

Short- and long-term outcomes of the Frey procedure for chronic pancreatitis: a single-center experience and summary of outcomes in Japan

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Received: 21 March 2017 / Accepted: 18 May 2017 / Published online: 8 June 2017
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Abstract

Purpose To evaluate the short- and long-term outcomes of the Frey procedure for chronic pancreatitis (CP).

Methods The subjects of this study were 12 patients who underwent the Frey procedure for CP between January, 2000 and December, 2016. We assessed pain relief, weight gain, and exocrine/endocrine insufficiency during follow-up.

Results The study population comprised 11 men and 1 woman (91.7% vs. 8.3%; mean age, 50.3 ± 6.8 years; range 39–61 years). Pancreatitis was caused by alcohol in 9 (75%) patients and was idiopathic in 3 (25%) patients. The mean follow-up period was 82.5 ± 46.5 months (range 16.9–152.1 months). There was no operative mortality, but three patients (25%) suffered postoperative morbidity. All patients were pain-free at the time of discharge. There was no case of new-onset diabetes mellitus after surgery, although one patient (8.3%) suffered exocrine insufficiency. The body weight and body mass index of all patients improved during follow-up. Only one patient continued to suffer pain in the long term.

Conclusion The findings of this long-term follow-up of patients who underwent the Frey procedure suggest that it offers effective pain relief and is a safe technique for the management of CP.

Keywords Chronic pancreatitis · Frey · Surgery · Pain · Long-term follow-up

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Introduction

Chronic pancreatitis (CP) is a long-standing inflammatory disease of the pancreas, manifesting as severe pain and malabsorption. Although the severe pain can often be managed with medication, some patients need surgical intervention. The surgical strategies involve resection of the inflammation and drainage of parenchymal pressure and ductal hypertension. The representative surgery for former is pancreaticoduodenectomy (PD). PD is useful for removing the inflammatory mass from the pancreatic head, but it is associated with high mortality and morbidity, including pancreatic fistula and cholangitis, despite CP being a benign disease [1–3]. To shift to a safer procedure, we have been performing the Frey procedure since 2000. The Frey procedure, which involves performing a longitudinal pancreaticojejunostomy with coring-out of the pancreatic head, is considered ideal for achieving both resection and drainage [4]. We performed the Frey procedure for 12 patients in our hospital and confirmed its therapeutic usefulness based on our experience. We report the short- and long-term outcomes of these patients.

Patients and methods

This was a retrospective study of 12 patients with CP, who underwent the Frey procedure at Hyogo College of Medicine between January, 2000 and December, 2016. The diagnosis of CP was based on clinical history and physical examination, as well as ultrasonography (US), computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) findings. The imaging examinations identified calcification of the pancreas in all patients.

Exocrine pancreatic dysfunction was based on the presence of steatorrhea. Patients were asked to answer a questionnaire about the number of stools passed per day, as well as the smell, appearance, and color of the stools. Steatorrhea was defined as more than three stools per day with a nauseating smell and a greasy and pale appearance [5]. Diabetes mellitus was defined as a blood glucose level of >200 mg/dl 2 h after a 75-g oral glucose load. Endocrine pancreatic dysfunction was assessed based on the level of glycosylated hemoglobin and the need to treat diabetes mellitus with diet, oral hypoglycemic agents, or insulin. The prescribed analgesics were classified according to the World Health Organization analgesic ladder as follows: class 1, acetaminophen; class 2, acetaminophen and weak opioid combinations; and class 3, opiates [6]. Pancreatic fistula (PF) was defined according to the International Study Group on Pancreatic Fistula (ISGPF) criteria [7]. Mortality and morbidity were defined, respectively, as death or complications occurring either within 30 days after surgery or during the hospital stay. The study was approved by the ethical committee of Hyogo College of Medicine (No. 2597).

Surgical procedure

The surgical procedure was performed as described by Frey and Smith [4]. The dilated main pancreatic duct (MPD) was incised from the anterior surface of the pancreas. The opening of the MPD was extended as much as possible to the pancreatic tail, and then to the head, which was cored out. The jejunum was dissected 20 cm distal to the Treitz ligament and opened longitudinally on the anti-mesenteric side. Longitudinal side-to-side pancreaticojejunostomy was performed using a 4-0 absorbable monofilament running suture, and finished with end-to-side jejunojejunal anastomosis. A closed suction drain was inserted into the splenic hilum through the cranial space of the pancreaticojejunostomy.

