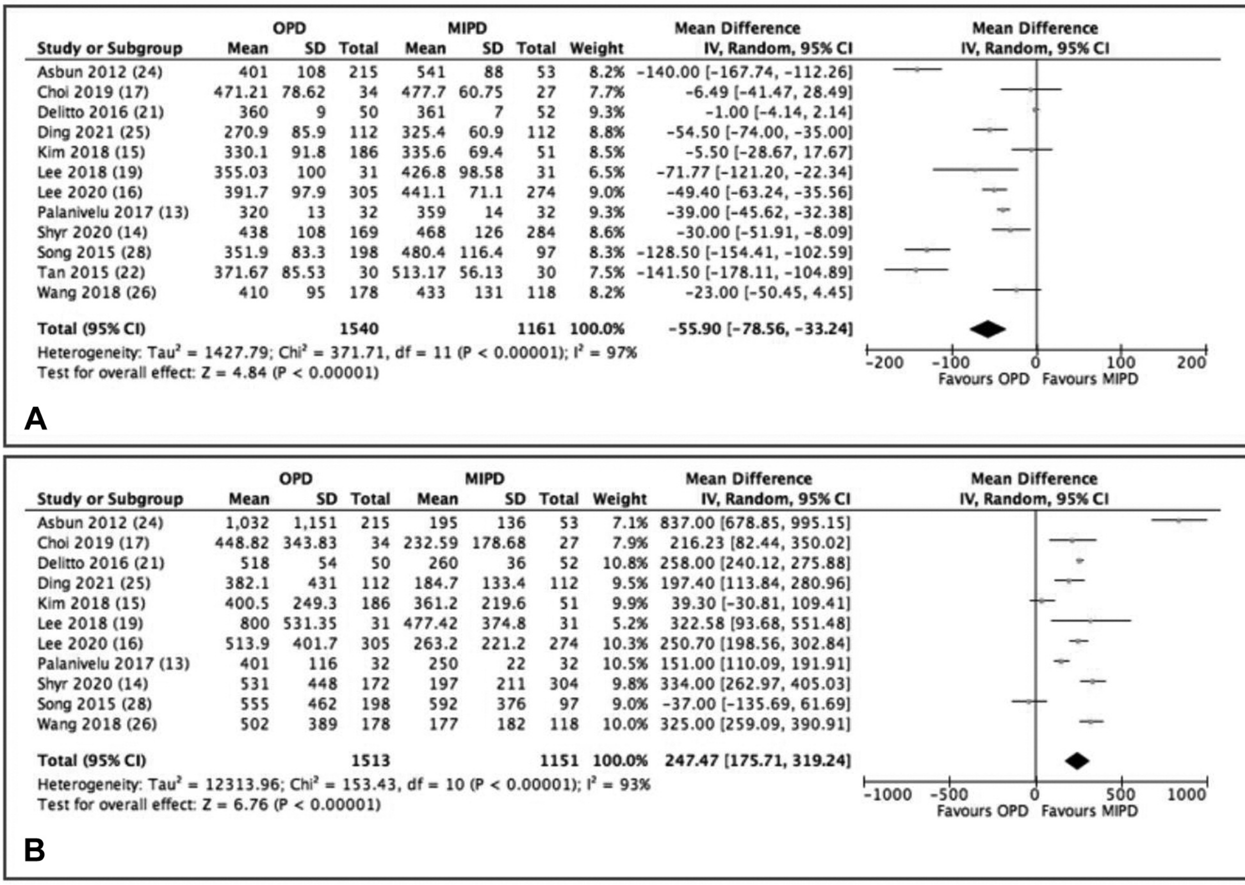

Figure 5. *Forest plot for comparison of per-operative variables between open (OPD) and minimally invasive pancreaticoduodenectomy (MIPD). (A) Operative time; (B) Blood loss.*

Table IV. *Postoperative and intraoperative outcomes.*

	N OPD	N MIPD	Diff. or OR	0.95 LL CI	0.95 UL CI
Soft pancreatic tissue	1,519	1,200	0.4	0.32	0.5
Mean duct diameter	557	384	0.77	0.57	0.97
Duct diameter ≥3 mm	434	232	1.67	1.12	2.48
Operative time (min)	1,540	1,161	–55.9	–78.56	–33.24
Blood loss (ml)	1,513	1,151	247.47	175.71	319.24
Length of stay (days)	1,203	855	1.12	–0.77	3.02
Mortality	2,128	1,803	1.08	0.59	1.95
Major complications (Clavien-Dindo≥3)	1,317	1,086	0.92	0.7	1.21
CR-POPF	2,284	1,688	1.21	0.87	1.68
POPF-C	1,199	754	0.62	0.35	1.11

