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Postpancreatectomy Hemorrhage—Incidence, Treatment, and Risk Factors in Over 1,000 Pancreatic Resections

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Abstract
Background Postpancreatectomy hemorrhage is a rare but often severe complication after pancreatic resection. The aim of this retrospective study was to define incidence and risk factors of postpancreatectomy hemorrhage and to evaluate treatment options and outcome.
Patients and Methods Clinical data was extracted from a prospectively maintained database. Descriptive statistics, univariate and multivariate risk factor analysis by binary logistic regression were performed with SPSS software at a significance level of $p=0.05$.
Results $N=1{,}082$ patients with pancreatic resections between 1994 and 2012 were included. Interventional angiography was successful in about half of extraluminal bleeding. A total of 78 patients (7.2 %) had postpancreatectomy hemorrhage (PPH), and 29 (2.7 %) were grade C PPH. Multivariate modeling disclosed a learning effect, age, BMI, male sex, intraoperative transfusion, portal venous and multivisceral resection, pancreatic fistula and preoperative biliary drainage as independent predictors of severe postpancreatectomy hemorrhage. High-risk histopathology, age, transfusion, pancreatic fistula, postpancreatectomy hemorrhage and pancreatojejunostomy in pancreatoduodenectomies were independent predictors of mortality.
Conclusions Our study identifies clinically relevant risk factors for postpancreatectomy hemorrhage and mortality. Interventional treatment of extraluminal hemorrhage is successful in about half of the cases and if unsuccessful constitutes a valuable adjunct to operative hemostasis. Based on our observations, we propose a treatment scheme for PPH. Risk factor analysis suggests appropriate patient selection especially for extended resections and pancreatogastrostomy for reconstruction in pancreatoduodenectomy.

Keywords Postpancreatectomy hemorrhage · Pancreatic surgery · Pancreatic resection · Postoperative pancreatic fistula · Risk factors

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Introduction

Postoperative bleeding can represent one of the most serious complications in pancreatic surgery.[1–8] Due to the clinical relevance and heterogeneity of bleeding an international consensus classification for postpancreatectomy hemorrhage (PPH) has been established by the International Study Group for Pancreatic Surgery (ISGPS).[7] Herein, PPH is categorized according to timing, severity and site of bleeding. Potentially life-threatening bleeding is defined as grade C. This feared complication usually occurs as erosion bleeding from the visceral arteries, most commonly the gastroduodenal artery stump, as a result of postoperative pancreatic fistula (POPF).[3,5,7,8] Few studies focused on delayed PPH but no comprehensive analysis of grade C PPH has been reported.[6] The aim of this study was to analyze incidence, risk factors,

treatment, and outcome of PPH and specifically severe PPH of grade C.

Patients and Methods

Patients and Operations

Patients who had received a major pancreatic resection at our institution were identified from a prospectively maintained database and baseline data was extracted. Major pancreatic resections were defined as pancreatoduodenectomy, duodenum-preserving pancreatic head resection, distal pancreatic resection and total pancreatectomy. PPH and POPF were defined according to the ISGPS criteria[7,9] and re-review of patient records was performed for exact classification. In brief, PPH and POPF are graded from A to C, where grade A does not result in significant deviation in the clinical course, grade B makes specific therapy and prolonged hospital stay necessary and grade C is potentially life-threatening requiring invasive treatment.

Procedures and Postoperative Treatment

Operations were performed as previously described.[10–12] The choice of the anastomotic technique was based on the surgeon's preference up to 2006. From 2006 to 2012, randomized trials comparing pancreatogastrostomy (PG) and pancreatojejunostomy (PJ) in pancreatoduodenecto my (PD) were performed at our institution.[12,13] In pancreatoduodenectomy, the gastroduodenal artery stump was routinely suture-ligated with non-absorbable monofilamentous 5–0 suture and additionally ligated with 2–0 polyfilamentous thread, without further covering or buttressing. Thromboembolic prophylaxis consisted of low-dose low-molecular heparin started 6 h after the operation. Novel platelet aggregation inhibitors were discontinued before the operation. Aspirin in patients with coronary artery stents was continued. Therapeutic anticoagulation was replaced by IV unfractionated heparin which was stopped before the operation and continued 6 h after the operation. All patients received proton pump inhibitor treatment starting the day before the operation.

Patients were transferred to the surgical intermediate care unit immediately after the operation. Amylase activity in abdominal drain secretions was measured routinely daily during the first week or until removal of drains. In pancreatoduodenectomy patients, a nasojejunal biluminal tube with an accessory gastric decompression lumen was placed intraoperatively. Enteral feeding was started on day one according to tolerance and supplemented by nasojejunal tube feeding in patients with pancreatoduodenectomy.

Statistics

Data collection and statistical analysis was performed with IBM SPSS Version 21 (SPSS Inc, Chicago, IL). Scale variables were expressed as median±range, categorial parameters as absolute count and percentage. For statistical testing of observed differences, two-sided Mann-Whittney and Chi-squared tests were used. Uni- and multivariate risk factor analysis was performed by binary logistic regression with conditional backward selection of predictor variables. The significance level was set to $p=0.05$.

Results

Baseline Data

Baseline data are shown in Table 1. From 1994 to 2012, $n=1{,}082$ patients (630 male and 425 female) of median age 60 years (range 9–89) received major pancreatic resections performed at the Clinic for General and Visceral Surgery of the University Medical Center of Freiburg. The patient cohort was divided into two equally sized parts which in result were operated from 1994 to 2005 and 2005 to 2012. Median BMI was 24 (range 15–41), 11 % had diabetes mellitus and 9 % presented with pancreatic insufficiency requiring enzyme replacement preoperatively. Median creatinine and bilirubin levels were normal (0.79 and 0.75 mg/dl) with ranges of 0.4–10.5 and 0.1–37.6, respectively. Rates of preoperative biliary drainage (PBD) and neoadjuvant therapy were 36 and 2 % (Table 1).