Figure 1 shows the following representative case. A 55-year-old man was admitted to our hospital for investigation of abdominal and back pain. Abdominal CT showed calcification in the pancreas (Fig. 1a). The Frey procedure was performed to treat CP and relieve the severe abdominal and back pain (Fig. 1b, c). Histological examination confirmed CP (Fig. 1d). The postoperative course was uneventful and the patient was discharged from hospital on postoperative day 15, since then he has not reported further pain in 9 years.

Postoperative follow-up

The patients were reviewed daily by an independent physician until their discharge from hospital. Blood tests, which

included serum amylase, hemoglobin, white blood cell count, platelet count, and liver function tests were done postoperatively. The peripancreatic drainage fluid was collected and measured and the amylase level was monitored postoperatively. Chest and abdominal radiography was performed postoperatively. The patients underwent follow-up examinations in an outpatient clinic every 3 months in the first year and then yearly thereafter.

Data collection

Data were collected during face-to-face interviews on admission to hospital and during follow-up examinations at the outpatient clinic. The information recorded in the interview included demographic information, analgesic requirements, exocrine/endocrine pancreatic function, and co-morbid conditions.

Statistical analysis

Quantitative data are expressed as mean \pm standard deviation and range. The Chi-squared test or Fisher's exact test were used to compare categorical variables, as appropriate. *P* values of <0.05 were considered to indicate significance. Statistical analyses were performed using SPSS version 19.0 software (SPSS Company, Chicago, IL, USA).

Results

Preoperative data

Table 1 shows the clinicopathological characteristics of the 12 patients (male, $n = 11$, 91.7%; female, $n = 1$, 8.3%; mean age, 50.3 ± 6.8 years, range 39–61 years) enrolled in the present study. The cause of CP was alcoholic in 9 patients (75%) and idiopathic in 3 patients (25%). The mean interval between the onset of symptoms and surgery was 5.3 ± 3.0 years. At the time of surgery, the mean body weight was 54.5 kg (range 40.8–77 kg) and the mean body mass index (BMI) was 19.6 ± 3.1 (range 15.5–26.9). Preoperatively, eight patients (66.7%) had diabetes mellitus and 4 patients (33.3%) had exocrine insufficiency. All patients used painkillers regularly for chronic abdominal or back pain. Pain control required class 1 analgesics in eight patients (66.7%), class 2 analgesics in three patients (25%), and class 3 analgesics in one patient (8.3%). Three patients were treated conservatively for CP prior to the Frey procedure, by pancreatic stenting in one, extracorporeal shock wave lithotripsy on one, and pseudocyst drainage in one.

