

Investigation of the influence of pancreatic surgery on new-onset and persistent diabetes mellitus

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Abstract

Aim: The management of diabetes mellitus (DM) after pancreatic surgery is a long-standing issue. We aimed to investigate DM concerning pancreatic surgery, including new onset diabetes mellitus (NODM), DM resolution, and the change in insulin excretion before/after pancreatic surgery.

Methods: We retrospectively investigated three different cohorts (total 403 patients) undergoing pancreatectomy. Of those, 275 patients without preoperative DM were investigated for the risk factors of NODM. Fifty-four patients without preoperative DM of the other cohort were assessed for pre/postoperative 24-hour urinary C-peptide excretion (24-hr CPR). To evaluate the influence of pancreatic surgery on DM treatment in patients with preoperative DM, 74 patients were investigated. In all those patients, the pancreatic volume in pre/postoperative images was assessed to estimate the resected pancreatic volume.

Results: NODM was observed in 60 patients (21%), and a lower ratio of remnant pancreatic volume (RRPV) was the only significant risk factor for NODM. Postoperative 24-hr CPR was significantly associated with two factors, RRPV and preoperative 24-hr CPR. Nine of 74 patients with preoperative DM achieved DM resolution after pancreatic surgery, and the presence of gastrointestinal anastomosis was a significant preferable factor for DM resolution.

Conclusions: Considering the management of DM after surgery, both predicting the postoperative pancreatic volume and the presence of gastrointestinal reconstruction are significant. We concluded that the combined assessment of the predicted remnant pancreatic volume and the preoperative 24-hr CPR value is useful to predict the postoperative pancreatic function.

KEYWORDS

DM resolution, NODM, pancreatic surgery

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1 | INTRODUCTION

Pancreatectomy is an optimal procedure for managing pancreatic diseases, including both malignant and premalignant diseases, despite its complications. New-onset diabetes mellitus (NODM) is a long-standing complication caused by pancreatectomy with a 3%-40% occurrence rate^{1,2} and is categorized as type 3c diabetes mellitus (DM) by the American Diabetes Association.³ Screening systems improve the detection of pancreatic disease,⁴ and the recent development of treatments for pancreatic disease has prolonged the survival time after surgery,^{5,6} leading to an increase in the long-term survival of patients undergoing pancreatectomy. DM is associated with an impaired quality of life with its long-term complications; however, the optimal management strategy for type 3c DM after pancreatectomy is unclear because DM due to pancreatectomy likely represents a phenotype that is clinically distinct from the majority of DM (type 1 or type 2).^{7,8}

Type 3c DM after pancreatic surgery consists of complicated situations because pancreatectomy resects pancreatic parenchyma-producing hormones related to both hyperglycemia and hypoglycemia, e.g. insulin, glucagon, and pancreatic polypeptide. In addition, gastrointestinal reconstruction, which is required in pancreaticoduodenectomy (PD) surgery, is regarded as one of the prophylactic options for NODM.^{9,10} The degree of endocrine deficiency might be related to the region of the pancreas resected due to the variation in the location of the islet. Previous reports concerning the risk factors for NODM after pancreatectomy indicated the following risk factors: pancreatic disease,¹⁰ surgery type (resection type, PD; distal pancreatectomy, DP; central pancreatectomy, CP) and the presence of gastrointestinal reconstruction,^{1,9,10} preoperative laboratory data associated with metabolic disease (cholesterol; glycated hemoglobin, HbA1c),^{11,12} body mass index,^{13,14} sex,¹³ and remnant pancreatic volume.^{1,12,13,15-18} However, those risk factors are controversial among previous reports. For example, Wu et al¹ demonstrated that the incidence of NODM was significantly different between surgery types in a systematic review ($n = 9873$ included in 36 studies; 21%, DP; 16%, PD; 6%, CP); conversely, according to their single-institute study, Nguyen et al¹⁹ suggested that NODM was unrelated to the type of surgery performed ($n = 472$; 45%, DP; 43%, PD). The association between resected pancreatic volume and NODM is not consistent. Three reports demonstrated that pancreatectomy of over 50% of the original pancreas volume was significantly accompanied by NODM,^{12,13,18} whereas other reports indicated no significant associations between the volume of the resected pancreas and NODM (including both patients undergoing PD and DP).¹⁵⁻¹⁷ As one of the reasons for these controversial results concerning risk factors for NODM, we suspected that the sufficient remnant pancreatic function differed in individuals and in order to consider the difference among individuals, not only the data of surgical information but also the data investigating pancreatic function needed to be collected. Several reports supported this speculation. Maxwell et al^{20,21} demonstrated that patients under the pre-diabetic range (5.7%-6.5%) tended to develop NODM after PD/DP.

Thus, we conducted this retrospective analysis, including three different cohorts (total 403 patients) who underwent pancreatectomy: to investigate the various data of the patients in association with NODM; to establish a readily available prediction tool using preoperative information that will enable the prediction of remnant pancreatic function; and to evaluate the influence of pancreatic surgery on anti-DM treatment.

