Outcomes After Minimally-invasive Versus Open Pancreatoduodenectomy

A Pan-European Propensity Score Matched Study

Sjors Klompmaker, MD,[*] Jony van Hilst, MD, MSc,[*] Ulrich F. Wellner, MD,[†††††††] Olivier R. Busch, MD, PhD,[*] Andrea Coratti, MD,[§] Mathieu D'Hondt, MD,[†] Safi Dokmak, MD,[‡] Sebastiaan Festen, MD, PhD,[***] Mustafa Kerem, MD,[††] Igor Khatkov, MD, PhD,[||||] Daan J. Lips, MD, PhD,[§§] Carlo Lombardo, MD,[§§§] Misha Luyer, MD, PhD,[¶] Alberto Manzoni, MD,[**] Izaäk Q. Molenaar, MD, PhD,[****] Edoardo Rosso, MD,[**] Olivier Saint-Marc, MD,[¶¶¶] Franky Vansteenkiste, MD,[†] Uwe A. Wittel, MD,[‡‡‡] Bert Bonsing, MD, PhD,[¶¶] Bas Groot Koerkamp, MD, PhD,[||] Mohammed Abu Hilal, MD, PhD, FRCS, FACS,[||||||] David Fuks, MD, PhD,[‡‡‡‡] Ignasi Poves, MD, PhD,[‡‡] Tobias Keck, MD,[††††††††] Ugo Boggi, MD,[§§§] and Marc G. Besselink, MD, MSc, PhD[*], for the European consortium on Minimally Invasive Pancreatic Surgery (E-MIPS)

Objective: To assess short-term outcomes after minimally invasive (laparoscopic, robot-assisted, and hybrid) pancreatoduodenectomy (MIPD) versus open pancreatoduodenectomy (OPD) among European centers.

Background: Current evidence on MIPD is based on national registries or single expert centers. International, matched studies comparing outcomes for MIPD and OPD are lacking.

Methods: Retrospective propensity score matched study comparing MIPD in 14 centers (7 countries) performing ≥10 MIPDs annually (2012–2017) versus OPD in 53 German/Dutch surgical registry centers performing ≥10 OPDs annually (2014–2017). Primary outcome was 30-day major morbidity (Clavien-Dindo ≥3).

Results: Of 4220 patients, 729/730 MIPDs (412 laparoscopic, 184 robot-assisted, and 130 hybrid) were matched to 729 OPDs. Median annual case-volume was 19 MIPDs (interquartile range, IQR 13–22), including the first MIPDs performed in 10/14 centers, and 31 OPDs (IQR 21–38). Major morbidity (28% vs 30%, $P = 0.526$), mortality (4.0% vs 3.3%, $P = 0.576$), percutaneous drainage (12% vs 12%, $P = 0.809$), reoperation (11% vs 13%, $P = 0.329$), and hospital stay (mean 17 vs 17 days, $P > 0.99$) were comparable between MIPD and OPD. Grade-B/C postoperative pancreatic fistula (POPF) (23% vs 13%, $P < 0.001$) occurred more frequently after MIPD. Single-row pancreatojejunostomy was associated with POPF in MIPD (odds ratio, OR 2.95, $P < 0.001$), but not in OPD. Laparoscopic, robot-assisted, and hybrid MIPD had comparable major morbidity (27% vs 27% vs 35%), POPF (24% vs 19% vs 25%), and mortality (2.9% vs 5.2% vs 5.4%), with a fewer conversions in robot-assisted- versus laparoscopic MIPD (5% vs 26%, $P < 0.001$).

Conclusions: In the early experience of 14 European centers performing ≥10 MIPDs annually, no differences were found in major morbidity, mortality, and hospital stay between MIPD and OPD. The high rates of POPF and conversion, and the lack of superior outcomes (ie, hospital stay, morbidity) could indicate that more experience and higher annual MIPD volumes are needed.

Keywords: hybrid, laparoscopic, minimally invasive, pancreas, pancreatic cancer, pancreatic tumors, propensity score matching, robot, robotic, surgery, Whipple

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Pancreatoduodenectomy is associated with high morbidity rates and a strong volume-outcome relationship.[1–3] Minimally invasive pancreatoduodenectomy (MIPD; laparoscopic, robot-assisted, or hybrid) could reduce morbidity and enhance postoperative recovery compared with open pancreatoduodenectomy (OPD),[1,2,4–12] but its implementation is lagging compared with minimally invasive distal pancreatectomy.[13,14]

Two factors may have delayed the implementation of MIPD. First, pancreatoduodenectomy is a demanding procedure with several anastomoses and potentially life-threatening complications. Indeed,

