Surgery Today (2023) 53:930–939
https://doi.org/10.1007/s00595-023-02653-5

ORIGINAL ARTICLE

Surgical outcomes of the Frey procedure for chronic pancreatitis: correlation between preoperative characteristics and the histological severity of pancreatic fibrosis

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Received: 5 September 2022 / Accepted: 8 December 2022 / Published online: 9 February 2023

Abstract

Purpose To evaluate the efficacy of the Frey procedure and clarify the relationship between preoperative characteristics and the histological severity of chronic pancreatitis (CP).

Methods Thirty patients who underwent the Frey procedure for CP between January, 2002 and December, 2020, at our hospital, were enrolled in this study. The specimen cored out of the pancreatic head was assessed for CP severity. We evaluated preoperative status and surgical outcomes according to CP severity.

Results Long-term pain relief was achieved in all 26 patients with sustained long-term follow-up, with complete pain relief attained in 19 (63%). Albumin levels were significantly higher 1 year postoperatively than preoperatively ($p=0.038$). Histological fibrosis was assessed in the 26 patients as follows: normal ($n=4$; 15%), mild ($n=8$; 31%), moderate ($n=2$; 8%), and severe ($n=12$; 46%). These patients were divided into two groups according to the severity of fibrosis: normal/mild ($n=12$) and moderate/severe ($n=14$). The rates of diffuse calcification on preoperative computed tomography (CT) (71% vs. 17%, $p=0.008$) and islet atrophy on insulin immunohistochemistry (100% vs. 33%, $p<0.001$) were significantly higher in the moderate/severe group than in the normal/mild group.

Conclusion The Frey procedure can achieve good pain relief and improve nutritional status. The severity of fibrosis can be predicted based on the extent of calcification on preoperative imaging studies.

Keywords Calcification · Diabetes mellitus · Histology · Islet atrophy · Pancreatitis

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Introduction

Chronic pancreatitis (CP) is a progressive inflammatory disease accompanied by irritable pain and functional disorders. Once CP develops with pain and morphological changes, therapeutic intervention is required. Conservative management with an analgesic agent is the first treatment strategy, followed by endoscopic intervention, with or without extracorporeal shock wave lithotripsy (ESWL) [1, 2]. When these treatments have proven ineffective [1], the final option is surgery, which has a higher success rate of pain relief [3].

Recent reports have shown that early diagnosis and intervention is important to improve the long-term outcomes of CP before inflammation and fibrosis become established and irreversible [2, 4]. The diagnostic criteria for early CP were proposed using endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) [5]. However, a prospective survey revealed that early CP did not progress in most patients, while, in some, it was able to be detected before progression to definite CP [6]. However, the actual clinical course and histological development of CP remain unknown. Since CP is most often treated conservatively or endoscopically, histological evidence is rarely obtained. However, prediction of the severity of CP based on morphologic changes using imaging studies might help in the selection of a suitable therapeutic approach. Surgery can provide the opportunity to understand the histological changes in the pancreatic tissue.

We conducted the present study to evaluate the efficacy of the Frey procedure for CP, focusing on the relationship between preoperative characteristics and histological grade using the specimen cored out from the pancreatic head.

Methods

Study participants

Between January, 2002 and December, 2020, 36 patients with CP were seen at Mie University Hospital. Two patients underwent pancreaticoduodenectomy (PD) because of the possibility of pancreatic cancer with duodenal stenosis in one, and without duodenal stenosis in the other. Four patients underwent distal pancreatectomy because of limited inflammation with pseudocysts in three, and pseudoaneurysm in one. The remaining 30 patients underwent surgical drainage of the entire length of the pancreatic duct with pancreatic head resection via lateral pancreaticojejunostomy (Frey procedure). We reviewed the data of these consecutive 30 patients.

