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Risk Factors for Life-threatening Grade C Postoperative Pancreatic Fistula After Pancreatoduodenectomy Compared to Grade B

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Abstract. *Background: The aim of the present study was to investigate risk factors for the development of grade C compared to grade B cases of postoperative pancreatic fistula (POPF). Materials and Methods: Clinicopathological data from 43 patients who developed grade B or C POPF were retrospectively analyzed. The following types of factors were analyzed: Patient-related, surgery-related, and pancreas-related, including the value of the drain amylase and the detection of gram-negative rod bacteria within the first 7 postoperative days (PODs). Results: Univariate analysis showed that male sex (p=0.0492) and detection of gram-negative rods within the first 7 PODs (p=0.0010) were risk factors for development of grade C POPF. Only detection of gram-negative rods within the first 7 PODs was a significant factor after multivariate analysis (p=0.0027). Conclusion: Sensitive and specific predictive criteria for early detection of grade C POPF should be developed to allow for a management approach appropriately tailored to this condition.*

Progress in surgical techniques and perioperative management have reduced operative mortality after pylorus-preserving pancreatoduodenectomy (PPPD) to less than 3% in high-volume centers. However, the rate of morbidity still remains as high as 30-50% (1-3). The most common complication after pancreatoduodenectomy (PD) is postoperative pancreatic fistula (POPF), which occurs in 5-25% (4, 5). POPF is associated with prolonged hospitalization and increased mortality. Recently, the International Study Group on Pancreatic Fistula (ISGPF) classified POPF into three categories (6). According to this definition, grade B and C POPFs are considered clinically important, which are associated with serious problems such as intra-abdominal abscess and hemorrhage. The presence of grade B or C POPF is strongly associated with abdominal infections after PPPD and continues to be a serious problem for pancreatic surgeons (7). Although grade B or C POPFs are certainly clinically important, grade C are more significant as they can be life-threatening. There have been several reports describing risk factors for grade B or C POPF but only two have focused on grade C (8, 9). Furthermore, the mechanism by which grade B POPF develops to grade C is still unclear.

The colonization and infection of drainage fluid after PD is associated with postoperative infectious complications. However, the association between bacteria cultured from drainage fluids and POPF as far as we are aware has never been investigated in detail, and whether infection increases the risk or severity of POPF after PD remains unclear (10, 11). Furthermore, there are no previous studies reporting the relationship between risk factors for grade C POPF and bacterial infection of the drainage fluid.

The aim of this study was to evaluate the risk factors of grade C POPF associated with this life-threatening condition after PPPD compared to grade B cases.

Materials and Methods

Patient selection. From September 2007 to September 2017, 186 consecutive patients underwent PD or PPPD at our Institute. The clinicopathological data of 43 patients who developed grade B or C POPF after PD or PPPD was retrospectively analyzed.

Operative technique. All surgeries were performed by experienced surgeons at our Institute. Technical variations of PD (such as pylorus-preservation, type of pancreaticojejunal anastomosis, ductal stenting, and insertion of nutrition tubes) were performed as previously reported (12). All patients had abdominal drains inserted into the foramen of Winslow and near the pancreaticojejunostomy.

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Key Words: Pancreas surgery, pancreatic anastomosis, pancreatic fistula grade C.

Perioperative antibiotic therapy. For antibiotic therapy for prevention of postoperative infections, patients with preoperative bile cultures were administered sensitive antibiotics. For patients without preoperative bile cultures, third-generation cephem antibiotics were administered prophylactically. For patients who showed elevated serum C-reactive protein level after surgery, antibiotics were changed appropriately according to the results of the postoperative culture.

Definitions. Mortality and morbidity were defined as postoperative death and complications occurring within 90 days of the operation or during hospitalization, respectively. All cultures of abdominal collections were peri-anastomotic (*i.e.* from the pancreaticojejunal anastomosis). POPF was defined (in accordance with the ISGPF guidelines) as amylase-rich fluid (an amylase concentration more than three times the serum concentration) collected by needle aspiration during intra-abdominal collection or from the intraoperatively placed drain on postoperative days (PODs) 1-7. Fluid was also collected for culturing from the vicinity of the pancreatojejunostomy on PODs 4, 7, and later. POPFs were graded according to the clinical impact on the patient's hospital course (grade A, B, or C) according to the ISGPF classification (6). The patients were variously treated with total parenteral or continuous enteral nutrition *via* a W-ED tube, nasogastric aspiration, and antibiotics. The parenchyma texture was classified by the operating surgeon as 'soft' or 'hard'. The main pancreatic duct was classified as being <3 or ≥3 mm in diameter.

