Original article

Postoperative infectious complications after pancreatic resection

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Background: **Although mortality associated with pancreatic surgery has decreased dramatically, high morbidity rates are still of major concern. This study aimed to identify the prevalence of, and risk factors for, infectious complications after pancreatic surgery.**

Methods: **The Japanese Society of Pancreatic Surgery conducted a multi-institutional analysis of complications in patients who underwent pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) between January 2010 and December 2012. Risk factors that were significantly associated with infectious complications in univariable models were included in a multivariable logistic regression model, and a nomogram was created to predict the risk of infectious complications after pancreatectomy.**

Results: **Infectious complications occurred in 1459 (35·2 per cent) of 4147 patients in the PD group and 426 (25·2 per cent) of 1692 patients in the DP group ($P < 0·001$). Nine risk factors for infectious complications after PD were identified: male sex, age 70 years or more, body mass index at least 25 kg/m^2, other previous malignancy, liver disease, bile contamination, duration of surgery 7 h or longer, intraoperative blood transfusion and soft pancreas. Five risk factors for infectious complications after DP were identified: chronic steroid use, smoking, duration of surgery 5 h or more, intraoperative blood transfusion and non-laparoscopic surgery. Occurrence of a postoperative infectious complication was significantly associated with mortality and reoperation after PD (odds ratio (OR) 4·33, 95 per cent c.i. 2·01 to 9·92 and OR 3·26, 1·86 to 5·82, respectively) and DP (OR 6·32, 1·99 to 22·55; OR 3·74, 1·61 to 9·04).**

Conclusion: **Prolonged operating time, intraoperative blood transfusion, bile contamination (PD) and non-laparoscopic surgery (DP) are risk factors for postoperative infectious complications that could be targeted to improve outcome after pancreatectomy.**

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Introduction

The number of pancreatic resections has increased, but postoperative mortality has decreased in recent years[1–4]. Although the perioperative mortality rate of pancreaticoduodenectomy (PD) in high-volume centres is now around 1–2 per cent, the morbidity rate is still relatively high at 20–50 per cent[2–7]. Infectious complications are the main cause of postoperative morbidity. In high-volume centres, infectious complications occurred in nearly one-third of patients who underwent PD and in one-quarter after distal pancreatectomy (DP)[8,9].

Optimal infection control is emerging as an indicator for quality in surgery. Most inventions aimed at reducing infectious complications have been applied to elective general surgery or non-abdominal procedures including either clean or clean-contaminated wounds[10,11]. Some studies[12–14] have focused on risk factors for infections associated with pancreatic resection, but a global analysis of the impact of infectious complications on short-term outcomes after pancreatic resections has not been undertaken.

The aim of this study was to assess the landscape of infectious complications after pancreatic surgery, and to

identify risk factors for infectious complications after PD and DP.

Methods

This nationwide multi-institutional analysis of infectious complications after major pancreatic surgery was conducted by the Japanese Society of Pancreatic Surgery (JSPS), which validates data through inspection of randomly selected institutions. Seventy-eight hospitals were invited to participate in the study. All patients who underwent PD or DP between January 2010 and December 2012 were included. Most institutions that participated in the study had advanced skills training facility certification for hepatobiliary–pancreatic surgery from the Japanese Society of Hepato-Biliary-Pancreatic Surgery. These institutions met requirements concerning strict data management and detailed case registration. In addition, the final database was carefully checked for clerical errors by two physicians and one statistician before analysis.

Definitions

Definitions of complications, including infectious complications, were almost identical to those of the American College of Surgeons National Surgical Quality Improvement Program criteria (NSQIP®)[15]. Infectious complications in the present study were defined as all postoperative infectious complications including surgical-site infection (wound infection, intra-abdominal abscess, infected postoperative pancreatic fistula (POPF)) and extraparietoabdominal infection (catheter infection, pneumonia, urinary tract infection). Infectious complications were also identified as a specific clinical condition that was related to infection by bacterium, fungus or virus in a specific organ/compartment. A positive culture that could not be linked to a specific clinical condition was not defined as an infectious complication.

As NSQIP® 30-day mortality rates underestimate the mortality rate for complicated surgical procedures such as PD[16], the present study used in-hospital mortality. Mortality was defined as death before postoperative day 30 (in and out of hospital), and death among patients who remained in hospital for 30 days or more after surgery and died in hospital[16]. Complication severity was graded according to the Dindo–Clavien classification[17]. Pancreatic fistula was defined according to the International Study Group on Pancreatic Fistula guidelines[18] by an amylase level over three times the normal serum amylase level in the drainage fluid on postoperative day 3. Infected pancreatic fistula was defined as clinically relevant fistula with infection proven 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, where 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.

