

Grade B pancreatic fistulas do not affect survival after pancreatectomy for pancreatic cancer: A multicenter observational study



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Background. Several studies have demonstrated that postoperative complications after pancreatectomy for pancreatic cancer adversely affect survival. The impact on survival of a pancreatic fistula according to the classification of the International Study Group for Pancreatic Surgery has not been fully evaluated. The aim of this multicenter, observational study was to evaluate the impact of pancreatic fistula on pancreatic cancer patients who had undergone pancreatectomy.

Methods. Between 2001 and 2012, 1,397 patients who underwent pancreatectomy for pancreatic cancer at 7 high-volume centers in Japan were reviewed retrospectively. The impact of pancreatic fistula on survival was evaluated by univariate and multivariate analysis.

Results. Pancreatic fistula occurred in 327 of 1,397 patients (23.4%) and was classified based on the International Study Group for Pancreatic Surgery as follows: grade A in 9.9%, grade B in 10.6%, and grade C in 2.9% of the patients. Median survival time in no fistula/grade A, grade B, and grade C were 23.6, 26.0, and 9.0 months, respectively. There was no significant difference in overall survival between patients with no fistula/grade A and those with grade B ($P = .403$); in contrast, overall survival in patients with grade C was worse than in patients without grade C ($P < .001$). The multivariate Cox proportional hazard analysis demonstrated that grade C pancreatic fistula was an independent prognostic factor (hazard ratio 1.59; 95% confidence interval, 1.03–2.45; $P = .035$).

Conclusion. Grade B pancreatic fistula after pancreatectomy does not adversely affect long-term survival, but a grade C pancreatic fistula has a negative impact on long-term survival of patients with pancreatic cancer. (Surgery 2016;160:293–305.)

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SEVERAL STUDIES HAVE DEMONSTRATED THAT POSTOPERATIVE COMPLICATIONS after resection for malignant disease, including esophageal, colorectal, and

metastatic hepatic cancer, are associated with poorer long-term outcome.^{1–3} In addition, several studies have reported that postoperative complications after pancreatectomy for pancreatic cancer adversely affect the survival outcome.^{4–6} Pancreatic fistula (PF), which occurs at relatively high rates ranging from 5–20%, is one of the most serious complications following pancreatectomy.^{7–10} Intra-abdominal hemorrhage or sepsis related to PF are life-threatening complications that lead to high mortality rates in short-term outcomes.^{11,12}

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Some studies have reported that PF has little to do with long-term survival in patients with pancreatic cancer.¹³⁻¹⁵ In contrast, Nagai et al¹⁶ reported that PF had a negative impact on peritoneal recurrence. It remains controversial if and how, PF adversely affects the long-term outcome for patients with pancreatic cancer because of the small number of studies. In addition, clinically relevant PF is classified into grade B and grade C based on the definitions of the International Study Group for Pancreatic Surgery (ISGPF). The difference between pancreatic fistula grade B and grade C on long-term survival has not been fully evaluated in patients with pancreatic cancer.

The aim of this study was to evaluate the impact of PF based on the ISGPF classification on long-term survival after pancreatectomy in patients with pancreatic cancer by performing a survey of high-volume centers for pancreatectomy in Japan.

METHODS

Patients. A database containing information from 7 high-volume surgical centers in Japan (the Multicenter Study Group of Pancreatobiliary Surgery) was established in 2001. From January 2001 to June 2012, 1,056 patients who underwent pancreatectomy at these centers were registered in the database. This study was approved by each center's institutional review board.

Modified Glasgow prognostic score. The modified Glasgow prognostic score (mGPS) is determined by a combination of the serum levels of C-reactive protein (CRP) and albumin.^{17,18} The GPS defined in the present study had been described in previous reports^{17,18} as follows: patients with both an increased CRP level (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were given a score of 2. Patients with only an increased CRP level (>1.0 mg/dL) were given a score of 1. Patients with CRP level ≤ 1.0 mg/L and any albumin concentration were given a score of 0.

Operative procedures, adjuvant therapy, and pathological assessment. Pancreatectomy and lymphadenectomy were performed in all patients without peritoneal dissemination and distant metastases. Patients with R2 resection were not registered in this study. Standard pancreatoduodenectomy, pylorus-resecting PD,¹⁹ or pylorus-preserving PD was selected for pancreatic head tumors. Pancreatic anastomosis, a 2-layer or single-layer fashion, including pancreaticojejunostomy or pancreaticogastrostomy, and the use of pancreatic duct stents were selected according to each surgeon's decision. Distal pancreatectomy with splenectomy was selected for pancreatic

body and tail tumors. Techniques of closure of the pancreatic remnant after distal pancreatectomy, including hand sewn closure, stapler closure, ultrasonic transection, or the use of bipolar scissors, was left to the individual surgeon's discretion. Vascular resections and reconstruction, including those of the portal vein, common hepatic artery, or celiac artery, as well as concomitant resections of neighboring organs were performed if necessary for curative resections. Peripancreatic drains were left routinely. Some patients received neoadjuvant treatment using chemotherapy or chemoradiotherapy. Postoperative adjuvant treatment using gemcitabine- or S-1-based chemotherapy was provided to patients, depending on the physicians' or patients' choice, unless contraindicated by a patient's condition.

