Fukushima J. Med. Sci.,
Vol. 66, No. 3, 2020

[Original Article]

Early intra-abdominal infection following pancreaticoduodenectomy : associated factors and clinical impact on surgical outcome

Naoya Sato, Takashi Kimura, Akira Kenjo, Yasuhide Kofunato, Ryo Okada, Teruhide Ishigame, Junichiro Watanabe and Shigeru Marubashi

Department of Hepato-Biliary-Pancreatic and Transplant Surgery, Fukushima Medical University

(Received June 8, 2020, accepted July 29, 2020)

Abstract

Early intra-abdominal infection (IAI) following pancreaticoduodenectomy (PD) is an initial event relating to morbidities caused by postoperative pancreatic fistula (POPF). The aims of this study were to determine factors associated with IAI, and to investigate its impact on postoperative outcome.

Consecutive patients, 113 in total, who underwent PD at Fukushima Medical University Hospital between January 2012 and September 2017 were included in this retrospective study. IAI was defined by positive bacterial culture from intra-abdominal drainage fluid any time through postoperative day 3 (POD3). Logistic regression analysis was used to identify the relevant factors associated with IAI. The clinical impact of the POD3 infection indicators related to POPF were assessed by multivariate analysis.

The incidence of IAI, POPF, and mortality were 36.1%, 36.1%, and 0%, respectively. Independent factors associated with IAI were preoperative biliary drainage (PBD) (OR=2.91, CI=1.16-7.33, $p=0.023$) and soft pancreas (OR=8.67, CI=2.37-31.77, $p=0.001$). Among infection markers on POD3, the significant factors for POPF were CRP (OR=1.18, CI=1.08-1.30, $p<0.001$), IAI (OR=7,37, CI=2.53-21.5, $p<0.001$), and drain amylase (OR=1.00, CI=1.00-1.01, $p=0.001$).

In conclusion, PBD, soft pancreas, and higher age were associated with IAI. IAI has a significantly negative impact on postoperative outcome.

Key words : pancreaticoduodenectomy, postoperative pancreatic fistula, surgical site infection, early intra-abdominal infection, preoperative biliary drainage

Introduction

With advances in surgical techniques and perioperative management, pancreaticoduodenectomy (PD) has become a relatively safe procedure at high-volume centers[1]. Postoperative mortality following PD has been reduced to less than 5%[2] ; however, morbidity remains high, with rates of 30-50%[3,4], and is especially high in patients over 80 years of age[5]. Among the most important risk factors for postoperative morbidity is postoperative pancreatic fistula (POPF), which can lead to life-threating surgical site infections (SSI) such as intra-abdominal abscess and/or postoperative hemorrhage due to pseudoaneurysm rupture.

Several reports have attributed various patient characteristics, intraoperative factors, or perioperative management to the development of clinically relevant POPF[2,6]. Considering how serious complications may arise from POPF, both early intra-abdominal infection and leakage of pancreatic juice from the cut surface of the pancreas must coexist initially. Behrman *et al.* demonstrated that infected fluid may accumulate relatively early in the postoperative course, often containing more than one bacterial species[7]. Previous studies investigating

Corresponding author : Shigeru Marubashi, MD, PhD. E-mail : s-maru@fmu.ac.jp

routes of intra-abdominal infection following PD have identified bacterial contamination of the lavage fluid during surgery[8] or bacterobilia[9] as triggers of POPF. However, there are a paucity of studies about contributing factors for developing IAI. Additionally, much remains to be understood regarding the impact of IAI on subsequent postoperative complications. In decision making for infection control practices following PD in the early postoperative course, understanding how much IAI impacts on POPF should be essential. Collectively, the aims of this retrospective study were to identify the factors associated with IAI following PD, as well as to evaluate the impact of IAI on postoperative outcome in patients undergoing PD.

Methods

This retrospective, single-center cohort study was approved by the ethics committee of Fukushima Medical University, which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki (Approval number : 3040).

Study population

Consecutive patients who underwent PD at Fukushima Medical University Hospital between January 2012 and September 2017 were enrolled in the present study. Patients who had pancreaticojejunostomy with internal drainage of the pancreatic duct using a lost stent were excluded. Demographics, comorbidities, laboratory data including physiological function tests, tumor pathology, and perioperative data were collected for all patients.

