ORIGINAL ARTICLE

Early biliary complications following pancreaticoduodenectomy: prevalence and risk factors

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Abstract

Background: Early biliary complications (EBC) following pancreaticoduodenectomy (PD) are poorly known. This study aimed to assess incidence, predictive factors, and treatment of EBC including bilio-enteric stricture, transient jaundice, biliary leak, and cholangitis.

Method: From 2007 to 2011, 352 patients underwent PD. Statistical analysis including logistic regression was performed to determine EBC predictive factors.

Results: 49 patients (14%) developed 51 EBC, including 7(2%) bilio-enteric strictures, 15(4%) transient jaundices, 9(3%) biliary leaks, and 20(6%) cholangitis with no mortality and a 18% reoperation rate. In multivariate analysis, male gender, benign disease, malignancy with preoperative chemoradiation, and common bile duct (CBD) diameter $\leq$5 mm were predictive of EBC. Of the 7 strictures, all were associated with CBD $\leq$5 mm and 5(71%) required reoperation. Transient jaundice resolved spontaneously in all 15 cases. Among 8 patients with serum bilirubin level >50 μmol/L (3 mg/dL) at POD3, 7(88%) developed bilio-enteric stricture. Biliary leak resolved spontaneously in 5(56%); otherwise, it required reoperation. Cholangitis recurred after antibiotics discontinuation in 5(25%).

Conclusions: EBC following PD do not increase mortality. EBC are more frequent with male gender, benign disease, malignancy with preoperative chemoradiation, and CBD $\leq$5 mm. Transient jaundice or cholangitis has a favorable outcome, whereas bilio-enteric stricture or biliary leak can require reintervention.

Received 12 October 2015; accepted 30 October 2015

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Introduction

In high-volume centers, pancreaticoduodenectomy (PD) is presently associated with a mortality rate below 5%, but perioperative morbidity remains significant, occurring in 40–50% of patients.[1,2] The most frequent complications following PD are pancreatic fistula, delayed gastric emptying, and hemorrhage, justifying the recent publications of their own grading system.[3–5] Incidence, risk factors, and management of these complications have been extensively studied, including through prospective randomized trials.[6–9] On the other hand, less frequent postoperative early complications such as ischemic complications,[10] infectious complications,[11] gastrojejunostomy fistula,[12] chylous leak,[13] or biliary complications[14,15] have been poorly investigated, and their management remain challenging. Particularly, early biliary complications (EBC) following PD are only reported as biliary leak or stenosis.[14,15] However, EBC consist of a wider spectrum also including cholangitis and transient jaundice, which have not been extensively characterized. The aim of the present study was to describe incidence, predictive factors, and management of the spectrum of EBC following PD.

This study was presented at the 11th World IHPBA Congress, 22-27 March 2014, Seoul.

Methods

Data acquisition

From January 2007 to December 2011, 352 patients underwent PD in the department of Hepato-Biliary and Pancreatic Surgery, Beaujon Hospital. Demographic, radiologic, postoperative course, and pathologic data were obtained from a prospective database with additional retrospective medical record review. All clinical, biochemical, and radiologic data were prospectively collected. The database was analyzed in regards to prevalence and risk factors of postoperative biliary complications.

