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ABSTRACT

Background: The aim of this study was to evaluate the impact of the level of neck transection on clinically relevant postoperative pancreatic fistula (CR-POPF) after standard pancreaticoduodenectomy (PD) with pancreaticojejunostomy.

Method: A total of 195 patients with an early postoperative CT scan were retrospectively analyzed and divided into 2 groups (CR-POPF and No CR-POPF) in order to seek potential risk factors for CR-POPF. We focused our analysis on the relationship between CR-POPF and the level of neck transection, defined by measuring the distance between the left side of the portal vein and the remnant pancreatic stump on the postoperative CT scan.

Result: CR-POPF occurred in 58 out of 195 PD (29.7 %); grade B (17 %) and grade C (12.7 %). The Clavien-Dindo ≥ 3 morbidity rate was 33 % (65/195) and the mortality rate was 2.5 % (5/195). Multivariate analysis indicated that a 'right-sided' level of neck transection (P = 0.007), a firm pancreatic texture (P = 0.001), and a PD for non-pancreatic ductal adenocarcinoma histology (P = 0.032) were independent risk factors for CR-POPF. A full neck resection with systematic transection ≥ 7 mm at the left side of the portal vein seems to prevent CR-POPF harboring a protective effect (OR 0.056; 95% CI 0.003 to 0.978; P = 0.039).

Conclusion: Here we further consolidate the concept describing the pancreatic neck as a vascular watershed, showing that a long remnant pancreatic neck could be an independent risk factor for CR-POPF after PD (NCT03850236).

Abbreviations

ASA, American Society of Anesthesiologists
POPF, Postoperative pancreatic fistula
CR-POPF, Clinically relevant postoperative pancreatic fistula
CT, Computed tomography
ISGPS, International Study Group of Pancreatic Surgery
ISGLS, International Study Group of Liver Surgery
PDAC, Pancreatic ductal adenocarcinoma
PD, Pancreaticoduodenectomy
POD, Postoperative day
SIRS, Systemic Inflammatory Response Syndrome
ROC-AUC, Receiver operating characteristic area under the curve
C.I., Confidence interval

Introduction

Pancreaticoduodenectomy (PD) is the gold standard treatment for resectable and malignant tumors of the pancreatic head and it remains a therapeutic option for the management of some benign lesions (1-5)

. PD is a complex surgical procedure, associated with significant morbidity rates of approximately 30 % and mortality rates ranging from 4 to 9 % (6-8). In most cases, postoperative morbidity is closely associated with postoperative pancreatic fistula (POPF). Since 2016, POPF is divided in two separate categories: biochemical leak (previous grade A) and clinically relevant POPF (CR-POPF: grade B/C) (9). CR-POPF, concerning 8 to 23 % of patients, significantly increases mortality, the length of hospital stay and hospital costs (10). Therefore, prevention and management of CR-POPF is a major concern for pancreatic surgery centers (8-9, 11-12).

There are numerous pre-, per-, and postoperative risk factors influencing POPF after PD. Body mass index (BMI), intraoperative blood loss, malignant histology, pancreatic texture, and main pancreatic duct diameter are independently associated with the occurrence of POPF and are included in the POPF risk score (12-14). Other debated risk factors, such as the type of pancreatic anastomosis, prophylactic administration of somatostatin analog, the surgeon's experience, and/or surgical center size, have also been identified (15-17). The study of these risk factors remains complex and regularly leads to discordant results (18).

Based on the general principle that a good anastomosis is tension-free, well vascularized, and performed in a non-septic atmosphere, we noted that reports describing pancreatic vascularization were rare. This is especially the case when considering vascularization of the pancreatic neck, routinely used to reconnect the pancreas to the digestive tract during reconstruction (19-21). In 1993, the "vascular watershed" anatomical concept described the pancreatic neck as an intermediate zone lacking proper vascularization, vascularized by both the head (through the celiac trunk and superior mesenteric artery) and the body/tail region (through the celiac trunk) (22). Resection of one of these two pancreatic areas, including its arteriovenous network, may compromise pancreatic neck vascularization, and thus promote POPF (Figure 1). Strasberg and al. have studied the impact of the defects of pancreatic stump vascularization on POPF and showed there is a statistically significant correlation (19-20). Together these anatomical observations on the pancreatic neck could explain the different discrepancies between the studies based on the type of pancreatic anastomosis as a risk factor of POPF after PD.

Given the anatomical findings reported here, and the fact that pancreatic transection is performed at the neck above the mesenterico-portal axis, our hypothesis is that the ‘actual’ physical level of pancreatic neck transection can significantly influence the rate of pancreatic fistula. The aim of this study was thus to evaluate the impact of the level of neck transection on CR-POPF after standard PD with pancreaticojejunostomy.

Methods

Study Design and Patients

We conducted an observational study between January 2009 and April 2018 at a single center to investigate the correlation between the level of neck transection and CR-POPF. Consecutive patients aged of at least 18 years-old who underwent PD for malignant or benign pathology were identified from a prospectively maintained database (n = 234). Patients excluded were those for whom postoperative measuring of neck transection level on postoperative CT was impossible (n = 2) and patients who did not undergo postoperative CT scans between postoperative day (POD) 7 and 10 (n = 28). We also excluded 9 patients with portal vein resection. In order to analyze perioperative risk factors for CR-POPF after PD, we divided the final cohort in 2 groups: CR-POPF and No CR-POPF (Figure 2). Informed consent for surgical procedures was obtained from each patient. The present study was approved by our local ethics committee and its protocol was declared on ClinicalTrials.gov (ID: NCT03850236) before statistical analysis (February 21, 2019). Data has been reported in line with STROCSS 2019 criteria (23).