Preoperative, intraoperative and postoperative variables

Patient demographics, performance status, smoking, medication use, co-morbidities, previous malignancies, previous operations, use of neoadjuvant therapy, and preoperative biliary drainage including biliary contamination were recorded. Details of the operation, concomitant resection of other visceral organs, duration of surgery, blood loss, intraoperative blood transfusion, texture of the pancreas (soft or hard) and perioperative antibiotic prophylaxis use (type and duration) were also recorded for each patient. Cut-off points were determined for each surgical procedure based on the median value for duration of surgery and estimated intraoperative blood loss.

The types of biliary drainage and the results of preoperative bile culture were also recorded for patients who underwent preoperative biliary drainage before PD. Percutaneous transhepatic biliary drainage and endoscopic nasobiliary drainage were categorized as external drainage, and endoscopic retrograde biliary drainage as internal drainage. Positive cultures of microorganisms in bile from a preoperative biliary stent or intraoperative bile collection indicated bile contamination. The types of microorganism collected from the site of infection were noted for patients with infectious complications.

Drain management

In most institutions (78 per cent), prophylactic drains were placed routinely anterior to the surfaces of the pancreaticojejunal anastomoses and dorsal to the choledochojejunal anastomoses for PD. Prophylactic drains were placed routinely on the side of the pancreas stump and/or left subphrenic space for DP in 92 per cent of the institutions. Drains were usually removed 3–7 days after operation[19].

Table 1 Complications following pancreaticoduodenectomy and distal pancreatectomy

	Pancreaticoduodenectomy ($n = 4147$)	Distal pancreatectomy ($n = 1692$)	P†
Age (years)*	70 (8–89)	68 (12–89)	
Sex ratio (M : F)	2516 : 1631	873 : 819	< 0·001‡
In-hospital death	77 (1·9)	22 (1·3)	0·191
Readmission	148 (3·6)	86 (5·1)	0·042
Reoperation	127 (3·1)	41 (2·4)	0·681
Duration of postoperative hospital stay (days)*	29 (5–921)	19 (2–205)	< 0·001‡
Patients with complication	2206 (53·2)	847 (50·1)	0·012
POPF (all)	1557 (37·5)	829 (49·0)	< 0·001
ISGPF grade A	670 (16·2)	413 (24·4)	< 0·001
ISGPF grade B	750 (18·1)	369 (21·8)	< 0·001
ISGPF grade C	137 (3·3)	47 (2·8)	0·323
Delayed gastric emptying	606 (14·6)	94 (5·6)	< 0·001
Intra-abdominal bleeding	206 (5·0)	46 (2·7)	0·012
Infectious complications	1459 (35·2)	426 (25·2)	< 0·001
Infected POPF	887 (21·4)	416 (24·6)	< 0·001
Intra-abdominal abscess	585 (14·1)	209 (12·4)	0·032
Wound infection	539 (13·0)	84 (5·0)	< 0·001
Central venous line catheter infection	206 (5·0)	43 (2·5)	< 0·001
Cholangitis	175 (4·2)	7 (0·4)	< 0·001
Sepsis	172 (4·1)	38 (2·2)	0·003
Pneumonia	123 (3·0)	43 (2·5)	0·578
Pseudomembranous colitis	61 (1·5)	16 (0·9)	0·464
Fungaemia	57 (1·4)	19 (1·1)	0·663
Liver abscess	45 (1·1)	9 (0·5)	0·095§
Urinary tract infection	38 (0·9)	12 (0·7)	0·147§
Dindo–Clavien grade for infectious complications			< 0·001
I	182 (4·4)	49 (2·9)	
II	597 (14·4)	153 (9·0)	
IIIa	554 (13·4)	179 (10·6)	
IIIb	38 (0·9)	14 (0·8)	
IVa	25 (0·6)	3 (0·2)	
IVb	8 (0·2)	4 (0·2)	
V	33 (0·8)	6 (0·4)	
Unknown	22 (0·5)	18 (1·1)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). POPF, postoperative pancreatic fistula; ISGPF, International Study Group on Pancreatic Fistula. †χ^2 test, except ‡Mann–Whitney U test and §Fisher's exact test.

Statistical analysis

Patient characteristics and clinical factors were compared using the Mann–Whitney U test for continuous variables and Fisher's exact test or χ^2 test for categorical variables. Risk factors that were significantly associated with infectious complications in univariable models ($P < 0·050$) were included in a multivariable logistic regression model. The coefficients derived from multivariable analysis were used as weights in a nomogram to predict infectious complications after pancreatic resection (PD and DP). The discriminatory power of the logistic regression model was summarized using the c-index and the model was validated by employing tenfold cross-validation. Calibration plots of the nomogram-predicted probabilities and the observed probabilities were constructed and the coefficients of determination (R^2) calculated. $P < 0·050$ was considered statistically significant. All statistical analyses were performed using SAS® version 8.2 (SAS Institute, Cary, North Carolina, USA).