2 | METHODS

2.1 | Patients

We investigated patients consisting of three different cohorts from three different standpoints.

All patients undergoing pancreatectomy in 2010-2014 were investigated for the incidence of NODM, and we excluded patients undergoing total pancreatectomy, patients undergoing pancreatectomy in whom the follow-up was less than 1 year postoperatively, and patients without sufficient information concerning DM before/after surgery. Consequently, 275 patients without preoperative DM were investigated for the incidence of NODM (Table 1; Figure S1).

For the assessment of remnant pancreatic function, all patients undergoing pancreatectomy from November 2018 to December 2019 were assessed for their preoperative 24-hour urinary C-peptide excretion (24-hr CPR), and postoperative 24-hr CPR was also checked at 1 month after surgery when the patients stayed and took enough food in the hospital without insulin-analog administration. Consequently, 54 patients without preoperative DM were assessed for the pre/postoperative 24-hr CPR (Table 2; Figure S2). When the level of 24-hr CPR was under 20 $\mu\text{g}/\text{d}$, the patients were regarded as having impaired insulin secretion, according to a previous report.²²

Information on treatment concerning DM after pancreatectomy in 74 patients who had been diagnosed with DM before surgery in 2010-2014 was obtained to evaluate the influence of pancreatic surgery on anti-DM treatments (Table 3; Figure S1). Patients with insufficient data concerning preoperative DM diagnosis were excluded from this study.

In our institute, we routinely administered pancreatic enzyme replacement therapy (PERT) to all patients undergoing pancreatectomy.

2.2 | Data collection

The data of patients before/after surgery were collected from existing medical records and used for analysis. Treatment histories of diabetes in other hospitals were obtained by referral letter of each patient.

We investigated various pre/postoperative variables, including patient factors, disease factors, and treatment factors (Tables 1-3). In our hospital, preoperative chemoradiation therapy for 2-3 months before surgery was usually performed for patients

TABLE 1 The characteristics of 275 patients without preoperative DM who underwent pancreatectomy in 2011-2014

	Median \pm SD or n
Patient factors (preoperative)	
Age (y)	66.0 \pm 9.4
Sex (M/F)	123/152
BMI (kg/m ²)	21.9 \pm 3.0
HbA1c (%)	5.6 \pm 0.6
Cholesterol (mg/dL)	195 \pm 51.4
Pancreatic volume in image (mL)	65 \pm 25.4
Pancreatic disease	
PDAC/IPMN/Other ^a	193/19/63
Treatment factors	
Surgery type (PD/DP/CP)	201/68/6
Gastrointestinal reconstruction (\pm)	201/74
Pancreatic reconstruction (None/PJ/PG)	68/5/202
Major vascular resection ^b (\pm)	57/218
Preoperative chemoradiation therapy (\pm)	171/104
BMI at 1 y after surgery (kg/m ²)	19.6 \pm 2.7
RRPV (%)	48.9 \pm 12.8
NODM (\pm)	60/215

Abbreviations: BMI, body mass index; CP, central pancreatectomy; DP distal pancreatectomy; HbA1c, hemoglobin A1c; IPMN, intraductal papillary mucinous neoplasm; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; PG, pancreaticogastrostomy anastomosis; PJ, pancreaticojejunal anastomosis; RRPV, ratio of remnant pancreatic volume.

^aOther disease included bile duct cancer, ampullary cancer, duodenum cancer, neuroendocrine neoplasm, other pancreatic cystic diseases, and metastasis in pancreas from other cancer.

^bVascular resection concomitant with pancreatectomy was performed if needed (e.g. portal vein, common hepatic artery, celiac artery, splenic artery).

undergoing pancreatectomy for advanced pancreatic ductal adenocarcinoma (PDAC)⁵; otherwise, upfront surgery was performed. The degree of postoperative complications such as pancreatic fistula was collected according to the International Study Group on Pancreatic Fistula.²³ This information was included in the treatment factors.

We also collected data on the change in pancreatic volume, the pancreatic volume was measured by software (Ziostation2, Ziosoft, Inc, Tokyo), and we outlined the borders of the pancreatic parenchyma, excluding the bile duct, vessels, identifiable tumors/cystic lesions and the dilated pancreatic duct. These CT images for the assessment of pancreatic volume were acquired within 4 weeks before surgery and at 1 week after surgery. The ratio of remnant pancreatic volume (RRPV) was calculated as the postoperative volume divided by the preoperative volume (Figure 1A).

To assess glucose tolerance, four related data (fasting plasma glucose, FPG; fasting plasma insulin, IR; homeostasis model assessment for β cell function, HOMA- β ; homeostasis model assessment

for insulin resistance, HOMA-IR) were obtained at the same time that pre/postoperative 24-hr CPR was measured in the 54 patients undergoing pancreatectomy in 2018-2019.

