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## Retrospective Study

# Influence of bile contamination for patients who undergo pancreaticoduodenectomy after biliary drainage

Keiichi Okano, Yasuyuki Suzuki

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## Abstract

### BACKGROUND

The influence of bile contamination on the infectious complications of patients undergoing pancreaticoduodenectomy (PD) has not been thoroughly evaluated.

### AIM

To evaluate the effect of preoperative biliary drainage and bile contamination on the outcomes of patients who undergo PD.

### METHODS

The database of 4101 patients who underwent PD was reviewed. Preoperative biliary drainage was performed in 1964 patients (47.9%), and bile contamination was confirmed in 606 patients (14.8%).

### RESULTS

The incidence of postoperative infectious complications was 37.9% in patients with preoperative biliary drainage and 42.4% in patients with biliary contamination, respectively. Patients with extrahepatic bile duct carcinoma, ampulla of Vater carcinoma, and pancreatic carcinoma had a high frequency of preoperative biliary drainage (82.9%, 54.6%, and 50.8%) and bile contamination (34.3%, 26.2%, and 20.2%). Bile contamination was associated with postoperative pancreatic fistula (POPF) Grade B/C, wound infection, and catheter infection. A multivariate logistic regression analysis revealed that biliary contamination (odds ratio 1.33,  $P = 0.027$ ) was the independent risk factor for POPF Grade B/C. The three most commonly cultured microorganisms from bile (*Enterococcus*, *Klebsiella*, and *Enterobacter*) were identical to those isolated from organ spaces.

### CONCLUSION

In patients undergoing PD, bile contamination is related to postoperative infectious complication including POPF Grade B/C. The management of biliary contamination should be standardised for patients who require preoperative biliary drainage for PD, as the main microorganisms are identical in both organ spaces and bile.



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**Core tip:** This study aimed to evaluate the effect of preoperative biliary drainage and bile contamination on the outcomes of patients who undergo pancreaticoduodenectomy (PD). The database of 4101 patients who underwent PD was reviewed. Preoperative biliary drainage was performed in 1964 patients (47.9%), and bile contamination was confirmed in 606 patients (14.8%). In patients undergoing PD, bile contamination is related to postoperative infectious complication including postoperative pancreatic fistula Grade B/C. The management of biliary contamination should be standardised for patients who require preoperative biliary drainage for PD, as the main microorganisms are identical in both organ spaces and bile.

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## INTRODUCTION

Pancreatoduodenectomy (PD) is a common and complex procedure in gastroenterological surgery. Although the perioperative mortality rate of PD in high-volume centres is reportedly 1% to 2%, the post-PD morbidity rate remains relatively high at 20% to 50%<sup>[1-7]</sup>. In a previous study, we reported that infectious complications are the main cause of postoperative morbidity after PD<sup>[8]</sup>. Nine risk factors for infectious complications after PD were identified: Male sex, age of 70 years or more, body mass index of at least 25 kg/m<sup>2</sup>, other previous malignancy, liver disease, bile contamination, surgery duration of 7 h or longer, intraoperative blood transfusion, and soft pancreas. Among these factors, bile contamination is the one that surgeons could control by appropriate perioperative management.

Obstructive jaundice is the most common symptom in patients with periampullary malignancy. Routine preoperative biliary drainage in patients undergoing surgery for cancer of the pancreatic head increases the rate of complications<sup>[9,10]</sup>. With the advent of neoadjuvant chemotherapy used to downstage potentially unresectable tumours in the hope of improving the outcome<sup>[11,12]</sup>, concern regarding preoperative biliary drainage during neoadjuvant treatment is clinically relevant. Preoperative endoscopic biliary procedures are widespread in the management of periampullary tumours<sup>[13]</sup>. The effect of endoscopic procedures on biliary contamination and the immediate outcomes of PD remain controversial, although the several studies reported increased mortality or morbidity rate<sup>[14-17]</sup>. This study aimed to identify the clinical features and outcomes after PD in patients with infected bile based on data from the Japanese Society of Pancreatic Surgery for future management of perioperative infectious complications.