CP was diagnosed based on the characteristic abdominal pain, as well as clinical history, physical examination, and imaging studies such as ultrasonography (US), computed tomography (CT), and MRCP. The indication for surgical treatment was pain unable to be managed by medical therapy or endoscopic intervention, with or without stones in the pancreatic duct. The following information about the patient background was collected: age, sex, height, weight, preoperative and postoperative endocrine status, and laboratory data. Body weight loss of 1 kg or more during the follow-up period was recorded. The pancreatic appearance was assessed on imaging studies, the diameter of the main pancreatic duct (MPD) was measured, and MPD irregularity, defined as MPD dilatation with partial narrowing in some parts, was evaluated on magnetic resonance imaging (MRI). We also checked images for the spread of calcification, pancreatic head enlargement with inflammation, and bile duct stenosis, defined as common bile duct (CBD) dilatation of 7 mm or more with narrowing in the pancreatic head area. Preoperative endoscopic intervention and ESWL were noted. Surgical outcomes were assessed by operation time, blood loss, postoperative mortality, morbidity, and length of hospital stay. Abdominal pain, blood sugar (BS) control by the maintenance dose of insulin or hypoglycemic agents, and the onset of diabetes mellitus (DM), were evaluated postoperatively. Information on postoperative pain relief was collected from the patients' medical records. Complete pain relief was defined as no pain and partial pain relief was defined as slight pain but improved from the preoperative degree of pain.

Surgical procedure

The Frey procedure was performed as described by Frey and Smith [7]. By cutting the right gastroepiploic artery and vein and dissecting the transverse mesocolon, the pancreatic surface was completely exposed. Kocher's maneuver was performed routinely, to control accidental bleeding during the coring out of the pancreatic head. After cholecystectomy, a bile duct stent was inserted through the cystic duct for intraoperative cholangiography and left in place postoperatively for biliary decompression because inflammation of the pancreatic head sometimes constricts the biliary passage. The MPD was identified by ultrasonography, then punctured and incised along the needle. Using an ultrasonic dissector, the MPD was opened longitudinally from the pancreatic head to the tail. A hemostatic suture was secured to occlude the blood flow in the anterior arcade of the gastroduodenal artery before coring out the pancreatic head. The pancreatic head was cored out, confirming the depth of the MPD as well as the location of the intrapancreatic bile duct. Pancreatic stones were removed to the maximum extent possible. When bile duct stenosis was seen to be severe on intraoperative

cholangiography, choledochoduodenectomy was performed. We adopted choledochoduodenectomy rather than choledochojejunostomy because of concerns about the kink of the afferent jejunum in the anal side of the pancreatojejunostomy when performing choledochojejunostomy. In patients without MPD dilatation, the MPD can be detected by incising the pancreatic parenchyma vertically in the pancreatic neck. If there was severe inflammation and/or stones in the pancreatic tail, we added pancreatic tail resection to the longitudinal opening of the MPD. The transected jejunum was lifted through the antecolic route, and a longitudinal side-to-side pancreatojejunostomy was performed.

Postoperative follow-up

The patients were followed up in the outpatient clinic every 3 months in the first year and annually thereafter. Postoperatively, pancreatic enzyme replacement therapy was administered routinely with pancrelipase. When patients complained of any symptoms or the lab data showed any abnormal findings, imaging studies were performed.

Histological assessment

The resected specimen obtained by coring out the pancreatic head was examined for the severity of CP by hematoxylin and eosin staining. We used the following fibrosis scoring system proposed by Kloppel and Maillet [8] to evaluate the extent and distribution of fibrosis. Perilobular (or interlobular) fibrosis is defined as the presence of connective tissue in the interlobular spaces. Intralobular fibrosis is defined as an extension of perilobular fibrosis into the acinar lobules with partial (mild: 10%–40%, moderate: 40%–80%), or (almost) complete (severe: 80%–100%) fibrous replacement of the acinar cells. They assessed the fibrosis levels categorized into two stages: focal and diffuse, with a final total score ranging from 1 to 12. Our study included only samples of a limited area that were obtained during coring out. Therefore, we could not perform "diffuse" assessment, so applied only a "focal" score. In a previous study, a total fibrosis score of ≤ 6 was defined as mild pancreatic fibrosis, a total score of 7–9 was defined as moderate, and a total score of 10–12 was defined as severe [9]. In our study, the "focal" score was doubled and classified as mild to severe grades. Islet aggregation and atrophy were assessed using insulin immunohistochemistry. A pathologist assessed the histological grade of fibrosis and islet atrophy in all cases.

Comparative study according to the severity of fibrosis

Patients with CP treated by the Frey procedure were divided into two groups according to the severity of fibrosis. We compared the patient background information, preoperative morphological findings on imaging, preoperative interventional treatment, perioperative and postoperative surgical outcomes, and pain relief, between the two groups.