Surgical Procedure and Postoperative Management

All patients underwent a standard Whipple procedure by at least one experienced pancreatic surgeon as previously described (24-26). We systematically avoided excessive posterior mobilization of the pancreatic stump after transection and the dorsal pancreatic artery was maintained. Pancreatic reconstruction was performed by a pancreaticojejunostomy. Pancreaticojejunostomy was an end-to-side wirsungojejunostomy carried out with an intraductal drain when the main pancreatic duct diameter was ≤ 3mm. Biliary reconstruction was achieved by end-to-side retrocolic hepaticojejunostomy. Finally, we carried out a precolic gastrojejunostomy. Two passive drains were systematically placed: the first one anterior to the hepaticojejunal anastomosis and posterior to the pancreatic anastomosis (right drain), and the second one posterior to the gastrojejunostomy and anterior to the pancreatic anastomosis (left drain).

All patients received intraoperative prophylactic antibiotics. Patients with preoperative biliary stenting received large spectrum antibiotics for at least 5 PODs (27). Depending on clinical course, therapy was extended if necessary and suitable antibiotics was prescribed (27). Most patients received epidural analgesia and were cared for in our intensive care unit for at least four days and then transferred to the ward.

Patients received a bolus of 100 µg octreotide during the surgery if the pancreatic texture was soft or fatty and a 600µg daily intravenous administration until the drain fluid amylase levels were assessed on POD 3 and POD 5. For patients lacking clinico-biological evidence of POPF on POD 5, drains were removed and the octreotide was stopped. For patients presenting POPF, we switched to intravenous somatostatin (6mg per day), then relayed with long-acting (LA) octreotide.

Nasogastric tubes were removed at POD 2 if the patient had no distension and daily output < 500mL. The patients recovered oral feeding at POD 2 with fluid diet then regular diet.

An enhanced abdominal CT scan was routinely performed between POD 7 and 10 or earlier in case of suspicion of intra-abdominal complication (hyperthermia, acute abdominal pain, SIRS), drain fluid appearance change (externalized bleeding, appearance of bilio-digestive, or pus), or following the presence of a biological inflammatory syndrome.

Definitions and data collected

POPF (biochemical leak or clinically relevant (Grade B or C)) was our primary outcome, defined according to the ISGPF 2016 definition (9). Only clinically relevant grade B/C leak were considered as POPF (CR-POPF). In case of grade C POPF, pancreas-preserving approaches were performed (pancreaticojejunostomy resection with external wirsungostomy, simple peritoneal drainage or refection of pancreaticojejunostomy).

The main pancreatic duct was assessed on preoperative imaging (CT or MRI). The diameter was measured on the transversal plane at the pancreatic neck just above the splenic vein superior mesenteric vein junction. The largest diameter obtained on the antero-posterior axis was noted. Pancreatic texture (firm or soft) was defined by the surgeon during the procedure and specimen examination.

The level of neck transection was defined by measuring the distance between the left side of the portal vein and the remnant pancreatic stump on the first postoperative CT scan by an independent and blinded radiologist. A multi-planar reconstruction was performed to obtain a modified coronal plane. The aim was to define, as a linear landmark, the drip line of the splenic vein superior mesenteric vein junction (left margin of the portal vein), as shown in Figure 3. Thus, if the transection level was above this landmark, the measurement was defined as 0 mm. We considered a negative distance value when the level of neck transection was deported on the right of the left side of the portal vein.

The following data was gathered from each patient's medical record: age, sex, BMI, preoperative comorbidities and ASA score, pathological findings, preoperative biliary drainage, neoadjuvant therapy, surgical procedures, period of surgery, duration of surgery, blood loss, morbidity, mortality, and length of postoperative hospital stay. We also collected biological data: preoperative albumin and bilirubin levels. Ninety-day postoperative morbidity was graded according to the Clavien-Dindo classification of surgical complications (28-29). Operative mortality was defined as death within 90 days following surgery. Post-pancreatectomy hemorrhage, delayed gastric emptying (DGE), and bile leakage were defined according to the ISGPS and ISGLS definitions (30-32).

Statistical analysis

Statistical analyzes were performed using SPSS V.21 software (IBM, USA). Continuous variables were reported as medians (range). The independent sample *t* test was used to detect differences between the means of continuous variables. Categorical variables were described using frequency distributions, then compared using Chi-squared test or the Fisher's exact test accordingly. *P* values < 0.050 were considered to be significant. A receiver operating characteristic area under the curve (ROC-AUC) was used in order to determine if a specific threshold of neck transection level was associated with lower rates of CR-POPF. In multivariate analysis, we included all variables with a *P* value < 0.100 from univariate analysis, and independent POPF risk factors of the original-FRS were forced into the model, which, although not significant, allowing the groups to be comprehensively analyzed (11).

These were then implemented into a logistic regression model to identify independent risk factors for POPF. The independent risk factors of the variables were expressed as odds ratios (Exp (B)) with their 95 % confidence intervals (c.i.). Two-sided *P* values were computed; a value of *P* < 0.050 was considered statistically significant.

Results

Study population and Surgical data

Out of the 370 pancreatectomies performed in our unit between 1st January 2009 and 4th April 2018, 234 patients required a PD. Following patient selection by inclusion/exclusion criteria, we analyzed data from 195 patients who underwent PD (F: 79 / M: 116). In the majority of cases, PD was required due to PDAC (68.7 %). Neo-adjuvant treatment by chemotherapy associated with or without radio-chemotherapy was administered to 16 patients. Demographic data are detailed in Table 1. PD was mostly performed by laparotomy (93.3 %). The median operating time was 315 minutes [126-585]. The R0 resection rate was 86.2 %. All surgical and histological data are detailed in Table 2.