All procedures were performed through laparotomy by three experienced surgeons (AS, SD, BA). PD were performed as previously described.[10] Pancreatico-enteric continuity was restored by pancreaticogastrostomy or pancreaticojejunostomy according to the surgeon's preference. In patients who had pancreaticogastrostomy, hepaticojejunostomy was performed on the first jejunal loop 60 cm upstream of the gastrojejunostomy. In patients who had pancreaticojejunostomy, hepaticojejunostomy was performed 40–50 cm downstream of the pancreatic anastomosis. Hepaticojejunostomy was routinely performed on the upper part of the common bile duct (CBD) in case of malignancy and on the CBD divided at the upper edge of the pancreas in case of benign disease. In the latter setting, low CBD division was chosen to obtain a larger diameter, and care was taken to avoid CBD devascularization caused by extensive dissection in the hepatic pedicle. Anastomosis modalities were driven by technical considerations. Briefly, interrupted sutures were preferentially used for the small CBD diameter ($\leq$5 mm), a running suture was used for the large CBD diameter (>1 cm), and a mixed technique (i.e., posterior running suture and interrupted anterior suture) was used otherwise. In case of a small CBD diameter, an enlargement plasty by either anterior ductal wall incision or side-to-side ductoplasty using a cystic duct was performed. Sutures were always performed with 5/0 or 6/0 monofilament synthetic absorbable sutures. No biliary stenting was used. A retrocolic gastrojejunostomy was performed 40–50 cm below the hepaticojejunostomy. A routine bile sampling was routinely performed at the beginning of PD for microbiological examination, including bacterial susceptibility to antibiotics. According to our institutional protocol, all patients with preoperative biliary stenting or ampulloma received a routine 5-days postoperative antimicrobial therapy, as previously reported.[2,11] At the end of the procedure, a multichannel, open silicone drain was placed close to both pancreatic and biliary anastomoses and externalized through a separate right flank incision.

Postoperative management and complications

Octreotide (Sandostatine®, 100 µg subcutaneously 3 times per day, Novartis, Rueil Malmaison, France) was given to patients with a soft pancreas and started intraoperatively. Postoperatively, biological assessment including amylase level in the drain fluid was routinely done on days 3, 5, 7, and 10. The bilirubin level in the drain fluid was only assessed in case of clinical suspicion of biliary leak.

The drain was removed incrementally over a course of days from postoperative day 5. Postoperative mortality included all deaths that occurred before postoperative day (POD) 90. Morbidity included all complications following surgery until discharge and/or readmission and was graded according to the Clavien-Dindo classification.[16] Major postoperative complication was defined as a Clavien-Dindo grade $\geq$3. Postoperative pancreatic fistula (POPF), hemorrhage, and delayed gastric emptying were defined according to the International Study Group of Pancreatic Surgery (ISGPS).[3,5]

Early biliary complications (EBC) (occurring within 90 postoperative days) were defined and treated as follows:

1 *Bilio-enteric stricture* was defined by a new onset of jaundice increasing continuously and related to obstruction confirmed by biliary dilatation on postoperative imaging (ultrasonography or CT). Strictures were managed by interventional radiology (percutaneous transhepatic balloon dilatation and stenting of the anastomosis) or reoperation, according to surgeon's preference.
2 *Transient jaundice* was defined by a temporary increase of serum bilirubin level 2 times above the upper limit of the normal range (i.e., above 35 µmol/L, 2 mg/dL). Imaging was usually performed to exclude intra-hepatic biliary dilatation. Apart from monitoring liver function tests, no specific treatment was given.
3 *Biliary leak* was defined by a bilious aspect of the drainage fluid confirmed biologically in patients without concomitant pancreatic fistula or bile duct ischemic complications.[10] Particularly, to avoid inclusion of patients with biliary fistula secondary to POPF, we excluded from the diagnosis of biliary leak every patient with amylase assay in the drainage fluid greater than three times the upper normal value at diagnosis of biliary leak. No fistulography was used. Biliary leak were managed by drainage until resolution or reoperation (revision of the bile duct anastomosis ± T tube) in case of sepsis or high output persistent fistula.
4 *Cholangitis* was defined by the association of clinical signs of infection (fever and chills), an increase in serum inflammatory markers, and abnormal liver functions tests improving over time under antibiotic therapy.