2.3 | Surgery

In this study, three kinds of pancreatectomy were performed, including PD, DP, and CP. PD was performed as stomach-preserving PD, and the pancreatic reconstruction technique (pancreaticojejunostomy, PJ; pancreaticogastrostomy, PG) was selected at each physician's discretion, mainly depending on the remnant pancreatic condition. Gastrointestinal reconstruction was performed in all PD surgeries. CP was performed only for small-sized pancreatic neuroendocrine neoplasms in this investigation, and the distal remnant pancreas underwent pancreatic reconstruction of PG. The actual cut line of the pancreas was individually determined during surgery, depending on the tumor disease and/or the tumor location.

2.4 | Follow-up for NODM and resolution of DM

Follow-up observations were performed as described previously.⁶ To detect NODM and the resolution of DM, three types of examinations were performed every 3-6 months for all patients: a routine physical examination (body weight information was also collected); laboratory tests including FPG and HbA1c; and radiological imaging, including chest and abdominal CT. The last follow-up date was December 2019.

NODM/preoperative DM were retrospectively diagnosed according to the World Health Organization criteria as follows: FPG > 126 mg/dL detected on two or more separate days or this abnormal FPG level detected once in addition to plasma glucose >200 mg/dL measured within 2 hours after a 75-g glucose drink. If the patients started any diabetic drugs or insulin treatment in other hospitals (including at family doctor clinics), they were also diagnosed with NODM/preoperative DM independent of FPG.

The resolution of DM was defined as being off antidiabetic medication with FPG levels being less than 126 mg/dL for 6 months, according to a previous report.⁹

2.5 | Statistical analysis

The data are expressed as the mean \pm standard deviation. The chi-squared test and Fisher's exact test were used for comparing categorical variables, as appropriate. To evaluate the correlation between two continuous variables, correlation analysis was performed by creating a scatterplot and performing calculations. Logistic regression was performed for the multivariate analysis. All analyses were performed using the JMP 14 software program (SAS Institute); *P* values < .05 were considered significant.⁶

TABLE 2 The characteristics of 54 patients without preoperative DM who underwent pancreatectomy in 2018-2019

	Median \pm SD or n	
Patient factors (preoperative)		
Age (y)	66.5 \pm 11.0	
Sex (M/F)	51/3	
BMI (kg/m ²)	21.4 \pm 2.5	
HbA1c (%)	5.6 \pm 0.4	
Cholesterol (mg/dL)	201 \pm 75.5	
Pancreatic volume in image (mL)	67.5 \pm 25.5	
Pancreatic disease		
PDAC/IPMN/Other ^a	33/3/18	
Treatment factors		
Surgery type (PD/DP)	40/14	
Gastrointestinal reconstruction (\pm)		
Pancreatic reconstruction (None/PJ/PG)	14/15/25	
Major vascular resection ^b (\pm)	5/48	
POPF, Grade B or C (\pm)	49/5	
Preoperative chemoradiation therapy (\pm)	30/24	
RRPV (%)	54.1 \pm 14.8	
Glucose tolerance-related factors		
	Preoperative	Postoperative
FPG (mg/dL)	96 \pm 13.5	101.5 \pm 17.4
IR (μ U/mL)	5.7 \pm 3.1	5.4 \pm 9.3
HOMA- β	57.1 \pm 64.9	47.5 \pm 56.0
HOMA-IR	1.3 \pm 1.0	1.2 \pm 3.0
24-hr CPR (μ g/d)	48.0 \pm 25.5	24.6 \pm 15.7
Change ratio of 24-hr CPR (Post/Pre, %)	44.2 \pm 27.0	

Abbreviations: BMI, body mass index; DP distal pancreatectomy; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance (FPG \times IR/405); HOMA- β , homeostasis model assessment for β cell function ((360 \times FPG)/(FPG-63)); IPMN, intraductal papillary mucinous neoplasm; IR, fasting plasma insulin; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; PG, pancreaticogastrostomy anastomosis; PJ, pancreaticojejunal anastomosis; POPF, postoperative pancreatic fistula; RRPV, ratio of remnant pancreatic volume.

^aOther diseases included bile duct cancer, ampullary cancer, neuroendocrine neoplasm, and other pancreatic cystic diseases.

^bVascular resection concomitant with pancreatectomy was performed if needed (e.g. portal vein, common hepatic artery, celiac artery, splenic artery).

2.6 | Informed consent

Informed consent was obtained from all individual participants in the study.

2.7 | Ethical considerations

This study protocol was approved by the ethics committee of the institution (No. 19225).