## MATERIALS AND METHODS

A nationwide multi-institutional analysis of infectious complications after major pancreatic surgery was conducted by the Japanese Society of Pancreatic Surgery. A database of 4101 patients who underwent PD during a 3-year period were analysed for this study. This study was approved by the Institutional Ethics Committee of Kagawa University.

### Definitions

The definitions of complications including infectious complications are almost identical to those of the American College of Surgeons-National Surgical Quality Improvement Program criteria (NSQIP)<sup>[18]</sup>. In the present study, infectious complications are defined as postoperative global infectious complications including

surgical site infection [*i.e.*, wound infection, intra-abdominal abscess, infected postoperative pancreatic fistula (POPF)] and extraparieto-abdominal infection (*i.e.*, catheter infection, pneumonia, urinary tract infection). Infectious complications are also identified as a specific clinical condition that was related to infection by bacteria, fungus, or virus in a specific organ/compartment. A positive culture without correlation to a specific clinical condition was not considered an infectious complication.

As the NSQIP 30-d mortality rates underestimate the mortality rate for complicated surgical procedures such as PD<sup>[7]</sup>, the present study applied in-hospital mortality. In-hospital mortality was defined as death before postoperative day 30, and death among patients who were hospitalised for 30 d or more after surgery and died during that time<sup>[7]</sup>.

Complication severity was graded according to the Clavien–Dindo classification<sup>[19]</sup>. Pancreatic fistula was defined according to the International Study Group on Pancreatic Fistula guidelines<sup>[20]</sup> as an amylase level in the drainage fluid on postoperative day 3 that is > 3 times the normal serum amylase level. Grade A fistulas presented with elevated drain amylase levels only, and they lacked any clinical consequences. Grade B fistulas, requiring therapeutic interventions, behaved in an intermediate fashion, with marginal increases in duration of hospitalisation and rates of complications. Grade C fistulas were the most severe, and patients frequently required intensive care unit transfer for sepsis management. An infected pancreatic fistula was defined as a clinically relevant fistula with proven infection by positive culture. Postoperative intra-abdominal haemorrhage was defined as bleeding requiring a blood transfusion, reoperation, or interventional radiology. An intra-abdominal abscess was defined as intra-abdominal fluid collection with positive cultures or organ/space surgical site infection in the abdominal cavity. A positive culture was not required to determine the presence of an infection, in cases in which NSQIP criteria were met and the clinical picture was consistent. Cultured organisms from organ space infections were determined by positive culture from the percutaneous drain, in patients with a clinical picture consistent with infection.

The types of biliary drainage and the results of preoperative bile culture were recorded for patients who underwent preoperative biliary drainage before PD. The preoperative biliary culture was performed in 1651 of 1964 patients (84.1%) who underwent biliary drainage in present study. Percutaneous trans-hepatic biliary drainage and endoscopic naso-biliary drainage were categorised as types of external drainage, and endoscopic retrograde biliary drainage was categorised as internal drainage. Positive results of cultured microorganisms in bile from a preoperative biliary stent or intraoperative bile collection were defined as bile contamination. Results of cultured microorganisms from overall infection site or organ space infections were collected from the patients with infectious complications. The standard perioperative management strategies were described previously<sup>[8]</sup>. Drains were usually removed at 3 to 7 postoperative days according to the early removal policy.

### Statistical analysis

All statistical analyses were performed using SAS 8.2 (SAS Institute Inc., Cary, NC, United States). Patient characteristics and clinical factors were compared using the Mann-Whitney *U* test for continuous variables and Fisher's exact test or the chi-squared test for categorical variables. Risk factors that were significantly associated with POPF Grade B/C in univariate models ( $P < 0.05$ ) were included in a multivariate logistic regression model. Throughout this study,  $P$  values < 0.05 were considered statistically significant.

