

Postpancreatoduodenectomy Hemorrhage: Association between the Causes and the Severity of the Bleeding

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Keywords

Pancreatoduodenectomy · Postpancreatoduodenectomy hemorrhage · Pseudoaneurysm

Abstract

Introduction: Of the complications following pancreatoduodenectomy (PD), postpancreatoduodenectomy hemorrhage (PPH) is the least common, but severe forms can be life-threatening without urgent treatment. While early PPH is mostly related to surgical hemostasis, late PPH is more likely due to complex physiopathological pathways secondary to different etiologies. The understanding of such etiologies could therefore be of great interest to help guide the treatment of severe, potentially life-threatening, late PPH cases.

Objective: The aim of this retrospective study was to assess the causes of PPH as a complication and explore a possible association between the causes and the severity of late PPH.

Methods: A retrospective study was performed at the HPB and Surgical Oncology Unit, Rambam Health Care Campus, Haifa, Israel. The charts of all patients submitted for PD were reviewed, and all patients with PPH were included. The timing, cause, and severity of PPH as well as other information were collected. A statistical analysis on the possible association between cause and severity of late PPH was performed.

Results: A total of 347 patients underwent PD, 18 of whom (5.18%) developed PPH. Early PPH was reported in 1 patient

(5.6%) with severe bleeding from the gastric staple line. Late PPH was reported in 17 patients (94.4%). The most common causes of late PPH were bleeding from a vascular pseudoaneurysm (PSA) reported in 6 patients, 1 with mild and 5 with severe hemorrhage, and bleeding from a gastroenteric anastomosis marginal ulcer reported in 6 patients, all with mild hemorrhage. No etiology was found in 5 patients with mild hemorrhage. A significant association was found between the severity of late hemorrhage and vascular PSA as the cause of the bleeding ($p = 0.001$). All PSA bleeding occurred in cases complicated by a postoperative pancreatic fistula (POPF), with a significant statistical association ($p < 0.001$).

Conclusions: The most common cause of PPH was bleeding from a vascular PSA; the majority of these cases involved severe bleeding with late presentation, and all were associated with a POPF formation. In such cases, early detection by computed tomography angiography is mandatory, thereby promoting urgent treatment by angiography of vascular bleeding complications following PD.

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Introduction

Pancreatoduodenectomy (PD) is a complex, highly challenging operation to perform. The first successful 1-stage PD was reported by Allen Whipple in 1945, when

he successfully anastomosed the pancreatic duct to the jejunum [1]. Although Whipple was the first to report the single-stage PD procedure, Verne Hunt was the first surgeon to successfully restore pancreaticoenteric anastomosis following PD in 1941 [2]. PD is the surgical procedure of choice for the treatment of benign and malignant diseases of the periampullary region (the head of the pancreas, ampulla of Vater, distal common bile duct, and second part of the duodenum), severe trauma to the pancreatic head and duodenum, and highly selective cases of chronic pancreatitis [3, 4]. The mortality rate following PD was initially high at almost 25%, but, as a result of the development of specialized centers, along with the improvement in perioperative care and advances in surgical techniques, mortality rates have fallen to <1%, especially in high-volume centers [5–8]. Nevertheless, the morbidity rate following PD remains high, with almost 30–40% of patients developing ≥ 1 complication [9, 10]. The most common complications following PD are delayed gastric-emptying, postoperative pancreatic fistula (POPF), intra-abdominal collections, biliary anastomotic leakage and post-PD hemorrhage (PPH), the last being the least frequent to occur. The incidence rate of PPH is 5–16%, with severe bleeding occurring in <10% of patients. The condition may be life-threatening if urgent treatment is not performed, and it is usually associated with high morbidity and mortality, especially if surgical intervention is required [11, 12].

According to the International Study Group of Pancreatic Surgery (ISGPS), PPH can be classified into early and late PPH [13, 14]. While early PPH is mostly related to surgical hemostasis, late PPH is more likely due to more complex physiopathological pathways. PPH that develops early following the index operation can be due to bleeding vessels (branches of the portal vein or the superior mesenteric artery [SMA]), or bleeding from one of the anastomoses. Late PPH could be due to a marginal ulcer (mostly at the gastroenteric anastomosis) or a bleeding vascular pseudoaneurysm (PSA), mostly involving the gastroduodenal artery (GDA) stump, and may develop following pancreatic leak and vessel erosion [15].

