

Management and Outcome of Late Post-Pancreatectomy Hemorrhage After Pancreaticoduodenectomy: Experience From a High-Volume UK Tertiary Center

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Abstract

Background: Delayed bleeding after pancreaticoduodenectomy (PD) is a serious complication with significant morbidity and mortality. The aims of the study were to evaluate the incidence, management, and outcomes of late (> 24 h) post-pancreaticoduodenectomy hemorrhage (PPH) after PD in a high-volume tertiary referral center.

Methods: A retrospective analysis of a prospectively maintained database of 1,184 patients who underwent PD between 2011 and 2023 was performed. Patients who developed late PPH were identified. Diagnostic investigations included computed tomography (CT) angiography, invasive angiography, and endoscopy. Interventions included endovascular treatment (embolization and/or stent graft placement) and laparotomy.

Results: Twenty-three patients (1.94%) developed late PPH, at a median onset of 15.6 days after surgery. Of late PPH cases, 62.5% were associated with pancreatic fistula. Eighteen patients (78.3%) underwent endovascular therapy, whilst five patients (21.7%) required surgery. The gastroduodenal artery (GDA) was the most common source of bleeding (43.5%). In-hospital mortality was 17.4%.

Conclusions: Late PPH after PD is a rare but serious complication with a high mortality rate. Early detection with CT angiography and endovascular treatment is effective in managing most cases, reducing

ing morbidity and mortality. Surgery remains a secondary option for refractory bleeding.

Keywords: Pancreaticoduodenectomy; Pseudoaneurysm; Bleeding; Arterial embolization

Introduction

Hemorrhage is one of the most serious complications following pancreaticoduodenectomy (PD). The incidence is relatively low (1.5–15%) but the associated mortality remains high (up to 38%) [1]. Recurrent bleeding after initial management can be significant as well (up to 30%) [1]. Bleeding within the first 24 h after the operation is termed early and is usually due to insufficient hemostasis in the surgical field. As per the International Study Group of Pancreatic Surgery (ISGPS) guidelines, any bleeding after the first postoperative day is classified as late and usually occurs within 1–4 weeks [2]. Bleeding can be in the peritoneal cavity or intraluminally within the gastrointestinal (GI) tract and the main contributing factor is pancreatic anastomotic leak. Other causes include vascular wall trauma or thermal injury during dissection, bile leak, mechanical irritation from surgical drains, staple line bleeding or early mucosal ulcers mainly in the stomach often in the region of gastrojejunostomy [3]. The typical scenario is intraperitoneal bleeding due to a pseudoaneurysm formation following pancreatic anastomotic leakage most commonly involving the gastroduodenal artery [2]. Late post-pancreaticoduodenectomy hemorrhage (PPH) commonly presents with a sentinel bleed, defined as evidence of minimal blood loss in the surgical drains or GI tract followed by an asymptomatic interval until the development of acute hemorrhagic shock, and is an important clinical indicator of pseudoaneurysm formation [4].

Currently, angiogram and endovascular treatment with embolization or stenting is considered the first option for definitive management for late PPH. Surgery may also be required, and indications include failed radiological control, recurrent bleeding, evidence of concomitant intraabdominal

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sepsis or lack of interventional radiology facilities [5]. When there are signs of delayed bleeding, early investigations and planned interventions (interventional radiology or surgery) result in definitive management and improved outcome.

Materials and Methods

This is a retrospective cohort study conducted in line with Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines after departmental approval at the University Hospitals Birmingham, United Kingdom, a tertiary center for pancreatic surgery [6]. Within a 12-year period (2011–2023) all patients that had any type of PD, classical or pylorus preserving, with or without vascular resection, were identified from a prospectively maintained database. Patients with signs of late postoperative hemorrhage (> 24 h) in the peritoneal cavity or in the GI tract, that underwent surgical or radiological intervention were included in the study. Patients that had suspected bleeding (e.g. hemoglobin drop, melaena, etc.) without any systemic response, transfusion requirement or radiological evidence of bleeding and did not require any intervention were excluded from the study. Investigations included computed tomography (CT) angiogram, invasive angiogram, routine blood tests, and upper GI endoscopy. Surgical intervention included suturing of bleeding vessel, packing and damage control surgery, and completion pancreatectomy. Endovascular treatment included embolization of pseudoaneurysm and stent graft insertion or both. Demographic, clinical biochemical, hematological, and radiological data were obtained from the hospital electronic records and the departmental prospectively maintained database.

