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Long-term outcomes after pancreaticoduodenectomy using pair-watch suturing technique: Different roles of pancreatic duct dilatation and remnant pancreatic volume for the development of pancreatic endocrine and exocrine dysfunction

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ABSTRACT

Background: We evaluated long-term outcomes including endo- and exocrine functions after pancreaticoduodenectomy (PD) with standardized pancreaticojejunostomy, paying attention to postoperative pancreatic duct dilatation (PDD) and remnant pancreatic volume (RPV), and examined whether postoperative pancreatic fistula (POPF) influenced the configuration of remnant pancreas.
Methods: We analyzed the records of 187 patients with PD who could have RPV measured by CT volumetry at 1 month after operation and had been followed for more than 6 months. We assessed the risk factors of diabetes mellitus (DM) and PDD, and evaluated association between RPV and pancreatic endo- and exocrine functions assessed by several markers such as albumin, cholesterol, amylase and HbA1c.
Results: Regarding RPV, pancreatic exocrine functions were significantly impaired in the small-volume group (SVG: less than 10 ml) than in the large-volume group (LVG: 10 ml or more). The incidence of new-onset or exacerbation of DM did not differ between SVG and LVG. PDD and the primary disease (pancreatic ductal adenocarcinoma compared to bile duct cancer) were selected as the independent risk factors of new-onset or exacerbation of DM by multivariate analysis. Unexpectedly, there was no significant association between POPF and PDD.
Conclusions: Early occurrence of POPF after PD did not influence the development of PDD in late period, and long-term follow-up should be made by paying attention to PDD and RPV, because PDD was recognized as the most important risk factor of new-onset or exacerbation of DM and the patients with small RPV suffered from prolonged exocrine dysfunction rather than endocrine dysfunction.

Introduction

Pancreaticoduodenectomy (PD) has been more often carried out in recent years as a safe and proper operation in patients with malignant and benign diseases of the pancreas head and distal bile duct region. The probability of operative mortality after PD is now notably decreased in many high-volume centers. Despite the fact that a low mortality rate has been observed, the incidence of postoperative pancreatic fistula (POPF), which most negatively affects the patient's outcome, can reach 20–50% [1–3]. Furthermore, long-term survival after PD has been increased recently because of recent improvements in surgical techniques and postoperative care [4], which in turn raise the importance of long-term patient's administration, including preservation of endocrine and exocrine pancreatic functions.

Even in high-volume centers, the procedures of pancreaticodigestive anastomosis have not been standardized and each institution have employed each preferring procedures such as pancreaticogastrostomy (PG), pancreaticojejunostomy (PJ), external tube drainage, lost stent method and invagination et al.,

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and this diversity of procedures made it difficult to evaluate the frequency of POPF and several remnant pancreatic functions which are highly influenced by the type of pancreaticodigestive anastomosis. We previously reported the study regarding the validation of duct-to-mucosa pancreaticojejunostomy, named the "pair-watch suturing technique (PWST)", which allowed us to completely standardize the anastomotic procedures regardless of type of primary disease, grand texture of pancreas and caliber of main pancreatic duct (MPD) [5,6].

Regarding pancreatic exocrine deficiency, which is highly influenced by remnant pancreatic volume (RPV) after PD, we previously revealed that the patients whose pancreas cut line was made at the left side of superior mesenteric artery (SMA) highly developed postoperative non-alcoholic fatty liver disease (NAFLD) caused by the disruption of exocrine function and suggested a significant efficacy of exocrine enzyme replacement for those patients [7]. Furthermore, our institution recently published a study in which actual RPV significantly influences the occurrence of NAFLD and postoperative nutrition until a year after the surgery [8].

On the other hand, despite the fact that new-onset of diabetes mellitus (DM) was reported to develop in about 20% after PD [2,9–11], the precise incidence and its mechanism have not yet been covered. It is important to investigate its cause and what kind of patient could be categorized as a high risk group since this disease could ruin the patient's quality of life for a long term after PD once it occurs. Risk factors of new-onset of DM after PD were reported to be body mass index (BMI), hard pancreatic texture and postoperative pancreatic duct dilatation (PDD) [2,12]. In addition, previous clinical study revealed that pancreatic duct obliteration significantly exacerbated postoperative endocrine function with compare to duct to mucosa anastomosis group [13]. According to these article, the development of postoperative DM and PDD might be closely interacted each other, but there has been few report in which those risk factors were comprehensively assessed for more than 3 years postoperatively.

Regarding the association between POPF and postoperative long-term outcome, POPF after PD is considered to influence long-term outcomes such as new-onset and exacerbation of DM. In fact, it would be logical hypothesis that POPF could lead to the stenosis of pancreaticodigestive anastomosis resulting in PDD, which could cause the remnant pancreatic atrophy and ruin the pancreatic function. However, whether POPF influences long-term outcomes or not has been uncovered. To the best of our knowledge, only the Japanese multi-center study showed that POPF is a significant risk factor for new-onset or exacerbation of DM [14], but this retrospective study also had a strong limitation because of the diversity of pancreaticodigestive anastomosis.