Technique of pancreaticoduodenectomy and perioperative management

Patients with objective jaundice due to Pancreatric, bile duct, or periampullary neoplasm were initially treated at a community hospital with biliary drainage, including endoscopic retrograde biliary drainage (ERBD) and percutaneous transhepatic biliary or gallbladder drainage (PT[G]BD).

For the operative procedure, the incision was wrapped with a wound protector (Alexis Wound Retractor ; Applied Medical, Rancho Santa Margarita, CA, USA). After dissection of the bile duct, the stump was clamped to avoid spillage of bile juice. Pancreatic texture was assessed intraoperatively by palpation, as described in a previous study[10]. Pancreaticojejunostomy was performed in all patients using two-layer duct-to-mucosa anastomosis ; the modified-Kakita method[11] with external drainage of the pancreatic duct by a stent. Ante-colic loop gastrojejunostomy was performed, and before wound closure, the abdominal cavity was lavaged with 6,000 mL of warm saline. One or two closed-suctioned drainage tubes were routinely placed around the pancreaticojejunal anastomosis. All patients received second- or third-generation cephem antibiotics prophylactically every 3 hours during surgery, which was continued until postoperative day 3 (POD3). Perioperative management was performed according to a clinical pathway designed by our department. No patient received thromboembolic prophylaxis with low-molecular-weight heparin.

Peripancreatic drainage fluid was collected for evaluating bacterial contamination and amylase levels on POD1, 3, and 7 routinely. Removal of the intra-abdominal drainage tube was considered after confirmation of no sign of abnormal infection. In cases where infectious POPF developed, contrast computed tomography was performed to evaluate the abdominal abscess, and the exchange of a drainage tube was considered more than 14 days after surgery.

Definition of early intra-abdominal infection and surgical outcomes

In the present study, IAI was defined as intra-abdominal infection within 3 days after PD, which was diagnosed by the presence of bacteria in surgical site drainage fluid. Additionally, POPF was defined as pancreatic fistula grade B or C by ISGPF[12]. Postoperative complications, such as incisional SSI, POPF, postoperative hemorrhage, delayed gastric emptying, and pneumonia, were prospectively noted and categorized as grade I to grade V, according to the modified Clavien-Dindo classification[13]. Postoperative complications of grade II or above were investigated in the present study.

Statistical analysis

Descriptive statistics were produced for demographic, clinical, and laboratory characteristics for the study subjects. Continuous variables are reported as the mean ± standard deviation (SD), and the values for the different subgroups were compared using the unpaired t-test. Categorical variables were expressed as prevalence, and differences in the proportion of the different patient groups were compared by the chi-square test. The whole study proceeded in two parts. Part 1 was conducted to determine the factors associated with IAI, in which the primary outcome was defined as IAI following

PD. We performed multivariate regression analysis using preoperative and intraoperative variables to determine the factors associated with IAI. A $p < 0.10$ in the unpaired t-test and chi square test was set for the multivariate logistic regression analysis. Part 2 was conducted to assess the clinical impact of IAI, in which potential surrogates of postoperative early infection status, including IAI, serum CRP, WBC, and drainage amylase, were used in a multivariate logistic regression model for predicting POPF. In the statistical analyses, a $p < 0.05$ was considered statistically significant. We used Stata (version 13, STATA Corp., College Station, TX, USA) for all statistical analyses.

Results

Patient characteristics

During the study period, 133 patients who met the eligibility criteria were included. Thirteen patients had received pancreaticojejunostomy with internal drainage using a lost stent and were therefore excluded from the analysis. The clinicopathologic characteristics of the 133 patients are outlined in Table 1. The entire study population had a mean age of 68.3 (SD±10.1) years, of whom 67.7% were male. PD was performed for pancreatic cancer in 45 patients (33.8%), biliary duct carcinoma in 40 patients (30.1%), carcinoma of the papilla of Vater in 20 patients (15%), and IPMN in 15 patients (11.3%).

Preoperative biliary drainage was performed in 81 patients (60.9%) with jaundice at onset : ERBD using a plastic stent for 75 patients and PTBD for six patients. The waiting period from the primary biliary drainage to surgery was almost 6 weeks, and 62% of the patients with preoperative biliary drainage (PBD) had cholangitis after the drainage, resulting in biliary stent replacement.