From the [*]Department of Surgery, Cancer Center Amsterdam, Academic Medical Center, University of Amsterdam, the Netherlands; [†]Department of Digestive and Hepatobiliary/Pancreatic Surgery, Groeninge Hospital, Kortrijk, Belgium; [‡]Department of HPB Surgery and Liver Transplantation, Beaujon Hospital, Clichy, France; [§]Department of Oncology and Robotic Surgery, Careggi University Hospital, Florence, Italy; [¶]Department of Surgery, Catharina Hospital Eindhoven, Eindhoven, the Netherlands; [||]Department of Surgery, Erasmus MC, Rotterdam, the Netherlands; [**]Department of Surgery, Fondazione Poliambulanza - Istituto Ospedaliero, Brescia, Italy; [††]Department of General Surgery, School of Medicine, Gazi University, Ankara, Turkey; [‡‡]Department of Surgery, Hospital del Mar, Barcelona, Spain; [§§]Department of Surgery, Jeroen Bosch Hospital, s-Hertogenbosch, the Netherlands; [¶¶]Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands; [||||]Department of Surgery, Moscow Clinical Scientific Center, Moscow, Russia; [***]Department of Surgery, OLVG, Amsterdam, the Netherlands; [†††]Department of Surgery, UKSH Campus Lübeck, Lübeck, Germany; [‡‡‡]Department of Visceral and General Surgery, University of Freiburg Medical Center, Freiburg, Germany; [§§§]Division of General and Transplant Surgery, University of Pisa, Pisa, Italy; [¶¶¶]Department of Surgery, Center Hospitalier Régional Orleans, Orleans, France; [||||||]Department of Surgery, Southampton University Hospital NHS Foundation Trust, Southampton, United Kingdom; [****]Department of Surgery, University Medical Center Utrecht, Utrecht, the Netherlands; [††††]Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV), Studien- Dokumentations- und Qualitätszentrum (StuDoQ|Pancreas), Berlin, Germany; and [‡‡‡‡]Department of Digestive, Oncological and Metabolic Surgery, Institut Mutualiste Montsouris, Université Paris Descartes, Paris, France.

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Reprints: Marc G. Besselink, MD, MSc, PhD, Sjors Klompmaker, MD, Cancer Center Amsterdam, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mails: m.g.besselink@amc.nl, s.klompmaker@amc.nl.

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MIPD has been associated with increased perioperative mortality compared with OPD in centers performing a fewer than 10 MIPDs annually.[15,16] Moreover, improved outcomes in centers performing more than 40 OPDs annually could indicate that the optimal volume cut-off for MIPD is also (much) higher.[17] Second, current evidence on the effectiveness and safety of MIPD consists mainly of registry studies with a large proportion of low-volume centers[14–16,18] or small-/single center retrospective studies from high-volume centers, suffering from reporting bias and/or insufficient adjustment for confounding by indication (surgical case selection).[1,8] The only published randomized trial on laparoscopic MIPD versus OPD (PLOT: Pancreatic Head and Periampullary Cancer Laparoscopic versus Open Surgical Treatment; NCT02081131) reported shorter length of hospital stay after MIPD but was underpowered to demonstrate a benefit regarding major morbidity.[19] Large multicenter (matched) studies on MIPD versus OPD are lacking.

The purpose of this study was to combine data from European centers performing at least 10 MIPDs annually in a multicenter propensity score matched cohort study on MIPD versus OPD. We hypothesized that MIPD is associated with equivalent morbidity and mortality compared with OPD, when performed in such centers, but with superior secondary outcomes (eg, shorter length of stay).

METHODS

We performed a retrospective multicenter propensity score matched cohort study comparing MIPD cases to OPD controls. MIPD patients were included from European centers performing at least 10 MIPDs per year. OPD patients were included from centers performing at least 10 OPDs per year in 2 Dutch and German surgical registries. This study was initiated by the European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS) and supported by the Scientific and Research Committee of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA). We used the STROBE guidelines[20] for design and reporting of the study, which included registration of a study protocol at clinicaltrials.gov (NCT03172572). Need for ethical approval was waived by the institutional review board at the Academic Medical Center in Amsterdam.

Eligibility and Data Collection

Inclusion criteria were elective MIPD (including laparoscopic, robot-assisted, or hybrid procedures) or OPD in adults, for solid premalignant tumors or cysts. Hybrid was defined as laparoscopic resection and open reconstruction via (limited) laparotomy. Exclusion criteria were chronic pancreatitis as indication for surgery, arterial resection, insufficient baseline data, or missing primary outcome data.

Included cases were consecutive patients undergoing elective MIPD between January 1, 2012 and July 31, 2017 at participating E-AHPBA and E-MIPS centers. Each center appointed a local study coordinator responsible for data collection and communication with the central study coordinators (SK and JH). All data was collected via an International Conference on Harmonization Good Clinical Practice (ICH-GCP) compliant on-line electronic case report form (eCRF) and data storage environment (CASTOR, CIWIT B.V., Amsterdam, the Netherlands). In addition, local study coordinators completed a survey (Google Survey, Mountain View, CA) with questions regarding methods of data collection, annual case volume, standard of care, and surgical case selection.

Included controls were consecutive patients undergoing OPD between January 1, 2014 and July 31, 2017 who were registered in the nationwide German Society for General and Visceral Surgery (DGAV) Studien-, Dokumentations- und Qualitätszentrum (StuDoQ|Pancreas),[21] and the Dutch Pancreatic Cancer Audit (DPCA)[22] registries. All centers were blinded to maintain anonymity on outcomes and prevent reporting bias.

Primary and Secondary Outcomes

The primary outcome was 30-day major morbidity (Clavien-Dindo 3a-5).[23] Secondary outcomes were 30-day mortality, grade-B/C pancreatic fistula (POPF), grade B/C postpancreatectomy hemorrhage (PPH), and length of hospital stay (day of surgery to day of discharge).

