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Predictors of postoperative pancreatic fistula after splenectomy with or without distal pancreatectomy performed as a component of cytoreductive surgery for advanced ovarian cancer

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ABSTRACT

Objective: Splenectomy with or without distal pancreatectomy is occasionally performed during cytoreductive surgery for advanced ovarian cancer. We investigated pre-, intra-, postoperative risk factors and predictors of clinically relevant postoperative pancreatic fistula (CR-POPF) in patients who underwent cytoreductive surgery for advanced ovarian cancer.
Methods: We investigated 165 consecutive patients with ovarian, fallopian tube, and peritoneal carcinoma categorized as stage III/IV disease, who underwent splenectomy with or without distal pancreatectomy as a component of cytoreductive surgery performed as initial treatment at Chiba University Hospital. Patient characteristics, clinical factors, and surgical outcomes were compared between those with and without CR-POPF.
Results: CR-POPF occurred in 20 patients (12%). There were no significant intergroup differences in the characteristics between patients with CR-POPF and patients without CR-POPF except for operative time, intraoperative blood loss, amylase (AMY) levels in drain fluid on postoperative day (POD)1 and POD3, and pancreatic stump thickness. Multivariate analysis showed that the POD3 drain fluid AMY level was the only significant risk factor and predictor of CR-POPF in patients who underwent cytoreductive surgery for advanced ovarian cancer. The receiver operating characteristic curve of the POD3 drain fluid AMY level, which predicted development of CR-POPF showed an area under the curve of 0.77, and the optimal cut-off value of AMY was 808 U/L. A pancreatic fistula did not occur in patients with POD3 drain fluid AMY levels <130 U/L.
Conclusion: The POD3 drain fluid AMY level can be early diagnostic predictor CR-POPF after splenectomy with or without distal pancreatectomy for advanced ovarian cancer.

Keywords: Ovarian Cancer; Cytoreductive Surgery; Splenectomy; Pancreatectomy; Pancreatic Fistula

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Author Contributions
Conceptualization: N.K.; Data curation: T.S.; Formal analysis: N.K.; Investigation: N.K., T.S., M.A., O.S.; Methodology: T.S.; Project administration: T.S., S.M.; Supervision: T.S., S.M.; Visualization: N.K.; Writing - original draft: N.K.; Writing - review & editing: T.S., M.A., O.S., S.M.

Synopsis

Pancreatic fistula is a common complication of Splenectomy with distal pancreatectomy. The postoperative day 3 drain fluid amylase (AMY) can predict clinically relevant postoperative pancreatic fistula. The receiver operating characteristic curve of the postoperative day (POD) 3 drain fluid AMY level showed an area under the curve of 0.77. The optimal cut-off value of the POD3 drain fluid AMY level was 808 U/L.

INTRODUCTION

Ovarian cancers often metastasize to the spleen and to the greater omentum near the splenic hilum. Splenectomy concomitant with distal pancreatectomy is occasionally required during cytoreductive surgery because the pancreatic tail is in close proximity to the splenic hilum. In fact, the pancreatic tail is often inseparable from the splenic hilum during interval debulking surgery owing to fibrosis observed after neoadjuvant chemotherapy.

Pancreatic fistula is a common complication of distal pancreatectomy with concurrent splenectomy. The incidence of pancreatic fistula after distal pancreatectomy performed for pancreatic tumors is 3%–49% [1-8]. Most patients with biochemical pancreatic juice leakage are asymptomatic. Usually, clinically relevant postoperative pancreatic fistula (CR-POPF) is treated using a conservative approach that includes percutaneous drainage and/or antibiotic administration. However, CR-POPF may occasionally lead to intra-abdominal abscess formation and life-threatening arterial bleeding. Reportedly, pancreatic fistula after distal pancreatectomy in patients with pancreatic cancer is associated with pancreatic parenchymal thickness [8,9], intraoperative blood loss, operative time [10,11], concomitant splenectomy [10], no elective ligation of the main pancreatic duct, pancreatic body transection [1], visceral fat area, and open passive drainage [11]. However, the risk factors and predictors of CR-POPF after cytoreductive surgery for ovarian cancer are unknown, and these may be different from those of pancreatic cancer because usually, the pancreas resected during ovarian cancer surgery is normal and is invariably smaller than that resected during pancreatic cancer surgery. Moreover, in addition to splenectomy with distal pancreatectomy, cytoreductive surgery includes multi-organ resections, which result in significant blood loss and a long operative time. Therefore, it is important to determine the specific risk factors and predictors for optimal management of CR-POPF in patients who undergo ovarian cancer surgery.

The postoperative drain fluid amylase (AMY) level is a known predictor of pancreatic fistula in patients who undergo distal pancreatectomy for pancreatic cancer [12-14]. Specifically, the AMY levels in the drain fluid analyzed on postoperative day (POD) 1 or POD3 can predict CR-POPF in cases of pancreatic cancer. Prediction of pancreatic fistula is useful to determine the appropriate timing for drain removal. However, whether the postoperative drain fluid AMY levels can predict the development of a pancreatic fistula in patients who undergo ovarian cancer surgery remains unclear. Following were the aims of this study: 1) To investigate the risk factors and predictors of CR-POPF and, 2) to confirm whether the drain fluid AMY level can predict the development of CR-POPF in patients who undergo ovarian cancer surgery.