Composition of isolated bacteria from intra-abdominal drainage fluid

IAI was observed in 48 patients (36.1%) in the present study. There were nine species of bacteria detected from surgical sites in the early phase, of which eight were Enterococci species (Table 2). The variety of bacteria isolated after POD7 increased to more than 15 species, which may have been the result of prolonged intra-abdominal infection. With regard to the spectrum of isolated bacteria after POD7, the proportions of species of Enterococcus or Candida remained larger ; however, gram-negative bacillus, such as Staphylococcus, MRSA, Klebsiella, and pseudomonas were newly detected. Therefore, polymicrobial infection was characterized in clinically relevant POPF.

Table 1. Baseline characteristics of the study population.

Variables	All patients (n = 133)
Mean age, years (SD)	68.3 (10.1)
Male sex, n (%)	90 (67.7)
Mean BMI, kg/m^2 (SD)	22.4 (3.6)
Pathological diagnosis, n (%)	
pancreatic adenocarcinoma	45 (33.8)
biliary duct carcinoma	40 (30.1)
Vater papillary carcinoma	20 (15.0)
intrapapillary mucinous neoplasm	15 (11.3)
duodenum cancer	7 (5.3)
pancreatic neuroendocrine tumor	3 (2.3)
others	3 (2.3)
Comorbidity, n (%)	
diabetes mellitus	37 (27.8)
Type of PBD, n (%)	
none	52 (39.1)
ERBD	75 (56.4)
PTBD	6 (4.5)
Cholangitis after BD, n (%)	32 (24.1)
Mean operation time, min (SD)	541.1 (122.4)
Mean blood loss, mL (SD)	780.8 (748.4)
Intraoperative transfusion, n (%)	21 (15.91)
Vascular reconstruction, n (%)	6 (4.51)
Soft pancreas	75 (56.82)

Abbreviations : SD, standard deviation ; BMI, body mass index ; ASA, American society of Anesthesiologists ; PBD, preoperative biliary drainage ; ERBD, endoscopic retrograde biliary drainage ; PTCD, percutaneous transhepatic biliary drainage ; BD, biliary drainage.

Part 1 : The factors associated with postoperative IAI following pancreaticoduodenectomy

The results of univariate and multivariate analyses using pre- and intra-operative variables with potential relationships to IAI are reported in Table 3. The univariate analysis showed that higher patient age (p = 0.001), PBD (p < 0.001), lower prothrombin time (p = 0.037), soft pancreas (p < 0.001), and biliary duct carcinoma (p < 0.001) were significantly related to the development of IAI. The multivariate logistic regression analysis showed that the independent associated factors were soft pancreas (p = 0.001), patient age (p = 0.009), and PBD (p = 0.023).

Table 2. Results of bacterial culture of drainage fluid.

Isolated bacterial species No. of patients	Within POD3 48	After POD7 63
Polymicrobial infection, *n* (%)	13 (27.0)	40 (71.7)
Gram-positive bacilli		
Enterococcus sp.	45 (78.9)	68 (43.0)
Staphylococcus sp.	1 (1.8)	13 (8.2)
MRSA	1 (1.8)	6 (3.8)
Streptococcus sp.	0	8 (5.1)
Clostridium sp.	0	2 (1.3)
Gram-negative bacilli		
Enterobacter sp.	1 (1.8)	5 (3.2)
Bacillus sp.	2 (3.5)	2 (1.3)
Citrobacter sp.	1 (1.8)	3 (1.9)
Lactococcus sp.	1 (1.8)	1 (0.6)
Klebsiella sp.	0	10 (6.3)
Pseudomonas sp.	1 (1.8)	5 (3.1)
Bacteroides sp.	0	3 (1.9)
E. coli	0	2 (1.3)
Candida sp.	4 (7.0)	13 (8.2)
Others	0	17 (10.8)
Total	57	158

Abbreviations : POD, postoperative day ; PD, pancreaticoduodenectomy ; MRSA, methicillin-resistant Staphylococcus aureus.

Table 3. The factors associated with postoperative early intraabdominal infection.