There were 729 pancreatoduodenectomies (PD), 188 distal pancreatic resections (DPR), 123 duodenum-preserving pancreatic head resections (DPPHR), and 42 total pancreatectomies. Reconstruction after PD was performed by pancreatogastrostomy (PG) in 38 % and pancreatojejunostomy (PJ) in 62 %. Median operative time was 405 min and 458 patients (42 %) received intraoperative red blood cell (RBC) transfusions. The rates of portal venous and multivisceral resections were 16 and 14 %, respectively. Additional organs involved in multivisceral resections were liver, stomach, colon, small bowel, kidney and other organs (adrenal, diaphragm, ovaries; see Table 1). Histopathological workup revealed pancreatic ductal adenocarcinoma, periampullary (duodenal, distal bile duct and ampullary) cancers, cystic neoplasms, neuroendocrine tumors, chronic pancreatitis and other diagnoses in 34, 15, 4, 33, and 11 %, respectively. Low-risk histopathology was defined as PDAC or chronic pancreatitis because pancreatic texture is usually hard in these conditions, as opposed to a

Table 1 Patient baseline parameters

Parameter	Category	Count/ median	%/range
Total patients	*n*	1082	100 %
Time period	1: 1994–2005	541	50 %
	2: 2005–2012	541	50 %
Age (years)		60	9–89
Sex	Female	452	41.8 %
	Male	630	58.2 %
Body mass index		23.7	14.5-41.2
Diabetes mellitus		116	10.7 %
Exocrine insufficiency		96	8.9 %
Creatinine (mg/dl)		0.79	0.40–10.45
Bilirubin (mg/dl)		0.75	0.10–37.60
Preoperative biliary drainage		389	36.0 %
Neoadjuvant therapy		23	2.1 %
Operation	PD	729	67.4 %
	DPR	188	17.4 %
	DPPHR	123	11.4 %
	PE	42	3.9 %
Pancreatic anastomosis	PG	279	38.3 %
	PJ	450	61.7 %
OP time		405	103-870
Intraoperative transfusion		458	42.30 %
Portal venous resection		170	15.7 %
Multivisceral resection	Colon resection	46	4.3 %
	Gastric resection	53	4.9 %
	Liver resection	41	3.8 %
	Small bowel resection	15	1.4 %
	Nephrectomy	5	0.5 %
	Other additional resection	37	3.4 %
	Total	155	14.3 %
Histopathology	PDAC	366	33.8 %
	Periampullary cancer	158	14.6 %
	CNP	38	3.5 %
	Neuroendocrine tumor	43	4.0 %
	Chronic pancreatitis	359	33.2 %
	Other	118	10.9 %
	High-risk total	357	33.0 %
	Low-risk total	725	67.0 %

The high-risk histopathology group was defined as patients with histopathological diagnoses other than PDAC or chronic pancreatitis

PD pancreatoduodenectomy, *DPR* distal pancreatic resection, *DPPHR* duodenum-preserving pancreatic head resection, *PE* pancreatectomy, *PG* pancreatogastrostomy, *PJ* pancreatojejunostomy, *OP* operation, *CNP* cystic neoplasms of the pancreas, *PDAC* pancreatic ductal adenocarcinoma

high-risk soft pancreas.[8,10,14–17] Thereby, 33 % of patients were assigned to the high-risk group.

Postpancreatectomy Hemorrhage

Detailed figures regarding PPH are depicted in Table 2. A total of 78 patients (7.2 %) had PPH, and 29 (2.7 %) were grade C PPH. Overall mortality in patients without PPH was 1.3 %, rose to 4.1 % with PPH of grade A/B and to 31.0 % with PPH grade C (Table 2).

Clinical PPH manifestation was extraluminal and intraluminal in 50 % of cases each. While intraluminal PPH was mostly grade A/B (74 %) and associated with 7.7 % (n=3) mortality. Two of these were episodes of delayed grade C erosion PPH with intraluminal manifestation from the pancreatoenteric anastomosis region, and one was grade B PPH due to erosive gastritis in a critically ill patient.

About half (49 %) of extraluminal PPH reached grade C, with associated mortality of 20.5 %. Extraluminal, but not intraluminal PPH was significantly associated with POPF (p=0.000 and 0.126, Chi-squared test) and mortality (p=0.000 and p=0.062, Chi-squared test). Intraluminal but not extraluminal PPH was associated with pancreatogastrostomy (p=0.000 and p=0.842, Chi-squared test).

Eighty-five percent of PPH were categorized as late (>24 h after operation) according to the ISGPS definition. These had an associated mortality of 16.7 %, while early PPH did not coincide with mortality.

The exact origin of bleeding could be identified in most cases. 31 % of PPH originated from the gastrointestinal tract and only 13 % of these were grade C. The second most frequent origin of bleeding were the visceral artery branches of the celiac trunk or superior mesenteric artery (24 % of PPH), 90 % of which were grade C. Bleeding from the pancreatic cut surface made up 17 % of PPH and was associated almost exclusively with reconstruction by PG as only one of 13 cases occurred after PJ (p=0.000, Chi-squared test).