Measuring the level of neck transection, reflecting the length of the remaining pancreatic neck, was feasible, reproducible, but highly variable (Figure 4-A). This variability followed a normal distribution. This initial observation led us to consider a potential correlation between the level of neck transection and CR-POPF.

Postoperative data

Postoperative outcomes are summarized in Table 3. Overall 90-day mortality after PD was 2.1% (n=5/234) during the study period. CR-POPF occurred in 58 out of 234 patients who underwent PD (24.5 %) and justified an early CT scan, giving a rate of 29.7 % in 195 patients matching inclusion criteria.

CR-POPF was grade B in 33 (17 %) and grade C in 25 (12.7 %) patients. A severe postoperative complication (Clavien-Dindo grade ≥ 3) occurred in 65 patients (33 %). Thirty-eight surgical re-interventions were performed (19.5 %), including 27 for CR-POPF. The median length of hospital stay was 14 [9-120] days and was significantly longer in the CR-POPF group (25 *versus* 13 days for No CR-POPF; *P* <0.001). Severe postoperative complications were significantly higher in the CR-POPF group (72.5 *versus* 17 %; *P* <0.001), with more hemorrhage, intra-abdominal fluid collections, bile leakage, delayed gastric emptying, and sepsis than in the No CR-POPF group. Ninety-day mortality was 2.5% (n=5/195) and was significantly higher in the CR-POPF group (8.5 *versus* 0 % for No CR-POPF; *P* <0.025). The causes of these five deaths were hemorrhage (n=2), septic shock (n=1), bowel (n=1) and liver ischemia (n=1) and were systematically associated to grade C POPF.

Risk factors for CR-POPF

The general risk factors evaluated, including the level of neck transection, are shown in Tables 1 and 2. The following risk factors were found significantly associated with CR-POPF *versus* No CR-POPF: (1) low preoperative albumin (*P* = 0.024), (2) no lateral portal vein resection (*P* = 0.042), (3) the absence of neoadjuvant treatment (*P* = 0.006), (4) pancreaticoduodenectomy for non-PDAC lesions (*P* < 0.002), (5) main pancreatic duct diameter < 3 mm (*P* < 0.001), (6) soft pancreatic texture (*P* < 0.001), and (7) the level of neck transection (-5.08 *versus* -0.25 mm; *P* < 0.002 (Figure 4-A)). Mean levels of neck transection in CR-POPF B *versus* C patients were both negative ('right-sided') and were not significantly different (*P* = 0.196; Figure 4-B).

As summarized in Table 4, these 7 variables associated with CR-POPF were then further analyzed by multivariate logistic regression in addition with blood loss and BMI (both with *P* values < 0.100). A soft pancreatic texture, PD for non-PDAC lesions, and the level of neck transection were identified as independent risk factors for CR-POPF.

We then sought to define if a specific threshold for neck transection level was associated with lower rates of CR-POPF. Guided by ROC-AUC prior to a second multivariate logistic regression analysis, we found that level of neck transection as a categorical variable (≤ or ≥ +7 mm; as shown in Table 2) remained an independent predictive factor for CR-POPF, with left-sided transection harboring a protective effect (OR 0.056; 95 %CI 0.003 to 0.978.; *P* = 0.039). In this second analysis, a soft pancreatic texture and PD for non-PDAC lesions still remained independent risk factors for CR-POPF.

Discussion

Pancreatic fistula after PD remains a major concern for patients and pancreatic surgeons given it represents a major cause of morbidity and mortality. There is an extensive literature illustrating many predictive patient-, operative-, and gland-related risk factors for POPF.

However, few studies have addressed variations in the level of pancreatic neck transection and a potential association with POPF. To our knowledge, this is the first study focusing on the level of neck transection on a large patient cohort (n = 195) requiring pancreaticoduodenectomy for benign or malignant lesions. We found that a ‘right-sided’ level of neck transection could be an independent risk factor for CR-POPF after PD. A full neck resection with systematic transection ≥ 7 mm at the left side of the portal vein seems to prevent CR-POPF. This further consolidates the "vascular watershed" anatomical concept used to describe the pancreatic neck by Strasberg et al (19). CR-POPF is likely a multifactorial severe complication. Our results suggest that the level of neck transection contributes to Cr-POPF occurrence in addition to other main independent risk factors strongly described in the literature, and included in the Fistula Risk Score (pancreatic texture and non-PDAC underlying lesions in the present study).

Several observations in this present study need clarifying with respect to our higher CR-POPF rate than generally found in published data. Firstly, one third of our patients in this study required a pancreaticoduodenectomy for non-PDAC lesions. This could have increased the CR-POPF rate as it has been described that a non-PDAC histology is an independent risk factor for CR-POPF (9). Secondly, our results were influenced by our systematic drainage policy, and the exclusion of 28 patients with uneventful postoperative course not requiring early CT-scan. However, if our grade C rate was higher than those usually reported (12, 33-36), we can highlight the fact that our overall mortality (2.5%) and grade C POPF-associated mortality were low (20%, n=5/43), evident of an aggressive but efficient postoperative management of CR-POPF (37).