Variables	Univariate analysis			Multivariate analysis		
	IAI (n = 48)	non-IAI (n = 85)	p value	OR	95% CI	p value
Male sex, *n* (%)	37 (77.1)	53 (62.4)	0.08	2.44	0.89-6.72	0.084
Age, yrs (SD)	72.1 (7.33)	66.2 (10.9)	**0.001**	1.09	1.03-1.16	**0.004**
BMI, kg/m^2 (SD)	22.5 (3.54)	22.3 (3.7)	0.75			
DM, *n* (%)	9 (18.8)	28 (32.9)	0.08	0.46	0.15-1.36	0.16
PBD, *n* (%)			**<0.001**	2.91	1.16-7.33	**0.023**
None	8 (16.7)	44 (51.8)				
ERBD	39 (81.3)	36 (42.4)				
PTBD	1 (2.1)	5 (5.9)				
Cholangitis after PBD, *n* (%)	18 (37.5)	14 (16.5)	**0.006**			
Serum albumin, g/dL (SD)	3.8 (0.46)	3.8 (0.50)	0.66			
Total bilirubin, mg/dL (SD)	1.28 (1.55)	0.96 (0.72)	0.12			
Prothrombin time, *n* (%)	95.3 (13.1)	100.4 (13.3)	**0.037**	0.96	0.93-1.00	0.061
Serum creatinine, mg/dL (SD)	0.84 (0.55)	0.75 (0.20)	0.19			
Preoperative CRP, mg/dl (SD)	0.72 (1.68)	0.43 (0.75)	0.18			
Soft pancreas, *n* (%)	39 (81.3)	36 (42.4)	**<0.001**	8.67	2.37-31.77	**0.001**
BDC, *n* (%)	33 (68.7)	27 (31.8)	**<0.001**	0.96	0.31-2.96	0.94
Operation time, min (SD)	566.8 (152.3)	526.4 (99.5)	0.068	1.00	0.99-1.01	0.12
Intraoperative transfusion, *n* (%)	11 (22.9)	10 (11.9)	0.096	0.86	0.25-3.00	0.81

Abbreviations : OR, odds ratio ; CI, confidence interval ; BMI, body mass index ; DM, diabetes mellitus ; PBD, Preoperative biliary drainage ; ERBD, endoscopic retrograde biliary drainage ; PTBD, percutaneous transhepatic biliary drainage ; CRP, c reactive protein ; BDC, Biliary duct carcinoma ; SD, standard deviation.
Continuous variables are reported as means and standard deviation, which were analyzed by Student's t-test. Categorical variables were analyzed by the chi square test.

Table 4. Surgical outcome according to early intraabdominal infection.

Postoperative complications, *n* (%)	Total (n = 133)	IAI (n = 48)	non-IAI (n = 85)	*P* value	OR	95% CI
Incisional SSI, *n* (%)	18 (13.5)	12 (25.0)	6 (7.1)	**<0.01**	3.54	1.42-8.83
Pancreatic fistula, Grade B/C, *n* (%)	48 (36.1)	35 (72.9)	13 (15.3)	**<0.01**	4.77	2.81-8.10
Postoperative hemorrhage, *n* (%)	6 (4.5)	4 (8.3)	2 (2.4)	0.11	3.54	0.67-18.6
Delayed gastric emptying, *n* (%)	14 (10.5)	5 (10.4)	9 (10.6)	0.98	0.98	0.35-2.77
Pneumonia, *n* (%)	1 (0.75)	1 (2.1)	0	0.18	-	-
Clavien-Dindo 3a, *n* (%)	41 (30.8)	26 (54.2)	15 (17.6)	**<0.01**	3.07	1.81-5.20
90-day mortality, *n* (%)	0 (0)	-	-	-	-	-

Abbreviations : IAI, early intraabdominal infection ; OR, odds ratio ; CI, confidence interval ; SSI, surgical site infection

Table 5. Difference in characteristics between the POPF and non-POPF groups in patients with non-IAI.