The understanding of the etiology of such a pathway could therefore be of great interest in cases of severe hemorrhage to guide the treatment of a potentially life-threatening condition that could be otherwise preventable. The aim of this retrospective study was to assess the cause of PPH as a complication and explore the possible association between the cause and severity of late PPH.

Methods

A retrospective study over a period of 8 years, from 1 January 2011 to 31 December 2018, was performed at the Hepato-Pancreato-Biliary (HPB) Unit of the General Surgery Department at Rambam Health Care Campus, Haifa, Israel. All patients aged ≥ 18

years who underwent PD were included in the study. Patients who underwent PD for severe trauma to the pancreatic head or duodenum, or other forms of pancreatic resection such as distal or total pancreatectomy, were excluded from the study. Patients were checked for readmission to our hospital or to other medical centers.

The 3 main outcomes were: timing of onset, cause of hemorrhage, and severity of hemorrhage. Other data included clinical manifestation of the hemorrhage, investigational modules used for diagnosis, management, and mortality rate. Possible risk factors for PPH relating to both surgical complications (e.g., POPF, intra-abdominal abscess) and the patient (e.g., anticoagulant or antiaggregant therapy and final pathology) were also registered.

Timing of PPH was classified according to the ISGPS, into early and late PPH; early is when the bleeding occurs within 24 h of the index operation and late is when bleeding develops >24 h after it [14, 15].

Causes of PPH were defined by the lesion found at the site of the bleeding. The cause was classified as unknown when no bleeding site was found on CT scan or endoscopy according to the clinical manifestation of the bleeding.

The severity of the hemorrhage was classified according to the ISGPS criteria into: mild PPH in case of small-medium blood loss (a decrease in hemoglobin level <3 g/dL) which leads to mild clinical impairment, and severe PPH (a decrease in hemoglobin level of ≥ 3 g/dL) which usually results in hemodynamic instability [14, 15].

The cases of POPF were registered according to the classification reported by Bassi et al. [16], with grade A POPF being replaced by biochemical leak.

Since it is in late PPH that the knowledge of a possible association between the cause and severity of PPH could be of interest in planning treatment, this association was statistically tested by comparing the respective frequency of causes in patients with mild PPH and patients with severe PPH.

The role of possible risk factors for PPH was investigated by comparing their frequency in patients without PPH and patients with PPH in a univariate analysis. The analysis was completed by investigating a possible association between clinically relevant potential risk factors, such as surgical complications and PSA as major causes of late PPH, by comparing the respective rates in patients with and without bleeding PSA.

Continuous variables are summarized as mean and SD and discrete variables are categorically expressed as n (%). Student's t test was used for continuous variables. The χ^2 or Fisher's exact test, depending on the results, was used for variables that were dichotomous. A p value <0.05 was considered significant.

Results

During the study period, 347 patients underwent PD for the management of diseases in the periampullary region. PPH was registered in 18 patients (5.2%), 10 males and 8 females (ratio 1.25:1). The average age was 68 years (range 22–85 years).

As reported in Table 1 and Figure 1, the timing of the bleeding was early in 1 patient (5.6%), and late in 17 (83.3%). The patient with early PPH had severe bleeding from the gastric staple line. In the cases of late PPH, the most common causes were bleeding from a vascular PSA