Results

Seventy-eight hospitals were registered in the study. Nine centres were excluded for not including patients or clerical errors, which left 69 hospitals. A total of 5839 patients who underwent pancreatectomy were analysed (4147 PD, 1692 DP). The median number of pancreatic resections during the 3 years of registration was 57 (range 10–238) for PD and 29 (range 1–106) for DP. In 59 participating hospitals (86 per cent), PD was performed in more than ten patients per year.

Table 2 Primary disease and infectious complications after pancreatic resection

	Pancreaticoduodenectomy ($n = 4147$)				Distal pancreatectomy ($n = 1692$)			
		Infectious complication				Infectious complication		
	Total no.	Yes ($n = 1459$)	No ($n = 2688$)	P*	Total no.	Yes ($n = 426$)	No ($n = 1266$)	P*
Pancreatic carcinoma	1804	524 (29·0)	1280 (71·0)	–	846	258 (30·5)	588 (69·5)	
Extrahepatic bile duct carcinoma	794	402 (50·6)	392 (49·4)	< 0·001	n.a.			
Ampulla of Vater carcinoma	448	197 (44·0)	251 (56·0)	< 0·001	n.a.			
IPMN	399	119 (29·8)	280 (70·2)	0·758	178	36 (20·2)	142 (79·8)	0·005
Duodenal carcinoma	122	55 (45·1)	67 (54·9)	< 0·001	n.a.			
Pancreatic neuroendocrine tumour	120	48 (40·0)	72 (60·0)	0·013	141	34 (24·1)	107 (75·9)	0·118
Pancreatic cystic tumour	60	16 (27)	44 (73)	0·687	190	40 (21·1)	150 (78·9)	0·008

Values in parentheses are percentages. IPMN, intraductal papillary mucinous neoplasm; n.a., not applicable. **Versus* pancreatic carcinoma (χ^2 test).

Postoperative (infectious) complications after pancreatectomy

The percentage of patients with postoperative complications was significantly higher after PD than DP (*Table 1*). Infectious complications occurred in 35·2 per cent in the PD group and 25·2 per cent in the DP group ($P < 0·001$). Some 18·8 and 15·9 per cent of patients developed minor (grade I–II) and major (III–V) infectious complications respectively after PD. In the DP group there was no difference in infectious complications between the patients who underwent closure of the pancreatic remnant with a stapler (666) or handsewn technique (527): 25·6 *versus* 24·8 per cent ($P = 0·780$). Grade B and C POPFs were found in 372 (63·6 per cent) of 585 patients with intra-abdominal abscess in the PD group, and 150 (71·8 per cent) of 209 with intra-abdominal abscess in the DP group.

Cultured microorganisms

Microorganisms were cultured from drain fluid (8·9 per cent), intra-abdominal abscesses (4·4 per cent), surgical wounds (1·6 per cent), bile (1·6 per cent), central venous catheters (1·2 per cent), blood (1·1 per cent), sputum (0·6 per cent), stool (0·4 per cent) and urine (0·2 per cent). The most commonly cultured organisms in the PD group were *Enterococcus* (10·3 per cent), *Enterobacter* (4·9 per cent), *Klebsiella* (3·5 per cent), *Pseudomonas* (2·9 per cent) and methicillin-resistant *Staphylococcus aureus* (2·7 per cent) (*Table S1*, supporting information). In the DP group, a different spectrum was found, including the microbiology of organ/space infections. There were no hospital outbreaks of multiresistant bacteria during the study interval.

Perioperative antibiotic prophylaxis was given for 3 (range 1–6) days in the PD and DP groups. The duration of antibiotic administration did not affect the incidence of infectious complications after either procedure. Second-generation cephalosporins were used most commonly in both PD (83·5 per cent) and DP (69·8 per cent).

Preoperative biliary drainage was performed in 1966 (47·4 per cent) of 4147 patients who underwent PD. Microorganisms were isolated from the bile in 606 (36·7 per cent) of 1651 patients. The organisms were *Enterococcus* (259 patients, 42·7 per cent), *Klebsiella* (161, 26·6 per cent), *Enterobacter* (86, 14·2 per cent), *Streptococcus* (77, 12·7 per cent) and *Escherichia coli* (72, 11·9 per cent). The three most commonly cultured microorganisms were identical to those isolated from organ spaces in patients with infectious complications.