Statistical analysis

Values are expressed as median (interquartile range, IQR), mean (standard derivation, SD), or number of patients and percentage, as appropriate. Univariate analysis was performed to test the association between the patients' characteristics and EBC occurrence using the Chi-squared test or Fisher's exact test when appropriate. Multivariate analysis was then performed to determine the main independent risk factors for EBC. All independent variables for which the p-value was $\leq$0.20 at the univariate

stage were introduced in a logistic regression model, and a backward selection of variables was used to obtain the final model. The Hosmer and Lemeshow test was run to assess the goodness-of-fit of this final model. The same analysis (univariate followed by multivariate analysis) was performed for each kind of EBC, i.e., bilio-enteric stricture, transient jaundice, biliary leak, and cholangitis, respectively. All tests were two-sided. For all tests, the statistical significance was defined by $p < 0.05$. Data were analyzed with the STATA 12 statistical software (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

Characteristics of the patients and surgical procedures

The pre-, intra-, and post-operative characteristics of the 352 patients are listed in Table 1. The study included 54% (n = 191) of male patients with a median age of 60 years (IQR 53–68). Indications for PD were ductal adenocarcinoma (43%, n = 151), intraductal papillary mucinous neoplasm (21%, IPMN, n = 75), endocrine tumor (11%, n = 39), ampullary carcinoma (7%, n = 23), bile duct carcinoma (6%, n = 19), chronic pancreatitis (4%, n = 14), duodenal carcinoma (3%, n = 13), and miscellaneous (5%, n = 18). Most of the PD were performed for malignancy (70%, n = 245), including after preoperative chemoradiation in 6% (n = 20) cases.

Preoperative biliary drainage has been performed in 29% (n = 102) of patients, and bile culture was positive in 32% (n = 114) of cases. At the time of surgery, 53% (n = 187) of patients were jaundiced. PD was usually performed with an antrectomy (70%, n = 245). For reconstruction, pancreaticogastrostomy was most frequently used (56%, n = 199). CBD diameter was ≤5 mm in 23% (n = 82) of patients. Bilio-enteric anastomosis was performed using interrupted sutures, running sutures, or a mixed technique in 13% (n = 45), 28% (n = 100),

Table 1 Distribution of patients' characteristics and surgical procedures according to occurrence of early biliary complications (EBC). Results are given as percentage and number of patients

	Overall% (n = 352)	EBC% (n = 49)	No EBC% (n = 303)	Univariate analysis (p)
Patient's characteristics				
Male gender	54 (191)	67 (33)	52 (158)	0.04
Age ≤ 60 y.	48 (169)	49 (24)	48 (145)	0.88
Preoperative biliary drainage	29 (102)	22 (11)	30 (91)	0.27
Pancreatic anastomosis				
Pancreaticogastrostomy	56 (199)	57 (28)	56 (171)	
Pancreaticojejunostomy.	44 (153)	43 (21)	44 (132)	0.78
Bilio-enteric anastomosis				
Interrupted sutures	28 (100)	39 (19)	27 (81)	
Continuous suture	13 (45)	8 (4)	13 (41)	0.18
Mixed	59 (207)	53 (26)	60 (181)	
Enlargement plasty	19 (68)	24 (12)	18 (56)	0.32
5/0 sutures	80 (281)	69 (34)	82 (247)	
6/0 sutures	20 (71)	31 (15)	18 (56)	0.05
Common bile duct diameter ≤ 5 mm	23 (82)	45 (22)	20 (60)	<0.001
Positive bile culture	32 (114)	22 (11)	34 (103)	0.1
Other intraoperative				
Venous resection	24 (84)	18 (9)	25 (75)	0.33
Pylorus preservation	30 (107)	47 (23)	28 (84)	0.01
Intraoperative blood transfusion	19 (67)	16 (8)	19 (59)	0.6
Histologic diagnosis				
Benign	30 (107)	51 (25)	27 (82)	
Malignant – no preoperative CRT	64 (225)	37 (18)	68 (207)	<0.001
Malignant with preoperative CRT	6 (20)	12 (6)	5 (14)	
Postoperative course				
Pancreatic fistula	33 (115)	45 (22)	31 (93)	0.05
Mortality	4 (13)	0 (0)	4 (13)	0.23

Table 2 Distribution, treatment, and outcome of early biliary complications following pancreaticoduodenectomy

Early biliary complications	Nb	Median delay of occurrence (day) (range)	Treatment		Grade ≥ Clavien3	Outcome	
			Interventional radiology	Surgery		Mortality	Late biliary complications
Overall	51	6 (1–90)	2	9	11	0	7
Bilio-enteric stricture	7	5 (4–15)	2	5	7	0	1
Transient jaundice	15	2 (1–5)	0	0	0	0	0
Biliary leak	9	7 (1–12)	0	4	4	0	1
Cholangitis	20	30 (5–90)	0	0	0	0	5

Late biliary complications include cholangitis ± abscess, stent obstruction, and bilio-enteric anastomotic stricture.

and 59% (n = 207) of patients, respectively. Nineteen per cent (n = 68) of patients had an enlargement plasty, and 5/0 sutures were used in 80% (n = 281) of patients.