Other extraluminal bleeding sources were found in 19 % of PPH, but in 10 % of PPH the definite origin could not be determined. Highest mortality rates were associated with bleeding from the branches of celiac trunk or SMA (21 %) and other extraluminal origins (29 %).

First-Line Treatment Approach to PPH

Detailed figures concerning PPH therapy and outcome are shown in Table 3. Primary and secondary treatment options were analyzed for intraluminal, extraluminal, and grade C PPH separately. Successful treatment was defined as a stop of bleeding without necessity of immediate secondary intervention. In some cases, no definite source of bleeding was found as target for therapy during primary endoscopy or angiography (Table 3).

Half of all cases of intraluminal PPH (49 %) were treated by endoscopy. Endoscopy reached a low failure rate (i.e.,

Table 2 Postpancreatectomy incidence and subclassification

Parameter		Number	% of category	Number	% of subcategory	Number	% of subcategory	Number	% of subcategory	Number	% of subcategory
Category	Subcategory	Total case numbers		PPH		PPH A/B		PPH C		Mortality	
PPH	PPH total	78	7.2							11	14.1
	PPH A/B	49	4.5							2	4.1
	PPH C	29	2.7							9	31.0
	No PPH	1004	92.8							13	1.3
PPH origin	GIT	24	30.8			21	87.5	3	12.5	2	8.3
	Pancreas cut surface	13	16.7			8	61.5	5	38.5	1	7.7
	CT/SMA	19	24.4			2	10.5	17	89.5	4	21.1
	Other	14	17.9			10	71.4	4	28.6	4	28.6
	Unknown	8	10.3			8	100.0	0	0.0	0	0.0
PPH bleeding site	Intraluminal	39	50.0			29	74.4	10	25.6	3	7.7
	Extraluminal	39	50.0			20	51.3	19	48.7	8	20.5
PPH time	Early	12	15.4			10	83.3	2	16.7	0	0.0
	Late	66	84.6			39	59.1	27	40.9	11	16.7
Operation	PD	729	67.4	61	8.4	38	5.2	23	3.2	19	2.6
	DPPHR	123	11.4	7	5.7	6	4.9	1	0.8	1	0.8
	DPR	188	17.4	8	4.3	3	1.6	5	2.7	2	1.1
	PE	42	3.9	2	4.8	2	4.8	0	0.0	2	4.8
Pancreatic anastomosis	PG	279	38.3	36	12.9	22	7.9	14	5.0	5	1.8
	PJ	450	61.7	25	5.6	16	3.6	9	2.0	14	3.1
POPF	No	759	70.1	38	5.0	31	4.1	7	0.9	10	1.3
	Yes	323	29.9	40	12.4	18	5.6	22	6.8	14	4.3

PPH/*POPF* postpancreatectomy/postoperative pancreatic fistula according to the International Study Group for Pancreatic Surgery (ISGPS) grading A–C, *PD* pancreatoduodenectomy, *DPR* distal pancreatic resection, *DPPHR* duodenum-preserving pancreatic head resection, *PE* pancreatectomy, *PG* pancreatogastrostomy, *PJ* pancreatojejunostomy, *OP* operation, *GIT* gastrointestinal tract, *CT* celiac trunk, *SMA* superior mesenteric artery

ongoing bleeding) of 5 %. On the other hand, in only 32 % a definite identification of bleeding origin with subsequent hemostasis was performed, as in most cases no target for therapy was identified (63 %). Operative intervention for intraluminal bleeding was successful in 92 % of cases, and most of these cases presented as bleeding from the pancreatic cut surface (7 of 12 cases). Four cases of intraluminal PPH were treated by angiography, 50 % of which were successful.

Extraluminal bleeding was managed by operation in 51 % of cases which was always successful. Angiography was used in 36 % of cases and had a 50 % success rate. Ten percent of extraluminal PPH was mild and self-limiting (grade A). Pseudo-intraluminal PPH represents a specific problem which was analyzed. There were four cases of extraluminal bleeding with primary manifestation as bleeding from the gastrointestinal tract, all more than 2 weeks after the operation, and three (75 %) thereof in patients with POPF. In one case primarily managed by endoscopy, secondary angiography was performed but not successful. Three cases were primarily managed by angiography, with successful interventional hemostasis in two and secondary operative hemostasis in one.

In separate analysis of severe grade C PPH, reoperation was the most frequent primary treatment (49 %) with 93 % success rate. The second most commonly employed intervention was angiography which stopped bleeding in 55 %. In contrast, endoscopy was only used in 14 % and had 25 % success rate.

To evaluate for a learning effect on the interventional radiology side, we compared the success rates of first-line angiography during the first and second time periods. Although there was an improvement from 29 to 36 %, this was not statistically significant (p=0.89). There were 11 successful first- and second-line angiographic interventions, with coil embolization in 9 and stenting in 2. Stenting was only performed during the second time period.