3 | RESULTS

3.1 | Pancreatectomy of over 50% of the original pancreas volume was a significant risk factor for NODM

Of 275 patients without preoperative DM undergoing pancreatectomy in 2010-2014, 201 patients (76%) underwent PD, 68 patients underwent DP, and the remaining six patients underwent CP. In this cohort, the median observation time was 60 months. NODM was detected in 60 patients (21.8%), and the median diagnosis time was 6 months after surgery (Figure 2A). The loss of body weight reached a steady-state value at 1 year after surgery, and the change in HbA1c was not distinct after surgery in this cohort (Figure 2B,C). To elucidate the risk factors for NODM, we compared various factors of the patients with and without NODM. In univariate analysis, preoperative level of cholesterol in blood, preoperative HbA1c value, sex, and RRPV were significantly associated with the occurrence of NODM. Using these four factors, multivariate analysis was performed and indicated that RRPV was the only significant factor related to NODM (<50% vs >50%, odds ratio 4.5, $P = .03$, Table 4). However, surgical variables, pancreatic disease or pre-DM status was not significantly associated with NODM (Table 4).

Using the preoperative images, the predicted cut line on the original pancreas in each image was set by two surgeons (DY and HT) who were not informed of the actual performed surgery. The predicted remnant pancreatic volume and the predicted remnant pancreatic volume ratio (p-RRPV) were calculated. To evaluate the predictive value of p-RRPV for actual RRPV, the RRPV was divided by its p-RRPV, and the two values were almost consistent: the mean value of p-RRPV/RRPV was 1.0 (± 0.3), yielding a high correlation value ($R = .869$, $P < .001$; Figure 1B).

3.2 | The postoperative amount of 24-hr CPR could be predicted by multiplication using preoperative information (preoperative 24-hour CPR \times p-RRPV)

Among the 54 patients without preoperative DM who underwent pancreatectomy in 2018-2019, 40 patients (74%) underwent PD, and the remaining 14 patients underwent DP. In our investigation, the mean preoperative 24-hr CPR was 48.0 \pm 25.5 μ g/d, the mean postoperative 24-hr CPR was 24.6 \pm 15.7 μ g/d, and impaired insulin secretion (<20 μ g/d) was detected in 25 patients (46%) after surgery. Three of the patients demonstrated an increase in insulin excretion after pancreatectomy (1.3- to 2.6-fold increase), and all of the cases showing a hyper-reaction were patients undergoing PD for periampullary tumors (two patients with PDAC and the remaining patient with bile duct cancer). In the comparison between patients with and without impaired insulin secretion at 1 month after surgery, both RRPV and preoperative 24-hr CPR were significant related factors (Table 5). However, other factors, including surgery type, perioperative treatment, pancreatic disease, and pre-DM status, were not related to the condition of impaired insulin secretion at 1 month after surgery (Table 5).

TABLE 3 The characteristics of 74 patients with preoperative DM who underwent pancreatectomy in 2011-2014

	Median \pm SD or n
Patient factors (preoperative)	
Age (y)	66.0 \pm 8.4
Sex (M/F)	42/32
BMI (kg/m ²)	22.7 \pm 3.1
HbA1c (%)	7.0 \pm 1.1
Cholesterol (mg/dL)	176 \pm 34.2
Pancreatic volume in image (mL)	60.5 \pm 18.5
Preoperative DM treatment (None or Drug/ Insulin)	34/40
Pancreatic disease	
PDAC/IPMN/Other ^a	62/4/8
Treatment factors	
Surgery type (PD/DP)	58/16
Gastrointestinal reconstruction (\pm)	
Pancreatic reconstruction (None/PJ/PG)	16/1/57
Major vascular resection ^b (\pm)	25/49
Preoperative chemoradiation therapy (\pm)	20/54
BMI at 1 y after surgery (kg/m ²)	19.5 \pm 3.5
RRPV (%)	45.5 \pm 13.1
Resolution of DM (\pm)	9/65

Abbreviations: BMI, body mass index; CP, central pancreatectomy; DM, diabetes mellitus; DP distal pancreatectomy; HbA1c, hemoglobin A1c; IPMN, intraductal papillary mucinous neoplasm; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; PG, pancreaticogastrostomy anastomosis; PJ, pancreaticojejunal anastomosis; RRPV, ratio of remnant pancreatic volume.

^aOther disease included bile duct cancer, ampullary cancer, neuroendocrine neoplasm, and other pancreatic cystic diseases.

^bVascular resection concomitant with pancreatectomy was performed if needed (e.g. portal vein, common hepatic artery, celiac artery, splenic artery).

Since both RRPV and preoperative 24-hr CPR were significantly related to postoperative 24-hr CPR, we expected that the multiplication of the values of preoperative 24-hr CPR and p-RRPV would enable us to predict the value of postoperative 24-hr CPR. The results of the multiplication correlated well with the value of postoperative 24-hr CPR ($R = .615$, $P = .006$, Figure 3A). Especially in patients undergoing DP, the multiplication more concisely predicted the value of postoperative 24-hr CPR ($R = .720$, $P = .008$, Figure 3B) than in patients undergoing PD ($R = .451$, $P = .006$, Figure 3C). For patients undergoing PD, several patients showed higher postoperative 24-hr CPR values than the calculated predicted value (Figure 3C). The multiplication yielded a higher predictive ability for insulin deficiency than that of the reported risk factors for NODM (positive likelihood ratio, 3.77; odds ratio, 6.77; Table S1).