## RESULTS

The median age of the 4101 patients included in this study was 68 years (range 6–89); 1920 patients (46.8%) were over 70 years old. The male to female ratio was 1.53:1. Preoperative biliary drainage was performed in 1964 of 4101 patients (47.9%), and bile contamination was confirmed in 606 patients (14.8%).

### Primary disease and infectious complications

The primary disease was significantly associated with preoperative biliary drainage and bile contamination (Table 1). Patients with extrahepatic bile duct carcinoma, ampulla of Vater carcinoma, and pancreatic carcinoma had a high frequency of preoperative biliary drainage (82.9%, 54.6%, and 5.80%) and bile contamination (34.3%, 26.2%, and 20.2%). In contrast, patients with intraductal papillary mucinous neoplasm, pancreas neuroendocrine tumour, and pancreas cystic tumour had a low

frequency of preoperative biliary drainage and bile contamination at 10% or less.

### **Background, outcomes, infectious complications, and cultured organisms**

There were significant differences in the age and sex ratio in patients with or without preoperative biliary drainage and bile contamination (Table 2). The incidence of postoperative infectious complications was 37.9% in patients with preoperative biliary drainage and 42.4% in patients with biliary contamination, respectively. Preoperative biliary drainage was performed in male and elderly patients frequently. Bile contamination was also confirmed in male and elderly patients frequently. Preoperative biliary drainage and bile contamination were not associated with the rate of readmission and mortality. Bile contamination was associated with prolonged surgery duration. Preoperative biliary drainage and bile contamination were associated with both overall complications and infectious complications. Preoperative biliary drainage was associated with wound infection. Bile contamination was associated with POPF Grade B/C, wound infection, and catheter infection.

### **Cultured organisms from the bile and organ space**

The most commonly cultured organisms from the bile were *Enterococcus* (42.7%), *Klebsiella* (26.6%), *Enterobacter* (14.2%), *Staphylococcus* (12.7%), and *E. Coli* (11.9%) (Table 3). The most commonly cultured organisms from the organ space ( $n = 596$ ) were *Enterococcus* (47.7%), *Enterobacter* (20.0%), *Klebsiella* (14.8%), *Pseudomonas* (13.8%), and *Staphylococcus aureus* (methicillin-resistant *S. aureus*) (10.6%). These organisms were mainly cultured from drain discharge ( $n = 398$ ) and intra-abdominal abscesses ( $n = 201$  patients) which were strongly suspected to be associated with pancreatic fistula. The three most commonly cultured microorganisms from bile (*Enterococcus*, *Klebsiella*, and *Enterobacter*) were identical to those isolated from organ spaces. Most of the participating institutions (49 of 69 institutions) changed their antibiotic prophylaxis based on bile culture results in the present study.

### **Risk factors influencing POPF Grade B/C**

Table 4 shows the results of multivariate analysis using risk factors that were significantly associated with POPF Grade B/C in univariate models. Six significant risk factors for infectious complications after PD were identified by multivariate analysis: male sex, age  $\geq 70$  years, body mass index  $\geq 25$  kg/m<sup>2</sup>, bile contamination, soft pancreas, and operative time  $\geq 7$  h. Preoperative biliary drainage was not independent significant risk factor.

The 1283 patients (40.5%) with high total bilirubin level ( $< 1.0$ g/dL) were compared with the 1886 patients (59.5%) with normal total bilirubin level ( $> 1.0$ g/dL) for incidence of all POPF and clinical relevant POPF (Grade B/C). There was no significant difference for all POPF (37.8% vs 39.5%,  $P = 0.55$ ) or clinical relevant POPF (21.4% vs 20.6%,  $P = 0.82$ ) between the patients with high and normal total bilirubin levels.

