Hepatobiliary anastomotic leakage: a narrative review of definitions, grading systems, and consequences of leaks

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Background and Objective: Hepatobiliary diseases are a longstanding and significant medical challenge which, despite advances in surgical techniques, still carry risks for postoperative complications such as anastomotic leaks (ALs), which can include both postoperative pancreatic fistula (POPF) and bile leaks (BL). These complications incur significant human and economic costs on all those involved, including the patient, healthcare providers, and hospital systems. The aim of this study was to construct a narrative review of literature surrounding definitions and grading systems for ALs in the context of hepato-pancreato-biliary (HPB) procedures, and consequences of POPF and BL.

Methods: A literature review was conducted by examining databases including PubMed, Web of Science, OVID Embase, Google Scholar, and Cochrane library databases. Searches were performed with the following search criteria: (((((((anastomosis) OR (anastomotic leak*)) OR (postoperative pancreatic fistula)) OR (bile leak*)) OR (pancreaticoduodenectomy)) OR (whipple)) AND ((hepatobiliary) OR (hepato-pancreato-biliary)) AND ((definition) OR (grading system*) OR (consequences) OR (outcomes) OR (risk factor*) OR (morbidity) OR (mortality))). Publications that were retrieved underwent further assessment to ensure other relevant publications were identified and included.

Key Content and Findings: A universally accepted definition and grading system for POPF and BL continues to be lacking, leading to variability in reported incidence in the literature. Various groups have worked to publish guidelines for defining and grading POPF and BL, with the International Study Group in Pancreatic Surgery (ISGPS) and International Study Group for Liver Surgery (ISGLS) definitions the current most recommended definitions for POPF and BL, respectively. The burden of AL on patients, healthcare providers, and hospitals is well documented in evidence from leak consequences, such as increased morbidity and mortality, higher reoperation rates, and increased readmission rates, among others.

Conclusions: AL remains a significant challenge in HPB surgery, despite medical advancements. Understanding the progress made in defining and grading leaks, as well as the range of negative outcomes that arise from AL, is crucial in improving patient care, reduce surgical mortality, and drive further advancements in earlier detection and treatment of AL.

Keywords: Anastomotic leak (AL); hepato-pancreato-biliary (HPB); postoperative pancreatic fistula (POPF); bile leak (BL); grading systems

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Introduction

Hepatobiliary diseases are a significant and longstanding medical challenge, with documentation extending as far back as 2000 BC, to reports of modern-day gallstones in Egyptian mummies (1). Since these first records, the field of hepato-pancreato-biliary (HPB) surgery (which involves the treatment of diseases found in the gall bladder, pancreas, liver, and bile ducts), has evolved massively (2). Nonetheless, complications may still arise, which carry significant consequences for patients, healthcare providers, and medical systems alike.

HPB procedures can be performed through an open procedure or laparoscopically, while the robotic approach is still being developed (3). These procedures include cholecystectomy, distal and total pancreatectomy, partial hepatectomy, total hepatectomy or liver transplants, pancreaticoduodenectomy (Whipple), and cholecystectomy (3).

There are many postoperative complications associated with HPB surgeries. One of the major complications arising from HPB surgery is anastomotic leaks (ALs). This includes postoperative pancreatic fistula (POPF), referring to the leakage of pancreatic fluid, and bile leak (BL) which refers to leakage of biliary contents. Major hospital centers have mortality rates associated with pancreatic AL under 5%, however, the morbidity remains high, at 30–50% (4,5). Hepatic surgeries may lead to BLs which occur in nearly 3.6–12.9% of cases after liver resection (6-12). Therefore, ALs are a major cause of concern, often increasing patient length of stay (LOS), and treatment cost, while lowering quality of life (4-7).

This narrative review provides a thorough synthesis of the latest advances in HPB surgery, in the context of ALs. Here, we focus on background information related to defining and classifying leaks, as well as the burden associated with the occurrence of leakage.

Terminology

This narrative review features a number of important acronyms, whose definitions are essential in understanding the context of the results presented here. As such, *Table 1* is included at the beginning of this paper, as an accessible reference for the various acronyms and definitions used throughout the results and discussion to come. We present this article in accordance with the Narrative Review reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-9/rc).

Methods

The most recent evidence from various databases was used to inform this narrative review, including PubMed, Web of Science, OVID Embase, Google Scholar, and Cochrane library databases. Literature searches were performed using the following search criteria: (((((((anastomosis) OR (anastomotic leak*)) OR (postoperative pancreatic fistula)) OR (bile leak*)) OR (pancreaticoduodenectomy)) OR (whipple)) AND ((hepatobiliary) OR (hepato-pancreato-biliary)) AND ((definition) OR (grading system*) OR (consequences) OR (outcomes) OR (risk factor*) OR (morbidity) OR (mortality))). No restrictions were placed on article type, except that articles must have been published in English or have an English translation. Inclusion was determined by the authors and their collaborators (see acknowledgements), aiming to include a broad, unbiased, and comprehensive range of relevant studies, including recent publications. *Table 2* summarizes the search strategy used for this narrative review. Figure S1 provides a more detailed flow-chart of the search strategy, using one database (PubMed) as an example.

Findings

POPF

Following a pancreatic procedure, an abnormal connection between the pancreatic ductal epithelium and another epithelial surface, such as the peri-pancreatic space or the peritoneal cavity, may be established, due to a disruption of the pancreatic duct (13). The collection of pancreatic fluid that has leaked into another cavity due to pancreatic duct disruption—termed 'pancreatic leak' or POPF allows pancreatic digestive enzymes to leak out of the pancreatic ductal system, disrupting other epithelial surfaces. POPF can significantly increase patient morbidity, with pain, ileus, fever, higher probability of abscess formation, and potential onset of sepsis and hemorrhages ultimately increasing hospital stay, and leading to poorer patient outcomes (13,14). Pancreatic enzymes erode the surrounding tissue, forming a pathway between the disrupted duct, and the connected epithelial surface (13).