All resected pancreatic tumors were confirmed pathologically to be invasive ductal carcinoma. Cases with invasive carcinoma derived from intra-ductal papillary mucinous neoplasms were not registered in this study. The tumor, node, metastasis (TNM) classification for pancreatic tumors by the seventh International Union Against Cancer (UICC) was applied. The tumor characteristics, including T and N status, tumor size, histologic type, operative margin status, and peritoneal cytology, were examined microscopically.²⁰

Postoperative complications. PF was defined by the guidelines of the ISGPF as an amylase level in fluid collection on postoperative day (POD) 3 that was more than 3 times the serum amylase level.²¹ PF were classified into 3 categories (grades A, B, or C) by the ISGPF clinical criteria based on the clinical course and postoperative management.²¹ A clinically relevant PF was defined as grade B and grade C. Removal of the intraoperative drain(s) under 3 weeks was defined as grade A in cases with no symptoms, no infection signs, and no treatment for pancreatic fistula. Pancreatic fistula-related symptoms, therapies, including conservative treatment, and every type of interventional drainage were defined as grade B PF.²² Pancreatic fistula-related reoperation, mortality without reoperation, or life-threatening complications, such as intra-abdominal bleeding or sepsis due to pancreatic fistula, were defined as grade C PF.²² All complications, including pancreatic fistulas, were graded from 0–V according to the Clavien-Dindo classification.²³ Severe complications in this study were defined as conditions that were grades III, IV, or V according to the Clavien-Dindo classification.²³ Thirty-day mortality was defined as death within 30 days after operation, and in-hospital mortality was defined as

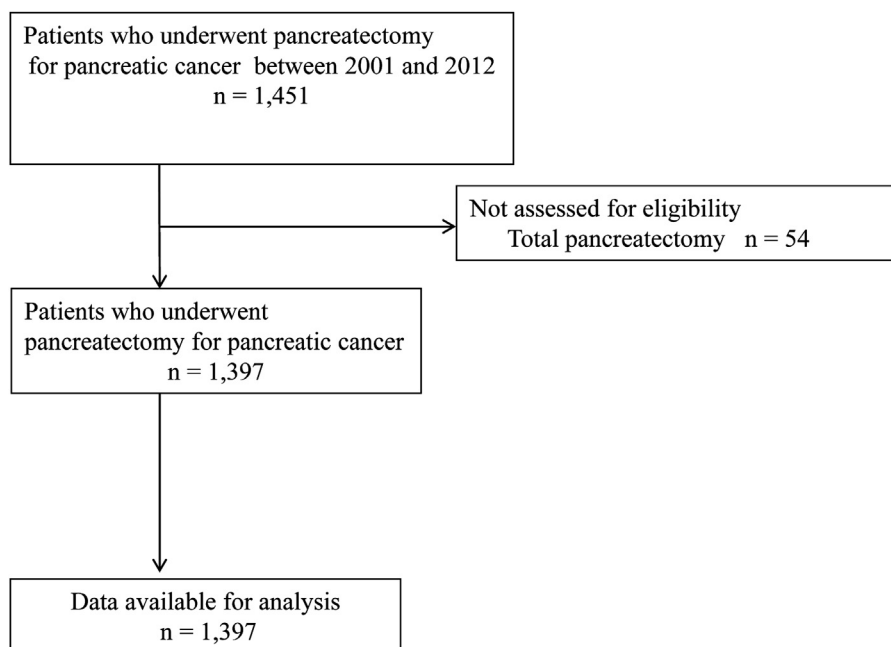


Fig 1. A flowchart for the patient enrolled in this study.

death related to the pancreatectomy during postoperative hospital stay.

Statistical analysis. Continuous variables were expressed as the mean values $\pm$ standard error. Overall survival was estimated using the Kaplan-Meier method, and the differences were tested using the log-rank test. Patients who were still alive at the time of the last follow-up were censored. The univariate and multivariate analyses were performed using a Cox proportional hazard model to evaluate prognostic predictors. The clinicopathologic and perioperative parameters were compared among no/grade A, grade B, and grade C based on ISGPF classification using χ^2 test or Fisher exact test. All statistical analyses were performed using SPSS software, version 20 (SPSS, Chicago, IL).

RESULTS

Of 1,451 patients who underwent pancreatectomy from January 2001 to June 2012, 54 underwent total pancreatectomy and were not assessed for eligibility, because PF did not occur in any patients with total pancreatectomy. The data for the remaining 1,397 patients who underwent pancreatectomy for pancreatic cancer were reviewed for our final analysis (Fig 1). There were 767 males and 630 females, with an average age of 66 ± 10 years (range, 27–91 years), of whom 966 underwent pancreatic head resection, and 431 patients

underwent pancreatic body and tail resection. In addition, 359 patients (25.7%) received neoadjuvant therapy, whereas 1,122 patients (80.3%) received postoperative adjuvant therapy with gemcitabine- or S-1–based chemotherapy.

Postoperative complications. A detailed summary of all postoperative complications after pancreatectomy is shown in Table I. The overall morbidity after pancreatectomy was 42.7%. Severe complications classified as III and IV, according to the Clavien-Dindo classification, occurred in 324 patients (23.2%). PF occurred in 23.4% of the patients (327 of the 1,397 patients). PF was classified into 3 categories based on the ISGPF guidelines as follows: grade A in 9.9%, grade B in 10.6%, and grade C in 2.9% of the enrolled patients. The 30-day mortality rate was 0.4% (6 of the initial 1,397 patients), and 90-day mortality was 1.4% (20 of the initial 1,397 patients). Reoperation and mortality related to the PF were 15 (1.1%) and 10 (0.7%), respectively. Pancreatic fistula-related reoperation and pancreatic fistula-related mortality occurred only in grade C PF.