Table 1. Summary of timing, site of bleeding, and severity of PPH

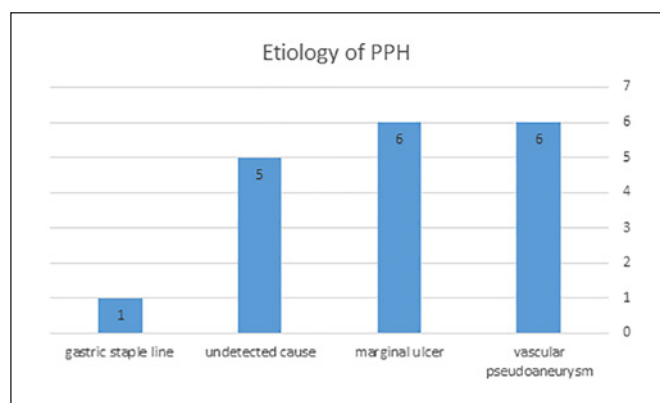
	Mild	Severe	Total
Early			
Gastric stapler line	0	1	1
Late			
Pseudoaneurysm	1	5	6
Marginal ulcer	6	0	6
Unknown	5	0	5
Total	12	6	18

in 6 patients (1 with mild and 5 with severe hemorrhage) and bleeding from a gastroenteric anastomosis marginal ulcer in 6 patients (all with mild hemorrhage). No etiology was found in 5 patients with mild hemorrhage. Overall, hemorrhage was mild in 12 (66.6%) and severe in 6 (33.3%) patients. According to the ISGPS classification, no Grade A bleeding was observed, 13 patients had Grade B bleeding, and 5 had Grade C bleeding.

Blood discharge from the drain was the most common presentation and was reported in 11 patients (61.1%). As our routine practice, 2 Jackson-Pratt drains are placed in the abdominal cavity of all patients undergoing PD. These are stationed in the right upper abdominal space near the pancreatico- and hepatico-jejeunal anastomosis. Patients are usually discharged with the drains and then followed up at our outpatient clinic a week later. Of these patients with blood discharge from the drain, 8 had been previously diagnosed with POPF, and none had sentinel bleeding into the drains upon their discharge. A total of 7 patients (38.9%) presented with signs of upper gastrointestinal bleeding, with hematemesis reported in 6 and a continuous bloody discharge from the nasogastric tube in the remaining patient.

The patient with early severe hemorrhage was hemodynamically unstable. Urgent surgery was performed. Active bleeding from the gastric stapler line was found and a hemostatic suture was used to stop the bleeding. During PD at our center, gastroenterostomy anastomosis is performed by means of a circular stapler inserted through an anterior wall gastrotomy, which is, in turn, closed with a linear stapler afterwards.

In the cases of late PPH, vascular PSA was the cause of bleeding in 6 patients, involving the GDA in 5 cases and the inferior pancreaticoduodenal artery in 1. One was a mild case and 5 involved severe hemorrhage. Computed tomography angiography (CTA) was diagnostic for all cases of bleeding PSA, which indicates a high specificity of this exam in the diagnosis of PPH. All patients were successfully treated by means of angiographic embolization using different methods.

**Fig. 1.** Distribution of causes of PPH.

Bleeding from a marginal ulcer of the gastroenteric anastomosis was found in 6 patients, all of whom had undergone PD with a Roux-en-Y reconstruction. PPH was late with mild hemorrhage in all of them. All were treated by endoscopy and had an average of 2 units of packed red blood cells (PRBC) transfused.

All patients with bloody discharges from the drain and an unknown etiology upon completing a hemorrhage screen workup presented as late PPH. A negative CTA scan and negative endoscopy were reported in 4 cases, while no diagnostic tests were performed in 1 case of limited bloody discharges from the drain. All cases were treated conservatively, with transfusion of an average of 3 units of PRBC per patient. In all cases, the bleeding responded to conservative treatment, leaving no merit to performing a surgical intervention.

Urgent surgery was performed in 1 patient due to hemorrhagic shock. Urgent CTA was performed in 10 patients with bloody discharge from the drain. Urgent endoscopy was performed in 6 patients with gastrointestinal bleeding. In 1 patient with mild hemorrhage, no diagnostic tests were performed. No mortality was registered due to PPH.

For the statistical analysis evaluating the association between the cause and severity of PPH, no severe bleeding from marginal ulcers and no severe unknown hemorrhage were diagnosed, so no χ^2 test was conducted. By grouping unknown etiology with marginal ulcer bleeding, PSA was found to be significantly associated with severe hemorrhage. The rate of PSA was 100% in patients with severe bleeding compared to 8.3% in patients with mild hemorrhage ($p = 0.001$, Fisher's exact test).