The incidence rate of leakages varies depending on the type of surgery performed, with Whipple procedures and pancreatectomies having incidence rates of approximately 13% and 31%, respectively (14). The mortality rate of secondary complications associated with POPF can be as high as 40% (14). The high morbidity and mortality

Table 1 Commonly used acronyms and definitions in HPB diseases and medical care

Acronym	Expanded name	Definition
HPB	Hepato-pancreato-biliary	HPB surgery encompasses the comprehensive surgical management of both non-cancerous and cancerous conditions affecting the liver, pancreas, gallbladder, and bile ducts. These procedures rank among the most demanding and intricate surgical interventions within the field of general surgery, demanding a considerable level of proficiency and precision
Whipple/PD	Pancreaticoduodenectomy	The Whipple procedure, also known as a pancreaticoduodenectomy, is a surgical procedure utilized to address tumors and various ailments affecting the pancreas, small intestine, and bile ducts. This intricate operation entails the removal of the pancreatic head, the initial section of the small intestine, the gallbladder, and the bile duct
		Primarily employed to treat pancreatic cancer that remains localized within the pancreas, the Whipple procedure is a high-stakes surgery associated with significant risks. Nevertheless, it frequently proves to be a life-saving intervention
AL	Anastomotic leak	Anastomotic leakage is defined as a defect of the gastrointestinal wall at the anastomotic site leading to a communication between the intra- and extraluminal compartments
POPF	Postoperative pancreatic fistula	POPF is one of the most severe complications after pancreatic surgeries. POPF develops as a consequence of pancreatic juice leakage from a surgically exfoliated surface and/or anastomotic stump, which sometimes cause intraperitoneal abscesses and subsequent lethal hemorrhage
ISGPF/ISGPS	International Study Group for Pancreatic Fistula/Surgery	In 2005, an international working group of 37 pancreatic surgeons (ISGPF) was convened to reach a universally accepted and objective definition of postoperative pancreatic fistula
DGE	Delayed gastric emptying	Gastroparesis, also called delayed gastric emptying, is a disorder that slows or stops the movement of food from your stomach to your small intestine, even though there is no blockage in the stomach or intestines
IAS	Intra-abdominal sepsis	Intra-abdominal infection describes a diverse set of diseases. It is broadly defined as peritoneal inflammation in response to microorganisms, resulting in purulence in the peritoneal cavity

Table 2 The search strategy summary

Items	Specification
Date of search	April 1, 2023 to November 1, 2023
Databases and other sources searched	PubMed, Web of Science, OVID Embase, Google Scholar, Cochrane Library Database
Search terms used	((((((anastomosis) OR (anastomotic leak*)) OR (postoperative pancreatic fistula)) OR (bile leak*)) OR (pancreaticoduodenectomy)) OR (whipple)) AND ((hepatobiliary) OR (hepato-pancreato-biliary)) AND ((definition) OR (grading system*) OR (consequences) OR (outcomes) OR (risk factor*) OR (morbidity) OR (mortality)))
Timeframe	All published literature (up to November 1, 2023)
Inclusion criteria	Articles published in English; no other restrictions
Selection process	Selection was completed by the study authors, with further consultation and consensus obtained in collaboration with experienced researchers and medical professionals (see Acknowledgments section). These collaborators span numerous institutions and countries

rates seen in POPF patients stems from the additional complications that arise due to the fistula, such as abdominal hemorrhages and abscesses, postoperative bleeding, and multiorgan failure (15). Major complications associated with pancreatic fistulas can be split into two broad categories: hemorrhage and sepsis. Both play a role in the development of additional consequences, including prolonged hospital stays, delayed gastric emptying (DGE), enteric fistulae, multiorgan failure, and death (16).

Moreover, patients who develop POPF are more likely to be impacted by additional complications, including wound infection; acute cardiac events; pulmonary, renal, thromboembolic, and septic complications; BLs; and intra-abdominal abscesses (16). POPF has also been linked to the development of DGE following Whipple procedures, resulting in poor nutritional outcomes which may further lengthen hospital stays (16).

A number of risk factors have been associated with POPF, including age >60 years, obesity, smoking, length of operation, pancreatic texture (soft—high risk), and pancreatic duct diameter (17-22). Body mass index (BMI) is a strong predictor of the risk of POPF, with increasing BMI significantly associated with exponentially increased POPF risk. This is due in part to the texture of the pancreas, which is majorly influenced by BMI. Overweight or obese patients with BMI ≥25 kg/m^2 have greater adipose deposits within the pancreas that contribute to the softer texture (20). This, in turn, leaves the pancreas friable and unable to effectively hold stitches from the anastomosis—providing the opportunity for fluid to leak out of the pancreas and cause POPF. BMI ≥30 kg/m^2 has been more predictive of clinically relevant POPF than BMIs over 25 kg/m^2. In addition, BMI ≥35 kg/m^2 is strongly associated with an increased development of DGE (20). Smoking is a modifiable risk factor that is debated and poorly understood, believed to result in ischemia and microvascular damage of small areas around the pancreatic anastomosis (18). This may slow down healing and increase risk of POPF. Several retrospective studies have found smoking as a risk factor on univariate analysis, although statistical significance from multivariate analysis remains mixed (18,23,24). The length and complexity of surgical procedures has been shown to be a risk factor not only for POPF, but as will be discussed below, BLs as well. Long, complicated surgeries, as well as those that are open or invasive all increase risk (24).