Definitions

Preoperative variables included baseline characteristics, such as age, sex, body-mass-index (BMI), and comorbidities (Charlson Comorbidity Index[24]), surgical history, computed tomography/magnetic resonance imaging (CT/MRI)-scan information (vascular/organ involvement), American Society of Anesthesiologists (ASA) classification[25], and Eastern Cooperative Oncology Group (ECOG) performance status. Conversion was recorded if a robot-assisted or laparoscopic MIPD was converted to OPD. The International Study Group on Pancreatic Surgery (ISGPS) 2005 definition[26] was used to classify POPF. Although a newer definition is available,[27] it was not used in the registry data and could therefore not be applied to compare outcomes. The ISGPS and International Study Group of Liver Surgery (ISGLS) definitions were used to classify delayed gastric emptying,[28] PPH,[29] and bile leakage.[30] Surgical site infections were defined using the Center for Disease Control and Prevention (CDC) definition.[31] All complications (minor or major) occurring during the initial hospitalization and subsequent readmissions were recorded. Patient were followed-up until discharge or 30 days postoperatively (whichever occurred later) in the German and Dutch registries and until the last hospital visit or phone call in the MIPD centers. Therefore, all primary and secondary outcomes in this study are limited to in-hospital or 30-day events.

Propensity Score Matching

Propensity score matching was applied to achieve a balanced exposure groups at baseline (ie, minimal confounding), in accordance with the recommendations by Lonjon et al.[32] The probability to undergo MIPD for each patient (ie, the propensity score) was obtained from a logistic regression model. The study entry survey was used to ensure all reported MIPD selection factors were included as covariates in the model to further reduce potential confounding by indication. Final covariates were age, sex, BMI, ASA, Charlson comorbidity index, ECOG, tumor location (pancreas vs periampullary/ distal common bile duct vs duodenum), suspected malignancy, organ involvement on imaging, multivisceral resection, porto-mesenteric vein resection, and pancreatic texture (Supplement 1, http://links.lww.com/SLA/B435). MIPD cases were analyzed intention-to-treat, regardless of conversion to open surgery, and matched in a 1:1 ratio to OPD controls based on the propensity score with a standard caliper width of 0.2.

Sensitivity Analyses

The association between treatment group (exposure) and primary and secondary outcomes was measured using odds ratios. A first sensitivity analysis assessed the impact of volume, learning curve, hybrid surgery, conversions, and laparoscopy. This was done using multivariable-adjusted odds ratios after respective exclusion of centers performing 10 to 20 MIPDs per year, the first 20 MIPD cases at each center, hybrid procedures, hybrid and converted procedures, and hybrid and laparoscopic procedures. A second sensitivity analysis was performed to mitigate differences in postoperative t-stage, histopathological diagnosis, and pancreatic duct diameter by replacing preoperative diagnosis by histological diagnosis, and by

including tumor stage and duct diameter in the propensity score model. A third analysis assessed baseline-, tumor-, and perioperative characteristics to identify new risk factors for POPF after MIPD, using multivariable logistic regression based on a univariable screen ($P < 0.1$) and backward stepwise elimination (if $P > 0.05$ and clinically irrelevant).

Statistics

Missing baseline and outcome data were resolved using chained multiple imputation[33], which reduces bias in combination with propensity score matching.[32] Categorical data were reported as proportions and continuous data as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. We used the standardized mean difference (SMD) to assess balance at baseline in both groups. Optimal balance on a parameter is generally achieved when the SMD is on or below 0.1. To test for statistical significance (alpha 0.05), we used the Fisher exact test for categorical variables, and the student *t*-test for continuous variables (applying the central limit theorem). All confidence intervals (CI) were 95%. All data were handled and analyzed using IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Orchard Road Armonk, New York, NY), STATA version 14.1 (StataCorp LP, College Station, TX), or R's programming environment (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We identified 903 MIPD patients from 26 E-AHPBA and E-MIPS centers and 4020 OPD patients from 70 German and Dutch centers. After exclusions, 730 MIPD patients from 14 E-MIPS centers and 3490 OPD patients from 53 high-volume DGAV and DPCA centers were included (see Fig. 1). Of all 14 MIPD centers, 7 performed laparoscopic, 4 both hybrid and laparoscopic, and 3 robot-assisted MIPD. The median annual pancreatoduodenectomy (MIPD and OPD combined) volume was 41 (IQR 17–69) among the MIPD centers and 31 (IQR 21–38) among the OPD centers. The median annual MIPD volume was 19 (13–22), which included the first MIPD case performed in 10 of 14 (71%) centers. Of all included patients, 729 of 730 MIPD cases could be matched (1:1) to an OPD control (Fig. 1).

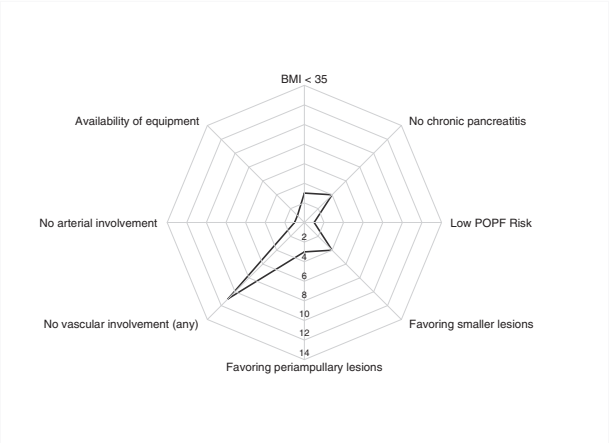

FIGURE 2. Self-reported Surgical Selection Factors for MIPD. Institutional or patient-related factors used by the 14 participating E-MIPS centers to select patients for MIPD. MIPD indicates minimally invasive pancreatoduodenectomy; POPF, postoperative pancreatic fistula.