Association between pancreatic fistula and the clinicopathologic parameters. The association between the classification of the PF and the clinicopathologic parameters of 1,397 patients are summarized in Table II. There were significant differences in PF classification according to sex and body mass index. With regard to the

Table I. Postoperative complications in patients who underwent pancreatectomy for pancreatic cancer ($n = 1,397$)

Complication	No. of patients (%)
Morbidity	596 (42.7)
Clavien-Dindo classification	
0–II	1,073 (76.8)
IIIa	244 (17.5)
IIIb	25 (1.8)
IVa	20 (1.4)
IVb	9 (0.6)
V	26 (1.9)
Severe complications*	
III–V	324 (23.2)
Pancreatic fistula†	
No fistula	1,070 (76.6)
Grade A	139 (9.9)
Grade B	148 (10.6)
Grade C	40 (2.9)
Intra-abdominal abscess	198 (14.2)
Intra-abdominal bleeding	32 (2.3)
Delayed gastric emptying	112 (8.0)
Wound infection	44 (3.1)
Reoperation related to pancreatic fistula	15 (1.1)
Mortality related to pancreatic fistula	10 (0.7)
30-day mortality	6 (0.4)
90-day mortality‡	20 (1.4)

*Severe complications were considered to be those classified as III and V according to the Clavien-Dindo classification.

†Pancreatic fistula was defined by the International Study Group on Pancreatic Fistula.

‡The 90-day mortality includes the number of deaths related to pancreatic fistula.

surgery-related parameters, the blood loss was significantly greater in those with grade C PF compared with those without grade C PF. There were no differences among PF classifications with regard to tumor-related parameters, such as lymph node status, surgical margin status, and UICC stage. In contrast, the rate of postoperative adjuvant therapy was less in patients with grade C PF than in those without (no fistula/grade A 81.5% versus grade B 84.6% versus grade C 37.5%, $P < .001$). Of the 40 patients with a grade C PF, 15 underwent reoperation related to pancreatic fistula; 15 had life-threatening complications requiring transfer to an intermediate or intensive care unit; and 10 (including 3 patients with reoperation) died due to pancreatic fistula. The prolonged poor physiologic condition or mortality in grade C PF may have decreased the rate of receiving adjuvant therapy significantly compared with grade A PF or grade B PF.

Survival according to PF. The median follow-up period was 25.3 months (range, 1.8–150.7 months). Median survival time (MST), according to the ISGPF classification, was as follows: no fistula/grade A, 23.6 months; grade B, 26.0 months; and grade C, 9.0 months (Fig 2). There was no difference in overall survival between patients with no fistula/grade A and those with grade B ($P = .403$), but overall survival in patients with grade C was much less than that in patients without grade C ($P < .001$).

In the grade C PF group, median overall survival in patients with adjuvant therapy was greater than in patients who did not receive adjuvant therapy (14.3 months versus 6.7 months, $P = .049$). In particular, median overall survival for completion of adjuvant chemotherapy, no completion of adjuvant chemotherapy, and no receipt of adjuvant chemotherapy were 15.4, 8.5, and 6.7 months, respectively. Median overall survival in patients with completion of adjuvant chemotherapy was greater than in patients who did not complete adjuvant chemotherapy ($P = .017$) or in patients who did not undergo adjuvant chemotherapy ($P = .026$). In contrast, survival did not vary in those who did not complete or receive adjuvant chemotherapy ($P = .664$). In the grade C PF group, completion of adjuvant chemotherapy appeared to improve median overall survival.

Median disease-free survival according to ISGPF classification was as follows: no fistula/grade A, 12.9 months; grade B, 14.0 months; and grade C, 7.4 months (Fig 3). There was no difference in disease-free survival between patients with no fistula/grade A and those with grade B ($P = .447$). Differences regarding disease-free survival were observed between patients with grade C and patients with no fistula/grade A ($P = .028$) and between patients with grade C and patients with grade B ($P = .017$; Fig 3). Concerning cancer-specific survival, median cancer-specific survival according to ISGPF classification was as follows: no fistula/grade A, 23.6 months; grade B, 26.0 months; and grade C, 9.0 months (Fig 4). There was no difference in cancer-specific survival between patients with no fistula/grade A and those with grade B ($P = .389$). In contrast, cancer-specific survival in patients with grade C was worse than that in patients with no fistula/grade A ($P = .005$) and that in patients with grade B ($P = .002$; Fig 4).

Prognostic factors after pancreatic resection for pancreatic cancer. Table III shows the results of the univariate and multivariate analyses of the

Table II. Association between classification of pancreatic fistula and clinicopathologic features in patients who underwent pancreatectomy for pancreatic cancer ($n = 1,397$)

