INTRODUCTION

To date, a pancreaticoduodenectomy (PD) still remains one of the most sophisticated procedures in visceral surgery. It is the standard procedure in cases of benign or malignant pancreatic head or periampullary duodenal lesions. Although the postoperative mortality has decreased to <5% within the last decades due to technical and medical advances, postoperative morbidity still remains high.1–3 Postoperative pancreatic fistulas (POPF) are present in 11%–16% of cases. They account for most of the complications and usually are treated conservatively.3–6

However, even experienced pancreatic surgery centers disclose relaparotomy rates of 5%–20%.7,8 The most severe complications are commonly induced by POPF leading to postoperative pancreatic hemorrhage (PPH), peritonitis and sepsis.5,9

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Pancreatic anastomotic leakages requiring revision surgery are defined as POPF grade C\textsuperscript{10}—a life-threatening complication and a nightmare for every pancreatic surgeon. Re-do procedures are associated with mortality rates of up to 50%.\textsuperscript{4,11,12} The aim of this retrospective study was to analyze the incidence, management, and outcome of patients with POPF grade C in the second largest pancreatic surgery center in Germany.

2 | MATERIALS AND METHODS

A chart review of our prospective data base was performed of all patients who underwent a pylorus-preserving PD (PPPD) or a PD between January 2007 and December 2016 in our high-volume pancreatic surgery center (St. Josef Hospital, Ruhr-University Bochum). Data of patients with insufficiency of the pancreatic anastomosis (pancreaticojejunostomy [PJ] or pancreaticogastrostomy [PG]) requiring revision surgery were analyzed and compared to the other patients. Clinicopathologic variables, laboratory values, operative notes, and hospital records were analyzed for all patients. This study was approved by the ethics committee of the Ruhr-University Bochum, Germany (permission no. 18-6497).

2.1 | Perioperative and operative management

All surgical procedures were performed by experienced pancreatic surgeons. Patients received preoperative antibiotic prophylaxis with 3rd generation cephalosporine + metronidazole or 2nd generation quinolone in the case of penicillin allergy. Subcutaneous Octreotide (200 µg, Sandostatin\textsuperscript{e}; Novartis) was administered preoperatively. The pancreatic duct diameter was measured on the pancreatic stump with a ruler intraoperatively. Two silicon drains were placed in all patients. One was placed next to the hepaticojejunostomy and the other next to the pancreatic anastomosis. Enzyme activity (lipase and amylase) in the drain output was measured every other day starting on postoperative day 3.

2.2 | Surgical technique of pancreaticojejunostomy

In our institution, the standard type of pancreatic anastomosis is a double layered end-to-side duct-to-mucosa PJ as described by Warren and Catell.\textsuperscript{13} The inner layer of the anastomosis is constructed by single sutures between the jejunal mucosa and the pancreatic duct using a non-absorbable 5-0 polypropylene suture. The outer layer is constructed by single sutures between the pancreatic parenchyma and capsule to the seromuscular layer of the jejunal loop using a 5-0 absorbable polydioxanone suture (Figure 1).

2.3 | Surgical technique of pancreaticogastrostomy

Mobilization of 3-4 cm of the pancreatic remnant is required prior to invagination into the stomach for the PG. The anterior wall of the stomach is incised by approximately 5 cm, followed by a 2-cm transgastric incision of the posterior stomach wall. A purse-string suture using 2-0 polydioxanone is prepared at the posterior wall of the stomach before the pancreatic remnant is pulled through the posterior incision. Once the pancreas is positioned 1.5-2.0 cm above the incision in the stomach, gastric seromuscular—pancreatic capsule—sutures using 4-0 polydioxanone can be placed. Afterwards the purse-string suture is tightened to secure the pancreatic anastomosis. Finally, the anterior wall of the stomach is closed with a continuous double layered 4-0 polydioxanone suture.

2.4 | Postoperative pancreatic fistula

First published in 2005 by the International Study Group of Pancreatic Fistula (ISGPF), the definition of POPF was amended and republished in 2017.\textsuperscript{10} A drain output of any measurable fluid volume with an amylase level...
greater than three times the upper limit of the institutional normal serum amylase activity is considered a POPF. Biochemical leaks formerly known as POPF grade A do not have a clinical impact and are no longer considered a complication. POPF grade B require antibiotic treatment due to infection without organ failure or requirement of angiographic, percutaneous or transgastric interventional treatments. POPF grade C involve organ failure, revision surgery or death.

