https://doi.org/10.1016/j.hpb.2023.02.010 HPB

ORIGINAL ARTICLE

Outcome of combined pancreatic and biliary fistulas after pancreatoduodenectomy

Ilgar Aghalarov[1], Elisabeth Beyer[1], Jennifer Niescery[2], Orlin Belyaev[1], Waldemar Uhl[1] & Torsten Herzog[1]

[1]Department of General and Visceral Surgery, St. Josef Hospital, Ruhr University Bochum, Germany, and [2]Department of Anesthesiology, St. Josef Hospital, Ruhr University Bochum, Germany

Abstract

Background: Postoperative pancreatic fistula (POPF) as well as postoperative biliary fistula (POBF) are considered the main source of postoperative morbidity and mortality after pancreatoduodenectomy (PD). However, little is known about the incidence and complications of combined POPF/POBF compared to isolated POPF or POBF.

Methods: This single-center study investigated retrospectively the incidence and postoperative outcome of combined POPF/POBF compared to isolated fistulas following PD in a tertiary German pancreatic center between 2009 and 2018.

Results: A total of 678 patients underwent PD for benign and malignant periampullary lesions. Combined fistulas occurred in 6%, isolated POPF in 16%, and isolated POBF in 2%. Pancreatic ductal adenocarcinoma and chronic pancreatitis had a protective effect on the occurrence of combined fistulas, whereas serous cystadenoma and pancreatic metastasis were risk factors. Morbidity (Grade C fistula, post-pancreatectomy hemorrhage, revisional surgery) and mortality was significantly higher in patients with combined fistulas than in those with isolated fistula. Moreover, the duration of ICU stay was longer.

Conclusions: A combined POPF/POBF is associated with a significant increase of morbidity and mortality compared to isolated fistulas after PD. Early surgical revision in these patients may improve the postoperative survival rate.

Received 20 October 2022; accepted 13 February 2023

Correspondence

Ilgar Aghalarov, Department of General and Visceral Surgery, St. Josef Hospital, Ruhr University Bochum, Germany. E-mail: ilgar.aghalarov@klinikum-bochum.de

Introduction

Pancreatoduodenectomy (PD) is a well-established therapy to treat chronic pancreatitis, periampullary tumors, and other lesions of the pancreatic head. Furthermore, for malignant tumors multimodal therapy including R0 surgical resection offers a chance for cure. However, PD still carries a high risk of potentially life-threatening complications. Reasons for that are the technically demanding pancreatic and bile duct anastomoses, the corrosive secretions of both organs, and the topographical proximity to major blood vessels (e.g., major branches of the coeliac trunk or the superior mesenteric artery). Thus, although the surgical technique has improved and patients are preferably treated in highly specialized tertiary pancreatic centers, morbidity rates remain high (30–50%).[1,2] Besides the length of hospital stay and economic aspects, this is problematic especially for cancer patients, as it delays the beginning of an adjuvant therapy and worsens quality of life.

Postoperative organ fistula is a significant source of morbidity. The incidences of the postoperative pancreatic fistula (POPF) and the postoperative biliary fistula (POBF) after PD are 9–21% and 4–12%, respectively. Both fistulas are associated with sepsis, multi-organ failure, bleeding, and death. However, a leakage of the pancreaticoenteric anastomosis is probably the most feared complication, as it may cause life-threatening post-pancreatectomy hemorrhage (PPH).[1–6] Thus, in highly specialized German hospitals the mortality after pancreatic resections is still 6.5%, while it is 11.5% in less specialized hospitals.[7]

Few authors mentioned the simultaneous presence of POPF and POBF after PD.[2,8,9] It can be assumed that a combined fistula is associated with higher morbidity and mortality rates than an isolated POPF or POBF, however, this has – to the best of our knowledge – not yet been analyzed. Thus, the presented retrospective single-center study investigated the incidence, morbidity and mortality of combined pancreatic and biliary fistulas

Please cite this article as: Aghalarov I et al., Outcome of combined pancreatic and biliary fistulas after pancreatoduodenectomy, HPB, https://doi.org/10.1016/j.hpb.2023.02.010

compared to isolated POPF or POBF after PD in a German tertiary pancreatic center. Potentially predisposing factors were additionally evaluated.

Methods

This retrospective single center study was performed at a German University hospital between 2009 and 2018. It was approved by the local Ethics committee of the Ruhr University Bochum (No.17-6251) and performed in accordance with the Helsinki Declaration as revised in 2013. Informed consent for surgery as well as for data collection and analysis was given by all patients.

