Clinical effects of early removal of an external stent from the viewpoint of postoperative pancreatitis following pancreaticoduodenectomy

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Research Article

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Abstract

Background: An external stent (ES) prevents clinically relevant postoperative pancreatic fistula (CR-POPF) after pancreaticoduodenectomy (PD), although it requires a longer postoperative hospital stay. Early ES removal has been suggested to overcome this issue. This study aimed to examine the effect of early ES removal on the pathophysiology of postoperative acute pancreatitis (POAP).

Methods: This retrospective cohort study was conducted between May 2018 and December 2020 at Amagasaki General Medical Center. The ES was removed on postoperative day 10 if the patient showed no clinical signs of postoperative pancreatic fistula (POPF). The early removal group included patients whose ES was removed within 10 days.

Results: Fifty consecutive patients underwent PD with an ES. The median length of postoperative hospital stay was 14.5 days in the early removal group and 19.5 days in the late removal group (P=0.0055). In the multivariate analysis, to eliminate the effects of postoperative complications, late ES removal was associated with a longer postoperative hospital stay (hazard ratio: 2.0, P=0.037). In the multivariate analysis of factors for early ES removal, early removal of the intra-abdominal tubes was statistically significantly associated with early ES removal (odds ratio: 8.4, P=0.03). Although patients with POAP showed a statistically significant delay in the removal of both ES and intra-abdominal drainage tubes, no statistically significant association was observed between CR-POPF and postoperative hospital stay.

Conclusions: An ES may manage POAP to reduce the risk of subsequent CR-POPF. Early removal of ES can be a method to shorten hospital stay.

Background

Clinically relevant postoperative pancreatic fistula (CR-POPF) is the leading contributor to major morbidity and mortality following pancreaticoduodenectomy (PD), with rates ranging from 8–17% [1–3]. Pathogenesis of CR-POPF is believed to involve a collapse of the pancreaticoenteral anastomosis due to POPF [4]. Various strategies have been tested to prevent the occurrence of CR-POPF, which include utilization of anastomotic stents and/or intraperitoneal drains, tissue sealants, administration of prophylactic somatostatin analogs, and selection of reconstruction sites and/or technical features of anastomosis [2, 3, 5]. However, the underlying pathogenesis of CR-POPF following PD has not been fully elucidated [6].

Postoperative acute pancreatitis (POAP) following PD is of particular interest to pancreatic surgeons since acute inflammation of the pancreatic remnant itself can cause local and systemic complications as well as collapse of the pancreaticoenteral anastomosis [7]. The definition of POAP proposed by Connor is based on biochemical evidence of pancreatic stump injury [1, 5]. Currently, there is considerable evidence that POAP is the underlying pathophysiology of CR-POPF [8, 9]. It is reported that appropriate

management of POAP including coordinated intraoperative fluid management and pharmacological interventions may reduce the incidence of CR-POPF [5].

Placement of an external stent (ES) through a pancreaticoenteral anastomosis is an attractive strategy to prevent the occurrence of CR-POPF [3]. Although the benefits of ESs have been identified through randomized controlled studies, only 2.1% of all surgeons always employ the ES method [10]. An ES is generally removed at 3–8 weeks after the operation [2, 3, 11–13]. The less frequent application of the ES method is attributed to its requirement of a longer postoperative hospital stay and greater need for postoperative management than internal stents (ISs) or no stents [12]. Early ES removal has been suggested to overcome this issue. The two purposes of this study were 1) to examine the effect of early ES removal and 2) to derive an optimal postoperative management method for ESs from the viewpoint of the pathophysiology of POAP following PD.

Methods

This retrospective cohort study involved all patients who underwent PD following the operative procedures and postoperative management between May 2018 and December 2020 at Amagasaki General Medical Center (Hyogo, Japan). The collected clinical characteristics included age, gender, white blood cell (WBC) count, serum C-reactive protein (CRP) level, serum amylase (S-AMY) level, CEA level, CA19-9 level, preoperative biliary drainage, diagnosis, pancreatic gland characteristics, and pancreatic duct size. The following characteristics of each patient were reviewed: portal vein resection, operative time, volume of blood loss, time to intra-abdominal tube removal, time to ES removal, the volume of pancreatic juice from the ES (maximum, on the day of removal), occurrence of POPF, Clavien-Dindo (CD) classification, and the length of postoperative hospital stay. The clinical patterns of POAP after PD were examined using the following records: postoperative S-AMY levels, serum CRP levels, drain amylase (D-AMY) levels, and the volume of pancreatic juice from the ES.

The surgical method was subtotal stomach-preserving PD. All reconstructions were performed using the modified Child method. Pancreaticoenteral anastomosis after PD was performed using a duct-to-mucosal, end-to-side pancreaticojejunostomy (PJ) for all enrolled patients. The details of the PJ procedure are shown in Fig. 1a. The procedure was modified based on the method used at Heidelberg University [14]. This method includes anastomosis of the pancreatic duct and the jejunum mucosa and five-layered sutures between the pancreatic surface and the seromuscular layer of the jejunum, covering the pancreatic stump by the jejunal serosa. A 4 or 5-French polyethylene pancreatic duct drainage tube was used for ES in all patients. The ES was guided externally from the elevated jejunum stump and was fixed to the jejunum wall of the anastomosis site using 4-0 VICRYL RAPIDE® sutures to prevent migration. The stent and the jejunum stump were fixed to the abdominal wall. No stent was used for biliary anastomosis. Two closed suction drains were placed over and behind the PJ (Fig. 1b).

All patients received proton pump inhibitors during the entire postoperative hospital course. No prophylactic somatostatin was administered. Oral diet was gradually resumed at 3 days after PD if there

was no evidence of delayed gastric emptying. Drain fluid volume and D-AMY levels from the intra-abdominal tube were measured daily until ES removal. The volume of pancreatic juice from the ES was measured daily. Intra-abdominal tubes were removed on postoperative day (POD) 3 if the patient showed no clinical signs of CR-POPF and if the D-AMY levels were within three times the normal upper limit of S-AMY regardless of the drain fluid volume. The ES was connected to a drainage bag and removed on POD 10. If there was evidence of pancreatic fistula, the ES was allowed to drain the pancreatic juice until the leakage resolved.

POPF was defined according to the International Study Group for Pancreatic Fistula definition and grading system [4]. POAP was defined according to the definition proposed by Connor and as elevation of serum S-AMY levels above the normal upper limit (S-AMY >132 U/L) on POD 0 or POD 1 [1]. Postoperative complications were classified according to the CD classification [15]. The early removal group included patients whose ES was removed within 10 days, and the late removal group included patients whose ES was removed at ≥11 days.