Variables	non-IAI patients (n = 85)		
	POPF (n = 13)	non-POPF (n = 72)	p value
Mean age, years (SD)	67.2 (12.5)	66.0 (10.7)	p = 0.444
Male, *n* (%)	9 (69.23)	44 (61.11)	p = 0.578
Mean BMI, Kg/m^2 (SD)	24.8 (3.92)	21.8 (3.49)	**p = 0.008**
PBD, *n* (%)	5 (38.46)	36 (50.00)	p = 0.444
Soft pancreas, *n* (%)	10 (76.92)	26 (36.11)	**p = 0.006**
Drain amylase on POD3, g/dL (SD)	5,385.8 (13,096.4)	767.73 (1,599.1)	**p = 0.004**
Serum CRP on POD3, mg/dL (SD)	18.2 (4.5)	12.5 (6.4)	**p = 0.003**

Abbreviations : POPF, postoperative pancreatic fistula ; BMI, body mass index ; PBD, preoperative biliary drainage ; POD3, postoperative day 3 ; CRP, C-reactive protein.
The unpaired t-test was used to compare the mean values of the different subgroups, and the chi-square test was used for testing the relationships between categorical variables.

Part 2 : Clinical impact of IAI on postoperative pancreatic fistula

The postoperative complications are shown in Table 4. The overall rates of IAI, POPF grades B or C, and mortality were 36.1%, 36.1% and 0%, respectively. Major complications defined as Clavien-Dindo classification 3a or above were observed in 30.8% of the patients. The rates of infectious complications such as incisional SSI and POPF (grade B or C) were significantly higher in the IAI group than in the non-IAI group. Interestingly, 13 of the 85 patients (15.3%) with non-IAI had POPF postoperatively, of whom 10 patients (76.92%) had a soft pancreas, high levels of drain amylase (mean, 5,385.8 g/dL) and serum CRP (18.2 mg/dL), as shown in Table 5.

In order to assess the clinical impact of IAI on clinically relevant POPF, multivariate logistic regression analysis using potential surrogates related to early infection status was performed, in which the cut-off values of continuous variables were determined via receiver operating characteristic analysis (Table 6). Among the potential surrogates, the significant factors for POPF (Grade B or C) were CRP on POD3 of 18 mg/dL or greater (Odds ratio = 5.81, CI = 2.05-16.43, p = 0.001), IAI (Odds ratio = 9.46, CI = 3.17-28.26, p < 0.001), and drain amylase POD3 of 583 mg/dL or greater (Odds ratio = 6.72, CI = 2.28-19.81, p = 0.001). When combining IAI and serum CRP on POD3, 31 of 35 patients (88.57%) with IAI and serum CRP on POD3 (≥ 18 mg/dL) had POPF, whereas seven of 66 patients (10.61%) with non-IAI and serum CRP (< 18 mg/dL) (Table 7) had POPF.

Discussion

The present study demonstrated that independent factors associated with IAI following PD were PBD, soft pancreas, and patient age (Results of Study, Part 1). IAI has a highly negative effect on clinically relevant POPF, requiring longer management of infection control. We believe that a combination of serum CRP levels (>18 mg/dL) and presence of IAI is useful for predicting complicated

Table 6. Multivariate logistic regression analysis using potential surrogate markers of postoperative early infection status.

Variables	OR	95% CI	p value
IAI (yes vs. no)	9.46	3.17-28.26	**<0.001**
CRP on POD3, mg/dL (< 18 vs ≥ 18)	5.81	2.05-16.43	**0.001**
Drain amylase, g/dL (< 583 vs ≥ 583)	6.72	2.28-19.81	**0.001**
WBC on POD3, /μL (< 9,300 vs ≥ 9,300)	1.74	0.59-5.15	0.319

Abbreviations : OR, odds ratio ; CI, confidence interval ; CRP, C-reactive protein ; POD3, postoperative day 3 ; WBC, white blood count ; IAI, early intra-abdominal infection.
Cut-off values of CRP on POD3, drain amylase, and WBC were determined by receiver operating characteristic analysis to predict postoperative pancreatic fistula.

Table 7. Occurrence of POPF (grade B or C) according to infection status on POD3.

Serum CRP on POD3	Non-IAI (−), n=85	IAI (+), n=48
<18 mg/dL	10.61% (7/66)	28.57% (4/13)
≧ 18 mg/dL	31.58% (6/19)	88.57% (31/35)

Abbreviations : POPF, postoperative pancreatic fistula ; POD, postoperative day.