Patients

We included all patients who underwent PD for resection of benign or malignant periampullary lesions (pylorus preserving Whipple procedure or classic Whipple operation). Patients who obtained any other pancreatic resection were excluded.

The following data were collected: age, gender, surgical procedure, underlying pathology, number of isolated POPF and POBF, combined POPF/POBF, PPH, length of hospital stay, length of ICU stay, need for re-surgery, 30- and 90-day mortality.

Surgical techniques

All procedures were conducted by 5 experienced pancreatic surgeons, who regularly performed more than 50 pancreatic resections per year, according to a standardized surgical technique. Pancreaticojejunostomy was carried out as end-to-side, duct-to-mucosa, double-layer anastomosis using interrupted polydioxanone (PDS) 5-0 sutures for the outer layer and interrupted polypropylene 5-0 sutures for the inner layer. Approximately 15 cm distal to the pancreaticojejunostomy, a single-layer end-to-side hepaticojejunostomy followed using interrupted PDS 5-0 sutures. Another 45–50 cm distal to the hepaticojejunostomy reconstruction was completed with antecolic duodenojejunostomy in a double-layer continuous PDS 4-0 suture technique as pylorus preserving Whipple procedure. In case of a classic Whipple procedure, a side-to-side Braun enteroenterostomy using double-layer continuous sutures with PDS 5–0 was added to gastrojejunostomy. In all cases two intraabdominal soft silicone drains were placed near the pancreaticojejunostomy and hepaticojejunostomy and derived separately in the left and right middle abdomen, respectively. The hepaticojejunostomy was splinted by T-tube in case of a tiny and thin-walled bile duct. All patients received 200 µg octreotide subcutaneous during induction of anesthesia.

Postoperative outcomes

POPF and PPH were defined according to the 2016 update of the International Study Group on Pancreatic Surgery (ISGPS).[10] The definition of POBF was based on the proposal of the International Study Group of Liver Surgery.[11] The simultaneous appearance of amylase, lipase, and bilirubin (each of them at least 3-times above the corresponding serum concentration) was labelled as combined fistula independent of the affected drain. The detection of a bile admixture in the drain near the pancreaticojejunostomy was defined as a combined retrograde fistula (Fig. 1).

Statistics

Data were expressed as percentages, mean ± standard deviation, or median with minimum–maximum range as appropriate. All parametric variables of independent samples were analyzed using t-Tests. To compare more than 2 groups the ANOVA was undertaken. The adjacent post hoc analysis helped to explore differences between groups. Nonparametric data were explored by means of Mann–Whitney U-test. To show a relationship between two nominal variables, the Pearson's Chi square test was performed. If statistically significant differences were observed, an ensuing in-depth analysis was performed among the groups. A p-value of <0.05 was considered statistically significant. The analysis was performed with SPSS software (SPSS Inc., Chicago, Ill., USA).

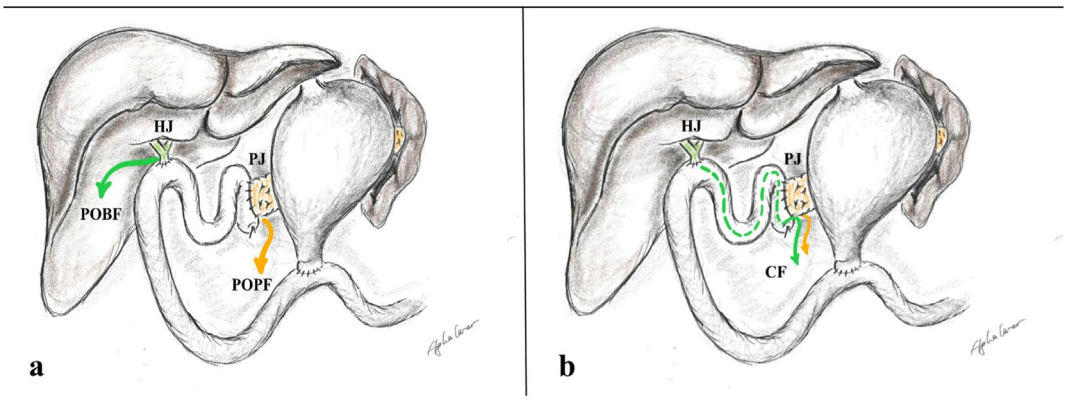

Figure 1 Sketch, clarifying *combined* (a) and *combined retrograde* (b) fistulas after PD: green shows flow direction of bile, yellow – of pancreatic juice, HJ – hepatico-jejunostomy, PJ – pancreatico-jejunostomy, POPF - postoperative pancreatic fistula, POBF - postoperative biliary fistula, CF- combined fistula