Literature evidence is minimal regarding the potential association between POPF and the quality of pancreatic stump vascularization after PD. In 1998, Strasberg and McNevin were the first to focus on this issue using a series of 40 consecutive PDs. Their methodology consisted in the analysis of pancreatic slice bleeding after neck transection with a cold blade: 16 patients presented no slice bleeding. This simple clinical finding was correlated with arterial Doppler signal obtained at the level of the neck transection (19). The same authors then reported a prospective study on 123 patients who underwent PD (20). A cut of the pancreatic neck to the left was suggested after a bleeding defect (38 %) was encountered following pancreatic section. This approach was associated with a reduction in pancreatic fistula rate compared to the authors' former cohort given that the publication of this paper was prior to the ISGPF definition of CR-POPF. Nonetheless, this study was the first to confront the vascular anatomy of the pancreas and the consequent surgical implications, highlighting the concept of 'impaired intraoperative pancreatic perfusion'.

More recently, a series of cases treated at the Montsouris Institute (Paris, France) were injected with indocyanine green during a laparoscopic PD. Similar results were evoked, with patients presenting areas of neck ischemia invisible to the naked eye (38). New prospective studies are needed to standardize intraoperative evaluations using indocyanine green, considering hemodynamic constants, post-injection time, and product elimination time.

The case-control study by Jwa et al. published in 2017 evaluated the interest of a 'left-sided' pancreatic transection, opposite the celiac trunk (extended pancreatic transection (EPT)), as a mean of preventing grade B/C pancreatic fistula (21). Grade B/C FP rates were significantly lower in the EPT group (5/19 patients) *versus* the standard neck transection group (25/49 patients; $P = 0.047$). Standard neck transection was defined as being opposite the left edge of the portal vein, with visualization of the spleno-mesaraic trunk and without mobilization of the pancreatic stump. The authors described a more favorable positioning of the main pancreatic duct in the EPT group; it would be more centered, less posterior at this level than at the pancreatic neck. They estimated with this technique to be able to remove an additional length of pancreatic (neck) parenchyma (on average approximately 3 cm) upon comparison to a conventional neck transection. No difference was found concerning endocrine and exocrine insufficiency between the 2 techniques (taking into consideration the small size of this study).

Our study presented here has several limitations. The design of the study was retrospective. The measuring of the pancreatic thickness at the cut surface was not performed, and the distance reflecting the level of neck transection was not assessed intraoperatively, but on postoperative CT scans. However, to limit this bias we took the left edge of the splenic vein as a reference - the superior mesenteric vein junction - which seems to be an anatomical constant (39). In addition, we also excluded patients who had a portal vein resection leading to a modified anatomy of the mesenterico-portal axis. The distance between the left edge of the portal vein and the right edge of the remaining pancreas was measured by an independent and blinded radiologist for postoperative course examination only. The present study showed that variation of the neck transection level is high. In order to provide a comprehensive explanation of this variation, we performed univariate analysis to reach variables influencing the neck transection level as a continuous and categorical variable ($\leq$ or $\geq$ +7 mm), and we failed to find significant factors (surgeon experience, open/laparoscopic approach) balancing the level of neck transection (data not shown). Our limited sample size meant that the potential risk of type II errors did not allow us to show an independent association between CR-POPF and the three major variables of the original Fistula Risk score (main pancreatic duct diameter, BMI, and the most debated: blood loss) (13, 40-41). In line with previous report, we found a trend of a protective effect of NAT on CR-POPF. The presence of a neoadjuvant treatment is a confounding factor that is strongly correlated with the pancreatic disease justifying PD (PDAC or not). The effect of the neoadjuvant treatment disappeared after logistic regression and only PD for a non-PDAC lesion remained an independent risk factor for CR-POPF.

These results suggest a role of the quality of pancreatic stump perfusion in CR-POPF, likely involving ischemic acute pancreatitis mechanisms. To date, there exists no randomized study dedicated to answering this question. For Strasberg et al. with their ‘blood supply-based technique’ (19-20), the design of such a study would raise ethical concerns as the question raised, following randomization, would be whether to perform an anastomosis on a pancreatic stump that does not bleed. The most relevant design could be that of a prospective randomized study evaluating ‘standard neck transection’ *versus* ‘extended pancreatic transection’. This was investigated in the retrospective study by Jwa et al (21), where they did not rely on bleeding from the pancreatic stump. Advances in imaging, and particularly in dynamic imaging, combined with a study on perfusion would surely allow progress to be made on this question concerning neck vascularization and impacts after PD. Measurements of future volume, degree of fibrosis, and fatty involution of the remnant pancreas have been more widely studied using either preoperative CT or MRI, and have shown associations with increased risk of POPF (42).

In contradiction, we know that some expert pancreatic surgeons choose to cut the dorsal pancreatic artery deriving from the splenic artery for cases of friable pancreas in order to prevent the risk of pancreatic stump bleeding. A compromise between a good pancreatic stump perfusion and bleeding risk must be considered. These results have led us to: (1) extend our pancreatic resections to the left of the mesenterico-portal axis, (2) control pancreatic stump hemostasis with sutures or cauterization rather than performing hemostatic suturing at the lower and upper edges of the pancreas, (3) avoid excessive posterior mobilization of the pancreatic stump after transection, and (4) continue carrying out wirsungojejunal anastomosis, which considerably reduces pancreatic stump hemorrhages in our experience.

Conclusion

In order to reduce CR-POPF rate, and thus morbidity and mortality after PD, the results of this present study require further prospective analyzes based on a systematic approach of shifting the level of neck transection > 7 mm ‘to the left’ of the mesenterico-portal axis in patients specifically with high risk of POPF. Additionally, the development of methods is required to enable systematic intraoperative evaluation of the vascularization of the remaining pancreatic parenchyma to allow for adaptation of the level of parenchymal section accordingly.