Selecting Patients for MIPD

Reported selection factors for MIPD were absence of vascular involvement (11 of 14 MIPD centers), smaller or periampullary tumors (7 of 14), absence of chronic pancreatitis (4 of 14), BMI $\leq$35 (3 of 14), low risk of POPF (1 of 14), absence of arterial involvement (1 of 14), and availability of minimally invasive equipment (1 of 14) (Fig. 2). One center indicated that MIPD selection factors had been stricter during the initial learning curve phase. The observed selection factors and their odds ratios are presented in Supplement 1, http://links.lww.com/SLA/B435, propensity score distributions in Supplement 2, http://links.lww.com/SLA/B435.

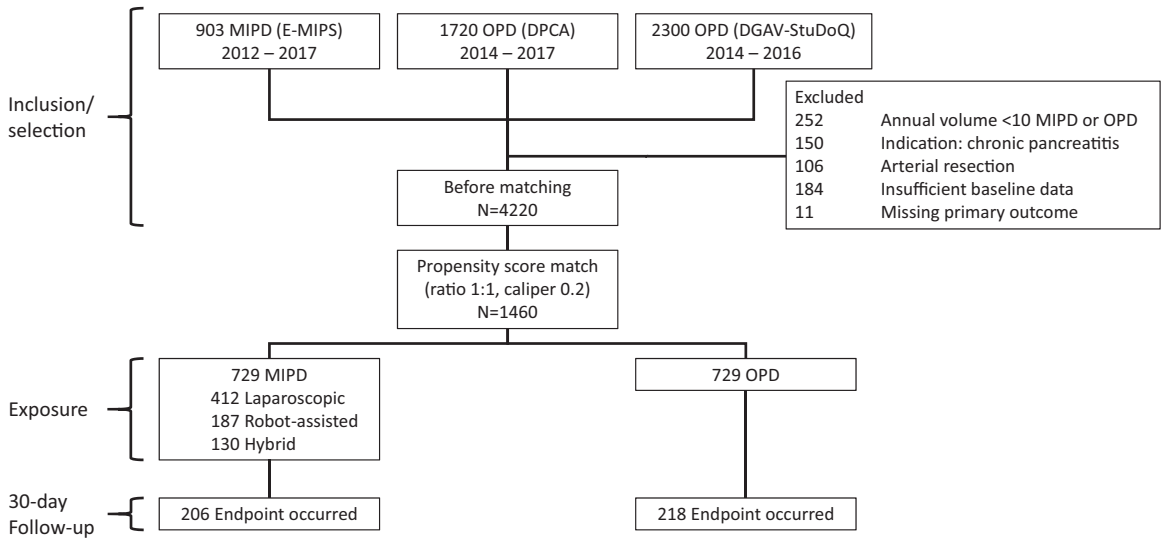

FIGURE 1. Study Flow-Chart. Endpoint was 30-day major morbidity. Annual indicates annual; DPCA, Dutch Pancreatic Cancer Audit; DGAV StuDoQ, German Society for General and Visceral Surgery Studien-, Dokumentations- und Qualitätszentrum; E-MIPS, European consortium on Minimally Invasive Pancreatic Surgery.