MATERIALS AND METHODS

1. Patients

This study was approved by the Institutional Review Board of Chiba University Graduate School of Medicine (Number 4139). Of 405 consecutive patients with ovarian, fallopian tube, and peritoneal carcinoma categorized as the International Federation of Gynecology and Obstetrics classification (FIGO) 2014 stage III/IV disease who received initial treatment at Chiba University Hospital between April 2008 and March 2021, we investigated 165 consecutive patients who underwent splenectomy with or without distal pancreatectomy as a component of cytoreductive surgery for initial treatment. Patient data were recorded from a prospectively maintained database. Patient characteristics, clinical factors, and surgical outcomes were obtained from the database and patients' medical records.

2. Splenectomy with or without distal pancreatectomy and intra-abdominal drain placement

After detachment of the perisplenic ligaments and those around the pancreatic tail, the TachoSil® tissue sealing sheet was wrapped around the pancreatic tail and the splenic vessels [15]. The pancreatic tail and surrounding tissue were gradually compressed for 5 min and transected over 5 min using a linear stapler (Endo GIA® or Signia®; Covidien, Tokyo, Japan) to prevent the pancreatic parenchyma from tearing [16]. We did not divide the splenic hilum and pancreatic tail to prevent pancreatic injury (specifically to prevent injury during interval debulking surgery after neoadjuvant chemotherapy) and to ensure complete tumor resection with presumed omental tail involvement between the splenic hilum and the pancreatic tail. In patients in whom the splenic hilum tumor was visible, the resection line of the pancreatic tail was immediately proximal to the splenic hilum tumor; however, in patients in whom the tumor was not visible during interval debulking surgery, we used a linear stapler to excise the pancreatic tail in a straight line that connected the upper and lower splenic poles. The length of the resected pancreatic tail ranged from 0.5 cm to 2 cm in most patients who underwent this procedure. The pancreatic tail was not included in the resection line in some patients.

Only the first two patients who were treated during the study period underwent pancreatic tail transection using a cold knife, pancreatic duct ligation, and hand-sewn closure.

A polyglycolic acid sheet (Neoveil; Gunze Co., Tokyo, Japan) was wrapped around the stump for stump coverage and closure, and fibrin glue (Beriplast; Behring, Marburg, Germany) was instilled along the sheet.

A closed-suction drain was inserted into the left subdiaphragmatic space, and a closed-suction drain was placed posterior to the transection stump of the distal pancreas in patients who underwent the operation after October 2016.

3. Management of drains and measurement of drain fluid AMY

AMY levels in the drain fluid were routinely measured on POD1 and POD3 and every 2 or 3 days thereafter until drain removal. In patients who had two drains around the pancreatic stump, the drain fluid which showed a higher AMY level was used for analysis. The drain was removed on POD6–8 after the drain fluid AMY level measured within three times the upper limit of institutional normal serum AMY level (<396 U/L) and the volume of drained fluid tended to decrease in principle. Even in patients with drain AMY levels higher than three times the upper limit of institutional normal serum AMY level at on POD6–8, the drain was

removed when fistulography (contrast agent injection into the drain under radiographic guidance) revealed only a simple tract; we did not observe spread of the contrast agent in the tissue surrounding the drain tract [17]. Among patients in whom a simple tract was not observed on POD6–8, the timing of drain removal was based on the following criteria: 1) drain AMY level measured within three times the upper limit of the institutional normal serum AMY level, or 2) fistulography performed every once or twice/week showed a mature tract without spread of the contrast agent and, or 3) drain fluid was serous in nature without signs of infection.

4. Definition of postoperative pancreatic fistula

Pancreatic fistula was defined based on the International Study Group on Pancreatic Surgery (ISGPS) definition updated in 2016 [18]. POPF grade B is defined as drain fluid with an AMY levels >3 times the upper limit of institutional normal serum AMY level accompanied by clinical symptoms such as persistent drainage >3 weeks that necessitate clinical interventions, including modifications in the management strategy, percutaneous or endoscopic drainage, and angiography for bleeding, or antibiotic administration for signs of infection without organ failure. POPF grade C refers to organ failure or clinical instability that necessitates reoperation. Grades B and C are categorized as CR-POPF.

Biochemical leakage (originally categorized as grade A based on the former ISGPS definition) is not considered to be CR-POPF according to the revised ISGPS definition because biochemical leakage is clinically insignificant and is not considered a true pancreatic fistula or an actual complication [18].