2.5 | Clavien-Dindo classification

Complications were classified according to the definition by Clavien and Dindo.14 Any deviation from the normal clinical course which could be treated conservatively was considered a minor complication (Clavien-Dindo ≤2). Major complications grade 3a required treatment under regional anesthesia involving interventional placement of drains, coils, or stents. Complications ≥3b at least required surgical revision and

| TABLE 1 | Demonstration of patient characteristics of all patients and patients with POPF C. Comparison of patient characteristics between patients with and without POPF |
|---|---|---|
| | All patients | POPF C | P-valuea |
| Total, n (%) | 722 (100%) | 23 (3.19%) |
| Age, mean ± SD (range), y | 61 ± 13 (14-86) | 63 ± 14 (37-85) | .397 |
| Sex, n (%) | | | .254 |
| Male | 367 (50.8%) | 9 (39.1%) |
| Female | 355 (49.2%) | 14 (60.9%) |
| Diagnosis,b n (%) | | | |
| Benign tumor | 91 (12.6%) | 3 (13.0%) |
| Malignant tumor | 454 (62.9%) | 12 (52.2%) |
| Chronic pancreatitis | 216 (29.9%) | 8 (34.8%) |
| Pancreas divisum | 9 (1.2%) | 1 (4.3%) |
| Autoimmune pancreatitis | 5 (0.7%) | 0 (0%) |
| Other | 8 (1.1%) | 0 (0%) |
| Preoperative stenting of the CBD,c n (%) | 384 (53.2%) | 12 (52.2%) | .893 |
| Protein level (66-87 g/L), mean ± SD | 68 ± 7 | 69 ± 6 | .211 |
| ASA score, n (%) | | | |
| I | 122 (16.9%) | 0 (0%) | .070 |
| II | 339 (47.0%) | 14 (60.9%) |
| III | 232 (32.1%) | 9 (39.1%) |
| IV | 29 (4.0%) | 0 (0%) |
| V | 0 (0%) | 0 (0%) |
| Additional potential risk factors, n (%) | | | |
| Diabetes mellitus | 199 (27.6%) | 6 (26.1%) | .872 |
| Cardiovascular diseases | 373 (51.7%) | 18 (78.3%) | .009 |
| Smoking | 196 (27.1%) | 5 (21.7%) | .551 |
| Alcohol consumption | 112 (15.5%) | 4 (17.4%) | .770 |
| Exocrine pancreatic insufficiencyd | 242 (33.5%) | 2 (8.7%) | .012 |
| Past abdominal surgical history | 429 (59.4%) | 14 (60.9%) | .885 |
| Body mass index, mean ± SD, kg/m² | 24 ± 4 | 25 ± 4 | .088 |

aUnivariate analysis.

bSome patients had multiple diagnoses.

cCommon bile duct.

dDefined as a fecal elastase concentration ≤ 200 µg/g.

Bold value indicates statistically significant result.
could be associated with single/multiorgan failure (4a, 4b) or patient demise (grade 5).

2.6 Statistical analysis

Data were expressed as percentages, mean ± standard deviation (SD) or median with interquartile range. The comparison of patients with POPF grade C requiring revision surgery with the other patients was performed using a two-tailed chi-squared test, a Fisher’s exact test, or a Mann-Whitney U test, as appropriate. A multivariate analysis was performed using a logistic regression model to identify risk factors of a POPF grade C for all variables being significant in univariate analysis. Statistical significance was present in the case of P-values < .05. Statistical analysis was performed with SPSS 21.0 (IBM Corp.).