Based on the results obtained from the long-term follow-up of patients who underwent PD using PWST, the present study was performed to evaluate how short-term outcomes such as POPF and RPV after PD influence long-term outcomes such as pancreatic functions, paying a special attention to PDD and the changes of RPV.

Patients and methods

Patients

All patients data including imaging studies were obtained from the electric medical records at Mie University Hospital Information Network Total System. The study design was approved by an ethics review board (*No.2857*). Among 284 patients who underwent PD from April 2007 to December 2015, PWST was performed in 263, of whom the subjects of the present study were 187 patients who could have RPV measured by CT volumetry at 1 month after operation and had been followed for more than 6 months (Fig. 1).

In these 187 patients, the median follow-up time was 26.6 months (6.1–114.2), the median age was 67.0 (39–86) years, and males/females were 112/75. The indication of PD was pancreatic ductal adenocarcinoma (PDAC) (n = 91), intraductal papillary mucinous neoplasm (IPMN) (n = 34), bile duct cancer (n = 34) and others (n = 28). Surgical procedure was conventional PD (n = 20), pylorus-preserving PD (PPPD) (n = 4) and subtotal stomach-preserving PD (SSPPD) (n = 163). Laparoscopic procedure was performed in 9 patients. Combined resection of the other organs was performed in 83 patients for the portal vein/superior mesenteric vein, in 11 for the hepatic artery, in 3 for the stomach, in 10 for the colon, in 5 for the liver and in 2 for the distal pancreas (middle pancreas was preserved). For the patients without PDAC, we did not perform the dissection of nerve plexus around SMA. Surgical reconstructions were performed according to our previous report: PJ using PWST, choledochojejunostomy, gastrojejunostomy (or duodenojejunostomy) and a Braun anastomosis were performed by turns [5].

At the time of 1 month after PD, we examined the status of pancreatic enzyme supplementation therapy: the dosage of pancreatic enzyme supplementation was no administration in 12 patient, low dose (pancreatin 1.5–3.0 g) in 15, and high dose (pancreatin 6 g or more or pancrealipase 900 mg or more) in 160.

After PD, all patients received enhanced multiditector-row computed tomography (MDCT) scan within one month to check the postoperative complications. The patients with the malignant disease such as PDAC or bile duct cancer had been followed by examining laboratory tests every 2 or 3 months and enhanced MDCT every 3 months within 2 years and every 6 months thereafter [15]. In the other patients, MDCT had been performed every 3–6 months with 2 years and thereafter every 6 or 12 months.

Methods

Assessment of pancreatic configuration

By using the images of preoperative MDCT, we evaluated the preoperative pancreatic configuration data such as MPD, pancreatic thickness, and MPD index which is the ratio of the MPD to pancreas body according to the previous literature [1]. Pancreatic duct size (3 mm or less, more than 3 mm) and the texture of the remnant pancreatic parenchyma were determined according to the medical records of intraoperative findings. RPV had been serially measured at 1, 3, 6, 12, 24 and 36 months after PD by CT volumetry according to our previous report [8].

Assessment of POPF after PWST

In all cases, amylase activities of abdominal drainage fluid and serum were measured on postoperative day 3–7. POPF was defined according to Bassi et al. [16]. Grading of POPF was calculated by using the web-based calculators which are available on Pancreas Club web site (http://pancreasclub.com/calculators/isgps-calculator/).

Association between RPV and NALFD or pancreatic functions

According to the RPV at 1 month, the 187 patients were classified into the two groups: small-volume group (SVG: RPV at 1 month of less than 10 ml) (n = 73) and large-volume group (LVG: RPV at 1 month of 10 ml or more) (n = 114) according to our previous study [8]. RPV ratio (RPV at 3 months or more/RPV at 1 month) was serially calculated to assess the shrinkage rate of the remnant pancreas.