Factors	Pancreatic fistula (ISGPF)*			P value
	No fistula/grade A, (%) ($n = 1,209$)	Grade B, (%) ($n = 148$)	Grade C, (%) ($n = 40$)	
Sex				
Male	635 (52.5)	97 (65.5)	35 (88)	<.001
Female	574 (47.5)	51 (34.5)	5 (13)	
Age, y				.448
Mean $\pm$ SD (range)	67 $\pm$ 10 (27–91)	66 $\pm$ 9 (45–90)	66 $\pm$ 7 (51–78)	
Body mass index, kg/m ²				
Mean $\pm$ SD (range)	21.4 $\pm$ 3.1 (13.2–35.1)	22.4 $\pm$ 3.2 (15.6–30.4)	23.3 $\pm$ 3.2 (18.2–33.2)	<.001
Diabetes mellitus				
Yes	483 (40.7)	61 (41.2)	19 (48)	.691
No	704 (59.3)	86 (58.8)	21 (52)	
Albumin, g/dL				
Mean $\pm$ SD (range)	3.8 $\pm$ 0.5 (2.0–5.5)	3.9 $\pm$ 0.5 (1.8–5.1)	3.8 $\pm$ 0.6 (2.5–4.5)	.065
CRP, mg/dL				
Mean $\pm$ SD (range)	0.7 $\pm$ 1.7 (0–18.2)	0.9 $\pm$ 2.2 (0–18.9)	1.3 $\pm$ 3.0 (0.1–12.9)	.120
mGPS†				
0	971 (83.6)	120 (81.6)	30 (79)	.075
1	98 (8.3)	16 (11.6)	1	
2	94 (8.1)	10 (6.8)	7 (18)	
Neoadjuvant therapy				
Yes	316 (26.2)	31 (20.8)	12 (30)	.303
No	893 (73.8)	117 (79.2)	28 (70)	
Location of cancer				
Head	875 (72.4)	68 (45.6)	23 (58)	<.001
Body and tail	334 (27.6)	80 (54.4)	17 (43)	
Length of operation, min				
Mean $\pm$ SD (range)	427 $\pm$ 154 (94–1,122)	401 $\pm$ 142 (141–1,015)	487 $\pm$ 180 (229–1,160)	.006
Blood loss, mL				
Mean $\pm$ SD (range)	1,213 $\pm$ 1,187 (5–26,042)	1,263 $\pm$ 1,172 (120–6,730)	1,724 $\pm$ 1,622 (110–9,163)	.044
Blood transfusion				
Yes	437 (36.7)	49 (34.0)	21 (53)	0.068
No	753 (63.3)	97 (66.0)	18 (48)	
UICC stage				
I–II	1,055 (87.3)	130 (87.9)	33 (83)	.650
III–IV	154 (12.7)	18 (12.1)	7 (18)	
UICC pT factor				
pT 1, 2	131 (10.8)	18 (12.1)	—	.707
pT 3, 4	1,078 (89.2)	130 (87.9)	37 (93)	
Lymph node status				
N0	432 (35.8)	56 (37.6)	11 (28)	.495
N1	775 (64.2)	920 (62.4)	29 (73)	
Surgical margin				
R0	909 (75.3)	105 (70.9)	32 (80)	.388
R1	299 (24.7)	42 (29.1)	8 (20)	
Reoperation related to pancreatic fistula				
Yes	0 (0)	0 (0)	15 (38)	<.001
No	0 (0)	0 (0)	25 (63)	
Mortality related to pancreatic fistula				
Yes	0 (0)	0 (0)	10 (25)	<.001
No	0 (0)	0 (0)	30 (75)	
CRP on POD 3, mg/dL				
Mean $\pm$ SD (range)	11.6 $\pm$ 5.9 (0.6–40.6)	17.4 $\pm$ 7.0 (1.4–30.7)	20.6 $\pm$ 6.6 (6.7–33.5)	<.001

(continued)

Table II. (continued)

Factors	Pancreatic fistula (ISGPF)*			P value
	No fistula/grade A, (%) (n = 1,209)	Grade B, (%) (n = 148)	Grade C, (%) (n = 40)	
Postoperative adjuvant therapy				
Yes	981 (81.5)	126 (84.6)	15 (38)	<.001
No	224 (18.5)	22 (15.4)	25 (63)	

*Pancreatic fistula was defined by the ISGPF.

†The Glasgow prognostic score was defined as follows: patients with both an elevated CRP level (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were given a score of 2. Patients with only an elevated CRP level (>1.0 mg/dL) were given a score of 1. Patients with a CRP level ≤1.0 mg/L and any albumin concentration were given a score of 0.

CRP, C-reactive protein; ISGPF, International Study Group on Pancreatic Fistula; mGPS, modified Glasgow prognostic score; SD, standard deviation; UICC, International Union Against Cancer; POD3, postoperative day 3.