Primary disease and infectious complications

The primary disease was associated with incidence of postoperative infectious complications (*Table 2*). Patients with extrahepatic bile duct carcinoma, ampulla of Vater carcinoma, duodenal carcinoma and endocrine tumour had a higher incidence of postoperative infectious complications than those with pancreatic carcinoma. Patients with pancreatic carcinoma had a higher incidence of postoperative infectious complications than those with intraductal papillary mucinous neoplasm or cystic tumour after DP.

Risk factors for infectious complications

Univariable analysis identified several risk factors for infectious complications after PD (*Table 3*). Multivariable analysis showed that male sex, age 70 years or more, body mass index (BMI) at least 25 kg/m^2, other previous malignancy, liver disease, bile contamination, duration of surgery 7 h or longer, intraoperative blood transfusion and soft pancreas were independent risk factors related to infectious complications after PD. Preoperative biliary drainage was not an independent statistically significant

Table 3 Risk factors for infectious complications after pancreaticoduodenectomy and distal pancreatectomy

	Pancreaticoduodenectomy ($n = 4147$)					Distal pancreatectomy ($n = 1692$)				
	No. of patients	Infectious complication (%)	P§	Multivariable analysis¶ Odds ratio*	P	No. of patients	Infectious complication (%)	P§	Multivariable analysis¶ Odds ratio*	P
Preoperative variables										
Male sex	2516 (60·7)	39·6	< 0·001	1·29 (1·04, 1·60)	0·019	873 (51·6)	31·4	< 0·001	1·05 (0·78, 1·41)	0·735
Age ≥ 70 years	1887 (45·5)	40·1	< 0·001	1·26 (1·04, 1·52)	0·013	711 (42·0)	29·0	0·2		
BMI ≥ 25 kg/m^2	605 (14·6)	49·5	< 0·001	1·53 (1·19, 1·97)	0·001	305 (18·0)	27·0	0·89		
Serum albumin < 3·5 g/dl	983 (23·7)	41·4	< 0·001	1·02 (0·79, 1·21)	0·830	174 (10·3)	32·0	0·16		
Lymphocyte count < 1000 /μl	705 (17·0)	35·6	0·62			335 (19·8)	22·9	0·11		
Total cholesterol < 130 mg/dl	493 (11·9)	37·9	0·6			86 (5·1)	31	0·55		
Total bilirubin ≥ 1·0 g/dl	1675 (40·4)	37·8	0·06			267 (15·8)	26·1	0·85		
Diabetes	1219 (29·4)	35·9	0·46			533 (31·5)	27·6	0·57		
Other previous malignancies	713 (17·2)	46·5	< 0·001	1·36 (1·06, 1·70)	0·012	345 (20·4)	33·1	0·02	1·33 (0·99, 1·79)	0·055
Liver disease	182 (4·4)	48·5	0·001	1·60 (1·21, 2·74)	0·008	115 (6·8)	27·0	0·99		
Previous laparotomy	1174 (28·3)	42·1	< 0·001	1·10 (0·89, 1·34)	0·350	516	(30·5)	29·8	0·25	
Chronic steroid use	83 (2·0)	47	0·09			39 (2·3)	49	0·011	2·21 (1·05, 4·57)	0·035
Smoking (≥ 20 pack-years)	1738 (41·9)	41·2	< 0·001	1·20 (0·97, 1·47)	0·083	628 (37·1)	34·7	< 0·001	1·68 (1·25, 2·25)	0·001
Preoperative biliary drainage	1966 (47·4)	37·9	0·003	1·15 (0·93, 1·41)	0·088	n.a.				
Bile contamination	664 (16·0)	42·4	< 0·001	1·32 (1·05, 1·65)	0·017	n.a.				
Operative variables										
Prolonged operation†	2633 (63·5)	40·4	< 0·001	1·41 (1·15, 1·76)	0·001	768 (45·4)	32·7	< 0·001	1·49 (1·06, 2·07)	0·022
High intraoperative blood loss‡	2397 (57·8)	39·1	< 0·001	1·05 (0·87, 1·32)	0·570	814 (48·1)	31·8	< 0·001	1·02 (0·76, 1·38)	0·881
Intraoperative blood transfusion	1215 (29·3)	41·9	< 0·001	1·24 (0·99, 1·52)	0·049	250 (14·8)	39·0	< 0·001	2·10 (1·52, 2·90)	< 0·001
Soft pancreas	2347 (56·6)	43·3	< 0·001	2·03 (1·69, 2·45)	< 0·001	1333 (78·8)	28·0	0·056		
Non-laparoscopic surgery	4064 (98·0)	36·5	0·55			1415 (83·6)	29·1	0·001	1·49 (1·04, 2·16)	0·027

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent c.i. †At least 7 h for pancreaticoduodenectomy, 5 h or more for distal pancreatectomy. ‡At least 640 ml for pancreaticoduodenectomy, 400 ml or greater for distal pancreatectomy. BMI, body mass index; n.a., not applicable. §χ^2 test (univariable analysis); ¶logistic regression.

risk factor for infectious complications. Independent risk factors for infectious complications after DP were chronic steroid use, smoking, duration of surgery 5 h or greater, intraoperative blood transfusion and non-laparoscopic surgery.