Statistical analyses

Categorical data were compared between the groups using the Chi-square and Fisher's exact tests, while continuous data were compared using the Mann–Whitney *U* test, and presented as medians and ranges. The Wilcoxon signed-rank sum test was performed to compare preoperative and postoperative laboratory data. Differences were considered significant at a p value of < 0.05. The study protocol was approved by the Medical Ethics Committee of Mie University Hospital (H2020-199).

Results

Whole patient analysis

Table 1 summarizes the backgrounds and characteristics of the patients with CP, who underwent the Frey procedure. We evaluated 30 patients (26 men (87%) and 4 women (13%), with a median age of 50 (35–71) years). The underlying cause of CP was alcohol consumption in 20 patients (67%) and it was idiopathic in 10 patients (33%). Body weight loss was evident in 5 of 22 patients with medical record data. Ten (33%) patients had DM, including seven treated with insulin, one treated with an oral hypoglycemic agent, and two with unknown treatment details. Laboratory investigation results of all patients were as follows: preoperative albumin, 4.0 (normal: 3.1–4.7) g/dL; total cholesterol, 159 (96–263) mg/dL; amylase 80 (9–392) U/L; and HbA1c, 5.7% (4.0%–10.3%).

Morphological characterization revealed that the median MPD diameter was 7.9 (1.0–13.3) mm. MPD irregularity was found on the MRI of 14 (52%) of 27 patients who underwent MRI. Pancreatic stones were found in 26 (87%) patients, which were limited to the pancreatic head in 12 and spread across the pancreas in 14. Pancreatic head enlargement was observed in 20 patients (67%) and pseudocyst was found in 13 (43%). Bile duct stenosis was found in 12 (40%) patients, 2 of whom underwent preoperative biliary drainage by ERBD. One of these two patients had preoperative jaundice.

Preoperative interventional treatment was performed for 20 (67%) patients. Fifteen (50%) patients underwent endoscopic drainage of the pancreatic duct, using endoscopic retrograde pancreatic drainage or endoscopic nasopancreatic drainage; one (3%) underwent EUS-guided drainage of a pseudocyst; and five (17%) underwent ESWL. Transcatheter

Table 1 Background and clinical characteristics of the patients with chronic pancreatitis who underwent Frey procedure

Variables	$n=30$
Age	50 (35–71)
Male: female	26: 4
BMI	20.1 (15.7–27.6)
Etiology alcoholic/non-alcoholic	20 (67%)/10 (33%)
DM	10 (33%)
Insulin use ($n=26$)	7 (23%)
Albumin (g/dL)	4.0 (3.1–4.7)
Total cholesterol (mg/dL)	159 (96–263)
Amylase (U/L)	80 (9–392)
HbA1c (%)	5.7 (4.0–10.3)
Morphological feature	
Maximum MPD diameter (mm)	7.9 (1.0–13.3)
MPD irregularity on MRI ($n=27$)	14 (52%)
Pancreatic head enlargement	20 (67%)
Pseudocyst	13 (43%)
Bile duct stenosis	12 (40%)
Stones	26 (87%)
Limited in pancreatic head/whole area	12 (40%) /14 (47%)
Preoperative interventional treatment	20 (67%)
ERPD, ENPD	15 (50%)
EUS-guided drainage	1 (3%)
ESWL	5 (17%)
TAE	3 (10%)
Previous operation for CP	1 (3%)
Duration before surgery (months)	28.5 (3–480)

BMI body mass index, *DM* diabetes mellitus, *HbA1c* glycated hemoglobin, *MPD* main pancreatic duct, *ERPD* endoscopic retrograde pancreas drainage, *ENPD* endoscopic nasopancreatic drainage, *EUS* endoscopic ultrasonography, *ESWL* extracorporeal shock wave lithotripsy, *TAE* transcatheter arterial embolization, *CP* chronic pancreatitis

arterial embolization (TAE) was performed preoperatively in three (10%) patients, who suffered spontaneous bleeding from a pseudoaneurysm. One patient had a history of Duval operation for CP and CT-guided drainage for delayed abscess. The period from the onset of symptoms to the operation was 28.5 (3–480) months.