Overall postoperative course

The mortality rate was 4% (n = 13). Causes of deaths were surgical complications in 62% (n = 8, including 3 ischemic complications, 2 pancreatic fistulas, and 3 hemorrhages), cardiopulmonary disorders in 23% (n = 3), and miscellaneous complications in 15% (n = 2). POPF occurred in 33% of patients (n = 115), including 15% (n = 52) and 5% (n = 17) of patients who developed grade B and C POPF, respectively. Delayed gastric emptying occurred in 15% (n = 53) of patients. One patient with ampullary carcinoma (1/23, 4%) and two patients with distal bile duct carcinoma (2/19, 11%) had positive biliary margins, respectively.

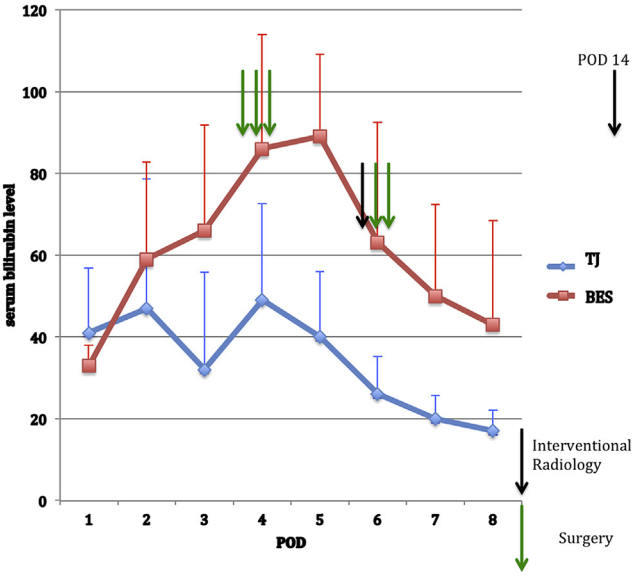

Figure 1 Evolution of serum bilirubin levels (expressed in µmol/L) in patients with bilio-enteric stricture and transient jaundice (100 µmol/L = 5.9 mg/dL). TJ: transient jaundice; BES: bilio-enteric stricture; POD: postoperative day

Early biliary complications: diagnosis, management, and outcome (Table 2)

Forty-nine patients developed 51 EBC, representing a 14% overall incidence. Bilio-enteric stricture occurred in 7 patients (incidence = 2%), transient jaundice in 15 (4%), biliary leak in 9 (3%), and cholangitis in 20 (6%, including 2 who also developed transient jaundice) (Table 2). In these 49 patients, median (IQR) postoperative follow-up was 9 (6–21) months.

Bilio-enteric stricture (n = 7)

Diagnosis of bilio-enteric stricture was made before or on postoperative day (POD) 5 in 6 patients (86%) or on POD 15 in one patient. In all 7 patients, presentation was new onset jaundice with serum bilirubin level increasing continuously until treatment (Fig. 1). Indeed, mean serum bilirubin level was 60 ± 20 µmol/L (3.5 ± 1 mg/dL) on POD 2 and 90 ± 33 µmol/L (5 ± 2 mg/dL) on POD 4, respectively. CBD diameter was ≤5 mm in all 7 patients. Bilio-enteric strictures were treated by surgical revision of anastomosis in 5 (71%) patients including T-tube insertion in 3 and by interventional radiology in 2 (29%) who underwent percutaneous transhepatic biliary drainage followed by balloon dilatation and stenting of the anastomosis. At reoperation, there were 2 complete short anastomotic strictures with technical insufficiency (including one transfixing suture), 2 cases of haemobilia with blood clots trapped in CDB above a partial stenosis, and 1 CBD stricture 1 cm above the anastomosis. Two complications (wound infection) occurred in the 5 re-operated patients. No patients treated by surgery developed late biliary complication, whereas one of the 2 patients treated by interventional radiology experienced stent occlusion requiring additional radiological procedure 2 months after the first one.

