

Association of surgical intervention within 1 year of treatment initiation with postoperative outcomes in chronic pancreatitis: a retrospective cohort study

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Abstract

Background

Chronic pancreatitis (CP) is a progressive inflammatory disease associated with intractable pain and functional impairment of the pancreas. Although early surgery has been advocated, the clinically relevant timing of surgical intervention remains unclear. This study evaluated the association between surgical timing and recurrent postoperative pain, endocrine function, and nutritional outcomes in patients with CP.

Methods

We retrospectively reviewed the medical records of 65 patients who underwent surgery for CP between 2005 and 2024 after malignancy was excluded. Early surgery was clinically defined as surgery performed within 12 months (≤ 12 months) after initiation of medical or endoscopic treatment; surgery after 12 months (> 12 months) was classified as delayed. Recurrent postoperative pain, new-onset diabetes mellitus (DM) among patients without preoperative DM, and nutritional parameters were assessed. Potential confounding by treatment era was also evaluated.

Results

Nineteen patients underwent early surgery, and 46 underwent delayed surgery. Recurrent postoperative pain occurred in 0/19 (0%) versus 14/46 (30.4%) patients ($p = 0.006$), and new-onset DM occurred in 0/16 (0%) versus 8/32 (25.0%) eligible patients without preoperative DM ($p = 0.039$), respectively. The frequency of both outcomes increased with increasing duration of preoperative treatment. Early/delayed group distribution did not differ significantly between 2005–2014 and 2015–2024 ($p = 0.357$), although adverse outcomes were more frequent in the earlier era. In an era-adjusted Firth model, delayed surgery remained associated with the unfavorable composite outcome (OR 20.1, 95% CI 2.26–2656). The prognostic nutritional index improved after surgery, particularly in patients with preoperative malnutrition.

Conclusions

Longer preoperative treatment duration was associated with progressively higher risks of clinically significant postoperative pain recurrence and new-onset DM after surgery for chronic pancreatitis. Patients who underwent surgery within 12 months had particularly favorable outcomes. These findings suggest that surgical referral at approximately 1 year may warrant consideration when durable disease control with medical or endoscopic treatment appears unlikely. Prospective multicenter studies are needed to determine the optimal timing of surgery.

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory disease characterized by recurrent pancreatic inflammation, resulting in fibrosis and the irreversible destruction of the pancreatic parenchyma. The condition is manifested by intractable pain and progressive exocrine and endocrine insufficiency, which leads to malnutrition due to the malabsorption of fats and impaired glucose metabolism, and a marked deterioration in patient quality of life (QOL) ¹. Because CP is a chronic inflammatory disease, the long-term preservation of QOL and pancreatic function is a major therapeutic goal.

Traditionally, endoscopic treatments that extract calculi and extracorporeal shock wave lithotripsy (ESWL) followed by the extraction of larger stones, along with stenting of an obstructed main pancreatic duct, have been considered as first-line therapies for painful uncomplicated CP, whereas surgery has been reserved for patients who do not obtain adequate relief from these conventional approaches². However, the prolonged inflammation associated with CP leads to progressive pancreatic fibrosis and irreversible pancreatic damage, resulting in refractory pain and permanent endocrine and exocrine dysfunction. Consequently, the concept of “early surgery” has emerged, which emphasizes surgical intervention before irreversible pancreatic damage occurs.

Recent evidence increasingly supports the benefits of early surgical intervention^{3–5}. The 2020 International Consensus Guidelines recommended early surgery to achieve long-term pain relief, instead of surgery performed at an advanced stage³. Furthermore, the 2021 Evidence-based Clinical Practice Guidelines for Chronic Pancreatitis discouraged prolonged repetitive endoscopic interventions and highlighted the evidence that early surgical intervention may provide better pain control and preservation of pancreatic function than delayed surgery⁴. More recently, long-term follow-up data from the ESCAPE trial demonstrated superior long-term pain control in patients undergoing early surgery compared with those managed by an endoscopy-first strategy, which suggests that the conventional step-up approach should be reconsidered⁵. Nevertheless, despite the accumulating evidence supporting early surgery, the optimal timing of surgical intervention remains unclear.

In addition to the need for pain control and pancreatic function preservation, nutritional impairment is a major clinical problem in patients with CP. Several studies have reported that surgical treatment for CP may improve patients’ nutritional status^{6,7}. However, the longitudinal changes in nutritional parameters, including body mass index (BMI), serum albumin (Alb) levels, and the prognostic nutritional index (PNI)⁸, have not been investigated sufficiently, particularly in relation to the timing of surgery.

Therefore, this study aimed to evaluate the association between surgical intervention performed within approximately 1 year after treatment initiation and postoperative outcomes in patients with CP, with a particular focus on recurrent pain, endocrine function, and nutritional status.

Methods

Ethics

This retrospective study was conducted with the approval of the Institutional Review Board of Nagoya City University Hospital (approval number: 60-18-0025).

Patients and study design

Surgical indications and decision-making

Surgical intervention was considered when durable disease control by medical or endoscopic management was considered difficult or when adequate symptom relief could not be achieved. The principal indications included: (1) pancreatic morphology considered difficult to manage endoscopically, such as impacted or cast-like pancreatic stones in the pancreatic head; (2) persistent or recurrent pain despite medical or endoscopic treatment; and (3) difficulty in definitive removal of a pancreatic duct stent, necessitating prolonged or repeated stenting. The timing of surgery was determined individually according to pancreatic morphology, clinical course, response to previous treatment, and feasibility of continued endoscopic management.