Institutional Review Board (IRB) approval

This study was conducted as a retrospective cohort service evaluation at University Hospitals Birmingham NHS Foundation Trust and was reviewed according to local governance procedures. In line with UK Health Research Authority (HRA) guidance, it does not constitute research and did not require IRB approval.

Ethical compliance with human subjects

All procedures were conducted in accordance with institutional ethical standards for service evaluations and UK Health Research Authority guidance for studies that do not constitute research.

Results

A total of 1,184 PDs were performed between 2011 and 2023. Twenty-three (1.94%) patients had evidence of late PPH at a median of 15.6 (range 1–43) days (Table 1). In patients with evidence of post-operative pancreatic fistula (POPF), the

median time to late PPH was 14 days. There were 18 male (78.3%) and five female patients (21.7%) with a median age of 62 years. Four patients (two male and two female) had a concomitant vascular resection. Fifteen (62.5%) patients had pancreatic fistula confirmed by biochemical test of drain fluid (fluid amylase > × 3 normal serum amylase) at the time of bleeding (Table 2).

The majority of patients (20/23, 86.9%) had a systemic response following bleeding, identified by the National Early Warning Score (NEWS) assessment. Ten patients (43.5%) had bleeding in the surgical drain, and 13 patients (56.5%) had bleeding within the upper GI tract mostly evident with hematemesis or blood in the nasogastric tube. The majority of patients 20/23 (86.9%) had a CT angiogram within 12–24 h from the onset of bleeding.

Upper GI endoscopy, which was mainly diagnostic, was performed in two patients without clearly identifying any active bleeding point. No endoscopic interventions were performed in any of those patients.

Five patients (21.7%) underwent surgery and 18 (78.3%) endovascular treatment. Of those undergoing endovascular treatment, eight (34.8%) underwent coil embolization of an artery pseudoaneurysm, seven (30.4%) had a stent-graft placement, two (8.7%) had both embolization and stent graft, and one (4.3%) had a failed embolization. Of the patients who underwent surgery, two had oversewing of the gastroduodenal artery (GDA) stump, one had oversewing of the gastrojejunostomy suture line, one underwent general hemostasis with no obvious bleeding point identified, and one had bleeding from the pancreatic stump controlled.

The GDA was the location of bleeding in 10 patients (43.5%). Other areas included the right, left or common hepatic artery, the superior mesenteric artery (SMA), the left gastric artery, and splenic artery branches. In two patients, there was no obvious bleeding point identified in repeated imaging or invasive angiogram and in two patients the site of bleeding was early ulceration of the gastrojejunostomy. The in-hospital mortality rate was 17.4% (4/23), although one patient died due to causes unrelated directly to the bleeding episode, but bleeding contributed to an overall systemic deterioration.

Of the six patients in whom bleeding originated from the common hepatic artery and/or its branches, five demonstrated transient deterioration in hepatic function after interventional radiology which subsequently recovered in the days following successful intervention. More importantly, none of those developed any further liver-related complications.