Continuous variables were expressed as medians and interquartile ranges (IQRs) and categorical variables were expressed as proportions. Categorical variables were compared using the $\chi 2$ test. All P-values were two-sided and P-values <0.05 were considered statistically significant. The length of hospital stay and the time to ES or intra-abdominal tube removal were measured as days from the date of surgery to the date of discharge and removal, respectively. They were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis of factors clinically relevant to postoperative hospital stay was performed to adjust for clinical variables using the Cox proportional hazards model. Multivariable logistic regression analysis was performed to evaluate the association between statistically significant clinical variables and early removal of ESs. Statistical analyses were performed using JMP software (version 8.0; SAS Institute, Cary, NC, USA).

Results

Clinical characteristics

Fifty consecutive patients underwent PD using PJ with an ES during the observation period. The clinical characteristics of the study are summarized in Table 1. The diseases included 28 pancreatic cancers, 10 bile duct cancers, five ampullary cancers, and seven others. The category of ‘others’ included intraductal papillary mucinous neoplasms in three cases, gastric cancer in two cases, duodenal cancer in one case, and solitary fibrous tumor in one case. Right hepatic artery resection was performed for two patients and multivisceral resection was performed for three patients. The median time to ES removal was 10 days. The median time to intra-abdominal tube removal was 4 days. The median postoperative hospital stay was 16 days. None of the patients had an intra-abdominal abscess or readmission due to early ES removal.

Table 1
Clinical Characteristics

	N=50
Age, years, median (IQR)	73.5 (67.8–78.3)
Gender, male / female	31(62%) / 19(38%)
WBC, 10^9/L, median (IQR)	5.5 (4.8–6.9)
CRP, mg/dl, median (IQR)	0.15 (0.07–0.81)
Amylase, U/L, median (IQR)	102 (73.5–118)
CEA, ng/mL, median (IQR)	3.85 (2.55–9.05)
CA19-9, U/mL, median (IQR)	31 (3.1–438)
Preoperative biliary drainage, yes / no	22(44%) / 28(56%)
Diagnosis, Pancreatic ca. / Bile duct ca. / Ampullary ca. / Others	28(56%) / 10(20%) / 5(10%) / 7(14%)
Pancreatic gland, hard / soft	25(50%) / 25(50%)
Duct size, >3mm / 3mm≥	32(64%) / 18(36%)
Portal vein resection, yes / no	23(46%) / 27(54%)
Operative time, minutes, median (IQR)	448 (380–543)
Volume of blood loss, ml, median (IQR)	879 (478–1356)
Time to intra-abdominal tube removal, median (IQR)	4 (3–5)
Time to external stent removal, median (IQR)	10 (10–11)
Volume of pancreatic juice (max.), median (IQR)	63 (18–134)
Volume of pancreatic juice (at the day of removal), median (IQR)	15.5 (0–60)
POAP, yes / no	34(72%) / 13(28%)
POPF, No / BC / Grade B	38(76%) / 9(18%) / 3(6%)
CD classification, 0–□ / □–□	37(74%) / 13(26%)
Postoperative hospital stay, median (min. –max.)	16 (10–72)
S-AMY POD1, median (IQR)	258 (123–333)

IQR: interquartile range, WBC: white blood cell, CRP:C-reactive protein, CD: Clavien-Dindo, ca.: cancer, POAP: postoperative acute pancreatitis, POPF: postoperative pancreatic fistula, BC: biochemical leak, S-AMY: serum amylase, D-AMY: drain amylase, POD: postoperative day

	N=50
S-AMY POD3, median (IQR)	48 (25–76)
S-AMY POD5, median (IQR)	35 (21–49)
CRP POD1, median (IQR)	7.7 (6.3–9.4)
CRP POD3, median (IQR)	15.9 (7.6–22.0)
CRP POD5, median (IQR)	4.5 (2.8–9.0)
CRP POD7, median (IQR)	4.2 (1.7–9.1)
D-AMY POD1, median (IQR)	1078 (48 –4522)
D-AMY POD3, median (IQR)	113 (21–316)
D-AMY POD5, median (IQR)	50 (32–867)
Volume of pancreatic juice POD1, median (IQR)	12 (0–44)
Volume of pancreatic juice POD3, median (IQR)	39 (5–76)
Volume of pancreatic juice POD5, median (IQR)	50 (4–97)
Volume of pancreatic juice POD7, median (IQR)	48 (4–108)
Volume of pancreatic juice POD9, median (IQR)	50 (1.5–97)
IQR: interquartile range, WBC: white blood cell, CRP:C-reactive protein, CD: Clavien-Dindo, ca.: cancer, POAP: postoperative acute pancreatitis, POPF: postoperative pancreatic fistula, BC: biochemical leak, S-AMY: serum amylase, D-AMY: drain amylase, POD: postoperative day	

Association between postoperative length of hospital stay and early ES removal

The median length of postoperative hospital stay was 15 days in the early removal group and 21 days in the late removal group (Fig. 2). Patients from the early removal group were discharged home or to a rehabilitation hospital significantly earlier than those from the late removal group (P=0.0055). The length of hospital stay was adjusted using CD classification, CR-POPF and POAP to eliminate the effects of postoperative complications. In the univariate analysis, late ES removal (hazard ratio [HR]: 2.3, 95% confidence interval [CI]: 1.2–4.4, P=0.007), CD grade ≥III (HR: 2.1, 95% CI: 1.1–4.6, P=0.027), and CR-POPF (HR: 3.9, 95% CI: 1.2–24, P=0.020) were significantly associated with a longer postoperative hospital stay. In the multivariate analysis, only late ES removal exhibited a significant association with a longer postoperative hospital stay (HR: 2.0, 95% CI: 1.0–4.0, P=0.037) (Table 2).