Other risk factors, such as blood pressure, alcohol consumption, and American Society of Anesthesiologists (ASA) score have been explored, but at this time provide less conclusive evidence than those described above, which based on current literature are the strongest predictors of POPF (25,26).

2005 International Study Group of Pancreatic Fistula (ISGPF) definition

Up until 2005, a commonly agreed upon definition of POPF was absent from literature. This led to conflicting opinions on grading, classification, and valuable comparison of leaks (27). For example, prior to the introduction of the commonly agreed on system, a leak could be graded based on many parameters, such as daily output and duration of the fistula, with a 2005 study identifying a striking 26 definitions of POPF in the literature (27). These variations in criteria, and multiple definitions and categorizations of pancreatic leaks created challenges in comparing surgical outcomes and patient/healthcare provider experiences.

In 2005, a panel of pancreatic surgeons came together as part of the ISGPF to properly define pancreatic leaks and produce a grading system for leak classification (27-29). POPF was defined as "an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid" (13). The formal diagnostic criteria was defined as "output via an operatively or a subsequently placed drain, of any measurable volume of drain fluid on or after postoperative day three, with an amylase content greater than three times the upper normal serum value" (27). Elaborating on this, a description of the appearance of drain fluid following the development of the leak, with a clear description of a range of colors the fluid may take was added. This ranged from a dark brown to greenish bilious fluid to a milky water to clear "spring water" like fluid that looks like pancreatic juice (27). The team also included several common signs of leaks that could be detected in patients, such as abdominal pain and distention, with impaired bowel function, DGE, fever, serum leukocyte count greater than 10,000 cells/mm^3 and increased C-reactive protein (CRP) (27). Despite progress made in defining leaks, the team feared that such a broad definition may be too inclusive, such that asymptomatic patients could fit in the definition of a POPF. These patients may not have a leak or be clinically ill, hence a grading system was proposed to properly classify types of leaks—including those which may be subclinical (27).

A three-class grading system was created, ranging from A to C to describe the pancreatic fistulae, with A being the least severe and C being the most severe (28). A Grade A leak was distinguished through elevated amylase in the drain fluid. Grade B leakage was identified by the need for modified postoperative management, such as use of antibiotics. Grade C leak was classified as those requiring severe departure from regular postoperative management, with the need for reoperation, or percutaneous drainage to manage the leak (28). For the next 11 years, the proposed system of classifying leaks became the standard system used by surgeons worldwide. Over time, a number of surgeons noted limitations with the system. In 2016, the system was

Table 3 2016 International Study Group in Pancreatic Surgery classification of and grading of postoperative pancreatic fistula

Grade	Definition
A/biochemical leak	Grade A leaks are defined as a measurable fluid output on or after post-operative day three, with an amylase content higher than three times the upper normal serum level (30). Grade A leaks are considered insignificant with respect to the postoperative pathway and are regarded as having no clinical impact on the pathway itself. These are usually treated through the slow removal of peri-pancreatic drain (14,30)
B	Grade B leakages are defined as leaks that result in a change in the patient's clinical management. As an example, the patient may need to have certain drains re-positioned due to a Grade B leak or receive antibiotic treatment (14,30). Grade B leaks are considered clinically significant, but through careful management, and proper monitoring, the leak can be dealt with using minimal changes in the patient's clinical management (14)
C	Grade C leaks are the most severe of the three leak grades, as they can often lead to organ failure (30). Grade C leaks are defined as leaks that require a major change in the patient's clinical management including intensive care unit level care, percutaneous drainage of undrained fluid collections, or operative re-exploration for further drainage or attempted anastomotic repair (14). Grade C leaks are associated with a major increase in hospitalization time as well as increased rates of complications and mortality (14)

revised by the ISGPF, now known as the International Study Group in Pancreatic Surgery (ISGPS) (27,28).

Limitations of original leak grading system

(I) Inclusion of Grade A leaks within the POPF definition as a postoperative complication. Grade A leak patients have a relatively uncomplicated recovery, and do not require changes to the patient's clinical management (28).

(II) Unclear distinction between Grade B and C leaks, and their associated inclusion criteria in the original paper (28). The use of percutaneous drainage was used to identify Grade C leaks in the paper, however the associated summary table listed it as a potential Grade B procedure. Therefore, subsequent classifications were based on different interpretations.

(III) Medical professionals were concerned regarding the conversion of Grade A leaks into Grade B leaks, especially after the patient had been discharged with the drain (28). This was a common occurrence at the time in patients who underwent distal pancreatectomies and did not experience any symptoms postoperatively.

Hence, the grading system was revised, along with the criteria for diagnosis (*Table 3*).

Revisions made to diagnosis and classification system

(I) An increased amylase content in the patient's abdominal fluid must be associated with another clinically significant condition, that is, it is causally linked with the pancreatic leak, for the diagnosis of a pancreatic leak (31).

(II) Grade A pancreatic leaks no longer existed under the revised system, and were termed as biochemical fistulas or biochemical leaks, which became a new asymptomatic pancreatic leak category (31).

(III) A greater distinction between Grade B and C leaks was established. Grade B leak diagnosis was modified to include some invasive procedures including percutaneous or endoscopic drainage, and angiographic procedure. A Grade C leak was characterized and limited to a subset of patients that developed a severe life-threatening condition such as organ failure that required a reoperation or died due to the leakage (31). ISGSP defined organ failure as follows: "the need for reintubation, hemodialysis, and/or use of inotropic agents for >24 hours because of respiratory, renal, or cardiac insufficiency respectively" (31).

This narrative review uses the updated version of the grading system proposed in 2016.