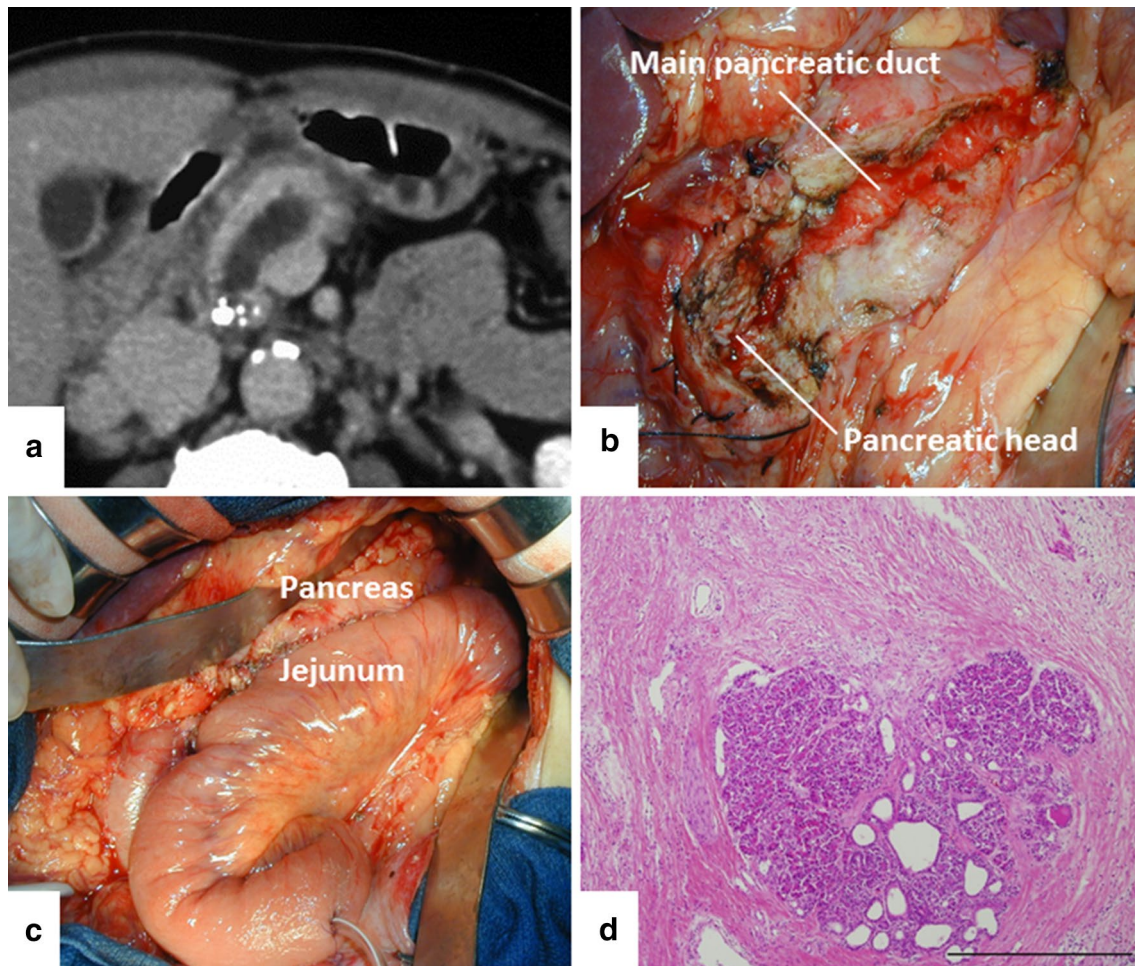


Fig. 1 **a** Abdominal computed tomography showed calcification in the pancreas. **b** The opening of the main pancreatic duct and the coring-out of the pancreatic head. **c** Longitudinal side-to-side pancreatico-

jejunostomy. **d** Histological examination revealed chronic pancreatitis (H&E staining $\times 100$)

Perioperative data

The mean operative time was 452 ± 84 min (range 371–610 min) and the mean blood loss was 481 ± 334 ml (range 10–1150 ml). The final histological analysis of all resected specimens confirmed CP. Postoperative surgical complications developed in three patients (25%). Grade B PF (which usually needs drainage) developed in association with infection in one patient (8.3%) and was treated with antibiotics. One patient suffered intra-abdominal hemorrhage and required blood transfusion. The remaining patient suffered adhesional ileus and was treated conservatively. The mean hospital stay was 28.9 days (range 15–62 days). There was no operative mortality.

Postoperative data

Table 2 summarizes the postoperative outcomes. The mean follow-up period was 82.5 ± 46.5 months (range 16.9–152.1 months). All patients presented with pain before surgery, but none had pain at the time of discharge. The incidence of diabetes mellitus did not increase after surgery. Although new-onset diabetes mellitus did not develop in any of the patients after surgery, pre-existing diabetes worsened in one patient. Exocrine insufficiency was observed before surgery in four patients (33.3%) and after surgery in five patients (41.7%). The mean body weight and BMI improved postoperatively. Figure 2 shows the changes in body weight. The pre- and postoperative mean body weights were 54.5 ± 11.7 kg and 57.1 ± 13.2 kg,