### **Outcome according to the type of drainage**

Table 5 shows the demographic characteristics, perioperative variables, and immediate outcome according to the type of drainage (external or internal drainage) in 1942 patients who received PD. External drainage was performed in 772 patients (endoscopic nasobiliary drainage in 499 cases and percutaneous transhepatic biliary drainage in 273 cases) and internal drainage (endoscopic retrograde biliary drainage) was performed in 1170 patients. The duration of surgery was significantly longer in the patients with internal drainage than in those with external drainage. There were no significant differences between the two groups concerning the incidence of postoperative complications such as infectious complication, POPF, delayed gastric emptying, and intra-abdominal bleeding.

## **DISCUSSION**

In this multicentre observational study, preoperative biliary drainage and bile contamination had a notable effect on the immediate outcomes after PD, with a high frequency of infectious complications. Especially, bile contamination had a strong association with POPF (Grade B/C). Bile contamination was present mainly in patients with pancreas cancer, bile duct carcinoma, and ampulla of Vater carcinoma. Furthermore, we found that the three most commonly cultured microorganisms from bile (*Enterococcus*, *Klebsiella*, and *Enterobacter*) were identical to those isolated from organ spaces. As the post-PD morbidity rate remains considerably high<sup>[1-7]</sup>, the prevention of bile contamination should be the most effective target to decrease the high morbidity after PD.

**Table 1 Primary disease and bile contamination in patients who received pancreaticoduodenectomy, n (%)**

| Disease                                 | Preoperative biliary drainage |               |          | Bile contamination |               |          |
|---|-------------------------------|---------------|----------|--------------------|---------------|----------|
|   | Yes (n = 1964)                | No (n = 2137) | P value  | Yes (n = 606)      | No (n = 2130) | P value  |
| Disease                                 |                               |               | < 0.0001 |                    |               | < 0.0001 |
| Pancreatic cancer                       | 955 (50.8)                    | 925 (49.2)    |          | 261 (20.2)         | 1029 (79.8)   |          |
| Bile duct carcinoma                     | 691 (82.9)                    | 143 (17.1)    |          | 208 (34.3)         | 399 (65.7)    |          |
| Intraductal papillary mucinous neoplasm | 19 (4.5)                      | 406 (95.5)    |          | 10 (5.1)           | 187 (94.9)    |          |
| Ampulla of Vater carcinoma              | 250 (54.6)                    | 208 (45.4)    |          | 78 (26.2)          | 220 (73.8)    |          |
| Pancreas neuroendocrine tumour          | 11 (8.9)                      | 113 (91.1)    |          | 3 (4.2)            | 69 (95.8)     |          |
| Pancreas cystic tumour                  | 3 (2.6)                       | 113 (97.4)    |          | 1 (2.9)            | 34 (97.1)     |          |
| Duodenal cancer                         | 23 (18.3)                     | 103 (81.7)    |          | 7 (9.7)            | 65 (90.3)     |          |

Several studies showed that early surgery without preoperative biliary drainage is the standard treatment in patients with resectable pancreatic head cancer presenting with jaundice<sup>[9,10]</sup>. However, early surgery is not always feasible, and preoperative biliary drainage may be still necessary for patients with high hyper-bilirubinaemia at diagnosis or for those undergoing neoadjuvant treatment. It is still controversial how biliary drainage-related complications affect the incidence of postoperative complications after PD. Jagannath *et al*<sup>[21]</sup> reported that a positive intraoperative bile culture was associated with higher morbidity rates after PD, and biliary drainage was not associated with increased morbidity. Cortes *et al*<sup>[22]</sup> also reported that bile contamination had a remarkable effect on the immediate outcomes after PD for tumours, with a higher rate of infectious complications including wound and intraabdominal abscesses. Kitahata *et al*<sup>[23]</sup> reported that patients undergoing internal drainage had a significantly higher incidence of cholangitis because of biliary drainage (22.4% *vs* 1.7% in the external drainage group). Internal drainage significantly increased the incidence of morbidity compared with external drainage (41.8% *vs* 22.3%). The present study analysed 772 and 1170 patients who received external and internal drainages, respectively, and no significant difference in postoperative complications was found between the internal and external drainage groups. The results suggested that the postoperative infectious complications for patients who underwent PD were not associated with type of biliary drainage.