5. Management of CR-POPF

Closed suction drainage was continued as long as the drainage was appropriate. Fistulography was performed on POD6–8 and once or twice a week thereafter. The drain was repositioned or a new drain was inserted under radiographic guidance in patients in whom the drain placed during cytoreductive surgery was not appropriately positioned. The drain was replaced with a new drainage tube to prevent retrograde infection in patients who required long-term drainage. Antibiotics were administered to patients with signs of infection. Total parental nutrition and somatostatin analogs were administered to only some patients during the early study period; most patients continued to receive oral feeds during the study period. The drain was removed when clinical symptoms showed improvement and infections were controlled only after the drain fluid AMY level was within three times the upper limit of institutional normal serum AMY level and the volume of fluid tended to decrease, or in patients in whom fistulography revealed a simple tract without spread of the contrast agent in the tissue surrounding the drain tract.

6. Area under the receiver operating characteristic (ROC) curve and optimal cut-off value of AMY for prediction of CR-POPF

The POD1 and POD3 drain fluid AMY levels were measured as predictors of CR-POPF. We calculated the area under the ROCs curve and the optimal cut-off values of AMY. The sensitivity and specificity of cut-off values were calculated. The optimal cut-off value was determined using the Youden index as follows: sensitivity+specificity-1. The Youden index ranged from 0 to 1 for each cut-off value. An optimal cut-off value was defined as the highest Youden index.

7. Statistical analysis

Using the chi-square test for categorical variables and the Wilcoxon's rank sum test for continuous variables, we analyzed the following clinical variables to determine their correlation with the incidence of CR-POPF: preoperative factors (age, primary site of cancer, patients' performance status, cancer stage, histopathological characteristics, serum albumin level before cytoreductive surgery), intraoperative factors (operative time, intraoperative blood loss, timing of cytoreductive surgery, the peritoneal cancer index [19,20], surgical complex score [21], residual disease, pancreatic involvement based on histopathological examination of the resected specimen), and postoperative factors (drain fluid AMY levels on POD1 and POD3, distance of the pancreatic stump and splenic hilum, and pancreatic stump thickness). Variables that were significant on univariate analysis were subjected to multiple logistic regression analysis. All statistical analyses were performed using the JMP software, version 11 (SAS, Cary, NC, USA), and a p-value <0.05 was considered statistically significant. Odds ratios for multivariable analysis were reported with corresponding 95% confidence intervals. Progression-free and overall survival were analyzed using Kaplan–Meier curves for patients who did and did not develop CR-POPF.

RESULTS

1. Patients characteristics

CR-POPF grade B occurred in 18 (10.9%) and CR-POPF grade C in 2 (1.2%) patients. Among 74 patients with POD3 drain AMY levels >3 times the upper limit of institutional normal serum AMY level on POD3, 16 patients developed CR-POPF and remaining 58 patients did not develop CR-POPF.

Table 1 summarizes the characteristics of patients with and without CR-POPF. We observed no significant intergroup differences except for the operative time, intraoperative blood loss, POD1 and POD3 drain fluid AMY levels, and pancreatic stump thickness.

The median POD1 and POD3 drain fluid AMY levels were 1685 U/L and 381 U/L, respectively, and these levels were significantly higher in patients with CR-POPF than in patients without CR-POPF (p=0.001 and p<0.001, respectively).

Pancreatic tail involvement was not observed on histopathological examination in 23 of 155 patients who underwent splenectomy with distal pancreatectomy. Splenectomy without distal pancreatectomy was performed in 10 patients in whom the pancreatic tail was sufficiently far and could be safely separated from the splenic hilum. The incidence of CR-POPF did not significantly differ between patients with and without pancreatic involvement based on histopathological examination of resected specimens (p=0.371).

The median period between surgery and removing drains in all patients was 10 days.

2. Histopathological findings in the resected specimen of pancreatic tail specimens

Histopathological evaluation showed carcinoma adjacent to the pancreatic capsule in one patient. No patient had carcinoma of the pancreatic parenchyma. However, we detected carcinoma in the connective tissue between the pancreatic tail and splenic hilum in 72 of the 132 patients (55%) in whom histopathological evaluation of the resected specimens showed

