Preoperative body mass index-to-prognostic nutritional index ratio predicts pancreatic fistula after pancreaticoduodenectomy

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Background: Estimating or scoring the risk of post-operative pancreatic fistula (POPF) may help with selection of high-risk patients and individualized patient consent. However, there are no simple and reliable preoperative predictors of POPF used in daily clinical practice.

Methods: We investigated the utility of body mass index-to-prognostic nutritional index (BMI/PNI) ratio as a preoperative marker to predict the development of POPF in 87 patients undergoing pancreaticoduodenectomy.

Results: The overall incidence of clinical (grade B/C) POPF was 17% (15 of 87 patients). Among various pre-, intra-, and post-operative variables analyzed, higher BMI and lower PNI were identified as independent predictors for POPF by multivariate analysis. We therefore investigated BMI/PNI ratio as a preoperative predictor for POPF. BMI/PNI ratio was significantly higher in patients with POPF than in those without POPF (0.54 vs. 0.45, $P=0.0007$). A receiver operating characteristic (ROC) curve analysis demonstrated a fair capability of BMI/PNI ratio to predict the occurrence of POPF (area under the ROC curve 0.781). With a cut-off value of 0.5, the sensitivity, specificity, and diagnostic accuracy of BMI/PNI ratio to predict POPF was 73%, 74%, and 74%, respectively. In particular, when restricted to a subgroup of elderly (≥ 75 years old) male patients, the sensitivity, specificity, and diagnostic accuracy of BMI/PNI ratio was 100%, 100%, and 100%, respectively.

Conclusions: The BMI/PNI ratio is a simple preoperative marker to predict the occurrence of POPF after pancreaticoduodenectomy.

Keywords: Pancreaticoduodenectomy; pancreatic fistula; risk factor; body mass index (BMI); prognostic nutrition index (PNI)

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Introduction

Despite a marked reduction in mortality after pancreaticoduodenectomy, post-operative pancreatic fistula (POPF) remains one of the most common and serious complications. According to a large-scale national survey in Japan, grade B and C POPF defined by the International Study Group on Pancreatic Fistula (ISGPF) occurred in 13.2% of 8,575 patients undergoing

pancreaticoduodenectomy (1). Although the majority of POPF can be managed by conservative therapy, some require reoperation (2). Furthermore, POPF leads to a prolonged hospital stay, substantial resource utilization, and sometimes to a life-threatening condition especially when associated with delayed massive bleeding (3,4).

Previous studies have identified a number of risk factors, most commonly intra- and post-operative variables, for

Table 1 Patient characteristics and outcomes

Characteristics/factors	All patients (n=87)
Age [yrs.]	70 [33–86]
Gender (M/F)	52/35
Disease	
Pancreatic ductal adenocarcinoma	29 (33%)
Ampullary cancer	17 (20%)
Bile duct cancer	16 (18%)
IPMN	8 (9%)
PNET	5 (6%)
Chronic pancreatitis	4 (5%)
Others	8 (9%)
Operative procedure	53/167
PPPD	69 (79%)
SSPPD	15 (17%)
PD	3 (3%)
Post-operative complications	
POPF Grade A	24 (23%)
POPF Grade B/C	15 (17%)

Values shown are median (range). M, male; F, female; IPMN, intraductal papillary mucinous neoplasms; PNET, pancreatic neuroendocrine tumor; PPPD, pylorus-preserving pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy; PD, pancreaticoduodenectomy; POPF, post-operative pancreatic fistula.

POPF (5). For example, soft pancreatic texture assessed during surgery is known as the most commonly reported risk factor for POPF (6,7). Furthermore, drain amylase level measured postoperatively has been also reported to be useful in predicting the development of POPF (7,8).

Estimating the risk of POPF could improve patient risk stratification preoperatively and help with individualized patient consent. In this respect, preoperative factors are more useful than intra- or post-operative factors. Several preoperative risk factors for POPF after pancreaticoduodenectomy have been reported, including higher body mass index (BMI) and lower prognostic nutritional index (PNI) (9–11). There are, however, no simple and reliable preoperative predictors of POPF used currently in daily clinical practice. In the present study, we investigated the utility of BMI-to-PNI (BMI/PNI) ratio as a preoperative marker to predict the development of POPF in 87 patients undergoing pancreaticoduodenectomy.