New classification of pancreatic leaks (2016)

The ISGPS defines a POPF as an output via an operatively or a subsequently placed drain, of any measurable volume of drain fluid on or after postoperative day three, with an amylase content greater than three times the upper normal serum value (27,31).

BL

BLs refer to the leakage of bile from the biliary tree, cut surface of remnant liver, or from a hepatoenteric anastomosis into the abdomen (32). Leaks formed from the cut surface of the remnant liver are referred to as peripheral BLs, while those that originate from the bile ducts are known as central BLs (33). BL can facilitate abnormal connections of the gallbladder with the biliary tree, and sometimes may even involve the GI tract (34). An abnormal connection involving the GI tract is known as an internal fistula, while a connection with the abdominal wall represents an external fistula (34).

The causes of the BL formation can vary depending on the type of surgical procedure. Following cholecystectomy, BL can be caused due to improper ligation of the cystic duct or accessory ducts, allowing the ligature to slip and come loose (35). In the case of hepatectomies, BL usually originates from the biliary anastomotic site, which can be caused by the dislodgement or removal of an external drainage tube, or iatrogenic bile duct injury (BDI) (35). In some cases, BLs can also occur following pancreatic surgeries. Similar to a cholecystectomy or hepatectomy, the cause of BL is mainly due to BDI, or in some cases leakage from a bilioenteric anastomosis, if one was created (36-42).

The reported incidence rates of BL following a cholecystectomy are relatively low at 0.3–2.7%. Hepatectomy patients have an incidence rate of 4.8–7.6% (37,42-45), and pancreatic patients who do not undergo iatrogenic biliary injury have an incidence rate of 2–10% (36-41), however if injury occurs the incidence rate rises to 24% (36,41,46).

Once a BL forms, the bile can seep from the injured duct or cut remnant liver and form distinct bile collections in the surrounding areas known as bilomas (47). This causes an inflammatory reaction and fibrosis in the area of the deposition (47). Left untreated, bilomas become an excellent medium for the proliferation of bacteria, owing to the mixture of bile, blood and devitalized tissues in the area surrounding the resected liver. Bacterial proliferation can impair the normal host defense mechanism, allowing sepsis development (37,43). This outcome is extremely dangerous for hepatectomy patients as septic conditions around the liver and reduction in liver volume can lead to liver failure (43). Additionally, BL can lead to peritonitis, multiple organ dysfunction syndrome, cholangitis, liver abscesses, and several other postoperative complications. These secondary complications contribute to the associated 5% mortality rate, as well as longer hospital stays and increased medical bills (44,45).

As with POPF, several strong risk factors/predictors of BL have emerged in the literature. These include BMI and nutritional status, operation duration, diabetes, and neoadjuvant chemoradiotherapy (24,48-51). With BMI an important indicator of a patient's nutritional status, patient BMIs <20 kg/m^2 have emerged as a risk factor for BL. For instance, in cancer patients, malnutrition is closely associated with the incidence of postoperative complications, length of hospital stay, and increased mortality, supporting findings that low BMI is a risk factor associated with BL (48). Diabetes increases the risk post-operative infections and mortality, with impacts on microcirculation disorders that can prevent/impact proper healing (49). The pathophysiology of diabetes also results in damage to the residual liver, increasing the risk of postoperative BLs. In line with this, it is recommended that pre-operative blood glucose control be emphasized in order to manage the impact of diabetes on overall patient recovery, including minimizing risk of BLs (49). For patients undergoing neoadjuvant therapy, particularly chemotherapy, this too has been noted as an important risk factor (50). Healing is negatively impacted by damage to the liver that makes it soft and fragile, increasing the risk of leaks. This was found to be most impactful when treatment was within 4 weeks of surgery, leading to more Grade A and Grade B leaks, with little effect on Grade C (see below for a description of leak grades) (50). As described above for POPF, operation duration is a risk factor for similar reasons in patients who go on to experience BLs (including complexity of surgery and invasiveness of procedure).

Definition

Prior to 2008, several definitions of BL existed, which provided a wide range of cutoffs for the volume of drain fluid and concentration of bilirubin within the drain fluid. In 2008, the International Study Group for Liver Surgery (ISGLS) proposed a system of diagnosis and grading for BLs (52).

BL was defined as "fluid with an elevated bilirubin level in the abdominal drain or intra-abdominal fluid on or after post-operative day three or the need for radiological intervention, owing to biliary collections or re-laparotomy due to biliary peritonitis" (52).

Elevated bilirubin concentration is defined as "a bilirubin concentration at least three times higher than the serum bilirubin level measured at the same time" (52). Additionally, a system of leak classification was developed, as is described in *Table 4*.

Postoperative consequences of leaks

Pancreatic leaks

Table 5 provides a summary of consequences experienced by patients with POPF, as well as burdens placed on healthcare systems as a whole.

BL

Table 6 provides a summary of postoperative consequences experienced by patients following development of BL. As the literature currently stands, the impact of BL on clinical and economic outcomes is less studied than that of POPF. However, it is clear that the development of a BL leads to increased costs, and poorer outcomes for patients.