Accurate methods for evaluation of pancreatic endocrine and

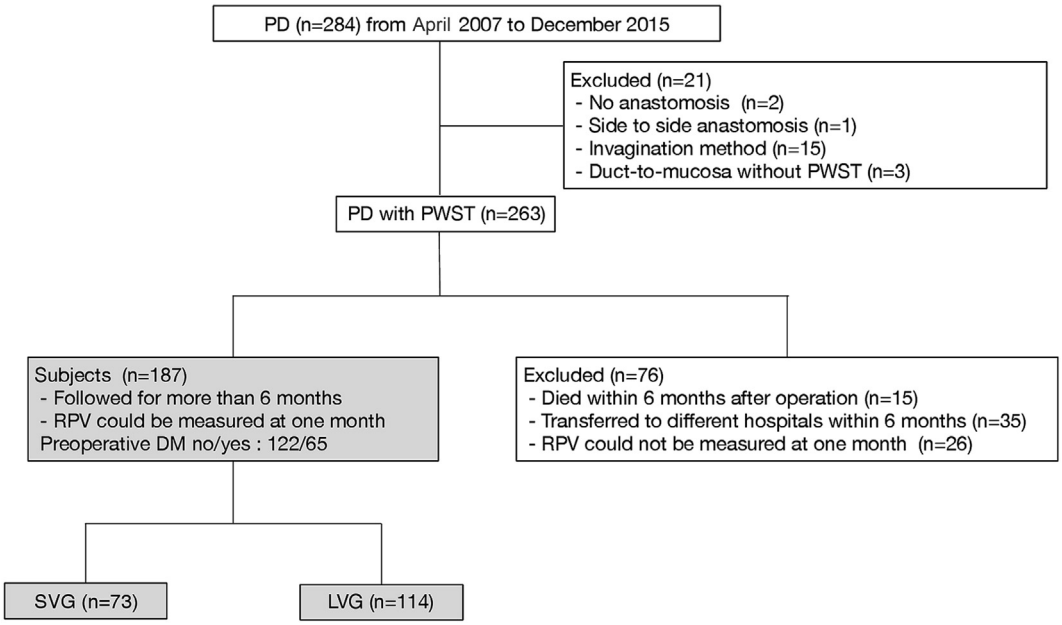

Fig. 1. Flow diagram of the subjects for the study. PD: pancreaticoduodenectomy, PWST: pair-watch suturing technique, RPV: remnant pancreatic volume, DM: diabetes mellitus, SVG: small-volume group, LVG: large-volume group.

exocrine functions are not widely available in clinical practice, and therefore we evaluated the remnant pancreatic functions assessed by several markers such as serum levels of albumin, cholesterol, amylase and HbA1c according to our previous report [8,17]. We examined these makers before and 1, 3, 6, 12, 24 and 36 months after pancreatectomy.

We measured the median CT attenuation value of the liver parenchyma, using a 5-point scale of certainty on plane CT, preoperatively and at 1–36 months after PD. NAFLD was defined as a hepatic CT value of less than 40 HU [7].

Definition of new-onset and exacerbation of DM and its risk factors

In the present study, the patients were diagnosed as DM when either one of fasting blood sugar of 126 mg/dl or more and HbA1c of 6.5% or more was found or when DM treatment had been introduced postoperatively. New-onset of DM in the nondiabetic patients after operation was defined according to the above-mentioned diagnostic criteria. In the patients with preoperative DM, exacerbation of DM was defined as an increase in the intensity of the treatment or amount of oral medications/insulin after PD compared with preoperative treatment according to Hirata et al. [2]. To clarify the risk factors of postoperative DM, we compared pre-, intra- and postoperative factors between the two groups of the patients with or without new-onset or exacerbation of DM.

Identification of risk factors of PDD after PWST

PDD was defined as greater than two-fold the pancreatic duct diameter at 3 months postoperatively by CT according to Tani et al. [9]. Among the subjects (n = 187), the duct diameter of the remnant pancreas could not be measured in 6 cases because of local recurrence around or within remnant pancreas and in 21 because of insufficient data, and the remaining 160 cases were classified into non-PDD group and PDD group. To identify risk factors of PDD, we compared the variables of pre-, intra- and postoperative factors between two groups. Furthermore, we added the factor of POPF because we hypothesized that POPF and following anastomotic stricture might be the main reason by which PDD occurred.

Statistical analysis

All statistical analyses were performed using the statistical software package SPSS for Macintosh (version 21.0, International Business Machines Co., Armonk, NY, USA). The results of the continuous variables were expressed as median and range, and the statistical significance was determined by Student's t-test or Mann-Whitney *U* test. Discrete variables were evaluated by $\chi 2$ analysis or Fisher's exact test, as appropriate. Risk factors associated with new-onset or exacerbation of DM, and PDD were analyzed by uni- and multivariate analysis (multivariate logistic regression). In the two groups of SVG and LVG, several markers to predict postoperative pancreatic functions, RPV and RPV ratio at each measuring points were individually analyzed by Student's t-test or Mann–Whitney *U* test, as appropriate. Serial changes of RPV ratio were analyzed by Tukey's multiple comparison test. Results were considered significant when the *P*-values were less than 0.05.

Results

Incidence of POPF after PWST

Among the subjects (n = 187), 28 (15.0%) were identified as having POPF: 13 (7.0%) in grade A, 15 (8.0%) in grade B, and none in grade C, and 159 (85.0%) developed non-POPF. During the study period of 8 years and 9 months, 28 surgeons had employed PWST in the 263 patients, of whom 70.6% patients had this procedure performed by surgeons who had experienced PD less than 20 times.

Incidence of new-onset or exacerbation of DM

Table 1 showed preoperative and postoperative DM status in the 187 patients: new-onset of DM (pink area) in 16 patients (13.1%) and exacerbation of DM (purple area) in 27 (41.5%), showing that the incidence of new-onset or exacerbation of DM were 23.0%.