POPF in the postoperative early phase (Results of Study, Part 2).

Soft pancreas is a widely recognized risk factor for anastomotic leakage of pancreaticojejunostomy or pancreaticogastrostomy. A previous study on a series of nearly 2,000 pancreaticoduodenectomies showed that soft pancreas was associated with a pancreatic fistula rate of 22.6, leading to a 10-fold increased risk of pancreas fistula compared to intermediate or hard pancreatic parenchyma[14]. It has been widely accepted that fragile pancreatic parenchyma due to soft pancreas makes anastomosis difficult to perform. Moreover, the amount of pancreatic juice secretion is higher in patients with soft pancreas than in patients with hard pancreas. Thus, there is a strong association between pancreatic texture and pancreatic leakage containing enteric bacteria. This could explain the results of the present study indicating that soft pancreas was an independent associated factor for IAI.

Our finding that PBD has an association with the development of surgical site infections is consistent with the findings of previous studies[8,15-17]. In the past decade, the pros and cons of PBD for patients with jaundice due to periampullary cancer have been discussed. Since the 1980s, hyperbilirubinemia has been recognized as a risk factor for poor surgical outcome[18,19]. Evidence suggests that PBD can improve immune functions and nutritional status[20,21] in jaundice patients. However, PBD has many drawbacks, such as biliary stent-induced bacterial contamination and cholangitis due to obstruction of the biliary duct stent. According to two recent meta-analyses[22,23], opinions were divided about whether PBD for patients with malignant obstructive jaundice has a beneficial effect on postoperative outcome or not. In terms of avoiding biliary infection, preoperative stenting of the common bile duct may be restricted on the basis of clear indication, such as cholangitis, severe symptomatic jaundice, or neoadjuvant chemotherapy.

With regard to preoperative biliary infection control, the method of biliary stenting must be discussed. ERBD using a plastic stent is associated with an increased incidence of cholangitis due to its lower patency[24]. In the present study, ERBD using a plastic stent was performed in over 90% of the BD patients. Furthermore, 70% of the patients with ERBD developed cholangitis while waiting for surgery and had biliary stent replacement. A meta-analysis investigating the safety and efficacy of nasobiliary drainage versus biliary stenting in malignant biliary obstruction suggested that endoscopic nasobiliary drainage has merit in terms of not only preoperative cholangitis but also postoperative pancreatic fistula[25]. Another promising approach for controlling IAI may be the prophylactic administration of antimicrobial agents for preoperative biliary bacterial contamination. A randomized controlled trial conducted by Okamura *et al.* demonstrated that preoperative bile culture-targeted administration of prophylactic antibiotics decreased surgical site infections in hepato-biliary-pancreatic surgery with biliary reconstruction[26].

In the present study, we could visualize the risk levels of POPF via the potential surrogates of postoperative early infection status (Table 6). Although IAI, serum CRP, and drain amylase were significantly associated with POPF, IAI had the most negative impact on POPF (Odds ratio : 9.46). We proposed that the combination of IAI and serum CRP levels (>18 mg/dL) can provide additional information to predict the development of clinically relevant POPF (Table 7), which may be of importance for making decisions for postoperative management, such as those of drain tube removal and administration of antibiotics. We believe that removal of the drainage tube in the early phase should not be performed in patients with IAI and high serum CRP.

Surveillance of bacteria isolated from the intra-abdominal surgical site is important for controlling intra-abdominal infection following PD. In the present study, we found that the most commonly isolated bacteria in IAI patients were Enterococcus species, under the prophylactic administration of cephem antibiotics. In cases of Enterococcus infection, administration of an antimicrobial agent to which the species is susceptible is crucial for infection control, due to its inherent resistance to cephem antibiotics. Interestingly, prevalence of polymicrobial infection was increased in intra-abdominal infection after POD7 (40 of 63 patients ; 76.9%), compared to IAI (13 of 48 patients ; 27%), in which the isolated bacteria resistant to multiple antibiotics may be increased, thereby making infection control difficult. Therefore, controlling the initial infection is crucial for postoperative management of PD, avoiding development of polymicrobial infection and the subsequent prolonged intra-abdominal infection. On the basis of our finding that Enterococcus species was isolated at a frequency of 78.9% in IAI patients, Gram staining may provide key information to determine which bacteria is responsible for postoperative intra-abdominal infection, although it takes a few days to incubate samples for testing bacterium.