Risk factors for in-hospital mortality, readmission and reoperation

Twelve potential risk factors were selected from the present study and previous reports[9,12,20–23] to identify the impact of infectious complications on in-hospital mortality, readmission and reoperation after pancreatectomy. Multivariable logistic regression revealed that BMI at least 25 kg/m^2, intraoperative blood transfusion and postoperative infectious complications (odds ratio (OR) 4·33, 95 per cent c.i. 2·01 to 9·92) were independent risk factors for in-hospital mortality after PD (*Table S2*, supporting information). An infectious complication was also an independent predictor of reoperation (3·26, 1·86 to 5·82).

A similar multivariable logistic regression analysis was performed for DP (*Table S3*, supporting information).

Table 4 Preoperative and operative risk score predicting infectious complications after pancreatic surgery

	Pancreatico-duodenectomy	Distal pancreatectomy
Preoperative risk factors		
Sex		
M	1	
F	0	
Age (years)		
≥ 70	1	
< 70	0	
BMI (kg/m^2)		
≥ 25	1	
< 25	0	
Other previous malignancies		
Yes	1	
No	0	
Liver disease		
Yes	2	
No	0	
Bile contamination		
Yes	1	
No	0	
Chronic steroid use		
Yes		2
No		0
Smoking (≥ 20 pack-years)		
Yes		1
No		0
Operative risk factors		
Prolonged operation*		
Yes	1	1
No	0	0
Intraoperative blood transfusion		
Yes	1	1
No	0	0
Pancreatic texture		
Soft	2	
Hard	0	
Surgical approach		
Open		1
Laparoscopic		0
Total points range	0–11	0–6

*At least 7 h for pancreaticoduodenectomy, 5 h or more for distal pancreatectomy. BMI, body mass index.

Postoperative infectious complication was also an independent risk factor for in-hospital mortality (OR 6·32, 1·99 to 22·55) and reoperation (OR 3·74, 1·61 to 9·04) after DP.

Nomogram for prediction of infectious complication after pancreatectomy

Multiple regression models estimated by the ordinary least squares method are shown for PD and DP in *Tables S4* and *S5* (supporting information) respectively. The total points of the risk score for a nomogram ranged from 0 to 11 (7 preoperative and 4 operative) for PD and 0 to 6 (3 preoperative and 3 operative) for DP (*Table 4*). The nomogram (*Fig. 1*) provides the probability of infectious complication by drawing a line horizontally from the preoperative and/or operative score total. Calibration plots for the nomogram-predicted probabilities and the observed probabilities for PD and DP are displayed in *Figs S1* and *S2* (supporting information). The coefficients of determination (R^2) were 0·976 for the PD and 0·673 for the DP nomogram.

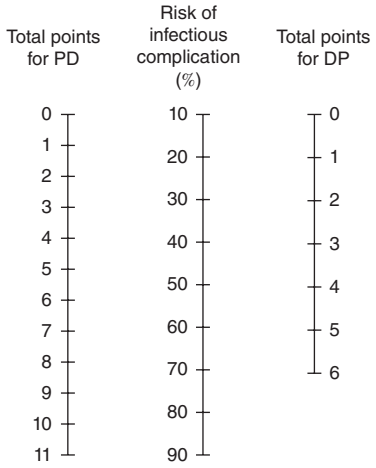

Fig. 1 Proposed nomogram for the prediction of infectious complication rates after pancreatectomy. To estimate the probability of infectious complication, a line is drawn horizontally from the preoperative and/or operative total score (*Table 4*). PD, pancreaticoduodenectomy; DP, distal pancreatectomy

Discussion

Infectious complications contribute to a complicated postoperative recovery and are associated with in-hospital death after pancreatic resection[13,16]. This multi-institutional study aimed to assess the incidence, severity and risk factors for infectious complications after pancreatic resection. Infectious complications were associated with in-hospital mortality and reoperations after pancreatic surgery. This is critical for patients undergoing pancreatectomy for malignancy, as infectious complications and a prolonged hospital stay may delay the initiation of adjuvant therapy. The primary disease was a predictor of infectious complications. It is important to consider this when counselling patients during the informed consent process.