Please cite this article as: Aghalarov I et al., Outcome of combined pancreatic and biliary fistulas after pancreatoduodenectomy, HPB, https://doi.org/10.1016/j.hpb.2023.02.010

Results

A total of 678 patients underwent open PD for benign and malignant periampullary lesions. An isolated POPF was observed in 16% (108/678), whereas 2% (16/678) suffered from an isolated POBF. A combined pancreatic-biliary fistula was seen in 6% (40/678). Patient demographics and the underlying diseases are presented in Table 1.

Malignancies represented most underlying diseases in all three groups (no fistula: $p < 0.001$; isolated fistula: 0.044; combined fistula: $p = 0.040$), however, malignancy itself was neither a risk factor nor protective to prevent the development of fistulas (all groups: $p = 0.312$; isolated vs. combined: $p = 0.437$).

A subgroup analysis revealed that the entities chronic pancreatitis and pancreatic ductal adenocarcinoma prevented the occurrence of combined fistulas ($p = 0.049$) and isolated fistulas ($p < 0.001$), respectively, whereas a serous cystadenoma (SCN) and pancreatic metastasis were risk factors for combined ($p = 0.014$) and isolated fistulas ($p < 0.001$) (Table 1).

Table 1 Patient demographics and underlying diseases

	No fistula (n = 514)	Isolated fistula (n = 124)	Combined fistula [a] (n = 40)	p-value
Gender [%]				
Male	56.5	48.4	57.5	
Female	43.5	51.6	42.5	0.258
Age [years]	62.0 ± 13.0	61.4 ± 13.8	62.6 ± 13.5	0.894
Underlying benign disease [n]	178	52	14	
Chr. Pancreatitis	120	32	3	**0.049**
IPMN	30	13	4	0.138
SCN	11	4	4	**0.014**
Other benign lesion	17	3	3	0.297
Underlying malignant disease [n]	336	72	26	
PDAC	261	40	14	< **0.001**
Ampullary CA	28	9	5	0.176
Duodenal CA	7	4	1	0.346
DCC	36	5	2	0.446
Metastasis	4	14	4	< **0.001**
PFRS [%]				
Negligible	9	7	5	0,368[b]
Low	56	38	10	< **0.001**[b]
Intermediate	30	40	60	< **0.001**[b]
high	5	15	25	< **0.001**[b]

IPMN – intraductal papillary mucinous neoplasm, SCN - serous cystic neoplasm, PDAC - pancreatic ductal adenocarcinoma, DCC – distal cholangiocarcinoma, PFRS - pancreatic fistula risk score (Callery et al.).
[a] 10 of combined fistulas are "combined retrograde" ones.
[b] No fistula vs fistula (isolated + combined).

Outcome parameters are presented in Table 2. The frequency of Grade C fistula, which is associated with severe morbidity and mortality, was significantly higher in patients with combined fistulas compared to isolated fistula ($p = 0.006$), whereas the less severe Grade A fistula were more frequently observed in patients with isolated fistula ($p = 0.026$). Furthermore, combined fistulas were more often complicated by PPH than isolated fistulas ($p < 0.001$).

Revisional surgery was performed significantly more often in patients suffering from isolated POBF or combined fistulas compared to isolated POPF ($p = 0.013$ and <0.001, respectively).

In 10 of 19 surgically revised patients with combined fistula a completion pancreatectomy with simultaneous re-do-hepaticojejunostomy was performed. In contrast to isolated POPF, no re-do-pancreaticojejunostomy was undertaken in this group. An erosive bleeding occurred twice in 2 patients after revisional surgery. Finally, 6 patients with combined fistula died after re-operation. There was no significant difference between all the groups concerning the revisional surgery related mortality.

The surgical procedures are presented in Table 2.

Patients with combined fistulas resided at ICU significantly longer than patients with isolated fistula ($p = 0.013$). Moreover, mortality was significantly higher in this group, especially due to complicated POPF ($p = 0.031$). Fig. 2 demonstrates significantly high rate of secondary complications in combined fistulas compared to isolated POPF and POBF.