Transient jaundice (n = 15)

In all 15 patients who developed transient jaundice, mean serum bilirubin levels always increased since POD 1, but they decreased spontaneously. The mean serum bilirubin level was 47 ± 17 µmol/L (2.7 ± 1 mg/dL) at POD 2, remained stable at 48 ± 18 µmol/L (2.8 ± 1 mg/dL) at POD 4, and decreased spontaneously to 17 ± 5 µmol/L (1 ± 0.3 mg/dL) at POD 8 (Fig. 1).

No specific treatment was provided for transient jaundice, except in 2 patients who also developed one episode of cholangitis one week and one month after transient jaundice, respectively. Both were treated by intravenous antibiotics.

Comparison of patients with bilio-enteric stricture and transient jaundice

In the early postoperative period, serum bilirubin levels were significantly higher in patients who developed stricture ($p < 0.001$) since POD 3, whereas no significant difference was present at POD 1 ($p = 0.71$) and POD 2 ($p = 0.1$). At the follow-up, among the 8 patients with serum bilirubin levels >50 µmol/L (3 mg/dL) at POD 3, 7 (88%) developed early bilio-enteric stricture. Contrarily, no patients with serum bilirubin level <50 µmol/L (3 mg/dL) at POD 3 developed ultimately bilio-enteric stricture.

Biliary leak (n = 9)

Of the 9 patients who developed a biliary leak, 6 (67%) developed this complication during the first post-operative week. In 8 patients, bilirubin levels in the drainage fluid were elevated (mean = 619 ± 390 µmol/L, 40.6 ± 23 mg/dL) and were normal in the last patient due to inefficient intra-abdominal drainage resulting in biliary peritonitis. No concomitant POPF was diagnosed at the same time as the biliary leak, but 2 patients developed POPF subsequently (5 and 9 days after diagnosis of biliary leak, respectively).

The biliary leak was resolved spontaneously in 5 (56%) patients treated by prolonged drainage with gradual drain removal. Reoperation was required due to sepsis or peritonitis in 4 (44%) patients who underwent anastomotic revision including T-tube insertion in 3. Two complications (1 wound infection and 1 pneumonia) occurred in the 4 re-operated patients. One of the 9 patients subsequently developed late biliary complications with bilio-enteric anastomotic stricture, requiring surgical revision.

Cholangitis (n = 20)

Cholangitis occurred in 20 patients, including 15 (75%) whose diagnosis was done after POD 15. In the 5 other patients, diagnosis was done during the first and second postoperative weeks in 2 (10%) and 3 (15%), respectively. Symptoms of cholangitis included fever and/or chills (100%), jaundice (n = 5, 25%), and right upper quadrant pain (n = 14, 70%). Bacteremia was proven by positive blood cultures in 10 (50%) patients. All patients were treated by antibiotics, which were chosen according to blood culture results if positive, and if no positive culture was available, the treatment was chosen according to the results of routine intraoperative bile culture or bacterial epidemiology in our unit. Cholangitis recurred after discontinuation of antibiotics in 5 (25%) patients (mean delay of 5 ± 8 months) who were treated by a second course of antibiotics. Out of these 5 patients, 2 patients developed small hepatic abscesses that resolved without drainage. No late bilio-enteric stricture was diagnosed after cholangitis.

Predictive factors of early biliary complications

Risk factors for overall complications

In the univariate analysis (Table 1), male gender, benign disease, malignancy treated by preoperative chemoradiation, pylorus preserving technique, CBD diameter ≤ 5 mm, pancreatic fistula, and use of 6/0 sutures for biliary anastomosis were associated with EBC. In the multivariate analysis, only male gender, benign disease, malignancy treated by preoperative chemoradiation, and a CBD diameter ≤5 mm were predictive of EBC (Table 3).