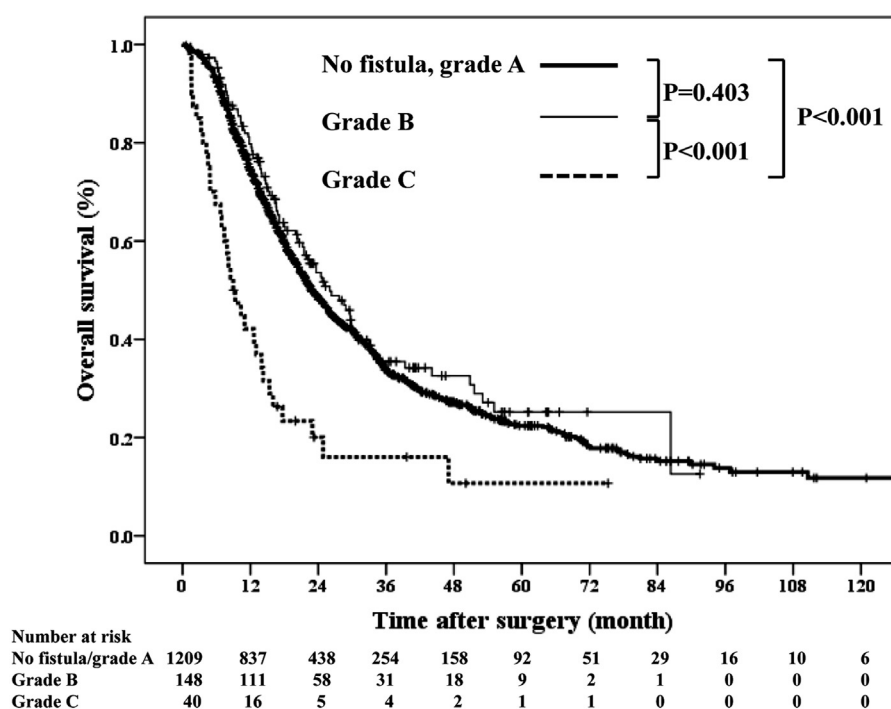


Fig 2. Overall survival based on the formation of pancreatic fistula. Median survival time was 23.6 months in the no fistula/grade A fistula group (solid thick line), 26.0 months in the grade B fistula group (solid thin line), and 9.0 months in the grade C fistula group (dotted line).

prognostic factors for overall survival in patients who underwent pancreatectomy for pancreatic cancer.

In the univariate analysis, age ≥70 years, mGPS of 2, location of the cancer, operative time ≥420 minutes, blood loss ≥1,000 mL, blood transfusion, UICC stage III and IV classification, pathologic portal or superior mesenteric vein invasion, lymph node status, surgical margin, the use of postoperative adjuvant therapy, postoperative complication, and pancreatic fistula were all identified as prognostic factors. With regard to adjuvant therapy, patients who received

postoperative chemotherapy exhibited an improved median survival compared with those without (25.1 months versus 12.4 months, $P < .0001$). In the univariate analysis of the postoperative complications, the development of severe postoperative complications (Clavien-Dindo III and IV) adversely affected the survival after pancreatectomy for pancreatic cancer (19.8 months versus 24.8 months, $P = .002$).

In the multivariate Cox proportional hazard analysis of the prognostic factors after pancreatectomy for pancreatic cancer, grade C PF was detected as an independent prognostic factor

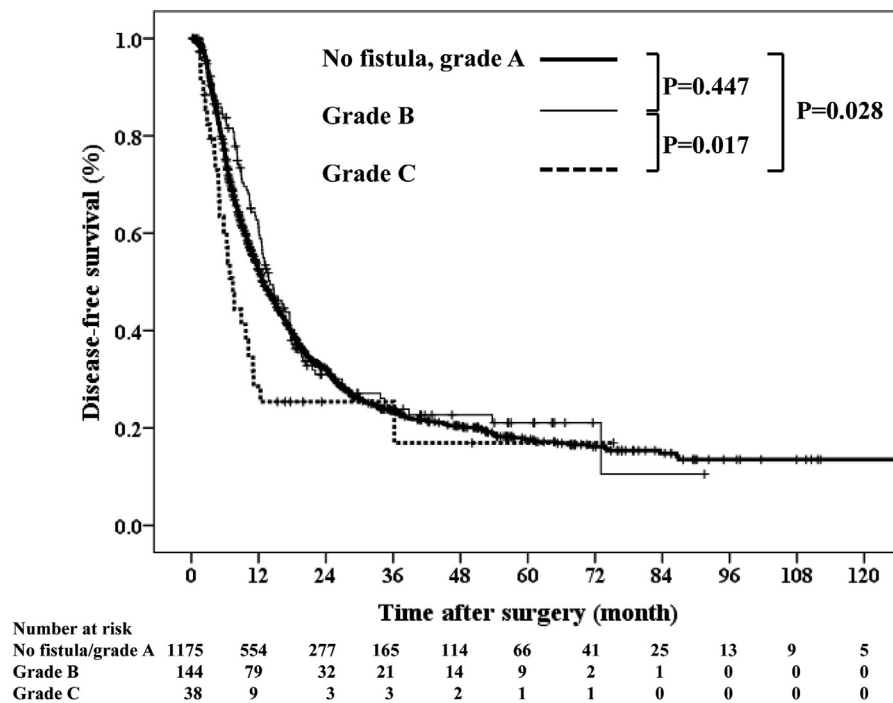


Fig 3. According to the International Study Group for Pancreatic Surgery classification, disease-free survival was as follows: no fistula/grade A, 12.9 months; grade B, 14.0 months; and grade C, 7.4 months. There was no significant difference in disease-free survival between patients with no fistula/grade A and those with grade B ($P = .447$). Significant difference regarding disease-free survival was observed between patients with grade C and patients with no fistula/grade A ($P = .028$) or between patients with grade C and patients with grade B ($P = .017$).

among postoperative complications (hazard ratio [HR] 1.59; 95% confidence interval [CI], 1.03–2.45; $P = .035$). With regard to demographic and tumor characteristics, the multivariate analysis also identified age ≥ 70 years (HR 1.22; 95% CI, 1.06–1.41; $P = .006$), mGPS of 2 (HR 1.40; 95% CI, 1.10–1.78; $P = .006$), blood transfusion (HR 1.52; 95% CI, 1.29–1.78; $P < .001$), UICC III or IV (HR 1.24; 95% CI, 1.01–1.51; $P = .037$), pathologic portal vein invasion (HR 1.44; 95% CI, 1.24–1.67; $P < .001$), lymph node status (HR 1.75; 95% CI, 1.49–2.06; $P < .001$), positive surgical margins (HR 1.37; 95% CI, 1.17–1.61; $P < .001$), and the use of adjuvant therapy (no therapy: HR 1.58; 95% CI, 1.32–1.88; $P < .001$) as predictors of poor prognosis.

