Clinical impact of atrophic changes in remnant pancreas on the development of nonalcoholic fatty liver disease after pancreaticoduodenectomy

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Abstract

Aim: The aim of this study was to evaluate risk factors for nonalcoholic fatty liver disease (NAFLD) after pancreaticoduodenectomy (PD), with a special focus on remnant pancreatic volume (RPV) as assessed using computed tomography (CT).

Methods: From February 2004 to June 2017, 101 patients who underwent PD in our institution were enrolled. We defined a CT attenuation value of less than 40 HU as hepatic steatosis and measured RPV at 7 days, 3 months, and 1 year after PD using the SYNAPSE VINCENT system. The incidence of NAFLD and RPV were compared between the two groups according to reconstruction with pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ).

Results: The incidence of NAFLD at 3 months after PD was 39.6% (40/101). The RPV ratio (RPV at 3 months or 1 year divided by RPV at 7 days after PD) at both 3 months and 1 year was significantly smaller in the PG group than in the PJ group (59% vs 73%, P < .001 and 53% vs 67% P < .01, respectively). A positive correlation between the RPV ratio and liver CT value at 3 months was found. The multivariate analysis identified three independent risk factors for NAFLD: female sex (odds ratio [OR] 8.16, 95% confidence interval [95% CI] 2.27-35.9, P < .001 and 53% vs 67% P < .01, respectively). A positive correlation between the RPV ratio and liver CT value at 3 months was found. The multivariate analysis identified three independent risk factors for NAFLD: female sex (odds ratio [OR] 8.16, 95% confidence interval [95% CI] 2.27-35.9, P < .001), PG reconstruction (OR 3.87, 95% CI 1.04-15.6, P = .04), and RPV ratio ≤60% (OR 3.44, 95% CI 1.06-11.8, P = .001).

Conclusion: Atrophic change in the remnant pancreas is significantly associated with the development of NAFLD, and PJ reconstruction may be superior to PG from the viewpoint of NAFLD development.

KEYWORDS
nonalcoholic fatty liver disease, pancreaticoduodenectomy, pancreaticogastrostomy, pancreaticojejunostomy, remnant pancreas
1 | INTRODUCTION

In the 1930s, Whipple introduced a radical surgery, pancreatectoduodenectomy (PD), for pancreatic tumors. PD has become the standard surgical procedure for malignant and benign disease in the periampullary region. In this procedure, the cut end of the pancreas is usually anastomosed to either the jejunum (pancreatecojejunostomy [PJ]) or stomach (pancreatecogastrostomy [PG]). These two types of anastomoses have been compared for a long time by many surgeons with regard to the incidence of postoperative pancreatic fistula (POPF), which is the leading cause of complication after PD in the early postoperative period. Some prospective randomized trials have reported no difference between PJ and PG. Additionally, the exocrine and endocrine functions of the remnant pancreas have been compared. No significant difference between PJ and PG in terms of pancreatic endocrine function has been reported; however, PG has been associated with equivalent or more severe pancreatic exocrine insufficiency than that following PJ. PD causes not only POPF but also various complications, such as anorexia, diarrhea, and nutritional disorders. Recently, hepatic steatosis, a type of nonalcoholic fatty liver disease (NAFLD), has been attracting attention as a complication after PD. Previous reports have shown that NAFLD developed in 8%-37% of patients who underwent PD. Although the exact mechanism responsible for the development of NAFLD after PD is still unclear, some studies have suggested that postoperative malnutrition caused by pancreatic exocrine insufficiency was significantly associated with NAFLD after PD. Furthermore, Tomimaru et al reported that reduced remnant pancreatic volume (RPV) after PD influences the development of NAFLD.

The aim of this study was to compare the change in RPV between PJ and PG reconstruction after PD with a special focus on perioperative pancreatic volume assessed using CT and investigating the occurrence rate of NAFLD. Moreover, we evaluated the risk factors for NAFLD after PD.

2 | PATIENTS AND METHODS

2.1 | Study design

We analyzed 101 patients who underwent PD for pancreatic cancer (pancreatic ductal adenocarcinoma, 96; other, five) at the Department of Gastroenterological Surgery, Kumamoto University Hospital between February 2004 and June 2017 retrospectively. Patients with fatty liver before surgery and those who had no postoperative follow-up were excluded from this study.