Table 2
Univariate and multivariate analyses for postoperative hospital stay

	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Late removal of external stent	2.3	1.2–4.4	0.007*	2.0	1.0–4.0	0.037*
CD classification ≥Ⅲ	2.1	1.1–4.6	0.027*	1.3	0.6–3.2	0.46
POPF	3.9	1.2–24	0.020*	2.8	0.7–19	0.16
POAP	1.5	0.8–2.8	0.23	1.3	0.6–2.5	0.49

HR: hazards ratio, CI: confidence interval, CD: Clavien-Dindo, POPF: postoperative pancreatic fistula, POAP: postoperative acute pancreatitis

Factors Associated With Early Es Removal

A comparison of clinical characteristics related to early and late ES removal is shown in Table 3. The following indicators showed statistical significance: preoperative WBC counts; pancreatic gland characteristics; time of removal of the intra-abdominal drainage tube; maximum volume of pancreatic juice; POPF (no/biochemical leak/Grade B); serum CRP levels on POD 3, POD 5, POD 7; and D-AMY levels on POD 1 and POD 3. Univariate and multivariate analyses were performed for serum CRP and D-AMY levels on POD 3. In the univariate analysis, the following variables were associated with early ES removal: lower preoperative WBC counts, hard pancreatic gland, early removal of the intra-abdominal drainage tube, biochemical leak compared to no POPF, a smaller maximum volume of pancreatic juice, lower serum CRP levels on POD 3, and lower D-AMY levels on POD3. In the multivariate analysis, only early removal of the intra-abdominal drainage tube was significantly associated with early ES removal (odds ratio [OR]: 8.4, 95% CI: 1.3–68) (Table 4).

Table 3
Comparison of clinical variables between patients with early and late removal of the external stent

	Late removal (n=18)	Early removal (n=32)	P value
Age, years, median>	12 (67%)	13 (41%)	0.077
Gender, male	14 (78%)	17 (53%)	0.085
WBC, 10^9/L, median>	12 (67%)	11 (34%)	0.028*
CRP, mg/dl, median>	9 (50%)	15 (47%)	0.83
Amylase, U/L, median>	7 (38%)	17 (54%)	0.28
CEA, ng/mL, median>	8 (44%)	17 (53%)	0.56
CA19-9, U/mL, median>	8 (44%)	17 (53%)	0.56
Preoperative biliary drainage, yes/no	10(56%) / 8(44%)	18(56%) / 14(44%)	0.96
Diagnosis			
Pancreatic ca. / Bile duct ca. / Ampullary ca. / Others	7(39%) / 5(28%) / 1(5%) / 5(28%)	21(66%) / 5(16%) / 4(12%) / 2(6%)	0.083
Pancreatic gland, hard / soft	5(28%) / 13(72%)	20(63%) / 37(8%)	0.018*
Duct size, >3mm / 3mm≥	24(75%) / 8(25%)	8(44%) / 10(56%)	0.030*
Portal vein resection, yes / no	6(33%) / 12(67%)	17(53%) / 15(47%)	0.18
Operative time, median>	10 (56%)	15 (47%)	0.56
Volume of blood loss, median>	10 (56%)	15 (47%)	0.56
Time to intra-abdominal tube removal, median>	11 (61%)	5 (16%)	0.0009*
Volume of pancreatic juice (maximum), median>	13 (72%)	11 (34%)	0.010*
Volume of pancreatic juice (at the day of removal), median>	10 (55%)	15 (47%)	0.56
POPF, No / BC / Grade B	10(56%) / 6(33%) / 2(11%)	28(88%) / 3(9%) / 1(3%)	0.040*
Non CR-POPF / CR-POPF	16(89%) / 2(11%)	1(3%) / 31(97%)	0.25
CD classification, 0–Ⅱ / Ⅲ–Ⅴ	11(61%) / 7(39%)	26(81%) / 6(19%)	0.12
CRP POD 1, median>	10 (56%)	15 (47%)	0.56

WBC: white blood cell, CRP:C-reactive protein, CD: Clavien-Dindo, POPF: postoperative pancreatic fistula, BC: biochemical leak, CR: clinically relevant, POD: postoperative day, D-AMY: drain amylase, POAP: postoperative acute pancreatitis

	Late removal (n=18)	Early removal (n=32)	P value
CRP POD 3, median>	14 (78%)	12 (38%)	0.0062*
CRP POD 5, median>	13 (72%)	12 (38%)	0.018*
CRP POD 7, median>	15 (83%)	10 (31%)	0.0004*
D-AMY POD 1, median>	13 (72%)	12 (38%)	0.018*
D-AMY POD 3, median>	13 (72%)	12 (38%)	0.018*
D-AMY POD 5, median>	6 (60%)	1 (20%)	0.14
POAP, yes / no	15(83%) / 3(17%)	19(66%) / 10(34%)	0.18

WBC: white blood cell, CRP:C-reactive protein, CD: Clavien-Dindo, POPF: postoperative pancreatic fistula, BC: biochemical leak, CR: clinically relevant, POD: postoperative day, D-AMY: drain amylase, POAP: postoperative acute pancreatitis

Table 4
Univariate and multivariate analyses for early external stent removal

	Univariate analysis		Multivariate analysis		
	OR	95%CI	Odds	95%CI	P value
WBC, median>	3.8	1.2–14	3.0	0.63–15	0.17
Pancreatic gland, hard	4.3	1.3–16	0.78	0.10–5.3	0.81
Duct size, >3mm	3.7	1.1–13	1.2	0.12–10	0.87
Time to intra-abdominal tube removal, Early removal	8.5	2.3–35	8.5	1.3–69	0.030*
Volume of pancreatic juice, median>	5.0	1.5–19	3.5	0.48–26	0.17
POPF, Grade B / BC	1.0	0.04–16	1.0	0.04–35	0.99
POPF, BC / No	5.6	1.2–31	1.4	0.10–13	0.85
CRP POD 3, median>	5.8	1.7–25	4.0	0.7–26	0.12
D-AMY POD 3, median>	4.3	1.3–16	3.5	0.38–43	0.29

OR: odds ratio, WBC: white blood cell, CRP:C-reactive protein, POPF: postoperative pancreatic fistula, BC: biochemical leak, D-AMY: drain amylase, POD: postoperative day

Clinical Factors Associated With Poap

Table 5 shows a detailed comparison of the clinical characteristics of patients with POAP. The following factors showed statistically significant association: serum CA 19-9 levels, diagnosis, pancreatic gland, portal vein resection, maximum volume of pancreatic juice, volume of pancreatic juice drainage on the day of ES removal, POPF (no/biochemical leak/grade B), serum CRP levels on POD 3 and POD 5, and D-AMY levels on POD 1 and POD 3. Patients with POAP showed a statistically significant delay in the removal of both ES and the intra-abdominal drainage tube (Fig. 3a, 3b). However, there was no statistically significant association among CR-POPF, CD grade ≥III, and postoperative hospital stay (Fig. 3c, Table 5).