We retrospectively reviewed the medical records of patients who underwent surgery for CP in our department between January 2005 and December 2024. This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Definitions and outcomes

The duration of preoperative treatment was defined as the time between the initiation of medical or endoscopic treatment and surgery. Postoperative recurrent pain was defined as postoperative pain requiring medical consultation and therapeutic intervention, including pharmacological treatment and/or hospitalization. Postoperative new-onset diabetes mellitus (DM) was defined as DM newly diagnosed after surgery and requiring pharmacological treatment; patients with preoperative DM were excluded from the denominator for this outcome. Unsuccessful medical or endoscopic treatment was defined as persistent or recurrent pain despite treatment, inability to achieve durable pancreatic duct decompression including difficulty in removing a pancreatic duct stent, or the presence of pancreatic morphology considered unlikely to be adequately controlled by continued endoscopic treatment.

Preoperative malnutrition was defined as the presence of at least one of the following: BMI < 20 kg/m², serum Alb level < 3.8 g/dL, or PNI < 50. To operationalize the institutional practice of considering surgery within approximately 1 year of treatment initiation, patients who underwent surgery within 12 months ($\leq$ 12 months) after treatment initiation were defined as the early-surgery group, whereas those who underwent surgery after 12 months ($>$ 12 months) were defined as the delayed-surgery group. The primary outcomes were recurrent postoperative pain and new-onset DM. An unfavorable composite

outcome was defined as recurrent postoperative pain and/or eligible new-onset DM; preoperative DM did not contribute to the DM component.

The prognostic nutritional index (PNI) was calculated using the Onodera formula: $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$.⁸

Statistical analysis

Data are presented as medians (interquartile range [IQR]) or numbers (%), as appropriate. The Mann–Whitney U test or Fisher’s exact test was used to compare two groups, as appropriate. The Wilcoxon signed-rank test was used to compare paired continuous variables before and after surgery. The Cochran–Armitage trend test was used to assess trends across ordered categories.

The Kaplan–Meier method and log-rank test were used to estimate and compare freedom from recurrent postoperative pain and new-onset DM; analyses of new-onset DM were restricted to patients without preoperative DM. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of preoperative treatment duration to predict postoperative outcomes. The maximum Youden index⁹ was used to identify a statistically optimal cutoff value, and a sensitivity-oriented analysis was performed to identify earlier thresholds that maintained maximal sensitivity.

To address potential era effects over the 20-year study period, the distribution of early versus delayed surgery and postoperative outcomes was compared between 2005–2014 and 2015–2024. Variables of clinical relevance and those associated with the composite outcome were evaluated using Firth penalized logistic regression because of the limited number of outcome events and complete separation. Surgical era (2015–2024 vs 2005–2014) was included as a covariate to account for potential temporal confounding. A sensitivity analysis was also performed by replacing the > 12-month treatment-duration variable with a ≥ 36 -month threshold.

A two-sided p value < 0.05 was considered statistically significant. IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA) was used for the primary statistical analyses. Firth penalized logistic regression analyses were performed using EZR version 1.68 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R.¹⁰

Results

The flowchart for patient selection is shown in Fig. 1. A total of 69 patients underwent surgery for CP at our department between 2005 and 2024. After exclusion of 4 patients with malignant disease, 65 patients were included in the retrospective analysis.

Table 1 summarizes the characteristics of the study patients. The median age was 54 (IQR, 46–60) years, and 80.0% of the patients were male. Alcohol-related pancreatitis was the predominant etiology

(75.4%), and pancreatolithiasis was present in 64.6% of patients. The median duration of preoperative treatment was 30 (IQR, 9–61) months, and 20.0% of patients required preoperative insulin therapy.

Table 1. Patient characteristics (N=65)

		All patients N=65	Male patients n=52 (80%)	Female patients n=13 (20%)
Age, years		54 (46 - 60)	56 (47-68)	49 (44-54)
BMI, kg/m²		21.1 (18.5 - 23.5)	21.4 (19.2- 23.6)	18.4 (17.1- 20.7)
Cause	Alcohol-related	49 (75.4 %)	43 (82.7 %)	6 (46.1 %)
	Idiopathic	16 (24.6 %)	9 (17.3 %)	7 (53.8 %)
Sub-diagnosis	Pancreatolithiasis	42 (64.6 %)	32 (61.5 %)	10 (76.9 %)
	Pancreatic pseudocyst	16 (24.6 %)	12 (23.1%)	4 (30.8%)
	Pancreatic fistula	5 (7.7 %)	5 (9.6%)	0 (0 %)
	Bile duct stricture	5 (7.7 %)	5 (9.6%)	0 (0 %)
	Pancreatic duct stricture	4 (6.1 %)	4 (7.6 %)	0 (0 %)
	Pseudoaneurysm	3 (4.6 %)	3 (5.8%)	0 (0 %)
	Abscess	2 (3.1%)	2 (3.1%)	0 (0 %)
Preoperative treatment duration, months		30 (9-61)	33 (14-77)	24 (6-43)
Treatment of DM prior to surgery	Insulin	13 (20.0%)	11 (21.2%)	2 (15.4%)
	Oral agents	3 (4.6%)	3 (5.8%)	0 (0%)
	Unknown treatment	1 (1.5%)	1 (1.9%)	0 (0%)
	None	48 (73.8%)	37 (71.2%)	11 (84.6%)

Continuous variables are presented as median (IQR), and categorical variables as n (%). BMI, body mass index; DM, diabetes mellitus; IQR, interquartile range.