Table 1 Clinicopathological characteristics of the patients

Patient	Age	Gender	Chief complaint	Etiology	Interval between symptoms and surgery (year)	Preoperative data						Postoperative data							
						Body weight	BMI	DM	HbA1c (%)	FBS (mg/dl)	Exocrine insufficiency	Analgesics	Body weight	BMI	DM	HbA1c (%)	FBS (mg/dl)	Exocrine insufficiency	Analgesics
1	54	F	Back pain	Idiopathic	5	46.4	18.9	+	6.7	152	–	Class 1	48	19.5	+	7.2	155	–	No
2	49	M	Back pain	Alcoholic	4	45.8	18.4	+	6.9	129	+	Class 3	48	19.3	+	7.3	153	+	No
3	59	M	Abdominal pain	Alcoholic	4	48	20.6	–	5.4	117	–	Class 2	45	19.3	–	5.6	104	–	No
4	50	M	Abdominal pain	Alcoholic	5	51	18	–	4.7	98	+	Class 1	52	18.4	–	4.7	102	+	No
5	39	M	Abdominal pain, back pain	Alcoholic	2	72	21.9	–	5.5	103	–	Class 2	79	24	–	5.4	118	–	No
6	61	M	Back pain	Idiopathic	3	77	26.9	+	8.8	193	–	Class 1	81	28.3	+	8.7	179	–	No
7	55	M	Abdominal pain, back pain	Idiopathic	2	54.6	18.6	+	7.8	260	–	Class 1	63	21.5	+	6.7	141	–	No
8	46	M	Back pain	Alcoholic	10	66.6	22.9	+	7.6	140	–	Class 1	65.5	22.5	+	7.6	132	+	No
9	42	M	Abdominal pain	Alcoholic	4	49.2	16.4	+	7.7	127	+	Class 1	52	17.4	+	7.8	131	+	No
10	52	M	Abdominal pain, back pain	Alcoholic	10	58.5	18.8	+	6.5	165	+	Class 1	63	20.3	+	6.5	146	+	No
11	54	M	Abdominal pain, back pain	Alcoholic	10	43.5	15.5	+	6.3	132	–	Class 1	48.5	17.3	+	8.5	212	–	No

Table 1 continued

Patient	Age	Gender	Chief complaint	Etiology	Interval between symptoms and surgery (year)	Preoperative data				Postoperative data									
						Body weight	BMI	DM	HbA1c (%)	FBS (mg/dl)	Exocrine insufficiency	Analgesics	Body weight	BMI	DM	HbA1c (%)	FBS (mg/dl)	Exocrine insufficiency	Analgesics
12	43	M	Abdominal pain, back pain	Alcoholic	5	40.8	17.9	–	5.2	85	–	Class 2	39.8	17.5	–	5.8	93	–	No
Patient	Age	Gender	Chief complaint	Etiology	Interval between symptoms and surgery (year)	Operation				Postoperative									
						Body weight	BMI	DM	HbA1c (%)	Operative time (min)	Intraoperative blood loss (ml)	Postoperative complications	Postoperative hospital stay (days)						
1	54	F	Back pain	Idiopathic	5		Frey		410	10	None	30							
2	49	M	Back pain	Alcoholic	4		Frey		610	1150	None	39							
3	59	M	Abdominal pain	Alcoholic	4		Frey		560	705	Ileus	62							
4	50	M	Abdominal pain	Alcoholic	5		Frey		393	415	Pancreatic fistula	60							
5	39	M	Abdominal pain, back pain	Alcoholic	2		Frey		540	240	None	25							
6	61	M	Back pain	Idiopathic	3		Frey		438	200	None	15							
7	55	M	Abdominal pain, back pain	Idiopathic	2		Frey		375	720	None	15							
8	46	M	Back pain	Alcoholic	10		Frey		384	285	None	19							
9	42	M	Abdominal pain	Alcoholic	4		Frey		371	400	None	26							
10	52	M	Abdominal pain, back pain	Alcoholic	10		Frey		524	960	None	21							
11	54	M	Abdominal pain, back pain	Alcoholic	10		Frey		375	310	Intra-abdominal hemorrhage	18							
12	43	M	Abdominal pain, back pain	Alcoholic	5		Frey		442	380	None	17							

BMI body mass index, DM diabetes mellitus, FBS fasting blood sugar

Table 2 The changes in general condition ($n = 12$)

	Preoperative	Postoperative	<i>P</i> value
Body weight (kg)	54.5 ± 11.7	57.1 ± 13.2	0.61
BMI	19.6 ± 3.1	20.4 ± 3.2	0.48
Diabetes mellitus	8 (66.7%)	8 (66.7%)	1
Exocrine insufficiency	4 (33.3%)	5 (41.7%)	0.67
Analgesics	12 (100%)	0 (0%)	<0.01
Class 1	8 (66.7%)	0 (0%)	
Class 2	3 (25%)	0 (0%)	
Class 3	1 (8.3%)	0 (0%)	

