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Completion Pancreatectomy After Pancreatoduodenectomy

Who Needs It?

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Objective: The objective of this study was to identify the indications for and report the outcomes of completion pancreatectomy (CPLP) in the postoperative course after pancreatoduodenectomy (PD).

Background: CPLP may be considered or even inevitable for damage control after PD.

Methods: A prospectively maintained database of all patients undergoing PD between 2001 and 2019 was searched for patients who underwent CPLP in the postoperative course after PD. Baseline characteristics, perioperative details, and outcomes of CPLP patients were analyzed and specific indications for CPLP were identified.

Results: A total of 3953 consecutive patients underwent PD during the observation period. CPLP was performed in 120 patients (3%) after a median of 10 days following PD. The main indications for CPLP included postpancreatectomy acute necrotizing pancreatitis [n = 47 (39%)] and postoperative pancreatic fistula complicated by hemorrhage [n = 41 (34%)] or associated with uncontrollable leakage of the pancreatoenteric anastomosis [n = 23 (19%)]. The overall 90-day mortality rate of all 3953 patients was 3.5% and 37% for patients undergoing CPLP.

Conclusions: Our finding that only very few patients (3%) need CPLP suggests that conservative, interventional, and organ-preserving surgical measures are the mainstay of complication management after PD. Postpancreatectomy acute necrotizing pancreatitis, uncontrollable postoperative pancreatic fistula, and fistula-associated hemorrhage are highly dangerous and represent the main indications for CPLP after PD.

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Pancreatoduodenectomy (PD) is the standard procedure for malignant and benign pathologies in the pancreatic head.[1–5] Advances in surgical technique along with improvements in perioperative care and better complication management have led to a decrease in mortality to <5% in high-volume centers. However, postoperative morbidity rates remain high.[6–10] Severe complications such as postoperative pancreatic fistula (POPF), postpancreatectomy acute (and even necrotizing) pancreatitis (PPAP), postpancreatectomy hemorrhage (PPH), or abdominal sepsis are feared complications associated with increased postoperative mortality of up to > 50%.[10–19] Herein, it is of importance to notice that POPF may not only result from leakage of the pancreatic anastomosis (1), but also from iatrogenic damage to the pancreatic remnant with rupture of the pancreatic duct system and capsule (2), from PPAP, especially in case of necrotizing pancreatitis (3), and from ischemia of the pancreatic remnant (4). Using modern interdisciplinary management including endoscopic/radiologic interventions or angiography to drain fluid collections or control bleeding, most of these complications can nowadays be managed conservatively without the need of reoperation.[20–23] Only with failure of interventional measures, the indication for surgical treatment is indisputable.[24,25] Although several pancreas-preserving surgical strategies such as necrosectomy and drainage, redo of the pancreatic anastomosis, and external wirsungostomy have been reported in the literature, completion pancreatectomy (CPLP) is the only therapeutic approach enabling the eradication of the underlying cause of morbidity in case of severe POPF or necrotizing PPAP.

The aim of this retrospective analysis was to identify indications for CPLP and to assess outcomes of CPLP in complication management after PD.

METHODS

The prospectively maintained pancreas database of the Department of General, Visceral and Transplantation Surgery was searched for all patients who had undergone PD at the