Table 1
Preoperative and postoperative diabetes mellitus (DM) status in the 187 patients and the patients who developed new-onset of DM (pink area) and exacerbation of DM (purple area).

		No. of cases	Postop DM (-)	Postop DM therapy		
				Diet	Oral medications	Insulin
Preop DM (-)		122	106	4	5	7
Preop DM therapy	Diet	21	0	12	4	5
	Oral medications	21	0	3	Unchanged 6	Increased 2 / 10
	Insulin	23	0	2	2	Unchanged 13 / Increased 6
Total		187	106	21	19	41

Preop: preoperative, Postop: postoperative, DM: diabetes mellitus.

Association between RPV and NAFLD or pancreatic functions during long-term follow-up

Patient characteristics in SVG (n = 73) and LVG (n = 114) are shown in Table 2. Compared to LVG, SVG showed significantly higher incidences of female, preoperative DM, PDAC, preoperative chemoradiotherapy (CRT), pancreatic duct size of more than 3 mm and hard pancreas. Furthermore SVG had significantly lower BMI, lower preoperative serum albumin, bigger main pancreatic duct diameter, thinner pancreatic thickness, bigger MPD index, longer operation time and larger blood loss, which were considered to be associated with significantly higher incidence of PDAC. The incidences of pancreatic stent placement and POPF (grade A, B and C) were significantly lower in SVG than in LVG. NAFLD was evaluated in the186 patients, excluding one patient who developed multiple liver metastasis in the early postoperative period. The 6 patients

Table 2
Patient characteristics in small-volume group (SVG) and large-volume group (LVG).

	SVG (n = 73)	LVG (n = 114)	P value
Age (years)	67 (39–86)	67 (43–86)	0.918
Sex: male/female	37/36	75/39	0.040
BMI (kg/m^2)	20.4 (15.2–27.9)	21.8 (15.1–40.0)	0.010
Preoperative DM (yes)	40 (54.8%)	25 (21.9%)	<0.001
Diagnosis			<0.001
PDAC	64 (87.7%)	27 (23.7%)	
IPMN	4 (5.5%)	30 (26.3%)	
Bile duct cancer	2 (2.7%)	32 (28.1%)	
Others	3 (4.1%)	25 (21.9%)	
Preoperative serum albumin (g/dl)	3.8 (2.9–4.6)	4.2 (2.9–5.1)	0.001
Preoperative CRT (yes)	56 (76.7%)	19 (16.7%)	<0.001
Pancreatic configuration data			
MPD (mm)	4.0 (1.0–11.5)	2.5 (1.0–8.0)	<0.001
Pancreatic thickness (mm)	11.5 (7.5–21.0)	15.5 (4.5–27.0)	<0.001
MPD index	0.329 (0.08–0.80)	0.158 (0.04–0.73)	<0.001
Operative procedure: PD/PPPD/SSPPD	7/0/66	13/4/97	0.325
Laparoscopic procedure (yes)	0	9 (7.9%)	0.013
Operation time (minutes)	577 (351–958)	503 (315–948)	0.001
Blood loss (ml)	1300 (110–20,983)	737 (50–7700)	<0.001
Pancreatic stent placement (yes)	28 (38.4%)	72 (63.2%)	0.001
Surgeon experience: less than 20/20 or more	53/20	79/35	0.629
Pancreatic duct size: 3 mm or less/more than 3 mm	27/46	67/47	0.004
Pancreatic consistency: soft/hard	8/65	72/42	<0.001
Pancreatic enzyme: none or low dose/high dose	6/67	21/93	0.053
POPF grades ABC (yes)	1 (1.4%, grade A: 1)	27 (23.7%, grade A: 12, B: 15)	0.001
RPV at 1 month	7.02 (1.92–9.99)	23.385 (10.15–68.13)	<0.001
RPV at 6 months	4.515 (1.49–9.72)	15.95 (5.82–39.66)	<0.001
NAFLD (yes)	40 (55.6%)	43 (37.7%)	0.017
New-onset of DM alone	5 (15.2%)	11 (12.4%)	0.764
Exacerbation of DM alone	16 (40%)	11 (44%)	0.750
PDD (yes)	6 (9.7%)	14 (14.3%)	0.391

SVG: small-volume group, LVG: large-volume group, BMI: body mass index, DM: diabetes mellitus, PDAC: pancreatic ductal adenocarcinoma.
IPMN: intraductal papillary mucinous neoplasm, CRT: chemoradiotherapy, MPD: main pancreatic duct, PD: pancreaticoduodenectomy, PPPD: pylorus-preserving PD.
SSPPD: subtotal stomach-preserving PD, POPF: postoperative pancreatic fistula, RPV: remnant pancreatic volume, NAFLD: non-alcoholic fatty liver disease.
PDD: postoperative pancreatic duct dilatation.

developed NAFLD preoperatively and the 78 patients (43.3%) developed NAFLD postoperatively. The incidence of NAFLD after PD was significant higher in SVG than in LVG (55.6% vs. 37.7%, p = 0.017).