Provenance and peer review

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Figures & tables

Table 1 – Demographic data, preoperative data and risk factors for CR-POPF

Table 2 – Surgical data, histological data and risk factors for CR-POPF

Table 3 - Postoperative outcome after pancreaticoduodenectomy according to CR-POPF

Table 4 - Multivariate logistic regression for CR-POPF

Figure 1 – Example of hypoperfusion (white arrow) of pancreatic neck during an arterial angio-CT scan (258 strips, Aquilion ONE +, Toshiba) following an injection of contrast product (standardized protocol, Iomeron 350, 4ml / sec, 20cc, unique volume acquisition at 16 seconds after the start of injection) from the celiac trunk (TC) by selective catheterization (5 F) during an interventional radiology procedure (chemoembolization for hepatocellular carcinoma).

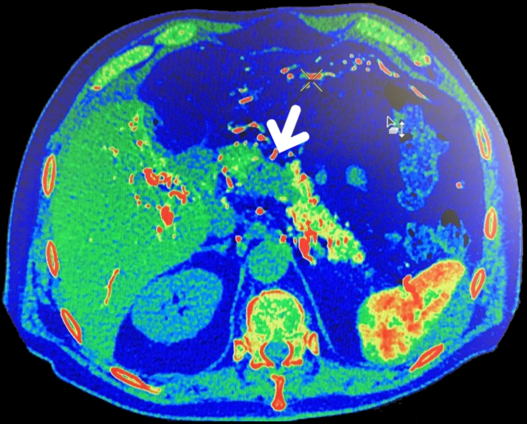
Figure 2 - Flowchart and study design

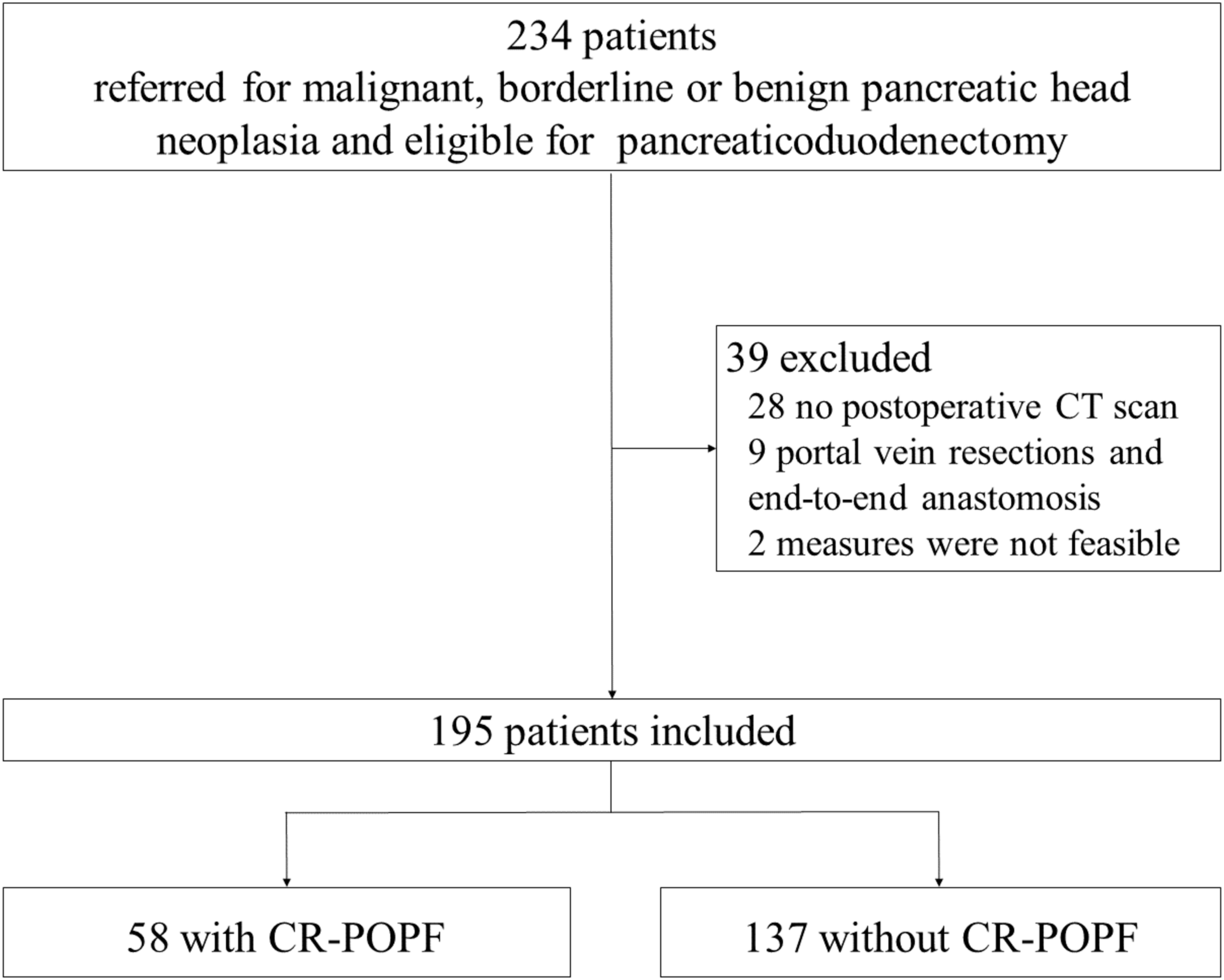
Figure 3 - Measuring the distance between the left side of the portal vein and the remnant pancreatic stump on the first postoperative CT scan after PD (A, B). The distance value was considered (B) negative when the level of neck transection was deported on the right of the left side of the portal vein and (C), nil or positive when the level of neck transection was above or on the left side of the portal vein, respectively (D).