The incidence of positive bile culture was reported to increase significantly in patients who underwent biliary drainage and presented complications such as cholangitis<sup>[22]</sup>. Yanagimoto *et al*<sup>[24]</sup> reported that preoperative cholangitis after biliary drainage was associated with development of POPF Grade B/C. The present study clearly revealed that significant association of bile contamination and POPF Grade B/C. The results strongly supported previous reports<sup>[22,24]</sup>. Stent occlusion was reported to cause preoperative cholangitis, and cholangitis occurred in 26% of patients who underwent internal drainage<sup>[9]</sup>. A possible mechanism to explain the association between cholangitis and internal drainage is the ascent of microorganisms from the open passage to the duodenum and subsequent reflux of duodenal contents<sup>[25,26]</sup>. However, internal biliary drainage permits physiological bile flow, which is important for intestinal immunity and the prevention of bacterial translocation<sup>[27-29]</sup>. Several studies reported that metallic stents have more advantages compared with plastic stents when used for preoperative biliary drainage in patients undergoing neoadjuvant therapy for pancreatic cancer<sup>[30-32]</sup>. In two previous studies, stent-related complications were significantly higher with plastic stents than with fully covered self-expandable metal stents with no differences in the rate of overall surgical complications<sup>[33,34]</sup>. Further studies are required to assess the fully covered self-expandable metal stents as preoperative biliary drainage affects the surgical procedure or perioperative outcome.

To our knowledge, this is the first report that clarified the specific causative microorganism profile for bile contamination in a large PD series. The *Enterococcus*, *Enterobacter*, and *Klebsiella* species were the more commonly cultured microorganisms from organ space infections and bile contamination. The illustration of different organisms is useful for selecting prophylactic antibiotics or considering drain management after pancreatic surgery. In addition, there were significant differences in the incidence of bile contamination among primary diseases. The results of cultured organisms suggest the need for tailored antibiotic prophylaxis for patients with a high risk of biliary contamination. In the present study, preoperative biliary culture was



**Table 2 Association of preoperative biliary drainage and bile contamination with immediate outcome after pancreaticoduodenectomy, *n* (%)**