In the present study, the incidence of overall and infectious complications was significantly higher after PD

compared with DP. Pancreatic fistula and readmission rates were significantly higher for DP. Most infectious complications in the DP group involved infected pancreatic fistula. Although the incidence of infectious complications after DP was not as high as that after PD, infected pancreatic fistula can be life-threatening. This is reflected by the in-hospital mortality rate for DP of 1·3 per cent and the high readmission rate, probably due to latent or delayed-onset infectious complications[24].

Some risk factors for infectious complications, such as total parenteral nutrition, coronary artery disease and perioperative hypotension, soft pancreas, BMI, prolonged operating time, bile contamination, blood transfusion and male sex, have already been reported[12–14,25,26]. The present study demonstrated that the presence of liver disease (such as hepatitis, liver cirrhosis) and previous malignancies were also independent risk factors for infectious complications after PD. Chronic steroid use, smoking and non-laparoscopic surgery were specific risk factors for DP. DP is a relatively simple surgical procedure that does not involve enteric reconstruction, and most of the infectious complications are associated with pancreatic fistula. Kelly and colleagues[9] proposed a preoperative risk scoring system for morbidity that includes male sex, high BMI, smoking and steroid use. The present study identified non-laparoscopic surgery as new risk factor for infectious complication in DP, but this needs confirmation in future studies. A nomogram for predicting infectious complications was established based on the independent risk factors. The nomogram could be clinically useful for preoperative counselling and perioperative management in order to reduce the rate of infections after pancreatic surgery.

Many previous studies[27–33] focused on preoperative biliary drainage in patients who underwent PD. It is evident that routine drainage in PD increases the incidence of postoperative complications[27]. Biliary contamination is a risk factor for postoperative infectious complications such as wound infection or intra-abdominal abscess[32]. Here, the three most commonly cultured microorganisms from bile were identical to those isolated from organ spaces in patients with infectious complications. Sudo and co-workers[33] recommended specific antibiotic prophylaxis based on bile culture for preventing infectious complications in patients undergoing PD with preoperative biliary drainage. Hence, preoperative bile culture should be considered in patients with biliary drainage.

The incidence of wound infection after PD has been reported to be 5–17 per cent[12,29,34–36]. The wound infection rate of 13·0 per cent in present study seems rather high. This may be explained by the fact that 47·4 per cent of patients who had PD also underwent preoperative biliary drainage, which has been reported as a risk factor for surgical-site infection after PD[30,32]. In addition, age (70 years or more) was an independent risk factor for infectious complication, and nearly half of the patients were over 70 years old.

Previous studies have reported on the prevalence of microorganisms at the surgical site[12,13] or in bile[32,33] in patients undergoing pancreatic resection. In the present study, gut-derived microorganisms were isolated predominantly after PD, most likely because the PD procedure involves intestinal reconstruction. In contrast, coagulase-negative *Staphylococcus* and methicillin-sensitive *S. aureus* were more frequently cultured from organ/space infections after DP than after PD. This suggests that the development of infected pancreatic fistula may involve retrograde migration of bacteria along a drain placed during surgery[37]. *E. coli* infections were confirmed in only 0·6 and 0·4 per cent of patients after PD and DP respectively. The most commonly used antibiotic prophylaxis (second-generation cephalosporins including cefotiam or flomoxef) covered the spectrum of *E. coli* infection, which may explain the low incidence of such infection. There is currently no consensus regarding the appropriate type and duration of antibiotic prophylaxis; a prospective study is warranted to provide evidence to validate appropriate antibiotic prophylaxis for PD and DP.

Several limitations of the study should be mentioned. First, the data were collected retrospectively, which is a potential source of bias. Second, although most of the 78 hospitals of the JSPS that participated in this study are leading institutions for pancreatic surgery in Japan[38–40], the results may have been influenced by hospital volume, hospital training status, hospital compliance and procedure-specific variables. Therefore, the study results do not necessarily reflect the outcome of pancreatic surgery nationwide. Third, some variables previously reported as risk factors for infectious complications, such as hypoxia[41], hypothermia[42] and American Society of Anesthesiologists classification[43], could not be studied. Finally, external validation using another data sets was not performed but is still warranted to confirm the clinical value of the nomogram.

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References

1 Teh SH, Diggs BS, Deveney CW, Sheppard BC. Patient and hospital characteristics on the variance of perioperative outcomes for pancreatic resection in the United States: a plea for outcome-based and not volume-based referral guidelines. *Arch Surg* 2009; **144**: 713–721.

2 Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J *et al.* 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J Gastrointest Surg* 2006; **10**: 1199–1210.