Discussion

Despite the advances in surgical technique the pancreaticojejunostomy as well as the hepaticojejunostomy remain very challenging and high-risky procedure in PD. The POPF presents the most common and feared complication with incidences between 9 and 50%.[3,5,12–14] In this study a POPF occurred in 22% (16% isolated POPF and 6% combined fistulas). The reported incidence of biliary leakage is comparatively lower and varies between 4 and 12%.[2,6,15,16] In our study group the incidence of biliary leakage was 8% (2% isolated POBF and 6% combined fistulas), which is within the expected range compared to other specialized centers.

In 6% of our patients a combined fistula was observed. A concomitant appearance of both, POPF and POBF, is rarely mentioned by other authors and thus, comparative values are difficult to demonstrate. Fu et al. presented a combined fistulas rate of 7.7% in 532 patients after PD, however, further details were not given.[8] El Nakeeb et al. analyzed 555 patients with biliary complications after PD. Ten of these patients (1.8%) developed a biliary leakage concomitant to POPF, and four patients underwent re-surgery due to biliary peritonitis and associated POPF.[17]

Please cite this article as: Aghalarov I et al., Outcome of combined pancreatic and biliary fistulas after pancreatoduodenectomy, HPB, https://doi.org/10.1016/j.hpb.2023.02.010

Table 2 Outcome parameters. * Multiple entries possible

	Isolated POPF (n = 108)	Isolated POBF (n = 16)	p-value (POPF vs. POBF)	Combined fistula (n = 40)	All patients (n = 678)	p-value (iso. vs. comb.)
Severity of fistula [%]						
Grade A	29 (31/108)	19 (3/16)	0.406	10 (4/40)	6 (38/678)	**0.026**
Grade B	58 (62/108)	56 (9/16)	0.880	55 (22/40)	14 (93/678)	0.111
Grade C	13 (15/108)	25 (4/16)	0.206	35 (14/40)	5 (33/678)	**0.006**
Post-pancreatectomy hemorrhage [%]	6 (6/108)	6 (1/16)	0.999	25 (10/40)	2.5 (17/678)	< **0.001**
CT-Drainage [%]	2 (2/108)	0	0.323	8 (3/40)	1 (5/678)	0.070
T- tube [%]	8 (9/108)	19 (3/16)		13 (5/40)	10 (65/678)	0.610
Revisional surgery* [%]	17 (18/108)	44 (7/16)	**0.013**	48 (19/40)	6.5 (44/678)	< **0.001**
Completion-PE	72 (13/18)	0	–	53 (10/19)	3 (23/678)	0.199
Re-do-HJ	0	57 (4/7)	–	53 (10/19)	2 (14/678)	0.794
Re-do-PJ	11 (2/18)	0	–	0	0.3 (2/678)	–
Other	167 (3/18)	43 (3/7)	0.422	47 (9/19)	2 (15/678)	0.776
ICU stay (days) [mean ± SD]	4.2 ± 9.9	3.4 ± 5.2	0.753	10.3 ± 16.2	1.8 ± 3.2	**0.013**
Hospital stay (days) [mean ± SD]	29.5 ± 25.5	31.5 ± 17.1	0.762	35.6 ± 17.1	14 ± 6.8	0.354
Mortality [%]						
30-days	2.8 (3/108)	0	0.807	7.5 (3/40)	2	0.136
90-days	4,6 (5/108)	6 (1/16)	0.522	15 (6/40)	2	**0.031**

PE – pancreatectomy, HJ – hepatico-jejunostomy, PJ – pancreatico-jejunostomy, ICU – intensive care unit, POPF – postoperative pancreatic fistula, POBF – postoperative biliary fistula.

The etiology of combined fistulas remains unclear, whereas the risk factors contributing to insufficiency of the pancreaticojejunostomy or the hepaticojejunostomy are widely investigated. A tiny and thin-walled bile duct (<5 mm), bile infection, and compromised blood supply may lead to biliary leak.[17] Soft pancreatic texture, pancreatic lipomatosis, and a small pancreatic duct (<3 mm) are variables that could cause a POPF.[3] In our study demographics did not influence the development of combined fistulas. However, chronic pancreatitis and pancreatic ductal adenocarcinoma prevented the occurrence of combined