When interpreting the clinical significance of IAI on postoperative outcome, it should be noted that POPF could be complicated even in non-IAI patients. In the present study, POPF was complicated in 13 (15.3%) of 85 patients initially diagnosed with non-IAI (Table 4). Characteristics of non-IAI patients developing POPF are higher BMI (24.8 Kg/m^2), soft pancreas (76.92%), high levels of amylase in drain fluid (5,385.8 g/dL), and serum CRP (18.2 mg/dl) on POD3 (Table 5). Therefore, we suggest that early removal of the drainage tube might not be determined only by absence of IAI. Indeed, in the present study, removal of the drainage tube within POD5 was not performed in non-IAI patients with POPF because of the high levels of amylase in the drainage fluid and serum CRP on POD3.

There are several limitations to the current study. First, the number of subjects was relatively small, and the study population was heterogenous in primary diagnosis for surgery. In the interpretation of the findings of the present study, the difference in prevalence of bile duct carcinoma between Western countries and East Asia should be taken into consideration. In East Asia, the proportion of patients with bile duct carcinoma, many of whom have a soft pancreas, is higher than that in Western countries. Second, the path of the bacteria causing the IAI was not fully examined in this study. In order to determine whether the bacterial species are derived from preoperative bacterial contamination of the bile duct, identification of microorganisms in preoperative and intraoperative bile juice is necessary.

Conclusions

The present study demonstrated that preoperative BD, soft pancreas, and higher age were factors associated with IAI, and that IAI has a significantly negative impact on postoperative outcome. Efforts to control IAI must be pursued to enhance the safety of PD.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose.

References

1. Kagedan DJ, Goyert N, Li Q, Paszat L, Kiss A, Earle CC, *et al.* The Impact of Increasing Hospital Volume on 90-Day Postoperative Outcomes Following Pancreaticoduodenectomy. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, **21**(3) : 506-515, 2017.
2. Aoki S, Miyata H, Konno H, Gotoh M, Motoi F, Kumamaru H, *et al.* Risk factors of serious postoperative complications after pancreaticoduode-

nectomy and risk calculators for predicting postoperative complications : a nationwide study of 17,564 patients in Japan. Journal of hepato-biliary-pancreatic sciences, **24**(5) : 243-251, 2017.