Preoperative and intraoperative data. Clinicopathological variables associated with the development of postoperative POPF were divided into three categories: (i) Patient-related factors, such as age, gender, and underlying disease; (ii) surgical procedure-related factors, such as operative time, blood loss, and associated procedures (*e.g.* combined vascular resection); and (iii) pancreas-related factors, such as the texture of the pancreatic remnant, and the diameter of the main pancreatic duct on the remnant's raw surface (<3 or ≥3 mm).

Statistical analysis. Our univariate analysis used the stepwise logistic regression test for quantitative nonparametric variables. A *p*-value of 0.05 or less was considered statistically significant. All variables demonstrating a *p*-value less than 0.05 in the univariate analysis were included in a multivariate analysis with a stepwise logistic regression model. The independent risk factors were expressed as odds ratios with their 95% confidence intervals.

Results

Clinicopathological findings. Of the 186 patients who underwent PD, 43 (23%) developed POPF (11 grade C and 32 grade B). The clinicopathological features of patients who developed POPF are summarized in Table I. In terms of sex, most females had grade B POPF (15/16, 94%). The underlying diseases included 11 cases (26%) of pancreatic carcinoma and 24 cases (56%) of cholangiocarcinoma. Pancreatic texture was considered to be firm in four (36%) patients with grade C and five patients (16%) with grade B. A pancreatic duct diameter ≥3 mm was found in six patients (55%) with grade C and eight patients (25%) with grade B. The median and mean amylase level in drain fluid from POD 1 to 3 was 2,693 IU/l and 7,752 IU/l in patients with grade C, and 1,460 IU/l and 4,047 IU/l in those with grade B, respectively. Finally, gram-negative rods were detected within the first 7 PODs in nine patients (82%) with grade C and five (16%) with grade B. After PPPD, grade C POPF occurred in 6% of patients and led to reoperation in 9%, while 81% needed endovascular embolization for postoperative bleeding. The mortality rate was 18%. Despite the small number of individuals in the subgroup with grade C POPF, the analysis showed that recurrent bleeding and surgical drainage of the anastomotic region due to sepsis were significantly associated with postoperative death. The history of postoperative antibiotics was not different significantly between two groups (data not shown).

Risk factors for development of grade C POPF. Univariate analyses of patient and surgical factors are summarized in Table II. Age, texture of the pancreas, diameter of the pancreatic duct, operative time, and operative blood loss were not found to be risk factors for development of POPF. There was no difference in the incidence of grade C POPF between patients who underwent combined vascular resection and those who did not. In terms of postoperative factors, maximum amylase level in drainage fluid on PODs 1-3 and 4-7 was not identified as a risk factor in either group. Univariate analysis determined that only male sex and detection of gram-negative rods within the first 7 PODs were risk factors for grade C POPF. The results of the multivariate analyses are summarized in Table III. Only detection of gram-negative rods within the first 7 PODs was a risk factor for grade C POPF.

Waterfall plotting of postoperative amylase level in drainage fluid. Figure 1 shows the waterfall plot of the postoperative value of amylase level in drainage fluid. From POD 1-3 and 4-7, the mean and median of the maximum value of drain amylase did not significantly differ between patients with grade B or C POPF.

Culture of drainage fluids within the first 7 PODs. The results of the culture of drainage fluid within the first 7 PODs are summarized in Figure 2. In patients with grade B POPF, almost all bacteria of drainage fluid within the first 7 PODs were gram-positive. On the other hand, in patients with grade C POPF, the detection of gram-negative rods was the only significant risk factor in multivariate analysis.