Preoperative treatments, surgical procedures, and perioperative outcomes are summarized in Table 2. Extracorporeal shock wave lithotripsy (ESWL) was the most frequently performed preoperative treatment (38.7%). The Frey procedure was the most commonly performed surgical procedure (40.0%), followed by the Frey procedure combined with distal pancreatectomy (15.4%). Recurrent postoperative pain was

observed in 21.5% of patients, with a pain remission rate of 78.5%. Postoperative new-onset DM was observed in 8 of 48 eligible patients (16.7%). The median follow-up period was 65 (interquartile range [IQR], 31–114) months.

Table 2
Preoperative Treatments, Surgical Procedures, and Perioperative Outcomes (N = 65)

Preoperative treatment	ESWL	25 (38.7%)
	MPD Stenting	18 (27.7%)
Surgical procedure	Frey	26 (40.0%)
	Frey + DP	10 (15.4%)
	DP	8 (12.3%)
	PD	7 (10.8%)
	Frey + CJ	7 (10.8%)
	Partington	2 (3.1%)
	Puestow	2 (3.1%)
	DP + LPJ	2 (3.1%)
	DP + Partington	1 (1.5%)
Operation time, min		495 (360–572)
Blood loss, mL		601 (298–1075)
PF ≥ Grade B		11 (16.9%)
Major complications, Clavien–Dindo ≥ Grade III		6 (9.2%)
Postoperative stay, days		22 (15–30)
Follow-up period, months		65 (31–114)
Postoperative pain		14 (21.5%)
Pain remission rate, %		78.5%
Postoperative new-onset DM*		8/48 (16.7%)

Data are presented as n (%) or median (IQR), as appropriate. *New-onset DM was evaluated only among the 48 patients without preoperative DM. ESWL, extracorporeal shock wave lithotripsy; MPD, main pancreatic duct; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; CJ, choledochojejunostomy; LPJ, lateral pancreaticojejunostomy; PF, postoperative pancreatic fistula; DM, diabetes mellitus; IQR, interquartile range.

A total of 15 patients discontinued outpatient follow-up, including 5 patients with a follow-up duration of less than 1 year. The reasons for early discontinuation were lost to follow-up in 4 (6.2%) patients and death from another disease in 1 (1.5%) patient. One patient died 3 months after surgery of an exacerbation of interstitial pneumonia. No patients developed pancreatic cancer during the follow-up period.

Changes in nutritional parameters were evaluated in patients with available data both before surgery and at 1 year after surgery (Table 3). Data at 1 year after surgery were missing in 5 (7.7% of 65) patients. BMI data were available for 24 (36.9% of 65) patients, whereas serum Alb levels and PNI data were available for 60 (92.3% of 65) patients. The change in BMI 1 year after surgery was not significant. At 1 year after surgery, serum Alb levels showed an upward trend ($p = 0.068$), and the PNIs increased significantly ($p < 0.001$).

Because patients with preserved preoperative nutritional status were unlikely to demonstrate further improvement, nutritional outcomes were additionally analyzed in patients with preoperative malnutrition (Table 3). In the low-BMI group, BMI showed a trend toward improvement at 1 year after surgery ($p = 0.066$). Serum Alb levels and PNI values increased significantly at 1 year after surgery, indicating improved nutritional status ($p = 0.004$ and $p < 0.001$, respectively).

Table 3
Changes in nutritional parameters (N = 65)

Variable n (%) or Median (IQR)	Patients for analysis	Before surgery	1 year after surgery	p value
All patients				
BMI	24 (36.9)	20.2 (17.9–22.4)	19.5 (18.6–21.1)	0.917
Alb	60 (92.3)	4.0 (3.5–4.2)	4.2 (3.9–4.4)	0.068
PNI	60 (92.3)	48.0 (43.0–52.8)	52.5 (47.0–55.5)	< 0.001
Patients with malnutrition before surgery				
BMI<20 kg/m ²	10 (41.7)	17.2 (16.6–18.0)	18.6 (18.5–19.6)	0.066
Alb<3.8 g/dL	20 (33.3)	3.5 (3.2–3.5)	4.1 (3.6–4.3)	0.004
PNI<50	35 (58.3)	44.5 (42.0–48.0)	51.0 (47.0–56.0)	< 0.001

Data are presented as medians (IQR). Comparisons were performed using the Wilcoxon signed-rank test. BMI, body mass index; Alb, albumin; PNI, prognostic nutritional index; IQR, interquartile range.

Comparisons of patient characteristics and perioperative factors between the early-surgery group (≤ 12 months; $n = 19$) and the delayed-surgery group (> 12 months; $n = 46$) are summarized in Table 4. The distribution of patients between the 2005–2014 and 2015–2024 eras did not differ significantly between

the groups ($p = 0.357$). The proportions receiving recorded preoperative interventions, including ESWL, pancreatic duct stenting, and drainage procedures, also did not differ significantly. The available dataset did not permit reliable reconstruction of the number of repeated treatment sessions for all patients. Other measured baseline and perioperative characteristics were broadly similar between groups.