Risk factors for each type of complications (Table 3)

All bilio-enteric strictures occurred in patients with a CBD diameter ≤ 5 mm. Another factor associated with stricture in multivariate analysis was the use of a 6/0 suture. Regarding transient jaundice, a CBD diameter ≤5 mm was the only significant risk factor identified. Cholangitis was significantly more frequently observed in cases of benign disease or malignancy

Table 3 Predictive factors of early biliary complication: multivariate analysis

	Adjusted OR	95% CI	p-value
Overall			
Male gender	2.0	1.0–3.8	0.05
Benign disease	2.2	1.1–4.7	0.002
Malignancy without preop. Chemoradiation (*ref*)	1		
Malignancy with preop. chemoradiation	6.3	2.1–19.1	
CBD diameter ≤5 mm	2.6	1.3–5.5	0.009
Pancreatic fistula	1.7	0.9–3.4	0.1
Bilio-enteric stricture			
CBD diameter ≤5 mm	100%		
6/0 suture caliber	5.3	1.1–25.5	0.03
Age ≤60 years	2.6	0.5–14.2	0.30
Blood transfusion	4.3	0.9–20.6	0.07
Transient jaundice			
Age ≤60 years	2.2	0.7–7.4	0.20
Venous resection	0.3	0.04–2.5	0.30
CBD diameter ≤5 mm	4.0	1.3–11.9	0.01
Cholangitis			
CBD diameter ≤5 mm	0.3	0.1–1.2	0.09
Benign disease	5.3	1.8–15.8	0.001
Malignancy without preop. Chemoradiation (*ref*)	1		
Malignancy with preop. chemoradiation	9.0	2.3–35.5	

OR = odds ratio; CI = confidence interval; CBD = common bile duct; preop = preoperative.

treated with preoperative chemoradiation. A CBD diameter ≤5 mm was not significant. Regarding biliary leak, no independent risk factor was identified (data not shown).

Discussion

The present study showed that EBC represent a significant part of the overall morbidity following PD, with an overall incidence of 14%. This relatively high incidence is probably explained by the conception of this study, which was to describe the full spectrum of EBC. While some EBC have a favorable outcome like transient jaundice or cholangitis, some other EBC like bilio-enteric stricture or biliary leak can lead to radiological or surgical intervention, leading to an overall 22% rate of Clavien-Dindo grade ≥3 complications. However, EBC did not increase mortality after PD. We identified male gender, benign disease, malignant disease treated by preoperative chemoradiation, and common bile duct diameter ≤5 mm as risk factors of EBC. This could be helpful to adopt specific policies of prevention and detection of EBC in high-risk patients undergoing PD.

EBC following PD are poorly described in the literature, mainly as biliary leak, and very few papers were specifically dedicated to these complications. Regarding biliary leak, 4 studies reported an incidence ranging from 2 to 8%.[14,15,17,18] Early bilio-enteric stricture has been scarcely studied[15] contrarily to delayed anastomotic stricture.[1,19–21] Regarding cholangitis, this complication is sometimes reported only in some large series but without any details.[22–24] Lastly, to our knowledge, transient jaundice following PD has not been previously reported, but, although it is not strictly a complication, it should be identified to be differentiated form early stricture to avoid an unnecessarily aggressive approach.

