Hepatobiliary & Pancreatic Diseases International 18 (2019) 67–72

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Original Article/Pancreas

Biliary leakage following pancreaticoduodenectomy: Prevalence, risk factors and management

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ARTICLE INFO

Article history:
Received 26 May 2018
Accepted 23 October 2018
Available online 28 October 2018

Keywords:
Pancreatic head carcinoma
Pancreaticodudenetomy
Postoperative pancreatic fistula
Biliary leakage

ABSTRACT

Background: Few studies investigated biliary leakage after pancreaticoduodenectomy (PD) especially when compared to postoperative pancreatic fistula (POPF). This study was to determine the incidence of biliary leakage after PD, predisposing factors of biliary leakage, and its management.

Methods: We retrospectively studied all patients who underwent PD from January 2008 to December 2017 at Gastrointestinal Surgery Center, Mansoura University, Egypt. According to occurrence of postoperative biliary leakage, patients were divided into two groups. Group (1) included patients who developed biliary leakage and group (2) included patients without identified biliary leakage. The preoperative data, operative details, and postoperative morbidity and mortality were analyzed.

Results: The study included 555 patients. Forty-four patients (7.9%) developed biliary leakage. Ten patients (1.8%) had concomitant POPF. Multivariate analysis identified obesity and time needed for hepaticojejunostomy reconstruction as independent risk factors of biliary leakage, and no history of preoperative endoscopic retrograde cholangiopancreatiography (ERCP) as protective factor. Biliary leakage from hepaticojejunostomy after PD leads to a significant increase in development of delayed gastric emptying, and wound infection. The median hospital stay and time to resume oral intake were significantly greater in the biliary leakage group. Non-surgical management was needed in 40 patients (90.9%). Only 4 patients (9.1%) required re-exploration due to biliary peritonitis and associated POPF. The mortality rate in the biliary leakage group was significantly higher than that of the non-biliary leakage group (6.8% vs 3.9%, $P = 0.05$).

Conclusions: Obesity and time needed for hepaticojejunostomy reconstruction are independent risk factors of biliary leakage, and no history of preoperative ERCP is protective factor. Biliary leakage increases the risk of morbidity and mortality especially if concomitant with POPF. However, biliary leakage can be conservatively managed in majority of cases.

Introduction

Pancreaticoduodenectomy (PD) is a standard surgical operation for management of localized periampullary tumors. PD is a sophisticated surgical procedure. In the last decade, the mortality rate declined down to less than 3% thanks to improvements in operative techniques and postoperative care. However, postoperative complication rate remains relatively high and may reach up to 40%, some of which may even require reoperation. Postoperative pancreatic fistula (POPF) develop in 8%–29% after PD [1–6].

When dealing with post PD complications, most of studies have focused mainly on POPF, delayed gastric emptying (DGE), post pancreatectomy hemorrhage, and surgical site infection. These have been widely addressed in previous publications and officially defined in the international study group for pancreatic surgery (ISGPS) [6–10]. On contrary, few studies in literature have investigated post-PD biliary complications. Although three classifications for biliary leakage have been proposed by international study group for liver surgery (ISGLS), classification by Burkhart et al., and classification produced by Miller [11–17], there is no accepted universal definition of post-PD biliary fistula, and accordingly no standard protocol for its management [11–14].

The incidence of biliary leakage post PD is 3%–8% at high volume centers. In the majority of literature available, there has been no mortality associated with hepaticojejunostomy leakages after PD. However, the outcome can be disastrous, resulting in biliary

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https://doi.org/10.1016/j.hbpd.2018.10.005

peritonitis, abdominal collection, prolonged hospital stay, and even mortality [11–13].

Several recent studies identified different factors that may lead to hepaticojejunostomy leakages like a poor surgical technique, compromised blood supply, excessive skeletonisation at the level of the bile duct, preoperative biliary stenting, small caliber of bile duct, and associated POPF. Hepaticojejunostomy leakages may be isolated or may be associated with POPF. Hepaticojejunostomy leakages were found to significantly prolong hospitalization, and increase health care costs and mortality [18–20].