|  | Preoperative biliary drainage |                       |                | Bile contamination    |                       |                |
|--|-------------------------------|-----------------------|----------------|-----------------------|-----------------------|----------------|
|  | Yes ( <i>n</i> = 1964)        | No ( <i>n</i> = 2137) | <i>P</i> value | Yes ( <i>n</i> = 606) | No ( <i>n</i> = 2130) | <i>P</i> value |
| Demographics                             |                               |                       |                |                       |                       |                |
| Age (yr), median                         | 69                            | 68                    | < 0.0001       | 69                    | 68                    | 0.0004         |
| Sex ratio (M:F)                          | 1.81:1                        | 1.34:1                | < 0.0001       | 2.11:1                | 1.56:1                | 0.0012         |
| Duration of hospital stay (d), median    | 29                            | 29                    | 0.29           | 29                    | 31                    | 0.11           |
| Readmission                              | 64 (3.3)                      | 84 (3.9)              | 0.25           | 19 (3.1)              | 91 (4.3)              | 0.33           |
| In-hospital death                        | 42 (2.1)                      | 34 (1.6)              | 0.21           | 8 (1.3)               | 46 (2.2)              | 0.19           |
| Operative variables                      |                               |                       |                |                       |                       |                |
| Estimated blood loss (g), median         | 855                           | 643                   | < 0.0001       | 875                   | 759                   | 0.053          |
| Duration of surgery (min), median        | 487                           | 461                   | < 0.0001       | 497                   | 483                   | 0.0005         |
| Postoperative complications              |                               |                       |                |                       |                       |                |
| Overall complications                    | 1084 (55.2)                   | 1114 (52.1)           | 0.049          | 356 (58.7)            | 1130 (53.1)           | 0.0014         |
| Infectious complications                 | 744 (37.9)                    | 714 (33.4)            | 0.003          | 257 (42.4)            | 746 (35.0)            | 0.0003         |
| Severe complications (grade III or more) | 340 (17.3)                    | 316 (14.8)            | 0.036          | 110 (18.2)            | 321 (15.0)            | 0.039          |
| POPF (all)                               | 739 (37.6)                    | 809 (37.9)            | 0.42           | 246 (40.6)            | 773 (36.3)            | 0.06           |
| Delayed gastric emptying                 | 111 (5.7)                     | 144 (6.7)             | 0.18           | 40 (6.6)              | 143 (6.7)             | 0.42           |
| Intra-abdominal bleeding                 | 67 (3.4)                      | 57 (2.7)              | 0.16           | 18 (3.0)              | 61 (2.9)              | 0.78           |
| Details of infectious complication       |                               |                       |                |                       |                       |                |
| POPF (ISGPF grade B or C)                | 444 (22.6)                    | 438 (20.5)            | 0.13           | 154 (25.4)            | 432 (20.3)            | 0.003          |
| Wound infection                          | 320 (16.3)                    | 216 (10.3)            | < 0.0001       | 93 (15.3)             | 263 (12.3)            | 0.045          |
| Intra-abdominal abscess                  | 289 (14.7)                    | 295 (14.0)            | 0.53           | 94 (15.5)             | 293 (13.8)            | 0.23           |
| Cholangitis                              | 79 (4.1)                      | 95 (4.5)              | 0.45           | 24 (4.0)              | 105 (4.9)             | 0.35           |
| Pneumonia                                | 61 (3.1)                      | 61 (2.9)              | 0.7            | 21 (3.5)              | 66 (3.1)              | 0.62           |
| Liver abscess                            | 21 (1.1)                      | 24 (1.2)              | 0.83           | 9 (1.5)               | 19 (0.9)              | 0.21           |
| Sepsis                                   | 86 (4.5)                      | 86 (4.2)              | 0.66           | 30 (5.0)              | 83 (3.9)              | 0.24           |
| Pseudomembranous enteritis               | 31 (1.6)                      | 30 (1.4)              | 0.68           | 13 (2.1)              | 27 (1.3)              | 0.12           |
| Catheter infection                       | 91 (4.7)                      | 115 (5.5)             | 0.24           | 41 (6.8)              | 98 (4.6)              | 0.029          |
| Fungaemia                                | 28 (1.5)                      | 28 (1.4)              | 0.8            | 8 (1.3)               | 25 (1.2)              | 0.75           |

The variables were identical to those of the American College of Surgeons–National Surgical Quality Improvement Program. POPF: Postoperative pancreatic fistula; ISGPF: Influencing postoperative pancreatic fistula.

performed in 1651 of 1964 patients (84.1%) who underwent biliary drainage. Bile contamination was confirmed in 606 of 1651 patients (36.7%). Most of the participating institutions (49 of 69 institutions) changed their antibiotic prophylaxis based on bile culture results in the present study. As the specific antibiotic prophylaxis based on bile culture results prevents infectious complications in PD patients with preoperative biliary drainage<sup>[35]</sup>, preoperative bile culture should be considered in patients with biliary drainage. However, as there is currently no consensus regarding the appropriate type of antibiotic prophylaxis, a prospective study is warranted to provide evidence to validate appropriate antibiotic prophylaxis for patients with biliary contamination.

This multicentre study has several limitations. First, data were retrospectively collected, which makes it a potential source for significant bias. Second, the results may have been influenced by hospital volume, hospital training status, hospital compliance, and procedure-specific variables. Third, in some patients who received immediate internal drainage, a preoperative biliary culture was not obtained. Although these limitations are recognised, we believe that our findings will contribute to improving quality control in pancreatic surgery. Further prospective, randomised studies are needed to overcome these limitations.