Table 5
Comparison of clinical variables between patients with and without postoperative acute pancreatitis

	Postoperative acute pancreatitis (n=34)	Non postoperative acute pancreatitis (n=13)	P value
Age, years, median>	18 (53%)	6 (46%)	0.68
Gender, male	20(59%)	10(77%)	0.25
WBC counts, median>	18 (53%)	5 (13%)	0.37
CRP, median>	18 (53%)	6 (46%)	0.68
Amylase, median>	18 (55%)	5 (58%)	0.33
CEA, median>	16 (47%)	8 (62%)	0.37
CA19-9, median>	14 (41%)	10 (77%)	0.028*
Preoperative biliary drainage, yes / no	22(65%) / 12(35%)	5(38%) / 8(62%)	0.10
Diagnosis			
Pancreatic ca. / Bile duct ca. / Ampullary ca. / Others	15(44%) / 9(26%) / 5(15%) / 5(15%)	12(92%) / 0(0%) / 0(0%) / 1(8%)	0.023*
Pancreatic gland, hard / soft	12(35%) / 22(65%)	12(92%) / 1(8%)	0.0005*
Portal vein resection, yes / no	12(35%) / 22(65%)	11(84%) / 2(15%)	0.0025*
Operative time, median>	16 (47%)	9 (69%)	0.17
Volume of blood loss, median>	17 (50%)	7 (54%)	0.81
Volume of pancreatic juice (maximum), median>	22 (65%)	1 (8%)	0.0005*
Volume of pancreatic juice (at the day of removal), median>	20 (59%)	3 (23%)	0.028*
POPF, No / BC / Grade B	22(65%) / 9(26%) / 3(9%)	13(100%) / 0(%) / 0(0%)	0.046*
Non CR-POPF / CR-POPF	31(91%) / 3(9%)	13(100%) / 0(0%)	0.27
CD classification, 0–□ / □–□	24(71%) / 10(29%)	10(77%) / 3(23%)	0.66
CRP POD 1, median>	18 (53%)	6 (46%)	0.68
CRP POD 3, median>	22 (65%)	3 (23%)	0.011*
CRP POD 5, median>	22 (65%)	2 (15%)	0.0025*

WBC: white blood cell, CRP:C-reactive protein, CD: Clavien-Dindo, POPF: postoperative pancreatic fistula, BC: biochemical leak, CR: clinically relevant, POD: postoperative day, D-AMY: drain amylase

	Postoperative acute pancreatitis (n=34)	Non postoperative acute pancreatitis (n=13)	P value
CRP POD 7, median>	19 (56%)	5 (38%)	0.29
D-AMY POD 1, median>	23 (68%)	1 (8%)	0.0002*
D-AMY POD 3, median>	23 (68%)	1 (8%)	0.0002*
D-AMY POD 5, median>	7 (50%)	0 (0%)	0.33
WBC: white blood cell, CRP:C-reactive protein, CD: Clavien-Dindo, POPF: postoperative pancreatic fistula, BC: biochemical leak, CR: clinically relevant, POD: postoperative day, D-AMY: drain amylase			

Clinical Patterns Of Poap After Pd

The median D-AMY levels on POD 1, POD 3, and POD 5 in patients with POAP were 259.3, 18.6, and 3.9 U/L, respectively. The median S-AMY levels on POD 1, POD 3, POD 5, and POD 7 were 294.5, 54, 28, and 33.5 U/L, respectively. The median serum CRP levels on POD 1, POD 3, POD 5, and POD 7 were 7.87, 17.96, 6.44, and 5.22 mg/dL, respectively. The volumes of pancreatic juice on POD 1, POD 3, POD 5, and POD 7 were 32.5, 112, 80.5, and 67 ml, respectively (Fig. 4). Postoperative changes in the D-AMY and S-AMY levels were homologous in terms of time in patients with POAP. Serum CRP levels and the volume of pancreatic juice were also homologous, which decreased after POD 5.

Discussion

Recent randomized controlled trials have demonstrated the benefits of utilizing an ES [3, 10, 11, 13, 16]. There are several factors supporting the effectiveness of ES in reducing the occurrence of CR-POPF. Theoretically, an ES has the advantage of diverting pancreatic juice more completely from the pancreaticoenteral anastomosis, thus preventing bile activation by pancreatic enzymes [13]. Stent placement of the pancreatic duct allows for more accurate placement of sutures during pancreaticoenteral anastomosis [3]. Patients who develop CR-POPF can be managed more efficiently and conservatively without requiring reoperation. Thus, ESs prevent the severity of CR-POPF [3, 13]. The results of the present study showed that soft pancreas, non-dilated pancreatic duct, and a higher volume of pancreatic juice prevented early ES removal, which is consistent with clinical factors associated with CR-POPF [2]. Higher serum CRP levels, higher D-AMY levels, and POPF were the postoperative factors associated with the prevention of early ES removal. However, CR-POPF was not associated with early ES removal. In addition, early ES removal was associated with early discharge home or to a rehabilitation hospital. The median duration of postoperative hospital stay was 16 days in the present study, which is shorter than that (29 days [IQR: 21–42 days]) from the National Clinical Database of Japan [17]. Even when early removal of ES was not possible, ES could be used to manage CR-POPF. These results suggest that an ES may suppress the deterioration of CR-POPF.

Potential complications are among the concerns with the use of an ES for pancreaticoenteral anastomosis [13]. It may increase the risks such as local skin infections, subcutaneous abscesses, and local peritonitis after tube removal [12, 18]. Although the ES can be locked earlier in the absence of pancreatic fistula, it has been placed at 3–8 weeks after PD in previous reports [3, 12, 13, 18]. ESs seem uncomfortable for patients who undergo PD and can be inadvertently removed [19]. The present study showed that the ES could be removed within 10 days regardless of the volume of pancreatic juice drained from it. No patient was readmitted or had an intra-abdominal abscess after ES removal. In cases where an intra-abdominal abscess is observed after ES removal, the peripheral part of the jejunum from the biliary anastomosis has been reportedly selected to guide the ES outside the jejunum [12]. Therefore, Development of postoperative intra-abdominal abscess due to ES may be suppressed by selecting the stump of the elevated jejunum to the abdominal wall (Fig. 1b).

An IS does not require additional postoperative management of drainage tubes. However, IS has been reported to cause a variety of stent-induced complications such as bile duct strictures, stones, liver abscesses, intestinal obstruction, and intestinal perforation [19]. In addition, proximal migration of the IS has also been reported [3]. Externalization of the stent prevents complications [3].