3 RESULTS

3.1 Patient characteristics

In the study period, 722 patients underwent a PPPD or a PD (Table 1). POPF grade C was detected in 23 patients (3.19%). Mean age was 61 ± 13 years (14-86) in the entire cohort and 63 ± 14 years (37-85) in the POPF C group. The overall male to female ratio was 367 (50.8%)/355 (49.2%) without significant differences compared to the POPF C group. The most common indications for surgery were...
### Table 3

Demonstration of postoperative outcome of all patients and patients with POPF C. Comparison of patient characteristics between patients with and without POPF

|                          | All patients | POPF C | P-value<sup>a</sup> |
|--------------------------|--------------|--------|----------------------|
| **Hospital stay, mean ± SD (range), d** |              |        |                      |
| Total                    | 26 ± 16 (4-243) | 51 ± 19 (16-101) | <.000001 |
| Postoperative            | 21 ± 15 (4-239) | 46 ± 20 (15-99)  | <.000001 |
| **Complications, n (%)** |              |        |                      |
| All patients with complications | 395 (54.7%) | 23 (3.19%) | <.000001 |
| Non-surgical             | 194 (26.9%) | 17 (73.9%) | <.000001 |
| Surgical                 | 309 (42.8%) | 23 (100%) |                      |
| **Clavien-Dindo, n (%)** |              |        |                      |
| ≤II                      | 209 (67.6%) | 0 (0%)  | <.000001 |
| III a                    | 25 (8.1%)   | 0 (0%)  |                      |
| III b                    | 32 (10.4%)  | 11 (47.8%) |                      |
| IV a                     | 27 (8.7%)   | 2 (8.7%) |                      |
| IV b                     | 2 (0.6%)    | 1 (4.3%) |                      |
| V                        | 14 (4.5%)   | 9 (39.1%) |                      |
| **POPF<sup>b</sup>, n (%)** |              |        |                      |
| Total                    | 125 (17.3%) |        |                      |
| Biochemical leak         | 20 (2.8%, 16% of POPF) |              | |
| Grade B                  | 82 (11.4%, 65.6% of POPF) |              | |
| Grade C                  | 23 (3.2%, 18.4% of POPF) |              | |
| **Secondary complications** |            |        |                      |
| Postoperative pancreatic hemorrhage | 54 (7.5%) | 18 (78.3%) | <.000001 |
| Delayed gastric emptying | 129 (17.9%) | 8 (34.8%) | .032 |
| Abscess/abdominal fluid collection | 104 (14.4%) | 8 (34.8%) | .005 |
| Bile leak                | 35 (4.8%)   | 3 (13.0%) | .096 |
| Wound infection          | 41 (5.7%)   | 5 (21.7%) | .001 |
| **Radiologic intervention, n (%)** |            |        |                      |
| Total                    | 41 (5.7%)   | 4 (17.3%) | .036 |
| Percutaneous drainage or puncture | 32 (78%) | 1 (25%) |                      |
| Coiling or stenting      | 9 (22%)     | 3 (75%)  |                      |
| **Readmission on ICU<sup>c</sup>** |            |        |                      |
| Total, n (%)             | 59 (8.2%)   | 19 (82.6%) | <.000001 |
| On postoperative day     | 10 ± 9 (1-54) | 10 ± 5 (3-21) | .129 |
| **Relaparotomy<sup>d</sup>** |            |        |                      |
| Total                    | 47 (6.5%)   | 23 (100%) | <.000001 |
| Postoperative day        | 15 ± 19 (1-91) | 12 ± 9 (1-45) | .983 |
| **Surgical procedure**   |              |        |                      |
| Remnant pancreatectomy ± SE | 24 (51.1%) | 19 (82.6%) | |
| Reconstruction of the PJ | 3 (6.3%)    | 3 (13.0%) | |
| Reconstruction of the HJ | 12 (25.5%)  | 3 (13.0%) | |
| Suturing of the PJ       | 1 (2.1%)    | 1 (4.3%)  | |
| Reconstruction of the GJ | 1 (2.1%)    | 0 (0%)    | |
| Other                    | 14 (29.8%)  | 3 (13%)   | |

(Continues)
malignant lesions (62.9%), followed by chronic pancreatitis (29.9%) and benign tumors (12.6%). Half of the patients in both groups were treated preoperatively by stenting of the common bile duct. Protein levels were normal in both groups. Most patients were classified as American Society of Anesthesiologists level II or III (47 and 32.1%, respectively). Cardiovascular diseases could be identified as an independent risk factor for POPF grade C in uni- and multivariate analysis ($P < .05$, Tables 1 and 4). They were present in 78.3% of the POPF C group and in 51.7% of the entire cohort. Exocrine pancreatic insufficiency seemed protective against the development of a POPF grade C ($P = .012$) in univariate analysis. Only two patients (8.7%) diagnosed with preoperative exocrine pancreatic insufficiency developed a POPF grade C. The mean prevalence was 33.5% of 722 patients. Diabetes mellitus, smoking, alcohol consumption, past abdominal surgical history, and body mass index could not be identified as risk factors for a POPF grade C.