We used the multivariate Cox proportional hazard analysis to evaluate how a grade C PF affected the disease-free and cancer-specific survival. Grade C PF was not associated with poor disease-free survival (HR 1.41; 95% CI, 0.94–2.13; $P = .100$; Table IV), but cancer-specific survival after pancreatectomy for pancreatic cancer in patients with a grade C PF was an independent prognostic factor (HR 1.68; 95% CI, 1.07–2.63; $P = .023$; Table V).

DISCUSSION

This multicenter study concluded that patients with grade B PF had favorable long-term survival similar to those with no fistula/grade A. In contrast, our study also showed that grade C PF had a negative impact on long-term survival in patients with pancreatic cancer. Several studies reported that PF did not adversely affect long-term survival in patients with pancreatic cancer. In those studies, both patients with grade B PF and grade C PF were analyzed regarding survival with no distinction between the two. Based on ISGPF, the clinical impacts of grade B PF and grade C PF are completely different. Therefore, grade B PF should be distinguished from grade C PF to achieve more reliable impact of PF on survival.

In contrast to the results of survival in patients with grade B PF, several previous studies demonstrated that postoperative complications adversely affect the survival outcome.^{14–16} The rate of receiving adjuvant therapy (84.6%) in patients with grade B PF was similar to that (81.5%) in patients with no fistula/grade A. A previous, randomized controlled trial demonstrated that adjuvant chemotherapy had a positive impact on the survival in patients with resectable pancreatic

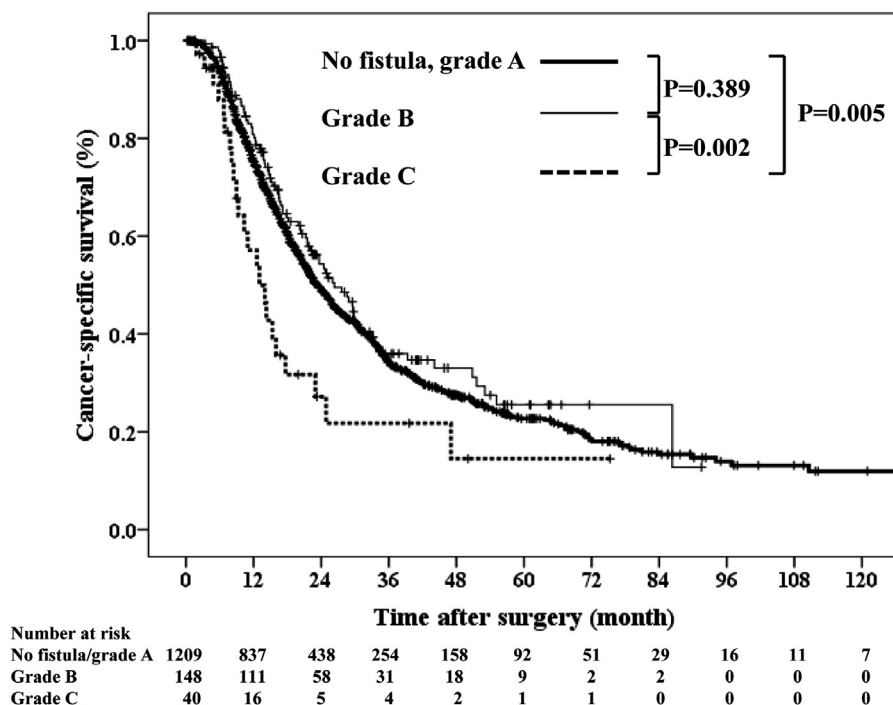


Fig 4. Cancer-specific survival and median cancer-specific survival times according to the International Study Group for Pancreatic Surgery classification were as follows: no fistula/grade A, 23.6 months; grade B, 26.0 months; and grade C, 9.0 months. There was no significant difference in cancer-specific survival between patients with no fistula/grade A and those with grade B ($P = .389$). However, cancer-specific survival in patients with grade C was significantly worse than that in patients with no fistula/grade A ($P = .005$) or than that in patients with grade B ($P = .002$).

cancer.²⁴ The multivariate analysis of this study also confirmed that adjuvant therapy provided a more favorable survival. In contrast, the rate of receiving adjuvant therapy in patients with grade C PF (37.5%) was less than that in patients without grade C PF ($P < .001$). Traverso²⁵ proposed that avoiding a delay in postoperative recovery after pancreatectomy is the most important factor in achieving effective adjuvant therapy. Early initiation of adjuvant chemotherapy after operation appears to improve overall survival in patients with pancreatic cancer. Generally, there are comparatively milder cases that were resolved successfully by conservative treatment in grade B PF. Most patients (84.6%) with grade B PF in the present study were able to receive adjuvant therapy after recovering from a poor physiologic condition relatively quickly. Consequently, grade B PF did not have a negative impact on long-term survival. In contrast, the poor physiologic condition in patients with grade C PF decreased the rate of adjuvant therapy. Consequently, the patients with grade C PF had worse survival compared with patients with no fistula/grade A and grade B PF.

