Usefulness of the abdominal fat area-based risk score for postoperative pancreatic fistula after pancreatoduodenectomy

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Abstract

Background

Pancreatic fistulas remain a significant concern after pancreatectomy, and it is not possible to perform preoperative risk stratification for all patients. This study aimed to evaluate the usefulness of a unique risk model, based on the abdominal fat area (AFA) calculated by computed tomography, for pancreatic fistula development after pancreatoduodenectomy and compare it with models based on the body mass index (BMI) or abdominal thickness.

Material and Methods

Patient characteristics, preoperative laboratory data, radiographic findings, and their association with pancreatic fistula development after pancreaticoduodenectomy were analysed for 158 patients who underwent resection between 2011 and 2017. Clinically relevant postoperative pancreatic fistulas (CR-POPF) were defined as Grade B or C fistulas based on the International Study Group of Pancreatic Surgery (ISGPS) 2016 consensus.

Results

CR-POPF developed in 38 patients (24.2%). Multivariate logistic analysis indicated that the AFA, BMI, and intra-abdominal thickness were potential candidates for predictive models for pancreatic fistula development, small pancreatic duct diameter, diabetes mellitus development, and the pathology of non-pancreatic cancers. When comparing the three risk models (AFA-, BMI-, and intra-abdominal thickness-based), the AFA-derived risk model was superior to the BMI-based and intra-abdominal thickness-based risk stratification models (area under the curve 0.836 vs 0.824 vs 0.826).

Conclusions

The risk model based on AFA calculation was superior to that based on BMI or intra-abdominal thickness measurements. The model must be validated further to elucidate the efficacy of the risk scoring system in more detail.

Introduction

Pancreaticoduodenectomy (PD) remains the surgery of choice for the majority of lesions involving the pancreatic head, uncus, and neck. There have been several improvements in the PD procedure and perioperative treatment approaches in recent decades[1], including the use of somatostatin analogues[2], pancreatic duct stenting[3], fibrin glue[3], suturing techniques that include duct-mucosa anastomosis[4], and sophisticated prophylactic drainage measures[5]. Despite these developments, postoperative pancreatic fistulas (POPFs) are commonly observed (22–26%)[6] and remain the most challenging complication following PD because they are the primary cause of mortality[7] and associated with high costs[8].

Some predictive indicators, such as body mass index (BMI), histological diagnosis of a tumour or pancreatic lesion, and main pancreatic duct (MPD) diameter, and scoring systems have been suggested to predict the development of POPF[9]. A factor referred to as the Alternative Fistula Risk Score (aFRS) is currently the most commonly used scoring system that applies BMI, pancreatic texture, and MPD diameter in risk calculations. Other risk scoring systems have included indicators such as abdominal thickness. Although the abdominal fat area (AFA) requires specific devices and accurate identification for calculation, of late, it has been recognised as a useful predictor and thought to directly affect the difficulty of PD. However, reports on the efficacy of risk stratification based on AFA are limited, and to the best of our knowledge, no study has reported on the evaluation of an AFA-derived risk model and its comparison with risk models derived from other body composition-based parameters. The present study aimed to evaluate a new risk stratification score that includes AFA, determine its correlation with the development of clinically relevant POPF (CR-POPF), and compare its efficacy with that of the BMI-based or abdominal thickness measurement-based scoring systems.

Material And Methods

Patients selection

All adult patients who underwent PD at our institution from April 2011 to October 2017 were included in this analysis. Patients who underwent pancreatic anastomosis by techniques other than the Child method described later, those with a history of other bowel surgeries such as esophagectomy or colectomy, and those with insufficient data were excluded. All patients provided informed consent for participating in this retrospective observational study using the “opt-out” method. This study was approved by the ethical committee of Keio University (No. 20140389).