As reported in Table 2, no significant association was found between possible risk factors for PPH (whether relating to surgical complications or patients) and the incidence rate. The overall rate of POPF was 26%, but this complication occurred in 8 (44.4%) patients with PPH, all

Table 2. A comparison between patients with and without PPH

	Patients with PPH	Patients without PPH	<i>p</i> value
Number of patients	18	329	
Average age, years (range)	68 (22–85)	64 (19–86)	0.16
Male-to-female ratio	1.25	1.27	0.97
Anticoagulant/antiaggregant treatment	15 (83.3)	279 (84.8)	0.87
Roux-en-Y classic PD performed	18 (100)	329 (100)	1
POPF	8 (44.4)	82 (24.9)	0.07
Intra-abdominal abscess	2 (11.1)	36 (10.9)	1
Pathology			
PDA	10 (55.5)	201 (61.1)	0.64
IPMN high-grade dysplasia	3 (16.7)	46 (14)	0.73
IPMN low-grade dysplasia	1 (5.6)	29 (8.8)	0.44
Neuroendocrine tumor	1 (5.6)	9 (2.7)	0.42
Duodenal adenocarcinoma	1 (5.6)	9 (2.7)	0.42
Distal CBD/ampulla adenocarcinoma	0	26 (7.9)	0.38
Pancreatic papillary pseudotumor	0	2 (0.6)	1
Normal pancreas	2 (11.1)	7 (2.1)	0.07

Values express *n* (%), unless otherwise indicated. PPH, postpancreatectomy hemorrhage; PD, pancreatoduodenectomy; PDA, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm; CBD, common bile duct; POPF, postoperative pancreatic fistula.

of whom had a biochemical leak. Although the difference in the rate of POPF in patients with and without PPH was 19.4%, the association between POPF and PPH was not statistically significant ($p = 0.07$); however, the estimated power of such a comparison is <50%. Moreover, although POPF was not found to be a risk factor for PPH, all patients who bled due to PSA were initially diagnosed with a biochemical leak (previously POPF grade A, according to the ISGPF definition of POPF). The association between POPF and PSA was found to be statistically significant with a POPF rate of 100% in patients with bleeding PSA and 26% in patients with no bleeding PSA ($p < 0.001$), suggesting the potential role of POPF in the development of a bleeding PSA as a cause of late PPH.

Discussion

The results of this study show that most of the patients suffered from late PPH, and that bleeding vascular PSA was the most common cause of severe late PPH. Moreover, a significant association was found between vascular PSA bleeding and an initial diagnosis of POPF.

It was a retrospective study, but all consecutive patients treated in the period already mentioned were included. Data are stored in a database that allows easy selection of cases of interest based on diagnosis, intervention, and postoperative complications. Rambam Health Care Campus is a referral center for 10 other hospitals that give medical cover for 2 million citizens, particularly

all patients for whom major pancreatic surgery is indicated. Our study should therefore be considered as having a low risk of selection bias.

Some concern should be advocated about the cases for which no etiology was found. A recent meta-analysis reported a sensitivity of 56% for CTA in identifying the source of bleeding following pancreatectomy [17], so the high incidence of false-negative diagnoses could affect the association found between several causes of late severe bleeding. No details about the original studies were provided in the meta-analysis, but the low sensitivity of CTA scan in diagnosing vascular PSA could be explained by the intermittent characteristics of the bleeding in cases of PPH [18]. Data on gastrointestinal bleeding reported in a recent review suggest that, in cases of massive gastrointestinal bleeding, the sensitivity and specificity of CTA scan are much higher. Moreover, a negative CTA scan could be considered a good prognostic result, as patients with no bleeding evident on the scan are unlikely to have massive bleeding [19]. This observation may be valid for gastrointestinal bleeding, but no data on PSA as a cause of PPH were found. According to a recent review, a self-limiting episode of bleeding, so-called sentinel bleeding, may be the initial manifestation of PPH [18]. In these cases, CTA scan may also be negative, but extra caution must be exercised due to the fact that sentinel bleeding may precede a severe PPH in 50–80% of cases, thus requiring intensive monitoring and specific diagnostic workup. In our series, the cases of bleeding with an unknown origin should not be considered as sentinel bleeding since they

were all self-limited and no further hemorrhage was observed in any of them.