Changes of RPV and RPV ratio were chronologically examined until 36 months (Fig. 2). Compared to RPV at 1 month, RPV at 3 months was decreased both in LVG and in SVG: 23.4 ml (10.2–68.1) vs. 18.8 ml (5.49–40.2) and 7.0 ml (1.9–10.0) vs. 5.3 ml (1.7–11.6), being not statistically significant, and thereafter RPV remained unchanged in both groups. When we focused on RPV ratio, which means the shrinkage rate of the remnant pancreas, the shrinkage rate and its pattern were very similar in both groups. RPV ratios at 3 and 6 months in both groups were significantly decreased (approximately 20% decrease at 3 months and 30% decrease at 6 months), followed by stabilization of change.

The chronological changes of several markers to assess the remnant pancreatic functions were compared between SVG and LVG (Fig. 3). Serum albumin levels (g/dl) were significantly lower in SVG than in LVG at 1–36 months. Serum cholesterol levels (mg/dl) were significantly lower in SVG than in LVG at preoperative status, 3, 6, and 12 months. Serum amylase levels (IU/L) were significantly lower in SVG than in LVG at preoperative status, 1–24 months. In contrast, HbA1c levels (%) were significantly higher in SVG than in LVG only at preoperative status, 1 and 36 month. These indicated that pancreatic exocrine functions assessed by serum albumin, cholesterol and amylase were significantly impaired in SVG, while that pancreatic endocrine function assessed by HbA1c did not significantly impaired in SVG, compared with those in LVG.

Risk factors for postoperative DM

As shown in Table 3, the ratio of SVG/LVG (45.5% vs. 35.9%) were very similar between groups with or without new-onset or exacerbation of DM. The incidence of PDD was significantly higher in the patients with new-onset or exacerbation of DM than in those without it: 23.7% vs. 9.0%, p = 0.025, revealing that PDD highly influenced new-onset or exacerbation of DM. By multivariate analysis, PDD (odds ratio 3.455, 95% CI 1.225–9.745, p = 0.019) and diagnosis (p = 0.035) were selected as the significant independent risk factors (Table 4). The risk factor of new-onset or exacerbation of DM in the patients with PDAC was higher than in those with IPMN (odds ratio 0.748, 95% CI 0.244–2.290, p = 0.611) and bile duct cancer (odds ratio 0.205, 95% CI 0.044–0.966, p = 0.045).

Risk factors for PDD

Among the subjects (n = 187), the duct diameter of the remnant pancreas could not be measured in 6 cases because of local recurrence around or within remnant pancreas and in 21 because of insufficient data, and the remaining 160 cases were classified into non-PDD group (n = 140) and PDD group (n = 20). To assess whether the development of POPF at early postoperative period influenced PDD at late postoperative period, we analyzed various risk factors for PDD. There was no significant difference in the incidence of PDD between non-POPF group and POPF group: 11.8% vs. 16.7%, p = 0.507, revealing that POPF did not influence the development of PDD. The other factors did not show significant difference between non-PDD group and PDD group (data not shown).

Discussion

Currently, we revealed the following things: 1) RPV (SVG) highly influenced pancreatic exocrine function, but did not significantly influence endocrine function; 2) PDD and diagnosis highly influenced new-onset or exacerbation of DM; 3) POPF did not influence the development of PDD.

We previously reported that pancreatic exocrine function assessed by nutrition markers after PD was highly associated with RPV which was divided into SVG (less than 10 ml) and LVG (10 ml or more): nutrition markers representing exocrine function in SVG were mostly deteriorated at one month after PD, followed by gradual improvement due to the effect of pancreatic enzyme supplementation [8]. When nutritional markers were compared between SVG and LVG, serum albumin, cholesterol and amylase levels were markedly lower in SVG than LVG from 1 to 12 months after PD. In the present study, we extended the follow-up period from 12 to 36 months after PD, and as a result these difference between two groups continued until 36 months. Our data consolidated the fact that RPV influence an exocrine function all through the 3 years, meaning that intensive nutritional supports including the enzyme replacement should be indispensable even 3 years after surgery especially for post-PD patients who categorized as SVG.