3. Conzo G, Gambardella C, Tartaglia E, Sciascia V, Mauriello C, Napolitano S, *et al.* Pancreatic fistula following pancreatoduodenectomy. Evaluation of different surgical approaches in the management of pancreatic stump. Literature review. Int J Surg, **21** Suppl 1 : S4-9, 2015.
4. Hua J, He Z, Qian D, Meng H, Zhou B, Song Z. Duct-to-Mucosa Versus Invagination Pancreaticojejunostomy Following Pancreaticoduodenectomy : a Systematic Review and Meta-Analysis. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, **19**(10) : 1900-1909, 2015.
5. Kim SY, Weinberg L, Christophi C, Nikfarjam M. The outcomes of pancreaticoduodenectomy in patients aged 80 or older : a systematic review and meta-analysis. HPB : the official journal of the International Hepato Pancreato Biliary Association, **19**(6) : 475-482, 2017.
6. De Pastena M, Paiella S, Marchegiani G, Malleo G, Ciprani D, Gasparini C, *et al.* Postoperative infections represent a major determinant of outcome after pancreaticoduodenectomy : Results from a high-volume center. Surgery, **162**(4) : 792-801, 2017.
7. Behrman SW, Zarzaur BL. Intra-abdominal sepsis following pancreatic resection : incidence, risk factors, diagnosis, microbiology, management, and outcome. The American surgeon, **74**(7) : 572-578 ; discussion 8-9, 2008.
8. Sugiura T, Mizuno T, Okamura Y, Ito T, Yamamoto Y, Kawamura I, *et al.* Impact of bacterial contamination of the abdominal cavity during pancreaticoduodenectomy on surgical-site infection. Br J Surg, **102**(12) : 1561-1566, 2015.
9. Ohgi K, Sugiura T, Yamamoto Y, Okamura Y, Ito T, Uesaka K. Bacterobilia may trigger the development and severity of pancreatic fistula after pancreatoduodenectomy. Surgery, **160**(3) : 725-730, 2016.
10. Usuba T, Misawa T, Ito R, Yoshida K, Hanyu N, Yanaga K. Safety of Non-stented Pancreaticojejunostomy in Pancreaticoduodenectomy for Patients with Soft Pancreas. Anticancer Res, **36**(12) : 6619-6623, 2016.
11. Kakita A, Yoshida M, Takahashi T. History of pancreaticojejunostomy in pancreaticoduodenecto my : development of a more reliable anastomosis technique. Journal of hepato-biliary-pancreatic surgery, **8**(3) : 230-237, 2001.
12. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, *et al.* The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula : 11 Years After. Surgery, **161**(3) : 584-591, 2017.
13. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, *et al.* The Clavien-Dindo classification of surgical complications : five-year experience. Annals of surgery, **250**(2) : 187-196, 2009.
14. Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. Journal of gastrointestinal surgery, **8**(8) : 951-959, 2004.
15. Povoski SP, Karpeh MS, Jr., Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. Annals of surgery, **230**(2) : 131-142, 1999.
16. Kyriazi MA, Arkadopoulos N, Smyrniotis V. Preoperative biliary drainage of severely jaundiced patients increases morbidity of pancreaticoduodenectomy : reply. World journal of surgery, **39**(3) : 804-805, 2015.
17. Lee H, Han Y, Kim JR, Kwon W, Kim SW, Jang JY. Preoperative biliary drainage adversely affects surgical outcomes in periampullary cancer : a retrospective and propensity score-matched analysis. Journal of hepato-biliary-pancreatic sciences, **25**(3) : 206-213, 2018.
18. Blamey SL, Fearon KC, Gilmour WH, Osborne DH, Carter DC. Prediction of risk in biliary surgery. Br J Surg, **70**(9) : 535-538, 1983.
19. Dixon JM, Armstrong CP, Duffy SW, Elton RA, Davies GC. Factors affecting mortality and morbidity after surgery for obstructive jaundice. Gut, **25**(1) : 104, 1984.
20. Roughneen PT, Gouma DJ, Kulkarni AD, Fanslow WF, Rowlands BJ. Impaired specific cell-mediated immunity in experimental biliary obstruction and its reversibility by internal biliary drainage. The Journal of surgical research, **41**(2) : 113-125, 1986.
21. Gouma DJ, Roughneen PT, Kumar S, Moody FG, Rowlands BJ. Changes in nutritional status associated with obstructive jaundice and biliary drainage in rats. Am J Clin Nutr, **44**(3) : 362-369, 1986.
22. Scheufele F, Schorn S, Demir IE, Sargut M, Tieftrunk E, Calavrezos L, *et al.* Preoperative biliary stenting versus operation first in jaundiced patients due to malignant lesions in the pancreatic head : A meta-analysis of current literature. Surgery, **161**(4) : 939-950, 2017.
23. Moole H, Bechtold M, Puli SR. Efficacy of preoperative biliary drainage in malignant obstructive jaundice : a meta-analysis and systematic review.

World J Surg Oncol, **14**(1) : 182, 2016.
24. Yanagimoto H, Satoi S, Yamamoto T, Toyokawa H, Hirooka S, Yui R, *et al.* Clinical impact of preoperative cholangitis after biliary drainage in patients who undergo pancreaticoduodenectomy on postoperative pancreatic fistula. The American surgeon, **80**(1) : 36-42, 2014.
25. Lin H, Li S, Liu X. The safety and efficacy of nasobiliary drainage versus biliary stenting in malignant biliary obstruction : A systematic review and meta-analysis. Medicine (Baltimore), **95**(46) : e5253, 2016.
26. Okamura K, Tanaka K, Miura T, Nakanishi Y, Noji T, Nakamura T, *et al.* Randomized controlled trial of perioperative antimicrobial therapy based on the results of preoperative bile cultures in patients undergoing biliary reconstruction. Journal of hepato-biliary-pancreatic sciences, **24**(7) : 382-393.