Hackert et al²² demonstrated that there was a strict difference between patients' interventional

drainage related to the PF or reoperation regarding outcomes. In this study, the mortality rate of patients with reoperation was greater than that of patients with other management in clinically relevant PF (20% vs 4.6%, $P = .046$). In addition, overall survival in patients with reoperation was worse than that in patients with other management in a clinically relevant PF (9.0 months versus 23.0 months, $P = .004$). Reoperation related to a PF was categorized as grade C PF and adversely affected long-term outcomes. There is a possibility that the adverse effect of grade C PF on long-term survival simply reflects the high postoperative mortality due to a life-threatening complication; however, to prove this hypothesis, both disease-free survival and cancer-specific survival were analyzed to evaluate whether grade C PF was associated oncologically with survival. As a result, grade C PF adversely affected not only overall survival, but also cancer-specific survival compared with those without a grade C PF, although the difference in disease-free survival between patients with and without grade C PF was not remarkable. The extremely short disease-free survival time due to an aggressive malignancy in pancreatic cancer might diminish the negative impact of grade C PF in disease-free survival.

Table III. Results of the univariate and multivariate analyses of the prognostic factors for overall survival in patients who underwent pancreatectomy for pancreatic cancer

Factors	Univariate analysis			Multivariate analysis		
	No. of patients	Median survival time (mo)	P value	Hazard ratio	95% CI	P value
Sex						
Male	767	21.9	.099			
Female	630	25.1				
Age, y						
<70	783	24.5	.038	Referent		
≥70	614	21.1		1.22	1.06–1.41	.006
Body mass index, kg/m ²						
<25	1,156	22.9	.172			
≥25	189	26.5				
Diabetes mellitus						
Yes	563	21.9	.270			
No	811	24.7				
mGPS*						
0	1,121	25.1	<.001	Referent		
1	115	25.1		.97	0.75–1.24	.787
2	111	17.7		1.40	1.10–1.78	.006
Neoadjuvant therapy						
Yes	359	25.6	.207			
No	1,038	22.3				
Blood loss, mL						
<1,000	702	30.6	<.001	Referent		
≥1,000	669	18.5		1.14	0.97–1.35	.113
Blood transfusion						
Yes	507	16.8	<.001	1.52	1.29–1.78	<.001
No	868	30.8		Referent		
UICC stage						
I–II	1,218	24.7	<.001	Referent		
III–IV	179	17.2		1.24	1.01–1.51	.037
Pathologic PV/SMV invasion						
Positive	450	17.0	<.001	1.44	1.24–1.67	<.001
Negative	939	27.6		Referent		
Lymph node status						
N0	499	36.4	<.001	Referent		
N1	896	19.4		1.75	1.49–2.06	<.001
Surgical margins						
R0	1,046	26.3	<.001	Referent		
R1	349	17.2		1.37	1.17–1.61	<.001
Postoperative adjuvant therapy						
Yes	1,122	25.1	<.001	Referent		
No	271	12.4		1.58	1.32–1.88	<.001
Postoperative complication(s)†						
Grade 0–II	1,073	24.8	.002	Referent		
Grade III–V	324	19.8		1.33	1.07–1.66	.011
Pancreatic fistula‡						
No fistula, grade A	1,209	23.6	<.001	Referent		
Grade B	148	26.0		.76	0.56–1.03	.079
Grade C	40	9.0		1.59	1.03–2.45	.035

*The mGPS was defined as follows: patients with both an elevated C-reactive protein level (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were given a score of 2. Patients with only an elevated C-reactive protein level (>1.0 mg/dL) were given a score of 1. Patients with a C-reactive protein level ≤1.0 mg/L and any albumin concentration were given a score of 0.

†Postoperative complications were classified according to the Clavien-Dindo classification.

‡Pancreatic fistula was defined by the International Study Group on Pancreatic Fistula.

Location of cancer and duration of the operation had no prognostic value.

CI, Confidence interval; mGPS, modified Glasgow prognostic score; PV/SMV, portal or superior mesenteric vein; UICC, International Union Against Cancer.

Table IV. Results of the univariate and multivariate analyses of the prognostic factors for disease-free survival in patients who underwent pancreatectomy for pancreatic cancer

Factors	Univariate analysis			Multivariate analysis		
	No. of patients	Median survival time (mo)	P value	Hazard ratio	95% CI	P value
Body mass index, kg/m ²						
<25	1,127	12.7	.062			
≥25	184	15.5				
mGPS*						
0	1,091	13.8	.062			
1	113	12.1				
2	107	10.2				
Neoadjuvant therapy						
Yes	356	15.1	.167			
No	1,001	12.6				
Blood loss, mL						
<1,000	681	17.0	<.001	Referent		
≥1,000	653	10.1		1.10	0.94–1.28	.253
Blood transfusion						
Yes	489	9.7	<.001	1.35	1.16–1.58	<.001
No	849	16.5		Referent		
UICC stage						
I–II	1,183	13.9	<.001	Referent		
III–IV	175	8.5		1.31	1.09–1.57	.004
Pathologic PV/SMV invasion						
Positive	426	9.7	<.001	1.47	1.28–1.68	<.001
Negative	924	15.6		Referent		
Lymph node status						
N0	489	24.4	<.001	Referent		
N1	867	10.2		2.03	1.74–2.35	<.001
Surgical margins						
R0	1,015	15.4	<.001	Referent		
R1	341	9.2		1.36	1.18–1.58	<.001
Postoperative adjuvant therapy						
Yes	1,098	13.8	.004	Referent		
No	257	8.6		1.33	1.12–1.59	.001
Postoperative complication(s)†						
Grade 0–II	1,043	13.3	.689			
Grade III–V	315	112.3				
Pancreatic fistula grade C‡						
Yes	39	6.9	.012	1.41	0.94–2.13	.100
No	1,319	13.1		Referent		

*The mGPS was defined as follows: patients with both an elevated C-reactive protein level (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were given a score of 2. Patients with only an elevated C-reactive protein level (>1.0 mg/dL) were given a score of 1. Patients with a C-reactive protein level ≤1.0 mg/L and any albumin concentration were given a score of 0.