TABLE 1. Baseline Characteristics Before and After Propensity Score Matching

Baseline	OPD Prematch N = 3490	OPD Postmatch N = 729	MIPD N = 729	Standard Difference Prematch	Standard Difference Postmatch
Age, mean (SD), y	66.9 (10.7)	64.6 (11.7)	64.5 (11.6)	−0.21	0.00
BMI, mean (SD), kg/m^2	25.7 (10.0)	24.8 (4.0)	24.9 (4.2)	−0.11	0.02
Charlson comorbidity index, median (IQR)	0.6 (.9)	0.5 (.9)	0.5 (.9)	−0.06	−0.02
Female sex (n), %	1512 (43.3)	363 (49.8)	357 (49.0)	0.11	−0.02
ASA-classification (n), %					
ASA 1	336 (9.6)	154 (21.1)	139 (19.1)	0.27	−0.06
ASA 2	1855 (53.2)	416 (57.1)	421 (57.8)	0.09	0.01
ASA 3-4	1275 (36.5)	149 (20.4)	162 (22.2)	−0.32	0.04
ASA Unknown	24 (.7)	10 (1.4)	7 (1.0)		
ECOG performance status (n), %					
ECOG 0-1	3116 (89.3)	667 (91.5)	614 (84.2)	−0.15	−0.21
ECOG 2	130 (3.7)	31 (4.3)	36 (4.9)	0.06	0.03
ECOG 3-4	133 (3.8)	5 (.7)	5 (.7)	−0.21	0.00
ECOG Unknown	111 (3.2)	26 (3.6)	74 (10.2)		
Preoperative tumor characteristics					
Localization (n), %					
Pancreas	2208 (63.3)	453 (62.1)	458 (62.8)	−0.01	0.01
Periampullary or CBD	466 (13.4)	76 (10.4)	101 (13.9)	0.01	0.10
Duodenum	187 (5.4)	39 (5.3)	36 (4.9)	−0.01	−0.02
Unknown	446 (12.8)	121 (16.6)	112 (15.4)	0.07	−0.04
Malignant indication (n), %	2474 (72.5)	453 (63.6)	451 (62.2)	−0.22	−0.03
Neoadjuvant treatment (n), %	69 (2.0)	7 (1.0)	7 (1.0)	−0.08	0.00
Unknown	1 (.0)		19 (2.6)		
Preoperative tumor size, mean (SD), mm	27.5 (20.3)	28.9 (26.8)	26.4 (13.9)	−0.06	−0.14
Unknown	2692 (77.1)	521 (71.5)	264 (36.2)		
Pathology					
Histology (n), %					
Adenocarcinoma - pancreas	1690 (48.4)	345 (47.3)	307 (42.1)	−0.13	−0.10
Adenocarcinoma - duodenum	149 (4.3)	23 (3.2)	14 (1.9)	−0.14	−0.07
Adenocarcinoma - other	769 (22.0)	165 (22.6)	132 (18.1)	−0.10	−0.11
NET	167 (4.8)	45 (6.2)	52 (7.1)	0.10	0.04
IPMN/MCN	226 (6.5)	50 (6.9)	81 (11.1)	0.16	0.15
Chronic pancreatitis	94 (2.7)	19 (2.6)	14 (1.9)	−0.05	−0.05
Intestinal adenoma	104 (3.0)	23 (3.2)	22 (3.0)	0.00	−0.01
Other	269 (7.7)	56 (7.7)	100 (13.7)		
Unknown	22 (.6)	3 (.4)	7 (1.0)		
T-stage (n), %					
Not adenocarcinoma*	882 (25.3)	196 (26.9)	276 (37.9)	0.27	0.24
Tis-T2	424 (12.1)	95 (13.0)	142 (19.5)	0.20	0.18
T3	1797 (51.5)	355 (48.7)	273 (37.4)	−0.29	−0.23
T4	137 (3.9)	35 (4.8)	19 (2.6)	−0.07	−0.12
Unknown	250 (7.2)	48 (6.6)	19 (2.6)		
Tumor size, mean (SD), mm	29.4 (17.3)	29.9 (18.5)	25.9 (13.9)	−0.22	−0.26
N-stage ≥1 (n), %	1764 (57.3)	382 (59.3)	305 (45.3)	−0.24	−0.28
Lymph node ratio, mean (SD)	0.1 (.2)	0.1 (.2)	0.1 (.2)	−0.10	−0.10
M-stage ≥1 (n), %	112 (3.4)	19 (2.8)	10 (1.5)	−0.12	−0.09

ASA indicates American Society of Anesthesiologists; BMI, body mass index; CBD, common bile duct; ECOG, Eastern Cooperative Oncology Group; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; MCN, mucinous cystic neoplasm; MIPD, minimally invasive pancreatoduodenectomy; NET, neuroendocrine tumor; OPD, open pancreatoduodenectomy.

*Pancreatic ductal-, duodenum-, distal bile duct-, or other type.

Baseline Characteristics

See Table 1 for baseline characteristics before and after matching. Almost all baseline variables were more balanced after propensity score matching. Some differences remained as a result of the matching by preoperative (and not postoperative) variables; the MIPD group had a fewer pathologic T-stage 3 tumors (37% vs 49%, SMD −0.23), smaller tumors (26 mm vs 30 mm, SMD −0.26), and a fewer N1-tumors (45% vs 59%, SMD −0.28) compared with the OPD group. However, the malignant lymph node ratio (0.1 vs 0.1, SMD −0.10) was similar between groups. Of note, among the 638 patients with reported pancreatic duct measurement (44% missing), the mean duct size was slightly larger in the OPD group (5 mm vs 6 mm, SMD −0.20).

Primary and Secondary Outcomes

See Table 2 for outcomes before and after matching. The MIPD group had longer operative times [mean 416 (SD 111) vs 330 (SD 103) minutes, $P < 0.001$] and more pancreatogastrostomies (19% vs 13%, $P < 0.002$). Rates of routine intraoperative drain placement were similar (91% vs 94%) between MIPD and OPD. In the MIPD group, 115 of 729 (15.8%) procedures were converted from laparoscopic (26%) or robot-assisted (5%, $P < 0.001$) MIPD to OPD, see Supplement 3, http://links.lww.com/SLA/B435. The rates of major morbidity (28% vs 30%, $P = 0.526$) and mortality (4.0% vs 3.3%, $P = 0.576$) were similar between MIPD and OPD. The rate of grade B/C POPF (23% vs 13%, $P < 0.001$) was higher after MIPD. The rate of grade B/C bile leakage was slightly lower after MIPD