One patient, who was initially discharged post-operatively, re-presented 4 weeks after pylorus-preserving pancreaticoduodenectomy (PPPD) with hematemesis. A CT angiogram demonstrated multiple collections surrounding the operative site, including a heterogeneous collection within the lesser sac concerning for internal hemorrhage, as well as locules of gas suggestive of an anastomotic leak at the pancreaticojejunostomy; however, no active bleeding source was identified on initial angiography. The patient continued to exhibit intraluminal bleeding over the subsequent 2 days and underwent repeat angiography, which identified the bleeding site and was treated with successful stent-graft placement. Despite this, the patient continued to deteriorate clinically, developed acute liver fail-

Table 1. Patients' Demographics, Intervention, and Outcome of Delayed Bleeding Post-PD

Patient No.	Sex	Age	Operation	Interval of delayed bleeding (days) > 24 h post-op	Bleeding site	Systemic response (tachycardia/hypotension, etc.)	Location of bleeding after/ endoscopy imaging including invasive angiogram	Type of intervention	Outcome
1	Male	75	PD	3	Surgical drain	Yes	GDA	IR	Deceased
2	Male	56	PD	9	Surgical drain	Yes	GDA	Surgery	Deceased
3	Male	48	PD	20	GI tract	Yes	Pancreatic branch from splenic artery	IR	Discharged
4	Male	81	PD	1	GI tract	No	Possibly left gastric	Surgery	Discharged
5	Male	67	PD	17	GI tract	Yes	GDA	IR	Discharged
6	Male	51	PD	28	Surgical drain	Yes	GDA	IR	Discharged
7	Female	48	PD + PV resection	4	GI tract	Yes	Right hepatic artery	IR	Discharged
8	Male	66	PD	1	Surgical drain	Yes	GDA	Surgery	Discharged
9	Female	60	PD	1	Surgical drain	Yes	Left hepatic	IR	Discharged
10	Female	78	PD	7	GI tract	Yes	GJ	Surgery	Discharged
11	Male	62	PD	5	GI tract	Yes	Pancreatic stump	Surgery	Discharged
12	Male	54	PD + PV resection	16	GI tract	Yes	SMA	IR (+ surgery for PV thrombosis)	Discharged
13	Male	83	PD	15	Surgical drain	Yes	Left hepatic artery	IR	Discharged
14	Male	72	PD	19	GI tract	No	GDA	IR	Discharged
15	Female	74	PD + PV resection	25	GI tract	Yes	Common hepatic artery	IR	Discharged
16	Male	44	PD + PV + SMA resection	27	GI tract	Yes	GDA	IR	Discharged
17	Male	58	PD	15	Surgical drain	Yes	Left hepatic	IR	Discharged
18	Male	74	PD	43	GI tract	Yes	GDA	IR	Discharged
19	Male	77	PD	5	Surgical drain	Yes	GDA	IR	Deceased but due causes not related to bleeding
20	Male	60	PD	29	GI tract	Yes	Common hepatic artery	IR	Deceased
21	Female	62	PD	40	GI tract	Yes	GDA	IR	Discharged
22	Male	70	PD	14	Surgical drain	No	Not identified	IR	Discharged
23	Male	51	PD	14	Surgical drain	No	Not identified	IR	Discharged

GDA: gastroduodenal artery; GI: gastrointestinal tract; GJ: gastrojejunostomy; IR: interventional radiology; PD: pancreaticoduodenectomy; PDA: pancreaticoduodenal artery; Post-op: postoperatively; PV: portal vein; SMA: superior mesenteric artery.