3 Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 2006; **244**: 10–15.

4 Vin Y, Sima CS, Getrajdman GI, Brown KT, Covey A, Brennan MF *et al.* Management and outcomes of postpancreatectomy fistula, leak, and abscess: results of 908 patients resected at a single institution between 2000 and 2005. *J Am Coll Surg* 2008; **207**: 490–498.

5 Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA *et al.* Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997; **226**: 248–257.

6 Büchler MW, Friess H, Müller MW, Wheatley AM, Beger HG. Randomized trial of duodenum-preserving pancreatic head resection *versus* pylorus-preserving Whipple in chronic pancreatitis. *Am J Surg* 1995; **169**: 65–69.

7 Simons JP, Shah SA, Ng SC, Whalen GF, Tseng JF. National complication rates after pancreatectomy: beyond mere mortality. *J Gastrointest Surg* 2009; **13**: 1798–1805.

8 Vollmer CM Jr, Sanchez N, Gondek S, McAuliffe J, Kent TS, Christein JD *et al.*; Pancreatic Surgery Mortality Study Group. A root-cause analysis of mortality following major pancreatectomy. *J Gastrointest Surg* 2012; **16**: 89–102.

9 Kelly KJ, Greenblatt DY, Wan Y, Rettammel RJ, Winslow E, Cho CS *et al.* Risk stratification for distal pancreatectomy utilizing ACS-NSQIP: preoperative factors predict morbidity and mortality. *J Gastrointest Surg* 2011; **15**: 250–259.

10 Pessaux P, Msika S, Atalla D, Hay J, Flamant Y; French Association for Surgical Research. Risk factors for postoperative infectious complications in noncolorectal abdominal surgery: a multivariate analysis based on a prospective multicenter study of 4718 patients. *Arch Surg* 2003; **138**: 314–324.

11 Haridas M, Malangoni MA. Predictive factors for surgical site infection in general surgery. *Surgery* 2008; **144**: 496–501.

12 Sugiura T, Uesaka K, Ohmagari N, Kanemoto H, Mizuno T. Risk factor of surgical site infection after pancreaticoduodenectomy. *World J Surg* 2012; **36**: 2888–2894.

13 Kent TS, Sachs TE, Callery MP, Vollmer CM Jr. The burden of infection for elective pancreatic resections. *Surgery* 2013; **153**: 86–94.

14 Su Z, Koga R, Saiura A, Natori T, Yamaguchi T, Yamamoto J. Factors influencing infectious complications after pancreatoduodenectomy. *J Hepatobiliary Pancreat Sci* 2010; **17**: 174–179.

15 Anonymous. *User Guide for the 2012 Participant Use Data File*. American College of Surgeons National Surgical Quality Improvement Program: Chicago, 2012.

16 Kimura W, Miyata H, Gotoh M, Hirai I, Kenjo A, Kitagawa Y *et al.* A pancreaticoduodenectomy risk model derived from 8575 cases from a national single-race population (Japanese) using a web-based data entry system: the 30-day and in-hospital mortality rates for pancreaticoduodenectomy. *Ann Surg* 2014; **259**: 773–780.

17 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.

18 Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al.*; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**: 8–13.

19 Kawai M, Tani M, Terasawa H, Ina S, Hirono S, Nishioka R *et al.* Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for 104 consecutive patients. *Ann Surg* 2006; **244**: 1–7.

20 Are C, Afuh C, Ravipati L, Sasson A, Ullrich F, Smith L. Preoperative nomogram to predict risk of perioperative mortality following pancreatic resections for malignancy. *J Gastrointest Surg* 2009; **13**: 2152–2162.

21 Venkat R, Puhan MA, Schulick RD, Cameron JL, Eckhauser FE, Choti MA *et al.* Predicting the risk of perioperative mortality in patients undergoing pancreaticoduodenectomy: a novel scoring system. *Arch Surg* 2011; **146**: 1277–1284.

22 Assifi MM, Lindenmeyer J, Leiby BE, Grunwald Z, Rosato EL, Kennedy EP *et al.* Surgical Apgar score predicts perioperative morbidity in patients undergoing pancreaticoduodenectomy at a high-volume center. *J Gastrointest Surg* 2012; **16**: 275–281.

23 House M, Fong Y, Arnaoutakis D, Sharma R, Winston C, Protic M *et al.* Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. *J Gastrointest Surg* 2008; **12**: 270–278.

24 Yanagimoto H, Satoi S, Toyokawa H, Yamamoto T, Hirooka S, Yamao J *et al.* Pancreaticogastrostomy following distal pancreatectomy prevents pancreatic fistula-related complications. *J Hepatobiliary Pancreat Sci* 2014; **21**: 473–478.