Table 4 Classification of BL

Grade	Definition
A	Grade A BL requires little to no change in a patient's postoperative management (52). The patients remain generally healthy, and the leak can be managed using an intra-abdominal drain. As a patient heals, the volume of drain fluid decreases along with its concentration of bilirubin. Abdominal imaging may be required to visualize the perihepatic fluid collections. Additionally, the time taken to drain the collection may prolong the patient's LOS. However, Grade A leakage that persists longer than a week is defined as Grade B BL (52)
B	Grade B BL requires a significant change in clinical management but can be treated without requiring a relaparotomy. Grade A leakage that continues for more than a week is also defined as Grade B leakage. Grade B leakages are usually accompanied by fevers and intraabdominal discomfort, which indicate an infection. Operative drains are commonly left in place to initiate the drainage of the fluid collection; however, these may not be able to completely drain the leakage. Clinical management includes antibiotic therapy, and image-guided percutaneous or endoscopic drainage of the collections. The hospital LOS is generally prolonged. Patients may be discharged with the drains intact to allow for further outpatient treatment (52)
C	Grade C leakage is the most severe form of BL and requires a relaparotomy to control the leak. Surgical techniques including suture closure of leaking bile ducts, and (re-) construction of bilioenteric anastomosis are performed to control the leak. Prophylactic drains may be placed intraabdominally for continuous drainage. These patients may suffer life threatening conditions, such as severe abdominal pain, bile peritonitis, multiorgan failure, and even death. Their care is often carried out in a critical care facility, where radiologic imaging is performed routinely for leak monitoring. Secondary postoperative complications like abdominal wound infection may result from the formation of the leak (52)

BL, bile leak; LOS, length of stay.

Table 5 Consequences of POPF

Consequence	Data from literature
Increased mortality	Mortality rates associated with POPF have remained at 1% for 25 years, while overall mortality rates for Grade C POPF is 25% (16,53). The increased mortality in patients with POPF can be attributed to the leak itself, as well as secondary complications. Khobragade *et al.* retrospectively studied the factors influencing POPF associated mortality following pancreaticoduodenectomy in 592 patients (54). They found that postoperative hemorrhages, BLs, chest complications, positive blood cultures, number of interventions performed on the patient, number of explorations performed, and pre-intervention serum albumin levels influenced mortality rates in patients with Grade C POPF (54)
Increased morbidity	Secondary complications can arise following POPF, including IAS and hemorrhage. Related patient morbidity is very high, with rates reported between 30% and 65% (15,27,55-61)
Prolonged LOS	For clinically relevant POPF, management usually leads to a prolonged LOS. This can be attributed to treatment of the leak, treatment of secondary POCs, or extended monitoring of patients
	A study by Veillette *et al.* retrospectively analyzed the cases of 581 patients undergoing PD. The overall incidence of fistulas was low at 12.9% (75/581). The patients that developed POPF had significantly longer LOS (23.6 *vs.* 8.7 days, P<0.001) (62)
	In another international, multicenter, retrospective study of 1,089 patients that underwent DP, the clinical outcomes of patients were compared based on the 2005 and 2016 ISGPS definition of POPF. In this study, van Hilst *et al.* found that, according to the 2016 International Study Group in Pancreatic Surgery definition, the median length of stay increased from 7 days in patients with no POPF or Grade A POPF, to 9 days in Grade B POPF. This number increased notably to 29 days for Grade C POPF (63)

Table 5 *(continued)*

Table 5 *(continued)*

Consequence	Data from literature
Increased reoperation rates	The incidence of Grade C POPF was reported as 1.3% following DP according to a meta-analysis of three studies with 2,635 patients (64). Following PD, this rate was reported as 1.3% in a retrospective systematic review of 5,115 patients at nine high-volume hepato-pancreato-biliary centres in China (65)
	Additionally, certain secondary conditions may also require surgical treatment, such as peritonitis, hemorrhage, and sepsis
	A study by Veillette *et al.* found that reoperation was required in 6.7% patients that developed POPF, *vs.* 2.2% patients that did not develop POPF (P=0.04) (62). A study by van Hilst *et al.* recorded a 13% percent reoperation rate in patients with clinically relevant POPF (CR-POPF), as opposed to 3% in the uncomplicated/Grade A cohort (63)
Increased readmission rates	Readmission to the hospital may be required in cases of late onset POPF, signs of which may not be recognized in the early postoperative period. In the 2008 Veillette *et al*. study (62), 46 patients suffered from CR-POPF. Of these patients, 33 were classified as having an overt fistula, that is, the signs of POPF were evident by POD 7. The remaining 13 patients were classified as occult fistulas, as the drain outputs did not meet clinical cutoffs to determine the presence of POPF initially, but the patients later experienced abscesses, PPH, or death that was associated with POPF. Among the overt fistula group, 30% of patients required readmission, whereas 77% of patients in the occult fistula groups required readmission (P=0.007). There was no significant difference found between reoperation, bleeding, or mortality among the overt and occult fistula groups. This may be because patients that present with late onset fistula are readmitted just for monitoring, even though they may not necessarily need readmission
	The study by Veillette *et al.* also found that readmission was required for 27% patients with POPF, while in the non-POPF cohort, only 11% of patients required readmission (62). Readmission rates varied from 6% in the uncomplicated/Grade A cohort, versus 32% in patients with CR-POPF, according to the van Hilst study (63)
Increased patient cost	Diagnosis of POPF, and treatment of POPF and of secondary complications results in increased patient costs. A 2022 retrospective study conducted by Jajja *et al.* on a cohort of 997 PD patients between 2010–2017 compared the mean cost for patients with POPF to those without in the United States. Patients with CR-POPF had median cost of $54,727, compared to $23,024 for patients without (P<0.001). They also found that POPF patients incur 2.4 times the overall median cost of PD. The most significant contributor to cost was the postoperative ward stay (median =$39,373). The group also noted a significant increment in cost tied to the grade of POPF with median costs of $32,164 ($13,053) for Grade A, $50,263 ($30,883) for Grade B, and $102,013 ($107,484) for Grade C POPF (P<0.001) (66)
	Topal *et al.* conducted a retrospective review of the records of 109 patients that received a curative PD for pancreatic or periampullary tumor. The POPF rate was 12.8%, while overall complication rate was 46.8% (67). The median LOS for the patient categories of POPF, other, and no complications were significantly different [26, 21, and 14 days, respectively (P<0.0001)]. The hospital cost per patient category was significantly correlated with the LOS (P<0.0001). The major factors responsible for increase in inpatient costs were hospitalization and medical staff, but not operating room costs (67)
	A similar study by Enestvedt *et al.* in 2010 found that the median cost for patients with the major POC after PD was $56,224, compared to a cost of $29,038 for uncomplicated recoveries (P<0.001) (68). This was a retrospective study that was conducted on data from 145 patients. A high morbidity rate of 26% resulted in longer LOS (21 *vs.* 11 days, P<0.001) and length of intensive care unit stay (0.89 *vs.* 5.3 days, P<0.001) in patients with complications. Multivariate analysis revealed that POPF resulted in 1.3 times the median cost of treatment in patients, compared to non-leak patients. Notably, median pharmacy charges went from $13,306 to $39,640 in patients with major post-operative complications (68)
Increased need for intensive care	Patients that develop CR-POPF usually require intensive care due to the high morbidity that includes life-threatening conditions such as septic shock, peritonitis, and multiorgan failure
	In the study of PD patients by Veillette *et al.*, it was found that development of POPF led to significantly increased time in the ICU [20 (SD 26.7) days *vs.* 17 (SD 3.4) days, P<0.001] (62). Similarly, van Hilst *et al.* found that percentage of patients that required ICU admission ranged from 2% in uncomplicated patients, or those with Grade A POPF, to 4% in Grade B POPF, to 59% in patients with Grade C POPF (63)