Surgical procedure

Eight attending physicians and 13 residents performed the surgical procedures. At our hospital, there are three different types of PD: classic (Whipple procedure), pylorus-preserving, and subtotal stomach-preserving PD. The procedure can be chosen at the surgeon’s discretion. After resection, anastomoses were constructed on a single jejunal loop, which was repositioned up into the supramesocolic compartment in a retrocolic manner. The Child method[3] or the Imanaga method[10,11] was performed for all patients who underwent reconstruction of the digestive tract. Management of the pancreatic stump consisted of a two-layer pancreaticojejunal (PJ) anastomosis (pancreatic duct-mucosa and pancreatic parenchyma-jejunal serosal muscular combined with peeling off the jejunal serosa); an internal or external pancreatic stent was used according to each surgeon’s preference. An end-to-side hepaticojejunostomy using absorbable 5 – 0 interrupted sutures was performed 20 cm distally to the pancreaticojejunostomy. Then, an end-to-side gastrojejunostomy was performed 50 cm downstream, using two-layer sutures. Two Blake drains (19-Fr; Ethicon, USA) were positioned; one was placed beneath the stomach up to the posterior surface of the pancreatic anastomosis, whereas the other was placed on the superior surface of the biliary and pancreatic anastomoses. Operative drains were managed at the discretion of the treating surgeon, usually based on drain amylase measurement on postoperative days 1, 3, 5, and 7[5]. Prophylactic somatostatin analogues were used at each surgeon's discretion; however, these were not routinely administered.

Definition and classification of POPF

The revised International Study Group for Pancreatic Surgery (ISGPS) definition and grading system of POPF[12] were adopted in this study. According to the updated criteria, POPF comprised three groups: those with biochemical leaks, grade B, and grade C. Grade B/C POPF was considered a CR-POPF.

Radiological findings

Radiological parameters, including the MPD diameter, AFA, subcutaneous fat area (SFA), and distance between the superior mesenteric vein and the abdominal wall (SMV distance), were determined from preoperative plain or contrast-enhanced computed tomography (CT). The AFA and SFA were measured semiautomatically by manually outlining them on the CT image at the third lumbar vertebra (L3) and setting the density at a threshold of -190 to -30 HU using OSIRIX®. The SMV distance was recorded on CT as the distance from the surface of the abdominal wall to the anterior plane of the SMV on the slice where the short axis of the pancreas could be observed. All the measurements and calculations described above were performed by the same examiners (TY and KA), who were blinded to the surgical outcome at the time of quantification.

Statistical analysis

We compared the clinical and radiological characteristics between the CR-POPF and non-CR-POPF groups. Categorical data were evaluated by the Chi-squared test or Fisher's exact test. Quantitative variables were compared using Student's t-test or the Wilcoxon rank-sum test and expressed as mean (± standard deviation) or median values (interquartile range). $P < 0.05$ was considered statistically significant. To identify independent predictors of CR-POPF, we conducted univariate and multivariate logistic regression analyses. Multivariate logistic analysis was performed using variables that showed a P value of < 0.05 in univariate analysis. Factors that showed a P value of < 0.20 in multivariate logistic analysis were considered for creation of the risk scoring system. For comparison of the risk scores, we generated the area under the receiver operating characteristic curve (AUC) and used the Akaike Information Criterion (AIC). All statistical analyses were conducted using JMP 12 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Overall, 157 patients were analysed. CR-POPF occurred in 38 (24.2%) patients. Patient characteristics, radiologic findings, intraoperative findings, and indications for PD are summarised in **Table 1**. The average age of all patients was 68 years, and 107 (67.7%) patients were male. Thirty-seven patients had a present history of diabetes mellitus (DM) and required dietary modifications, exercise, or medication, including insulin. Pathologic diagnoses were pancreatic cancer (n=68, 43%), intraductal papillary mucinous neoplasm (IPMN; n=29, 18%), pancreatic neuroendocrine neoplasms (PanNEN; n=11, 6.9%), solid pseudopapillary neoplasms (SPN; n=1, 0.6%), pancreatic cystic lesions (n=1, 0.6%), bile duct cancer (n=30, 18.9%), duodenal cancer (n=7, 4.4%), and others (n=11, 6.9%). Preoperative drainage was conducted in 52 patients (pancreatic cancer; n=31, PanNEN; n=2, bile duct cancer; n=15, duodenal cancer; n=2, others; n=2). All patients who underwent preoperative treatment were diagnosed with pancreatic cancer. Classic PD was performed in 9 patients with a previous history of gastrectomy. Pylorus-preserving PD (PPPD) was more likely to be performed in patients with bile duct cancer, while subtotal stomach-preserving PD (SSPPD) was more likely performed in patients with other diseases. The technique chosen was mainly based on each surgeon’s preference. Thirty-three patients with pancreatic cancer and two with IPMN underwent vascular resection.