Table 2 shows the surgical outcomes. The operative time was 427 (248–676) min and blood loss was 561 (50–2094) ml. Simultaneous choledochoduodenostomy was performed in all 12 (40%) patients with preoperative bile duct stenosis, to avoid postoperative jaundice being caused by poor biliary passage in intraoperative cholangiography. The length of the postoperative hospital stay was 16 (10–76) days. Complications of Clavien–Dindo (C-D) classification [10] grade 3a or higher developed in seven (23%) patients, and included bleeding from a pseudoaneurysms in six (20%). The bleeding points included the gastroduodenal artery (GDA) in two patients, the dorsal pancreatic artery in two, the posterior superior pancreatic duodenal artery in one, and the splenic artery in one. A pseudoaneurysm was found in the peripheral branch of the artery in four patients, whereas bleeding occurred from the preoperatively embolized GDA and the root of the splenic artery in two. No mortality was recorded. Long-term pain relief was achieved by the Frey procedure for all 26 patients with sustained follow-up. Complete pain relief was achieved for 19 (63%) of these patients.

With sustained follow-up, BS control improved after surgery, with a reduction of insulin or hypoglycemic agent dosage in four (44%) of the nine patients with DM. In contrast, new-onset DM developed in 4 (24%) of 17 patients without preoperative DM, after the Frey procedure. In the postoperative nutritional condition as an assessment of exocrine function, the albumin level was significantly higher than the preoperative level, 1 year after surgery ($p=0.038$). However, the total cholesterol, amylase, and C-reactive protein (CRP) levels did not change significantly after the operation (Fig. 1).

During long-term follow-up, pancreatic body cancer developed in one patient, who underwent PD 11 years after the Frey procedure. Another patient suffered recurrent pancreatitis in the pancreatic head with bile duct stenosis, possibly caused by drinking alcohol again, with insufficient drainage of the pancreatic head in the initial operation. This patient underwent PD 8 years after the Frey procedure.

The resected specimen was assessed histologically in 26 of the 30 patients who underwent the Frey procedure for CP. According to the fibrosis scoring system for CP [8], the findings were classified as normal pancreas in 4 patients (15%), as mild fibrosis in 8 (31%), as moderate fibrosis in 2 (8%), and as severe fibrosis in 12 (46%). Islet atrophy was observed in 18 (69%) of the 26 patients for whom islet assessment was possible using insulin immunohistochemistry (Fig. 2).

Comparative study according to fibrosis grade

The 26 patients were divided into 2 groups according to the grade of fibrosis: normal/mild ($n=12$) and moderate/severe ($n=14$). Table 3 summarizes the patients' background data. According to the preoperative morphological features, the rate of diffuse calcification was significantly higher in the moderate/severe group than in the normal/mild group (71% vs. 17%, $p=0.008$). Other morphological features were similar between the two groups and the preoperative patient characteristics and laboratory data did not differ significantly between the groups.

Table 4 shows the surgical outcomes. The operation time, blood loss, and postoperative complications were similar in the two groups. However, histological examination revealed that the rate of islet atrophy was significantly higher in the

Table 2 Surgical outcomes of the patients with chronic pancreatitis who underwent Frey procedure

Surgical outcomes	$n=30$
Simultaneous choledochoduodenostomy	12 (40%)
Operation time (min)	427 (248–676)
Blood loss (ml)	561 (50–2094)
Complications (C-D ≧ IIIa)	7 (23%)
Bleeding from pseudoaneurysm	6 (20%)
Postoperative hospital stay (days)	16 (10–76)
Lab data 1 year after operation	
Albumin (g/dL)	4.2 (3.2–5.0)
Total cholesterol (mg/dL)	139 (105–237)
Amylase (U/L)	91 (9–153)
Pain relief ($n=26$)	26 (100%)
Complete pain relief ($n=26$)	19 (63%)
New onset of DM in non-diabetic patients ($n=17$)	4 (24%)
DM improvement after surgery in diabetic patients ($n=9$)	4 (44%)
Pathological findings	
Pathological fibrosis grade ($n=26$) normal/mild/ moderate/ severe	4 (15%)/8 (31%)/2 (8%)/12 (46%)
Islet cell atrophy (insulin staining) ($n=25$)	18 (69%)
Reoperation during long-term follow-up	
Pancreatic body cancer	1 (3%)
Recurrence of inflammation in pancreatic head	1 (3%)