3.2 | Intraoperative data

PPPD was the dominating procedure performed in 645 patients (89.3%) whereas 77 patients (10.7%) underwent a PD (Table 2). There was no significant difference in the occurrence of POPF grade C between PPPD and PD ($P = .727$). A PJ was constructed in 708 patients (98.1%) and a PG in 14 patients (1.9%). POPF grade C occurred in 22 patients with a PJ (3.11%) and in one patient with a PG (7.14%). Multivisceral resections were performed in 65 patients (9%). None of them suffered a POPF grade C. The mean pancreatic duct diameter was 5.41 mm in the entire population, while it was 3.26 mm in the study group. Patients with POPF grade C had significantly smaller pancreatic duct diameters ($P = .001$) in univariate analysis. Soft pancreatic texture was also significantly more common in patients with POPF grade C in univariate analysis ($P = .00002$). Multivariate analyses are demonstrated in Table 4. Modified single-loop reconstruction according to Aghalarov et al$^{15}$ had no impact on the occurrence of POPF grade C. Intraoperative blood loss (mean $377 \pm 248$ mL), intraoperative blood transfusions (24 patients, 3.3%), and mean operative time (366 min) were not identified as risk factors. Mean blood loss was $377 \pm 248$ mL. It was documented in only 171 of the 722 patients, explaining the increased SD.

### Table 4

Multivariate analyses using binary logistic regression of variables with a $P$-value $< .05$ in univariate analysis

| Influencing variable for POPF C | $P$-value | Odds ratio (95% confidence level) |
|---------------------------------|-----------|----------------------------------|
| Cardiovascular diseases         | .032      | 3.068 (1.101-8.547)               |
| Exocrine pancreatic insufficiency | .161     | 0.343 (0.077-1.532)               |
| Pancreatic texture              | .014      | 1.964 (1.149-3.354)               |
| Pancreatic duct diameter (mm)   | .119      | 0.821 (0.640-1.052)               |

3.3 | Postoperative outcome

The total and postoperative hospital stay were significantly longer with POPF grade C (51 and 46 days vs 26 and 21 days, respectively; $P < .05$, Table 3). Complications occurred in 395 patients (54.7%); most of them were surgical complications (309 patients, 42.8%). Most patients with POPF grade C also suffered from non-surgical complications (309 patients, 42.8%). Most patients with POPF grade C also suffered from non-surgical complications (17/23, 73.9%; $P < .05$). While most complications were classified as Clavien-Dindo $\leq 2$ in the entire population, predominant forms of complications in the study population were Clavien-Dindo type $3b$ ($n = 11, 47.8\%$) and type $V$ ($n = 9, 39.1\%$). The overall rate of clinically relevant POPF was 14.6% ($n = 105$).

PPH occurred in 54 patients (7.5%) overall and in 18 patients (78.3%) in the POPF grade C group ($P < .05$). Also, delayed gastric emptying ($n = 8, 34.8\%$ vs $n = 129, 17.9\%$), abscess/intrabdominal fluid collection ($n = 8, 34.8\%$ vs $n = 104, 14.4\%$), and wound infection ($n = 5, 21.7\%$ vs $n = 41, 5.7\%$) occurred significantly more often in the study population ($P < .05$).
Radiologic interventions in terms of percutaneous drainage/puncture or angiographic coiling or stenting were also significantly more often required with POPF grade C (n = 4, 17.3%) than without it (n = 41, 5.7%).

Overall, readmission to an ICU ward was rarely required (n = 59, 8.2%). However, 82.6% of the patients with POPF grade C required readmission to the ICU after having been transferred to a normal ward.