TABLE 2. Outcomes Before and After Propensity Score Matching

Perioperative	OPD Prematch N = 3490	OPD Postmatch N = 729	MIPD N = 729	P***
Operative time, median (SD), min	328.4 (99.6)	324.2 (93.9)	415.8 (110.9)	<0.001
Median (IQR)	316 (259–382)	312 (255–377)	400 (330–487)	
Type of resection (n), %				
Pylorus preserving pancreatoduodenectomy	2289 (65.6)	501 (68.7)	481 (66.0)	0.289
Classic Whipple	1201 (34.4)	228 (31.3)	240 (32.9)	0.537
Additional organs resected*(n), %	294 (8.4)	19 (2.6)	17 (2.3)	0.866
Unknown	94 (2.7)	17 (2.3)	10 (1.4)	
Veins resected**(n), %	423 (12.1)	71 (9.7)	64 (8.8)	0.588
Unknown	20 (.6)	5 (.7)	10 (1.4)	
Type of anastomosis (n), %				
Pancreatojejunostomy	2886 (82.7)	612 (84.0)	548 (75.2)	<0.001
Pancreatogastrostomy	456 (13.1)	92 (12.6)	136 (18.7)	0.002
Other	148 (4.2)	25 (3.4)	45 (6.2)	
Hard/firm pancreas	1038 (29.7)	243 (33.3)	255 (35.0)	0.544
Unknown	623 (17.9)	116 (15.9)	107 (14.7)	
Postoperative (30 days)				
Morbidity (n), %				
Clavien-Dindo 0–2 (none or minor)	2382 (68.3)	511 (70.1)	523 (71.7)	0.526
Clavien-Dindo 3a–4b (major)	958 (27.4)	194 (26.6)	177 (24.3)	0.336
Clavien-Dindo 5 (death)	150 (4.3)	24 (3.3)	29 (4.0)	0.576
Pancreatic fistula grade B/C (n), %	469 (13.5)	92 (12.7)	164 (22.6)	<0.001
Bile leakage grade B/C (n), %	160 (4.6)	37 (5.1)	22 (3.0)	0.047
Hemorrhage grade B/C (n), %	274 (7.9)	53 (7.3)	69 (9.5)	0.156
Delayed gastric emptying grade B/C (n), %	475 (13.6)	95 (13.1)	77 (10.6)	0.167
Reoperation (n), %	449 (13.1)	90 (12.6)	80 (11.0)	0.329
Length of hospital say, mean (SD), d	18.8 (14.6)	17.4 (14.6)	18.2 (19.5)	<0.001
Median (IQR)	14 (11–21)	13 (10–19)	14 (9–21)	
German and Dutch centers only	18.8 (14.6)	17.4 (14.6)	17.0 (12.3)	>0.99
Median (IQR)	14 (11–21)	13 (10–19)	14 (9–20)	
Unplanned readmission (n), %	402 (11.8)	90 (12.6)	69 (9.8)	0.11

*Other than pancreatic head, duodenum, gallbladder, or pylorus.
**Such as porto-mesenteric vein, superior mesenteric vein.
***P-value for the difference between OPD and MIPD after propensity-score matching.
IQR indicates interquartile range; MIPD, minimally invasive pancreatoduodenectomy; OPD, open pancreatoduodenectomy.

(3.0% vs 5.1%, $P = 0.047$). However, the overall rates of endoscopic reintervention (3.7% vs 2.2%, $P = 0.068$), percutaneous catheter drainage (12% vs 12%, $P = 0.809$), reoperation (11% vs 13%, $P = 0.329$), and intensive care unit admission (6.3% vs 6.5%, $P = 0.500$) were similar between MIPD and OPD.

Lengths of hospital stay [mean 18 (SD 20) vs 17 (SD 15) days and median 14 vs 13 days, $P < 0.001$] were significantly longer in the MIPD group. As expected through variation in discharge policy between countries, there was a considerable difference in hospital stay after MIPD between 7 Belgian/Dutch/German (mean 16, median 13 days) and 5 French/Italian (mean 23, median 17 days) centers. When comparing MIPD versus OPD in Dutch and German centers, no differences in hospital stay were found [mean 17 (SD 12) vs 17 (SD 15) days – median 13 vs 14 days, $P > 0.99$]. Equally, no significant differences were found after excluding all patients with grade B/C POPF [mean 15 (SD 11) vs 15 (SD 10) days – median 12 vs 13 days, $P = 0.389$].

Sensitivity Analyses

MIPD was not associated with major morbidity before (odds ratio, OR 0.85, $P = 0.072$) or after (OR 0.92, $P = 0.489$) propensity score matching. MIPD was also not associated with 30-day mortality before (OR 1.03, $P = 0.869$) or after (OR 1.36, $P = 0.269$), but there was an association with POPF before (OR 1.87, $P < 0.001$) and after propensity score matching (OR 2.01, $P < 0.001$). These estimations remained stable across all sensitivity analysis scenarios (Fig. 3, Supplement 4, http://links.lww.com/SLA/B435). Between laparoscopic, robot-assisted and hybrid procedures, the unadjusted rates of major morbidity (27% vs 27% vs 35%), POPF (24% vs 19% vs 25%), and 30-day mortality (2.9% vs 5.2% vs 5.4%) were similar, see Supplement 3, http://links.lww.com/SLA/B435. Volume-outcome associations for major morbidity and POPF are presented in Supplement 5, http://links.lww.com/SLA/B435.

In a second sensitivity analysis (n = 600), adding pancreatic duct diameter, histopathological diagnosis, and T-stage as propensity score matching variables, MIPD was not associated with increased 30-day major morbidity (OR 1.11, $P = 0.581$) or mortality (OR 1.61, $P = 0.253$), and the association with POPF (OR 1.53, $P = 0.087$) remained similar.