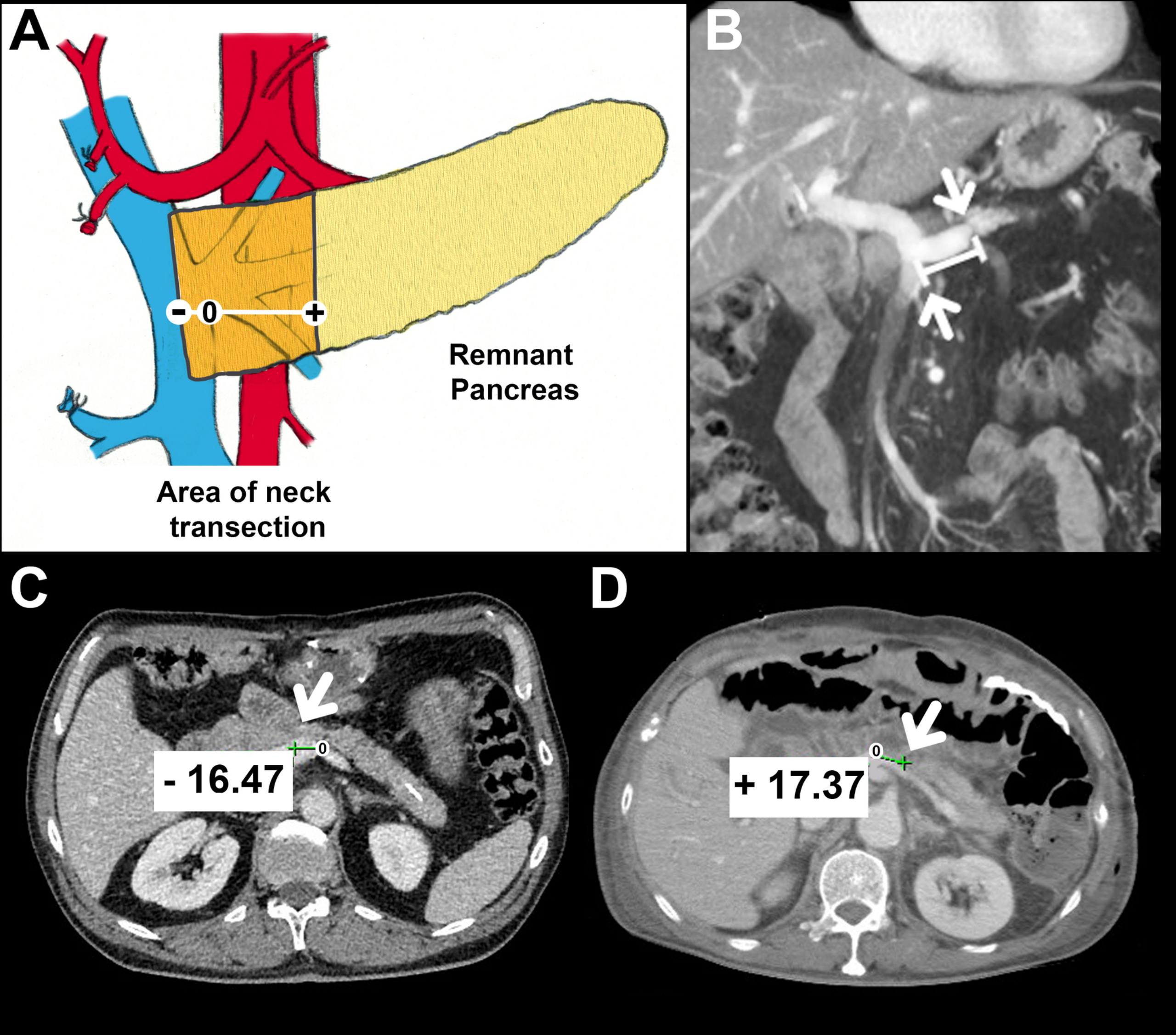
Figure 4 - Level of neck transection during PD according to CR-POPF and No CR-POPF groups: (A) a 'right sided' level of neck transection was significantly associated with CR-POPF (-5.08 *versus* 0.25 mm; p <0.002). A 0 value means that the pancreatic stump was above the left side of the portal vein. A negative value means that the pancreatic stump was deported to the right of the left side of the portal vein (long neck). A positive distance value means that the pancreatic stump was on the left side of the portal vein (short neck or totally resected neck); (B) Mean levels of neck transection in CR-POPF B *versus* C patients were both negative ('right-sided') and were not significantly different (p = 0.196); (C) Receiver operating characteristic area under the curve (ROC-AUC) was 0.621 (95 % c.i 0.525-0.698).

COI/Disclosure statement

All authors declare no competing interests.




234 patients
referred for malignant, borderline or benign pancreatic head neoplasia and eligible for pancreaticoduodenectomy
39 excluded
28 no postoperative CT scan
9 portal vein resections and end-to-end anastomosis
2 measures were not feasible
195 patients included
58 with CR-POPF
137 without CR-POPF