To the best of our knowledge, our study is the first report in

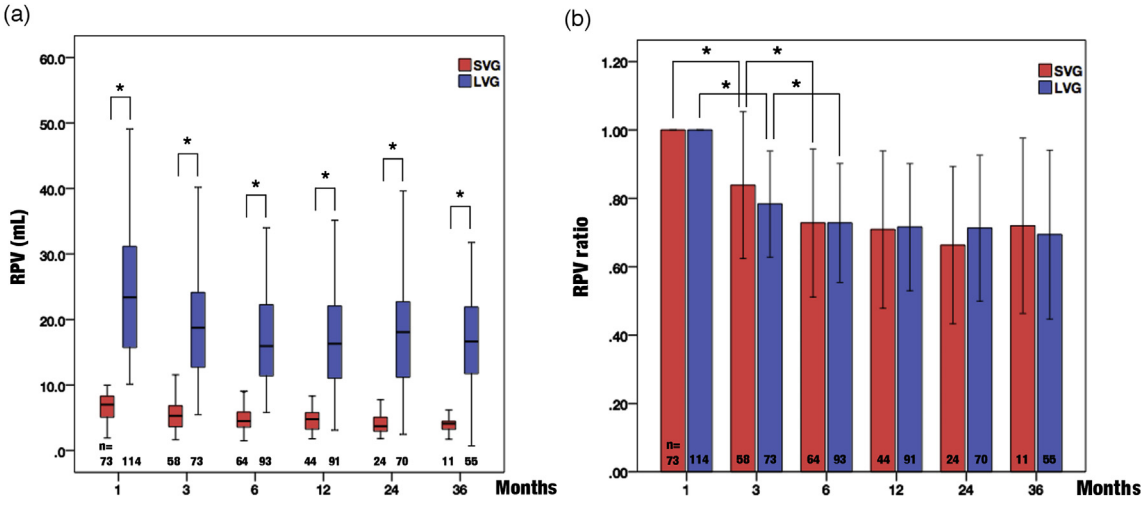

Fig. 2. Changes of remnant pancreatic volume (RPV) in the patients with small-volume group (SVG) and with large-volume group (LVG) (a) and changes of RPV ratio in the patients with SVG and with LVG (b). *P < 0.05. RPV: remnant pancreatic volume, SVG: small-volume group, LVG: large-volume group.

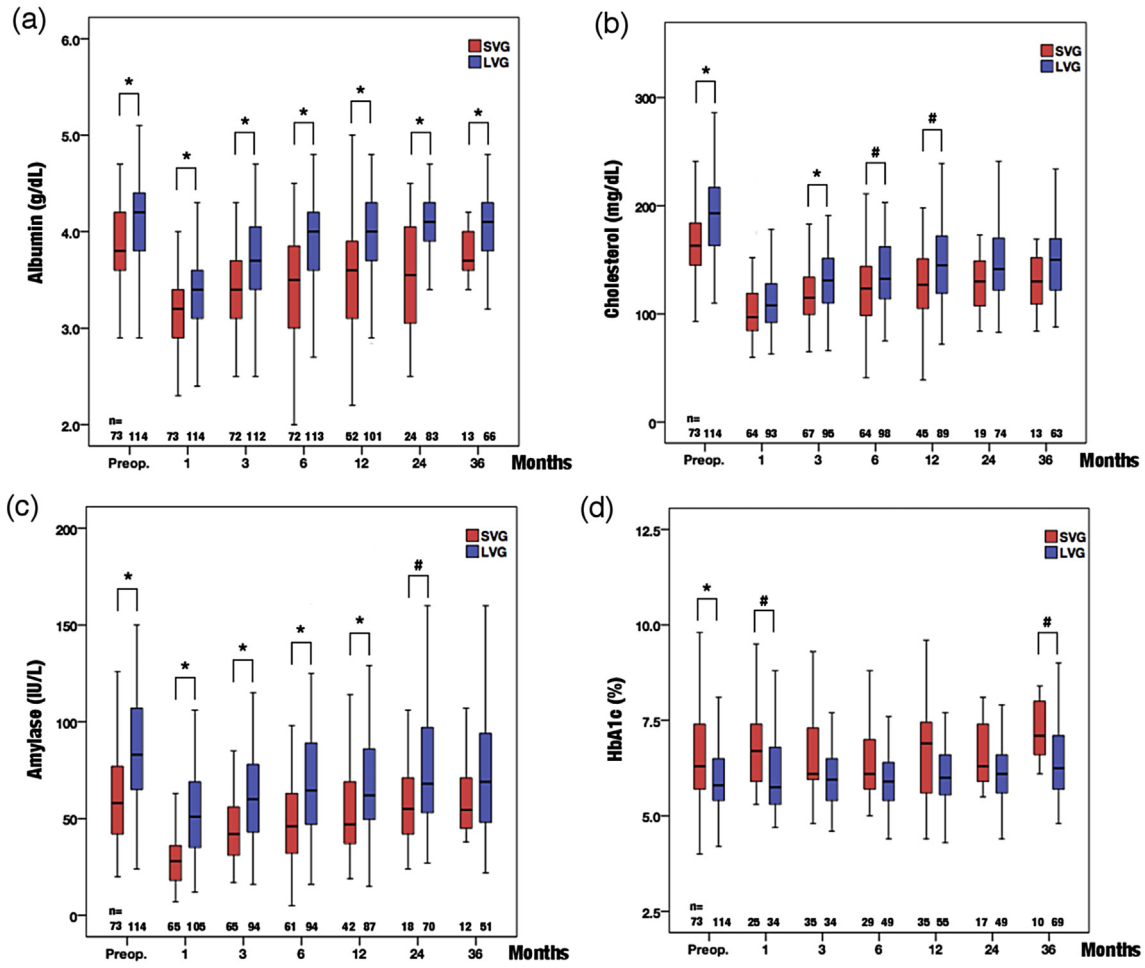

Fig. 3. Changes of postoperative serum albumin, cholesterol, amylase and HbA1c in the patients with small-volume group (SVG) and with large-volume group (LVG): albumin (a), cholesterol (b), amylase (c) and HbA1c (d). *P < 0.05 with Bonferroni collection, # rough P < 0.05. SVG: small-volume group, LVG: large-volume group.