CR-POPF: Clinically relevant postoperative pancreatic fistula (ISGPS grade B or C); POPF-C: grade C postoperative pancreatic fistula; OPD: open pancreatoduodenectomy; MIPD: mini-invasive pancreatoduodenectomy; Diff: difference; OR: odds ratio; LL CI: lower limit confidence interval; UL CI: upper limit confidence interval.

approaches have permitted several important advantages, including faster patient recovery, reduction in postoperative pain, morbidity, and length of hospital stay (36, 37). Such benefits have been demonstrated for a number of abdominal minor and major procedures, including colorectal and liver surgery (38-40). The robotic surgical systems have further

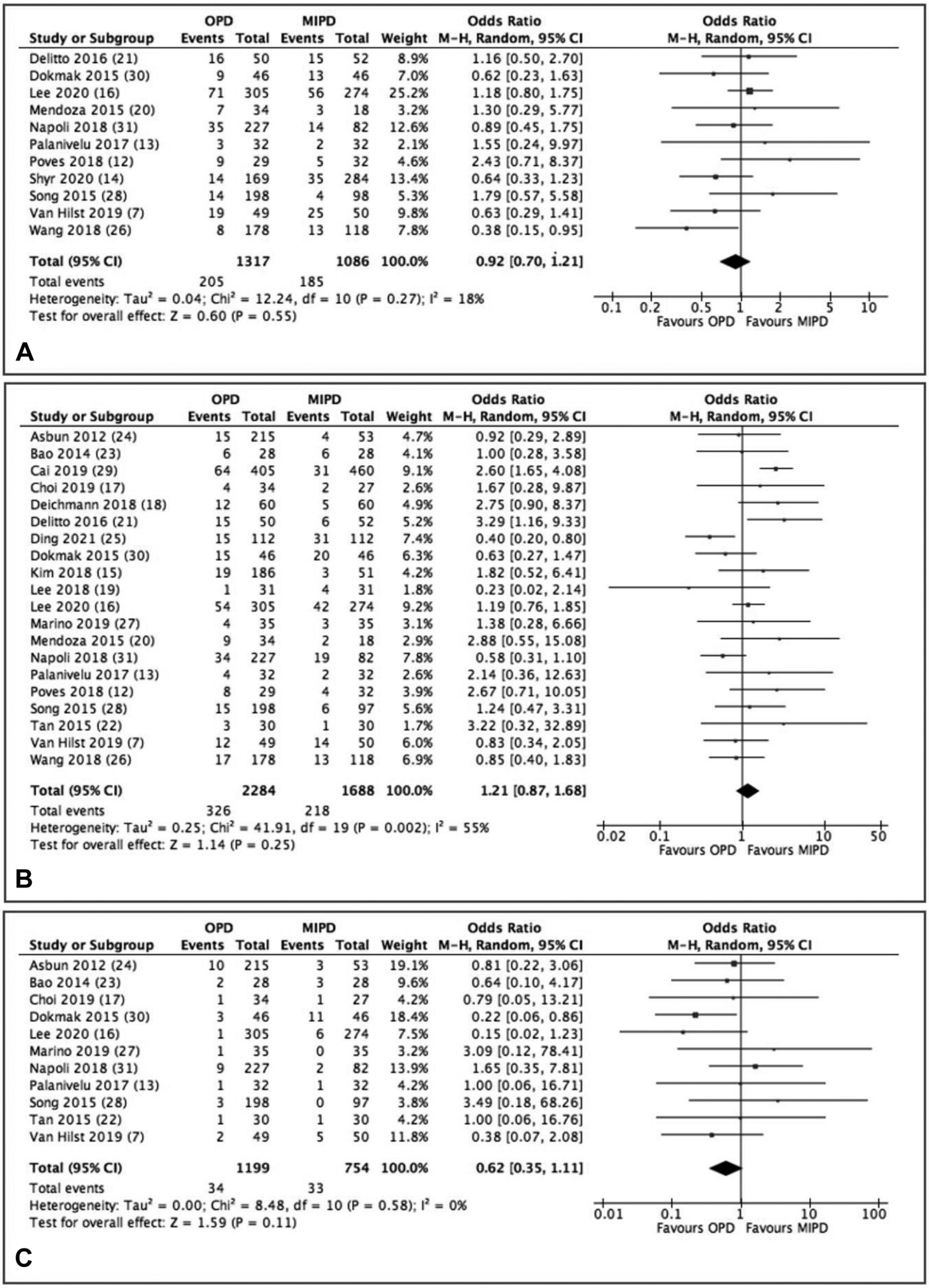

Figure 6. *Forest plot for comparison of postoperative surgical complications between open (OPD) and minimally invasive pancreaticoduodenectomy (MIPD). Odds ratio <1 indicates superiority of first intervention over second intervention. (A) Clavien-Dindo ≥3; (B) Clinically relevant pancreatic fistula; (C) Pancreatic fistula with grade C.*