The overall relaparotomy rate was 6.5% (n = 47). Every patient suffering from POPF grade C underwent relaparotomy (n = 23, 100%) on average on postoperative day 12 ± 9. The indications for relaparotomy were mostly POPF grade C, insufficiency of the hepaticojejunostomy, fulminant necrotizing pancreatitis, or hematomas/infections requiring wound revision. Preoperatively, patients with POPF grade C had significantly elevated pancreatic enzyme levels in the drainage fluid (mean: amylase 6441.91 U/L, lipase 15 686.73 U/L). Furthermore, the readmission rate was significantly higher in the study population (P < .05). Nearly every patient (13/14, 93%) surviving the complication required stationary readmission within 90 days of discharge. Last, the mortality rate was significantly higher in the study group. 21.7% of the patients (n = 5) with POPF grade C died within 30 days and 39.1% (n = 9) within 90 days. The most common cause of death was persistent sepsis with multiorgan failure. The mean postoperative time to reoperation for patients surviving a POPF grade C was exactly the same as for patients who died (postoperative day 11.7). Multivariate analysis using a binary logistic regression showed a significant association between mortality and POPF grade C (P = .000), postoperative pancreatic hemorrhages (P = .001) and non-surgical complications (P = .001).

### 3.4 Comparison of patients with POPF grade B and C

To discriminate the different impact of risk factors and outcomes between patients with POPF grade B and C, all

| Table 5 Comparison of patients with POPF B and POPF C |
|------------------------------------------------------|
| **Total (n)** | POPF B | POPF C | **P-value** |
|----------------|--------|--------|-------------|
| **ASA score** | | | | |
| I  | 11 (13.4%) | 0 (0%) | .074 |
| II | 50 (61.0%) | 14 (60.9%) | | |
| III | 20 (24.4%) | 9 (39.1%) | | |
| IV | 1 (1.2%) | 0 (0%) | | |
| **Cardiovascular diseases** | | | | |
| | 49 (59.8%) | 18 (78.3%) | .104 |
| **Exocrine pancreatic insufficiency** | | | | |
| | 15 (18.3%) | 2 (8.7%) | .272 |
| **Pancreatic texture** | | | | |
| Soft | 45 (54.9%) | 17 (73.9%) | .349 |
| Hard | 27 (32.9%) | 5 (21.7%) | | |
| Not specified | 10 (12.2%) | 1 (4.3%) | | |
| **Pancreatic duct diameter (mm, mean, standard deviation)** | 3.52 ± 2.67 | 3.26 ± 1.29 | .672 |
| **Postoperative hospital stay (d, range)** | 24 (11-121) | 46 (15-99) | <.001 |
| **Non-surgical complications** | 27 (32.9%) | 17 (73.9%) | <.001 |
| **Postoperative pancreatic hemorrhage** | 8 (9.8%) | 18 (78.3%) | <.001 |
| **Delayed gastric emptying** | 18 (22.0%) | 8 (34.8%) | .210 |
| **Abscess/Fluid formation** | 35 (42.7%) | 8 (34.8%) | .498 |
| **Wound infection** | 6 (7.3%) | 5 (21.7%) | .047 |
| **Radiologic intervention** | 13 (15.9%) | 4 (17.3%) | .860 |
| **Readmission to ICU** | 11 (13.4%) | 19 (82.6%) | <.001 |
| **Readmission within 90 d** | 17 (20.7%) | 13 (56.5%) | .001 |
| **Mortality** | | | | |
| Within 30 d | 1 (1.2%) | 5 (21.7%) | <.001 |
| Within 90 d | 2 (2.4%) | 9 (39.1%) | <.001 |

**Abbreviations:** ASA, American Society of Anesthesiologists; ICU, intensive care unit; POPF, postoperative pancreatic fistula.

**Bold value indicates statistically significant result.**
variables which showed a statistically significant difference in Tables 1-4 underwent a Mann-Whitney U test for comparison. A significant difference in univariate analysis was observed for the postoperative hospital stay, non-surgical complications, postoperative pancreatic hemorrhages, wound infections, readmission to an ICU, hospital readmission within 90 days of surgery, and the 30- and 90-day mortality ($P < .05$, Table 5).

4 | DISCUSSION

To this day, pancreatic surgery remains one of the most sophisticated surgical specialties. It is technically demanding, exhausting, and requires comprehensive anatomic and pathophysiologic knowledge and surgical skills.