which the change of RPV after PD had been observed for a long-term period, revealing that the shrinkage rate and its pattern were very similar in SVG and LVG, showing approximately 20% decrease at 3 months and 30% decrease at 6 months, followed by the stabilization of RPV. Tomimaru et al. [18] compared the changes of the parenchymal thickness between patients with PG and with PJ until 1 year after PD: parenchymal thickness started to be decreased just after PD and its change was almost stabilized by 1 year after PD, although these change were significantly severe in PG. It is speculated that early postoperative shrinkage of the remnant pancreas might be caused by the decrease of blood flow occurring just after transection of the pancreas regardless of RPV.

We assumed that RPV highly influenced the development of new-onset or exacerbation of DM after PD; however, the incidence of new-onset or exacerbation of DM did not differ between SVG and LVG. PDD and the primary disease (pancreatic ductal adenocarcinoma compared to bile duct cancer) were the significant independent risk factors for new-onset or exacerbation of DM. According to the previous literatures, new-onset of DM was found in about 20% of the patients with PD [2,9–12], and thus it is important to investigate its cause and what kind of patient would be categorized as a high risk group since this disease could undermine patient's quality of life for a long term after surgery once it occurs. Risk factors of new-onset of DM after PD were reported to be BMI, hard pancreatic texture and PDD [2,12]. As of RPV, Eom K et al. [19] recently examined the relationship between RPV after PD and new-onset of DM by CT volumetry: RPV was comparable between the patients with and without new-onset of DM (24.4 ml vs. 20.0 ml), showing the results similar to those in present study. As of PDD, Fujino Y et al. [12] evaluated the long-term outcomes such as the remnant pancreatic duct size, exocrine and endocrine functions in the 25 PD patients in whom duct size could be evaluated at 2 or 3 years postoperatively. The incidence of endocrine dysfunction was significantly higher in the dilated group than in the nondilated group: 50% (7/14) vs. 9% (1/11), p = 0.038, although they did not examine the relation between RPV and endocrine function, and furthermore they did not mention the reason why PDD was associated with pancreatic endocrine function.

In the present study, by evaluating the various risk factors for new-onset or exacerbation of DM, PDD was selected as the most significant risk factors by multivariate analysis. Major question arising from this result is how PDD is associated with new-onset or exacerbation of DM after PD. The previous experimental study reported that acini became atrophic and fibrotic but islets and β-cell morphology unchanged 4 weeks after pancreatic duct ligation in an exocrine pancreas-insufficient pig model; despite the fact that total amount of insulin secretion was maintained, fasting glucose concentrations became significantly higher. These results suggested that glucose utilization was impaired in an exocrine pancreas-insufficient model [20]. In setting of clinical randomized study, Tran K et al. [13] revealed that the incidence of new-onset of DM was significantly higher in pancreatic duct obliteration group in

Table 3
Univariate analysis of risk factors for new-onset or exacerbation of diabetes mellitus (DM).

	With new-onset or exacerbation of DM (n = 43)	Without new-onset or exacerbation of DM (n = 144)	P value
Age (years)	66 (46–86)	67.5 (39–86)	0.479
Sex: male/female	25/18	87/57	0.789
BMI (kg/m^2)	21.9 (15.2–28.0)	20.9 (15.1–40.0)	0.424
Diagnosis			0.069
PDAC	23 (53.5%)	68 (47.2%)	
IPMN	7 (16.3%)	27 (18.8%)	
Bile duct cancer	3 (7.0%)	31 (21.5%)	
Others	10 (23.3%)	18 (12.5%)	
Preoperative serum albumin (g/dl)	3.9 (2.9–4.8)	4.0 (2.9–5.1)	0.726
Preoperative CRT (yes)	21 (48.8%)	54 (37.5%)	0.183
Pancreatic configuration data			
MPD diameter (mm)	3.0 (1.0–8.0)	3.0 (1.0–11.5)	0.942
Pancreatic thickness (mm)	13.5 (8.0–26.5)	13.5 (4.5–27.0)	0.948
MPD index	0.23 (0.05–0.73)	0.21 (0.04–0.80)	0.992
Operative procedure: PD/PPPD/SSPPD	4/1/38	16/3/125	1.000
Laparoscopic procedure (yes)	2 (4.7%)	7 (4.9%)	1.000
Operation time (minutes)	558 (327–760)	527 (315–958)	0.517
Blood loss (ml)	980 (110–4930)	879 (50–20,983)	0.694
Pancreatic stent placement (yes)	23 (53.5%)	77 (53.5%)	0.999
Surgeon experience: less than 20/20 or more	28/15	104/40	0.370
Pancreatic duct size: 3 mm or less/more than 3 mm	23/20	71/73	0.630
Pancreatic consistency: soft/hard	17/26	63/81	0.624
Pancreatic enzyme: none or low dose/high dose	9/34	18/126	0.215
POPF grade ABC (yes)	7 (16.3%)	21 (14.6%)	0.784
RPV: SVG/LVG	21/22	52/92	0.133
PDD (yes)	9 (23.7%)	11 (9.0%)	0.025