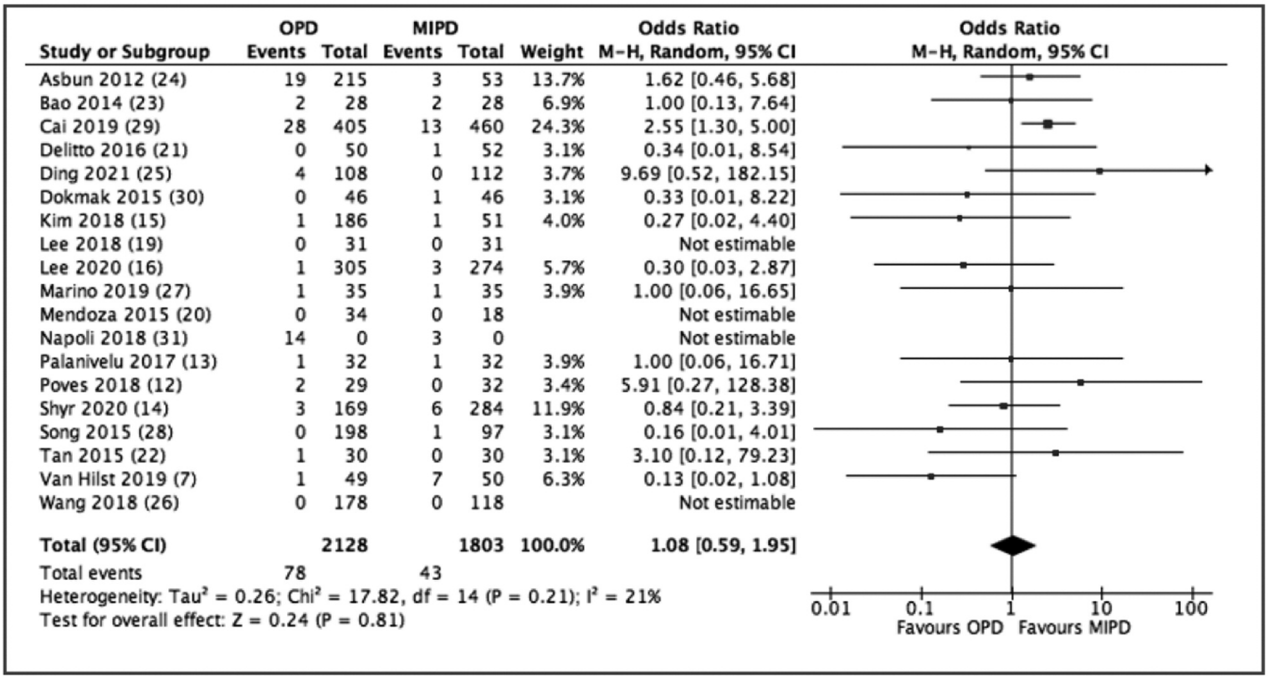

Figure 7. *Forest plot for comparison of postoperative mortality between open (OPD) and minimally invasive pancreaticoduodenectomy (MIPD). Odds ratio <1 indicates superiority of first intervention over second intervention.*

pushed the spread of minimally invasive surgery, permitting to overcome some limitations of laparoscopy, such as two-dimensional imaging, restricted instrument movement, and trembling.

In the setting of pancreatic surgery, minimally invasive distal pancreatectomy has been demonstrated to reduce the morbidity rate and shorten recovery compared to open surgery by multicentric studies, randomized controlled trials (RCT), and meta-analyses (41, 42). Meta-analyses have also reported comparable oncologic outcomes (43-45).

Pancreaticoduodenectomy represents a highly complex procedure, including a demanding demolition phase and reconstruction with a digestive, biliary, and pancreatic anastomosis. MIPD was at first reported by Gagner *et al.* (46) but the need of advanced technical laparoscopic skills and the long operative times hindered its widespread use (46). Improvements in laparoscopic skills, instrumentation, the spreading of robotic platforms, and the increased experience of digestive surgeons have permitted an increased use of MIPD, including both laparoscopic and robotic procedures. Single institutions series, RCTs, and meta-analyses have analyzed the current role of MIPD focusing on different aspects and have suggested feasibility of MIPD and non-inferiority to open PD (47-50).