Heidelberg University Hospital, Germany, between October 1, 2001, and December 31, 2019. Those patients in whom CPLP was necessary in the postoperative course after PD were identified and analyzed. Partial PD included pylorus-preserving PD, pylorus-resecting PD, and the classic Whipple procedure. Standard anatomic reconstruction was performed with end-to-side pancreaticojejunostomy in a double-layer technique, a single-layer, end-to-side hepaticojejunostomy, and a double-layer, antecolic duodenojejunostomy or gastrojejunostomy. Abdominal drains were removed whenever the amount of fluid output decreased to <500 mL/24 h and drain amylase or drain lipase activity was <3 times above the upper limit of normal. Indications for CPLP included emergency relaparotomy for damage control in complicated postoperative courses. Patients who underwent CPLP for oncologic reasons addressing incomplete tumor resection, which was identified only in the final histopathologic examination and not intraoperatively by frozen section during PD, were excluded from the analysis. The study was approved by the institutional review board of the Ethics Committee of the Medical Faculty of the University of Heidelberg; written informed consent for data collection and analysis had been obtained from each patient at the time of admission for surgery. Patient characteristics included age, sex, body mass index, American Society of Anesthesiologists performance status, and neoadjuvant treatment. Operative details of both PD and CPLP were assessed comprising operation time, estimated blood loss, and intraoperative blood transfusion (packed red blood cells and fresh frozen plasma). Postoperative short-term outcomes including surgical complications, length of hospital stay, and 90-day mortality were analyzed. POPF and PPH were classified according to the International Study Group of Pancreatic Surgery definitions.[26–28] The decision to perform CPLP was at the surgeons' discretion and based on the patients' condition and intraoperative findings during relaparotomy. Hence, 4 main indications for CPLP, specifically (1) acute necrotizing pancreatitis, (2) uncontrollable leakage of the pancreaticojejunostomy, (3) hemorrhage, and (4) other reasons were classified. The diagnosis of PPAP and postpancreatectomy acute necrotizing pancreatitis was based on characteristic histopathologic findings of the resected pancreatic remnant. Histopathology was reevaluated by 2 pathologists (B.G. and T.A.) specialized in pancreas pathology and blinded for clinical outcomes. Laboratory parameters such as serum and drain amylase/lipase levels, as well as C-reactive protein levels, were also assessed in the postoperative course. Medical management of patients with suspicion of PPAP included close clinical observation and nasogastric tube insertion for nausea and/or vomiting. In case of worsening of the patients' clinical condition, computed tomography (CT) imaging was performed and the patient was admitted to the intermediate or intensive care unit, if necessary. If intra-abdominal fluid collections were detected, these were addressed by radiologic interventional drain placement. Antibiotic therapy was started for signs of an abdominal infection.

Statistical Analysis

R software (version 4.0.3) was used for statistical analyses. Quantitative parameters are expressed as median with interquartile range (IQR). The nonparametric Kruskal-Wallis test was used to compare quantitative parameters between CPLP subgroups. Categorical parameters are presented as absolute and relative frequencies and compared between the groups using the χ^2 test. Two-sided P values < 0.05 were computed and since this was an exploratory study, they have to be interpreted in a descriptive sense.

RESULTS

Baseline Patient Characteristics and Short-term Outcomes After PD

During the study period, 3953 PDs were performed and 120 patients (3%) underwent postoperative CPLP. Specific details regarding the entire cohort of 3953 patients have been published recently.[6] The median age of the 120 CPLP patients was 68 years (IQR, 61–74 years) and most patients were men [n = 83 (69%)]. The median body mass index was 27 kg/m^2 (IQR, 24–30 kg/m^2) and the vast majority of patients were classified American Society of Anesthesiologists II and III (97%) before PD. The most common indication for PD was pancreatic adenocarcinoma [n = 43 (36%)], followed by intraductal papillary mucinous neoplasm [n = 15 (12%)], distal cholangiocarcinoma [n = 13 (11%)], periampullary carcinoma [n = 12 (10%)], chronic pancreatitis [n = 11 (9%)], serous and mucinous cystic neoplasms [n = 9 (8%)], and neuroendocrine tumors [n = 7 (6%)]. Regarding the underlying diagnosis for PD, patients with distal cholangiocarcinoma had the highest rate of CPLP (18.6%) followed by serous and mucinous cystic neoplasms (7.7%), other indications (6.4%), neuroendocrine tumors (3.8%), and intraductal papillary mucinous neoplasm (3.5%). Of the 1901 patients with pancreatic ductal adenocarcinoma, 43 had to undergo CPLP (2.3%). Seventy-three patients (61%) underwent pylorus-preserving PD, 32 (27%) pylorus-resecting PD, and 15 (12%) a classic Whipple procedure. Fourteen patients (12%) had venous, 16 (13%) multivisceral, and 2 (2%) arterial resections along with PD. The median operation time of PD was 358 minutes (IQR, 310–434 minutes) and the median blood loss 1000 mL (IQR, 800–1600 mL). Detailed patient characteristics are shown in Table 1.