Comparison between CR-POPF and non-CR-POPF groups

The CR-POPF group primarily included male patients with diabetes. Laboratory findings showed no significant differences between the CR-POPF and non-CR-POPF groups. A high BMI, AFA, SFA, and SMV distance were all associated with the incidence of CR-POPF. The CR-POPF group was likely to require a longer operation time, exhibit greater blood loss, and require a longer hospital stay (CR-POPF group vs non-CR-POPF group: 475 min vs 346 min, P=0.012; 510 ml vs 260 ml, P=0.0002; 40 days vs 27 days, P<0.0001, respectively). There was a slight but not significant difference in the development of POPF according to the experience of the operator (board-certified or trainee; CR-POPF: board-certified vs. trainee, 23.4% vs. 27.6%, P=0.63). Among patients with grade C fistulas, one died of multiple organ failure. The total mortality rate in the whole group of patients was 0.6% (1/157).

Risk factors for CR-POPF and predictive models

Univariate analysis for POPF (**Table 2**) revealed that male sex (OR; 2.6, P=0.03), present history of DM (OR; 2.9, P=0.01), pathology of non-pancreatic cancer (OR; 7.7, P<0.0001), BMI (OR; 1.3, P<0.0001), MPD (OR; 0.73, P<0.0001), AFA (OR; 1.01, P=0.0002), SFA (OR; 1.01, P=0.018), SMV distance (OR; 1.03, P=0.0013), and SMV/portal vein (PV) resection (OR; 0.07, P=0.03) were significantly associated with the incidence of CR-POPF. The rate of CR-POPF did not correlate with age; laboratory findings, including albumin and CRP levels; smoking status; and treating surgeons.

Multivariate logistic analysis was performed using variables that showed a P value of <0.05 in univariate analysis. There was multicollinearity between BMI, AFA, SFA, and SMV distance; therefore, predictive models were separately created. In this analysis, a history of DM, a non-pancreatic cancer pathology, and a small MPD diameter were similarly independent factors for CR-POPF. The BMI model, AFA model, and SMV distance model were adopted, whereas the SFA model did not meet the criteria mentioned previously (**Table 3**). Each risk model was compared based on the AUC and AIC. The AFA model showed a higher AUC and lower AIC than did the BMI model and SMV distance model (AUCs for the AFA model vs BMI model vs SMV distance model were 0.834 vs. 0.824 vs. 0.826, while AICs were 136.323 vs. 137.917 vs 138.318, respectively; **Figure 1**).

Discussion

In this study, we demonstrated that pancreatic fistulas occurred after PD in 24% patients, a finding similar to those in other studies[13]. Like previous studies[14], our results showed that a small pancreatic duct, DM, and a non-pancreatic cancer pathology were predictive factors for pancreatic leakage after PD. Moreover, parameters associated with body composition, including BMI, AFA, and SMV distance, were identified as predictors. After detecting the risk factors, we devised potent risk models using these variables. Among them, the AFA model showed a greater AUC than did the BMI model and SMV distance model. There have been several risk scoring systems for predicting CR-POPF after pancreaticoduodenectomy[9,14]; however, our study provides new insight into the usefulness of the AFA for predicting CR-POPF.

Generally, visceral fat is a major factor influencing the technical difficulty during abdominal surgery. It has been shown in several studies[15–17] that obese patients are associated with a higher rate of complications such as wound infection, anastomotic fistula, and longer hospital stay. Recently, it was reported that a high amount of visceral fat was associated with a significantly higher rate of overall complications and pancreatic fistula development after PD[15,18]. Operating on patients with a high AFA involves surgical difficulties associated with obstruction of the field of view during surgery, which can be challenging when handling fragile pancreatic tissue. Moreover, an abundant amount of abdominal fat around the pancreaticojejunostomy anastomosis site may be catalysed into triglycerides and free fatty acids by pancreatic lipase. This may have a deteriorating impact on a developing CR-POPF, according to recent clinical and experimental studies on intraabdominal lipolysis[19]. This may be why there was no significant difference in the rate of CR-POPF between the trainees and skilled surgeons (CR-POPF vs non-CR-POPF, 23.4% vs 27.6%, $P = 0.63$) in this study. BMI has been widely used to estimate the status of obesity because it can be calculated easily using weight and height. However, BMI does not always accurately measure the amount of visceral fat because of the variation in fat tissue distribution among individuals[20]. Thus, AFA is considered a better surrogate marker. However, AFA would need to be measured with an imaging application, while BMI or SMV distance can be determined in a general clinical setting. A more concise way to estimate intra-abdominal fat is needed in the future.