Recent published studies on PPH have no homogeneous methodology. A literature research limited to the past 10 years found studies reporting PPH complicating a series of pancreatectomies [20–26]. Others, like this study, have focused on PD [27–33], and some report results mainly related to late PPH [26, 30, 32]. Other studies produced results about the treatment of PPH cases [34–44] and focused mainly on series of late PPH. In 1 series, PPH was classified according to the timing as early, intermediate, or late, but the only reported cases were intermediate or late [45].

The reported rate of PPH varies from 3 to 16.8% across studies, i.e., those covering all types of pancreatectomy [20–26], and those focusing on PD [27–29, 31, 45]. Only a handful has reported a rate >10% [21, 24, 26, 29]. All series also reported that late PPH occurred more frequently than early PPH, with a rate >75% compared to 90% in our study. Only 1 study from Italy [26] reported a rate of late presentation of 45%. This particular study had the biggest series of pancreatectomies, 2,429 cases in 13 years; the lower rate of late PPH is related to the finding that 77% of the patients had Grade B bleeding. The overall rate of late PPH as a complication of pancreatic surgery varies from 2.3 to 13.1% in the more recent studies [20, 22, 23, 25–27, 29–33]. These results are comparable to previous studies included in a meta-analysis that reported an overall rate of late PPH of 3.3% (range 1.6–12.3%) [46].

Severe late PPH, classified as Grade C by the ISGPS, is, however, the less common type. In our study, 29.4% of late PPH cases were severe. The data reported in the literature ranges mainly from 26.6 to 53.8% [20, 22, 23, 25, 26, 30–33]. However, 1 small series of 87 PD in over 3 years reported a rate of severe late PPH of 90% [27].

As recommended in a recent review, the best approach should be tailored based on the clinical manifestation and the timing and severity of the bleeding [18]. However, the cause of bleeding also plays a role in PPH treatment strategy. Intraluminal bleeding may be approached by endoscopy first, while CTA is preferred for extraluminal bleeding. In cases where the site of bleeding cannot be found at the first examination, a diagnostic workup should be completed [47]. Based on nonanalytic data, some authors suggest performing a CTA scan, even in cases of a diagnosed cause of intraluminal bleeding on endoscopy. The finding of a mild bleeding cause might distract the physician from further severe bleeding causes, which can delay intervention and worsen the outcome [18]. This conclusion is not confirmed by the data of our study.

In all cases of intraluminal bleeding, a cause was found at endoscopy. In the cases of extraluminal bleeding, the cause was found in only 6/10 patients. In patients with no apparent cause of bleeding, a full thorough diagnostic

workup was completed, with a negative endoscopy in all cases. All 4 of these patients manifested with self-limited bleeding with no clinical worsening of the PPH.

Early PPH is usually due to the technical failure of hemostatic factors used during surgery, and it can be mild or severe. In our study, 1 patient developed early PPH, manifesting as a bloody discharge from the nasogastric tube. Due to continuous bleeding, along with a severe decrease in hemoglobin level, she underwent a reoperation, during which a bleeding from the gastric staple line was detected, a primary suture was placed, and the bleeding stopped.

Late bleeding could be due to marginal ulcers, or bleeding from the resection bed, the anastomosis, or the vascular stump, or an arterial PSA. The majority of our patients suffered from late PPH (94.4%), with a bleeding vascular PSA the most common cause of late severe bleeding (6/17 patients, 5 with a GDA PSA and 1 with an inferior pancreaticoduodenal artery PSA). Recent studies focusing on PD [27–33, 45] have confirmed that the GDA stump is the most common site of bleeding. However, the clear description of a PSA is not always reported, and it may not always be clear whether the bleeding indeed arose from direct leakage from the artery stump, or a PSA that formed after surgery. Of 7 PSA cases, an extravasation of contrast material (suggesting active bleeding) was observed in only 2 patients, and 2 others showed signs of active bleeding with no PSA reported [31].