We analyzed the records of 101 patients who underwent postoperative unenhanced CT approximately 7 days and 3 months after PD (mean, 3.0 months; range, 1.5-6.0). Twenty-five patients died within 12 months after surgery. Among them, 21 died due to recurrence. CT images at 12 months were missing in four patients. Therefore, CT of all patients at 7 days and 3 months after PD were analyzed. We finally analyzed a total of 76 patients' postoperative unenhanced CT approximately 12 months after PD (mean, 12.0 months; range, 10.0-15.0). Primary endpoint was incidence of NAFLD at 3 months after PD. We also set the atrophic change of remnant pancreas at 1 year after PD as second endpoint. Variables, including pancreatic CT parameters and RPV, were compared between the two groups according to reconstruction with PG or PJ after PD. Reconstruction methods were decided according to the attending surgeon's clinical judgement. However, the reconstruction method varied over time: PG was mainly performed until 2011, and the number of PJ was increased from 2012. Tumor stages were classified according to the TNM staging system of the International Union Against Cancer (UICC) version 7.

Our cohort in this study had 23 patients that experienced neo-adjuvant chemotherapy with gemcitabine plus 5FU regimen and 91 who received adjuvant chemotherapy. No patients received adjuvant chemotherapy. The regimen of adjuvant chemotherapy varied over time. Hepatic arterial infusion of 5-FU plus systemic gemcitabine was performed from 2005 to 2010, and gemcitabine or 5FU were administered starting in 2011 according to the clinical evidence.

2.2 | Evaluation of postoperative NAFLD

Unenhanced CT evaluation of the liver was performed with a 16-slice multi-detector CT (MDCT) (IDT16, PHILIPS), a 40-slice MDCT (PHILIPS), a 64-slice MDCT (PHILIPS), and 320-slice MDCT (Aquilion ONE Vision Edition, TOSHIBA). Unenhanced image acquisition of the liver was performed during a single breath hold at 120 kVp. All unenhanced images were reconstructed using contiguous 5-mm intervals.

The CT image analysis in this study consisted of liver attenuation measurement using a standard region of interest (ROI) technique. Care was taken to measure representative areas of the liver parenchyma, avoiding visible vessels, visible bile ducts, and focal lesions. For each patient, the average CT attenuation values in five sectors were monitored to evaluate hepatic fat content. In this study, we defined a CT value of <40 Hounsfield units (HU) as representing NAFLD (Figure 1A). We calculated RPV on postoperative CT images using a SYNAPSE VINCENT system (Fujifilm Medical Co., Ltd.). A sequence of transverse CT images acquired in the equilibrium phase was obtained at 2.5-mm intervals. The pancreatic parenchyma was manually outlined on each slice using a free-hand ROI, and the outlined area was automatically calculated (Figure 1B). Major vessels and dilated pancreatic ducts (≥3 mm) were excluded. The product of the pancreatic area and slice thickness represented the volume of the pancreas in a single slice. The total pancreatic volume was computed by summing all slice volumes.
2.4 | Statistical analysis

All continuous variables are expressed as the median with interquartile range and were compared using the Mann-Whitney U test. The ability of each continuous variable, including the CT parameters, to predict NAFLD after PD and the best cutoff values were evaluated based on a receiver operating characteristic curve (ROC) analysis. Comparisons between categorical variables were analyzed using Fisher’s exact test. A P-value < .05 was considered statistically significant. Potentially important variables with a P-value < .1 in the univariate analysis were included in the multivariate analysis to identify independent risk factors for NAFLD after PD. A multivariate analysis was performed using the logistic regression method with a backward stepwise selection model. Statistical analyses were performed using JMP version 8 (SAS Institute).

2.5 | Ethics

This study was a retrospective, non-interventional, observational study, and was approved by the institutional review board at Kumamoto University Hospital (admission number #1000). Written informed consent was obtained from all included patients. This study complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.21 All procedures in this study were performed in accordance with the guidelines of the Declaration of Helsinki.

3 | RESULTS

3.1 | The incidence of NAFLD after PD is significantly higher in the PG group

The patients included 48 men and 53 women (median age, 67 years; range, 37-82). The mean liver CT attenuation values were 57.3 ± 7.4 preoperatively and 50.0 ± 15.0 at 3 months postoperatively, respectively. The incidence of NAFLD at 3 months after PD was 39.6% (40/101). Table 1 shows a comparison of the clinical features between patients in the PG and PJ groups. Significant differences between the PG and PJ groups were found with respect to operative time (689 min vs 497 min, P < .0001), blood loss (1041 mL vs 693 mL, P = .043) and blood transfusion (50% vs 27%, P = .024). Interestingly, the incidence of NAFLD at 3 months after PD was significantly higher in the PG group than in the PJ group (57% vs 24%, P = .0005).