In many studies, a soft pancreatic texture has been widely recognised as the most significant risk factor for POPF[14]. Generally, pancreatic cancer is associated with the development of substantial pancreatic fibrosis, which results in hardening of the pancreatic texture. Histopathological analysis, rather than a surgeon’s impression of the texture, has been adopted as the most reliable method for histopathological categorisation of pancreatic texture. Univariate analysis showed a significant statistical difference between the two groups (ORs 7.7, 95% CI 2.9–25, $P < 0.0001$), suggesting that patients with soft pancreatic parenchyma were more likely to develop a POPF after PD than were patients with a hard pancreas. Furthermore, multivariate logistic regression analysis indicated that a soft pancreas was an independent risk factor for the development of POPF. This result was consistent with those in previous studies[9,14,21]. The lower rate of POPF in patients with hard pancreatic parenchyma may be associated with pancreas exocrine dysfunction resulting from long-term pancreatic fibrosis[22]. Our previous study that involved quantitative assessments of pancreatic fibrous tissue[22] suggested that a lower proportion of fibrous tissue would likely lead to POPF, but not CR-POPF. This result indicated that pancreatic fibrosis was associated with the amount of pancreatic secretions, although it was not the sole culprit behind CR-POPF development. Other factors such as perioperative management, including the pancreaticojejunostomy method, would be influenced. In our suturing method, 6–8 stitches are placed during pancreatic parenchyma-jejunal seromuscular anastomosis, as previously mentioned. Procedures that use fewer stitches such as the modified Blumgart method[4,23] should be taken into consideration for better results, as they might help in preventing pancreatic juice leakage from suturing holes.

Previous studies have consistently demonstrated that a small MPD diameter is a strong predictor of POPF[14]. Similarly, our study showed that patients with a smaller MPD diameter were more likely to experience CR-POPF (CR-POPF vs non-CR-POPF: median 2.15 mm vs 4.11 mm, respectively; $P = 0.0007$). The main reason could be that a small MPD is technically difficult to anastomose. Several intraoperative procedures for overcoming this obstacle have been developed, such as external stenting[24], pancreatic duct holders[25], and pancreaticogastrostomy[26]; however, practical approaches are limited. More interventions need to be investigated.

In our cohort, DM was associated with a higher risk of POPF. Theoretically, patients with DM are likely to experience delayed wound healing because numerous cytologic factors contribute to impaired wound healing in patients with diabetes[27]. Diabetes is a particularly important risk factor for the development of chronic wounds from neuropathy and vasculopathy, which increase the risk of infection and delay healing. Some studies have investigated the association between the presence of DM and POPF[28,29]. However, the results were inconsistent. Some papers have demonstrated results that conflicted with our outcomes[17,30,31], while others suggested that DM was associated with neither negative nor positive predictors of POPF[32,33]. The various proportions of patients with type 2 DM in the studies might explain this[34]. The pancreatic acinar cells and Langerhans islets cells are scarce because of fibrous tissue substitution in patients with pancreatic cancer. In this situation, both endocrine and exocrine functions are diminished. Therefore, the development of POPF is likely to decrease. Differences in the proportion of patients with this type of DM and other types of DM in the previous cohorts may have led to an inconsistent result.

The present study has some limitations, including its retrospective nature and the limited number of enrolled patients in a single institution. Second, this study did not include a validation set analysis because of the rather low patient number. In addition, other techniques for performing pancreaticojejunostomy, such as the Kakita and Blumgart methods, and pancreaticogastrostomies were excluded because we intended to exclude the influence of methodological differences in POPF treatment. Further validation is needed for the various anastomotic procedures.

In conclusion, the AFA-based risk model was superior to the BMI- or abdominal thickness- derived model. Thus, AFA calculation might result in better prediction of POPF after PD. Further validation of the AFA-based model is warranted to identify the most suitable risk stratification model.

Declarations

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Conflict of interests

The authors have no conflicts of interest to declare.

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Tables

Due to technical limitations, Tables 1 - 3 are only available for download from the Supplementary Files section.