Table 5 *(continued)*

Table 5 *(continued)*

Consequence	Data from literature
	It should be noted that admission to the ICU can vary by center based on the facilities available in the surgical ward. While some centers are better equipped to handle complications, such that only organ failure warrants an ICU admission, other centers, other centers may have a lower clinical threshold for this (62)
DGE	DGE is a common complication following pancreatic surgery, characterized by prolonged retention of food within the stomach without mechanical obstruction. This complication is divided into three grades (A, B, and C) based on nasogastric intubation, type of diet a patient can tolerate, a patient's general health, whether a prokinetic drug is used, and the need for further tests (69). DGE can lead to symptoms such as nausea, vomiting, bloating, and early satiety, significantly impacting postoperative recovery and quality of life. Beyond impacts on patients alone, DGE places significant burden on healthcare systems, whereby patients with DGE may require additional medical interventions, prolonged hospital stays, nutritional support, and medications, leading to higher healthcare costs (69)
	In a prospective study of 267 patients undergoing pancreaticoduodenectomy (>80% pylorus-preserving, antecolic-reconstruction), 49 patients (17.8%) developed DGE, with 5.1% classified as Grade B and 3.6% as Grade C (70). DGE patients were more likely to present with multiple complications (32.6% *vs.* 4.4%, ≥3 complications, P<0.001), including POPF (42.9% *vs.* 18.9%, P=0.001) and IAA (16.3% *vs.* 4.0%, P=0.012). They also had a longer hospital stay (median, 12 *vs.* 7 days, P<0.001) and were more likely to require transitional care upon discharge (24.5% *vs.* 6.6%, P<0.001). Multivariate analysis revealed that predictors for DGE included POPF [OR =3.39 (1.35–8.52), P=0.009] and IAA [OR =1.51 (1.03–2.22), P=0.035] (70). A separate study by Futagawa *et al.* found that DGE (particularly Grade C) negatively affects cancer-specific survival, using data from 383 patients who underwent pancreaticoduodenectomy (140 with DGE) (71). Five-year overall survival rates were 32.7% and 41%, respectively, for the DGE versus non-DGE group (P=0.02), highlighting the seriousness of this complication (71)
PPH	Hemorrhages are most commonly caused due to a pseudoaneurysm of a large visceral artery that develops due to the artery being in contact with pancreatic fluid, which is high in proteolytic digestive enzyme. Some commonly afflicted arteries include the common hepatic, splenic, gastroduodenal and superior mesenteric artery. If these are left untreated, the pseudoaneurysm may expand and rupture, which is associated with severe hemorrhage and hemodynamic instability. In these scenarios, early intervention is critical (16). Generally, the rate of PPH varies from 3% to 16.8% (72-75)
	A retrospective study of 347 patients that underwent PD was conducted by Khuri *et al.* 18 (5.18%) of which suffered from PPH (72). Of these, 5.6% (1/18) suffered early PPH, while the remaining 94.4% (17/18) suffered late PPH. Pseudoaneurysm was recorded as the cause for 6/17 late PPH. Significance was shown in the severity of late PPH and vascular pseudoaneurysms (P=0.001) (72)
	In another retrospective study of 1,122 patients, the rate was reported as 3% for both pancreatectomies and PD (74). Rate of early PPH was 21% and tended to extraluminal. Late PPH was intraluminal in 18/26 patients (69%). The study found that PPH significantly increased LOS (P<0.01), but not mortality rates. Additionally, PPH occurred following discharge in 39% of patients (74)
Postoperative sepsis	Sepsis can result from bacterial infection due to contamination of the operative field by biliary and enteric contents, which may explain why it is more common following Whipple than DP (16). The complication presents itself clinically as the development of a fever, DGE, abdominal pain, rising inflammatory markers such as C-reactive proteins, and turbidity of drain fluid (16,76). Drain fluid can be assessed through Gram stain, bacterial cultures, and microscopy. Patients presenting these symptoms must be assessed for peripancreatic fluid collections with CT scans (16). These collections can usually be managed through image guided percutaneous or endoscopic drainage (16)
	In a retrospective analysis, Behrman *et al.* studied 192 patients that underwent elective pancreatectomies (77). 16.3% (32/192) patients developed IAS. The risk factors for IAS included an early onset POPF, and soft pancreatic texture (77). The study found prolonged LOS (28.5 *vs.* 15.2 days), and a higher mortality rate (15.8% *vs.* 1.8%) in patients with IAS compared to patients without IAS

POPF, postoperative pancreatic fistula; BL, bile leak; LOS, length of stay; POCs, post-operative complications; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; ISGPS, International Study Group in Pancreatic Surgery; POD, post-operative day; PPH, postoperative pancreatic hemorrhage; ICU, intensive care unit; SD, standard deviation; DGE, delayed gastric emptying; IAA, intra-abdominal abscess; OR, odds ratio; PPH, postoperative pancreatic hemorrhage; CT, computed tomography; IAS, intra-abdominal sepsis.