Methods

Study subjects

The study included a total of 87 consecutive patients underwent pancreaticoduodenectomy at our institution from May 2008 to March 2014. The patient characteristics are summarized in *Table 1*. There were 52 male and 35 female patients with a median age of 70 (range, 33–86) years. Indications for surgery included pancreatic ductal adenocarcinoma (29 patients), ampullary cancer (17 patients), bile duct cancer (16 patients), intraductal papillary mucinous neoplasm of the pancreas (eight patients), pancreatic neuroendocrine tumor (five patients), chronic pancreatitis (four patients), and other diseases. The operative procedures performed included pylorus-preserving pancreaticoduodenectomy (PPPD) in 69 patients, subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) in 15 patients, and conventional Whipple operation (pancreaticoduodenectomy) in the remaining three patients.

Surgical techniques

Pancreaticoduodenectomy was done as previously described (12). Pancreaticojejunostomy was performed using a modified Kakita's method (13). Adhesive sutures were placed through the pancreatic stump and run through the subserosal layer of the jejunum. A mucosa-to-mucosa anastomosis of the pancreaticojejunostomy was performed with interrupted sutures using 5–0 monofilament absorbable sutures (PDS, Ethicon Inc., Tokyo, Japan). A pancreatic duct drainage tube [a 4–6 Fr tube with an expanded segment selected according to the size of the main pancreatic duct (MPD)] was placed from the jejunal loop to the MPD. The pancreatic duct drainage tube was fixed at the anastomotic site using absorbable suture material and then externalized from a stab incision in the anterior abdominal wall. One or two intraabdominal drainage tubes were placed in the vicinity of the pancreaticojejunostomy.

Post-operative management and POPF

After surgery, all patients received intravenous antibiotics for three days [on the operation day and post-operative day (POD) 1 and 2]. In general, oral intake was gradually resumed around on day 3–5 if there was no evidence of intra-abdominal complications. The drain fluid amylase levels were measured on POD 3. The peripancreatic drains were removed usually on or after POD 7 if there was no

evidence of leakage. When there was evidence of leakage or suspicion of an infectious complication, the peripancreatic drains were left and changed once a week.

The diagnosis of POPF was made by drain output of any measurable volume of fluid on or after POD 3 with amylase content 3 times greater than serum amylase activity, according to the International Study Group for Pancreatic Fistula (ISGPF) (14). In addition, the severity of POPF was graded as grade A, B, or C (14). In the present study, grade B and C POPF was defined as clinically relevant POPF.

Clinical variables for risk analysis of POPF

The medical records were reviewed for the following clinical variables: patient age, sex, BMI, PNI [calculated as $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$ (15)], serum albumin level and total lymphocyte count as components of PNI (but not used in the multivariate analysis), pancreatic gland texture (soft or hard), dilatation of the MPD at operation (5 mm or greater in diameter), operative time, intraoperative blood loss, drain amylase level on POD 3, and the volume of post-operative pancreatic juice output (during POD 1–3).

Data presentation and statistical analysis

The results of parametric data were expressed as medians (range). A univariate analysis of risk factors associated with POPF was performed using the Fisher's exact probability test for categorical data and the Mann-Whitney U test for continuous data. A multivariate analysis was done for all variables with P-values of less than 0.2 using a logistic regression analysis. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were done using JMP 10 software (SAS Institute Inc., Cary, NC, USA).

Results

Post-operative pancreatic fistula (POPF)

Overall, POPF was diagnosed in 39 (45%) of 87 patients according to the ISGPF criteria. The severity of POPF was classified as grade A in 24 patients, grade B in 14, and grade C in 1 (Table 1). Therefore, clinically relevant (grade B/C) POPF occurred in 15 patients (17%). There was no 30-day mortality in this series.

Comparison of factors between patients with POPF and those without POPF

First, we compared various pre-, intra-, and post-operative variables between patients with POPF of all grades (n=39) and those without POPF (n=48). Univariate analysis revealed BMI ($P=0.131$), pancreatic consistency ($P=0.0021$), MPD dilatation ($P=0.0060$), and drain amylase level on POD3 ($P<0.0001$) to be significantly different between the groups. However, multivariate analysis including these significant variables failed to identify independent risk factors for POPF (data not shown).

Comparison of factors between patients with clinical POPF and those without clinical POPF

We then compared these variables between patients with clinical (grade B/C) POPF (POPF group, n=15) and those without clinical POPF (No-POPF group, n=72) (Table 2).

Among the preoperative factors, older age and male sex tended to be associated with the development of POPF, although the differences were not statistically significant. BMI was significantly higher in the POPF group than in the No-POPF group (23.3 vs. 21.2, $P=0.0080$). Preoperative PNI tended to be lower in the POPF group than in the No-POPF group ($P=0.0533$).