Second-Line Treatment Approach of PPH

Regarding second-line treatment, it has to be emphasized that case numbers for secondary interventions were relatively small (n=9 intraluminal and n=9 extraluminal PPH). There was a shift towards the use of angiography (56 %) for

Table 3 Postpancreatectomy treatment and outcome

		Intraluminal PPH					Extraluminal PPH					PPH grade C				
		Number	%	Outcome	Number	%	Number	%	Outcome	Number	%	Number	%	Outcome	Number	%
Primary intervention	Self-limited	4	10	Failed	0	0	4	10	Failed	0	0	0	0	Failed	0	0
				Success	4	100			Success	4	100			Success	0	0
				No target	0	0			No target	0	0			No target	0	0
	Angiography	4	10	Failed	1	25	14	36	Failed	5	36	11	38	Failed	5	45
				Success	2	50			Success	7	50			Success	6	55
				No target	1	25			No target	2	14			No target	0	0
	Operation	12	31	Failed	1	8	20	51	Failed	0	0	14	48	Failed	1	7
				Success	11	92			Success	20	100			Success	13	93
				No target	0	0			No target	0	0			No target	0	0
	Endoscopy	19	49	Failed	1	5	1	3	Failed	1	100	4	14	Failed	2	50
				Success	6	32			Success	0	0			Success	1	25
				No target	12	63			No target	0	0			No target	1	25
Secondary intervention	Self-limited	0	0	Failed	0	0	0	0	Failed	0	0	0	0	Failed	0	0
				Success	0	0			Success	0	0			Success	0	0
				No target	0	0			No target	0	0			No target	0	0
	Angiography	5	56	Failed	0	0	2	22	Failed	1	50	2	18	Failed	1	50
				Success	1	20			Success	1	50			Success	1	50
				No target	4	80			No target	0	0			No target	0	0
	Operation	2	22	Failed	0	0	7	78	Failed	0	0	8	73	Failed	0	0
				Success	2	100			Success	7	100			Success	8	100
				No target	0	0			No target	0	0			No target	0	0
	Endoscopy	2	22	Failed	0	0	0	0	Failed	0	0	1	9	Failed	0	0
				Success	1	50			Success	0	0			Success	1	100
				No target	1	50			No target	0	0			No target	0	0

PPH/POPF postpancreatectomy/postoperative pancreatic fistula according to the International Study Group for Pancreatic Surgery (ISGPS) grading A–C, *PD* pancreatoduodenectomy, *DPR* distal pancreatic resection, *DPPHR* duodenum-preserving pancreatic head resection, *PE* pancreatectomy, *PG* pancreatogastrostomy, *PJ* pancreatojejunostomy, *OP* operation, *GIT* gastrointestinal tract, *CT* celiac trunk, *SMA* superior mesenteric artery

intraluminal PPH, with only 20 % success rate as 80 % of interventions did not identify a target. For extraluminal PPH however, angiography remained successful in about 50 %. Seven patients received operative hemostasis after unsuccessful angiography. In five (71 %) of these, the bleeding site was already identified during angiography, thus contributing to the operative strategy (Table 3).

There were only two cases where the same non-operative intervention was repeated as secondary treatment, under stable hemodynamic condition: One patient had a second endoscopy with successful clipping of PPH at the anterior gastrotomy site, another patient had unsuccessful repeat angiography for recurrent PPH from the PG site, which was then managed operatively.

Operative Interventions for PPH

In total, 39 patients (3.6 % of total) were reoperated because of PPH as first- or second-line treatment. Seventeen (1.5 % of total) of these cases had late erosion PPH with associated POPF or postoperative pancreatitis, which occurred 5–26 days after the initial operation. Completion pancreatectomy was performed in 9 such cases (0.8 % of total) with associated mortality of 33 %.

Risk Factor Analysis for PPH Grade C and Mortality

Because PPH and especially PPH grade C was strongly associated with mortality, risk factor analysis for PPH grade C and mortality were performed. This was performed for the whole study population and for the subgroup of pancreatoduodenectomy (Tables 4 and 5). For multivariate analysis, stepwise conditional backward elimination was employed in a binary logistic regression model (Table 6). To account for possible learning effects, the patient cohort was divided into two equally sized parts operated from 1994 to 2005 and 2005 to 2012. Histopathology and time period were categorized as already mentioned into high risk versus low risk and first- and second-time period, respectively (Tables 4, 5 and 6).

Univariate risk factors for PPH grade C were high-risk histopathology, higher age and BMI, reconstruction by pancreatogastrostomy, intraoperative transfusion, portal venous and multivisceral resection and POPF (Table 4). In the pancreatoduodenectomy subgroup, risk factors for PPH grade C were the same except for high-risk histopathology which did not achieve the significance level (p=0.008) (Table 5).

Multivariate modeling by binary logistic regression with backward elimination (Table 6) disclosed nine factors as independently predicting PPH grade C in all pancreatic resections: higher age and BMI, male sex, intraoperative transfusion, portal venous and multivisceral resection, and POPF. Protective factors were operation in the recent time period and preoperative biliary drainage. Results were similar in the panceatoduodenectomy subgroup, where gender and multivariate resection did not qualify as independent variables (Table 6).

Risk factors significantly associated with perioperative mortality in univariate analysis comprised higher age, BMI and bilirubin, POPF and PPH (Table 4). In the pancreatoduodenectomy subgroup, higher age, POPF and PPH qualified as risk factors (Table 5). Multivariate analysis (Table 6) in the whole patient collective disclosed high-risk histopathology, higher age, intraoperative transfusion, POPF, and PPH as independent predictive factors. In the pancreatoduodenectomy group, higher age, POPF, PPH, and PJ were identified as independent risk factors for mortality.

The finding that PG was associated with reduced mortality was investigated further. Mortality under critical conditions was lower with PG versus PJ: in patients with PPH 8 vs 28 %, with extraluminal PPH 17s vs 33 % and with completion pancreatectomy 20 vs 67 %.

Discussion

We performed a comprehensive analysis of PPH in a collective of over 1,000 pancreatic resections. Our results provide insights on risk factors for severe grade C PPH and mortality as well as treatment strategies and their effectiveness. The patient collective can be regarded as representative of a high-volume academic center for pancreatic surgery at the University Medical Center Freiburg. The most frequently performed pancreatic resection procedure was pancreatoduodenectomy, which was also the procedure with the highest rate of PPH. Therefore we also analyzed this subgroup for severe PPH and mortality. Overall incidence of PPH and PPH grade C was 7.2 and 2.7 %, respectively. Nevertheless, valid statistical analysis was possible due to the large case number.