Table 4

Comparisons between patient characteristics and perioperative outcomes in the 2 groups (N = 65)

Age, years	Early-surgery group (≤ 12 months; n = 19)	Delayed-surgery group (> 12 months; n = 46)	p value
	51 (44–57)	55 (46–60)	0.593
Sex			0.214
Male	15 (78.9%)	37 (80.4%)	
Female	4 (21.1%)	9 (19.6%)	
BMI	20.5 (18.5–23.5)	21.3 (18.4–23.5)	0.960
Surgical procedure			0.612
Frey	8 (42.1%)	18 (39.1%)	
Frey + DP	3 (15.8%)	7 (15.2%)	
DP	4 (21.1%)	4 (8.7%)	
PD	2 (10.5%)	5 (10.9%)	
Frey + CJ	2 (10.5%)	5 (10.9%)	
Partington	0	2 (4.3%)	
Puestow	0	2 (4.3%)	
DP + LPJ	0	2 (4.3%)	
DP + Partington	0	1 (2.2%)	
Blood loss, mL	763.0 (350.0–1061.5)	464.0 (284.5–1065.0)	0.579
Treatment for preoperative DM			0.301
Insulin	3 (15.8%)	10 (21.7%)	
Oral agents	0	3 (6.5%)	
Unknown treatment	0	1 (2.2%)	
None	16 (84.2%)	32 (69.6%)	
PF $\geq$ Grade B			0.802
Grade B	2 (10.5%)	6 (13.0%)	
Grade C	1 (5.3%)	1 (2.2%)	
Major complications,			0.705

Age, years	Early-surgery group (≤ 12 months; n = 19)	Delayed-surgery group (> 12 months; n = 46)	p value
	51 (44–57)	55 (46–60)	0.593
Clavien–Dindo $\geq$ III			
Bleeding	1 (5.3%)	3 (6.5%)	
Abscess	1 (5.3%)	1 (2.2%)	
Postoperative stay, days	26 (18–39)	29 (21–39)	0.707
Surgical era			0.357
2005–2014	3 (15.8%)	13 (28.3%)	
2015–2024	16 (84.2%)	33 (71.7%)	
Any recorded preoperative intervention	12 (63.2%)	33 (71.7%)	0.560
ESWL	6 (31.6%)	19 (41.3%)	0.579
Pancreatic duct stenting	6 (31.6%)	15 (32.6%)	1.000
Drainage procedures	4 (21.1%)	12 (26.1%)	0.761

Preoperative intervention categories were derived from recorded treatment descriptions. Pancreatic duct stenting included endoscopic pancreatic stenting, endoscopic retrograde pancreatic drainage, and pancreatic duct stent records; drainage procedures included endoscopic nasopancreatic drainage, endoscopic ultrasound-guided drainage, or transpapillary drainage records. Repeated-session counts were not structured consistently in the source dataset and are therefore not reported. ESWL, extracorporeal shock wave lithotripsy.

BMI, body mass index; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; CJ, choledochojejunostomy; LPJ, lateral pancreaticojejunostomy; DM, diabetes mellitus; PF, postoperative pancreatic fistula.

Table 5 compares recurrent postoperative pain and new-onset DM according to duration of preoperative treatment. In the early-surgery group (≤ 12 months), recurrent postoperative pain was not observed (0/19). Among patients without preoperative DM, new-onset DM was also not observed (0/16). In the delayed-surgery group (> 12 months), recurrent postoperative pain occurred in 14/46 (30.4%) patients and new-onset DM occurred in 8/32 (25.0%) eligible patients. When treatment duration was stratified into ≤ 12 months, 13–35 months, and ≥ 36 months, recurrent pain increased from 0% to 15.8% and 40.7% (p for trend < 0.001), while new-onset DM increased from 0% to 15.4% and 31.6% among eligible patients (p for trend = 0.012). Compared with early surgery, delayed surgery was associated with a higher rate of recurrent postoperative pain (Fisher’s exact p = 0.006) and new-onset DM among patients without

preoperative DM (Fisher's exact $p = 0.039$). The Haldane–Anscombe odds ratio for recurrent pain was 17.4 (95% CI 1.0–307.6). Because the new-onset DM analysis used outcome-specific denominators after excluding preoperative DM, its principal comparison is presented as event rates and Fisher's exact p value rather than an odds ratio based on the full cohort.

Table 5
Recurrent postoperative pain and new-onset DM according to duration of preoperative treatment

Outcome	Early surgery	Delayed surgery		OR* (95% CI)	p for trend
	≤ 12 months	13–35 months	≥ 36 months		
	(n = 19)	(n = 19)	(n = 27)		
Postoperative pain	0/19 (0%)	3/19 (15.8%)	11/27 (40.7%)	17.4 (1.0–307.6)	< 0.001
New-onset DM	0/16 (0%)	2/13 (15.4%)	6/19 (31.6%)	—	0.012

*For recurrent postoperative pain, the odds ratio (OR) was calculated for delayed surgery (>12 months) versus early surgery (≤12 months) using the Haldane–Anscombe correction. New-onset DM denominators exclude patients with preoperative DM. p for trend was calculated using the Cochran–Armitage trend test. The 1-year cutoff was expressed as ≤12 months versus >12 months because treatment duration was recorded in completed months.

Kaplan–Meier analyses were performed for recurrent postoperative pain and new-onset DM. No recurrent pain was observed in the early-surgery group during follow-up. In the delayed-surgery group, recurrent pain occurred predominantly during the early postoperative period; the latest recorded pain recurrence occurred at 22 months. For new-onset DM, the analysis was restricted to patients without preoperative DM. No new-onset DM occurred in the early-surgery group, whereas events occurred in the delayed-surgery group, including one late event at 136 postoperative months. These findings are shown in Fig. 2A and B.