Of the 120 patients undergoing CPLP, 102 patients (85%) developed POPF and 23 patients (19%) bile leakage after PD. Based on histopathology, acute pancreatitis was diagnosed in 105 patients (88%), including 57 patients (48%) with edematous and 48 (40%) with necrotizing PPAP. Characteristic histopathologic findings of patients with acute pancreatitis and acute necrotizing pancreatitis are shown in Figure 1. PPH occurred in 51 patients (42%). Thirty-five patients had percutaneous CT-guided drain placement for intra-abdominal fluid collections before CPLP and POPF was found in 32 (91%) of these 35 patients. Microbiology was positive in all 35 specimens. Following PD, clinical deterioration of the patients' condition required admission to the intensive care unit in 82 patients (68%) before CPLP. Thirty-three patients (28%) were re-intubated for respiratory failure, and 35 patients (29%) were dependent on catecholamines for cardiocirculatory failure. Fifty-seven patients (48%) developed single-organ failure and 30 patients (25%) had multiple-organ failure. Details on perioperative parameters before and during CPLP and postoperative short-term outcomes after CPLP are shown in Table 2.

Intraoperative Findings During CPLP and Outcomes of CPLP

CPLP was performed after a median of 10 days (IQR, 6–15 days). The median reoperation time was 165 minutes (IQR, 130–235 minutes) and the median blood loss during CPLP was 1450 mL (IQR, 500–3000 mL). Ninety-four patients (78%) needed an intraoperative blood transfusion and the median number of packed red blood cells was 3 (IQR, 1–8). Intraoperative findings that required CPLP included acute necrotizing pancreatitis [n = 47 (39%)], PPH [n = 41 (34%)], and uncontrollable leakage of the

TABLE 1. Characteristics of Patients Undergoing PD

Parameters	Entire Patient Cohort (N = 3953)	All Patients (N = 120)	Acute Necrotizing Pancreatitis (n = 47)	Pancreaticojejunostomy Leakage (n = 23)	PPH (n = 41)	Other Reasons (n = 9)	*P*
Sex							0.094
Male	2283 (58)	83 (69)	33 (70)	18 (78)	29 (71)	3 (33)	
Female	1670 (42)	37 (31)	14 (30)	5 (22)	12 (29)	6 (67)	
Age (y)	64 (55–72)	68 (60–74)	68 (61–74)	69 (64–78)	65 (55–73)	70 (60–75)	0.241
ASA classification							0.221
ASA I	140 (3.8)	2 (2)	1 (2)	1 (5)	0 (0)	0 (0)	
ASA II	2198 (59)	52 (45)	23 (52)	6 (27)	20 (49)	3 (33)	
ASA III	1378 (37)	60 (52)	20 (45)	15 (68)	20 (49)	5 (56)	
ASA IV	14 (0.4)	2 (2)	0 (0)	0 (0)	1 (2)	1 (11)	
Missing	223	4	3	1	0	0	
BMI (kg/m^2)		27 (24–30)	28 (25–30)	26 (24–30)	27 (24–29)	25 (22–27)	0.145
<25	1983 (52)	38 (32)	14 (30)	8 (35)	12 (29)	4 (44)	
25 to ≤ 30	1311 (34)	55 (46)	20 (43)	10 (43)	20 (49)	5 (56)	
≥ 30	406 (11)	27 (22)	13 (28)	5 (22)	9 (22)	0	
Missing	121 (3)	0	0	0	0	0	
Neoadjuvant therapy	325 (8)	11 (9)	1 (2)	1 (4)	7 (17)	2 (22)	0.039
Histology							0.048
Pancreatic carcinoma	1901 (48)	43 (36)	13 (28)	6 (26)	18 (44)	6 (67)	
Periampullary carcinoma	523 (13)	12 (10)	3 (6)	2 (9)	7 (17)	0 (0)	
IPMN	423 (11)	15 (12)	9 (19)	1 (4)	5 (12)	0 (0)	
NET	184 (5)	7 (6)	1 (2)	2 (9)	4 (10)	0 (0)	
SCN/MCN	117 (3)	9 (8)	6 (13)	3 (13)	0 (0)	0 (0)	
Distal cholangiocarcinoma	70 (2)	13 (11)	7 (15)	5 (22)	1 (2)	0 (0)	
Chronic pancreatitis	579 (15)	11 (9)	5 (11)	1 (4)	4 (10)	1 (11)	
Other	156 (4)	10 (8)	3 (6)	3 (13)	2 (5)	2 (22)	
Pancreatoduedenectomy							0.163
Pylorus preserving	2667 (68)	73 (61)	29 (62)	12 (52)	27 (66)	5 (56)	
Pylorus resecting	768 (19)	15 (12)	5 (11)	1 (4)	6 (15)	3 (33)	
Classic Whipple	518 (13)	32 (27)	13 (28)	10 (43)	8 (20)	1 (11)	
PD+venous resection	712 (18)	14 (12)	7 (15)	1 (4)	3 (7)	3 (33)	0.017
PD+multivisceral resection	425 (11)	16 (13)	5 (11)	6 (26)	2 (5)	3 (33)	
PD+arterial resection	39 (1)	2 (2)	0 (0)	0 (0)	2 (5)	0 (0)	
Estimated blood loss(mL)	650 (400–1000)	1000 (800–1600)	1000 (700–1700)	1200 (850–1500)	1000 (700–1500)	1700 (1450–2850)	0.033
Operation time (min)	325 (275–390)	358 (310–434)	346 (310–415)	375 (330–440)	355 (280–448)	340 (330–427)	0.594