Table 6 Consequences of BLs

Consequence	Data from literature
Increased mortality	Higher mortality rates are seen among patients with clinically relevant BL. A multi-institutional study by the ACS NSQIP that evaluated outcomes of hepatectomy in 6,859 patients saw a 7.7% rate of BL (78). Mortality rates differed greatly among BL and non-BL patients at 6.0% *vs.* 1.7% (P<0.001), respectively. These rates also related strongly with the rates of septic shock [28.3% in BL cohort *vs.* 4.8% in non-BL cohort (P<0.001)] (78)
	Additionally, a multicenter, prospective study of 949 patients conducted by Brooke-Smith *et al.* found a mortality rate of 1.6% (15/949) (6). This study recorded that the risk of mortality was 6.8 times higher for a patient that experienced BL (P<0.001). These deaths were a result of cardiac arrest, liver failure, pneumonia, and multi-organ failure (6)
	Moreover, reoperation further increases the perioperative mortality associated with hepatic resections. The retrospective analysis conducted by Barbas *et al.* evaluating 1,281 patients of hepatic resection found that 6.8% required reoperation (79). One of the most common causes was repair of fascial dehiscence (16.1%), and intra-abdominal hemorrhage (27.6%). Among the patients that required reoperation, 23.0% suffered perioperative mortality, *vs.* 3.4% among patients that did not require reoperation (P<0.001) (79)
	BL also impacts long-term survival of patients. A study by Fong *et al.* analysed the records of 711,454 cholecystectomy patients between 2005 and 2014 (80). BL occurred in 3,551 patients (0.50%). Mortality analyses found that mortality rates of BL patients are higher at the 1-year (2.4% *vs.* 1.4%, P<0.001) and 3-year (5.8% *vs.* 4.8%, P<0.05) mark compared to non-BL patients. Multivariate regression analysis supported this claim as well (OR =1.8, 95% CI: 1.4–2.3, P<0.001). This impact, however, was only noted in patients greater than 40 years of age. It should be noted that the mortality rate of 2.4% in BL patients in the first year was found after adjusting for sepsis and cholangitis. This indicates that even in the absence of infection, BL can be highly detrimental to healing (80)
	Mortality resulting from BL is usually associated with resulting comorbidities, such as IAS. In the absence of complete liver function, IAS can cause liver failure
Increased morbidity	Clinically relevant BL can severely increase postoperative morbidity (78). A study by Martin *et al.* in conjunction with the ACS NSQIP found that BL was independently associated with increased risk of postoperative morbidity (OR =4.55; 95% CI: 3.72–5.56; P<0.001) (78)
	As per a review conducted by Kapoor and Nundy, it was illustrated that while mortality associated with BL has reduced to less than 5% in high volume centres, postoperative morbidity remains in a range of 20–50% (35,81). Increased morbidity following BL can be attributed to prolonged drainage, intra-abdominal collections, and abscesses
Prolonged LOS	Patients who present with a clinically relevant BL, on average spend more time in the hospital than non-leak patients. A prospective, multicenter, international study of 949 patients undergoing hepatobiliary surgery was conducted by Brooke-Smith *et al.* (6). The rate of BL was 7.3%. In this cohort, LOS associated with BL patients was significantly higher than that of non-BL patients. On average, BL patients spent a median of 15 days (IQR, 8–29 days) in the hospital, compared to median 7 days (IQR, 7–15 days) for non-BL patients (P<0.001). The LOS was also significantly related with length of intensive care unit stay in BL patients (P<0.001) (6)
	The analysis of 6,589 hepatectomy patients by Martin *et al.* also illustrates the increased LOS associated with BL (78). The median length of stay for leak patients being 9 days (IQR, 6–15 days), while the non-BL patients had a median length of stay of 5 days (IQR, 4–7 days) (78)
	It has also been noted that patients requiring readmission have significantly increased LOS. In the retrospective analysis conducted by Barbas *et al.*, it was found that of 14.4% patients that required readmission, the cumulative LOS was 21.9 days (SD 15.7 days) *vs.* 9.0 days (SD 8.6 days) in patients that did not require readmission (P<0.001) (79)
	The increased LOS results from a need for prolonged drainage, monitoring of the patient, and treatment of any comorbidities resulting from BL
Increased readmission rates	Due to the onset of the clinical symptoms associated with BL, many patients that present with severe leaks are re-admitted if the leak developed during their discharge period. This subsequently increases LOS and patient costs
	The ACS NSQIP analysis by Martin *et al.* which contained 6,589 patients that underwent hepatectomy found that readmission was required in 12.1% of patients in the BL cohort, as opposed to 2.2% of patients in the non-BL cohort (P<0.001) (78)