The aim of this retrospective study is to identify incidence of biliary leakages after PD, risk factors that may cause postoperative biliary leakages, and report our center experience in dealing with this complication.

Methods

Study design

This study included all patients who underwent PD between January 2008 and December 2017 at Gastrointestinal Surgery Center, Mansoura University, Egypt. Patient data were retrieved from a prospectively maintained database for analysis. Collected data included preoperative data, operative details, and postoperative morbidity and mortality. Written informed consent was obtained from each patient after explaining the nature of the disease, proposed surgical procedure and its complications and other possible lines of management. This study was approved by the local Institutional Review Board of Mansoura University, Egypt.

Preoperative assessment

As obstructive jaundice was the usual presentation, patients were usually diagnosed with a magnetic resonance cholangiopancreatography (MRCP). A further assessment with a pancreatic protocol abdominal computed tomography (CT) was done to confirm the diagnosis and evaluate resectability. Preoperative endoscopic biliary stenting was done only in patients with cholangitis or other correctable medical conditions which require postponing surgery [3,6,8,10].

Surgical procedures

A standard subtotal stomach preserving PD was done in all cases. Pancreatic anastomosis was performed either to the remaining stomach by pancreatico-gastrostomy (PG) or to the jejunum by pancreatico-jejunostomy (PJ) based on surgeon preference. Bilioenteric anastomosis was done in form of retrocolic end to side to hepaticojejunostomy. Hepaticojejunostomy was done as a single layer using Vicryl or Polydioxanone (PDS) (4–0 or 5–0) sutures (interrupted, continuous or combined). Gastro-jejunal anastomosis (GJ) was done side to side either antecolic or retrocolic in 2 layers.

Postoperative management

All patients were admitted to the intensive care unit for close monitoring on day of surgery then transferred to the general ward the next day. Two doses of prophylactic third generation cephalosporins were administered intra-operatively and continued for 4 days post-operatively. Patients with high risk for development of a pancreatic fistula (soft pancreas and small pancreatic duct <3 mm) were given prophylactic octreotide subcutaneously both intra- and postoperatively for 4 days.

Vital parameters, fluid charts, and drain outputs were recorded daily. Patients were allowed to start oral fluids once bowel movements were confirmed. Drains were removed and patients were discharged after tolerating semisolid diets and follow-up abdominal ultrasound was routinely done to exclude any intra-abdominal collections.

Definitions

Biliary leakage was defined as presence of bile in the drainage fluid that persists to postoperative day (POD) 4. POPF was defined by International Study Group of Pancreatic Fistula (ISGPF) as any volume of drained fluid on or after POD 3 with amylase content 3 times more than the serum amylase activity. POPF was graded into Grades A, B, and C according to the clinical course. DGE was defined as output from a nasogastric tube of greater than 500 mL per day that persisted beyond POD 10, the failure to maintain oral intake by POD 14, or reinsertion of a nasogastric tube [21]. Postoperative morbidities were graded according to Dindo–Clavien classification [22]. Postoperative mortality was defined as death within 30 days of operation.

Statistical analysis

Data analysis was done by SPSS software (Version 17.0, SPSS Inc., Chicago, IL, USA). Median and range were used to describe continuous variables. Categorical variables were described using frequency distributions. Wilcoxon rank sum test was used to detect differences in the median of continuous variables and Chi-square test was used for frequency distribution. *P* values were considered significant when the value was ≤0.05. Significant variables were analyzed by a logistic regression model to identify independent risk factors of postoperative biliary leakage. The independent risk factors of the variables were expressed as odds ratios (OR) with their 95% confidence intervals (CI).

Results

Demographic data

The study included 555 consecutive patients who were divided into two groups based on the development of postoperative biliary leakage. Group (1) included 44 patients (7.9%) who developed biliary leakage and group (2) included 511 patients (92.1%) without biliary leakage. Demographic and preoperative data are presented in Table 1. There was no significant difference between groups as regards age, presence of diabetes mellitus, clinical presentation, preoperative serum albumin and preoperative bilirubin. Preoperative biliary drainage by endoscopic retrograde cholangiopancreatography (ERCP) and BMI > 25 kg/m^2 were found to be significantly associated with a higher rate of postoperative biliary leakage.