Data refer to the time of PD and not to the time of CPLP; all values are median (IQR) and n (%).

ASA indicates American Society of Anesthesiologists; BMI, body mass index; IPMN intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumor; SCN, serous cystic neoplasm.

pancreaticojejunostomy [n = 23 (19%)]. Nine patients (8%) underwent CPLP for other reasons, which included iatrogenic rupture of a soft pancreatic remnant during relaparotomy (n = 1) and early postoperative celiac axis occlusion/thrombosis with consecutive ischemia of the liver, stomach, and/or pancreas (n = 8). In 1 patient with acute necrotizing pancreatitis, the main indication for CPLP was severe bleeding. Histopathology confirmed acute necrotizing pancreatitis of the pancreatic remnant in all 48 patients with intraoperative diagnosis of acute necrotizing pancreatitis. Acute pancreatitis was diagnosed in another 57 patients. The rate of CPLP increased over the years from 1.5% before 2011 to 4.1% after 2010 (Supplemental Digital Content Table 1, http://links.lww.com/SLA/D852) and CPLP was performed earlier in the postoperative course after PD. The median time from PD to CPLP was 12 days before 2011 and 9 days after 2010. The 30- and 90-day mortality rates after CPLP were 21% and 37%, respectively. The 90-day mortality rate decreased from 63% before 2011 to 30% after 2010 (Supplemental Digital Content Table 1, http://links.lww.com/SLA/D852). Stratified by indication for CPLP, patients undergoing CPLP for PPH (n = 41) had the highest 90-day mortality rate (46%) and all but 1 of these 41 patients had POPF (98%) and 82% had PPAP. The 90-day mortality rate of patients undergoing CPLP for necrotizing PPAP was 28%. The vast majority of patients with acute necrotizing pancreatitis also had POPF (83%). Uncontrollable leakage of the pancreaticojejunostomy as the main indication for CPLP was associated with a 90-day mortality rate of 39%. Of the 102 patients with POPF, 91 patients also had PPAP (89%).

Postoperative Serum and Drain Amylase Levels After PD

Serum amylase levels in the early postoperative course after PD have been shown to be associated with both PPAP and POPF. Stratified by reason for CPLP, median serum amylase levels on postoperative day (POD) #1 after PD were highest in patients with necrotizing PPAP [537 U/L (IQR, 333–693 U/L)] followed by patients with uncontrollable leakage of the pancreatic anastomosis