25 Kaiser AB, Herrington JL Jr, Jacobs JK, Mulherin JL Jr, Roach AC, Sawyers JL. Cefoxitin *versus* erythromycin, neomycin, and cefazolin in colorectal operations. Importance of the duration of the surgical procedure. *Ann Surg* 1983; **198**: 525–530.

26 Coppa GF, Eng K. Factors involved in antibiotic selection in elective colon and rectal surgery. *Surgery* 1988; **104**: 853–858.

27 van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ *et al.* Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010; **362**: 129–137.

28 Kitahata Y, Kawai M, Tani M, Hirono S, Okada KI, Miyazawa M *et al.* Preoperative cholangitis during biliary drainage increases the incidence of postoperative severe complications after pancreaticoduodenectomy. *Am J Surg* 2014; **208**: 1–10.

29 Pisters PW, Hudec WA, Hess KR, Lee JE, Vauthey JN, Lahoti S *et al.* Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg* 2001; **234**: 47–55.

30 Hodul P, Creech S, Pickleman J, Aranha GV. The effect of preoperative biliary stenting on postoperative complications after pancreaticoduodenectomy. *Am J Surg* 2003; **186**: 420–425.

31 Povoski SP, Karpeh MS Jr, Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. *Ann Surg* 1999; **230**: 131–142.

32 Cortes A, Sauvanet A, Bert F, Janny S, Sockeel P, Kianmanesh R *et al.* Effect of bile contamination on immediate outcomes after pancreaticoduodenectomy for tumor. *J Am Coll Surg* 2006; **202**: 93–99.

33 Sudo T, Murakami Y, Uemura K, Hayashidani Y, Hashimoto Y, Ohge H *et al.* Specific antibiotic prophylaxis based on bile cultures is required to prevent postoperative infectious complications in pancreatoduodenectomy patients who have undergone preoperative biliary drainage. *World J Surg* 2007; **31**: 2230–2235.

34 Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR *et al.*; Pancreas Cancer Working Group. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. *Surgery* 2005; **138**: 618–628.

35 Grobmyer SR, Pieracci FM, Allen PJ, Brennan MF, Jaques DP. Defining morbidity after pancreaticoduodenectomy: use of a prospective complication grading system. *J Am Coll Surg* 2007; **204**: 356–364.

36 Schmidt C, Powell ES, Yiannoutsos CT, Howard TJ, Wiebke EA, Wiesenauer CA *et al.* Pancreaticoduodenectomy: a 20-year experience in 516 patients. *Arch Surg* 2004; **139**: 718–725.

37 Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R *et al.* Early *versus* late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg* 2010; **252**: 207–214.

38 Tani M, Kawai M, Hirono S, Hatori T, Imaizumi T, Nakao A *et al.* Use of omentum or falciform ligament does not decrease complications after pancreaticoduodenectomy: nationwide survey of the Japanese Society of Pancreatic Surgery. *Surgery* 2012; **151**: 183–191.

39 Kawahara R, Akasu G, Ishikawa H, Yasunaga M, Kinoshita H. A questionnaire on the educational system for pancreatoduodenectomy performed in 1134 patients in 71 institutions as members of the Japanese Society of Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 2013; **20**: 173–185.

40 Kato H, Usui M, Isaji S, Nagakawa T, Wada K, Unno M *et al.* Clinical features and treatment outcome of borderline resectable pancreatic head/body cancer: a multi-institutional survey by the Japanese Society of Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 2013; **20**: 601–610.

41 Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic. The effect of inspired oxygen on infection. *Arch Surg* 1984; **119**: 199–204.

42 Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med* 1996; **334**: 1209–1215.

43 Garibaldi RA, Cushing D, Lerer T. Risk factors for postoperative infection. *Am J Med* 1991; **91**(3B): 158S–163S.

Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Micro-organisms cultured from patients who underwent pancreatectomy (Word document)

Table S2 Multivariable logistic regression model to identify factors associated with in-hospital mortality, reoperation and readmission after pancreaticoduodenectomy (Word document)

Table S3 Multivariable logistic regression model to identify factors associated with in-hospital mortality, reoperation and readmission after distal pancreatectomy (Word document)

Table S4 Multiple regression model for infectious complications after pancreaticoduodenectomy estimated by ordinary least squares method (Word document)

Table S5 Multiple regression model for infectious complications after distal pancreatectomy estimated by ordinary least squares method (Word document)

Fig. S1 Calibration of the nomogram for pancreaticoduodenectomy (Word document)

Fig. S2 Calibration of the nomogram for distal pancreatectomy (Word document)

Appendix S1 Participating institutions (Word document)