A
B
C
D
- 0 +
Remnant
Pancreas
Area of neck
transection
- 16.47
0
+ 17.37
0

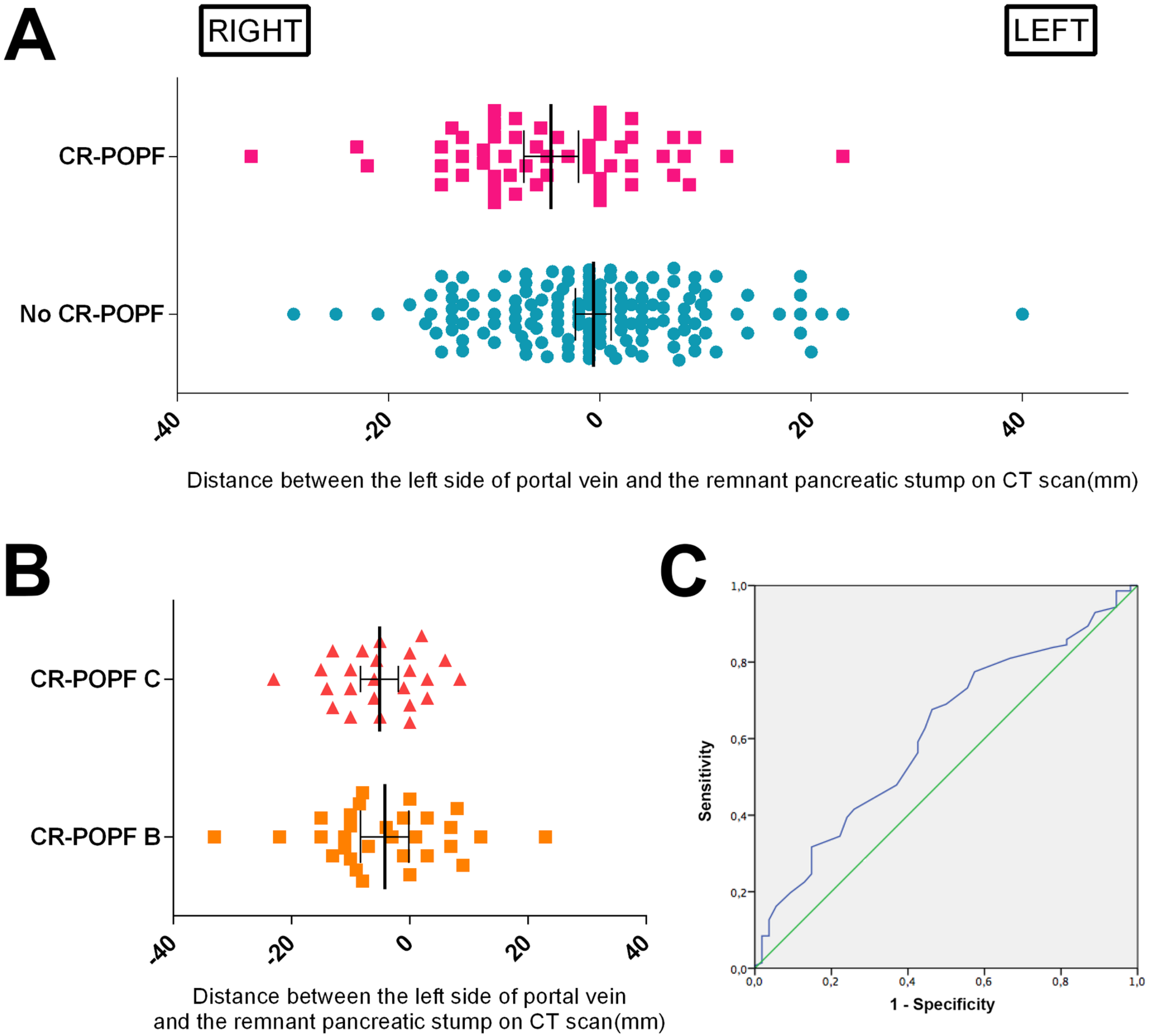

A
RIGHT
LEFT
CR-POPF
No CR-POPF
-40
-20
0
20
40
Distance between the left side of portal vein and the remnant pancreatic stump on CT scan(mm)
B
CR-POPF C
CR-POPF B
-40
-20
0
20
40
Distance between the left side of portal vein
and the remnant pancreatic stump on CT scan(mm)
C
Sensitivity
1,0
0,8
0,6
0,4
0,2
0,0
0,0
0,2
0,4
0,6
0,8
1,0
1 - Specificity

Table 1 - Demographic data, preoperative data and risk factors for CR-POPF

Variables	Total (n=195)	CR-POPF (n=58)	No CR-POPF (n=137)	*P*
Gender				
Female	79 (40.5)	21 (36)	58 (42)	_
Male	116 (59.5)	37 (64)	79 (58)	0.425‡
Period				
2009-2013	103 (53)	27 (46.5)	76 (55.5)	_
2013-2018	92 (47)	31 (53.5)	61 (44.5)	0.254‡
Age (years), median (range)	74 (18-92)	74 (18-92)	74 (29-90)	0.689¶
BMI (kg/m2), median (range)	24.5 (17-52)	25.4 (17-32)	24.2 (17-52)	0.099¶
ASA score				
Grade I	38 (19.5)	8 (14)	30 (22)	_
Grade II	118 (60.5)	40 (69)	78 (57)	0.135‡
Grade III	37 (19)	10 (17)	27 (20)	0.540‡
Grade IV	2 (1)	0 (0)	2 (1)	1.000§
Comorbidities				
High Blood Pressure	75 (38.5)	24 (41)	51 (37)	0.586‡
Cardiovascular disease	91 (46.5)	30 (52)	61 (44.5)	0.357‡
Smoker	29 (15)	6 (10)	23 (17)	0.248‡
Drinking habit	7 (3.5)	1 (2)	6 (4)	0.676§
Respiratory disease	16 (8)	6 (10)	10 (7)	0.478‡
Diabetes mellitus	27 (14)	8 (14)	19 (14)	0.989‡
Previous pancreatitis	9 (4.5)	2 (3.5)	7 (5)	0.613§
Renal dysfunction	6 (3)	3 (5)	3 (2)	0.365§
Previous abdominal surgery	78 (40)	28 (48)	50 (36.5)	0.125‡
Neoadjuvant therapy	16 (8)	0 (0)	16 (12)	0.006§
Chemotherapy	12 (6)	0 (0)	12 (9)	_
Chemotherapy plus radio-chemotherapy	4 (2)	0 (0)	4 (3)	_
Preoperative bilirubin (µmol/l), median (range)	147.5 (2-514)	149 (2-514)	127.5 (2-478)	0.367¶
Preoperative albumin (g/l), median (range)	42 (20-51)	36 (20-50)	45 (20-51)	0.024¶
Biliary drainage	66 (34)	17 (29)	49 (36)	0.384‡