Table 1. Patients' characteristics

| Characteristics	All (n=165)	No CR-POPF (n=145)	CR-POPF (n=20)	p-value
Preoperative variable				
Age, median [IQR]	64 [51–71]	65 [52–72]	60 [46–71]	0.119
Primary site				0.074
Ovary	90	78	12	
Fallopian tube	66	61	5	
Peritoneum	9	6	3	
Performance status				0.533
0	26	22	4	
1	75	69	6	
2	51	43	8	
3	13	11	2	
FIGO stage				0.078
IIIA	0	0	0	
IIIB	2	1	1	
IIIC	79	74	5	
IVA	18	15	3	
IVB	66	55	11	
Histology				0.815
High-grade serous	143	126	17	
Non high-grade serous	22	19	3	
Low-grade serous	2	2	0	
Clear	11	10	1	
Endometrioid	3	2	1	
Mucinous	1	1	0	
Carcinosarcoma	5	4	1	
Pretreatment serum albumin (g/dL), median [IQR]	3.1 [2.7–3.6]	3.1 [2.7–3.6]	3.4 [2.6–4.0]	0.270
Intraoperative variables				
Operative time (min), median [IQR]	620 [524–716]	609 [521–703]	718 [610–820]	<0.001
Intraoperative blood loss (mL), median [IQR]	2,050 [1,290–3,273]	1,945 [1,230–3,163]	2,980 [2,046–4,353]	0.014
Timing of cytoreductive surgery				
Primary	31	24	7	0.065
Interval	134	121	13	
Peritoneal cancer index, median [IQR]	20 [16–24]	20 [16–24]	19 [17–22]	0.388
Surgical complex score, median [IQR]	15 [13–16]	15 [13–16]	15 [13–17]	0.122
Residual disease				0.239
0 cm	151	133	18	
0.1–1 cm	12	11	1	
>1 cm	2	1	1	
Involvement of pancreas in histological examination of resected specimen	132	114	18	0.371
Postoperative variables				
POD1 drain amylase level, median [IQR]	1,685 [785–4,498]	1,505 [704–3,831]	4,274 [1,845–7,537]	0.001
POD3 drain amylase level, median [IQR]	381 [138–821]	355 [128–726]	1,369 [449–3,231]	<0.001
Length of the pancreatic stump and splenic hilum, median [IQR]	1.5 [1.0–2.2]	1.5 [1.0–2.0]	2.0 [1.4–3.0]	0.061
Pancreatic stump thickness, median [IQR]	1.0 [0.5–1.2]	1.0 [0.5–1.2]	1.1 [1.0–1.7]	0.004

CR-POPF, clinically relevant postoperative pancreatic fistula; FIGO, The International Federation of Gynecology and Obstetrics; IQR, interquartile range; POD, postoperative day.

pancreatic involvement. On histopathological evaluation, the median distance between the carcinoma and the pancreatic tail capsule was 5 mm (interquartile range [IQR]=3–8 mm) and that between the splenic hilum and pancreatic tail was 2 mm (IQR=1–6 mm) (**Fig. 1**).

3. Outcomes of patients who developed CR-POPF

All 18 patients who developed POPF grade B recovered with percutaneous drainage and antibiotic administration. The median duration of drainage was 26 days. Two of 18 patients developed latent POPF on POD20 and 29; one patient underwent reinsertion of the drain into the left upper abdomen and recovered after 16 days of drain placement and the other underwent endoscopic ultrasonography guided pseudocyst drainage.
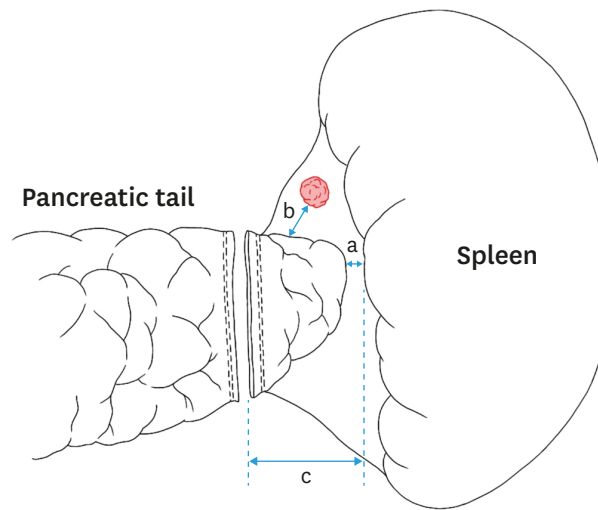
Fig. 1. Location of carcinoma between splenic hilum and pancreatic tail on histopathological evaluation. (a) Distance between splenic hilum and pancreatic tail (median, 2 mm). (b) Distance between the carcinoma (highlighted in red) and the pancreatic tail capsule (median, 5 mm). (c) Distance between splenic hilum and pancreatic stump (median, 15 mm).

Of the two patients with POPF grade C, one patient developed intra-abdominal bleeding from the right external iliac artery on POD10 and underwent reoperation; however, she died of multi-organ failure on POD57. The other patient was readmitted to our hospital on POD29 with left upper abdominal pain and fever and was diagnosed with latent POPF. She underwent pancreatic body resection and main pancreatic duct ligation on POD44, following a reduction in the drain output; however, pancreatic leakage persisted. On POD63, the patient underwent endoscopic pancreatic stenting and endoscopic ultrasound-guided biopsy of a low echoic lesion of the pancreatic head. Subsequently, we observed resolution of the pancreatic fistula. Histopathological evaluation suggested microscopic carcinoma of the pancreatic head; however, this diagnosis could not be confirmed. Preoperative computed tomography and intraoperative finding did not reveal a pancreatic head tumor. Moreover, histopathological evaluation of resected specimens of the pancreatic tail and body did not show carcinoma. Computed tomography performed 4 months after the initial cytoreductive surgery revealed pancreatic head cancer (3 cm lesion), and she received chemoradiotherapy using tegafur-gimeracil-oteracil potassium.

4. ROC curve for cut-off values of variables associated with CR-POPF

The cut-off values of variables associated with CR-POPF were analyzed using the ROC curve and the Youden index.