Despite advances in surgical techniques and perioperative management within the last decades, the postoperative morbidity remains high with a complication rate of at least 45%.1‒3 While most postoperative complications such as POPF grade B or delayed gastric emptying can be treated conservatively, POPF grade C represent a nightmare for every pancreatic surgeon (Figures 2 and 3). According to the revised classification of the ISGPS, POPF grade C usually requires revision surgery (as in 100% of our cases) and are generally associated with a high level of morbidity and mortality.4,10 The mean postoperative hospital stay is significantly longer compared to regular cases (46 vs 21 days; $P < .05$). The mortality rate due to POPF grade C ranges between 36.7% and 50%4,11; this was confirmed by our data (39%). Nonetheless, only 9 of the 722 patients of our cohort died due to a POPF grade C (1.2%). The overall mortality rate was 2.6%.

Fortunately, the incidence of POPF grade C ranges between 3% and 5%, while the average occurrence rate of POPF is 11%-16%.3‒6,8,11 The incidence in our pancreatic surgery center was only 3.2%, which supports the recommendation that pancreatic surgery should only be performed in specialized centers where the level of expertise is higher.2,16

No type of pancreatic anastomosis, neither PJ nor PG, has shown any superiority in the literature. Several technical variations of the construction of a PJ have been proposed, also with no favorable results for any technique.2,17

Local inflammation due to leakage of the pancreatic anastomosis is induced by activated pancreatic enzymes on the one hand and simultaneous leakage of enteric bacteria on the other hand.18 Secondary complications such as PPH or delayed gastric emptying are typically associated with POPF3,9,19 as validated by our data ($P < .05$). PPH arise due to erosion of peripancreatic arteries such as the gastroduodenal stump or the hepatic arteries due to aggressive activated pancreatic enzymes. Delayed gastric emptying is a consequence of local inflammation due to activated pancreatic juice surrounding the small bowel and stomach. POPF are also associated with intraabdominal abscesses, wound infections, and need for radiologic interventions ($P < .05$).

Several factors which every pancreatic surgeon must know contribute to the development of a POPF. There are technical and perioperative factors on the one hand and patient related factors on the other hand.

As with intestinal anastomoses, an anastomosis between the pancreas and the jejunal limb/stomach must be constructed tightly. However, sutures must not be tied too vigorously but gently adapted to the various tissues (Figure 1). Especially pancreatic tissue is generally much softer than the small bowel and prone to be cut through by sutures tied too tightly. As a

**FIGURE 2** Intraoperative photos of patients who survived a POPF grade C. A, Semicircular insufficient pancreaticojejunostomy in a patient with secondary postoperative hemorrhage due to erosion bleeding from the peripancreatic vessels. The tip of the Overholt (O) forceps is placed in the formerly anastomosed jejunal loop (J). The white arrow demonstrates the main pancreatic duct of the subtotally exposed pancreatic remnant. B, Complete insufficiency of the pancreaticojejunostomy. The jejunal loop (J) with view of its lumen (L) and the pancreatic remnant (P) are held apart. The portal vein can be seen in between (V)
result, local ischemia of the small bowel/stomach or the pancreatic tissue with consecutive local necrosis and development of POPF can occur. The margins of the jejunal loop/stomach and pancreas must provide a good blood supply to guarantee sufficient healing. Thus, the jejunal loop must be relocated without any tension in the mesentery towards the pancreatic remnant. Only careful and subtle hemostasis should be applied in the region of the anastomosis to maintain sufficient blood supply.

Pre- and postoperative administration of a somatostatin analogue seems to decrease the perioperative morbidity but not the mortality. Further well-designed studies are required for a definitive statement of this matter.

In contrast to technical features on which the surgeon has an influence, patient related factors also contribute to the development of POPF. Soft pancreatic tissue, a small pancreatic duct diameter <3 mm and a body mass index ≥25 kg/m² have been described as independent risk factors for POPF.

Our data confirm that soft pancreatic tissue and a smaller pancreatic duct diameter are associated with POPF grade C. The mean diameter in the POPF grade C group was 3.26 mm in contrast to 5.41 mm in the entire group. 73.9% of the patients in the study group had a soft pancreatic texture vs 27.8% in the entire cohort. As a novelty, we observed that sicker patients with higher American Society of Anesthesiologists levels and specifically those suffering from cardiovascular disease were more likely to develop a POPF grade C. The latter might predispose to local hypoperfusion and anastomotic ischemia with resulting insufficiency.