Table 6 *(continued)*

Table 6 *(continued)*

Consequence	Data from literature
	Barbas *et al.* conducted a retrospective analysis of 1,281 patients that had liver resections (79). Of these patients, 14.4% required readmission. The most common reason for reoperation was postoperative fluid collections (27.2%), while other common reasons included wound complications (14.7%), and pleural effusions (6.5%). They also found that patients that underwent reoperation had increased risk of readmission (41.4% *vs.* 12.4%, P<0.001) (79)
Increased reoperation rates	Reoperation may be required if non-operative management techniques are not effective at managing the leak. This is done for Grade C BL. Reoperation can further affect the rates of readmission, mortality, and LOS
	In the analysis of 949 consecutive patients, Brooke-Smith *et al.* found that 7.3% patients had BL (6). Only 6 patients (0.6%) had a Grade C leak out of 69. 55% BL patients required intervention, including 8.7% that required relaparotomy (6)
	Additionally, as per the analysis of 6,589 patients by the ACS NSQIP, reoperation was required in 35.7% of patients in the BL cohort, as opposed to 8.5% of patients in the non-BL cohort (P<0.001) (78)
Increased hospital cost	Fong *et al.* found in their 2018 analysis of 711,454 cholecystectomies that the cumulative medical cost for BL patients can be as high as $17,130 more than non-leak patients within the first 30 days following their operation ($38,037 *vs.* $20,907, P<0.001) (80). The costs remained stable after the first month. The higher costs can be attributed to increased LOS, the need for reoperations and readmission, as well as treatment of secondary complications arising from BL (80)
Liver failure	Postoperative BL is frequently associated with liver failure (82). Yamashita *et al.* hypothesized that following a hepatic resection, an empty space where the remaining liver used to be is filled with blood, bile and devitalized tissues (42). These areas can act as breeding ground for bacteria, thereby impairing the patient's host defenses and promoting onset of sepsis. The combination of the septic conditions along with the loss of a significant portion of the liver has been shown to frequently result in liver failure, leading to a poor patient outcome (42)
	The analysis of 6,589 patients by Martin *et al.* recorded a BL rate of 7.7% (78). Of these patients, 20.2% patients in the BL cohort suffered from liver failure, while 4.1% patients in the non-BL cohort faced liver failure (P<0.001) (78). As per the analysis of 949 patients conducted by Brooke-Smith *et al.*, the risk of liver failure is increased by 2.9 times in BL patients (P<0.001) (6)
Intra-abdominal abscess	Infection from BL into the abdomen can lead to abscess formation, often progressing to sepsis. A significant challenge with BLs is their tendency to go unnoticed, allowing bile to accumulate in the abdomen rather than being drained (83). It is therefore vital to take immediate action upon discovering BLs to drain the bile and stop the leakage, preventing the onset or severity of these complications (84)
	In a retrospective study by Lee *et al.*, 21 patients experienced a bile collection, with 11% of them also developing an abscess (83). Late detection of these leaks was a critical factor in patients progressing to abscess formation. This was seen again in a case study by Huang *et al.*, where a patient experienced an extensive retroperitoneal abscess due to a BL (84). In both studies, patients were unable to recover from the abscess until the leak was addressed, with bile collections drained from the abdomen
Postoperative hemorrhage	Although post-operative hemorrhage and BLs are frequently mentioned together, some evidence suggests that hemorrhaging may actually manifest as a clinical presentation of BLs (52). BL into the abdomen causes the erosion of blood vessels, increasing the risk of hemorrhage (85). In addition, literature has associated late hemorrhage with infectious hepatic complications following surgery (86)
	In 2008 a prospective study on biliary leak complications was conducted by Ferrero *et al.* (85). This paper highlights the importance of PTBD to prevent complications from BLs. None of the patients who experienced hemorrhaging in this study underwent PTBD. The authors hypothesized that if bile had been drained from any leaks the risk and severity of bleeding may have been reduced

BL, bile leak; ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; OR, odds ratio; CI, confidence interval; LOS, length of stay; IQR, interquartile range; SD, standard deviation; PTBD, percutaneous biliary drainage; IAS, intra-abdominal sepsis.

Conclusions

Despite the ongoing progress in clinical medicine, addressing ALs in the context of HPB procedures remains a formidable challenge. A universally accepted grading system is yet to be established, but significant strides have been taken to conceptualize and define leaks of varying severity. Understanding these grading systems is crucial in both clinical and research settings, as issues in accurate identification and classification of leaks pose major limitations for diagnosis, incidence estimates, and proper patient categorization in research analyses.

Beyond diagnostic challenges, the gravity of leaks cannot be overstated. Marked by high morbidity and mortality, an increased rate of secondary postoperative complications, elevated reoperation rates, and prolonged hospital stays, the burdens extend not only to patients experiencing POPF or BL, but also impact their healthcare teams and broader medical system. The urgent need to alleviate these serious consequences underscores the necessity for further research in this domain. Recognizing that ALs persist as a reality in HPB surgical procedures, there is a compelling call to focus on exploring strategies for early detection—and consequently, treatment—of this severe and potentially life-threatening complication.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-9/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-9/coif). O.R. is a full-time permanent employee of FluidAI Medical, a medical device company that works on early prediction of postoperative complications, including anastomotic leaks. The company contributes to research associated with this manuscript in the following ways: clinical interest in the topic of this manuscript; attendance at conferences/educational events related to this article's content, travel related to this article's content, and stock options with the company. M.S. is a full-time permanent employee of FluidAI Medical, a medical device company that works on early prediction of postoperative complications, including anastomotic leaks. The author holds clinical interest and professional expertise in the topics explored within this article. The author also attends meetings/travel related to content in this article through their role at FluidAI Medical, and owns stock options with the company. N.H. is a full-time employee at FluidAI Medical which focuses on the early predication of leaks after gastrointestinal surgery. The author's role at FluidAI involves expertise in the topics explored within this article. The author also holds stock options with FluidAI. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are 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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