†Postoperative complications were classified according to the Clavien-Dindo classification.

‡Pancreatic fistula was defined by the International Study Group on Pancreatic Fistula.

Sex, age, presence of diabetes, location of cancer, and duration of the operation had no prognostic value.

CI, Confidence interval; mGPS, modified Glasgow prognostic score; PV/SMV, portal or superior mesenteric vein; UICC, International Union Against Cancer.

The mechanism underlying how grade C PF causes worse survival in patients with pancreatic cancer has not been investigated fully. Several studies have reported that anastomotic leakage in patients with colorectal cancer is significantly associated with worse survival.^{1,26,27} Such leakage results in the release of proinflammatory

lymphocytes, cytokines, and chemokines secondary to a systemic inflammatory response syndrome (SIRS), which may cause immunosuppression and consequently may enhance the spread and metastasis of residual tumor cells.^{28,29} CRP has been reported to be one of the postoperative biochemical markers of SIRS in pancreatic cancer.³⁰ In

Table V. Results of the univariate and multivariate analyses of the prognostic factors for cancer-specific survival in patients who underwent pancreatectomy for pancreatic cancer

Factors	Univariate analysis			Multivariate analysis		
	No. of patients	Median survival time (mo)	P value	Hazard ratio	95% CI	P value
Sex						
Male	767	22.6	.165			
Female	630	25.8				
Age, y						
<70	783	25.0	.043	Referent		
≥70	614	21.6		1.24	1.07–1.43	.004
Body mass index, kg/m ²						
<25	1,156	23.7	.070			
≥25	189	28.6				
Diabetes mellitus						
Yes	563	22.9	.533			
No	811	24.8				
mGPS*						
0	1,121	25.8	<.001	Referent		
1	115	25.6		1.09	0.81–1.04	.162
2	111	18.0		1.10	0.75–1.08	.243
Neoadjuvant therapy						
Yes	359	26.2	.146			
No	1,038	22.7				
Blood loss, mL						
<1,000	702	32.8	<.001	Referent		
≥1,000	669	18.5		1.17	0.99–1.38	.066
Blood transfusion						
Yes	507	17.8	<.001	1.52	1.29–1.80	<.001
No	868	32.3		Referent		
UICC stage						
I–II	1,218	25.1	<.001	Referent		
III–IV	179	17.7		1.26	1.03–1.54	.028
Pathological PV/SMV invasion						
Positive	450	17.7	<.001	1.24	1.07–1.68	<.001
Negative	939	28.4		Referent		
Lymph node status						
N0	499	37.4	<.001	Referent		
N1	896	2.1		1.76	1.49–2.07	<.001
Surgical margins						
R0	1,046	27.6	<.001	Referent		
R1	349	17.8		1.37	1.17–1.60	<.001
Postoperative adjuvant therapy						
Yes	1,122	25.1	<.001	Referent		
No	271	16.0		1.41	1.18–1.70	<.001
Postoperative complication(s) [†]						
Grade 0–II	1,073	24.8	.145			
Grade III–V	324	22.1				
Pancreatic fistula grade C [‡]						
Yes	40	13.0	.002	1.68	1.07–2.63	.023
No	1,357	24.2		Referent		

*The mGPS was defined as follows: patients with both an elevated C-reactive protein level (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were given a score of 2. Patients with only an elevated C-reactive protein level (>1.0 mg/dL) were given a score of 1. Patients with a C-reactive protein level ≤1.0 mg/L and any albumin concentration were given a score of 0.

[†]Postoperative complications were classified according to the Clavien-Dindo classification.

[‡]Pancreatic fistula was defined by the International Study Group on Pancreatic Fistula.

Location of cancer and duration of the operation had no prognostic value.

CI, Confidence interval; mGPS, modified Glasgow prognostic score; PV/SMV, portal or superior mesenteric vein; UICC, International Union Against Cancer.

addition, some studies have reported that SIRS is associated with poor survival in patients undergoing potentially curative resection for pancreatic cancer.^{31,32} In the present study, CRP on POD 3 in grade C PF was greater than in no fistula/grade A and grade B PF (grade C PF versus no fistula/grade A PF; $P < .001$, grade C PF versus grade B PF; $P = .045$, respectively). It is possible that grade C PF might increase the magnitude and duration of SIRS, which is associated with poor survival in patients with pancreatic cancer.

One limitation of our study is missing data because of the retrospective nature of the data collection, but there were few missing data points in the database that was established from 7 high-volume surgical centers for pancreatic surgery. Another addition was that only CRP levels before operation and on POD 3 were available to evaluate SIRS in the present database. Another limitation regarding the association between grade C PF and long-term survival was that the results were based on a relatively small numbers of patients with grade C PF. A larger prospective cohort study will be required to confirm the impact of grade C PF on survival.

In conclusion, grade B PF after pancreatectomy did not adversely affect long-term survival in patients with pancreatic cancer; in contrast, the development of grade C PF has a negative impact on long-term survival of patients with pancreatic cancer. Improved perioperative management or operative procedure to prevent grade C PF may lead to more favorable survival in patients with pancreatic cancer.

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