Most frequent PPH origins were the gastrointestinal tract and the visceral arteries. In line with previous studies,[6] the latter constituted the most severe PPH events with a high associated mortality. There were also few cases of diffuse extraluminal bleeding not attributable to a major visceral vessel that carried a comparable risk. We observed an overall association of PPH with pancreatogastrostomy due to an increased number of intraluminal PPH originating from the pancreas cut surface. In some cases of non-severe (PPH grade A/B), the exact source of bleeding remained unknown.

Regarding clinical presentation as extraluminal or intraluminal PPH, grade C was more frequent in extraluminal bleeding. In contrast to intraluminal PPH, extraluminal PPH was significantly associated with POPF and mortality, pointing to the role of erosion bleeding.

Table 4 Univariate analysis of risk factors for PPH grade C and mortality in all pancreatic resections

Univariate analysis		PPH grade C					Mortality				
		No		Yes		*p*	No		Yes		*p*
		Count/ median	% row/ range	Count/ median	% row/ range	Logreg	Count/ median	% row/ range	Count/ median	% row/ range	Logreg
Period	Period 1	527	97.4	14	2.6	0.851	528	97.6	13	2.4	0.680
	Period 2	526	97.2	15	2.8		530	98.0	11	2.0	
Histopathology	Low-risk	711	98.1	14	1.9	*0.034*	708	97.7	17	2.3	0.687
	High-risk	342	95.8	15	4.2		350	98.0	7	2.0	
Age		60	9–89	68	44–83	*0.003*	60	9–89	70	44–83	*0.000*
Sex	Female	442	97.8	10	2.2	0.421	440	97.3	12	2.7	0.411
	Male	611	97.0	19	3.0		618	98.1	12	1.9	
Body mass index		23.6	14.5–41.2	27.0	20.6–32.7	*0.000*	23.7	14.5–41.2	26.3	18.8–33.2	*0.011*
Diabetes	No	938	97.1	28	2.9	0.228	945	97.8	21	2.2	0.776
	Yes	115	99.1	1	0.9		113	97.4	3	2.6	
Exocrine insufficiency	No	958	97.2	28	2.8	0.318	963	97.7	23	2.3	0.425
	Yes	95	99.0	1	1.0		95	99.0	1	1.0	
Preop biliary drainage	No	671	96.8	22	3.2	0.185	677	97.7	16	2.3	0.787
	Yes	382	98.2	7	1.8		381	97.9	8	2.1	
Neoadjuvant therapy	No	1030	97.3	29	2.7	0.998	1035	97.7	24	2.3	0.998
	Yes	23	100.0	0	0.0		23	100.0	0	0.0	
Creatinine (mg/dl)		0.79	0.4–10.5	0.80	0.46–1.30	0.616	0.79	0.40–10.5	0.82	0.50–2.12	0.343
Bilirubin (mg/dl)		0.75	0.1–37.6	0.70	0.30–34.30	0.188	0.75	0.10–37.60	1.25	0.10–34.30	*0.032*
Operation	PD	706	96.8	23	3.2		710	97.4	19	2.6	
	DPR	183	97.3	5	2.7		186	98.9	2	1.1	
	DPPHR	122	99.2	1	0.8		122	99.2	1	0.8	
	PE	42	100.0	0	0.0		40	95.2	2	4.8	
	other	0	0.0	0	0.0		0	0.0	0	0.0	
Operation group	other	347	98.3	6	1.7	0.171	348	98.6	5	1.4	0.220
	PD	706	96.8	23	3.2		710	97.4	19	2.6	
Pancreatic anastomosis	PG	265	95.0	14	5.0	*0.029*	274	98.2	5	1.8	0.283
	PJ	441	98.0	9	2.0		436	96.9	14	3.1	
Operative time		405	103–870	420	229–565	0.905	405	103–870	473	229–630	0.118
IntraOP transfusion	No	600	96.2	24	3.8	*0.009*	614	98.4	10	1.6	0.115
	Yes	453	98.9	5	1.1		444	96.9	14	3.1	
PVR	No	892	97.8	20	2.2	*0.026*	891	97.7	21	2.3	0.663
	Yes	161	94.7	9	5.3		167	98.2	3	1.8	
Multivisceral resection	No	907	97.8	20	2.2	*0.012*	906	97.7	21	2.3	0.797
	Yes	146	94.2	9	5.8		152	98.1	3	1.9	
POPF	No	752	99.1	7	0.9	*0.000*	749	98.7	10	1.3	*0.004*
	Yes	301	93.2	22	6.8		309	95.7	14	4.3	
PPH	No						991	98.7	13	1.3	*0.000*
	Yes						67	85.9	11	14.1	

p values derived from two-sided binary logistic regression (logreg). Time period 1/2 referring to the first/second half of all operations (1994–2005 and 2005–2012)

PPH/*POPF* postpancreatectomy/postoperative pancreatic fistula according to the International Study Group for Pancreatic Surgery (ISGPS) grading A–C, *PD* pancreatoduodenectomy, *DPR* distal pancreatic resection, *DPPHR* duodenum-preserving pancreatic head resection, *PE* pancreatectomy, *PG* pancreatogastrostomy, *PJ* pancreatojejunostomy, *OP* operation, *GIT* gastrointestinal tract, *CT* celiac trunk, *SMA* superior mesenteric artery, *PVR* portal venous resection

Statistically significant *p* values (<0.05) are written in italics

Choice of treatment options for PPH depends on clinical presentation. We therefore analyzed treatment and outcome separately in extraluminal and intraluminal PPH.