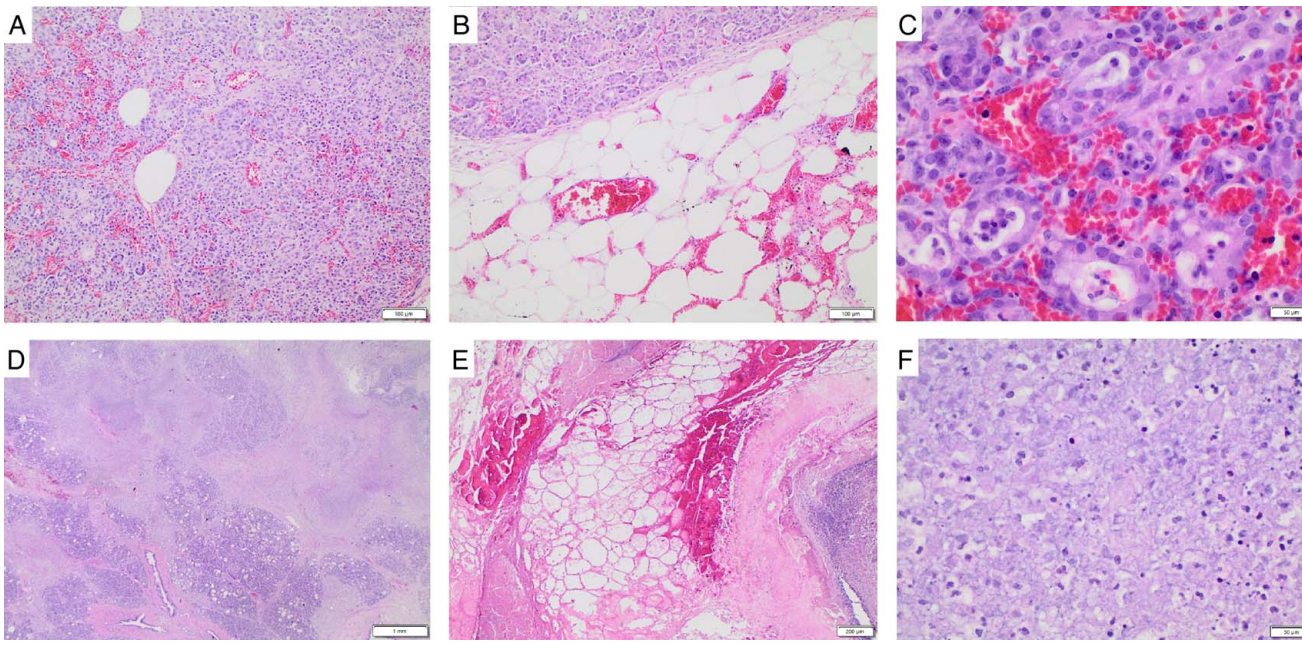

FIGURE 1. Histopathology of pancreatitis in CPLP specimen. A–C, Acute pancreatitis was characterized by interstitial edema, diffuse hemorrhage both in the parenchyma and peripancreatic adipose tissue and peripherally accentuated infiltration of neutrophilic granulocytes. D–F, In necrotizing pancreatitis, patchy areas of confluent parenchymal necrosis were noted with abundant cell debris surrounded by loosely packed neutrophilic aggregates and extensive fat necrosis. Original magnifications: A, B: ×100; C, F: ×400; D: ×12.5; E: ×40.

[287 U/L (IQR, 145–370 U/L)], patients with PPH [243 U/L (IQR, 82–368 U/L)], and patients undergoing CPLP for other reasons [29 U/L (IQR, 14–141 U/L)]. Drainage amylase levels on POD#1 were also highest in patients with acute necrotizing pancreatitis [5187 U/L (IQR, 1479–9289 U/L)] followed by patients with uncontrollable leakage of the pancreaticojejunostomy [1910 U/L (IQR, 524–2670 U/L)], patients with PPH [1506 U/L (IQR, 333–2911 U/L)] and patients with CPLP for other reasons [6 U/L (IQR, 5–7 U/L)]. Laboratory parameters are summarized in Table 3.

DISCUSSION

To our knowledge, this is the largest single-center study investigating the sequalae of postoperative complications requiring CPLP after PD. Herein, not only clinical parameters before CPLP and intraoperative findings during CPLP were used to assess the indications for CPLP, but also histopathology of the resected pancreatic remnants. Only very few patients (3%) needed CPLP after PD in our study cohort. The vast majority of patients with complicated postoperative courses after PD could be managed using conservative interventional measures or limited surgical procedures. Necrotizing PPAP and POPF complicated by either uncontrollable leakage of the pancreatic anastomosis or bleeding were the 2 most important indications for CPLP. Our finding that most patients with the need for CPLP developed both PPAP (88%) and POPF (85%) in the postoperative course after PD suggests that the combination of PPAP and POPF is a highly dangerous scenario and may play a causative role leading to the deterioration of the patients' condition requiring CPLP.