Operative data

There was no significant difference between groups regarding liver status, tumor size, common bile duct (CBD) diameter, pancreatic texture, type of pancreatic reconstruction, method of hepaticojejunostomy reconstruction, and blood loss. Small pancreatic duct diameter (≤3 mm) was significantly prevalent in patients who developed biliary leakage (50.0% vs 30.5%, $P < 0.05$).

Time of hepaticojejunostomy reconstruction was significantly prolonged in patients who developed biliary leakage (40 vs 30 min, $P < 0.01$) (Table 2).

Postoperative data

DGE (47.7% vs 17.8%, $P = 0.0001$) and wound infection (13.6% vs 3.7%, $P = 0.0020$) were significantly more frequent in patients who developed biliary leakage than those not. The length of hospital

Table 1
Demographic and preoperative data.

Variables	Biliary leakage (n = 44)	Non-biliary leakage (n = 511)	P value
Age (yr, median)	56 (34–80)	54 (11–88)	0.26
≤60 yr	28 (63.6%)	365 (71.4%)	0.27
>60 yr	16 (36.4%)	146 (28.6%)	
Gender			
Male	31 (70.5%)	295 (57.7%)	**0.02**
Female	13 (29.5%)	216 (42.3%)	
BMI			
≤25 kg/m^2	18 (40.9%)	313 (61.3%)	**0.01**
>25 kg/m^2	26 (59.1%)	198 (38.7%)	
DM	8 (18.2%)	114 (22.3%)	0.25
Jaundice	36 (81.8%)	460 (90.0%)	0.90
Abdominal pain	30 (68.2%)	358 (70.1%)	0.79
Pre-operative biliary drainage	27 (61.4%)	227 (44.4%)	**0.03**
Pre-operative serum albumin (g/dL)	4.1 (2.9–5.0)	3.9 (2.9–4.5)	0.46
Pre-operative serum bilirubin (mg/dL)	3.1 (0.4–35.0)	4.2 (0.4–37.0)	0.31

BMI: body mass index; DM: diabetes mellitus.

Table 2
Operative data.

Variables	Biliary leakage (n = 44)	Non-biliary leakage (n = 511)	P value
Liver cirrhosis	7 (15.9%)	66 (12.9%)	0.86
Child–Pugh score A	6 (13.6%)	63 (12.3%)	
Child–Pugh score B	1 (2.3%)	3 (0.6%)	
Mass size (cm, median)	3.0 (0.5–6.0)	3.0 (0.5–12.0)	0.25
≤2 cm	14 (31.8%)	224 (43.8%)	0.12
>2 cm	30 (68.2%)	287 (56.2%)	
CBD diameter (mm)	15 (5–30)	15 (4–30)	0.38
Pancreatic duct diameter (mm)	3 (1–12)	4 (1–15)	
≤3 mm	22 (50.0%)	156 (30.5%)	<**0.01**
>3 mm	22 (50.0%)	355 (69.5%)	
Pancreatic texture			
Soft	22 (50.0%)	247 (48.3%)	0.38
Firm	22 (50.0%)	264 (51.7%)	
Type of reconstruction			
Continuous	21 (47.7%)	259 (50.7%)	0.85
Interrupted	6 (13.6%)	56 (11.0%)	
Posterior continuous and anterior interrupted	17 (38.6%)	196 (38.4%)	
Types of suture material			
Vicryl	30 (68.2%)	397 (77.7%)	0.15
PDS	14 (31.8%)	114 (22.3%)	
Type of pancreatic reconstruction			
PG	28 (63.6%)	386 (75.5%)	0.20
PJ	16 (36.4%)	125 (24.5%)	
Operative time (h)	5.25 (3.50–10.00)	5.00 (3.00–10.00)	0.57
Time of hepaticojejunostomy reconstruction (min)	40 (20–45)	30 (20–40)	**0.0001**
Blood loss (mL)	400 (50–5000)	500 (50–4000)	0.54

CBD: common bile duct; PDS: Polydioxanone; PG: pancreatico-gastrostomy; PJ: pancreatico-jejunostomy.

stay was 15 days in patients who developed biliary leakage and 9 days in patients who did not develop biliary leakage (P = 0.0001). The time to resume oral intake was 6 days in the biliary leakage group patients and 5 days in the non-biliary leakage group (P = 0.02).