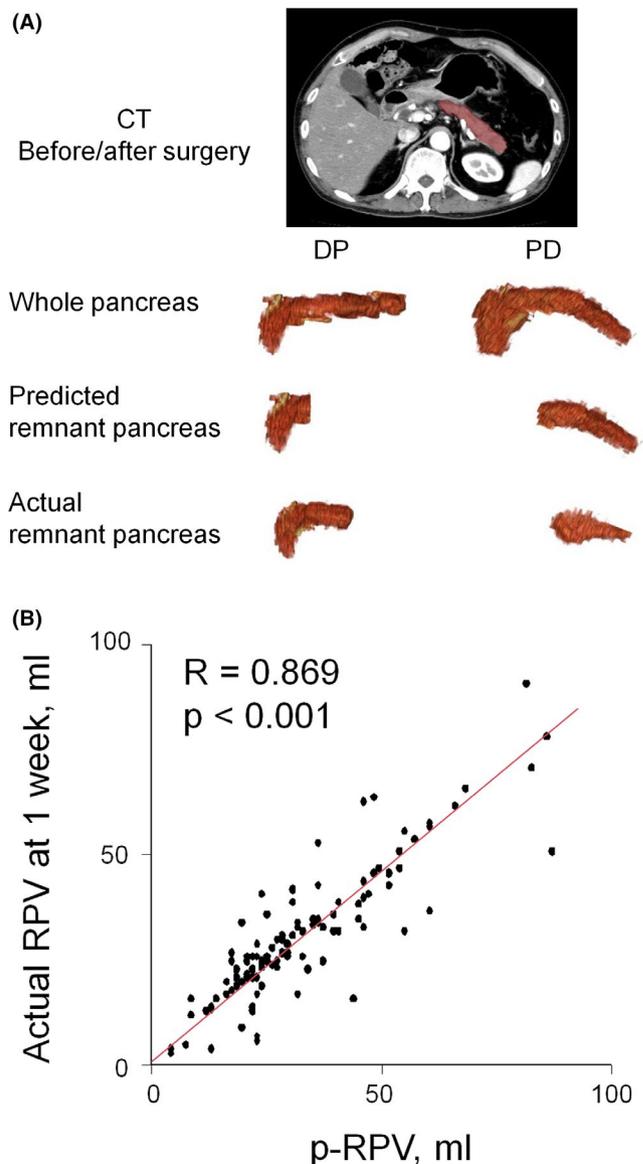


FIGURE 1 Pancreas volumetry using CT images by software. A, Outlined areas are depicted in CT images (upper panel). The whole pancreas was outlined before surgery, and the remnant pancreas was outlined at 1 wk after surgery. The pancreas constructed by software is depicted below. Using preoperative CT images, the whole pancreas was constructed, and the predicted remnant pancreas was constructed by diminishing the expected resection site and estimating the remnant volume by using the constructed image. B, The correlation between the predicted remnant pancreatic volume (p-RPV) and actual remnant pancreatic volume (RPV) is depicted as a scatterplot. The correlation coefficient is depicted as the R value

3.3 | PD surgery was a significant preferable factor for DM resolution, regardless of the resected pancreatic volume

To evaluate the influence of pancreatic surgery on patients suffering from DM, we investigated 74 patients with preoperative DM