Most studies reporting on CPLP refer to the complication management of severe POPF after PD.[8,11–13,24,25] Only few articles are available with a direct focus on CPLP and complications requiring CPLP after PD.[29–33] The rate of CPLP after PD reported in most studies was low ranging from 2.5% to 3.8%. Nentwich et al[29] published one of the most recent studies on CPLP. The authors analyzed 521 patients after Kausch-Whipple resections. Of these 521 patients, 20 patients (3.8%) had to undergo CPLP for damage control of postoperative complications. The mortality rate of CPLP was 55%. Indications for CPLP included leakage of the pancreaticojejunostomy leading to POPF in 14 patients, severe PPH in 6 patients and portal vein thrombosis in 1 patient. In 7 patients (35%), the clinical course was complicated by acute pancreatitis. The findings of this 521-patient series are basically comparable to ours. However, the authors did not use histopathologic examinations of the resected pancreatic remnants.[29] This may explain the relatively lower rate of PPAP in their analysis compared with our study. Farley et al[30] published outcomes of 17 patients undergoing CPLP in a cohort of 458 patients following PD. The CPLP and mortality rates were 3.7% and 24%, respectively. Indications for CPLP included leakage of pancreaticojejunostomy in 8 patients, acute pancreatitis in 7 patients, and bleeding in 1 patient. Similar to the study by Nentwich and colleagues, only intraoperative findings were used to assess PPAP.[30] Therefore, the rate of PPAP may have been underestimated and it remains unclear whether more patients undergoing CPLP had PPAP, for example, those patients with uncontrollable leakage of the pancreaticojejunostomy. Tamijmarane et al[31] published outcomes of 25 CPLP (3.6%) in 677 patients after PD (n = 599), distal or subtotal pancreatectomy (n = 78). The mortality rate was 57%. Indications for CPLP included POPF with or without peritonitis (n = 12), PPH (n = 5), and POPF with bleeding (n = 8). The authors reported that the pancreatic remnants were either inflamed or surrounded by inflamed or necrotic tissue. However, the exact rate and severeness of histologically diagnosed pancreatitis remain unclear.[31] Only Gueroult et al[32] reported specific details on POPF and PPAP. In

TABLE 2. Perioperative Data of Patients Undergoing CPLP and Short-term Outcomes After CPLP

Parameters	All Patients (N = 120)	Acute Necrotizing Pancreatitis (n = 47)	Pancreaticojejunostomy Leakage (n = 23)	PPH (n = 41)	Other Reasons (n = 9)	*P*
Findings directly before CPLP						
Intensive care unit preoperative	82 (68)	32 (68)	18 (78)	26 (63)	6 (67)	0.678
Reintubation preoperative	33 (28)	10 (21)	8 (35)	13 (32)	2 (22)	0.569
Catecholamine required preoperative	35 (29)	13 (28)	7 (30)	12 (29)	3 (33)	0.986
Blood loss	1450 (500–3000)	850 (500–1700)	900 (500–2000)	3800 (2800–6750)	500 (300–800)	< 0.001
Operation time	165 (130–235)	150 (120–215)	132 (110–200)	200 (155–280)	175 (137–240)	0.002
Packed red blood cells	3 (1–8.5)	2 (0–4)	2 (1–3)	10 (5–18)	1 (0–5)	< 0.001
Fresh frozen plasma	2 (0–8)	0 (0–2)	0 (0–3)	8 (5–15)	2 (0–4)	< 0.001
Days to CPLP	10 (6–15)	7 (4–11)	12 (8–20)	14 (9–20)	2 (1–3)	0.003
Intraoperative diagnosis during CPLP						
POPF	102 (85)	39 (83)	23 (100)	40 (98)	0 (0)	< 0.001
Bleeding	51 (42)	7 (15)	2 (9)	41 (100)	1 (11)	< 0.001
Bile leakage	23 (19)	12 (26)	1 (4)	9 (22)	1 (11)	0.167
Bowel fistula	22 (18)	12 (26)	3 (13)	6 (15)	1 (11)	0.433
Acute pancreatitis	57 (48)	0	19 (83)	33 (80)	5 (56)	< 0.001
Acute necrotizing pancreatitis	48 (40)	47 (100)	0	1 (2)	0	< 0.001
Peritonitis	68 (57)	36 (77)	13 (57)	17 (41)	2 (22)	< 0.001
Single-organ failure	57 (48)	22 (47)	10 (43)	20 (49)	5 (56)	0.963
Multiple-organ failure	30 (25)	12 (26)	6 (26)	10 (24)	2 (22)	0.996
Intraoperative findings during CPLP						
Packed red blood cells	14 (8–29)	11 (6–24)	10 (5–37)	26 (15–39)	12 (8–13)	0.018
Fresh frozen plasma	10 (3–18)	5.5 (0–12)	4 (0–12)	19 (11–37)	10 (4–11)	0.002
Albumin	3 (0–12)	5 (0–17)	1 (0–4)	3 (0–9)	5 (1–11)	0.800
ICU	9 (4–21)	12 (4–27)	9.5 (4–26)	8 (3–14)	4 (4–6)	0.125
IMC	8 (4–17)	10 (5–20)	6.5 (3–17)	8 (3–16)	5 (2–11)	0.229
Length of hospital stay	42 (23–63)	52 (31–80)	46 (23–57)	36 (22–61)	30 (9–43)	0.245
30-d mortality	25 (21)	4 (9)	4 (17)	14 (34)	3 (33)	0.021
90-d mortality	44 (37)	13 (28)	9 (39)	19 (46)	3 (33)	0.334