3.2 | Change in RPV after PD in the PG and PJ groups

The change in RPV at 7 days, 3 months, and 1 year after PD was compared between the PG and PJ groups. No significant differences in RPV at 7 days after PD were observed between the two groups. Although the RPV at 3 months and 1 year was smaller in the PG group than in the PJ group, the difference between the two groups was not statistically significant (8 vs 10 cm³, P = .06 and 8 vs 9.5 cm³, P = .06, respectively, Figure 2A). Additionally, we compared the “change ratio” of RPV (RPV ratio) from 7 days to 3 months and 7 days to 1 year after PD between the PG and PJ groups. Intriguingly, the RPV ratio at both 3 months and 1 year were significantly smaller in the PG group than in the PJ group (59% vs 73%, P < .001 and 53% vs 67% P < .01, respectively, Figure 2B). These data indicate that PG reconstruction after PD results in atrophy of the remnant pancreas for at least 1 year.

3.3 | The RPV ratio at 3 months after PD correlates with liver CT attenuation value

To evaluate the influence of RPV on the liver CT attenuation value after PD, we analyzed the correlation between RPV and liver CT attenuation value. We found a positive correlation between the RPV ratio, but not RPV, and liver CT attenuation value at 3 months after PD (Figure 3A,B). However, both RPV and the RPV ratio had no correlation with the liver CT attenuation value at 1 year after PD (data not shown). Because NAFLD was defined as CT attenuation value...
<40 HU, these results suggest that a smaller RPV ratio at 3 months after PD relates to the development of NAFLD.

### 3.4 PG reconstruction and the RPV ratio are independent risk factors for NAFLD after PD

Table 2 shows the results of the univariate and multivariate analyses of risk factors for NAFLD after PD. According to the univariate logistic analysis, age <65 years, female sex, operative time >580 min, blood loss >880 mL, portal vein resection, PG reconstruction, RPV <10 mL, and RPV ratio ≤60% were significant factors. The multivariate analysis identified three independent risk factors for NAFLD after PD: female sex (odds ratio [OR] 8.16, 95% confidence interval [95% CI] 2.27-35.9, $P < .001$), PG reconstruction (OR 3.87, 95% CI 1.04-15.6, $P = .04$), and RPV ratio ≤60% (OR 3.44, 95% CI 1.06-11.8, $P = .001$).

In recent years, prevalence of NAFLD as a liver disease in metabolic syndrome has increased, and the progression from NAFLD to cirrhosis and hepatocellular carcinoma has been reported. As NAFLD has attracted increasing attention, the number of reports on NAFLD after PD have been increased. In the current study, 40 out of 101 patients (39.6%) developed NAFLD within 3 months after PD for pancreatic cancer. The incidence of NAFLD after PD was significantly higher in the PG group than in the PJ group. Furthermore, the RPV decreased significantly more in patients who underwent PG than in those who underwent PJ. Interestingly, the change ratio of RPV was more strongly associated with the development of NAFLD at 3 months after PD than RPV itself. A multivariate analysis revealed that female sex, PG reconstruction, and the RPV ratio ≤60% were independent factors associated with NAFLD after PD.
Postoperative NAFLD and malnutrition often resulted in a lower quality of life for patients treated with PD, thus impeding the introduction and continuation of adjuvant chemotherapy. Okamura et al reported that NAFLD after PD might affect the long-term prognosis after pancreatectomy. Therefore, the prevention and treatment of NAFLD after PD have become clinically important issues. It has been suggested that malnutrition due to pancreatic exocrine insufficiency is one of the causes of NAFLD after PD because supplementation with high-dose pancreatic enzyme reduces the likelihood of its development. Nakagawa et al evaluated pancreatic exocrine insufficiency using a 13C-Labeled Mixed Triglyceride Breath Test to determine risk factors for the development of postoperative NAFLD, and reported that postoperative pancreatic exocrine insufficiency was the only significant risk factor in multivariate analysis. Pancreatic exocrine insufficiency after PD is associated with fat malabsorption, resulting in fatty acid deficiency, which leads to increased conversion of carbohydrates into fat (i.e. increased fat deposition) in the liver.

A reduced RPV is highly associated with impaired postoperative pancreatic function. Previous reports showed that a reduced postoperative pancreatic parenchymal thickness correlated with pancreatic exocrine insufficiency after PD. Another recent study showed that reduced RPV was a risk factor for the development of NAFLD after PD. Although our results were consistent with those of previous studies, the factor correlated with the development of NAFLD at 3 months after PD was the RPV ratio, but not RPV itself. Furthermore, RPV was one of the risk factors for the development of NAFLD in the univariate analysis, but it was not an independent predictive factor in the multivariate analysis.