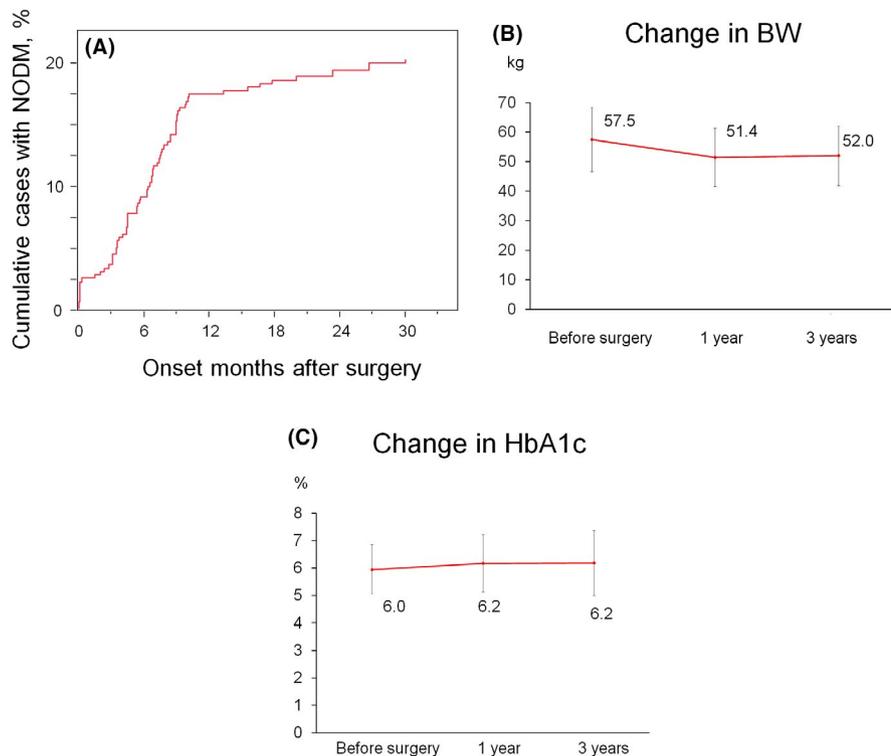


FIGURE 2 The occurrence time of NODM and the change in body weight (BW) and HbA1c after pancreatic surgery. A, The Kaplan-Meier curve showed cumulative cases with NODM. The median months of the diagnosis of NODM was 6.3 months after surgery, and 91% of patients with NODM were diagnosed within 12 months after surgery. The changes in BW (B) and HbA1c (C) after surgery are depicted. The value of BW decreased by 10% from the primary value in 1 y, and the value did not show a remarkable change after 1 y. The value of HbA1c did not show a distinct change after surgery

who underwent pancreatectomy in 2010-2014. In this cohort, the median observation time was 61 months. Of 74 patients with preoperative DM, nine patients (12%) quit anti-diabetic medicine without abnormal glucose tolerance. To investigate whether any peri-surgical factors affected DM resolution after surgery, we compared various factors of patients with and without DM resolution. DM resolution was detected in only the patients undergoing PD surgery (Table S2). More patients with preoperative non-insulin-dependent DM achieved DM resolution than patients with preoperative insulin-dependent DM (IDDM); however, one of the 40 patients (2.5%) with preoperative IDDM achieved DM resolution after PD surgery (Table S2). Other factors, including pancreatic disease (PDAC or non-PDAC) and RRPV, were not related to DM resolution (Table S2).

4 | DISCUSSION

Our results indicated that saving a remnant pancreatic volume of over 50% is a considerable surgical option; moreover, both simulating the resected pancreatic volume and measuring the preoperative 24-hr CPR enable the prediction of postoperative pancreatic function, especially for pancreatic surgery without gastrointestinal reconstruction (e.g. DP and CP). Our results contribute to simulating the cut-line that enables the preservation of sufficient pancreatic function not accompanied by NODM.

The multiplication of the p-RRPV and preoperative 24-hr CPR values predicted the postoperative 24-hr CPR well; however, the degree of insulin excretion might not directly correspond to NODM due to pancreatic surgery. In patients with type 2 DM, the majority

of patients with values under 20 $\mu\text{g}/\text{d}$ in the 24 hour CPR test had impaired insulin excretion and required insulin use for DM treatment.²² In our investigation, the rate of NODM after pancreatic surgery (21%) was lower than the rate of patients with impaired insulin excretion (46%). Since the result of NODM in our investigation did not conflict with the findings of previous reports (the reported range was 3%–40%),^{1,2} it is assumed that DM due to pancreatic surgery was not completely linked to insulin deficiency. Thus, other factors concerning NODM after pancreatic surgery should be considered. Bariatric surgery, including gastrointestinal bypass surgery, improved antidiabetic treatment and was associated with a low rate of antidiabetic treatment initiation in obese patients,²⁴ with the postulated mechanisms of the resolution of DM including the foregut (food bypasses the duodenum and proximal jejunum to facilitate insulin excretion by suppressing secretion of anti-incretin hormones) and hindgut (food passage directly into the distal jejunum, increasing insulin excretion by enhancing release of incretin hormones) theories,^{9,25} which are also applicable to nonobese patients. In our study, we found 16% DM resolution after PD, whereas none of the patients undergoing DP achieved DM resolution. In addition, the resected pancreatic volume was not associated with DM resolution. In sub-analysis, RRPV of patients with DP was a little bit higher than those of patients with PD, despite the lack of significance (PD/DP, RRPV $45 \pm 5\%/55 \pm 8\%$, $P = .056$). Nevertheless, both the rate of NODM and the rate of impaired insulin excretion in patients with PD were a little bit lower than those in the patients with DP (PD/DP, NODM 21%/25%, Impaired(+) 43%/57%). These facts might imply that the gastrointestinal reconstruction in pancreatic surgery reduced the rate of occurrence of NODM with its prophylactic effect.

TABLE 4 The comparison of parameters among cohorts of patients with and without the development of NODM