As a result, the exact prevalence of PSA in cases of late PPH may be underestimated. The rate of PSA as a cause of late severe bleeding is reported to be 28.5–38.8% in late PPH [17–19, 35, 44]. A statistical association between PSA and bleeding has not yet been explored. The most interesting finding of our study was the statistically significant association between late severe bleeding and arterial PSA as a cause of bleeding. Moreover, 83.3% of severe bleeding was caused by PSA, and the second-most common site of bleeding was the pancreaticoduodenal artery, a rare site of bleeding that has previously been reported only as a sight of sporadic bleeding [34, 37, 40].

Of the post-PD complications, POPF has been reported to increase the risk of PPH and has been associated with late bleeding in 48.1–78.5% of cases [30, 31, 45]. Our finding of 44.4% of POPF in PPH could be considered congruous with the data reported in the literature.

Interventional radiology (IR) has become a valuable diagnostic approach, allowing a definitive treatment by embolizing or stenting bleeding arteries in cases of extraluminal PPH. All the cases in our study were treated successfully by IR. Whether embolization or stent placement insertion is performed depends mainly on the site of the bleeding as well as the length of the GDA stump. In cases of a short GDA stump, hepatic artery stenting to bypass the bleeding site is the preferred management method,

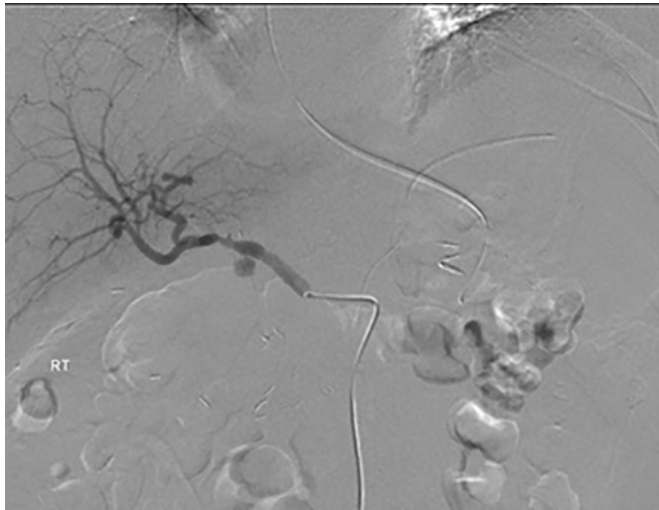


Fig. 2. Selective angiography of the celiac artery reveals PSA of the GDA (arrow).



Fig. 3. Control of bleeding was achieved by stent insertion into the hepatic artery to bypass the PSA (arrow).

Table 3. Description of patients that presented with PPH due to bleeding vascular PSA

Case No.	Age, years	Sex	Indication for PD	Postoperative complications	Vascular resection	Presentation	Findings on CTA	Angiographic management
1	80	M	MD-IPMN	PE, BL	No	hematemesis	PSA of the GDA	stent graft into the CHA (Fig. 2, 3)
2	84	M	PDA	BL	No	blood in drains	PSA of the GDA	stent graft into the CHA
3	67	F	LG-PIN	BL	No	blood in drains	PSA of the GDA (Fig. 4)	coil embolization of the CHA
4	68	M	PDA	BL	No	hematemesis	no active bleeding	stent graft into the CHA
5	68	M	PDA	BL	No	hematemesis	active bleeding from branch of SMA (Fig. 5)	glue embolization
6	74	F	PDA	BL	No	blood in drains	PSA of the GDA	stent graft into the CHA

M, male; F, female; PD, pancreaticoduodenectomy; MD-IPMN, main duct intraductal mucinous neoplasm; PDA, pancreatic duct adenocarcinoma; LG-PIN, low-grade pancreatic intraepithelial neoplasm; PE, pulmonary embolism; BL, biochemical leak; CTA, computed tomography angiography; PSA, pseudoaneurysm; GDA, gastroduodenal artery; IPDA, inferior pancreaticoduodenal artery; CHA, common hepatic artery; SMA, superior mesenteric artery.

while long GDA stumps are usually embolized with coils or glue (Table 3; Fig. 2–4). In 1 patient, the bleeding originated from a branch of the SMA, suspected to be the inferior pancreaticoduodenal artery stump (Fig. 5). This allowed a definitive treatment without major complications following the procedure. In the literature, the role of IR is well documented [34–44], but the reported success rate varies. Relapse bleeding, requiring more than an IR approach before treatment could be considered as definitive (reported in up to 47.6%) [36–44]. A failure of IR was reported in up to 13% of cases in most of the studies [34, 36, 38, 41, 43, 44], with 1 [42] reporting a failure rate of 35%.