Table 5 Univariate analysis of risk factors for PPH grade C and mortality in pancreatoduodenectomy

Univariate analysis		PPH grade C				*p*	Mortality				*p*
		No		Yes			No		Yes		
		Count/ median	Row %/ range	Count/ median	Row %/ range	Logreg	Count/ median	Row %/ range	Count/ median	Row %/ range	Logreg
Period	Period 1	356	96.7	12	3.3	0.869	357	97.0	11	3.0	0.514
	Period 2	350	97.0	11	3.0		353	97.8	8	2.2	
Histopathology	Low-risk	465	97.7	11	2.3	0.080	463	97.3	13	2.7	0.772
	High-risk	241	95.3	12	4.7		247	97.6	6	2.4	
Age		62	9–89	70	44–83	*0.012*	62	9–89	71	44–80	*0.003*
Sex	Female	301	97.4	8	2.6	0.455	298	96.4	11	3.6	0.172
	Male	405	96.4	15	3.6		412	98.1	8	1.9	
Body mass index		23.7	14.5–41.2	26.3	20.6–32.7	*0.002*	23.9	14.5–41.2	25.2	18.8–32.7	0.140
Diabetes	No	625	96.6	22	3.4	0.309	631	97.5	16	2.5	0.528
	Yes	81	98.8	1	1.2		79	96.3	3	3.7	
Exocrine insufficiency	No	662	96.8	22	3.2	0.713	666	97.4	18	2.6	0.868
	Yes	44	97.8	1	2.2		44	97.8	1	2.2	
PreOP biliary drainage	No	377	95.9	16	4.1	0.133	381	96.9	12	3.1	0.415
	PBD	329	97.9	7	2.1		329	97.9	7	2.1	
Neoadjuvant therapy	No	691	96.8	23	3.2	0.999	695	97.3	19	2.7	0.999
	Yes	15	100.0	0	0.0		15	100.0	0	0.0	
Creatinine (mg/dl)		0.79	0.40–6.28	0.80	0.46–1.30	0.778	0.79	0.40–6.28	0.8	0.54–1.74	0.662
Bilirubin (mg/dl)		0.88	0.20–37.60	0.90	0.30–34.30	0.273	0.87	0.20–37.60	1.3	0.40–34.30	0.292
Pancreatic anastomosis	PG	265	95.0	14	5.0	*0.029*	274	98.2	5	1.8	0.283
	PJ	441	98.0	9	2.0		436	96.9	14	3.1	
Operation time		430	170–870	430	229–565	0.162	427	170–870	475	229–630	0.842
Intraop transfusion	No	384	95.3	19	4.7	*0.013*	394	97.8	9	2.2	0.484
	Yes	322	98.8	4	1.2		316	96.9	10	3.1	
Portal venous resection	No	569	97.6	14	2.4	*0.025*	567	97.3	16	2.7	0.641
	Yes	137	93.8	9	6.2		143	97.9	3	2.1	
Multivisceral	No	640	97.4	17	2.6	*0.012*	640	97.4	17	2.6	0.923
	Yes	66	91.7	6	8.3		70	97.2	2	2.8	
POPF	No	503	98.6	7	1.4	*0.000*	504	98.8	6	1.2	*0.001*
	Yes	203	92.7	16	7.3		206	94.1	13	5.9	
PPH	No						659	98.7	9	1.3	*0.000*
	Yes						51	83.6	10	16.4	

p values derived from two-sided binary logistic regression (logreg). Time period 1/2 referring to the first/second half of all operations (1994–2005 and 2005–2012)

PPH/*POPF* postpancreatectomy/postoperative pancreatic fistula according to the International Study Group for Pancreatic Surgery (ISGPS) grading A–C, *PD* pancreatoduodenectomy, *DPR* distal pancreatic resection, *DPPHR* duodenum-preserving pancreatic head resection, *PE* pancreatectomy, *PG* pancreatogastrostomy, *PJ* pancreatojejunostomy, *OP* operation, *GIT* gastrointestinal tract, *CT* celiac trunk, *SMA* superior mesenteric artery

Statistically significant *p* values (<0.05) are written in italics

Angiography has been advocated as the primary intervention for extraluminal PPH.[1,6] The rationale is to avoid technically difficult reoperation, damage to sensitive anastomotic regions and systemic inflammatory response resulting from operative trauma. A recent meta-analysis even demonstrated reduced mortality with angiography versus laparotomy, however there is a possibility of selection bias.[6] Our data show an overall success rate of 50 % for interventional angiography in extraluminal PPH in terms of identification of bleeding origin and hemostasis. In the remaining 50 %, there was no target because of intermittent bleeding stop, or seldomly venous bleeding origin, or interventional hemostasis was technically not feasible. The latter required operative intervention, which was successful in all cases.