	Univariate analysis		Multivariate analysis		
	NODM (+)	NODM (-)	P-value	OR (range)	P-value
	Median \pm SD or n				
Patient factors					
Age (y)	65.5 \pm 1.4	63.5 \pm 0.7	.211		
Sex (M/F)	35/25	88/127	.015	0.28 (0.07-1.01)	.052
BMI (kg/m ²)	22.4 \pm 0.4	22.0 \pm 0.2	.350		
HbA1c (%)	5.7 \pm 0.06	5.5 \pm 0.03	.003	3.10 ^a (0.89-10.7)	.075
Cholesterol (mg/dL)	216.5 \pm 10.9	193.6 \pm 5.3	.031	2.74 ^a (0.77-9.74)	.120
Pancreatic volume in image (mL)	68.8 \pm 4.7	71.5 \pm 2.2	.600		
Tumor factors					
PDAC/IPMN/Other ^b	42/4/14	151/15/49	.993		
Treatment factors					
Surgery type (PD/DP/CP)	43/17/0	158/51/6	.350		
Gastrointestinal reconstruction (\pm)	43/17	158/57	.733		
Pancreatic reconstruction (None/PJ/PG)	17/0/43	51/5/159	.400		
Major vascular resection ^c (\pm)	10/50	47/168	.366		
Preoperative chemoradiation therapy (\pm)	35/25	136/79	.468		
BMI at 1 y after surgery (kg/m ²)	19.6 \pm 0.4	19.8 \pm 0.2	.608		
RRPV (%)	44.8 \pm 2.3	50.9 \pm 1.1	.020	4.51 ^a (1.14-17.9)	.032

Abbreviations: BMI, body mass index; CP, central pancreatectomy; DP distal pancreatectomy; HbA1c, hemoglobin A1c; IPMN, intraductal papillary mucinous neoplasm; NODM, new onset diabetes mellitus after surgery; OR, odds ratio; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; PG, pancreaticogastrostomy anastomosis; PJ, pancreaticojejunal anastomosis; RRPV, ratio of remnant pancreatic volume.

^aContinuous variables were divided into two groups according to previous reports [11-13,18]; HbA1c, >5.7% vs <5.7% [12]; Cholesterol, >200 mg/dL vs <200 mg/dL [11]; RRPV, <50% vs >50% [12,13,18].

^bOther disease included bile duct cancer, ampullary cancer, duodenum cancer, neuroendocrine neoplasm, other pancreatic cystic diseases, and metastasis in pancreas from other cancer.

^cVascular resection concomitant with pancreatectomy was performed if needed (e.g. portal vein, common hepatic artery, celiac artery, splenic artery).

In our investigation, the specificity of the formula for insulin deficiency in patients undergoing DP was 100%, whereas that value in patients undergoing PD was 81.8%. In our study, some patients showed a paradoxical increase in insulin excretion even after pancreatectomy, which was found in patients only after PD. Park et al²⁶ reported similar cases, and they assumed that obstructive pancreatitis due to periampullary PDAC exacerbated glucose tolerance by inhibiting insulin secretion, and pancreatectomy for the periampullary tumor sometimes recovered the function in the remnant pancreas by releasing obstruction. In summary, insulin excretion was directly dependent on the resected pancreatic volume in patients undergoing DP, whereas patients undergoing PD did not always correspond to the sole factor of resected pancreatic volume. Thus, we suspected that NODM was mainly caused by pancreatectomy according to the resected volume in the patients undergoing DP, whereas the hyperglycemia in the blood of the patients undergoing PD was possibly blunted by several factors, including the presence of gastrointestinal reconstruction or the improvement of insulin excretion following pancreatectomy.

The present study has some limitations, including its retrospective nature, the investigation in a single center and the different cohorts of patients for the investigation of insulin excretion and for the investigation of NODM. Thus, the cut-off values of postoperative 24-hr CPR, which indicate NODM after pancreatic surgery, were not detected (we expected that the cut-off value would be different between patients undergoing PD and DP). Increasing the number of patients who have pre/postoperative 24-hr CPR levels measured with observation for over 1 year after surgery would endorse our findings and enable us to calculate the optimal cut-off value of the multiplication, which finely predicts NODM after pancreatic surgery. As we advocated above that the postoperative endocrine pancreatic function was reflected by their own original function, the investigation of the risk factors which affect the pancreatic endocrine function is needed for the hospital in which the assessment of preoperative 24-hr CPR is difficult to routinely perform. Although we did not investigate what affected the original/preoperative pancreatic

TABLE 5 The comparison of parameters among cohorts of patients with and without impaired insulin excretion

	Univariate analysis		P-value
	Impaired ^a (+)	Impaired ^a (-)	
	Median ± SD or n		
Patient factors			
Age (y)	63.2 ± 2.2	63.4 ± 2.1	.953
Sex (M/F)	23/2	28/1	.465
BMI (kg/m ²)	21.1 ± 0.5	22.1 ± 0.5	.122
HbA1c (%)	5.7 ± 0.1	5.6 ± 0.1	.353
Cholesterol (mg/dL)	210.3 ± 14.2	207.8 ± 16.3	.906
Pancreatic volume in image (mL)	71.6 ± 5.8	74.5 ± 5.0	.706
Pancreatic disease			
PDAC/non-PDAC	17/8	16/13	.333
Treatment factors			
Surgery type (PD/DP)	17/8	23/6	.345
Gastrointestinal reconstruction (±)			
Pancreatic reconstruction (None/PJ/PG)	8/9/8	6/6/17	.142
Major vascular resection ^b (±)	4/21	1/27	.113
POPF, Grade B or C (±)	2/23	3/26	.766
Preoperative chemoradiation therapy (±)	15/10	15/14	.541
RRPV (%)	47.1 ± 3.2	55.0 ± 2.8	.036
Glucose tolerance-related factors			
Preoperative FPG (mg/dL)	100.6 ± 2.1	95.1 ± 2.0	.065
Preoperative IR (μU/mL)	5.9 ± 0.6	6.9 ± 0.6	.269
Preoperative HOMA-β	50.8 ± 7.5	70.0 ± 6.9	.066
Preoperative HOMA-IR	1.4 ± 0.2	1.4 ± 0.2	.922
Preoperative 24-h CPR (μg/d)	46.2 ± 5.1	64.2 ± 4.6	.012