Discussion

Management of POPF after PPPD is various, and ranges from simple monitoring to emergency interventional procedures (including surgery). It is important to recognize patients who are likely to develop life-threatening grade C POPF. Therefore, although several studies have reported risk

Table I. *Clinicopathological features for grade B and C postoperative pancreatic fistula (POPF).*

Variable	POPF		*p*-Value
	Grade B (n=32)	Grade C (n=11)	
Age			
Median (range)	70 (54-80)	67 (56-80)	0.6799
Gender, n (%)			
Female	15 (47%)	1 (9%)	0.0492
Male	17 (53%)	10 (91%)	
Disease, n (%)			
Pancreatic carcinoma	5 (16%)	6 (55%)	0.3583
Cholangiocarcinoma	19 (59%)	5 (45%)	
Other	8 (25%)	0 (0%)	
Preoperative, n (%)			
Cholangitis	12 (33%)	4 (36%)	0.9832
Biliary drainage	28 (88%)	9 (82%)	0.8853
Texture of pancreas, n (%)			
Firm	5 (16%)	4 (36%)	0.1557
Soft	27 (84%)	7 (64%)	
Diameter of pancreatic duct, n (%)			
<3.0 mm	8 (25%)	6 (55%)	0.2951
≥3.0 mm	24 (84%)	5 (45%)	
Operative time (min)			
Median (range)	430 (275-650)	460 (375-600)	0.6479
Operative blood loss (g)			
Median (range)	743 (20-1350)	845 (190-2856)	0.1295
Combined vascular resection, n (%)			
Yes	4 (13%)	2 (18%)	0.6408
Maximum amylase level in drainage fluid, U/l			
POD 1-3: Median (range)	4047 (44-25791)	7752 (33.50080)	0.2732
Mean	1460	2693	
POD 4-7: Median (range)	2453 (45-85813)	587 (31-19610)	0.2838
Mean	8464	2357	
GNR detection until POD 7, n (%)			
Positive	5 (16%)	9 (82%)	0.0010

GNR: Gram-negative rods; POD: postoperative days.

factors for grades B and C, we believed that it was crucial to explore risk factors associated with progression of POPF to grade C. To the best of our knowledge, this is the first report to investigate in detail the risk factors for grade C POPF after PPPD in relation to postoperative factors and culture of drainage fluids. Focusing on patients who are likely to develop grade C POPF is pertinent, since despite the extensive range of suggested methods for reducing the incidence of this condition, it still occurs in 10-30% of patients, with a steady mortality rate of 2-10% (13, 14).

Although POPF of grade B or C increased the duration of postoperative hospitalization, in this study grade B was considered unlikely to be life-threatening. In a logistic regression univariate analysis, soft pancreas (p=0.0004), pancreatic duct diameter of <3.0 mm (p=0.0100), and new method of pancreaticojejunostomy (p=0.0135) were identified as prognostic risk factors for only grade B and C POPF considering the whole patient cohort (data not shown). However, the purpose of this study was to detect grade C POPF as early as possible as compared with grade B POPF, since we consider that grade C POPF will develop from grade B POPF. Our retrospective analysis showed that male sex and detection of gram-negative rods within the first 7 PODs were significant risk factors for developing grade C POPF. Multivariate analysis showed that only detection of gram-negative rods remained a significant risk factor.

The postoperative drain amylase value is often reported as a risk factor for grade B or C POPF after PPPD. However, even though the value of drain amylase was high, it did not relate to grade C POPF. In our study, the maximum amylase level in drainage fluid from PODs 1-3 and 4-7 was not a significant risk factor. It is difficult to determine whether drainage of the pancreatic juice is successful if a POPF has developed and to distinguish between grade B and C POPFs based on drainage fluid amylase level. This may account for our negative result.