The ROC curve for operative time and intraoperative blood loss showed an area under the curve (AUC) of 0.70 and of 0.67, respectively (**Fig. 2A and B**). The most accurate cut-off values for operative time and intraoperative blood loss calculated using the Youden index were 703 min (sensitivity 60%, specificity 75%) and 2,570 mL (sensitivity 70%, specificity 64%), respectively.

The ROC curve for POD1 and POD3 drain fluid AMY levels for prediction of CR-POPF showed an AUC of 0.72 and 0.77, respectively (**Fig. 2C and D**). The most accurate cut-off values for POD1 and POD3 drain fluid AMY levels calculated using the Youden index were 1,765 U/L (sensitivity 85%, specificity 57%) and 808 U/L (sensitivity 65%, specificity 79%), respectively.
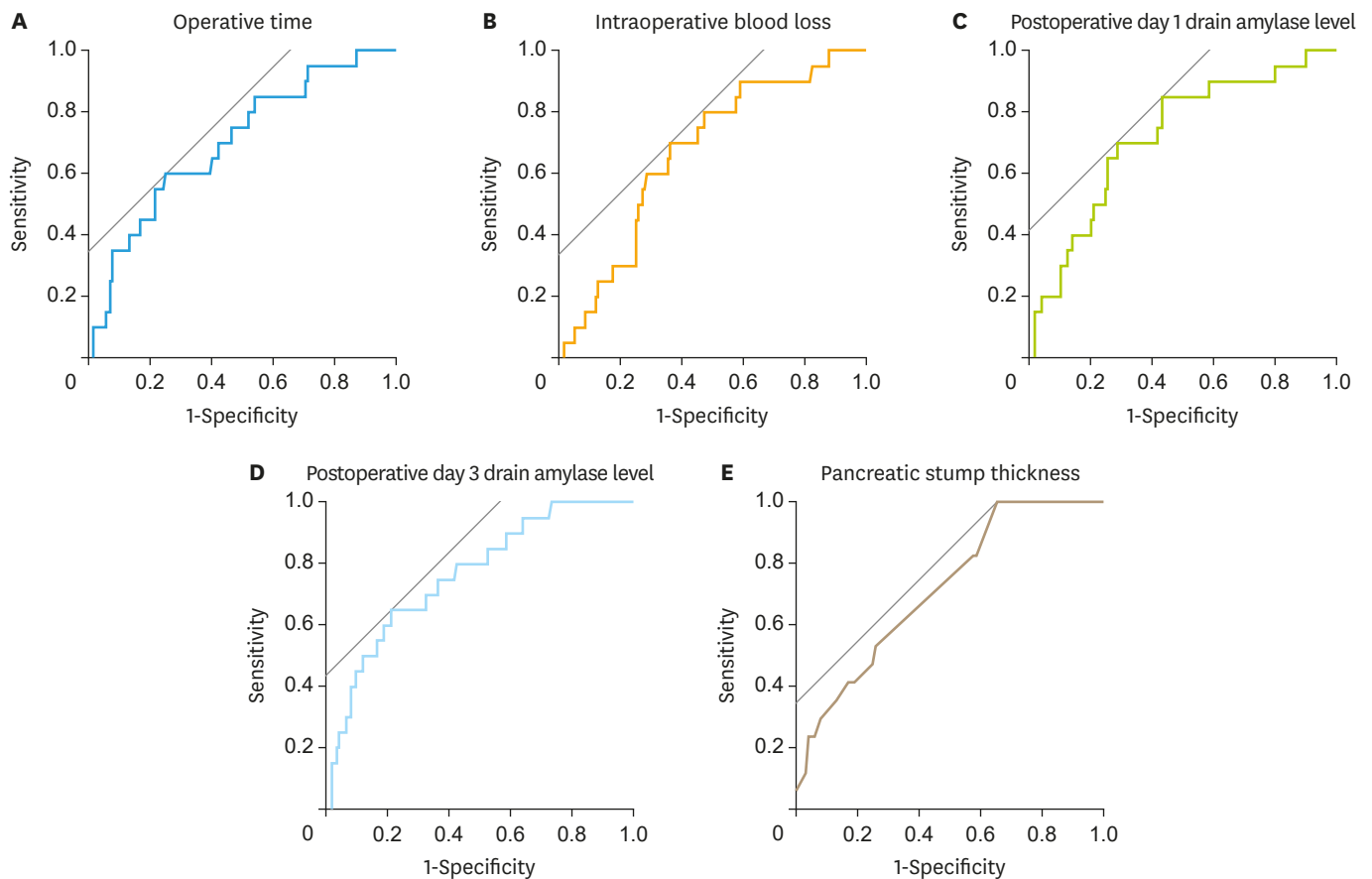
Fig. 2. Receiver operating characteristic curve for cut-off values of variables associated with clinically relevant postoperative pancreatic fistula. (A) Operative time, AUC 0.70. (B) Intraoperative blood loss, AUC 0.67. (C) Postoperative day 1 drain amylase level, AUC 0.72. (D) Postoperative day 3 drain amylase level, AUC 0.77. (E) Pancreatic stump thickness, AUC 0.72.
AUC, area under the curve.