There was no significant difference between groups as regards the development of POPF. Ten patients had combined biliary leakage with POPF (7 patients had POPF grade B and 3 patients POPF grade C).

Re-exploration was done in 9 patients (20.5%) who developed biliary leakage (4 patients had biliary peritonitis, 2 patients internal hemorrhage, 2 patients obstructed GJ, and 1 patient GJ leakage). Thirty-four patients (6.7%) without biliary leakage were re-explored for different reasons: internal hemorrhage (14 patients), obstructed GJ (7 patients), bleeding from PG (5 patients), GJ leakage (2 patients), POPF grade C (4 patients), burst abdomen (1 patient) and mesenteric vascular ischemia (1 patient).

The overall mortality rate was 23 patients (4.1%). There was a significant difference between groups as regard hospital mortality 3/44 (6.8%) in the biliary leakage group (two patients died from sepsis due to POPF grade C combined with biliary leakage and one patient due to pulmonary embolism) and 20/511 (3.9%) in the non-biliary leakage group [8 patients died due to sepsis secondary to POPF, 4 patients due to pulmonary embolism, 2 patients due to bleeding, 2 patients due to heart failure, 1 patient due to severe pancreatitis, 1 patient due to liver failure, 1 patient due to cerebral hemorrhage, and 1 patient due to severe chest infection (Table 3)].

Univariate analysis showed that biliary leakage was more frequent among male patients, BMI > 25 kg/m^2, longer time for hepaticojejunostomy reconstruction, pancreatic duct diameter ≤ 3 mm, and preoperative ERCP and stenting. Multivariate analysis identified that obesity, and time needed for hepaticojejunostomy reconstruction were independent risk factors for biliary leakage and no history of preoperative ERCP as a protective factor (Table 4).

Benign biliary stricture post PD after one year was 17/555 (3.1%). All patients presented by recurrent attacks of cholangitis. In the biliary leakage group three out of four patients needed redo hepaticojejunostomy and one patient managed by interventional ultrasound balloon dilatation. In the non-biliary leakage group 9

Table 3
Postoperative data.

Variables	Biliary leakage (n = 44)	Non-biliary leakage (n = 511)	P value
Hospital stay (d)	15 (10–45)	9 (4–71)	**0.0001**
Time to oral intake (d)	6 (4–35)	5 (4–56)	**0.02**
Total amount of drainage (mL)	2000 (800–15,000)	800 (65–35,000)	**0.0001**
Drain removal (d)	15 (10–45)	8 (5–71)	**0.0001**
Postoperative D1 serum bilirubin (mg/dL)	2.4 (0.5–32.0)	3.5 (0.5–29.5)	0.50
Postoperative D5 serum bilirubin (mg/dL)	1.6 (0.5–17.8)	2.3 (0.5–27.7	0.49
Dindo-Clavien grade			
I	15 (34.1%)	74 (14.5%)	**0.0001**
II	8 (18.2%)	44 (8.6%)	
III	18 (40.9%)	34 (6.7%)	
IV and V	3 (6.8%)	20 (3.9%)	
Pancreatic fistula	10 (22.7%)	46 (9.0%)	0.56
Grade B	7 (15.9%)	35 (6.8%)	0.30
Grade C	3 (6.8%)	11 (2.2%)	
DGE	21 (47.7%)	91 (17.8%)	**0.0001**
Pulmonary complications	2 (4.5%)	16 (3.1%)	0.61
Internal hemorrhage	2 (4.5%)	14 (2.7%)	0.49
Gastrojejunostomy leakage	3 (6.8%)	6 (1.2%)	**0.004**
Pancreatitis	1 (2.3%)	7 (1.4%)	0.63
Bleeding PG	0	5 (1.0%)	0.51
Wound infection	6 (13.6%)	19 (3.7%)	**0.002**
Re-operation	9 (20.5%)	34 (6.7%)	**0.0001**
Hospital mortality	3 (6.8%)	20 (3.9%)	0.05
Biliary stricture after one year	4 (9.1%)	13 (2.5%)	**0.02**

DGE: delayed gastric emptying; PG: pancreatico-gastrostomy.