Table II. *Univariate analysis of risk factors for grade C postoperative pancreatic fistula.*

Variable	Odds ratio	95% CI	*p*-Value
Age			
Per year	0.981	0.895-1.075	0.6799
Gender			
Female	1	1.008-77.273	0.0492
Male	8.824		
Texture of pancreas			
Firm	1	0.068-1.536	0.1557
Soft	0.324		
Diameter of pancreatic duct			
<3.0 mm	1	0.517-8.768	0.2951
≥3.0 mm	2.130		
Preoperative cholangitis			
No	1	0.879-1.023	0.7465
Yes	1.006		
Preoperative biliary drainage			
No	1	0.994-1.035	0.6487
Yes	1.051		
Operative time			
Per min	1.002	0.993-1.011	0.6479
Operative blood loss			
Per ml	1.001	1.000-1.003	0.1295
Combined vascular resection			
No	1	0.243-9.995	0.6408
Yes	1.556		
Maximum drainage amylase			
POD 1-3	1.005	0.995-1.008	0.2732
POD 4-7	1.007	0.968-1.015	0.2838
Detection of GNR until POD 7			
No	1	3.318-114.587	0.0010
Yes	19.500		

CI: Confidence intervaI; GNR: Gram-negative rods; POD: postoperative days.

Table III. *Multivariate analysis of risk factors for grade C postoperative pancreatic fistula.*

Variable	Odds ratio	95% CI	*p*-Value
Gender			
Female	1	0.611-72.265	0.1199
Male	6.649		
Detection GNR until POD 7			
No	1	2.659-104.994	0.0027
Yes	16.708		

CI: Confidence intervaI; GNR: Gram-negative rods; POD: postoperative days.

Our study revealed a significant association between detection of gram-negative bacteria in drainage fluids and development of grade C POPF. This suggests that infection with these bacteria is associated with the development and severity of POPF and that the onset of grade C POPF may be triggered by infection. Although some kind of substance caused by gram-negative rods may be linked to tissue destruction, further research *in vitro* might be necessary to elucidate its mechanism. Bile contamination and preoperative cholangitis are often reported as risk factors for infectious complications after PD (10, 11); however, the origin of bacteria isolated from the intra-abdominal fluid was unknown because no relationship was found between bacteria from the drainage fluids and those in bile during preoperative bile culture (data not shown). The reason for this might be that preoperative biliary culture is not performed in all cases and that intraoperative bile culture examination was not performed. To our knowledge, no previous studies have examined the association between bacterial infection and grade B and C POPF. Our study showed that neither preoperative biliary drainage nor cholangitis were independent risk factors for grade C POPF.

Cephem antibiotics are commonly used to prevent postoperative infection. However, to efficiently target these bacteria, it is necessary to administer broad-spectrum antibiotics such as carbapenem. Although bacterial antibiotic sensitivity tests are important, it might be necessary to administer broad-spectrum antibiotics immediately after an operation for patients at high risk for postoperative infection, such as those with preoperative cholangitis, in order to prevent bacterial contamination of the ascitic fluid. More prospective studies are needed to identify the most appropriate perioperative antibiotic regimen for patients undergoing PPPD.

The present study demonstrated that around 5% of patients undergoing PPPD will have grade C POPF and around 10% of those will consequently die. Although successful drainage of infected fluid through appropriate drain management is most important in order to avoid POPF developing to grade C, it is difficult to clearly detect when drainage has become defective. With this in mind, incorporating the two risk factors identified in this study may be useful in the clinical practice. Male patients who develop POPF and have gram-negative rods in their drainage fluids must receive close monitoring and aggressive conservative management, including imaging-guided percutaneous drainage of collection if necessary, and enhanced washing or an intra-abdominal cavity drain. Our new anastomotic method, previously reported, dramatically reduced the incidence of grade C POPF (12). However, it is not possible to be completely reduce grade B and grade C POPF, and grade C POPF remains a life-threatening complication after PPPD. Therefore, even if a new anastomosis method is performed, we believe that POPF will not disappear and the predictors of this study are therefore important. Moreover, endovascular treatment should be the initial modality used for bleeding after PPPD (15, 16). It should be noted that those patients who were at a high risk of developing grade C POPF received aggressive management in the Intensive Care Unit.