Based on the definition proposed by Connor, the reported rate of POAP was between 53% and 64% [7]. The rate of POPF was 72.3% in the present study. S-AMY levels have been reported to peak at POD 1 and to normalize at POD 4–5 during the postoperative course [7], which is consistent with the results of the present study. Serum CRP levels peaked at POD 3 and decreased at POD 5–7, and the volume of pancreatic juice from the ES increased until 5 days after PD. These results indicate that POAP may resolve at 5–7 days after PD and the pancreatic remnant may start to recover functionally. The results from the present study showed that POAP was associated with the time to ES removal and the time to intra-abdominal tube removal. However, POAP was not associated with postoperative hospital stay, CR-POPF, or postoperative complications. This suggests that ESs may control POAP in the early postoperative period. Considering the results regarding the clinical pattern of POAP and the purpose of an ES, an ES might be removed earlier, since POAP management needs only 5–7 days after PD.

The present study indicated that early removal of the abdominal tube was the only factor associated with early removal of ES (OR: 8.5, 95% CI: 1.3–69, P=0.03) in the multivariate analysis. Various discussions have been conducted on intra-abdominal drains during PD [20, 21]. Two points should be considered regarding the drainage of amylase-rich ascites: it contains proteases and it can cause infection. Leakage of pancreatic juice from the pancreatic remnant starts intraoperatively [22]. Proteases, rather than amylases in the pancreatic juice, can damage the tissues around the pancreaticoenteral anastomosis, leading to the development of POPF [23, 24]. Particularly, the area of peritoneal fluid collection around the pancreaticoenteral anastomosis has been significantly associated with the development of CR-POPF [25]. Thus, sufficient drainage of amylase-rich ascites through an intra-abdominal tube is essential to prevent POPF. In contrast, an intra-abdominal drain tube can directly injure the pancreaticoenteral anastomosis [26]. In addition, long-term drainage via an intra-abdominal tube can increase the risk of infection, which in turn increases the risk of CR-POPF [21, 27]. Microbial detection in CR-POPF can lead to life-threatening

conditions [23, 28]. Early removal of the intra-abdominal tube immediately after the disappearance of amylase-rich ascites is a reasonable strategy to decrease the risk of CR-POPF.

The present study has several limitations. It was a single-institution retrospective analysis with a small number of patients and limited clinical variables. No comparisons were performed with the absence of a pancreatic stent or an IS. Moreover, this study did not perform a comparison between the 10-day removal group and the conventional ≥3-week removal group. The effects of ES on POAP need to be evaluated carefully, since the stent removal period was not based on patients with or without POAP in the present study. A comparative study between an IS group and an early ES removal group among patients with a high risk of POAP is desirable in the future.

Conclusions

An ES may manage POAP to reduce the risk of subsequent CR-POPF. Early removal of an ES is possible regardless of the fluid volume of pancreatic juice. Early removal of ES can be a method to shorten hospital stays.

Abbreviations

ES
External stent
CR-POPF
Clinically relevant postoperative pancreatic fistula
PD
Pancreaticoduodenectomy
POAP
Postoperative acute pancreatitis
POPF
Postoperative pancreatic fistula
IS
Internal stent
WBC
White blood cell
CRP
C-reactive protein
S-AMY
Serum amylase
CD
Clavien-Dindo
D-AMY
Drain amylase

PJ
Pancreaticojejunostomy
POD
Postoperative day
IQR
Interquartile ranges
HR
Hazard ratio
CI
Confidence interval
OR
Odds ratio

Declarations

Ethics approval and consent to participate: This study was approved by the ethical review board at Amagasaki General Medical Center (2-196). Preoperative written informed consent was obtained from each participant for the use of clinically recorded data. This study was a retrospective cohort study and carried out by the opt-out method at our hospital.

Consent for publication: Written informed consent for publication of clinical data was preoperatively obtained from each participant.

Availability of data and materials: The datasets analyzed during this study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing of interests.

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Authors' contributions: MKurimoto, KY, and JT designed the study. Mkurimoto and KY analyzed the data. YH, AS, HA, KH, MKayano and MT collected the data. MKurimoto wrote the first draft of the manuscript and KY revised the previous versions of the manuscript. All authors have read and approved the final manuscript.

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References

1. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. HPB. 2016;18:642–651.
2. Ecker BL, McMillan MT, Asbun HJ, et al. Characterization and Optimal Management of High-risk Pancreatic Anastomoses During Pancreatoduodenectomy. Ann Surg. 2018;267:608–616.
3. Pessaux P, Sauvanet A, Mariette C, et al. External pancreatic duct stent decreases pancreatic fistula rate after pancreaticoduodenectomy: prospective multicenter randomized trial. Ann Surg. 2011;253:879–885.
4. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161:584–591.
5. Bannone E, Andrianello S, Marchegiani G, et al. Postoperative Acute Pancreatitis Following Pancreaticoduodenectomy: A Determinant of Fistula Potentially Driven by the Intraoperative Fluid Management. Ann Surg. 2018;268:815–822.
6. Partelli S, Tamburrino D, Andreasi V, et al. Implications of increased serum amylase after pancreaticoduodenectomy: toward a better definition of clinically relevant postoperative acute pancreatitis. HPB. 2020;22:1645–1653.
7. Loos M, Strobel O, Dietrich M, et al. Hyperamylasemia and acute pancreatitis after pancreatoduodenectomy: Two different entities. Surgery. 2021;169:369–376.
8. Kühlbrey CM, Samiei N, Sick O, Makowiec F, Hopt UT, Wittel UA. Pancreatitis After Pancreatoduodenectomy Predicts Clinically Relevant Postoperative Pancreatic Fistula. J Gastrointest Surg. 2017;21:330–338.
9. Birgin E, Reeg A, Téoule P, et al. Early postoperative pancreatitis following pancreaticoduodenectomy: what is clinically relevant postoperative pancreatitis?. HPB. 2019;21:972–980.
10. McMillan MT, Malleo G, Bassi C, Sprys MH, Vollmer CM Jr. Defining the practice of pancreatoduodenectomy around the world. HPB. 2015;17:1145–1154.
11. Motoi F, Egawa S, Rikiyama T, Katayose Y, Unno M. Randomized clinical trial of external stent drainage of the pancreatic duct to reduce postoperative pancreatic fistula after pancreaticojejunostomy. Br J Surg. 2012;99:524–531.
12. Tani M, Kawai M, Hirono S, et al. A prospective randomized controlled trial of internal versus external drainage with pancreaticojejunostomy for pancreaticoduodenectomy. Am J Surg. 2010;199:759–764.
13. Poon RT, Fan ST, Lo CM, et al. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg. 2007;246:425–435.
14. Z'graggen K, Uhl W, Friess H, Büchler MW. How to do a safe pancreatic anastomosis. J Hepatobiliary Pancreat Surg. 2002;9:733–737.