ROC curve analysis was performed to evaluate preoperative treatment duration as a predictor of recurrent postoperative pain and new-onset DM (Fig. 3A, B). For recurrent postoperative pain, the AUC was 0.760 and the maximum-Youden cutoff was 38 months; the highest threshold retaining 100% sensitivity was 14 months. For new-onset DM, restricted to the 48 patients without preoperative DM, the AUC was 0.764 and the maximum-Youden cutoff was 58 months; the highest threshold retaining 100% sensitivity was 13 months. Thus, the statistically balanced cutoffs were substantially later than the clinically oriented sensitivity thresholds.

Table 6 summarizes Firth penalized logistic regression analyses for the unfavorable composite outcome. The composite outcome occurred in 18/65 (27.7%) patients and was absent in the early-surgery group. Because the corrected DM eligibility changed the composite membership of one patient

and because outcomes differed by treatment era, the multivariable model was recalculated with surgical era included as a potential confounder.

In univariable Firth analyses, delayed surgery (> 12 months), alcohol-related etiology, and treatment in the earlier era were associated with the unfavorable composite outcome. Age, sex, preoperative BMI, and preoperative PNI were not significantly associated with the outcome.

In the multivariable Firth penalized logistic regression model including delayed surgery, alcohol-related etiology, and surgical era, the variable of delayed surgery remained associated with the unfavorable composite outcome (OR 20.1, 95% CI 2.26–2656; $p = 0.003$). The wide confidence interval indicates substantial imprecision, and the estimate should therefore be interpreted cautiously. In a sensitivity analysis using a ≥ 36 -month threshold, the association was attenuated after adjustment for surgical era (OR 3.44, 95% CI 0.96–13.17; $p = 0.057$), further underscoring that this study does not establish a single optimal timing threshold.

Table 6
Univariable and multivariable analyses for composite outcome

Analysis	Variable	Univariable OR (95% CI)	<i>p</i> value	Multivariable OR (95% CI)	<i>p</i> value
Primary analysis	Age	0.985 (0.941–1.032)	0.519	—	—
	Male sex	1.24 (0.344–5.45)	0.752	—	—
	Alcohol-related etiology	19.4 (2.36–2525)	0.002	16.6 (1.80–2220)	0.009
	Preoperative treatment duration > 12 months	25.3 (3.11–3293)	< 0.001	20.1 (2.26–2656)	0.003
	Surgical era 2015–2024	0.185 (0.054–0.598)	0.005	0.228 (0.049–0.914)	0.037
	Preoperative BMI	0.884 (0.742–1.025)	0.106	—	—
	Preoperative PNI	1.006 (0.938–1.087)	0.870	—	—
Sensitivity analysis	Alcohol-related etiology	19.4 (2.36–2525)	0.002	16.9 (1.86–2279)	0.007
	Preoperative treatment duration ≥ 36 months	5.67 (1.84–19.61)	0.002	3.44 (0.962–13.17)	0.057
	Surgical era 2015–2024	0.185 (0.054–0.598)	0.005	0.247 (0.057–0.979)	0.046

Firth penalized logistic regression was used because of the limited number of events and complete separation. The corrected composite outcome incorporated new-onset DM only among patients without preoperative DM. The primary multivariable model included preoperative treatment duration >12 months, alcohol-related etiology, and surgical era (2015–2024 vs 2005–2014). The sensitivity model replaced the

>12-month variable with a ≥ 36 -month threshold. OR, odds ratio; CI, confidence interval; BMI, body mass index; PNI, prognostic nutritional index.

Discussion

Traditionally, endoscopic treatment centered on ESWL and ERCP was considered the first-line therapy for CP, whereas surgery was reserved for refractory cases^{11,12}. However, prolonged inflammation can lead to irreversible neural remodeling, pancreatic fibrosis, and progressive pancreatic dysfunction^{13–16}. With this background, the concept of “early surgery” emerged during the 2010s. The concept emphasized surgical intervention before the establishment of irreversible pancreatic damage^{17,18}. The 2020 International Consensus Guidelines for Surgery and the Timing of Intervention in Chronic Pancreatitis supported early surgical intervention for improved long-term pain control and preservation of pancreatic function³. Consistent with this concept, observational studies of patients undergoing the Frey procedure have also demonstrated favorable postoperative pain control and preservation of pancreatic function^{22,23}. In addition, long-term follow-up data from the ESCAPE trial showed that superior long-term pain control was provided by early surgery compared with an endoscopy-first strategy, further challenging the conventional step-up approach in CP management^{5,19}. The 2021 Japanese clinical practice guidelines have discouraged administering repetitive endoscopic treatments over a long time period (> 2–3 years), and recommended considering surgical intervention when durable pain relief could not be achieved endoscopically⁴. However, the clinically relevant timing of surgical referral and intervention remains insufficiently defined.

Surgery at our institution has generally been considered within approximately 1 year of treatment initiation. We therefore expressed the primary clinical cutoff as surgery within 12 months (≤ 12 months) versus after 12 months (> 12 months). Neither recurrent postoperative pain nor new-onset DM occurred in the early group, whereas both outcomes occurred in the delayed group and increased stepwise with longer treatment duration. These findings demonstrate an association between longer preoperative treatment duration and adverse postoperative outcomes, but they do not establish that surgery within 12 months is an optimal or causal threshold. Rather, approximately 1 year may represent a clinically relevant point at which surgical referral should be reconsidered in appropriately selected patients when durable disease control with continued medical or endoscopic treatment appears unlikely.