Major hepatic complications have been reported in up to 23.8% of cases [48]. The risk of hepatic failure or hepatic abscess formation increased when performing an embolization of the hepatic artery following a pancreatectomy involving the head of the pancreas. In such cases, stenting is the preferred method of treatment.

Among PPH cases, a mortality rate ranging from 0 to 39.7% has been reported, and is associated with early PPH, late PPH, and treatment complications [20, 22, 23, 25, 26, 28–32, 34, 37–41, 43–45]. Studies focusing on late PPH report a mortality rate in the range of 7.1–23.8% [34, 37–41, 43, 44]. In our study, no mortality was registered.



Fig. 4. On abdominopelvic CTA, a PSA of the GDA was demonstrated with contrast blush (arrow). A J-P drain inserted during operation can be seen next to the bleeding site.

The results of our study confirm most of the literature findings on PPH and include clinical presentations and late severe PPH treatment. A significant association between severe late PPH and PSA bleeding is of clinical importance. A finding of 1 PSA with mild bleeding suggests that PSA may form with no initial clinical importance but may nevertheless cause severe hemorrhage in the following stages. Although this would not alter the therapeutic approach, it should also be studied, to distinguish true PSA from bleeding secondary to arterial stump leakage.

Conclusion

PPH is a less common, yet well-known complication following PD, with a wide range of incidence rates. A significant association was found between the cause and severity of the bleeding, with PSA as the cause of all severe cases of late PPH, and a bleeding marginal ulcer as the cause of mild PPH. POPF was also found to be associated with PSA, which, in turn, was the major cause of late severe bleeding. In future studies, the distinction between true PSA and arterial stump leakage should be made.

Statement of Ethics

This article does not contain any experimental studies with human participants or animals performed by any of the authors. The study was approved by the Ethics Committee. Due to the retrospective nature of the study, informed consent was waived. The study was approved by the review board of our Department.

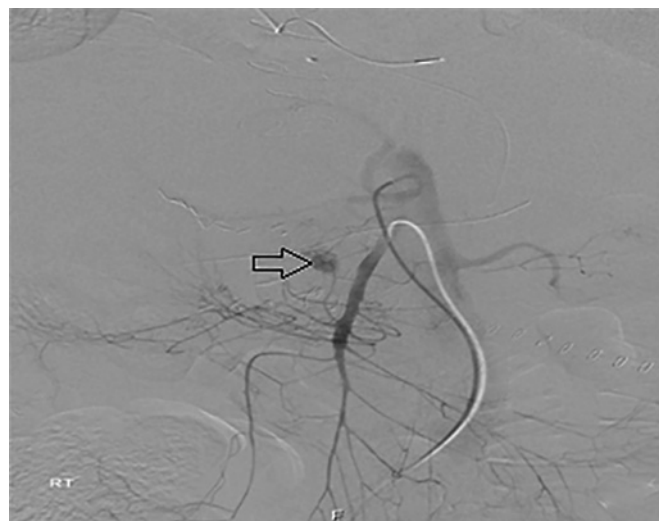


Fig. 5. Selective angiography of the superior mesenteric artery (SMA), showing an active bleeding from a branch of the SMA suspected to be from the inferior pancreaticoduodenal artery stump (arrow).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There were no funding sources.

Author Contributions

Acquisition of the data was made by Ameer Azzam and Amir Obeid and analysis and interpretation were done by Safi Khuri. The paper was drafted by Safi Khuri and Subhi Mansour, and critical revision and final approval of the published version was done by Yoram Kluger and Giuseppe Borzellino. All parties agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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