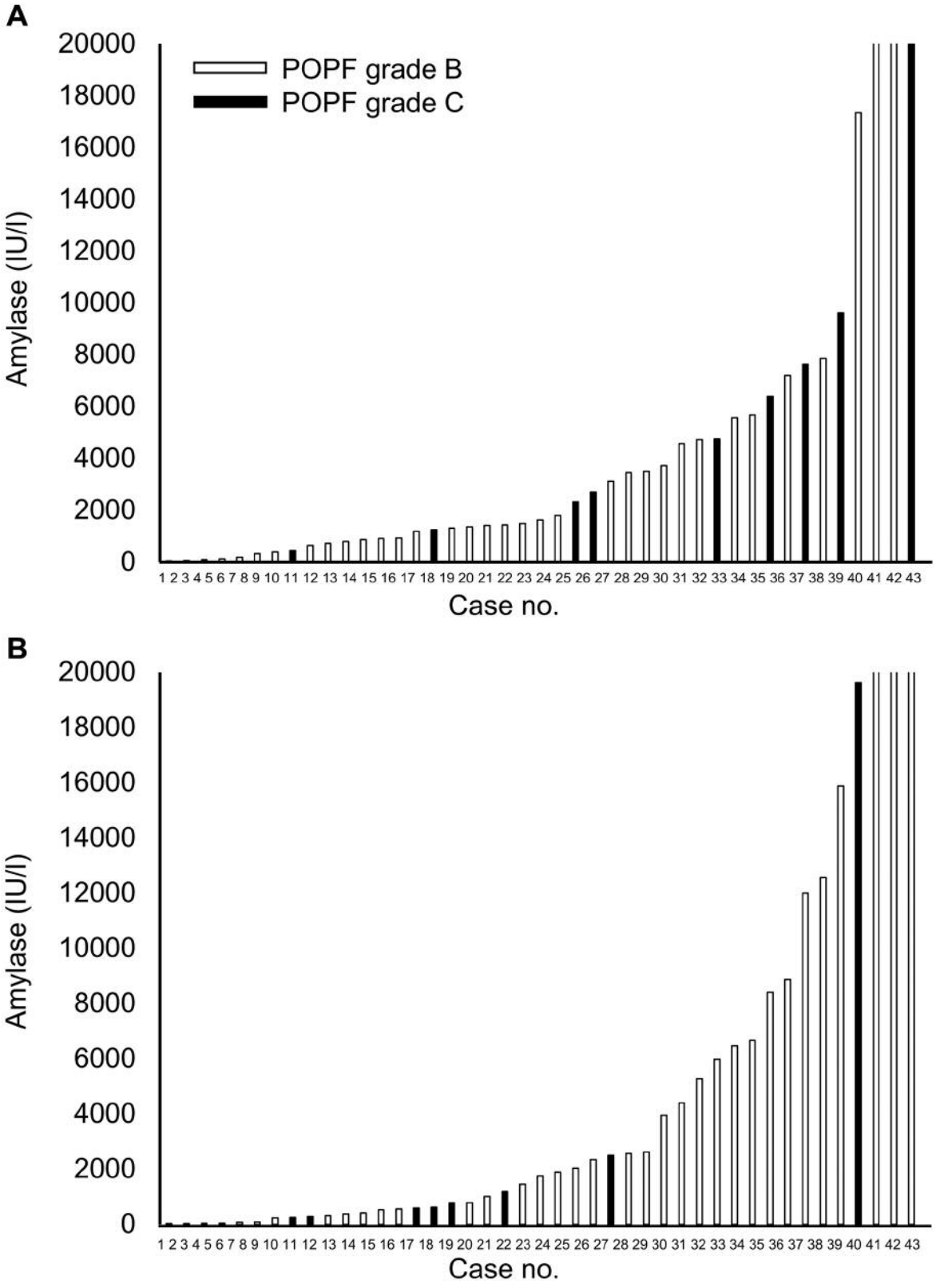

Figure 1. *Waterfall plot of postoperative amylase level in drainage fluid. The mean and median of the maximum amylase level from postoperative days (POD) 1-3 (A) and 4-7 (B) was not significantly different between patients with grade B or C postoperative pancreatic fistula.*