15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–213.
16. Winter JM, Cameron JL, Campbell KA, et al. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg. 2006;10:1280–1290.
17. Kimura W, Miyata H, Gotoh M, et al. A pancreaticoduodenectomy risk model derived from 8575 cases from a national single-race population (Japanese) using a web-based data entry system: the 30-day and in-hospital mortality rates for pancreaticoduodenectomy. Ann Surg. 2014;259:773–780.
18. Zhang GQ, Li XH, Ye XJ, et al. Internal Versus External Drainage With a Pancreatic Duct Stent For Pancreaticojejunostomy During Pancreaticoduodenectomy for Patients at High Risk for Pancreatic Fistula: A Comparative Study. J Surg Res. 2018;232:247–256.
19. Park SH, Kim JH, Noh SY, et al. Migration of Internal Pancreaticojejunostomy Stents into the Bile Ducts in Patients Undergoing Pancreatoduodenectomy. J Gastrointest Surg. 2015;19:1995–2002.
20. Witzigmann H, Diener MK, Kienkötter S, et al. No Need for Routine Drainage After Pancreatic Head Resection: The Dual-Center, Randomized, Controlled PANDRA Trial (ISRCTN04937707). Ann Surg. 2016;264:528–537.
21. Kawai M, Tani M, Terasawa H, et al. Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for 104 consecutive patients. Ann Surg. 2006;244:1–7.
22. de Reuver PR, Gundara J, Hugh TJ, Samra JS, Mittal A. Intra-operative amylase in peri-pancreatic fluid independently predicts for pancreatic fistula post pancreaticoduodectomy. HPB. 2016;18:608–614.
23. Taniguchi K, Matsuyama R, Yabushita Y, et al. Prophylactic drain management after pancreaticoduodenectomy without focusing on the drain fluid amylase level: A prospective validation study regarding criteria for early drain removal that do not include the drain fluid amylase level. J Hepatobiliary Pancreat Sci. 2020;27:950–961.
24. Molinari E, Bassi C, Salvia R, et al. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. Ann Surg. 2007;246:281–287.
25. Hirono S, Kawai M, Okada KI, et al. Modified Blumgart Mattress Suture Versus Conventional Interrupted Suture in Pancreaticojejunostomy During Pancreaticoduodenectomy: Randomized Controlled Trial. Ann Surg. 2019;269:243–251.
26. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg. 2010;252:207–214.
27. Correa-Gallego C, Brennan MF, D'angelica M, et al. Operative drainage following pancreatic resection: analysis of 1122 patients resected over 5 years at a single institution. Ann Surg. 2013;258:1051–1058.

28. Loos M, Strobel O, Legominski M, et al. Postoperative pancreatic fistula: Microbial growth determines outcome. Surgery. 2018;164:1185–1190.

Figures

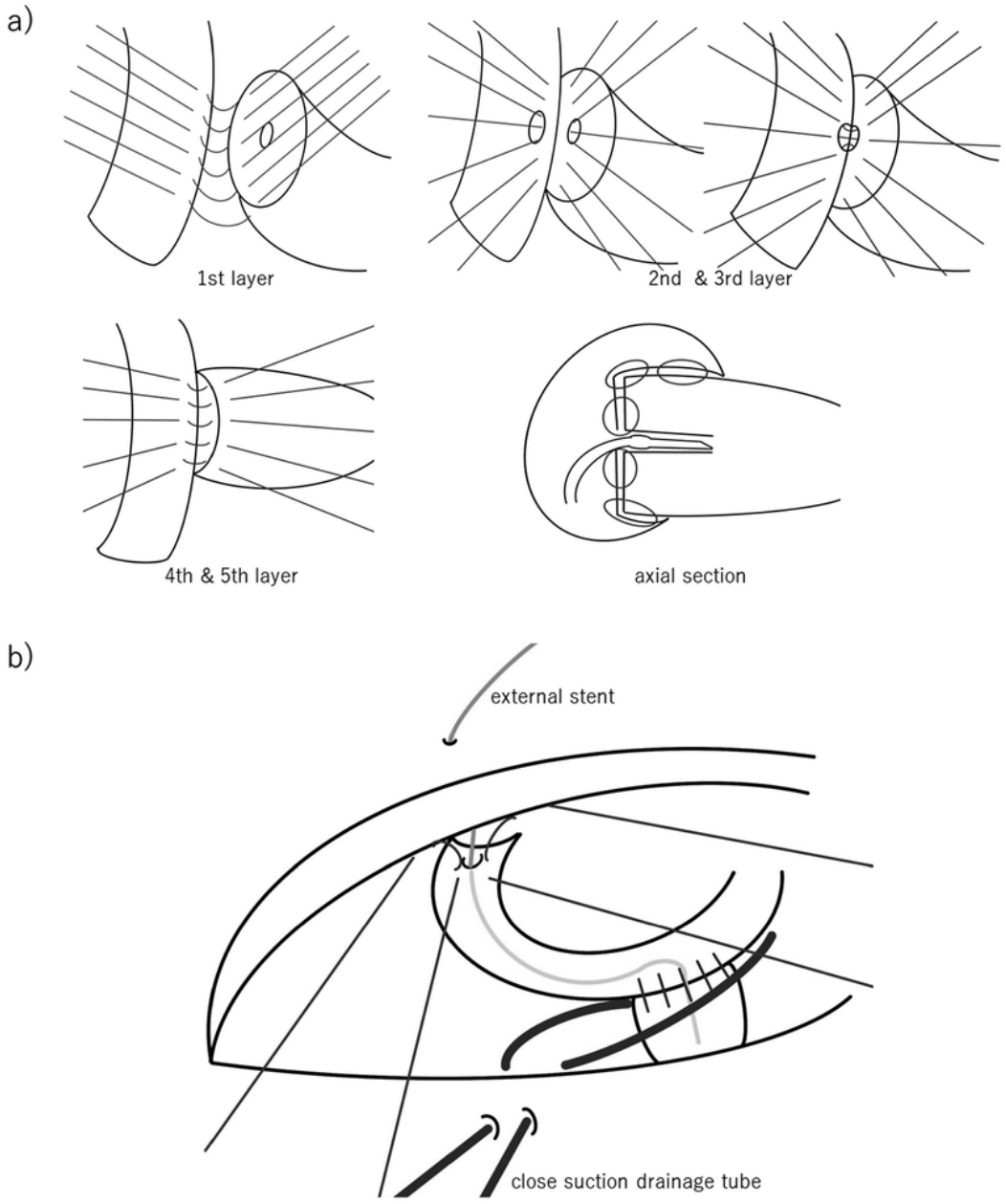

Figure 1

Five-layered pancreaticojejunostomy

We used 4-0 polypropylene for the first, fourth, and fifth-layer sutures between the pancreatic surface and the seromuscular layer of the jejunum and 5-0 polydioxanone for the second and third-layer sutures between the pancreatic duct and the jejunum mucosa. The external stent is guided externally from the elevated jejunum stump (a) and the jejunum stump is fixed to the abdominal wall (b).