In a third analysis comparing MIPD patients with- (n = 164) and without (n = 563) POPF, some known and new risk factors were identified, see Supplement 6A, http://links.lww.com/SLA/B435. After multivariable adjustment, the most important newly identified risk factor for POPF in MIPD was single-row pancreatojejunostomy (OR 2.95, $P < 0.001$) as opposed to double-row pancreatojejunostomy or pancreatogastrostomy, see Supplement 6B, http://links.lww.com/SLA/B435. In patients with OPD, no association between single-row pancreatojejunostomy and POPF was found.

DISCUSSION

This large pan-European propensity score matched cohort study in centers performing at least 10 MIPDs per year found no differences in 30-day major morbidity, mortality, and length of stay between MIPD and OPD. However, MIPD was associated with a

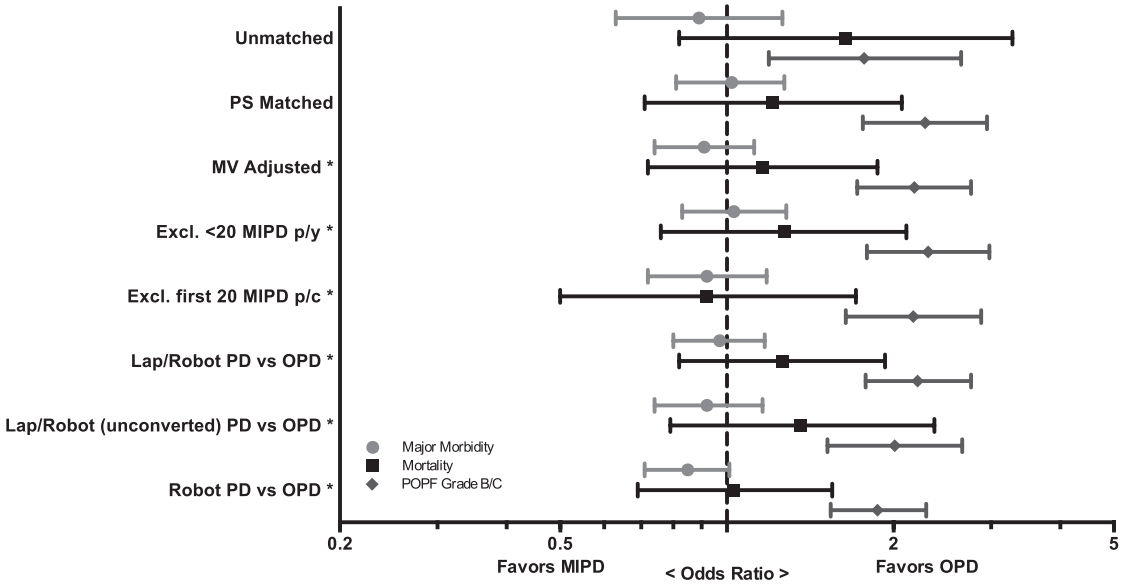

FIGURE 3. Main Outcomes and Sensitivity Analyses. Overview of the association between approach and primary (major morbidity) and secondary (mortality, postoperative pancreatic fistulae) outcomes in primary and sensitivity analysis. Underlying data is presented in Supplement 3, http://links.lww.com/SLA/B435. * Adjusted for: propensity score, age, sex, BMI, ASA, Charlson comorbidity index, ECOG, tumor location, preoperative organ involvement, multivisceral resection, porto-mesenteric vein resection and histological diagnosis. ASA indicates American Society of Anesthesiologists; BMI, body mass index; c, center; ECOG, Eastern Cooperative Oncology Group; Excl., excluding; MV, multivariable; p, per; y, year.

10% higher rate of grade B/C POPF and longer (90 minutes) operative times, but no increase in bile leakage. These results remained similar after excluding, respectively, centers performing 10 to 20 MIPDs per year, the first 20 MIPD procedures per center, hybrid procedures, conversions, and hybrid and laparoscopic procedures. No differences in risk of major morbidity, mortality, and POPF were observed between laparoscopic, robot-assisted, and hybrid MIPD, but the conversion rate was lower after robot-assisted- versus laparoscopic MIPD (5% vs 26%). Single-row pancreatojejunostomy was a newly identified risk factor for POPF in MIPD.

In keeping with these findings, 2 recent systematic reviews comparing MIPD versus OPD found no difference in 30-day mortality, but increased operative times after MIPD.[1,8] In contrast to our findings, these studies found similar rates of POPF, lower rates of delayed gastric emptying, and shorter hospital stays after MIPD. One review also found fewer postoperative complications and a lower rate of delayed gastric emptying after robot-assisted- versus laparoscopic MIPD. As was noted in one of the reviews, considerable publication bias has likely influenced these positive results for MIPD.[1] Two US nationwide registry studies on MIPD versus OPD for pancreatic ductal adenocarcinoma found higher rates of 30-day mortality in centers performing a fewer than 10 MIPDs annually, compared with equivalent rates in higher volume centers.[15,16] Two other registry studies on MIPD versus OPD found that laparoscopic MIPD was associated with lower rates of overall complications and shorter hospital stays.[14,18] Shorter hospital stays were also reported by the recent PLOT trial including 64 patients.[19] The absence of a clinical benefit of MIPD in the current study is an important finding. However, given the current early experience and relatively low annual volume of MIPD in most participating centers it may be too soon for definitive conclusions on the merits of MIPD.