ROC analyses provided complementary rather than prescriptive timing information. The maximum-Youden cutoffs were 38 months for recurrent pain and 58 months for new-onset DM, whereas sensitivity-oriented thresholds were much earlier, at 14 and 13 months, respectively. The Youden index identifies a statistically balanced discrimination point and should not be interpreted as the optimal time for surgery. Notably, the sensitivity-oriented thresholds were close to the institutionally based 1-year boundary, supporting further evaluation of surgical referral around 1 year in patients with persistent symptoms. Observational series of the Frey procedure have likewise reported favorable pain relief and pancreatic functional outcomes after surgical treatment^{21,22}.

Importantly, these findings do not contradict recommendations discouraging prolonged repetitive endoscopic treatment. Rather, they suggest that selected patients with persistent symptoms may merit surgical assessment earlier than the 2–3-year upper limit discussed in guidelines. However, the present data do not establish 12 months as a universal causal threshold. The 1-year boundary should be regarded as a clinically interpretable hypothesis that was supported by the absence of adverse outcomes in the early group and by sensitivity-oriented ROC thresholds, and it requires external validation.

Malnutrition is common in patients with CP because of chronic pain, reduced oral intake, malabsorption, and impaired glucose metabolism²⁰. Previous studies examining the relationship between surgery for CP and postoperative nutritional status have been limited, although improvements in BMI, serum albumin levels, and nutritional indices after the Frey procedure have been reported^{6,7,21}. In this study, PNI improved significantly at 1 year after surgery in the overall cohort, whereas BMI and serum albumin did not show statistically significant changes. However, among patients with preoperative malnutrition, the levels of serum albumin and PNIs improved significantly, and the BMI values showed a trend toward improvement. These findings suggest that surgical treatment for CP may contribute to postoperative nutritional recovery, particularly in patients with impaired nutritional status before surgery.

Limitations

This study has several limitations. First, it was a retrospective single-center study with only 65 patients, 19 of whom underwent surgery within 12 months, and the number of outcome events was small. Estimates from Firth regression therefore had wide confidence intervals and should be considered exploratory. In particular, the association observed for alcohol-related etiology should be interpreted cautiously because of the very wide confidence interval. Second, the study spanned 20 years, during which endoscopic therapy, perioperative management, patient selection, and institutional surgical experience evolved. Although the proportion of early versus delayed surgery did not differ significantly between 2005–2014 and 2015–2024, adverse outcomes were more frequent in the earlier era, and era remained associated with the composite outcome after adjustment. Residual temporal confounding therefore cannot be excluded. Third, residual confounding related to disease severity, pancreatic morphology, treatment selection, the intensity and number of repeated endoscopic procedures, and lifestyle factors such as alcohol consumption could not be addressed fully. Preoperative treatment types were compared between groups, but repeated-session counts could not be reconstructed reliably from the available dataset. Fourth, objective evaluation of postoperative exocrine function was difficult because all patients received pancreatic enzyme replacement therapy. Fifth, nutritional analyses were limited by missing data, particularly for BMI. Finally, postoperative pain was assessed retrospectively based on the need for medical consultation and therapeutic intervention rather than using a validated pain assessment tool, such as the Izbicki pain score²⁴. Because the detailed information required to calculate the Izbicki pain score retrospectively was not consistently available in the medical records, quantitative assessment of pain severity and changes in pain intensity was not feasible. Consequently,

our definition may have captured clinically significant pain recurrence but may not have reflected milder pain or changes in pain-related quality of life adequately.

In summary, our findings suggest that, for patients with CP who remain symptomatic despite medical or endoscopic treatment, surgical referral at approximately 1 year of treatment initiation may be clinically appropriate in selected patients and may be associated with lower risks of recurrent postoperative pain and endocrine deterioration compared with later intervention.

Conclusions

Longer preoperative treatment duration was associated with progressively higher risks of clinically significant postoperative pain recurrence and new-onset DM after surgery for chronic pancreatitis. Patients who underwent surgery within 12 months had particularly favorable outcomes, and the association between delayed surgery and the composite outcome persisted after adjustment for surgical era. However, the small sample size, wide confidence intervals, retrospective design, and temporal changes in care preclude causal inference or determination of a single optimal timing threshold. These findings suggest that, in appropriately selected patients, surgical referral within approximately 1 year of treatment initiation may be a clinically relevant strategy and warrant prospective multicenter validation.

Abbreviations

Alb, albumin; AUC, area under the curve; BMI, body mass index; CI, confidence interval; CJ, choledochojejunostomy; CP, chronic pancreatitis; DM, diabetes mellitus; DP, distal pancreatectomy; ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; IQR, interquartile range; LPJ, lateral pancreaticojejunostomy; MPD, main pancreatic duct; OR, odds ratio; PD, pancreaticoduodenectomy; PF, postoperative pancreatic fistula; PNI, prognostic nutritional index; QOL, quality of life; ROC, receiver operating characteristic; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of Nagoya City University Hospital (approval number: 60-18-0025) and was conducted in accordance with the Declaration of Helsinki. The requirement for individual informed consent was waived by the Institutional Review Board because of the retrospective nature of the study. Information regarding the study was disclosed to patients, who were provided with the opportunity to opt out of participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

YU conceived the study, collected and analyzed the data, and drafted the manuscript. YH, YD, KN, HM, TK, KS, TSh, YY, and HS contributed to data collection and interpretation. TSa critically revised the manuscript. YM and ST supervised the study. All authors reviewed and approved the final manuscript.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and ethical considerations but are available from the corresponding author upon reasonable request.