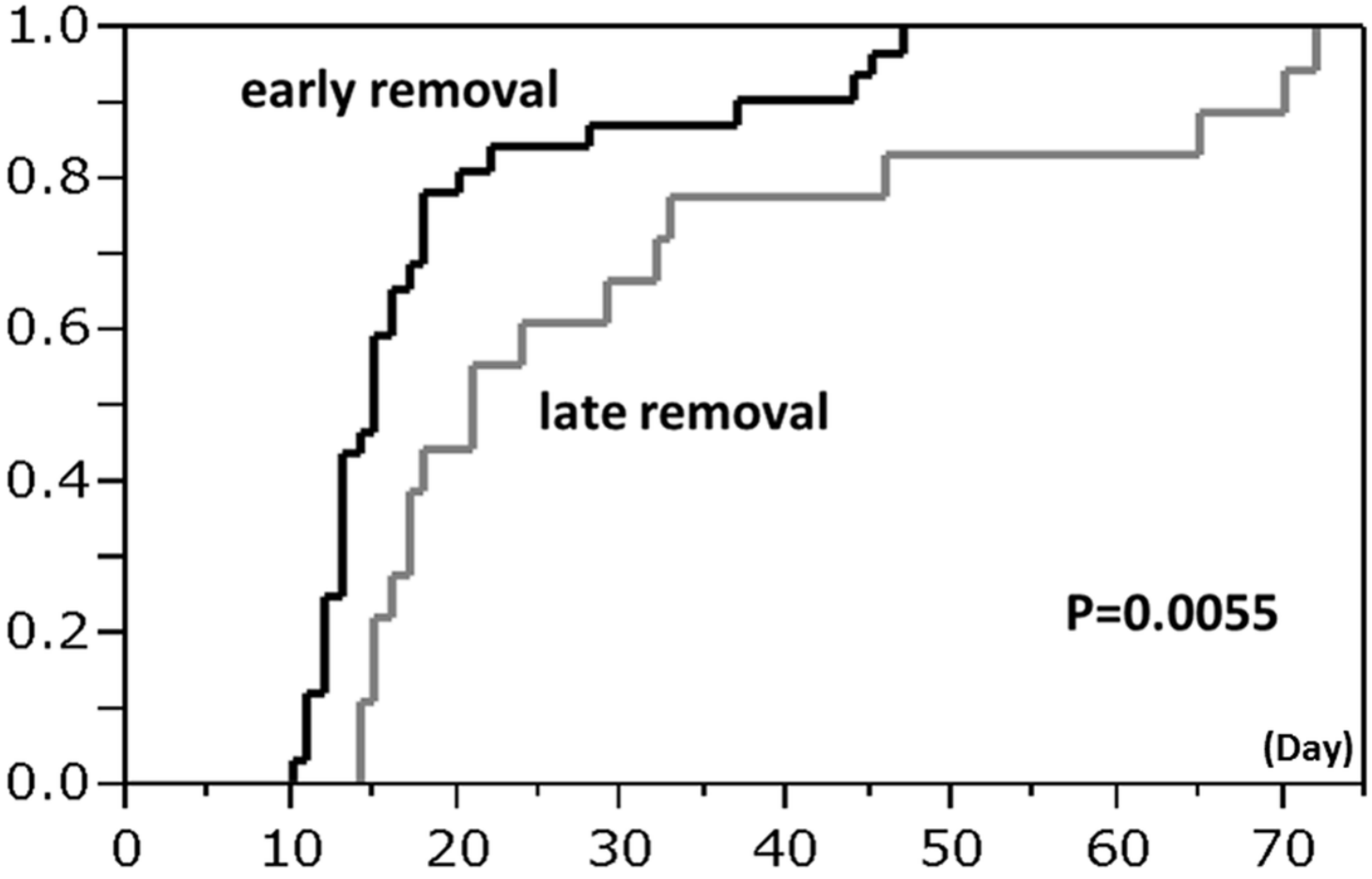

Figure 2

Comparison of the length of postoperative hospital stay between the early external stent (ES) removal and the late ES removal groups