C-D Clavien–Dindo classification, *DM* diabetes mellitus

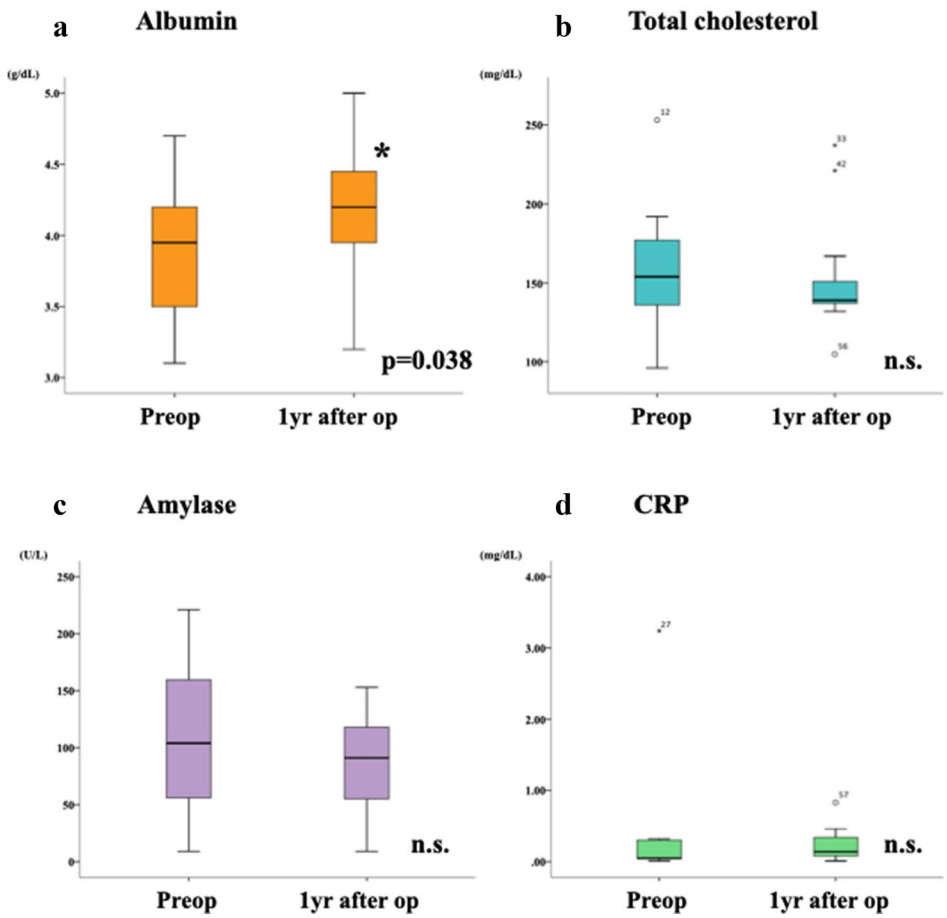
moderate/severe group than in the normal/mild group (100% vs. 33%, $p<0.001$).

Discussion

The Frey procedure for CP provided pain relief to all patients in the present series, achieving complete pain relief in 63%. Although new-onset DM developed in 24% of the non-diabetic patients, BS control improved after surgery in 44% of the patients with existing DM. Albumin levels were significantly elevated after surgery, reflecting an improvement in nutritional status. Histological examination of the resected specimens revealed that the severity of pancreatic fibrosis was correlated with islet atrophy. Furthermore, the finding of diffuse calcification in the entire pancreatic area on preoperative imaging studies was predictive of pancreatic fibrosis.

The present study demonstrated the Frey procedure to be a feasible operation that provided pain relief to all our patients. The success rates of pain relief achieved by surgical intervention for patients with CP have been reported to be as high as 80% [11]. In a meta-analysis comparing the outcomes of endoscopic and surgical treatment for CP, pain relief was significantly better after surgery (80.4%) than after endoscopy (72.6%) [3]. Therefore, the International Consensus Guidelines recommend early surgery within the first 2–3 years after diagnosis or symptom onset, and before five endoscopic procedures [11], because less pain relief after surgery was achieved when patients had been on long-term opioids and when conversion to surgery from endoscopic treatment was done [12–14]. A recent randomized clinical trial (RCT) comparing early surgery to step-up practice also showed lower pain scores in the early surgery group than in the endoscopy-first approach group during 18 months of follow-up [15]. In our study, the symptomatic period before surgery was 28.5 months, which was longer than that in a previous RCT study, and 67% of the patients had undergone endoscopic intervention or ESWL several times before surgery. However, pain relief was achieved in all our patients. Our strategy is to consider surgery whenever a patient with unmanageable pain is referred, regardless of the length of the symptomatic period.