Of the intraoperative variables, a soft pancreatic texture was significantly more frequent in the POPF group than in the No-POPF group (100% vs. 64%, $P=0.0040$). There was no significant difference in the MPD dilatation (5 mm or greater), operative time, and intraoperative blood loss between the groups. With regard to the MPD dilatation, the difference was not significant ($P=0.7625$) even when the definition was changed to 3 mm or greater in diameter.

Regarding the post-operative variables, drain amylase level (on POD3) was significantly higher in the POPF group than in the No-POPF group (1,719 vs. 282 IU/L, $P=0.0007$). Furthermore, the volume of post-operative pancreatic juice output (during POD 1–3) was significantly larger in the POPF group than in the No-POPF group (276 vs. 151 mL, $P=0.0206$).

Multivariate analysis for factors associated with POPF

We then performed a multivariate analysis for factors predicting the development of clinical POPF using a logistic regression analysis. Because pancreatic consistency is assessed subjectively by the surgeon, this factor was

Table 2 Univariate analyses of risk factors for clinical POPF after pancreaticoduodenectomy

Factor	Patients with POPF (n=15)	Patients without POPF (n=72)	P value
Preoperative factors			
Age [yrs.]	73 [52–86]	68 [33–85]	0.1128
Gender (male)	80% (12/15)	56% (40/72)	0.0914
BMI (kg/m ²)	23.3 (18.0–42.3)	21.2 (15.8–31.0)	0.0080*
PNI	45.7 (34.7–51.4)	47.4 (30.4–62.0)	0.0533
Serum albumin (g/mL)	3.6 (2.8–4.3)	3.9 (2.6–5.1)	0.0591
Total lymphocyte counts	1,381 [280–2,691]	1,590 [727–3,837]	0.0963
Intraoperative factors			
Pancreatic consistency (soft)	100% (15/15)	64% (46/72)	0.0040*
MPD dilatation	27% (4/15)	36% (26/72)	0.5633
Operative time [min]	526 [365–780]	512 [314–720]	0.5365
Intraoperative blood loss [mL]	575 [120–2,300]	425 [100–4,700]	0.5625
Post-operative factors			
Drain amylase level on POD3 [U/mL]	1,719 [67–16,766]	282 [7–37,512]	0.0026*
Pancreatic juice output during POD1–3 [mL]	276 [95–570]	151 [0–750]	0.0206*

*, statistically significant. Values shown are medians (range); POPF, post-operative pancreatic fistula; BMI, body mass index; PNI, prognostic nutritional index; PDAC, pancreatic ductal adenocarcinoma; MPD, main pancreatic duct; POD, post-operative day.

Table 3 Multivariate analysis of risk factors for clinical POPF after pancreaticoduodenectomy

Factor	Category	Odds ratio	95% CI	P value
Age	Per 1 year	1.05	0.97–1.15	0.2175
Gender	Male/female	11.8	1.62–220.1	0.0120*
BMI	Per 1 kg/m ²	1.52	1.22–2.10	<0.0001*
PNI	Per 1	0.82	0.68–0.98	0.0251*
Pancreatic juice output during POD1–3	Per 1 mL	1.00	0.98–1.01	0.8567

*, statistically significant. POPF, post-operative pancreatic fistula; CI, confidential interval; BMI, body mass index; PNI, prognostic nutritional index; POD, post-operative day.

excluded from the multivariate analysis. We also excluded drain amylase level because this consists of the definition of POPF. The multivariate analysis (including age, gender, BMI, PNI, and pancreatic juice output) revealed gender (male, $P=0.0120$), higher BMI ($P<0.0001$) and lower PNI ($P=0.0251$) to be independent factors associated with the development of clinical POPF (Table 3).

Analysis of BMI/PNI ratio as a preoperative predictor for POPF

We thought to determine if a combination of two independent factors, BMI and PNI, could be more useful

in predicting the development of POPF. We therefore compared the BMI/PNI ratio between the POPF and No-POPF groups. The BMI/PNI ratio was significantly higher in the POPF group than in the No-POPF group (0.54 *vs.* 0.45, $P=0.0007$).

A receiver operating characteristic (ROC) curve analysis demonstrated a fair capability of BMI/PNI ratio to predict the occurrence of POPF (area under the ROC curve 0.781) (Figure 1). The area under the curve (AUC) of BMI/PNI ratio was higher as compared to that of BMI (0.719) or PNI (0.659) alone.