The ROC curve of pancreatic stump thickness showed an AUC of 0.72, and the most accurate cut-off value of pancreatic stump thickness was 0.8 cm (sensitivity 100%, specificity, 35%) (**Fig. 2E**).

Analysis of data from 132 patients with pancreatic involvement (confirmed on histopathological examination of resected specimens) showed that the variables significantly associated with CR-POPF and their cut-off values were the same as those observed on analysis of data from all 165 patients included in the study.

5. Univariate and multivariate analysis of predictors of CR-POPF

Univariate analysis showed that operative time >703 min, intraoperative blood loss >2,570 mL, POD1 drain fluid AMY levels >1,765 U/L, POD3 drain fluid AMY levels >808 U/L, and pancreatic stump thickness >0.8 cm were significantly associated with CR-POPF (**Table 2**). However, the POD3 drain fluid AMY level >808 U/L was the only significant predictor observed on multivariate analysis.

Multivariate analysis of data from 132 patients with pancreatic involvement on histopathological evaluation of resected specimens showed that POD3 drain fluid AMY level >808 U/L was the only significant predictor of CR-POPF (**Table S1**).

Table 2. Univariate and multivariate analysis of predictors of clinically relevant postoperative pancreatic fistula

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Operative time >703 min	3.84	1.47–10.27	<0.001	2.33	0.63–8.77	0.202
Intraoperative blood loss >2,570 mL	3.32	1.28–9.33	0.014	2.96	0.80–11.90	0.103
POD1 drain amylase level >1,765 I/U	5.29	1.82–19.23	0.002	3.28	0.82–17.00	0.096
POD3 drain amylase level >808 I/U	5.72	2.16–15.98	<0.001	5.52	1.61–21.19	<0.001
Pancreatic stump thickness >0.8 cm	3.32	1.00–15.06	0.049	2.16	0.55–10.90	0.278

CI, confidence intervals; POD, postoperative day.

Table 3. Sensitivity, specificity, and positive and negative predictive values of different cut-off levels for postoperative day 3 drain fluid amylase levels

Postoperative day 3 drain amylase level (U/L)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
130	100%	35%	17%	100%
350	80%	48%	19%	94%
800	65%	79%	32%	94%
1,400	50%	87%	37%	92%
2,000	35%	92%	41%	90%
4,000	20%	96%	44%	89%
5,000	15%	97%	43%	88%

6. Sensitivity, specificity, and positive and negative predictive values of different cut-off levels for POD 3 drain fluid AMY levels

Table 3 shows the sensitivity, specificity, as well as positive and negative predictive values of different cut-off values for POD3 drain fluid AMY levels. POD3 drain fluid AMY levels <130 U/L ruled out CR-POPF with 100% sensitivity and showed 100% negative predictive value. POD3 drain fluid AMY levels >5,000 U/L showed the highest specificity (97%).

7. Survival

The median observation period in this study was 38 months. We observed no significant intergroup difference in progression-free survival (median: 22 months in patients with CR-POPF and 32 months in patients without CR-POPF, p=0.568, log-rank test) and overall survival (median: not reached in patients with CR-POPF and 80 months in patients without CR-POPF, p=0.873, log-rank) (**Fig. 3**).
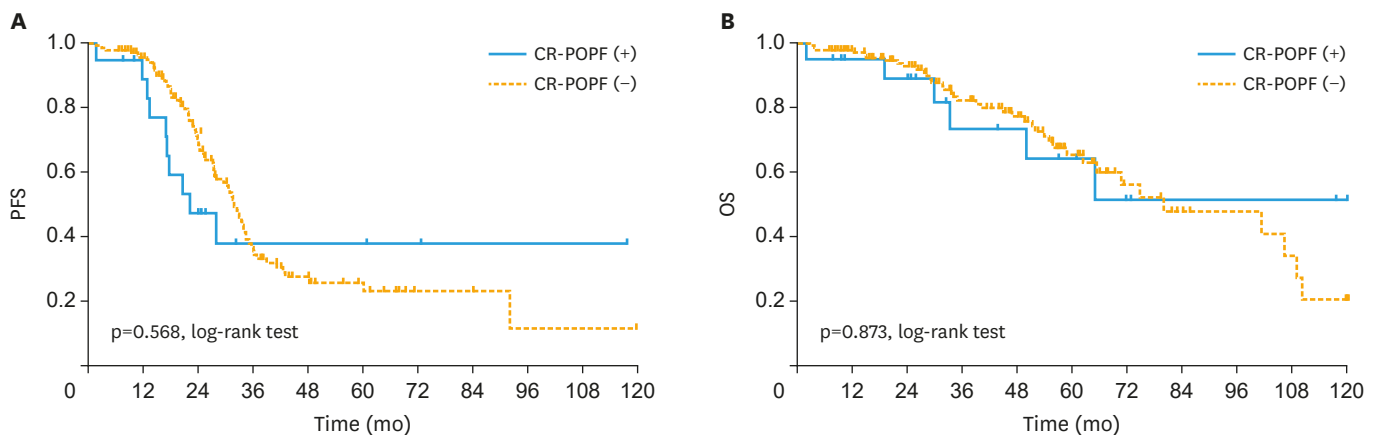
Fig. 3. Survival in patients with clinically relevant postoperative pancreatic fistula and without clinically relevant postoperative pancreatic fistula. (A) Progression-free survival, median: 22 months in patients with CR-POPF and 32 months in patients without CR-POPF, p=0.568, log-rank test. (B) Overall survival, median: not reached in patients with CR-POPF and 80 months in patients without CR-POPF, p=0.873, log-rank.
CR-POPF, clinically relevant postoperative pancreatic fistula; OS, overall survival; PFS, progressive-free survival.