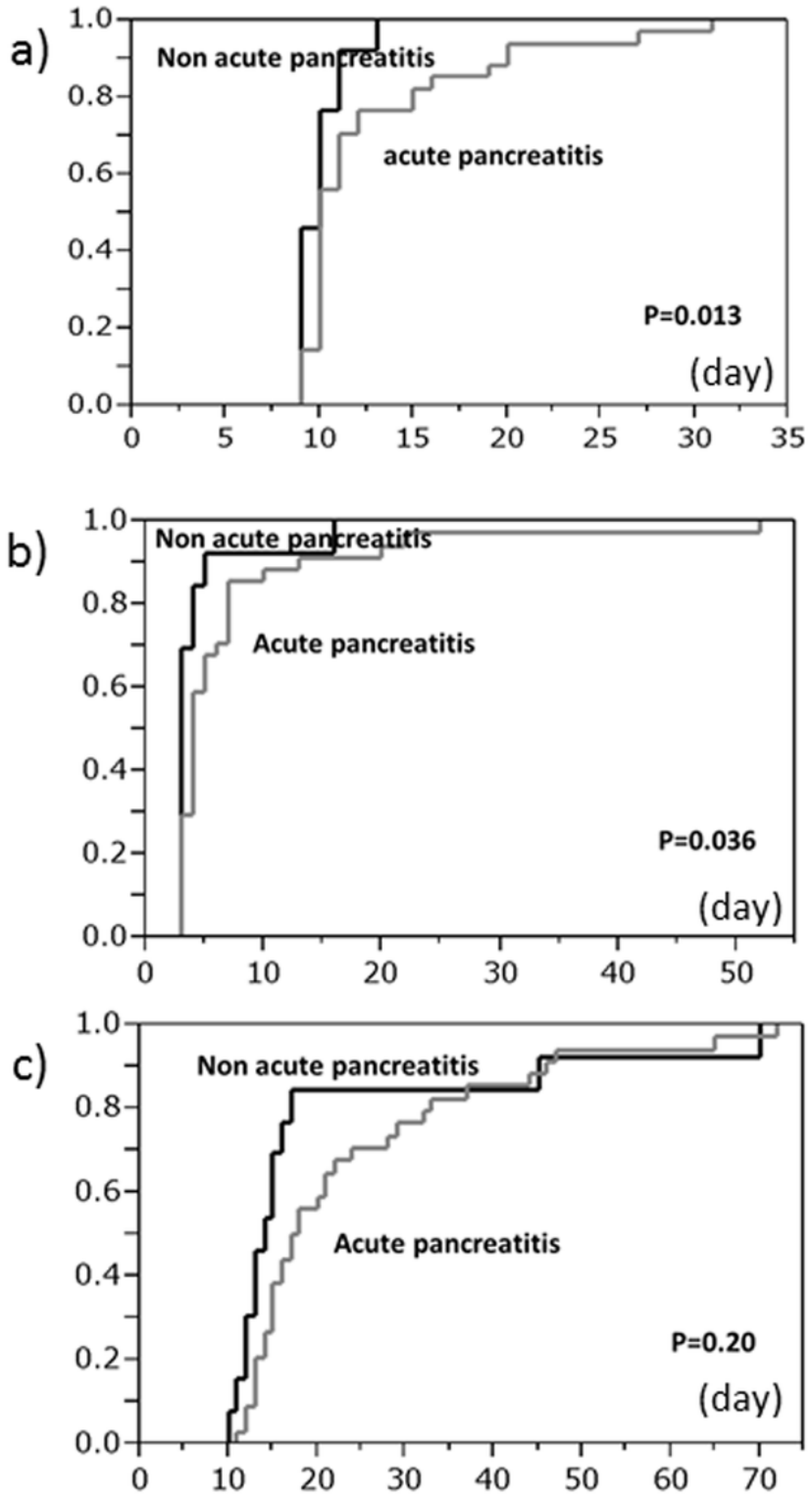

Figure 3

Time to external stent removal (a), time to intra-abdominal tube removal (b), and the length of postoperative hospital stay (c)

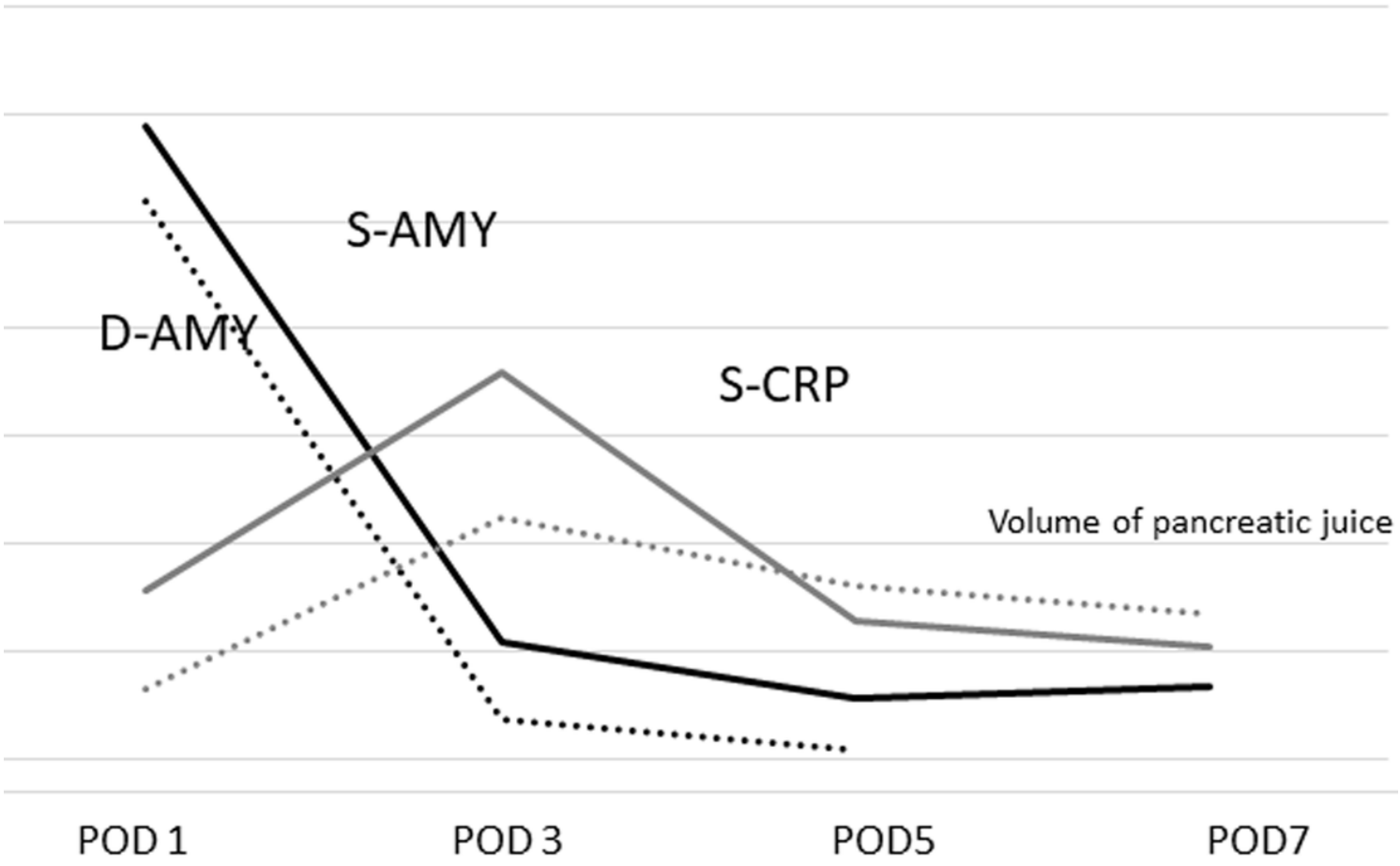

Figure 4

Postoperative changes in the serum amylase (S-AMY) levels, drain amylase (D-AMY) levels, serum C-reactive protein (S-CRP) levels, and volume of pancreatic juice in patients with postoperative acute pancreatitis (POAP)