In the present study, early bilio-enteric anastomotic strictures occurred in 2% of cases and were suspected when postoperative serum bilirubin level exceeded the threshold of 50 μmol/L (3 mg/dL) with associated dilatation of intra-hepatic bile ducts contrasting with the absence of preoperative bile duct dilatation. This 2% incidence is lower than the 4% previously reported in one study[15] and is comparable to the 2–2.5% incidence reported for delayed stenosis.[1,19–21] In the present study, risk factors of early stricture were CBD diameter ≤5 mm and use of 6/0 sutures, reflecting the technical difficulties of performing bilio-enteric anastomosis on a small CBD. Small CBD diameter has been identified previously as a risk factor of early stricture following PD[15] and was also as risk factor of biliary stenosis in hepato-biliary surgery.[25] Interestingly, enlargement plasty did not prevent early stricture in our experience, and the risk factors of early strictures we identified seem different from that of delayed stricture, such as preoperative and postoperative biliary stenting.[1] Contrasting with the management of delayed bilio-enteric strictures, which mainly rely on interventional radiology,[1,20] we treated early stricture mainly by reoperation. Reoperation was decided because the biliary anastomosis was considered difficult and failed because of the small diameter of CBD at PD, and subsequently the occurrence of a biliary dilatation suggested that redoing the anastomosis at a higher (more proximal) level after resection of the stenosis would be easier. Also, reoperation could avoid the discomfort related to a prolonged transhepatic calibration by internal-external stent when interventional radiology procedures are performed. Surgery seems more appropriate than percutaneous prolonged stenting which also exposes to frequent drain obstruction requiring repeated procedures and ultimately refractory stenosis, leading to reoperation in up to 25% of cases.[15,20] Indeed, in all 5 reoperated patients, a tight and short stenosis was present, and all 5 were successfully treated by reoperation.

Transient jaundice occurred twice as frequently as early bilio-enteric strictures. Diagnosis of transient jaundice may be suggested by association of normal preoperative serum bilirubin level followed by a rise not exceeding 50 μmol/L (3 mg/dL) at POD 3 and no biliary tract dilatation on postoperative imaging. Transient jaundice is important to diagnose since indications of PD without preoperative biliary obstruction and CBD dilatation (e.g., IPMN or neuroendocrine tumors) are increasing.[21,26] A moderate and relatively stable jaundice combined with no postoperative biliary dilatation seems very suggestive of this diagnosis and should lead to a "wait and see" attitude. Conversely, in the present study, out of the 8 patients with serum bilirubin level >50 μmol/L (3 mg/dL) at POD 3, 7 (88%) developed early bilio-enteric stricture, which was proved by imaging and reintervention. The presumed mechanism of transient jaundice is anastomotic edema becoming partially obstructive due to the small CBD caliber. Indeed, we identified a common bile duct diameter ≤5 mm as the only significant risk factor. Transient jaundice was always completely reversible within a short delay after PD (median 4 days with a maximum of 8 days). Besides that, delay needed for complete regression of cholestasis is unknown since cholestasis following PD is frequently present for several weeks,[27] and we did not compare postoperative liver function tests in patients with or without transient jaundice.

Biliary leak is an uncommon complication following PD with an incidence ranging from 2 to 8%.[14,15,17,18] Biliary leak and POPF can be, but are unlikely, associated with the technique of reconstruction after the PD we use. Our diagnostic criteria were strict to avoid inclusion of patients with "mixed fistula", since we excluded from the diagnosis of biliary leak every patient with amylase assay in the drainage fluid exceeding three times the upper normal value at diagnosis of biliary leak. We observed a 3% incidence of biliary leak and did not identify any risk factor from our multivariate analysis. In the literature, reported risk factors of bile leaks were male gender,[14] obesity,[17] decreased serum albumin level,[14] endoscopic biliary drainage,[17] CBD diameter ≤5mm,[15] anastomosis on the segmental bile ducts,[17] and absence of biliary leak testing.[18] Biliary leak seems mainly related to weakness of the biliary wall. In the present series, bile

duct wall ischemia seems unlikely since we routinely prevent ischemia in the celiac axis territory by preoperative CT-scan screening of celiac axis stenosis coupled with intraoperative gastroduodenal artery clamping test.[10] Probably, most biliary leaks are due to needle holes in the biliary wall, thus explaining that about 50% of leaks resolve spontaneously provided peri-anastomotic drainage is maintained.[14,17] The reason why some leaks can lead to biliary peritonitis or require radiological or surgical intervention is not fully understood.[14,22,28] In the majority of studies[14,15,17] and in the present one, mortality due to biliary leak was nil; however, deaths secondary to biliary leaks have already been reported.[29]