Table 4
Predictors of biliary leakage.

Variables	B	SE	Wald	P value	Exp(B)	95% CI for Exp(B)
Gender (male)	−0.709	0.379	3.493	0.062	0.492	0.234–1.035
Body mass index > 25 kg/m^2	1.017	0.361	7.941	**0.005**	2.764	1.363–5.604
No history of preoperative ERCP	−0.747	0.358	4.349	**0.037**	0.474	0.235–0.956
Pancreatic duct diameter ≤ 3 mm	0.121	0.208	0.340	0.560	1.129	0.751–1.696
Time of hepaticojejunostomy reconstruction	0.236	0.038	37.957	**<0.010**	1.266	1.175–1.365

ERCP: endoscopic retrograde cholangiopancreatoraphy.

Table 5
Outcome of biliary leakage and management in the biliary leakage group (n = 44).

Variables	Values
Time of onset of biliary leakage (d)	2 (1–7)
Time of stoppage of biliary leakage (d)	15 (10–45)
Amount of biliary leakage (mL)	2000 (800–15,000)
Presentation	
Bile in the drain	44 (100%)
Collection	17 (38.6%)
Peritonitis	4 (9.1%)
Non-surgical treatment	
Maintenance of abdominal drain for long time	10 (22.7%)
Withdrawal of the drain and re-positioning	13 (29.5%)
Ultrasound-guided tubal drainage	17 (38.6%)
Surgical treatment	
Surgical drainage	3 (6.8%)
Re-hepaticojejunostomy over external stent	1 (2.3%)

patients managed by redo hepaticojejunostomy and 4 patients managed by interventional ultrasound balloon dilatation (Table 3).

Management and outcome of biliary leakage

Non-surgical management was done in 40 (90.9%) patients; prolonged need for the abdominal drain (23 patients), or ultrasound guided tubal drainage (17 patients). Only 4 (9.1%) patients required re-exploration due to biliary peritonitis and associated POPF (Table 5, Fig. 1).

Discussion

PD is a complex procedure with extensive dissection and three reconstructions (pancreatic reconstruction, hepaticojejunostomy and GJ). Recently, with improvement of the perioperative management, surgical techniques and patient selection, operative mortality declined to less than 3%–5%. However, the postoperative morbidity remains in the range of 40%–60% [3–5]. Most of literatures addressed on type of pancreatic reconstruction and postoperative morbidity stressed on POPF, DGE, and postoperative hemorrhage [1,5–8,23].

Hepaticojejunostomy leakage after PD is not fully addressed in most of studies after PD. The incidence of biliary leakage after PD is ranging from 2% to 8% [11–14, 18–20]. Our reported 7.9% of biliary leakage after 555 patients who underwent PD is consistent with that reported in literature. A few studies reported that the risk factors for development of biliary leakage included older age, longer operative time, POPF, small caliber CBD, post pancreatectomy hemorrhage, low serum albumin, DGE, and sepsis [12,20,24–27]. de Castro et al. [19] studied 486 PDs, and they found that previous ERCP, obesity, anastomosis of small bile ducts were independent risk factors associated with biliary leakage. Antolovic et al. [24] studied 300 PDs, showing that preoperative chemotherapy and associated hepatectomy were independent factors associated with biliary leakage. Andrianello et al. [12] studied 1618 consecutive PDs at single institution and reported that hepaticojejunostomy leakage is multifactorial but technical factors represent the major role, and that prolonged operative time, obesity, and small CBD diameter are risk factors for development of biliary leakage. The present study adds evidence to these cited studies,