The 10% absolute increase of POPF after MIPD warrants further inquiry as this has been reported in small single center cohort studies,[34,35] but not in large registry studies[14–16,18] or systematic reviews.[1,5,8] Because no differences in radiologic drainage or reoperations were observed between groups, the higher POPF rate is likely the result of prolonged drainage (ie, leaving the surgical drain in situ). Besides the approach itself, 2 other factors could have influenced this outcome; insufficient balance between groups at baseline (residual confounding) or underreporting of POPF in the German and Dutch registry data. First, residual confounding seems less likely, as OPD control patients were retrieved from unselected populations, with less than 5% MIPD use, and important risk factors associated with POPF (BMI, pancreatic texture, vascular involvement)[36,37] were controlled for. Although pancreatic duct size was often missing, the result of a secondary matched analysis on patients with available duct size was not different from the primary analysis. Second, although the rates of grade B/C POPF in the German and Dutch data on OPD were similar (11%), the 2005 ISGPS definition[26] can be interpreted in different ways[38] and POPF may not always be accurately scored postdischarge in registry databases. Indeed, recent large retrospective single-center studies on OPD have reported grade B/C POPF rates between 17%[5,39] and 28%[40] and prospective studies have reported rates between 17%[41] and 25%.[42] These proportions are closer to the 23% POPF rate after MIPD found by this study. Moreover, the Indian PLOT trial found no increase in grade B/C POPF between laparoscopic MIPD and OPD (6% vs 13%, $P = 0.311$) with an annual volume over 40 pancreatectomy procedures and a total experience of over 150 MIPDs.[19] Ultimately, more (multicenter) randomized trials are needed to compare POPF rates between MIPD and OPD.

This study has some limitations. First, we collected OPD controls from validated nationwide surgical registries with $< 5\%$ MIPD implementation and applied propensity score matching to minimize confounding by indication (surgical case selection). However, this type of bias can only be maximally avoided by randomization. Second, because MIPD data were retrieved from

institutional databases and OPD data was retrieved from nationwide registries, differences in data collection and follow-up methods may have introduced information bias. Because major morbidity (requiring reinterventions), mortality, and length of stay are hard outcomes, this is less of a concern for the main study conclusions. Third, we could not compare levels of estimated blood loss or grade A POPF (ie, biochemical leak), because these variables were not recorded in the nationwide registries. Blood loss, however, is not an essential risk factor in the recent alternative fistula risk score (aFRS).[36] Fourth, a variety of centers with different settings (academic vs nonacademic) and geographical characteristics were included. The result is substantial heterogeneity in preoperative workup, treatment strategies, and postoperative management between centers. Although this improves the external validity of the study, it reduces the accuracy of measuring the association between the approach and outcomes.

This is the first international multicenter matched study on MIPD versus OPD to date. A predefined study protocol was registered at clinicaltrials.gov to improve the study's validity and centers were offered anonymity to reduce reporting bias. The results give valuable insights into the outcomes of MIPD in the early experience of European centers performing at least 10 MIPDs per year. Consequently, our results only apply to centers with similar characteristics.

Moving forward, there are 2 major determinants of successful dissemination of MIPD: (i) the use of dedicated training programs and (ii) total- and annual procedure-specific case volumes. First, as previously shown in the Netherlands for laparoscopic distal pancreatectomy (LAELAPS-1)[43] and laparoscopic pancreatoduodenectomy (LAELAPS-2),[44] nationwide training programs can result in safe implementation of minimally invasive pancreatic surgery. In addition, a reproducible Institutional Training and Fellowship program for robot-assisted pancreatoduodenectomy, like the Pittsburgh example, has been shown to produce excellent outcomes.[10,45] For example, their grade B/C POPF rate improved from 27.5% to 14.4% ($P = 0.04$) after the first 40 MIPDs. The LAELAPS-3 program was based on the Pittsburgh program and is currently being used, including Pittsburgh-based proctors, to implement robot-assisted MIPD within the Dutch Pancreatic Cancer Group.[46] Second, 2 recent US nationwide studies found a volume-outcome associations for MIPD and defined a minimum volume cut-off of 22 to 25 MIPDs per year to achieve comparable outcomes to OPD.[47,48] In the current study, no clear association between volume and POPF was found, but it should be noted that only 6 of 14 centers performed more than 20 MIPDs per year and only one center performed more than 40 MIPDs per year. Future studies with more centers reaching higher annual case-volumes are therefore needed.

This study found that MIPD is associated with similar 30-day major morbidity, mortality, and length of stay, but longer operative times and a 10% higher rate of grade B/C POPF compared with OPD. No differences in outcomes were found between robot-assisted-, laparoscopic- and hybrid MIPD, with lower conversion rates after robot-assisted MIPD, although this sub group analysis was not the primary aim of the current study. In contrast to prior expectations, this study did not find the secondary benefits (eg, shorter hospital stays) to support the immediate widespread implementation of MIPD. We conclude that MIPD does not increase major morbidity or 30-day mortality in centers performing at least 10 MIPDs per year. However, the impact of anastomotic technique, higher annual case-volumes, and experience on outcomes (eg, grade B/C POPF) should be addressed in (prospective) studies before the true impact of MIPD can be established.

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