Table 2. Interval to Investigations for Patients With Delayed Bleeding After PD

Patient No.	Interval time to CT angiogram after signs of bleeding	Interval time to IR angiogram after signs of bleeding	Evidence of pancreatic fistula	Type of IR	Location of bleeding after/endoscopy imaging including invasive angiogram	Type of surgery
1	1 day	2 days	Yes	Embolization of hepatic artery	GDA	N/a
2	12 h	N/a patient too unstable	Yes	N/a	GDA	Gastroduodenal stump bleeding oversewn
3	12 h	24 h	Yes	Embolization of pseudoaneurysm arising from a branch of the splenic artery	Pancreatic branch of the splenic artery	N/a
4	24 h	24 h	Yes	N/a	Left gastric	General hemostasis, no obvious bleeding point identified
5	72 h	72 h	Yes	Embolization of GDA stump and hepatic artery stent graft	GDA	N/a
6	24 h	6 days	Yes	Hepatic artery stent graft	GDA	N/a
7	4 days	4 days	Yes	Mesenteric angiography and embolization of hepatic artery pseudoaneurysm	Right hepatic artery	N/a
8	12 h	N/a patient too unstable	Yes	N/a	GDA	GDA stump oversewn
9	12 h	12 h	No	Embolization of the left hepatic artery	Left hepatic	N/a
10	12 h	Not performed	No	N/a	GJ	Gastrojejunostomy suture line oversewn
11	12 h	12 h	Yes	N/a	Pancreatic stump	Pancreatic stump bleeder oversewn
12	24 h	24 h	Yes	1. Splenic artery embolization for portal vein reduced flow within the PV graft 2. SMA stent	1. Thrombosed PV 2. SMA pseudoaneurysm	Laparotomy for thrombosed portal repaired with interposition vein graft, but no surgical intervention for bleeding.
13	12 h	12 h	No	Coil embolization left hepatic artery	Left hepatic artery	N/a
14	24 h	24 h	No	Common Hepatic Artery Stenting across leaking GDA stump	GDA	N/a
15	12 h	12 h	No	Common hepatic artery pseudoaneurysm embolization	Common hepatic artery	N/a
16	12 h	24 h	No	Failed Spontaneous Bleeding stopped after monitoring	GDA	N/a
17	12 h	48 h	Yes	Stenting of the left hepatic artery	Left hepatic	N/a
18	12 h	24 h	Yes	Embolization of GDA	GDA	N/a
19	6 days	6 days	No	Stent graft IN common hepatic artery across GDA	GDA	N/a
20	24 h	24 h	No	Stent-graft of common hepatic artery	Common hepatic artery	N/a
21	12 h	12 h	Yes	Embolization and stent-graft across the GDA	GDA	N/a
22	12 h	24 h	Yes	Embolization of GDA stump	Not identified	N/a
23	12 h	24 h	Yes	Stent graft common hepatic artery	Not identified	N/a

CT: computed tomography; IR: interventional radiology; PD: pancreaticoduodenectomy.

Table 3. Proposed Classification of PPH: Clinical Condition, Diagnostic and Therapeutic Consequences

Grade	Time of onset, location, severity, and clinical impact of bleeding		Clinical condition	Diagnostic consequence	Therapeutic consequence
A	Early, intra- or extraluminal, mild		Well	Observation, blood count, ultrasonography and, if necessary, computed tomography	No
B	Early, intra- or extraluminal, severe	Late, intra- or extraluminal, mild ^a	Often well/intermediate, very rarely life-threatening	Observation, blood count, ultrasonography, computed tomography, angiography, endoscopy ^b	Transfusion of fluid/blood, intermediate care unit (or ICU), therapeutic endoscopy ^b , embolization, relaparotomy for early PPH
C		Late, intra- or extraluminal, severe	Severely impaired, life-threatening	Angiography, computed tomography, endoscopy ^b	Localization of bleeding, angiography, and embolization, endoscopy ^b or relaparotomy, ICU

^aLate, intra- or extraluminal, mild bleeding may not be immediately life threatening to patient but may be a warning sign for later severe hemorrhage ("sentinel bleed") and is therefore grade B. ^bEndoscopy should be performed when signs of intraluminal bleeding are present (melena, hematemesis, or blood loss via nasogastric tube). Reprinted from Reference [8] with permission from Elsevier. ICU: intensive care unit; PPH: pancreaticoduodenectomy hemorrhage.

ure, and ultimately died in the intensive care unit (ICU) from multi-organ failure.

Discussion

Late bleeding, although rare, is a significant factor for increased morbidity and mortality after PD and is usually associated with evidence of pancreatic fistula and sepsis [7].