In contrast, exocrine pancreatic insufficiency (EPI) has been proven to be significantly protective against POPF grade C in univariate analysis, most likely because these patients produce less aggressive pancreatic enzymes endangering the pancreatic anastomosis. Because EPI is significantly more common in patients with a hard pancreatic texture which correlates with a large pancreatic duct diameter, multivariate analysis did not show a significant correlation between EPI and POPF grade C.

The overall complication rate following PPPD or PD was 54.7%. The majority of those (75.7%) could be treated conservatively without requiring reoperation.

We did not observe a difference in the occurrence of POPF grade C between PJ and PG. However, of note, most of our patients underwent a PJ (n = 708, 98.1%).

73.9% of the patients with POPF grade C also suffered from non-surgical complications, which demonstrates that POPF grade C rarely come alone as stated before.

Risk factors for POPF have been investigated thoroughly as stated above. We further investigated differences between patients with POPF grade B and C (Table 5) and did not identify differences of classic risk factors such as soft pancreatic tissue or pancreatic duct diameter. However, the postoperative course is significantly more dramatic meaning a longer postoperative hospital stay, higher rates of ICU/hospital readmission and mortality as well as more association with postoperative pancreatic hemorrhages, non-surgical complications and wound infections.

All patients requiring reoperation had significantly elevated amylase and lipase levels in the drainage fluid (mean amylase level: 6441 U/L, lipase-level 15 686 U/L). In contrast to the ISGPF proposal, we suggest to not only test the amylase levels

| TABLE 6 | Obligate criteria for revision surgery with completion pancreatectomy in case of a POPF grade C |
|-----------------|---------------------------------------------|
| + Significant POPF (usually amylase levels >10 000 U/mL) |
| + Septic signs |
| Tachycardia |
| Catecholamine—requiring hypotension |
| Massive elevated inflammatory parameters |
| + Progressive abdominal pain |
| (+) Angiographic treatment failure with continuous intraabdominal bleeding |
| (+) Persistent sepsis with antibiotic treatment resistance and failure of transgastric drainage placement |
in the drainage fluid but also the lipase concentration which can be extremely elevated, also.\textsuperscript{10} Conservative treatment is always the first approach in case of a POPF. However, significant POPF combined with signs of sepsis such as tachycardia, catecholamine—requiring hypotension, massive elevated inflammatory parameters, and progressive abdominal pain are an indication for immediate reoperation (Table 6). Also, POPF combined with angiographic treatment failure to stop a bleed or with percutaneous/transgastric drainage treatment failure with persistent sepsis require a reoperation.\textsuperscript{10,12}

The mean time to reoperation in our cohort was the 12th postoperative day, which seems to be the most critical period in which special attention should be paid by the surgeon.

There are three reoperation strategies in cases of POPF grade C: suturing the leaky pancreatic anastomosis, renewal of the pancreatic anastomosis, or completion pancreatectomy. Pancreas-preserving techniques bear the risk of continuous POPF with associated complications such as sepsis, PPH, and re-relaparotomy. Completion pancreatectomy leads to direct insulin dependent diabetes mellitus and exocrine pancreatic insufficiency. While not statistically significant, our data show that the mortality rate was much higher with pancreas-preserving techniques in the form of renewal of the pancreatic anastomosis (2/3 patients, 67%). In comparison, only 7/19 (36.8%) patients died after completion pancreatectomy. Therefore, we propose completion pancreatectomy as the treatment of choice in cases of POPF grade C to keep postoperative morbidity and mortality rates low.

Regarding the updated ISGPS definition, POPF grade C is a rare complication following PPPD or PD; however, it is also one of the most feared complications due to the high level of morbidity and a mortality rate of nearly 40%. Completion pancreatectomy is the treatment of choice and must be initiated as quickly as possible to reduce local peritonitis and arrosion of the peripancreatic arteries.

**CONFLICT OF INTEREST**

None declared.

**AUTHOR CONTRIBUTIONS**

All authors meet the four criteria required for authorship defined by the guidelines of the International Committee of Medical Journal Editors (ICMJE).

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