DISCUSSION

This study highlighted that the POD3 drain fluid AMY level is an early diagnostic predictor of CR-POPF after splenectomy with or without distal pancreatectomy performed for ovarian cancer. Prediction and early diagnosis of CR-POPF enables accurate and safe management of patients in the early postoperative period. The POD3 drain fluid AMY level is useful to identify patients who require accelerated postoperative care for CR-POPF and to identify those in whom early drain removal can be attempted. POD3 drain fluid AMY levels >808 U/L necessitate intensive postoperative care, such as switching the patient's antibiotic to a different agent, computed tomography imaging, and drain replacement to prevent serious abdominal infection or bleeding. Based on the 100% sensitivity and negative predictive values observed in our study, we conclude that early drain removal is safe in patients with POD3 drain fluid AMY levels <130 U/L.

Intra- or postoperative variables could predict CR-POPF in this study. Univariate analysis showed that operative time, intraoperative blood loss, POD1 and POD3 drain fluid AMY levels, and pancreatic stump thickness were associated with CR-POPF. In contrast, preoperative factors could not predict CR-POPF in this study. These results concur with the results of a previous study that reported POPF after distal pancreatectomy in patients with pancreatic cancer [1,10-14]. Several studies have reported that the POD1 drain fluid AMY level serves as a predictor of CR-POPF in patients who undergo distal pancreatectomy for pancreatic cancer [12-14], and a few studies have observed that the POD3 drain fluid AMY level was also a predictor of CR-POPF in this patient population [22,23]. Although univariate analysis performed in our study showed that the POD1 and POD3 drain fluid AMY levels were predictors of CR-POPF, the POD3 drain fluid AMY level was the only predictor observed on multivariate analysis. In most patients who did not develop CR-POPF, the drain AMY level rapidly decreased from POD1 to POD3 [14]. Therefore, a high drain AMY level detected on POD3 indicates a delay in reduction of the AMY level from POD1 to POD3, which suggests an abnormal postoperative course.

Studies performed in patients with pancreatic cancer who underwent distal pancreatectomy have reported varied optimal cut-off levels for the prediction of POPF. The cut-off level was defined by the most balanced sensitivity and specificity, high sensitivity, and high negative predictive values. Based on the most balanced sensitivity and specificity, simplicity and easy clinical applicability, we observed that the POD3 drain fluid AMY level of 800 U/L was the optimal cut-off value in this study. Yoshino et al. investigated patients who developed POPF after distal pancreatectomy for pancreatic cancer and observed that the POD3 drain fluid AMY level of 1029 U/L was an optimal cut-off value for POPF using ROC analysis [22]; notably, this level was higher than that observed in our study. The AUC was 0.76, and the sensitivity and specificity were 73.1% and 75.8%, respectively in the study reported by Yoshino et al. [22]. Newhook et al. [23] reported that POD3 drain fluid AMY levels <26 U/L could exclude POPF with 100% sensitivity; notably, this level was lower than that observed in our study. It is necessary to determine a specific cut-off level in patients who undergo ovarian cancer surgery because usually, the pancreas resected during ovarian cancer surgery is smaller than that resected in patients with pancreatic cancer. Moreover, the pancreatic parenchyma is normal, and bowel resection is often performed concomitant with splenectomy. Furthermore, the resection procedure and techniques used for stump closure differ across departments and hospitals. Therefore, it is necessary to establish a specific cut-off level that is applicable for each department and hospital.

Early drain removal is widely implemented to reduce infection and consequent POPF in patients with pancreatic cancer [24,25]. Kawai et al. [24] reported that drain infections occurred on approximately POD7. Based on our results, we concluded that drains could be removed on POD3 in patients with drain fluid AMY levels <130 U/L (100% sensitivity and negative predictive value). The timing of drain removal should be carefully determined to avoid the reinsertion of drains. No study has described early drain removal after distal pancreatectomy performed for ovarian cancer surgery; however, early drain removal is known to reduce the risk of retrograde infection and length of hospitalization in patients at a low risk of development of CR-POPF.