BMI body mass index

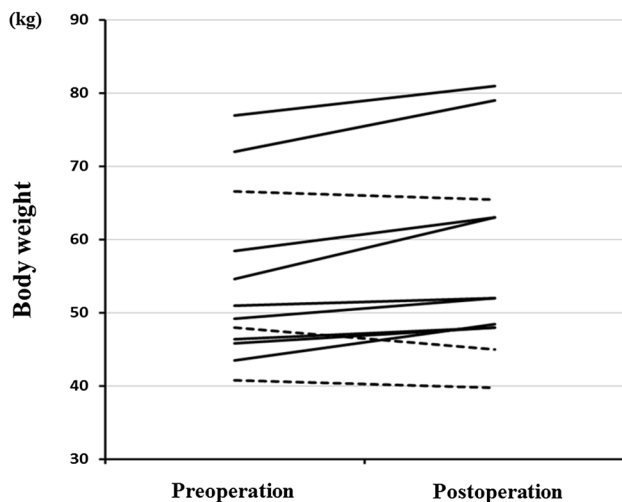


Fig. 2 Changes in body weight. Patients who gained weight and those who lost weight are shown as *solid* and *dotted* lines, respectively

Table 3 The outcomes of the patients with long-term follow-up ($n = 6$)

	Preoperative	Postoperative	<i>P</i> value
Body weight (kg)	58.3 ± 13	61.2 ± 13.3	0.71
BMI	20.0 ± 3.8	21.0 ± 3.7	0.65
Diabetes mellitus	4 (66.6%)	4 (66.6%)	1
Exocrine insufficiency	3 (50%)	2 (33.3%)	0.56
Analgesics	6 (100%)	1 (16.7%)	<0.01
Class 1	4 (66.6%)	1 (16.7%)	
Class 2	1 (16.7%)	0 (0%)	
Class 3	1 (16.7%)	0 (0%)	

BMI body mass index

respectively, with a mean body weight gain of 2.6 kg. 3 of the 12 patients lost weight after surgery. There were no significant differences between pre- and postoperative body weight ($P = 0.61$).

Six patients were followed up for more than 5 years. Table 3 summarizes the changes in their general condition. None of the patients suffered new-onset diabetes mellitus or new-onset exocrine insufficiency during the long-term follow-up period. Only one patient suffered pain during the long-term follow-up period. The general conditions of these patients have remained almost stable for more than 5 years.

Three of the nine patients with alcoholic pancreatitis (33%) stopped drinking and six (67%) reduced their alcohol intake. Pancreatic cancer did not develop in any of the patients during our surveillance.

Discussion

The present study analyzed outcomes of the Frey procedure performed for CP. Our data support that the Frey procedure can be performed safely, without mortality and with a low rate of severe morbidity. In fact, the general condition of all our patients improved, and they remained well even after 5 years.

The aims of surgery for CP are pain relief and preservation of the endocrine and exocrine functions of the pancreas. In the past, conventional PD and pylorus-preserving PD were considered the standard procedures for CP in patients with pancreatic head complications [8]. While these procedures can achieve pain relief, they are associated with high mortality and morbidity rates and poor results in terms of postoperative digestive function, with slow weight gain [1–3]. Moreover, diabetes mellitus develops in approximately 20% of patients who undergo these techniques [9, 10]. Duodenum-preserving resection of the head of the pancreas (described by Beger and Krauzberger) or local pancreatic head resection with a longitudinal pancreatojejunostomy (described by Frey and Smith) has been introduced as alternative surgical therapies. These procedures preserve the pancreatic parenchyma.

Since the introduction of the Frey technique, controversy has arisen about optimal surgical management, particularly in relation to possible improvement in functional outcome, perioperative morbidity, and quality of life. The Frey procedure is associated with an operative mortality rate of <1% and a morbidity rate of 9–39% [11–13].