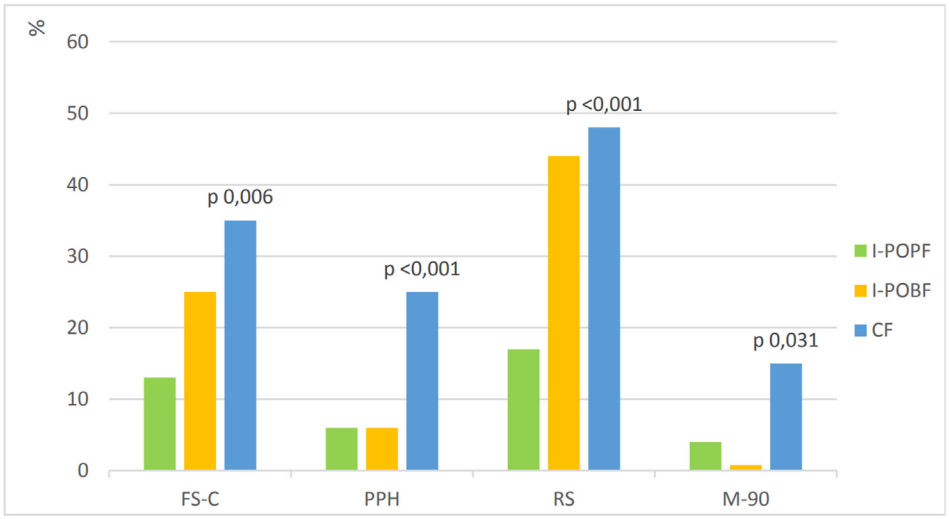

Figure 2 Diagram demonstrates significantly high rate of secondary complications in combined fistulas compared to isolated POPF and POBF: FS-C – fistula severity grad C, PPH – postpancreatectomy hemorrhage, RS – revisional surgery, M–90 – 90-day mortality, I-POPF – isolated POPF, I–POBF – isolated POBF, CF – combined fistula

Please cite this article as: Aghalarov I et al., Outcome of combined pancreatic and biliary fistulas after pancreatoduodenectomy, HPB, https://doi.org/10.1016/j.hpb.2023.02.010

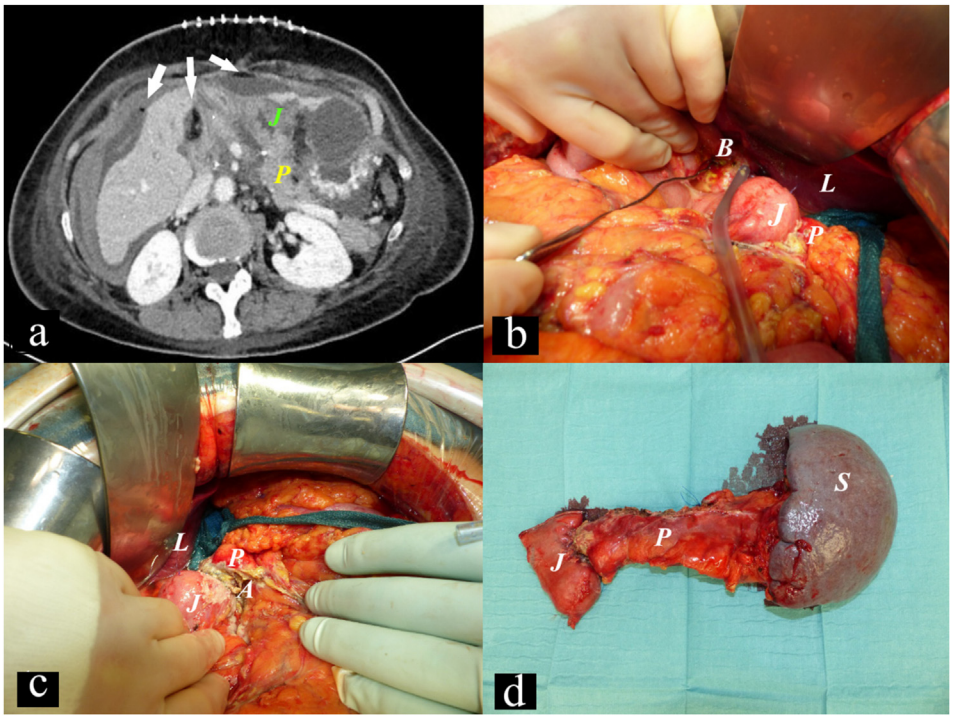

Figure 3 CT-scan (a) and intraoperative images of combined fistula Grade C (b - POBF, c - POPF) as well as specimen after completion pancreatectomy (d): narrows show perihepatic ascites with free intraperitoneal air; A – insufficiency of pancreatico-jejunostomy, B – insufficiency of hepatico-jejunostomy, J-jejunum, L - liver, P - pancreas, S - spleen