DM: diabetes mellitus, BMI: body mass index, PDAC: pancreatic ductal adenocarcinoma, IPMN: intraductal papillary mucinous neoplasm, CRT: chemoradiotherapy.
MPD: main pancreatic duct, PD: pancreaticoduodenectomy, PPPD: pylorus-preserving PD, SSPPD: subtotal stomach-preserving PD, POPF: postoperative pancreatic fistula.
RPV: remnant pancreatic volume, SVG: small-volume group, LVG: large-volume group, PDD: postoperative pancreatic duct dilatation.

Table 4
Multivariate analysis of risk factors for new-onset or exacerbation of diabetes mellitus (DM).

	Odds ratio	95%CI	P value
Diagnosis			0.035
PDAC	1		
IPMN	0.748	0.244–2.290	0.611
Bile duct cancer	0.205	0.044–0.966	0.045
Others	2.309	0.850–6.271	0.101
PDD (yes)	3.455	1.225–9.745	0.019

DM: diabetes mellitus, CI: confidence interval, PDAC: pancreatic ductal adenocarcinoma, IPMN: intraductal papillary mucinous neoplasm.
PDD: postoperative pancreatic duct dilatation.

which alcoholic prolamine solution was injected into pancreatic duct than in duct-to-mucosa anastomosis group after PD. Furthermore, islet distribution/density in the pancreatic tail is more than twice as high as that in the head and body [21]. Taken together, we believe that a certain number of endocrine cells, which is enough to maintain endocrine function, could be preserved in the pancreatic tail even if pancreatic parenchyma is resected at the left of SMA level, resulting in small RPV. However, PDD, which might be caused by late anastomotic strictures, may cause impairment of glucose utilization at first and gradually disrupt the function of endocrine cells located in the remnant pancreas, resulting in development of new onset or exacerbation of DM after PD.

We hypothesized that POPF occurring on early postoperative period could influence the configuration of the remnant pancreas, especially main pancreatic dilatation which might be caused by scarring after inflammation; however, it did not influence the development of PDD and we could not identify any significant risk factors of PDD. In general, type of pancreaticodigestive anastomosis, CRT and postoperative intra-abdominal complications such as POPF have been considered to cause the changes of the remnant pancreatic configuration, which in turn influence pancreatic functions. In the present study, the incidence of PDD was 15.4% in the 13 patients with POPF grade B who had median follow-up of 45.0 months (12.7–72.4 months), which is very similar to 11.8% (16/136) in non-POPF group. These results suggest that the remnant pancreas with POPF might be regenerated well rather than be scarred. To the best of our knowledge, there have been few studies concerning how the development of POPF affects long-term outcome of remnant pancreas such as the configuration and functions after PD. According to the Japanese multi-center study on the 1066 patients who underwent pylorus-preserving PD, new-onset or exacerbation of DM was found in 10.9%, and univariate analysis (multivariate analysis not available) revealed that PG and POPF were significant risk factors for DM, although configurational change of the remnant pancreas was not examined [14]. You et al. [10] examined the relationship between POPF and new-onset or aggravation of DM after PD in the single institutional 55 patients cohort: POPF was not associated with new-onset or aggravation of DM, and furthermore the atrophy of the remnant pancreas did not affect the new-onset of DM, although they did not examine the relationship between POPF and the changes of remnant pancreas such as atrophy and main pancreatic duct dilatation.

The incidence of PDD (12.5%) after using our PWST technique was considered to be comparable to those of 2.2 and 13.3% after duct-to-mucosa PJ anastomosis previously reported [9,22]. In contrast to the duct-to-mucosa PJ anastomosis, its incidences after total external stent method without duct-to-mucosal PJ anastomosis, invagination for PJ anastomosis and PG anastomosis were 48.3%, 25% and 100%, respectively, being significantly higher than those after the duct-to-mucosa PJ anastomosis [9,18]. These results indicate that duct-to-mucosa PJ anastomosis is preferable in terms of preventing PDD.

In conclusion, early occurrence of POPF after PD did not influence the development of PDD in late period, and long-term follow-up should be made by paying much more attention to the configuration change of remnant pancreas such as PDD and RPV, because

PDD was recognized as the most important risk factor of new-onset or exacerbation of DM and the patients with small RPV suffer from prolonged exocrine dysfunction rather than endocrine dysfunction.

Conflict of interest

The authors have no conflicts of interests to disclose.

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