Data refer to the time of CPLP and not to the index procedure (PD); all values are median (IQR) and n (%).
ICU indicates intensive care unit; IMC, intermediate care unit.

their cohort of 282 patients undergoing PD, 7 patients (2.5%) had complications requiring CPLP. Another patient with the need for CPLP, who was transferred from another hospital, was also included in the analysis. Three of these 8 patients died (38%). The authors found a high prevalence of both POPF and PPAP. The reasons for CPLP included leakage of the pancreaticojejunostomy (100%) in combination with peritonitis and/or acute pancreatitis (87.5%). In 2 patients, necrotizing pancreatitis was found during CPLP.[32] When analyzing outcomes reported in the latter studies, it is intriguing that even though the authors of these studies were well aware of PPAP following PD, most of them concluded that leakage of the pancreatic anastomosis with either bleeding or sepsis were the most important indications for CPLP. The role of PPAP in these patients was not further evaluated or commented. In our cohort of 3953 patients, 120 patients had to undergo CPLP for postoperative complications and most patients had both POPF (85%) and PPAP (88%). The most frequent indication for CPLP was necrotizing PPAP. There is no doubt that POPF complicated by uncontrollable leakage of the pancreatic anastomosis or bleeding is among the most feared complications in pancreatic surgery. However, the role of PPAP in this scenario remains to be elucidated. Further data from high-quality (randomized controlled) studies are warranted to improve our understanding of PPAP in context with POPF.

Furthermore, it is also important to anticipate that the quality of conservative treatment measures such as interventional radiologic abdominal drain placement to address intra-abdominal fluid collections resulting from pancreatic leakage as well as angiographic coiling and/or stenting of arteries to control erosional bleeding complications have to be considered when comparing outcomes of patients with POPF, PPH, and/or PPAP and the prevalence of CPLP.

In a recent multicenter cohort study and meta-analysis, Groen et al[33] compared pancreas-preserving procedures and CPLP in patients undergoing relaparotomy for POPF. There were 786 patients (16%) with grade B/C POPF in 4877 patients after PD. Relaparotomy for POPF was performed in 162 patients (3%) including mostly pancreas-preserving procedures [n = 126 (78%)] such as surgical drainage (n = 80), repair of the pancreatic anastomosis (n = 20), disconnection of the pancreatic anastomosis with preservation of the pancreatic remnant (n = 21), and redo of the pancreatic anastomosis (n = 5). CPLP was performed in only 36 patients (22%). In another 10 patients with a primarily pancreas-preserving approach, CPLP had to be performed secondarily in an additional operation. The mortality rate of patients undergoing CPLP was found to be higher (56%) in comparison to pancreas-preserving procedures (32%). Patients undergoing CPLP more often had single-organ or multiple-organ failure 24 h before relaparotomy. In the multivariable analysis, CPLP was associated with fatal outcome (adjusted odds ratio, 2.55; 95% confidence interval, 1.07–6.08; $P = 0.035$). In addition, the authors performed a systematic review and meta-analysis and identified 35 studies which reported on patients

TABLE 3. Laboratory Parameters After PD

Parameters	All Patients (N = 120)	Acute Necrotizing Pancreatitis (n = 47)	Pancreaticojejunostomy Leakage (n = 23)	PPH (n = 41)	Other Reasons (n = 9)	*P*
CRP (mg/dL)						
POD#1 CRP (mg/L)	105 (75–148)	118 (77–161)	113 (91–152)	94 (61–132)	75 (60–128)	0.101
POD#2 CRP (mg/L)	185 (151–239)	205 (171–268)	168 (146–204)	183 (148–234)	145 (115–173)	0.020
POD#4–5 CRP (mg/L)	209 (147–276)	242 (196–305)	160 (139–248)	189 (130–269)	99 (90–181)	0.010
Missing POD#1	11	2	3	6	0	
Missing POD#2	18	7	4	6	1	
Missing POD#4/5	5	1	2	2	0	
Amylase POD#1 (U/L)	330 (128–568)	537 (333–693)	287 (145–370)	243 (82–368)	29 (14–141)	< 0.001
> 53	97 (91)	42 (98)	19 (95)	33 (89)	3 (43)	< 0.001
> 159	73 (68)	37 (86)	14 (70)	21 (57)	6 (86)	< 0.001
Missing	13	4	3	4	2	
Drainage Amylase (U/L)POD#1 (U/L)	2157 (907–7026)	5187 (1479–9289)	1910 (524–2670)	1506 (333–2911)	6 (5–7)	0.023
Missing	73	26	17	23	7	