fistulas. Explanations might be that both entities are associated with a rather hard pancreatic tissue, as well as enlarged pancreatic and bile duct diameter. In contrast, pancreatic metastasis and SCN were risk factors for fistulas, as the tissue of the pancreas is soft, and the ducts are mostly small. Besides that, a reciprocal potentiation of bile and pancreatic juice may increase the severity of the fistula. It has been reported bile activates phospholipase A2 and it converts biliary lecithin to lysolecithin. The last ones demonstrate high cytotoxic activity. Moreover, bile provides an optimal alkaline pH at 8–8.5, which contributes to converting of trypsinogen to trypsin due to enteric enterokinase. Furthermore contaminated bile contains lipopolysaccharids, which potentiate the activity of pancreatic enzymes. These mechanisms demonstrate a high potentiating effect of bile on pancreatic juice, increasing proinflammatory and detrimental impact in case of combined fistulas.[18]

In 25% of our patients, the combined fistulas were classified as retrograde fistulas. Here, a retrograde bile flow towards the pancreaticojejunostomy could be of impact.[19] In case of retrograde bile fistulas, the reconstructive technique could matter. Double loop reconstruction and other modifications, including a modified single loop reconstruction, could prevent the reflux of bile toward the pancreaticojejunostomy as recently described.[20] There are few RCTs and observational clinical studies comparing PG (pancreaticogastrostomy) vs PJ and showing no significant difference between these techniques concerning the rate of POBF and POPF. The occurrence of combined fistulas is not described in these studies explicitly. Nevertheless, PG might prevent a combined *retrograde* fistula, as well as a double loop or a modified single loop reconstruction. Probably the biliary reflux is one of the possible but not only cause of combined fistula particularly in case of concomitant but pure POPF and POBF. Splinting the hepaticojejunostomy by T-tube is used in patients with thin bile duct diameter or fragile bile duct wall. However, this technique does not prevent the biliary leakage. It solely aims to avoid re-surgery in case of insufficiency of the hepaticojejunostomy.[21]

The analysis of the severity of fistulas in each group showed a significantly prevelance of Grade C fistulas in patients with combined insufficiency of the hepaticojejunostomy and the pancreaticojejunostomy. Along with that, Grade A fistulas ammounted the majority in patients with isolated POPF and POBF. It emphasizes an elevated morbidity of combined fistulas regardless of the mechanism of occurrence (retrogradely or separately). This is also reflected in the need for a longer ICU-stay, as well as in the increased 90-days mortality rate. Furthermore, our data correspond to the results of a study conducted by Jester et al., who investigated 924 patients after PD. A combined insufficiency of the hepaticojejunostomy and the pancreaticojejunostomy was seen in 31 patients (3%). This group had a significantly increased morbidity (58%), a longer median length of stay (14 days vs. 7–9 days), as well as a higher

Please cite this article as: Aghalarov I et al., Outcome of combined pancreatic and biliary fistulas after pancreatoduodenectomy, HPB, https://doi.org/10.1016/j.hpb.2023.02.010

90-day mortality (32% vs. 3.6%) compared to isolated POPF or no leak.[22]

One of the most feared complications, the PPH, was observed in 17 patients in our study (10% of patients with fistulas). This corresponds to incidences reported by others (5–16%).[23,24] Detailed examination revealed that patients with combined fistulas were significantly more often affected by PPH than those with isolated fistula. The potentiating effect of bile leakage on PPH has already been reported.[25]

The primary therapeutic approach in case of insufficiency of the pancreaticojejunostomy is rather conservative. Revisional surgery with completion pancreatectomy remains an ultima ratio (Fig. 3) and is associated with a high morbidity and mortality rate.[26] In contrast, the bile leakage can be successfully repaired surgically, especially in the early postoperative period.[17] Certainly, the willingness for (early) surgery in patients with combined fistulas is higher to avert complications such as PPH, peritonitis, and sepsis, as well as to reduce the related mortality. That is why patients underwent revisional surgery more frequently than patients with isolated POPF in this study. However, it should be mentioned that some patients required repetitive re-surgeries (isolated and combined fistulas), which is associated with a significant increase of mortality (13–55%).[27,28]

This study demonstrated that a combined POPF/POBF fistula is associated with a significant increase of morbidity and mortality compared to isolated fistulas after PD. Chronic pancreatitis and pancreatic ductal adenocarcinoma prevent the occurrence of combined fistulas, whereas pancreatic metastasis and serous cystadenoma were risk factors. Early surgical revision in patients with combined fistulas may improve the postoperative survival rate.