In total, 3.6 % of patients were operated because of PPH, 1.7 % in the setting of late erosion PPH with associated POPF, and 0.8 % had completion pancreatectomy. The role of angiography in this situation has to be emphasized. Successful interventional hemostasis on the one hand may avoid reoperation but on the other

Table 6 Multivariate analysis of risk factors for PPH grade C and mortality

Multivariate analysis		*p*	Odds ratio	95 % confidence interval	
				Lower	Upper
PPH in all pancreatic resections	Time period 2 (recent)	0.000	0.174	0.067	0.452
	Age	0.005	1.058	1.018	1.100
	Male sex	0.012	3.484	1.320	9.198
	Body mass index	0.003	1.163	1.053	1.284
	Preop biliary drainage	0.013	0.264	0.092	0.758
	Intraop transfusion	0.008	0.222	0.073	0.674
	Portal venous resection	0.001	4.677	1.822	12.006
	Multivisceral resection	0.013	3.166	1.273	7.874
	POPF	0.000	8.432	3.279	21.684
PPH in pancreatoduodenectomy	Period 2 (recent)	0.002	0.185	0.064	0.532
	Age	0.033	1.049	1.004	1.095
	Body mass index	0.008	1.175	1.043	1.322
	Preop biliary drainage	0.003	0.187	0.062	0.561
	Intraop transfusion	0.008	0.189	0.055	0.650
	Portal venous resection	0.005	3.934	1.507	10.274
	POPF	0.001	5.589	2.120	14.737
Mortality in all pancreatic resections	High-risk histopathology	0.045	0.351	0.126	0.975
	Age	0.000	1.081	1.037	1.127
	Intraop transfusion	0.010	3.386	1.335	8.587
	POPF	0.041	2.607	1.039	6.541
	PPH	0.000	12.384	4.686	32.732
Mortality in pancreatoduodenectomy	Age	0.009	1.077	1.019	1.139
	POPF	0.003	5.127	1.717	15.311
	PPH	0.000	16.902	5.322	53.681
	Pancreatojejunostomy	0.005	5.784	1.711	19.553

p values and odds ratio derived from two-sided binary logistic regression with conditional backward elimination of parameters. Shown are only independent predictors of outcome. Time period 1/2 referring to the first/second half of all operations (1994–2005 and 2005–2012)

PPH/*POPF* postpancreatectomy/postoperative pancreatic fistula according to the International Study Group for Pancreatic Surgery (ISGPS) grading A–C

hand provides the possibility of revision procedures or completion pancreatectomy under stable conditions.

Most patients in our series were treated by coil embolization, and stenting became an option during the second (recent) time period. Stenting seems more adequate than coil embolization in situations where occlusion of major visceral vessels has to be avoided during interventional hemostasis, but we can not yet draw definite conclusions from limited experience with stenting for PPH.

Even unsuccessful angiography is of value in patients undergoing operative hemostasis. In about 70 %, the bleeding site was identified preoperatively, facilitating planning of the operation.

Indication and timing of completion pancreatectomy remains a matter of debate among pancreatic surgeons. Emergency completion pancreatectomy can be very complex and carries a high risk of mortality. While some authors advocate early indication,[18,19] others have tried to prevent completion pancreatectomy by special drainage procedures.[20–24] With regard to PPH, we performed completion pancreatectomy in the setting of erosion bleeding due to POPF, when it was felt that the bleeding site could not be securely compartmented and drained to avoid recurrent erosion.

For intraluminal bleeding, endoscopy was the most frequently chosen option but did not have a high success rate because frequently no target was identified. On the other hand, frank failure to stop bleeding was only observed in one case. These observations are in line with other series, where success rates between 20 and 42 % have been reported for primary endoscopy.[8,25] Upper gastrointestinal endoscopy was not felt to be appropriate during the first ten postoperative days because stomach and bowel distension from gas insufflation can potentially damage pancreatoenteric and bilioenteric anastomoses. Therefore, early bleeding from the pancreatic cut surface was preferentially treated operatively. Operative hemostasis as the primary intervention was successful in all intra- and extraluminal PPH but one case.

Pseudo-intraluminal PPH, i.e., extraluminal bleeding with primary manifestation as bleeding from the gastrointestinal tract at the anastomotic site, represents a specific problem. Early recognition is necessary for correct management. From our data, we draw the conclusion that in patients presenting with late gastrointestinal bleeding associated with an ongoing POPF, pseudo-intraluminal PPH should be suspected. Angiography or operative intervention is indicated instead of endoscopy in these cases (Fig. 1).

Out data regarding treatment of the grade C PPH subgroup disclosed figures similar to overall analysis in terms of success rates.

For secondary interventions after failure of primary treatment, there was a shift towards the use of secondary interventional angiography for intraluminal PPH. There is a possibility to perform the same non-operative intervention twice in case of recurrent bleeding. We do not advocate this approach and believe it should only be followed in patients which are hemodynamically stable. However, the numbers of secondary interventions are too small to draw definite conclusions.

Due to the large patient cohort of this study, we were able to perform multivariate analysis for risk factors of PPH grade C and mortality. Previous studies have assessed risk factors for the endpoint PPH or delayed PPH, however to date there is no report for specific analysis of grade C PPH. Multivariate analysis provides the opportunity of adjustment for confounding factors, leading to more valid identification of risk factors than univariate analysis.[26] Several patient- and surgeon-side predictors of PPH grade C could be identified.

Independent patient-side risk factors for grade C PPH included high age and BMI and male gender. While age[2,27] and BMI[10,28] are known to adversely influence operative risk, a clear explanation for higher risk in male patients is lacking.