Data refer to the time of PD; all values are median (IQR).
CRP POD#4/5: The higher value on either day 4 or 5 is shown.
CRP indicates C-reactive protein; POD, Postoperative day.

undergoing relaparotomy for POPF after PD. Thirty-two studies and their own study were included in the meta-analysis comprising 745 patients who had undergone relaparotomy following PD. The mortality rates ranged from 0% to 100% and CPLP was associated with death (odds ratio, 1.99; 95% confidence interval, 1.03–3.84; $P = 0.004$). The authors concluded that a pancreas-preserving procedure seems preferable to CPLP in patients undergoing relaparotomy for POPF after PD.[33] One of the main problems with these previous data on the role of CPLP in the treatment of POPF is that most studies are small retrospective cohort series with a high risk of selection bias. The decision to perform CPLP instead of a pancreas-preserving procedure is depending on the patients' condition before and during relaparotomy and on the intraoperative findings. To assume that both pancreas preservation and CPLP were equivalent options is highly unlikely. Most surgeons will consider CPLP only in those patients without other surgical options and vice versa will consider pancreas-preserving procedures such as redo of the pancreatic anastomosis only in those patients with fairly good intraoperative conditions. Therefore, comparison of the 2 patient cohorts (namely those undergoing relaparotomy with pancreas-preserving procedures and those undergoing CPLP) is at least limited or even not possible.

Early identification of patients with deleterious postoperative courses might be helpful to improve outcomes. An increase in early postoperative serum amylase levels on POD#0 to #2 has been shown to be associated with PPAP. Most articles on PPAP used the definition of PPAP published by Connor in 2016.[34] However, the prevalence of PPAP reported from different centers using the Connor definition of PPAP was exceedingly high (> 50%) and suggests an overestimation of PPAP after PD.[14,18,35,36] Thus far, virtually no data are available on the cutoff levels of postoperative serum amylase for reliable diagnosis of postpancreatectomy acute necrotizing pancreatitis. Serum amylase levels were highest in patients with acute necrotizing pancreatitis [537 U/L (IQR, 333–693 U/L)]. Therefore, serum amylase on POD#1 might be helpful to identify patients at risk of developing PPAP. However, a reliable cutoff needs to be determined in further studies. We used histopathology to confirm PPAP which theoretically represents the gold standard. However, this diagnostic modality is only possible in the case of resection of the pancreatic remnant in CPLP.

This study has limitations. The limitations originate from the study design, being a single-center study from a highly specialized pancreatic surgery institution. This limits the generalizability of our results. Further studies (eg, prospective multicenter trials) are needed to validate our data. Given the retrospective study design and the long study period, there may be some heterogeneity in indications for PD, extent of resection, and complication management after PD, especially of PPAP, POPF, and PPH. Indeed, pancreatic ductal adenocarcinoma as an indication for PD decreased from 45% before 2014 (n = 22) to 30% after 2013 (n = 21). Moreover, the extent of resection including venous, multivisceral, and arterial resections increased during the study period from 16% (2001–2004) to 29% (2017–2019). The median time from PD to CPLP decreased from 12 days before 2011 to 9 days after 2010. Nonetheless, the study cohort should reliably represent the postoperative complication management after PD in daily practice in other national and international pancreas centers.

Our finding that only very few patients (3%) have to undergo CPLP suggests that conservative, interventional and pancreas-preserving surgical measures are the mainstay of complication management after PD. The sequelae of adverse postoperative events requiring CPLP seem to evolve mostly from the combination of postpancreatectomy acute (necrotizing) pancreatitis with POPF. Early identification of these patients with laboratory parameters and timely use of CT imaging may help to improve outcomes of this subgroup of patients. Postoperative serum amylase levels are highly elevated in patients with postpancreatectomy acute necrotizing pancreatitis and could therefore be useful to identify those patients. However, further studies are warranted to better understand the role of PPAP in patients with adverse short-term outcomes after PD, especially in those patients with simultaneous POPF.

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