There may be some possible limitations in this study. The first one is its retrospective design. The second limitation concerns to the limited number of patients in each group, particularly in the group of isolated POBF and combined fistulas. Third, it is difficult to differentiate between combined retrograde fistula and disruption of both anastomoses only basing on drain investigation, particularly in case of amylase/lipase and bilirubin elevation in the same drain. Fourth, there is a little number of prior studies, thus extensive comparison of results is difficult. Further research is needed to shed more light on the pathogenesis and prevention options of combined fistulas after PD.

Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

Ilgar Aghalarov – acquisition, analysis and interpretation of data, drafting the paper, revising, final approving.

Elisabeth Beyer – acquisition, analysis and interpretation of data, revising, final approving.

Jennifer Niescery – analysis and interpretation of data, drafting the paper, revising, final approving.

Orlin Belyaev – analysis and interpretation of data, revising, final approving.

Waldemar Uhl – research design, analysis and interpretation of data, revising, final approving.

Torsten Herzog – research design, analysis and interpretation of data, revising, final approving.

Funding

No funding received.

Conflict of interest

None declared.

References

1. He J, Ahuja N, Makary MA, Cameron JL, Eckhauser FE, Choti MA *et al*. (2014) 2564 resected periampullary adenocarcinomas at a single institution: trends over three decades. *HPB* 16:83–90.
2. Burkhart RA, Relles D, Pineda DM, Gabale S, Sauter PK, Rosato EL *et al*. (2013) Defining treatment and outcomes of hepaticojejunostomy failure following pancreaticoduodenectomy. *J Gastrointest Surg*, 451–460.
3. Pedrazzoli S. (2017) Pancreatoduodenectomy (PD) and postoperative pancreatic fistula (POPF): a systematic review and analysis of the POPF-related mortality rate in 60,739 patients retrieved from the English literature published between 1990 and 2015. *Medicine (Baltim)* 96(19): e6858.
4. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR *et al*. (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 142.
5. Dusch N, Lietzmann A, Barthels F, Niedergethmann M, Rückert F, Wilhelm TJ. (2017) International study group of pancreatic surgery definitions for postpancreatectomy complications: applicability at a high-volume center. *Scand J Surg* 106:216–223.
6. Herzog T, Belyaev O, Hessam S, Uhl W, Chromik AM. (2014) Management of isolated bile leaks after pancreatic resections. *J Invest Surg*, 273–281.
7. Krautz C, Nimptsch U, Weber GF, Mansky T, Grützmann R. (2018) Effect of hospital volume on in-hospital morbidity and mortality following pancreatic surgery in Germany. *Ann Surg* 267:411–417. https://doi.org/10.1097/SLA.0000000000002248.
8. Fu S-J, Shen S-L, Li S-Q, Hu W-J, Hua Y-P, Kuang M *et al*. (2015) Risk factors and outcomes of postoperative pancreatic fistula after pancreaticoduodenectomy: an audit of 532 consecutive cases. *BMC Surg* 15:34.
9. Suzuki Y, Fujino Y, Tanioka Y, Ajiki T, Hiraoka K, Takada M *et al*. (2003) Factors influencing hepaticojejunostomy leak following pancreaticoduodenal resection; importance of anastomotic leak test. *Hepato-Gastroenterology* 50:254–257.
10. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M *et al*. (2017) The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Surgery* 161:584–591.
11. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L *et al*. (2011) Bile leakage after hepatobiliary and pancreatic surgery: a

Please cite this article as: Aghalarov I et al., Outcome of combined pancreatic and biliary fistulas after pancreatoduodenectomy, HPB, https://doi.org/10.1016/j.hpb.2023.02.010

definition and grading of severity by the International Study Group of Liver Surgery. *Surgery* 149:680–688.