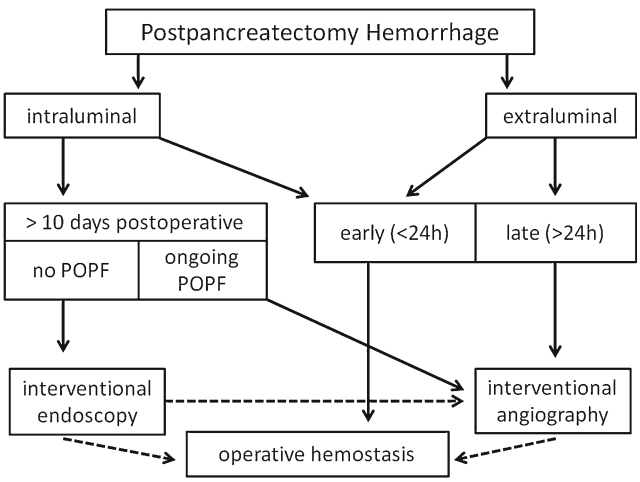

Fig. 1 Proposed treatment algorithm for postpancreatectomy hemorrhage. *Dotted arrows* denote secondary treatment options in case of primary treatment failure. Abbreviations: *HD* hemodynamically, *POPF* postoperative pancreatic fistula

Multivisceral and portal venous resections as well as intraoperative transfusion are risk factors that can be influenced by the surgeon in terms of patient selection and operative technique. Of note and contrary to several single-center series, PVR has also been identified as a risk factor for perioperative morbidity and mortality in the scope of the National Surgical Quality Improvement Program.[29]

There was also evidence of a learning effect over time. With increasing numbers of pancreatic resections over time (first half of resections over 12 years, next half over 8 years), the incidence of PPH grade C decreased significantly (odds ratio 0.174). We also noted a non-significant improvement regarding the success rates of first-line angiography for PPH. These data constitute a strong argument for centralization of pancreatic surgery as suggested by large-scale survey of pancreatic surgery.[30]

The fact that PBD was an independent protective factor may be interpreted. PBD is often necessary in large tumors which also obstruct the main pancreatic duct (MPD), leading to MPD dilatation and fibrotic changes in the remnant pancreas and reduced risk of POPF. On the other hand, PBD for cholestasis improves vitamin K deficiency and hepatic function, both of which theoretically contribute to better hemostasis and wound healing. We know however from a randomized trial that PBD significantly increases infectious complications after PD[31,32] and therefore share other authors' opinion that PBD should be avoided if possible.

As PPH was strongly associated with perioperative mortality, we conducted uni- and multivariate risk factor analysis for mortality, too. PPH indeed was the strongest independent predictor with an odds ratio of over 12 in the total collective and pancreatoduodenectomy subgroup. In line with etiology of PPH grade C and confirming large-scale survey,[33] POPF was another independent risk factor for mortality. Based on previous studies from our institution and others,[3,8,10,14–17] we empirically defined conditions usually associated with a soft pancreas as high-risk because there is an elevated risk for POPF. This categorization is validated by the fact that a high-risk pancreas was an independent predictor of mortality.

The observation that intraoperative transfusion and PJ were independent risk factors of mortality is important because these can be influenced by the surgeon. The fact that PG, while associated with more bleeding from the pancreatic cut surface, was independently and significantly associated with decreased mortality is a strong argument in favor of this anastomotic technique. We observed that mortality in critical conditions like extraluminal PPH and completion pancreatectomy for PPH was lower in patients with PG compared to PJ. Our interpretation is that PPH and underlying POPF and septic conditions tend to resolve better with PG than with PJ. This is supported by recent randomized studies showing reduced POPF and

complication rates with PG.[34–36] Furthermore, completion pancreatectomy is less technically complex when pancreatic anastomosis and hepaticojejunostomy are physically well separated like in the case of PG.

Empirical measures against the observed intraluminal bleeding from the PG may be suggested. The first is meticulous hemostasis of small arteries on the pancreatic cut surface, with non-absorbable suture material preferred over electrocoagulation. Another is the routine use of proton pump inhibitors to reduce erosion of the pancreatic surface. However, these measures have not been evaluated for effectiveness in a clinical study.

Limitations of the current study are its retrospective nature and the low incidence of the subject under examination. In order to obtain data amenable to statistical evaluation, we used a very large case number for this study. Prospective randomized studies evaluating treatment options of PPH have not been performed and will hardly be feasible due to the low incidence numbers and heterogeneity of clinical presentation.

In summary, we performed one of the largest and the most detailed comprehensive analysis of incidence, risk factors, and treatment of PPH so far. Several conclusions of clinical relevance can be drawn from our study.

Regarding treatment, we conclude that interventional angiography is a valid option to avoid reoperation or supplement operative treatment by identification of bleeding origin, even when interventional hemostasis is only possible in about half of cases. Endoscopy often does not identify the origin of mild intraluminal bleeding and should be avoided when pseudointraluminal PPH is to be suspected. Our recommended algorithm of treatment is depicted in Fig. 1.

Pancreatic surgeons should be aware of the identified risk factors for grade C PPH and mortality. Centralization of pancreatic surgery is associated with better outcome and less grade C PPH. Our data suggest that elderly patients with high BMI are poor candidates for portal venous or multivisceral resection procedures. In addition, the high-risk group of cystic neoplasms of the pancreas and non-pancreatic periampullary cancers can frequently be diagnosed or at least suspected before the operation. Even though PBD was associated with reduced PPH, we do not advocate it due to reasons discussed above. Intraoperative bleeding and transfusion should be minimized to lower the risk of PPH, probably at the expense of operative time which was not a predictor of PPH. One of the strongest risk factors is POPF, which means that by lowering POPF rate, PPH and mortality can be reduced. As reconstruction by pancreatogastrostomy was associated with more intraluminal bleeding events, we recommend careful suture hemostasis and routine perioperative proton inhibitor therapy. In spite of that, pancreatogastrostomy seems to be safer than pancreatojejunostomy in terms of overall mortality after pancreatoduodenectomy.

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