Three different grades of bleeding, A, B and C, are defined by the ISGPS according to the time of onset, location, actions required, and overall outcome, estimating a cumulative risk and clinical severity of the hemorrhage (Table 3) [8, 9]. The overall incidence of all grades of PPH varies from 3% to 29%, with a significantly increased mortality rate of 7–31% for grade C specifically [10]. The pathogenesis of late bleeding after PD is directly related to the complexity of surgery (extensive dissection and lymphadenectomy, vascular skeletonization and reconstruction, soft pancreas, and high-risk anastomosis), making vessels susceptible to bleeding due to local factors (e.g. pancreatic/biliary fistula, abscess) [11]. Several studies have investigated other independent risk factors that may predict late bleeding including high body mass index (BMI), younger age, prolonged operative time, intraoperative blood loss, and vascular reconstruction [12]. Interestingly those factors were also associated with an increased incidence of POPF, and the severity of bleeding was also associated with the degree of pancreatic fistula and its complications [3]. In one study, the presence of gas, rim enhancement, and isolation of candida species were identified as independent risk factors for late bleeding in patients with a pancreatic fistula and associated intrabdominal collection [13].

It is important to identify the source and early signs of late bleeding and initiate the appropriate investigations and treatment. Approximately one-third of patients (28.2%) present with GI tract bleeding, whereas the rest have intra-abdominal hemorrhage as reported in one study [11].

Immediate CT angiography after appropriate resuscita-

tion, when signs of bleeding occur or is suspected, regardless of severity and location, is strongly recommended. In our unit, we have a very low threshold for performing imaging and the majority of patients had a CT angiogram within 24 h after the onset of bleeding as shown in Table 1. Diagnostic and therapeutic endoscopy is an additional option and may be of value in controlling bleeding from a staple line or an early anastomotic ulcer but does not replace CT or formal angiogram to identify a pseudoaneurysm which must always be ruled out [11]. In fact, patients with pseudoaneurysms may remain asymptomatic without any evidence of bleeding. In one study, 27% of pseudoaneurysms were incidentally detected on routine CT imaging for other indications [3]. In our unit, we routinely perform a CT angiogram in all high-risk patients who have evidence of clinical or radiological pancreatic fistula before discharge even if they have no signs of bleeding to rule out an uncomplicated pseudoaneurysm. A meta-analysis of 14 studies reported the sensitivity of CT angiogram to identify the source of late bleeding to be only 67%. Sentinel bleed is also another scenario where CT may be initially negative [14]. Khalsa et al reported an overall sentinel bleed prevalence of 33% and found that this has been associated with a higher relaparotomy and mortality rate compared to late bleeding patients without a sentinel bleed episode [15].

Invasive angiogram offers both diagnostic and therapeutic options and can be considered when there is evidence of ongoing bleeding even with initially negative CT findings [16]. Angiography may be more sensitive and can identify hemorrhage when the bleeding rate is low (0.5 mL/min). Super-selective catheter placement may be required to maximize benefit [1]. Transcatheter arterial embolization has been widely accepted as the first-line treatment in the management of a bleeding pseudoaneurysm after PD and has a success rate of 67–100%, morbidity rate of 14–25%, and mortality rate of 0–14% [2, 16, 17]. Stent grafting is an alternative option instead of or in addition to embolization in selected patients. It offers the advantage of providing continued perfusion to the end-organ (e.g. liver) and may be useful in cases of a short stump or recur-

rent bleeding after previous embolization [17, 18]. Anatomical variations or acute arterial angulation may cause technical difficulties in the placement of the stent-graft. Routine post-procedure anticoagulation is not usually recommended [19].

Patients with ongoing bleeding but with radiologically negative findings to identify the source, may benefit from empiric embolization especially if they become systemically unstable. The GDA appears to be the most common site of bleeding (35–45%) in many studies [15]. In our series, the majority of bleeding was related to the GDA or SMA branches (47.8%). Yekebas et al reported a success rate of 80% in five patients who had empiric embolization of either GDA or SMA branches [20]. In our series, two patients were successfully treated with empiric GDA embolization or stenting (due to short stump).