12. Eshmuminov D, Schneider MA, Tschuor C, Raptis DA, Kambakamba P, Muller X *et al*. (2018) Systematic review and meta-analysis of 73 post-operative pancreatic fistula rates using the updated 2016 International Study Group Pancreatic Fistula definition in patients undergoing pancreatic resection with soft and hard pancreatic texture. *HPB*, 992–1003.
13. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al*. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 138:8–13.a Strobel O, Büchler MW. (2019) Postoperative Pankreasfistel: update der Definition und Klassifikation. *Chirurg* 90:89.
14. Crippa S, Salvia R, Falconi M, Butturini G, Landoni L, Bassi C. (2007) Anastomotic leakage in pancreatic surgery. *HPB* 9:8–15. https://doi.org/10.1080/13651820600641357.
15. Antolovic D, Koch M, Galindo L, Wolff S, Music E, Kienle P *et al*. (2007) Hepaticojejunostomy–analysis of risk factors for postoperative bile leaks and surgical complications. *J Gastrointest Surg* 11:555–561.
16. Suzuki H, Shimura T, Mochhida Y, Wada S, Araki K, Kubo N *et al*. (2014) To stent or not to stent hepaticojejunostomy–analysis of risk factors for postoperative bile leaks and surgical complication. *Hepato-Gastroenterology* 61:920–926.
17. El Nakeeb A, El Sorogy M, Hamed H, Said R, Elrefai M, Ezzat H *et al*. (2019) Biliary leakage following pancreaticoduodenectomy: prevalence, risk factors and management. *Hepatobiliary Pancreat Dis Int* 18:67–72. https://doi.org/10.1016/j.hbpd.2018.10.005. Epub 2018 Oct 28. PMID: 30413347.
18. Machado MC, da Cunha JE, Bacchella T, Bove P. (1976) A modified technique for the reconstruction of the alimentary tract after pancreatoduodenectomy. *Surg Gynecol Obstet* 143:271–272. PMID: 941087.
19. Hata T, Mizuma M, Motoi F, Nakagawa K, Masuda K, Ishida M *et al*. (2020) Early postoperative drainage fluid culture positivity from contaminated bile juice is predictive of pancreatic fistula after pancreaticoduodenectomy. *Surg Today* 50:248–257.
20. Aghalarov I, Herzog T, Uhl W, Belyaev O. (2018) A modified single-loop reconstruction after pancreaticoduodenectomy reduces severity of postoperative pancreatic fistula in high-risk patients. *HPB* 20:676–683. https://doi.org/10.1016/j.hpb.2018.01.011. Epub 2018 Feb 16. PMID: 29456198.
21. Herzog T, Belyaev O, Bakowski P, Chromik AM, Janot M, Suelberg D *et al*. (2013) The difficult hepaticojejunostomy after pancreatic head resection: reconstruction with a T tube. *Am J Surg* 206:578–585.
22. Jester AL, Chung CW, Becerra DC, Molly Kilbane E, House MG, Zyromski NJ *et al*. (2017) The impact of hepaticojejunostomy leaks after pancreatoduodenectomy: a devastating source of morbidity and mortality. *J Gastrointest Surg* 21:1017–1024. https://doi.org/10.1007/s11605-017-3406-1. Epub 2017 Mar 24. PMID: 28342120.].
23. Balachandran P, Sikora SS, Raghavendra Rao RV, Kumar A, Saxena R, Kapoor VK. (2004) Haemorrhagic complications of pancreaticoduodenectomy. *ANZ J Surg* 74:945–950.
24. Karim SAM, Abdulla KS, Abdulkarim QH, Rahim FH. (2018) The outcomes and complications of pancreaticoduodenectomy (Whipple procedure): cross sectional study. *Int J Surg* 52:383–387.
25. Tien Y-W, Lee P-H, Yang C-Y, Ho M-C, Chiu Y-F. (2005) Risk factors of massive bleeding related to pancreatic leak after pancreaticoduodenectomy. *J Am Coll Surg* 201:554–559.
26. Smith CD, Sarr MG, vanHeerden JA. (1992) Completion pancreatectomy following pancreaticoduodenectomy: clinical experience. *World J Surg* 16:521–524.
27. Standop J, Glowka T, Schmitz V, Schäfer N, Overhaus M, Hirner A *et al*. (2009) Operative Re-intervention following pancreatic head resection: indications and outcome. *J Gastrointest Surg* 13:1503–1509. https://doi.org/10.1007/s11605-009-0905-8.
28. Lessing Y, Pencovich N, Nevo N, Lubezky N, Goykhman Y, Nakache R *et al*. (2019) Early reoperation following pancreaticoduodenectomy: impact on morbidity, mortality, and long-term survival. *World J Surg Oncol* 17:26–76.

Please cite this article as: Aghalarov I et al., Outcome of combined pancreatic and biliary fistulas after pancreatoduodenectomy, HPB, https://doi.org/10.1016/j.hpb.2023.02.010