Among the several surgical procedures for CP, the Frey procedure is the first choice at our institution because it achieves ductal decompression and removes inflammatory masses in the pancreatic head. The Frey procedure accounted for 83% of all CP operations at our institution. Recently, duodenum-preserving pancreatic head resection (DPPHR), including the Frey [7] and Beger [16] procedures, has become the standard practice for CP. A meta-analysis of RCTs comparing PD and DPPHR for CP showed that DPPHR had significantly better perioperative outcomes with



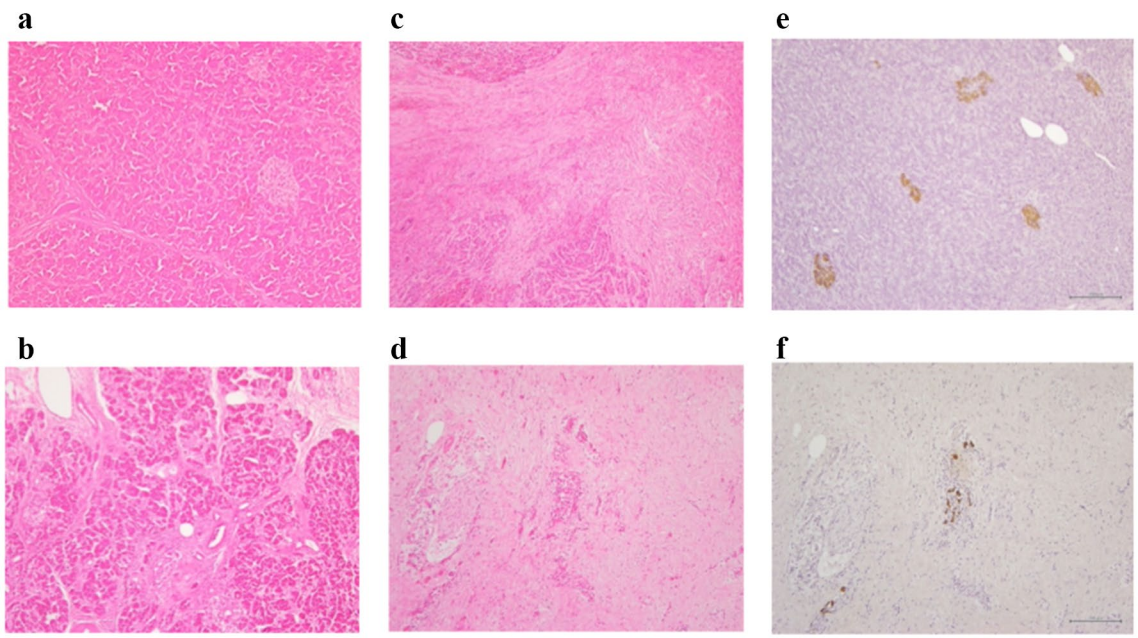


Fig. 1 Changes in laboratory parameters before and 1 year after the Frey procedure for chronic pancreatitis—**a** albumin, **b** total cholesterol, **c** amylase, **d** CRP

Fig. 2 Histology of a specimen resected during the Frey procedure **a**–**d**: H&E staining × 10; **e**, **f**: insulin immunohistochemistry × 10. **a** Normal pancreas, **b** mild fibrosis, **c** moderate fibrosis, **d** severe fibrosis, **e** normal islet tissue, **f** islet atrophy

Table 3 Backgrounds of the patients with chronic pancreatitis who underwent Frey procedure according to the severity of histological fibrosis in resected specimens

	Normal/mild group, $n=12$	Moderate/severe group, $n=14$	p value
Age	51.5 (35–71)	50.5 (35–69)	n.s
Male: female	11: 1	12: 2	n.s
BMI	19.1 (15.7–24.3)	20.1 (16.6–27.1)	n.s
Alcoholic/non-alcoholic	8 (67%)/4 (33%)	10 (71%)/4 (29%)	n.s
DM	2 (17%)	5 (36%)	n.s
Insulin use	1 (10%)	5 (39%)	n.s
Albumin (g/dL)	3.6 (3.5–4.6)	4.0 (3.1–4.7)	n.s
Total cholesterol (mg/dL)	177 (124–263)	134 (96–253)	n.s
Amylase (U/L)	94 (39–221)	78 (9–392)	n.s
HbA1c (%)	5.3 (4.9–8.6)	5.8 (4.0–10.3)	n.s
Morphological feature			
Maximum MPD diameter (mm)	7.5 (1.9–10.4)	7.7 (1.0–13.3)	n.s
MPD irregularity on MRI ($n=23$)	4 (40%)	7 (54%)	n.s
Pancreatic head enlargement	7 (64%)	11 (79%)	n.s
Pseudocyst	4 (33%)	9 (64%)	n.s
Bile duct stenosis	5 (42%)	5 (36%)	n.s
No stone or limited in pancreatic head/ stone in whole area	10 (83%)/2 (17%)	4 (29%)/10 (71%)	0.008
Preoperative interventional treatment	8 (67%)	10 (71%)	n.s
Endoscopic treatment	8 (67%)	8 (57%)	n.s
Duration before surgery (months)	15 (3–67)	44 (3–480)	n.s