Currently, the risk factors and predictors of CR-POPF after cytoreductive surgery for advanced ovarian cancer remain unknown. A few reports have discussed POPF after distal pancreatectomy performed in patients with advanced ovarian cancer; however, only approximately 20 patients underwent this operation [26,27]. Therefore, it is difficult to definitively establish the risk factors and predictors based on investigation of a small number of patients. Sozzi et al. [26] reported that hyperthermic intraperitoneal chemotherapy and cholecystectomy were independently associated with POPF in 22 patients who underwent distal pancreatectomy during ovarian cancer surgery. However, to date, hyperthermic intraperitoneal chemotherapy is not accepted as the standard treatment in clinical practice, and cholecystectomy is rarely performed as a component of advanced ovarian cancer surgery. To date, our study, which included 165 patients in whom we investigated the incidence of POPF after splenectomy with or without distal pancreatectomy for ovarian cancer, is the largest study to discuss this subject. The POD3 drain fluid AMY level, which was an early diagnostic predictor of CR-POPF in our study, is easy to measure in routine clinical practice and our findings will certainly serve as guidelines for prediction of POPF in patients who undergo ovarian cancer surgery.

The rate of distal pancreatectomy among patients who underwent splenectomy was higher in this study than that reported by other studies that have described this operation in patients with ovarian cancer; the rate of distal pancreatectomy ranged from 4.5% to 41% in other studies [28-31]. The high rate of distal pancreatectomy observed in our study is attributable to the fact that 134 of 165 (81%) patients underwent interval debulking surgery. Division of the pancreatic tail from the splenic hilum is relatively easy during primary debulking surgery. However, division of the pancreatic tail from the splenic hilum is challenging during interval debulking surgery secondary to post-chemotherapy fibrosis and shortening of the distance between the pancreatic tail and splenic hilum, which are invariably observed in these patients. In view of the distance between the splenic hilum and pancreatic tail capsule (median 2 mm) and that between the pancreatic capsule and carcinoma (median 5 mm) observed on histopathological evaluation of the resected specimens in our study, it was reasonable to conclude that division of the splenic hilum and pancreatic tail would be unsafe. Therefore, our hospital's surgical policy for splenectomy with or without distal pancreatectomy involves complete tumor resection with omental resection for presumed metastases between the splenic hilum and pancreatic tail in addition to metastatic splenic tumor removal and avoiding injury to the pancreatic capsule. Although the rate of distal pancreatectomy in this study was higher than that reported by previous studies among patients who underwent ovarian cancer surgery, the incidence of CR-POPF was not higher than that observed in those studies (5.5%–33%) [29,30,32]. In our study, the incidence of CR-POPF did not significantly differ between patients with and without pancreatic involvement based on histopathological examination of resected specimens. Predictors and cut-off

values were the same between patients with and without pancreatic involvement based on histopathological examination of resected specimens.

Histopathological evaluation showed metastatic carcinoma between the pancreatic tail and splenic hilum in more than 50% of the patients included in our study, although we did not detect pancreatic parenchymal invasion in any patient. A few studies have reported the histopathological findings in patients with ovarian cancer, who underwent distal pancreatectomy during primary cytoreduction. Kehoe et al. reported peripancreatic and pancreatic parenchymal metastasis in 12 and 1 patient, respectively among 17 patients who underwent distal pancreatectomy during primary cytoreduction [28]. Xiang et al. [32] reported pancreatic parenchymal invasion in two of nine patients who underwent distal pancreatectomy during primary cytoreduction. The aforementioned studies included a small number of patients, and the timing of cytoreduction differed from that used in our study; therefore, it is difficult to compare the histopathological findings observed in our study with those reported by previous studies. We did not observe pancreatic parenchymal invasion, which may be attributed to the high rate of interval debulking surgery performed in our study. Our surgical procedure was aimed at resection of peripancreatic metastases located within 10 mm of the pancreatic capsule; the median distance between the pancreatic stump and splenic hilum was 1.5 cm in our study.

Following are the limitations of this study: 1) The retrospective single-center design is a drawback of this study. Whether the optimal cut-off values identified in this study are generalizable across hospitals should be clarified in future studies. 2) Resection procedures and stump closure techniques differ across hospitals. However, in our study, the surgical procedures adopted during the study period were all performed by the same surgical team that included the same gynecologic oncologists. Therefore, the data from our study are uniform. Moreover, to date, ours is the largest study that investigated splenectomy with distal pancreatectomy in patients who underwent ovarian cancer surgery.

In conclusion, the POD3 drain fluid AMY level serves as an early diagnostic predictor of CR-POPF after splenectomy with or without distal pancreatectomy in patients who undergo ovarian cancer surgery. Prediction and early diagnosis of CR-POPF enables accurate and safe management of patients in the early postoperative period. Further research is warranted to validate the optimal cut-off value of the drain fluid AMY level across hospitals.

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SUPPLEMENTARY MATERIAL

Table S1

Univariate and multivariate analysis of predictors of clinically relevant postoperative pancreatic fistula in 132 patients with pancreatic involvement confirmed on histopathological examination of resected specimens

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