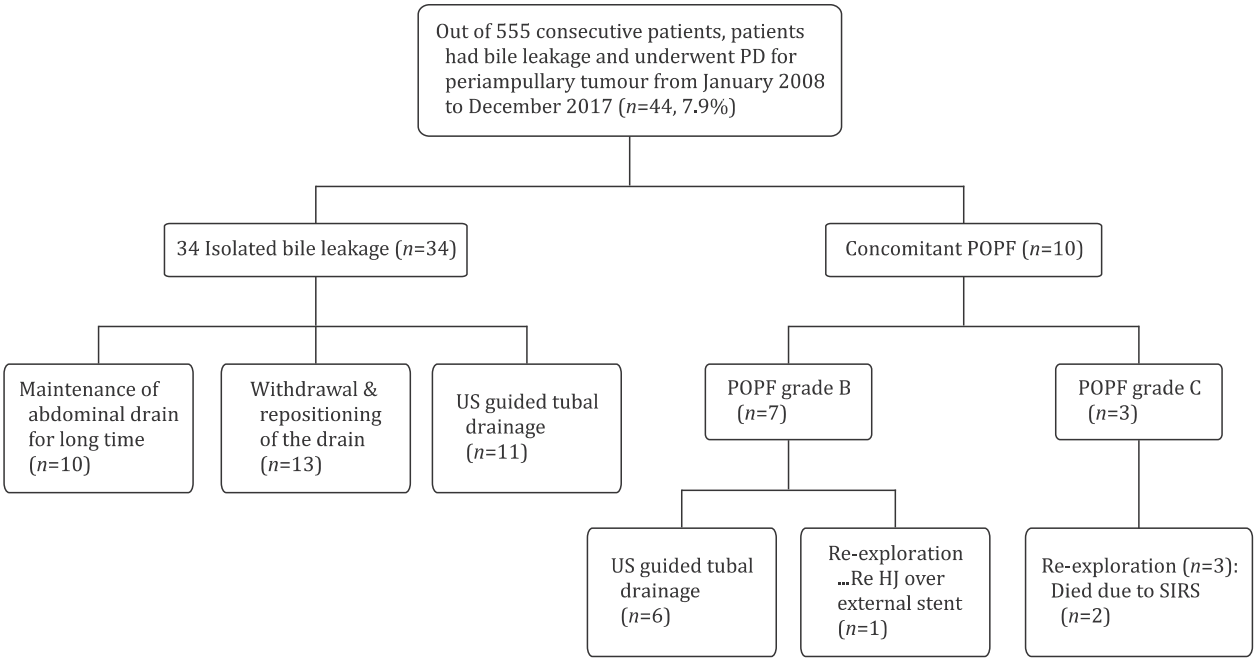

Fig. 1. Types and management of biliary leakage after PD. PD: pancreaticoduodenectomy; POPF: postoperative pancreatic fistula; US: ultrasound; HJ: hepaticojejunostomy; SIRS: systemic inflammatory response syndrome.

with advantage of a large surgical series of PDs at a single surgical center. The present study identified obesity, and time needed for hepaticojejunostomy reconstruction as independent risk factors of biliary leakage and no history of preoperative ERCP as a protective factor.

Asymptomatic biliary leakage from hepaticojejunostomy after PD results in no changes in patients' clinical pathway and has no impact on complication rate [15–17]. In this study, symptomatic biliary leakage from hepaticojejunostomy after PD leads to a significant increase of DGE, and wound infection. Biliary leakage resulted in prolonged hospital stay and time to resume oral intake.

Outcomes of biliary leakage after PD are quite variable. It may lead to surgical site infection, prolonged hospital stay, intra-abdominal collection, biliary peritonitis, or even death. The reason why biliary leakage can lead to peritonitis or need intervention is not fully understood. In the absence of signs of systemic infection and local signs of collection, biliary leakage could resolve spontaneously in 50% of cases or easily managed by non-surgical measures even in outpatient clinic [12,13,18,19]. Non-surgical management (including maintenance of abdominal drain for long time, withdrawal and re-positioning of the drain or ultrasound guided tubal drainage) is successful in management of majority of patients. Surgical management is needed if there is abdominal collection (not candidate for tubal drainage because it is septated and multiloculated) or biliary peritonitis. In the majority of the studies the mortality related to biliary leakage and its sequlae is none [1l–15,19,20]. However in the present study, two cases died as a complication of biliary leakage especially when associated with POPF.