Figures

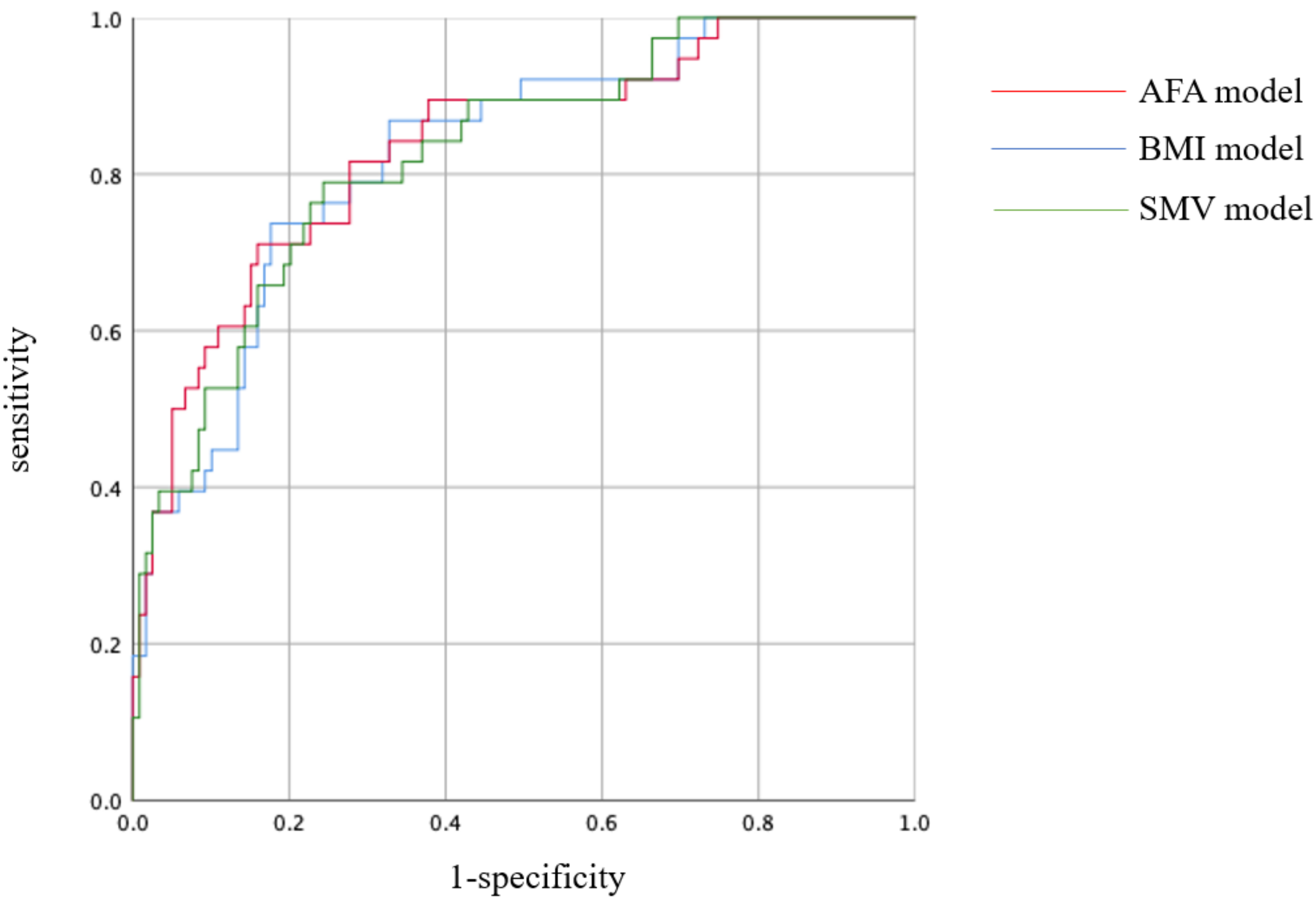

Figure 1

Receiver-operator characteristic (ROC) analysis for the three risk models The area under the ROC curve (AUC) for the AFA model, BMI model, and SMV model is 0.835, 0.825, and 0.825 ($p<0.0001$), respectively. AFA: abdominal fat area; BMI: body mass index; SMV: superior mesenteric vein.

Supplementary Files

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