BMI body mass index, *DM* diabetes mellitus, *HbA1c* glycated hemoglobin, *MPD* main pancreatic duct, *CP* chronic pancreatitis

Table 4 Surgical outcomes of the patients with chronic pancreatitis who underwent Frey procedure according to the severity of histological fibrosis in the resected specimens

Surgical outcomes	Normal/mild group, $n=12$	Moderate/severe group, $n=14$	p value
Simultaneous choledochoduodenostomy	5 (42%)	5 (36%)	n.s
Operation time (min)	393 (248–571)	428 (324–676)	n.s
Blood loss (ml)	577 (160–1297)	598 (50–2094)	n.s
Complication (C-D ≧ IIIa)	4 (40%)	2 (15%)	n.s
Bleeding from pseudoaneurysm	3 (30%)	2 (15%)	n.s
Postoperative hospital stay (days)	23 (10–43)	15.5 (10–76)	n.s
Lab data 1 year after operation			
Albumin (g/dL)	4.4 (4.0–4.6)	4.2 (3.6–5.0)	n.s
Total cholesterol (mg/dL)	149 (137–237)	139 (105–221)	n.s
Amylase (U/L)	113 (91–153)	58 (9–126)	n.s
Pain relief ($n=22$)	11 (100%)	11 (100%)	n.s
Complete pain relief ($n=22$)	8 (73%)	8 (73%)	n.s
Pathological findings ($n=25$)			
Islet cell atrophy	4 (33%)	14 (100%)	<0.001

C-D Clavien–Dindo classification

a shorter operation time and less need for blood transfusion, with a reduced length of hospital stay, postoperative morbidity, and better weight gain and quality of life than PD, although there were no significant differences in pain relief [17]. In contrast, a meta-analysis comparing the Frey and Beger procedures revealed that the Frey procedure required a shorter operation time and lower morbidity than the Beger procedure [18]. Moreover, the Frey procedure is superior technically, being a simpler procedure. In Japan, the guidelines recommend the Frey procedure for CP with an inflammatory mass in the pancreatic head per the DPPHR procedure [1] because the Beger procedure is rarely performed,

accounting for only 0.2% of the 476 surgical cases from 2005 to 2014. Regarding complications after the Frey procedure, a previous meta-analysis revealed that 24.73% of patients who underwent DPPHR suffered morbidity during the follow-up period [17]. An RCT comparing early surgery with DPPHR and the step-up approach also identified postoperative complications in 27% of the patients in the early surgery group. In our series, the rate of postoperative complications of C-D grade 3a or higher was 23%, comparable to that in previous reports. The majority of complications were bleeding from the pseudoaneurysm, and the rate was higher than that reported previously. However, all bleeding was managed successfully by immediate angiography and TAE. Notably, there was just one case of pancreatic fistula. The bleeding site involved various branches of the artery, but mainly the peripheral branches. Therefore, bleeding might be caused by insufficient arterial sealing during transection of the pancreatic parenchyma. During the surgical procedure, tight sutures in the pancreatojejunostomy and reliable hemostatic suturing of the gastroduodenal artery branch should be important to prevent bleeding.