Hepaticojejunostomy in PD should be above the cystic duct level especially in malignant cases whatever its diameter. Biliary leakage is usually related to CBD wall weakness, ischemia and needle holes in CBD wall. The optimal preventive measures to decrease the biliary leakage after PD included correct surgical technique in high specialized center, use of internal or external stent in difficult cases (including small caliber CBD, very thick and inflamed CBD or friable CBD wall), and use interrupted suture in difficult cases. Use of 6/0 suture with less number of stitches to avoid ischemia and large needle holes. Detection of celiac axis stenosis is important to avoid biliary leakage due to ischemia [12,13,20,28–30].

Biliary leakage concomitant to POPF increase the overall effect of the two fistulae alone [12,13,31]. Andrianello et al. [12] reported that pure biliary leakage is less harmful than mixed biliary leakage with POPF. Mixed biliary leakage with POPF increased the rate of postoperative mortality. The concomitant biliary leakage and POPF results in 65% of post pancreatectomy hemorrhage and a 34.8% mortality rate. In the current study, biliary leakage associated with POPF was represented in 10 (22.7%) cases. Four patients who had mixed biliary leakage with POPF required re-exploration due to biliary peritonitis. Two patients died from sepsis due to POPF grade C combined with biliary leakage.

Many classifications for biliary fistula exist including Burkhart et al. classification, ISGLS classification, and modified Accordion classification [15–17]. All of them are based on the severity of biliary leakage depending on its clinical pathway and management. Most of classifications show overlap between the grades of biliary leakage in terms of total cost and length of hospital stay. ISGLS classification, and modified Accordion classification are more reliable and accurate. Although presence of concomitant biliary leakage and POPF greatly affects the surgical outcomes and prognosis, none of these classifications have taken this point into consideration. Therefore, we strongly recommend that any further new classification for biliary leakage after PD should include presence of concomitant POPF and its management.

In this study, benign biliary stricture post PD was 17/555 (3.1%) in one year. House et al. [18] reported biliary stricture developed in 42 of 1595 patients (2.6%) independent of type of tumor. The median time to stricture formation was 13 months (range, 1–106). The pathogenesis of biliary enteric anastomotic stricture following a PD is multifactorial. Tension at anstomosis and ischemia may be the most important factors. All strictures were initially managed with preoperative biliary balloon dilatation and stenting and only two patients managed by redo hepaticojejunostomy. Duconseil et al. [11] found that thirty out of 397 patients underwent PD experienced a biliary complications; 13 biliary leakage (3.3%) and 17 biliary stricture (4.3%). A thin bile duct < 5 mm was the only

risk factor for developing biliary leakage and biliary stricture. Malgras et al. [13] found that 49 patients (14%) developed 51 biliary complications including 7 (2%) biliary stricture, 9 (3%) biliary leakages, 15 (4%) transient jaundice and 20 (6%) cholangitis, and reported that male gender, benign disease, malignancy chemoradiation, and CBD < 5 mm were risk factors for development of biliary complications.

Several limitations are inherent to this study. Firstly, it is a retrospective study despite all patient data being recorded in a prospectively maintained database. Secondly, all patients presented by biliary leakage after PD including patients with concomitant POPF and biliary leakage.

In conclusion, biliary leakage is an uncommon complication after PD. Obesity, time needed for hepaticojejunostomy reconstruction are independent risk factors of biliary leakage after PDs and history of no preoperative ERCP is a protective factor. Biliary leakage leads to a prolonged hospital stay and increased the incidence of DGE. Biliary leakage can resolve spontaneously or easily managed by non-surgical measures even in outpatient clinic in majority of cases. Surgical intervention is required only in case of biliary peritonitis. A pure biliary leakage from hepaticojejunostomy is not considered harmful. However, biliary leakage concomitant to POPF is severe and life-threatening.

Contributors

ENA designed the research. ENA, HH, and SR analyzed the data. ENA and ESM wrote the paper. All authors contributed to the design and interpretation of the study and to further drafts. ENA is the guarantor.

Funding

None.

Ethical approval

This study was approved by the Institutional Review Board and local ethical committee at Faculty of Medicine, Mansoura University.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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