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Figures

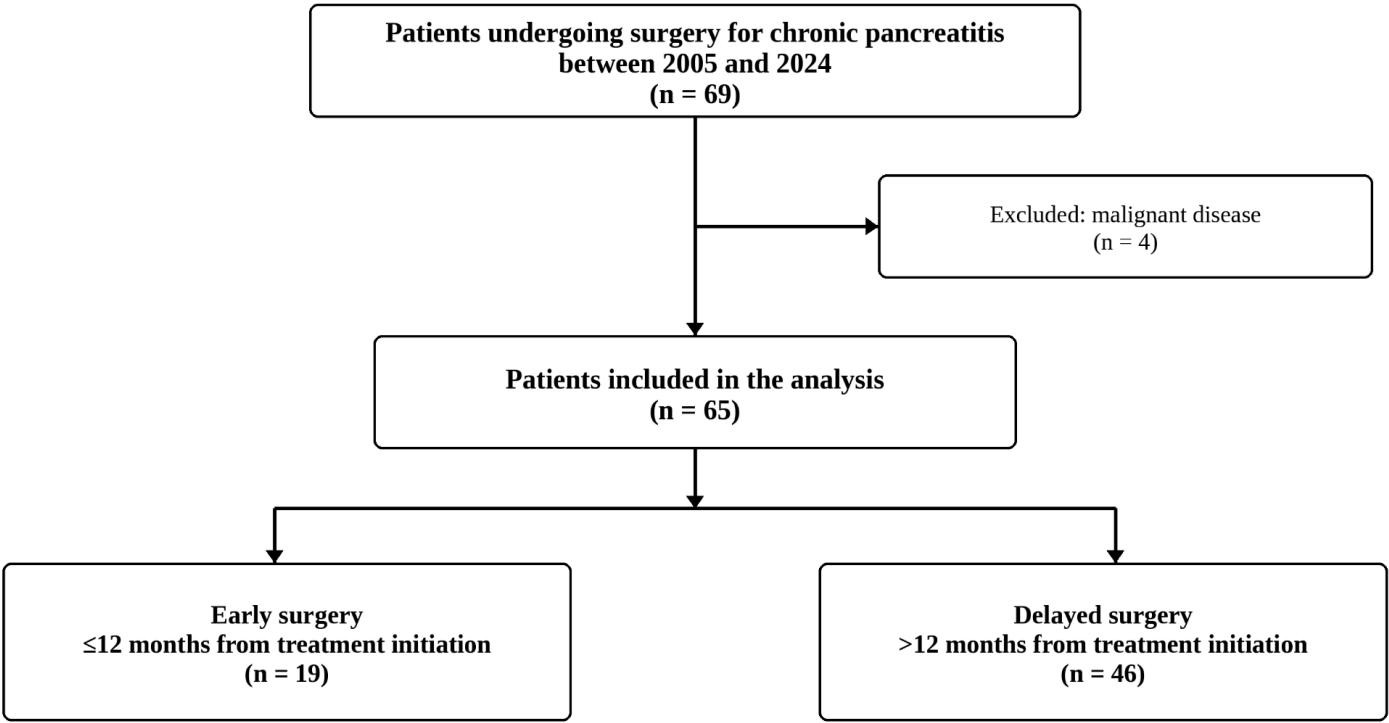


Figure 1

Flow diagram showing enrollment of the study patients

A total of 69 patients underwent surgery for chronic pancreatitis between 2005 and 2024. After exclusion of 4 patients with malignant disease, 65 patients were included in the analysis. These patients were categorized into an early-surgery group (≤ 12 months from treatment initiation; $n = 19$) and a delayed-surgery group (> 12 months; $n = 46$).

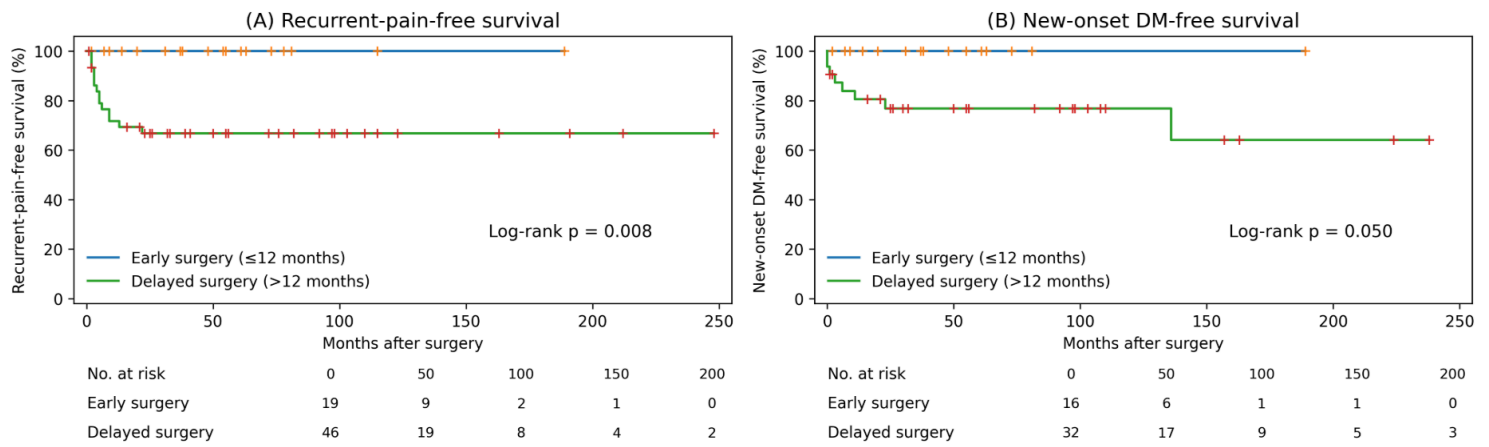


Figure 2

Kaplan–Meier curves for postoperative outcomes.