Surgical management of bleeding is associated with higher mortality and morbidity compared to endovascular treatment [16]. This is possibly reflecting the fact that these patients: 1) often require urgent intervention due to severe bleeding and instability, 2) may have recurrent intractable bleeding with previous failed endovascular treatment, multiple transfusions, and coagulopathy, 3) may have high volume hemoperitoneum that would require washout, and 4) may have associated intraabdominal sepsis from pancreatic fistula and require control of both sepsis and bleeding [20]. In cases of failed endovascular treatment, the angiography performed at the time may still be helpful to identify the location of bleeding facilitating operative strategy [21]. In our study, 5/23 patients (21.7%) had surgical intervention all of them during the early part of the 12 years study period. Surgery may be very useful when bleeding is intraluminal (staple lines, early ulceration) and endoscopy fails to control. Various surgical techniques have been described aiming to prevent pseudoaneurysm formation intraoperatively including: 1) performing the pancreaticojejunostomy as far away as possible from the coeliac trunk and portal vein, or putting an omental flap around it, and 2) the use of the round ligament around the GDA stump. The real benefits of these modifications remain at the level of local expertise [2, 4]. In a recent systematic review by Montorsi et al focusing in methods that can prevent and mitigate PHH, there were three randomized controlled trials (RCTs) identified that have proved to reduce the risk of PPH following specific surgical strategies including: 1) performing a smaller jejunal incision when creating the end to side duct to mucosa pancreaticojejunostomy, 2) creating a falciform ligament patch around the GDA or hepatic artery, and 3) performing a pancreaticojejunostomy instead of a pancreaticogastrostomy [22]. In our unit, when arterial resection and reconstruction is undertaken (e.g. hepatic artery), we perform total pancreatectomy to prevent pseudoaneurysm formation from possible pancreatic fistula.

The management of patients with recurrent bleeding after first treatment either surgery or interventional radiology remains challenging. The re-bleeding rate has been reported to be 28% after the first treatment in one study [1]. Possible causes include persistent surgical bed inflammation and infection from ongoing pancreatic leak, which can also cause new bleeding sites (28.6% of patients in one study), and failed endovascular treatment (coil migration, insufficient covered stent placement, endoleaks, recanalization of vessels) [14].

This study has several limitations. First, its retrospective design may introduce selection and information bias. In addition, the analysis relies primarily on descriptive statistics without inferential statistical testing, which limits the ability to identify independent predictors of late hemorrhage. Furthermore, other potentially relevant clinical variables, such as tumor characteristics, pancreatic texture, details of vascular resection or reconstruction, perioperative liver function, and management of pancreatic fistula prior to bleeding, were not systematically analyzed and may have influenced outcomes.

Conclusions

Late bleeding after PD commonly but not always is related to pancreatic leak. Early intervention after signs of bleeding results in the location of bleeding and potential definitive intervention. Endovascular treatment remains the most effective approach. When no source of bleeding can be identified, empiric embolization/stenting of the GDA provides an alternative option. Surgery may also be required in cases where ongoing sepsis causes recurrent bleeding episodes not amenable to endovascular treatment.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

Dobrzycka MA: data curation (lead); formal analysis (lead); project administration (lead); visualization (lead); investigation (lead); writing – review and editing (equal); final approval of manuscript (equal). Chatzizacharias N: writing – review and editing (supporting); final approval of manuscript (equal). Bisht H: data curation (supporting); investigation (supporting); writing – review and editing (supporting); final approval of manuscript (equal). Raza SS: writing – review and editing

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Data Availability

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request and with appropriate institutional approvals.

Abbreviations

BMI: body mass index; CT: computed tomography; GDA: gastroduodenal artery; GI: gastrointestinal; HRA: Health Research Authority; ICU: intensive care unit; IRB: Institutional Review Board; ISGPS: International Study Group of Pancreatic Surgery; NEWS: National Early Warning Score; PD: pancreaticoduodenectomy; PPH: pancreaticoduodenectomy hemorrhage; POPF: post-operative pancreatic fistula; RCT: randomized controlled trial; SMA: superior mesenteric artery; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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