Good postoperative exocrine function was reflected by the fact that the albumin level was significantly elevated 1 year after the operation. The albumin level is affected by nutritional status and the degree of inflammation. However, the CRP level remained low and unchanged preoperative and postoperatively. We consider that the elevated albumin level was indicative of nutritional improvement through better exocrine function. However, we did not assess exocrine function using the pancreatic function diagnostic test or checking for steatorrhea. Previous studies have shown that 19%–90% of patients with CP experience pancreatic exocrine insufficiency after the Frey procedure [19–21]. Among comparative studies of perioperative and postoperative exocrine function, one found no change in the presence of steatorrhea [20], whereas another showed weight gain after the Frey procedure [22]. On the other hand, better outcomes of exocrine insufficiency were noted in patients who underwent DPPHR than in those who underwent PD [17]. The authors of that study considered that the larger remnant pancreatic volume after DPPHR helped to preserve exocrine function better than PD. Previous experimental studies on CP have shown that the pancreatic secretion of amylase and lipase was restored in early surgery groups but not in late surgery groups [23]. However, in the clinical setting, RCTs comparing early surgery with step-up practice did not show differences in post-treatment exocrine function [15]. The reason for the nutritional status improvement after the Frey operation in our study is unclear; however, we speculate that decompression of the pancreatic duct contributes to mitigation of the progression of pancreatic atrophy with exocrine deficiency. On the other hand, non-surgical factors, such as pancreatic enzyme replacement therapy or cessation of drinking, might improve nutritional status because we administered pancrelipase routinely before and after surgery.

Regarding DM status, new-onset DM developed in 24% of the non-diabetic patients, whereas BS control improved postoperatively in 44% of the diabetic patients. In previous reports, new-onset DM developed in 7%–18% of patients after the Frey procedure for CP [22–25]. However, it is not clear how many patients would develop DM during the natural course of CP. The fact that DM improved after the Frey procedure in 44% of the diabetic patients in our study suggests that decompression of the pancreatic duct might prevent progression of endocrine deficiency. A previous study also showed that early surgical intervention with pancreatojejunostomy could sustain integrated serum C-peptide secretion [26]. In an RCT comparing early surgery with step-up practice, endocrine insufficiency developed more often in the endoscopy-first approach group than in the early surgery group, although the difference was not significant [15]. These reports support our conclusion that the Frey procedure can recover endocrine function in some CP patients.

To our knowledge, this is the first study to evaluate the histological findings of resected specimens obtained during coring out in the Frey procedure. Previously, histological changes were assessed in large specimens obtained by PD, DP, and total pancreatectomy or autopsy [8, 9, 27]. However, such a large specimen is rarely obtained in the era of DPPHR, as in most CP operations. Moreover, most patients with CP are treated initially with analgesic agents or endoscopic interventions with/without ESWL and there are no true histological findings. Even pancreatojejunostomy without pancreatic head resection, such as by the Puestow or Partington procedure, does not provide any specimens for histological examination. Therefore, it is unclear how accurately the severity of CP can be assessed by imaging studies, laboratory data, and symptoms. In our study, preoperative diffuse calcification in the whole pancreatic area on imaging was a sign of severe fibrosis in the pancreatic tissue. In a previous study, Amman et al. [9] revealed that marked progression of fibrosis with the duration of CP was associated with an increased incidence of pancreatic calcification, but they did not evaluate the extent of calcification. Another study showed that MRI features were significantly correlated with pancreatic fibrosis; however, there were no cases of pancreatic calcification included [27]. On the other hand, our moderate/severe fibrosis group had a significantly higher rate of islet atrophy than our normal/mild fibrosis group and the DM rate was slightly higher in the former group, although the difference was not significant. These findings may reflect atrophy of the islet cells. DM is a frequent complication of CP, with a point prevalence of approximately 40% [28, 29]. In a large cohort reported from USA, CP patients with DM were more likely to have pancreatic calcifications, atrophy, and exocrine insufficiency [30]. These findings suggest that

the morphological progression of CP is correlated with the severity of DM. In our study, the preoperative duration was longer in the moderate/severe group than in the normal/mild group, but without significance because of the small sample size. This may imply that pancreatic disease progression is proportional to the duration of illness. Moreover, pancreatic fibrosis seems to develop with calcification and islet atrophy over time.

The main limitation of our study was that it was a retrospective single-center study with small sample size. Postoperative pain assessment and exocrine and endocrine functions should be assessed prospectively using objective pain scores such as the Izbicki pain score, the *N*-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) test, and the oral glucose tolerance test (OGTT), respectively. Therefore, these results should be confirmed by studies on a larger cohort.

In conclusion, the Frey procedure achieved good pain relief for patients with CP and improved their nutritional status, as evidenced by increased albumin levels. While the degree of histological fibrosis varied in the histological examination of resected specimens, the severity of fibrosis correlated with the extent of calcification seen on imaging studies and islet atrophy in the histological analyses.

Data availability Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

Declarations

Conflict of interest We have no conflict of interest to declare.

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