Values are numbers (percentage) unless otherwise indicated. CR-POPF indicates clinically relevant postoperative pancreatic fistula; BMI, body mass index; ASA, American Society of Anesthesiologists. ‡ Chi-2 test. § Fisher's exact test and ¶ Student *t*- test.

Table 2 - Surgical data, histological data and risk factors for CR-POPF

Variables	Total (n=195)	CR-POPF (n=58)	No CR-POPF (n=137)	*P*
Surgical approach				
Laparotomy	182 (93)	54 (93)	128 (93)	_
Laparoscopy	13 (7)	4 (7)	9 (7)	1.000§
Intraoperative features				
Duration of surgery (min), median (range)	315 (126-585)	420 (170-585)	315 (126-530)	0.145¶
Intraoperative blood loss (ml), median (range)	425 (0-3200)	75 (0-3200)	425 (0-3000)	0.889¶
Intraoperative transfusion	32 (16.5)	9 (15.5)	23 (17)	0.827‡
Lateral venous resection	20 (10.3)	2 (3.5)	18 (13)	0.042§
Pathological data				
Main pancreatic duct diameter				
<3 mm	97 (50)	43 (74)	54 (39.5)	_
≥3 mm	98 (50)	15 (26)	83 (60.5)	<0.001‡
Pancreatic texture				
Soft	107 (55)	52 (89.5)	55 (40)	_
Hard	88 (45)	6 (10.5)	82 (60)	<0.001‡
Level of Neck Transection (mm), median (range)	-1.68 [-33 +40]	-5.08 [-33 +23]	-0.25 [-29 +40]	0.002¶
< +7 mm	156 (80)	52 (89.5)	104 (76)	_
≥ +7 mm	39 (20)	6 (10.5)	33 (24)	0.028‡
Final histology				
PDAC	134 (68.7)	31 (53.5)	103 (75)	_
Others	61 (31.3)	27 (46.5)	34 (25)	0.002‡
Tumor size (mm), median (range)	12,5 (0-100)	25 (0-75)	20 (0-100)	0.656¶
Resection margin				
R0	168 (86.2)	53 (91.5)	115 (84)	_
R1	27 (13.8)	5 (8.5)	22 (16)	0.255§

Values are numbers (percentage) unless otherwise indicated. CR-POPF indicates clinically relevant postoperative pancreatic fistula; PDAC, pancreatic ductal adenocarcinoma. ‡ Chi-2 test. § Fisher's exact test and ¶ Student t- test.

Table 3 - Postoperative outcome after pancreaticoduodenectomy according to CR-POPF

Variables	Total (n=195)	CR-POPF (n=58)	No CR-POPF (n=137)	*P*
Primary outcome				
Neither BL or POPF	114 (58.5)	-	114 (83)	
BL	23 (11.8)	-	23 (17)	
POPF grade B	33 (17)	33 (57)	-	
POPF grade C	25 (12.7)	25 (43)	-	
Secondary outcomes				
Hemorrhage	9 (4.5)	7 (12)	2 (1.5)	0.005§
Intra-abdominal fluid collection	52 (26.5)	34 (58.5)	18 (13)	<0.001‡
Biliary leakage	20 (10)	11 (19)	9 (7)	0.009‡
DGE	55 (28)	25 (43)	30 (22)	<0.003‡
Sepsis	50 (25.5)	34 (58.5)	16 (12)	<0.001‡
Reoperation	38 (19.5)	27 (46.5)	11 (8)	<0.001‡
Major complications (Clavien-Dindo ≥3)	65 (33)	42 (72.5)	23 (17)	<0.001‡
90-days postoperative mortality	5 (2.5)	5 (8.5)	0 (0)	0.025§
LOS (days), median (range)	38 (19.5)	25 (9-120)	13 (9-56)	<0.001‡

Values are numbers (percentage) unless otherwise indicated. CR-POPF indicates clinically relevant postoperative pancreatic fistula; BL, biochemical leak; POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying, LOS, length of stay. ‡ Chi-2 test. § Fisher's exact test and ¶ Student t- test.

Table 4 – Multivariate logistic regression for CR-POPF

	Odds Ratio (95% C.I for Exp(B))	*P*
BMI	1.027 (0.892 - 1.182)	0.713
Preoperative serum albumin	1.091 (0.920 - 1.295)	0.317
Absence of neoadjuvant treatment	1.085(0.748 - 1.325)	0.998
Main pancreatic duct < 3 mm	1.091 (0.457 - 11.060)	0.319
Firm pancreatic texture	0.033 (0.005 - 0.247)	0.001
Blood loss	0.794 (0.999 - 1.001)	0.794
No lateral venous resection	1.322 (0.104-16.779)	0.830
Level of neck transection	0.875 (0.794 - 0.964)	0.007
Non-PDAC lesion	6.397 (1.172 - 34.917)	0.032

C.I indicates confidence interval; BMI, body mass index.