When a cut-off value of BMI/PNI ratio was set to 0.5, the sensitivity, specificity, and diagnostic accuracy to predict

Figure 1 A receiver operating characteristic (ROC) curve analysis demonstrated a fair capability of BMI/PNI ratio to predict the occurrence of post-operative pancreatic fistula (POPF) (area under the ROC curve 0.781). BMI, body mass index; PNI, prognostic nutritional index.

POPF was 73%, 74%, and 74%, respectively. In particular, when restricted to a subgroup of elderly (≥ 75 years old) male patients ($n=10$), the sensitivity, specificity, and diagnostic accuracy of BMI/PNI was 100%, 100%, and 100%, respectively.

Discussion

In this study, we retrospectively reviewed our series of 87 patients undergoing pancreaticoduodenectomy to identify risk factors for POPE. The major findings obtained were as follows: (I) the incidence of clinical POPF was 17%; (II) univariate analysis comparing patients with or without clinical POPF showed significant differences in BMI, pancreatic gland texture, drain amylase level, and the amount of pancreatic juice output; (III) multivariate analysis revealed a higher BMI and lower PNI to be independent risk factors for clinical POPF; (IV) BMI/PNI ratio was significantly higher in patients with POPF than in those without POPF; (V) a ROC curve analysis revealed AUC of BMI/PNI ratio to be 0.781; and (VI) the sensitivity, specificity, and diagnostic accuracy of BMI/PNI ratio to predict POPF was 73%, 74%, and 74%, respectively. These

findings suggest that BMI/PNI ratio is a simple and reliable preoperative marker to predict the development of POPF after pancreaticoduodenectomy.

The reported risk factors for POPF after pancreaticoduodenectomy include preoperative variables (older age, male gender, a higher BMI, impaired preoperative nutritional status, type of disease, jaundice/biliary drainage, cholangitis, and normal exocrine function), intraoperative variables (soft pancreatic texture, small pancreatic duct, longer operative time, and increased blood loss during surgery), and post-operative variables (high amylase levels in the drain fluid and a larger volume of pancreatic juice output) (1,5-8,11,16-27). In addition to these individual risk factors, scoring systems combining several factors have been proposed to more accurately predict the risk of POPF (26,28). However, these scoring systems are sometimes too complex to use in daily clinical practice. In the present study, we combined only two preoperative factors, BMI and PNI, which were shown to be independently associated with POPF by multivariate analysis. Although high BMI and impaired preoperative nutritional status have been already recognized as risk factors for POPF (11), the clinical utility of BMI/PNI ratio has not been evaluated in previous studies. Because BMI and PNI can be obtained easily from physical examinations and basic laboratory data even at the first outpatient visit, BMI/PNI ratio may be a simple and useful preoperative marker for predicting the risk of POPF.

The strategy to decrease the incidence of POPF involves controlling its risk factors. In this respect, BMI/PNI can provide opportunities to select patients who could benefit from nutritional support. A previous study showed that preoperative immunonutrition decreases post-operative complications by modulating prostaglandin E2 production and T-cell differentiation in patients undergoing pancreaticoduodenectomy (29). However, there is no sufficient evidence to support the efficacy of preoperative nutritional support to prevent POPF after pancreatectomy. Based on our present results, we introduced preoperative oral nutritional supplements (Ensure H, Abbott Japan) for a relatively short period (usually from the day of first visit to the day of surgery) in patients with a BMI/PNI ratio of >0.5 . The efficacy of this preoperative nutritional support in patients at high risk for POPF should be prospectively evaluated in future studies.

In the present study, the sensitivity, specificity, and diagnostic accuracy of BMI/PNI ratio was 100%, 100%, and 100%, respectively, when restricted to a subgroup

of elderly (≥ 75 years old) male patients. The reason why the diagnostic accuracy was particularly higher in this subgroup is unknown, but in general older age and male gender are also risk factors for POPF. Recently, increasing number of elderly patients become candidates for pancreaticoduodenectomy. Therefore, BMI/PNI ratio could be used to estimate the risk of POPF and help determine the indication of pancreaticoduodenectomy especially in elderly patients.

The present study has several limitations. First, this study is a retrospective analysis and the possibility of bias related to the historical background cannot be eliminated. Second, the number of patients (especially the number of patients who developed clinical POPF) in this study is relatively small and may be underpowered for some statistical analyses. To further validate our present findings, a prospective study in a larger number of patients is needed.

In summary, our present study demonstrates that BMI/PNI ratio is a simple preoperative marker to predict the occurrence of POPF after pancreaticoduodenectomy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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