### FIGURE 3
Correlation analysis of RPV, RPV ratio, and liver attenuation value. RPV ratio, but not RPV, had positively correlated with the liver attenuation value ($p = 0.35, P = 0.0003$)

### TABLE 2 Risk factors for NAFLD at 3 months after PD

| Characteristics | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|----------------------|
| Age <65 (vs ≥65) | 2.92 (1.28-6.81) .01 | 1.79 (0.58-5.57) .30 |
| Female (vs Male) | 4.06 (1.75-9.95) .001 | 8.16 (2.27-35.9) .001 |
| BMI 25≤ | 3.02 (0.85-12.3) .09 | 5.40 (0.72-47.9) .10 |
| Diabetes mellitus | 1.39 (0.59-3.29) .44 |                     |
| NAC Present | 0.98 (0.37-2.50) .96 |                     |
| Operative time ≥580 | 3.20 (1.41-7.58) .005 | 1.09 (0.26-4.73) .91 |
| Blood loss ≥880 | 2.39 (1.07-5.53) .03 | 3.37 (0.81-16.1) .10 |
| Portal vein resection (Present) | 2.81 (1.22-6.63) .02 | 1.91 (0.51-7.21) .33 |
| PG reconstruction (vs PJ) | 4.59 (1.98-11.1) .0003 | 3.87 (1.04-15.6) .04 |
| Postoperative complication | 1.13 (0.50-2.57) .75 |                     |
| Pathological Stage ≥ II (vs 0-I) | 1.36 (0.40-5.39) .63 |                     |
| RPV ≤10 cm³ | 3.31 (1.41-8.23) .005 | 2.82 (0.77-11.4) .12 |
| RPV ratio ≤60% | 6.15 (2.59-15.4) <.0001 | 3.44 (1.06-11.8) .04 |
Several reports of prospective randomized trials (RCTs) have compared postoperative complications between PG and PJ reconstruction after PD.5-7,30,31 Four studies found no difference in short-term morbidity,5,6,32 while two studies found that pancreatic fistula rates were significantly lower in the PG group than in the PJ group.30,31 However, long-term pancreatic function outcomes have not yet been reported; therefore, it remains unclear which reconstruction is better after PD. Hirono et al reported that atrophic change in the remnant pancreas in the PG group was more severe than that in the PJ group, and PG reconstruction was an independent risk factor for pancreatic exocrine insufficiency after PD.33 In addition, potential reasons for the remnant pancreatic atrophies being predominant in the PG group were chronic inflammation of the remnant pancreas arising from the gastric mucosa over healing and covering the anastomotic or reflux of gastric juice into the main pancreatic duct. Therefore, the postoperative morphologic changes may lead to the exocrine insufficiency in the PG group.23 Our study found similar results, and PG reconstruction was one of the independent risk factors for NAFLD after PD.

Female sex was also identified as the independent risk factor for NAFLD after PD with the highest OR in our study. Although this result was consistent with previous reports,28,34 the mechanism underlying the significant correlation between female sex and NAFLD after PD remains unclear. One possible reason may be the withdrawal of estrogens in postmenopausal woman, a population that has a higher prevalence of NAFLD.35,36 Menopause markedly accelerates the accumulation of visceral fat, which may induce insulin resistance.37,38 One recent study reported that female sex was a significant risk factor for intractable NAFLD even after pancreatic enzyme supplementation. This observation suggests that not only pancreatic exocrine insufficiency but also insulin resistance influences the development of NAFLD after PD in women.14

This study had several limitations. First, NAFLD was diagnosed based only on CT imaging; there were no data of histological findings for NAFLD. Second, there were no data from patients who died within 3 months postoperatively. Third, because not all patients in this study had data regarding pancreatic enzyme supplementation therapy after PD, we were not able to investigate the correlation between the development of NAFLD and pancreatic enzyme preparation. Fourth, PJ was mainly performed since 2012 instead of PG. The difference in the reconstruction method may have affected the perioperative factors. Finally, this study was a retrospective study, and there is a selection bias because the patients were enrolled at a single center. Further prospective studies are needed to investigate the mechanism of NAFLD and its treatment.

In conclusion, three independent risk factors—female sex, atrophic change in the remnant pancreas, and PG reconstruction—significantly influenced the development of NAFLD after PD. Perioperative CT assessment of the pancreas may be helpful for preventing the development of NAFLD after PD and may also contribute to the prevention and early treatment of this late complication of PD.

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DISCLOSURE
Conflict of Interest: H.B. is an Editorial Board Member of AGS.
Ethical Approval: The study was approved by the Institutional Review Board of Kumamoto University Hospital (admission number #1000).
Informed Consent: Written informed consent was obtained from all included patients.

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