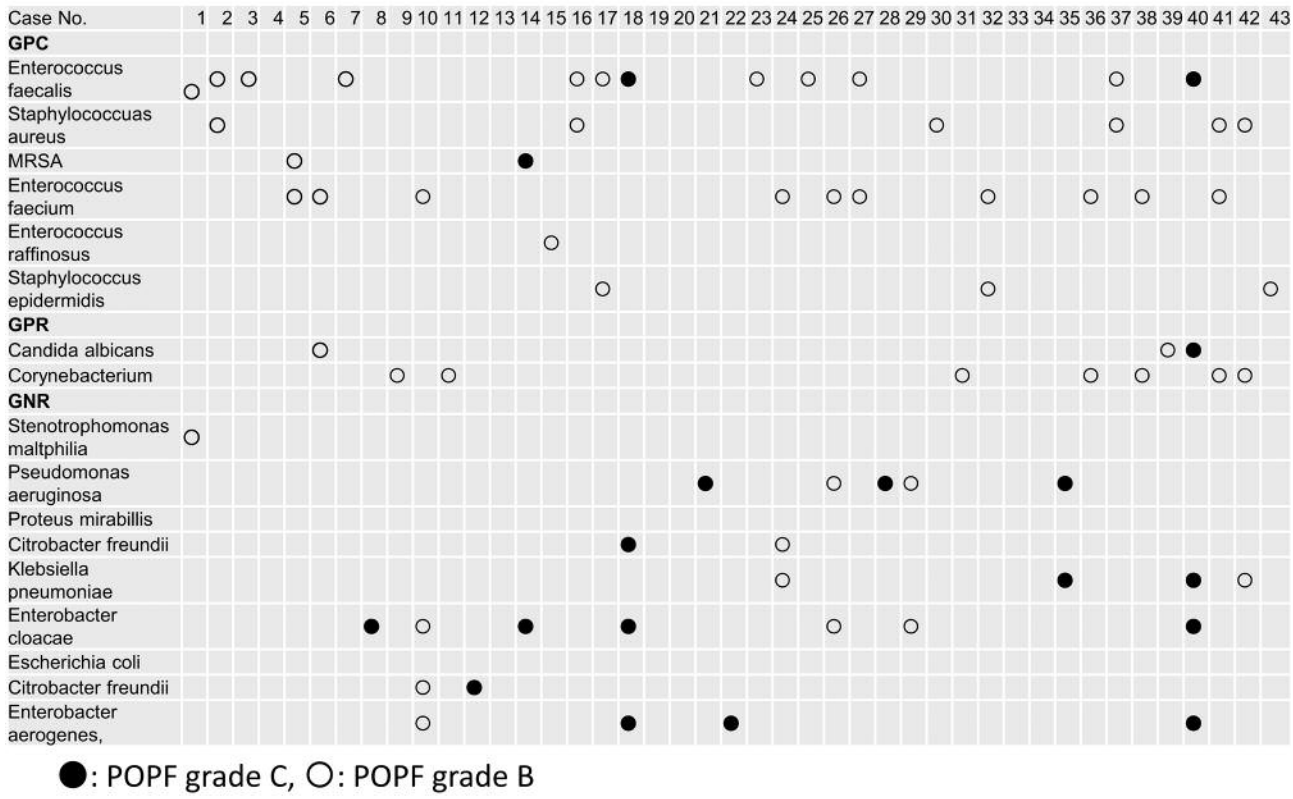

Figure 2. *Results of bacterial culture of drainage fluids within the first 7 postoperative days (POD). In patients with grade B postoperative pancreatic fistula, almost all bacteria of drainage fluid within the first 7 PODs was gram-positive. On the other hand, in patients with grade C POPF, the detection of gram-negative rods (GNR) was the only significant risk factor in multivariate analysis. GPC: Gram-positive cocci; MRSA: methicillin-resistant Staphylococcus aureus.*

Conclusion

Despite the success of conservative management, a minority of patients will inevitably develop grade C POPF after PPPD and the condition is associated with a 10% mortality rate. Therefore, accurate and early predictive criteria, namely male patients who develop POPF and have gram-negative rods in their drainage fluids within 7 POD, are important to enable appropriate management of potential grade C cases.

Conflicts of Interest

All Authors declare no conflicts of interest in regard to this study.

Authors' Contributions

Study design: N. Chiba, and S. Kawachi; Acquisition of data: N. Chiba; Operation procedures: All Authors; Analysis and interpretation: N. Chiba; Manuscript drafted by N. Chiba; Revision: N. Chiba and S. Kawachi.

Ethical Consideration

This research was approved by Tokyo Medical University Hachioji Medical Center Ethics Committee.

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