In conclusion, preoperative biliary drainage and bile contamination had a notable effect on immediate outcomes after PD, with high frequency of infectious complications. Particularly, bile contamination is related to POPF Grade B/C. Management of biliary contamination should be standardised for patients who

**Table 3 Comparison of cultured organisms from bile and organ space infections**

| Characteristic                      | n (%)      |
|-------------------------------------|------------|
| Cultured from bile                  | 606        |
| <i>Enterococcus</i>                 | 259 (42.7) |
| <i>Klebsiella</i>                   | 161 (26.6) |
| <i>Enterobacter</i>                 | 86 (14.2)  |
| <i>Streptococcus</i>                | 77 (12.7)  |
| <i>E.coli</i>                       | 72 (11.9)  |
| Other Gram negative rods            | 59 (9.7)   |
| <i>Citrobacter</i>                  | 42 (6.9)   |
| <i>Pseudomona</i>                   | 38 (6.3)   |
| Coagulase negative staphylococcus   | 34 (5.6)   |
| <i>Candida albicans</i>             | 23 (3.8)   |
| <i>Staphylococcus aureus</i> (MRSA) | 20 (3.3)   |
| <i>Staphylococcus aureus</i> (MSSA) | 10 (1.7)   |
| Cultured from organ space           | 596        |
| <i>Enterococcus</i>                 | 284 (47.7) |
| <i>Enterobacter</i>                 | 119 (20.0) |
| <i>Klebsiella</i>                   | 88 (14.8)  |
| <i>Pseudomona</i>                   | 82 (13.8)  |
| <i>Staphylococcus aureus</i> (MRSA) | 63 (10.6)  |
| <i>Candida albicans</i>             | 58 (9.7)   |
| Coagulase-negative Staphylococcus   | 55 (9.2)   |
| <i>Streptococcus</i>                | 51 (8.6)   |
| <i>Staphylococcus aureus</i> (MSSA) | 48 (8.1)   |
| <i>E.coli</i>                       | 26 (4.4)   |

MRSA: Methicillin-resistant *S. aureus*; MSSA: Methicillin-sensitive *S. aureus*.

require preoperative biliary drainage for PD, as the main microorganisms are identical in both infected POPF and bile. These findings contribute to the proper management of patients with biliary drainage for PD and may help to establish perioperative therapeutic strategies for biliary contaminations.

**Table 4 Multivariate analysis for risk factors influencing postoperative pancreatic fistula (Grade B/C) patients who received pancreaticoduodenectomy**

| Risk factor                   | Significance ( <i>P</i> value) | Odds ratio | 95%CI       |
|-------------------------------|--------------------------------|------------|-------------|
| Male sex                      | < 0.0001                       | 1.815      | 1.459-2.266 |
| Age ≥ 70                      | 0.032                          | 1.250      | 1.018-1.535 |
| BMI (kg/m <sup>2</sup> ) ≥ 25 | < 0.0001                       | 2.095      | 1.610-2.718 |
| Other previous malignancies   | 0.079                          | 1.253      | 0.971-1.612 |
| Liver disease                 | 0.119                          | 1.422      | 0.903-2.200 |
| Preoperative biliary drainage | 0.461                          | 1.087      | 0.869-1.361 |
| Bile contamination            | 0.026                          | 1.338      | 1.033-1.729 |
| Soft pancreas                 | < 0.0001                       | 4.594      | 3.650-5.824 |
| Operation time (h) ≥ 7        | 0.0021                         | 1.441      | 1.143-1.822 |

BMI: Body mass index; NA: Not available; POPF: Postoperative pancreatic fistula; ISGPF: International Study Group on Pancreatic Fistula; CI: Confidence interval.