In the present study, the perioperative mortality rate was 0%, but complications developed in three patients (25%). According to the Japan Clinical Oncology Group (JCOG) postoperative complications criteria, the complications in this study were graded as IIIa for one patient with PF, II for one patient with intra-abdominal hemorrhage, and IIIa for one patient with ileus [14]. The variability in the rate of PF after the Frey procedure (0–12%) is probably explained by the various definitions applied in the literature [13, 15]. In our study, the rate of PF was 8.3%. One patient suffered intra-abdominal hemorrhage, which was treated conservatively, although the patient required blood transfusion. In previous studies, reoperation was required for postoperative hemorrhage after the Frey procedure [16, 17]. Therefore, careful hemostasis during the Frey procedure is imperative. Exocrine insufficiency was evident postoperatively in 41.7% of the whole cohort and in 33.3% of the patients who were followed up over 5 years. Oral enzyme supplementation is now given systematically after major pancreatic surgery in many hospitals. New-onset diabetes mellitus developed during the follow-up period in 13–25% of patients in previous reports [18], but did not develop in any of our patients, although pre-existing diabetes deteriorated in one patient. None of our patients complained of pain during the short-term follow-up period. Ueda et al. [16] reported good long-term outcomes, including long-term pain relief after the Frey procedure for CP. In our study, one (16.7%) patient required pain killers in the long term. With regard to quality of life, Strate et al. [19] reported that 44% of their patients were able to return to professional work after surgery. Our results were even better, with 83.3% of the patients returning to their occupations.

To assess the strength of our assertions, we reviewed five Japanese studies on the Frey procedure [16, 17, 20–22]. Table 4 summarizes the clinicopathological characteristics and clinical outcomes reported in these studies vs. those in our study. The mean rate of pain relief after the Frey procedure was 95.2% in these five studies vs. 100% in our study; however, pain control was required even after 5 years by one patient who continued to drink. The mean rates of morbidity and mortality after the Frey procedure were 17.5% and 0% in the five studies vs. 25% and 0% in our study. PF and postoperative bleeding were the most common complications, followed by abdominal abscess. The mean rate of new-onset diabetes mellitus after the operation was 12.2% in the five studies vs. 0% in our study, although one of our patients suffered new-onset exocrine insufficiency soon after the operation.

A previous study reported that the mean rates of pain relief, morbidity, and mortality after the Frey procedure in Western countries were 87, 26.1, and 0.3%, respectively [23]. Despite the small sample size in Japan, the mean rates

Table 4 Clinicopathological characteristics and outcomes of Japanese patients who underwent the Frey procedure as documented in the six studies

Author	Year	Number of patients	M/F	Mean age	Etiology alcoholic/idiopathic/other	Mean interval between symptoms and surgery (year)	Preoperative pain (%)	Mean operative time (min)	Mean intraoperative blood loss (ml)	Morbidity (%)	Mortality (%)	Mean hospital stay (day)	Pain relief (%)	Mean weight gain (kg)	New-onset diabetes mellitus (%)	New-onset exocrine insufficiency (%)
Amikura [20]	1997	11	10/1	51.2	11/0/0	–	100	–	–	18	0	–	90	–	16.7	–
Egawa [17]	2010	71	66/5	48	61/6/4	–	100	244 ^a	439 ^a	14.1	0	19 ^a	100	–	–	–
Aimoto [21]	2013	6	6/0	51.5	5/1/0	–	100	362	718	16.7	0	28	100	–	0	0
Tanaka [22]	2014	28	26/2	47 ^a	24/3/1	–	100	335 ^a	662 ^a	21.4	0	20 ^a	96.4	–	25	–
Ueda [16]	2015	41	34/7	49	36/4/1	5.3	100	299	514	17.1	0	20	89.7	2.6	6.9	0
Our study	2017	12	11/1	50.3	9/3/0	5.3	100	452	481	25	0	28.9	91.6	2.6	0	8.3

^a Median

of pain relief, morbidity, and mortality after the Frey procedure appear to be better than those in Western countries.

In conclusion, the Frey procedure showed good efficacy and safety, in terms of morbidity and pain relief, for patients with CP. The benefits were evident throughout the long-term period. However, as the population of the present study was small, further studies on a greater number of patients will be necessary.

Compliance with ethical standards

Conflict of interest We declare no conflict of interest in association with the present study.

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