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; PDAC, pancreatic ductal adenocarcinoma; PD, pancreatoduodenectomy; DP distal pancreatectomy; PJ, pancreaticojejunal anastomosis; PG, pancreaticogastrostomy anastomosis; POPF, postoperative pancreatic fistula; RRPV, ratio of remnant pancreatic volume; FPG, fasting plasma glucose; IR, fasting plasma insulin; HOMA-β, homeostasis model assessment for β cell function ((360 × FPG)/(FPG-63)); HOMA-IR, homeostasis model assessment for insulin resistance (FPG × IR/405).

^a When the level of 24-hr CPR was under 20 μg/d, the patients were regarded as having impaired insulin secretion, according to a previous report [22].

^b Vascular resection concomitant with pancreatectomy was performed if needed (e.g. portal vein, common hepatic artery, celiac artery, splenic artery).

function in this study, previous reports indicated that fatty infiltration in pancreatic parenchyma²⁷ or the obstruction of main pancreatic duct would influence endocrine pancreatic function,²⁶ and these investigations would be a help to develop the prediction tool of NODM. To further validate our findings, we need to prospectively accumulate data on the predictive ability from multiple centers, referring to whether preoperative data predict the development of NODM.

We investigated the influence of pancreatic surgery on new-onset and persistent diabetes mellitus. Considering the management of DM after surgery, both predicting the postoperative pancreatic volume and the presence of gastrointestinal reconstruction are significant. We assumed that the combined assessment of the predicted remnant pancreatic volume and the preoperative 24-hr CPR value is useful to predict the postoperative pancreatic function.

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DISCLOSURE

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CONFLICT OF INTEREST:

Authors declare no conflict of interests for this article.

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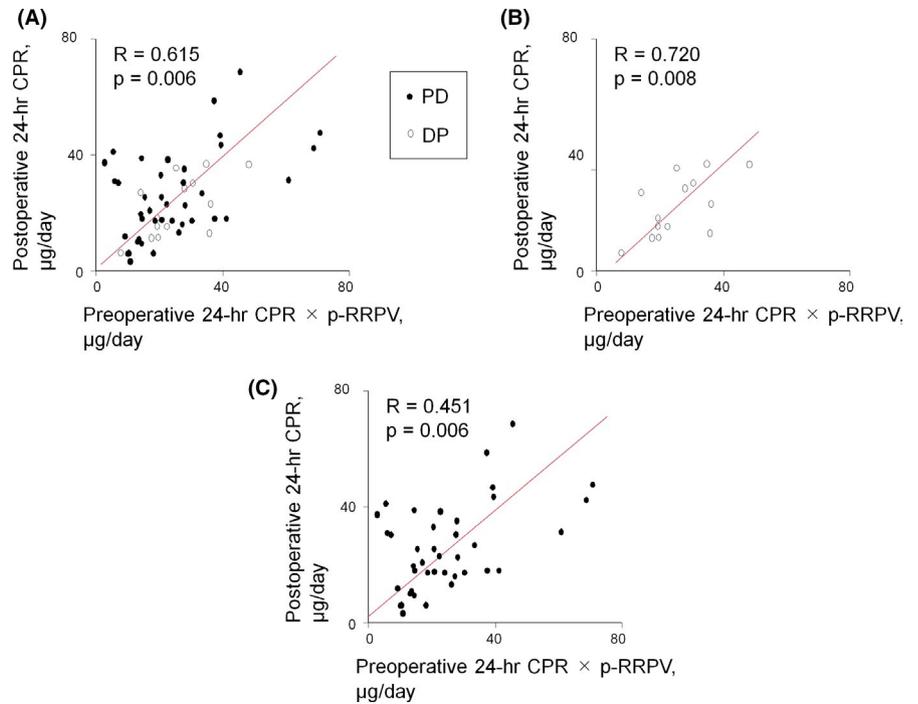
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FIGURE 3 The correlation between the calculated value with the multiplication (preoperative 24-hr CPR \times p-RRPV) and the postoperative 24-hr CPR is depicted as a scatterplot. The correlation coefficient is depicted as the R value. The value of patients undergoing PD is depicted as a black plot, and an empty plot indicates those of patients undergoing DP. The analysis for all patients (A), only patients undergoing PD (B), and only patients undergoing DP (C) are depicted



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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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