**Table 5 Comparison of complications and immediate outcome according to the type of drainage (external or internal) after pancreaticoduodenectomy, *n* (%)**

|  | Type of biliary drainage   |                             | <i>P</i> value |
|--|----------------------------|-----------------------------|----------------|
|  | External ( <i>n</i> = 772) | Internal ( <i>n</i> = 1170) |                |
| Demographics                             |                            |                             |                |
| Age (yr), median                         | 64                         | 62                          | 0.025          |
| Sex ratio (M:F)                          | 1.97:1                     | 1.84:1                      | 0.99           |
| Duration of hospital stay (d), median    | 30                         | 28                          | 0.72           |
| Readmission                              | 29 (3.8)                   | 36 (3.1)                    | 0.32           |
| In-hospital death                        | 15 (1.9)                   | 27 (2.3)                    | 0.58           |
| Operative variables                      |                            |                             |                |
| Estimated blood loss (g), median         | 855                        | 860                         | 0.75           |
| Duration of surgery (min), median        | 475                        | 500                         | 0.0004         |
| Postoperative complications              |                            |                             |                |
| Overall complications                    | 433 (56.1)                 | 646 (55.2)                  | 0.7            |
| Infectious complications                 | 293 (38.0)                 | 445 (38.0)                  | 0.77           |
| Severe complications (grade III or more) | 127 (16.5)                 | 211 (18.0)                  | 0.35           |
| POPF (all)                               | 284 (36.8)                 | 450 (38.5)                  | 0.57           |
| POPF (ISGPF grade B or C)                | 164 (21.2)                 | 277 (19.4)                  | 0.19           |
| Delayed gastric emptying                 | 97 (12.6)                  | 166 (14.2)                  | 0.37           |
| Intra-abdominal bleeding                 | 36 (4.7)                   | 68 (5.8)                    | 0.32           |

The variables were identical to those of the American College of Surgeons–National Surgical Quality Improvement Program Percutaneous transhepatic biliary drainage and endoscopic nasobiliary drainage were categorized as the types of external drainage and endoscopic retrograde biliary drainage was categorized as internal drainage. External drainage was performed in 772 patients (endoscopic nasobiliary drainage in 499 cases, percutaneous transhepatic biliary drainage in 241 cases, and PTGBD in 32 cases) and internal drainage was performed in 1170 patients. POPF: Postoperative pancreatic fistula.

## ARTICLE HIGHLIGHTS

### Research background

Preoperative endoscopic biliary procedures are widespread in the management of periampullary tumours. The influence of bile contamination on the infectious complications of patients undergoing pancreaticoduodenectomy (PD) has not been thoroughly evaluated.

### Research motivation

The large data of clinical features and outcomes after PD in patients with infected bile will help improve future clinical outcome.

### Research objectives

This study aimed to identify the clinical features and outcomes after PD in patients with infected bile based on data from the Japanese Society of Pancreatic Surgery for future management of perioperative infectious complications.

### Research methods

We retrospectively reviewed the database of 4101 patients who underwent PD. Preoperative biliary drainage was performed in 1964 patients (47.9%), and bile contamination was confirmed in 606 patients (14.8%).

### Research results

The incidence of postoperative infectious complications was 37.9% in patients with preoperative biliary drainage and 42.4% in patients with biliary contamination, respectively. Patients with extrahepatic bile duct carcinoma, ampulla of Vater carcinoma, and pancreatic carcinoma had a high frequency of preoperative biliary drainage (82.9%, 54.6%, and 50.8%) and bile contamination (34.3%, 26.2%, and 20.2%). Bile contamination was associated with postoperative pancreatic fistula (POPF) Grade B/C, wound infection, and catheter infection. A multivariate logistic regression analysis revealed that biliary contamination (odds ratio 1.33,  $P = 0.027$ ) was the independent risk factor for POPF Grade B/C. The three most commonly cultured microorganisms from bile (*Enterococcus*, *Klebsiella*, and *Enterobacter*) were identical to those isolated from organ spaces.

### Research conclusions

In patients undergoing PD, bile contamination is related to postoperative infectious complication including POPF Grade B/C.

### Research perspectives

The management of biliary contamination should be standardised for patients who require preoperative biliary drainage for PD, as the main microorganisms are identical in both organ spaces and bile.

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