However, even if results of MIPD are encouraging, and outcomes are comparable or even better than those of open PD in several relevant studies (12, 13, 18-20, 26), robotic PD represents only 3% of PDs, and laparoscopic 10% (50). One of the major arguments against the adoption of MIPD is the potential increase in the risk of POPF. The pancreatic anastomosis is technically demanding, most surgeons are used to perform it in open surgery; the risks in case of failure of the anastomosis are high and may lead to patient death or to a long and difficult recovery. Existent data are conflicting, and it is not clear what the impact of minimally invasive surgery on the rate and severity of POPF is (26, 28). It is very difficult to assess this outcome with a RCT, because a very large study population will be needed (28). Previous meta-analyses reported no differences (49, 50-60), or lower POPF rate of MIPD (61). Recent studies have demonstrated a significant reduction in POPF using innovative techniques such as the "clip on staple method" (62) and reinforced triple-row staplers, especially in obese patients with a BMI >25 kg/m^2 (63).We felt that an updated meta-analysis, using the novel ISPGS definition4 and including recent relevant studies, was needed in this rapidly evolving field. The topic is very relevant because POPF may have severe consequences on the postoperative outcomes, but also on the administration of adjuvant therapies, which may be delayed or cancelled in case of severe POPF.

The present meta-analysis highlights that patients undergoing MIPD are younger and have a lower probability to be classified as ASA 3, therefore they generally have a lower rate of severe associated diseases. Furthermore, the MIPD group has a lower proportion of pancreatic adenocarcinoma, and MIPD patients have a smaller pancreatic duct diameter. Soft pancreas is found significantly more frequently in the MIPD group. No differences were found in BMI and the rate of neoadjuvant therapy. These results stress some differences in patients' selection for MIPD or OPD, related mainly to the characteristics of the observational and retrospective studies. MIPD is preferentially performed in younger patients, with less comorbidities and benign pancreatic diseases. During surgery, operative time is significantly increased in the MIPD group, which is concordant with the need of docking times, and with single studies showing increased operative times for both laparoscopic and robotic techniques. Blood loss is lower in patients who underwent MIPD, and it may be related to different patients' and disease' characteristics, but also to more precise dissection and the need of a very clean field when the operation is minimally invasive. The rate of pancreatojejunostomy was similar in the two groups. Concerning postoperative outcomes, MIPD and OPD are comparable in the rate of POPF, grade C POPF, postoperative mortality, complications Clavien-Dindo ≥3, and length of hospital stay. Oncologic and long-term outcomes were not assessed.

Our results are in line with those of the majority of reports and underline that 1) MIPD is preferentially performed in selected patients (younger, lower rate of ASA 3, lower rate of pancreatic adenocarcinoma); 2) MIPD is associated to longer operative time but lower blood loss; 3) postoperative outcomes of MIPD and OPD are comparable.

Our results are partially concordant with previous RCTs. Palanivelu *et al*. (13) compared for the first time OPD and laparoscopic pancreaticoduodenectomy (LPD) postoperative outcomes in a randomized controlled setting. The results showed no significant differences between OPD and LPD in postoperative outcomes, except for blood loss and length of stay, that were significantly lower in the mini-invasive group. The results in favor of the non-inferiority of MIPD were furtherly implemented by the PADULAP trial (12), that demonstrated a lower incidence of severe postoperative complications in the MIPD group. These results were in line with previous studies (49). However, in 2019, the LEOPARD (27) showed a significantly higher mortality rate in the laparoscopic group (14% *vs*. 2%), for which the trial was interrupted prematurely. Even though the complication-related deaths in the laparoscopic group were higher, no significant difference was found in the incidence of severe complications and POPF between the OPD and MIPD groups. This result might strengthen the idea that LPD has to be performed by highly specialized surgeons (51), as the centers involved in the LEOPARD 2 trial performed a median of 11 LPD annually.

Limitations. We stress that these results are obtained by the meta-analysis of studies mostly published by referral centers for minimally invasive pancreatic surgery, which may constitute a selection bias. It is unknown whether the use of MIPD by less experienced centers may jeopardize the postoperative outcomes. Furthermore, oncologic outcomes were not reported as our major outcomes and the main aim was the evaluation of POPF rate and short-term morbidity, which in our opinion, is one of the main arguments against the adoption of MIPD, as also shown by the LEOPARD 2 trial (7). A third limitation is represented by the fact that some of the authors performing MIPD, fashioned pancreatic anastomosis through a mini-laparotomy. Fourth, we decided to combine data of laparoscopic and robotic pancreaticoduodenectomy, based on a recent meta-analysis showing no difference between the two procedures in term of postoperative morbidity (52); however, it is possible that the robotic platform will be considered in the future able to guarantee better postoperative outcomes.

In conclusion, MIPD was associated to younger patients' age, lower rate of ASA 3 status, and a diagnosis of pancreatic adenocarcinoma compared to OPD. Operative time was lower for OPD, whereas blood loss was higher. No differences were found between OPD and MIPD in POPF rate, grade C POPF, major postoperative complications, postoperative mortality, and length of hospital stay.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

PA approved the final version to be published. NP and AC conceived, designed, and wrote the study, FDF, MP and DG provided data, GN and SV collected data, RK and TD analyzed the data, GR and FDA critically revised the manuscript.

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