(A) Recurrent-pain-free survival. No recurrent postoperative pain occurred in the early-surgery group. In the delayed-surgery group, recurrences occurred predominantly during the early postoperative period; the latest recorded pain recurrence was at 22 months. Log-rank $p = 0.008$.

(B) New-onset diabetes mellitus (DM)-free survival among the 48 patients without preoperative DM (early surgery, $n=16$; delayed surgery, $n=32$). No new-onset DM occurred in the early-surgery group. Eight events occurred in the delayed-surgery group, including one late event at 136 postoperative months. Log-rank $p=0.050$.

Numbers at risk are shown below each graph.

Figure 3. ROC Analysis for Disease Duration Predicting Postoperative Pain Recurrence and New-Onset Diabetes Mellitus

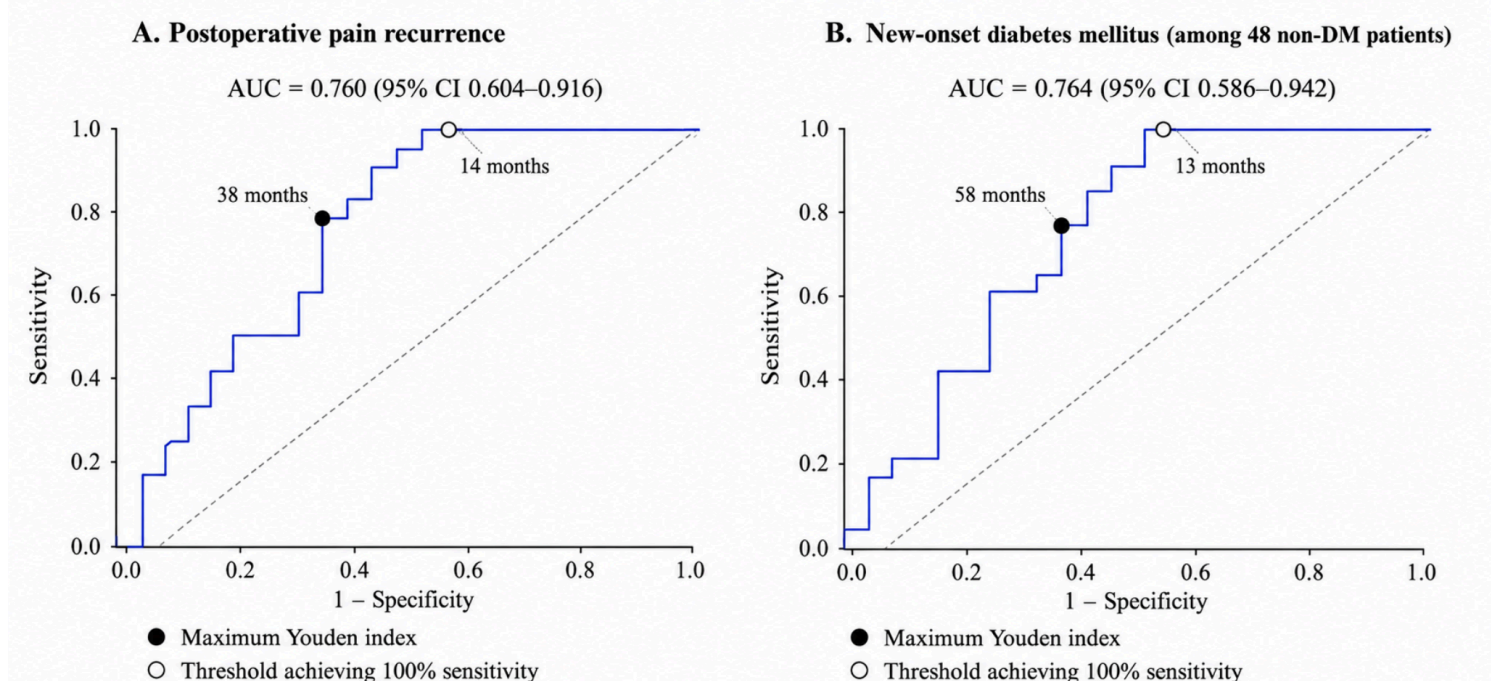


Figure 3

ROC curves for preoperative treatment duration and postoperative outcomes

(A) Recurrent postoperative pain. The maximum-Youden cutoff for preoperative treatment duration was 38 months (AUC = 0.760). The highest threshold retaining 100% sensitivity was 14 months.

(B) New-onset diabetes mellitus (DM), analyzed among the 48 patients without preoperative DM. The maximum-Youden cutoff was 58 months (AUC = 0.764). The highest threshold retaining 100% sensitivity was 13 months.

Closed circles indicate cutoff values determined by the maximum Youden index, whereas open circles indicate sensitivity-oriented thresholds used for clinical interpretation.

AUC, area under the curve; DM, diabetes mellitus.