Cholangitis was the most common EBC in the present series with a 6% incidence. This rate is slightly higher than the 1%–5% incidence previously reported.[22,24,26] In our series, cholangitis mainly occurred during the third postoperative week or later. This is in accordance with the findings of the Massachusetts General Hospital group that reported 2% of readmissions due to cholangitis with a median time to readmission of 22 days.[23] We observed that cholangitis was significantly more frequent in the case of benign disease or malignancy treated with preoperative chemoradiation. Despite these findings, pathophysiology of early cholangitis following PD is unknown. Several mechanisms could be implicated, possibly in association such as minimal bilio-enteric stricture, delayed gastric emptying or ileus, obstruction by alimentary debris, or bile contamination by germs resistant to antimicrobial prophylaxis. The latter mechanism is probably very rare in our series, since, in case of preoperative biliary stenting, we use a specific antimicrobial therapy that is immediately suitable in 85% of the cases and adapted 48 h later to the antibiogram, if necessary.[11] We also observed a high rate (25%) of cholangitis recurrence after the first course of antibiotics with occurrence of liver abscess in some cases, that could be due to persisting bowel motility disorders downstream of the bilio-enteric anastomosis during the early postoperative period. This hypothesis is supported by the fact that no late bilio-enteric strictures were diagnosed after cholangitis.

Prevention of EBC following PD is difficult to standardize. In case of PD for benign diseases, it can be hypothesized that performing the anastomosis below the confluence with the cystic duct allows the use of a wider CBD with a lower risk of EBC. Conversely, when PD is indicated for malignancy, the biliary anastomosis should be performed on the upper CBD whatever its diameter, exposing to a high risk of EBC when this diameter is less than 5 mm. Detection of celiac axis stenosis is also very important to avoid EBC due to CBD ischemia.[10] Prevention of early bilio-enteric stricture seems difficult. We observed that stricture was favored by the use of 6/0 caliber sutures, which could be due to ischemic phenomenons secondary to an excessive number of stitches when small caliber sutures were used. To our knowledge, the value of internal stenting of bilio-enteric anastomosis has never been evaluated and that of external stenting has been assessed by only one retrospective comparative study that demonstrated no benefit and even a higher rate of postoperative cholangitis comparatively to non-stented anastomosis.[30] Jaundiced patients are overall less exposed to early bilio-enteric strictures and transient jaundices but can develop biliary leaks and cholangitis since small CBD was not significantly associated with these two specific complications in the present study. Prevention of biliary leak in jaundiced patients with a large CBD only relies on a meticulous surgical technique. Prevention of cholangitis could rely of appropriate perioperative antimicrobial therapy according to the risk of bile contamination and routine bile sampling.[11]

Several limitations are inherent to this study. Firstly, even if we excluded patients with concomitant pancreatic fistula, it is possible that some biliary leaks originated in part from pancreatic anastomosis. Secondly, diagnosis of cholangitis is sometimes difficult to do, especially in patients with preoperative obstructive jaundice who experienced postoperative recurrence of jaundice. Some other causes of sepsis such as urinary tract infection or venous access infection can be confusing but we only took into consideration the patients with both signs of infection and abnormal liver function tests improving under antibiotic therapy. Thirdly, we have not collected data over a long-term follow-up on the whole series to bring out every late biliary complication, so we could not determine if EBC increases the risk of late biliary symptoms or anastomotic stenosis.

In conclusion, early postoperative biliary complications following PD are more frequent than previously reported in the literature and are sometimes misleading (transient jaundice). EBC are more frequent in case of male gender, benign disease, malignancy treated by preoperative chemoradiation, and a common bile duct diameter $\leq$5 mm. While some EBCs have a favorable outcome like transient jaundice or cholangitis, others like strictures or leaks can be severe and lead to radiological or surgical intervention. Importantly, EBC does not increase mortality after PD. Diagnosis and treatment of EBC requires a close collaboration between surgeons and radiologists.

Funding sources

None.

Conflict of interest

None to declare.

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