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Original Article

A comprehensive study on postoperative complications and postoperative pancreatic fistula in sporadic non-functional pancreatic neuroendocrine tumors: A retrospective cohort study

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Backgrounds/Aims: Balancing surgical risks and benefits is crucial for managing non-functional pancreatic neuroendocrine tumors (NF-PNETs). Despite high postoperative pancreatic fistula (POPF) rates, studies on postoperative complications of sporadic NF-PNETs are scarce. Thus, this study aimed to investigate postoperative complications and identify risk factors for POPF.

Methods: A retrospective review of 166 NF-PNET surgeries performed at Severance Hospital between February 2000 and August 2023 was conducted.

Results: Age > 65 years and higher American Society of Anesthesiology (ASA) grade were not significantly correlated with severe complications (odds ratio [OR]: 1.10, $p = 0.871$ and OR: 1.47, $p = 0.491$, respectively). Surgical procedures included enucleation (13.9%), distal pancreatectomy (50.0%), central pancreatectomy (4.8%), pancreaticoduodenectomy (PD) (26.5%), and total pancreatectomy (4.8%). Severe complications occurred in 12.05% of surgeries. The overall incidence of all POPFs including biochemical leaks was 53%, while clinically relevant POPF (grade B or C) occurred in 7.8% of patients. Logistic regression showed that PD (OR: 3.94, $p = 0.092$) tended to be risk factor for POPF and that diameter of the main pancreatic duct (MPD) ≤ 3 mm was a significant risk factor for POPF (OR: 0.22, $p = 0.008$). A pancreas thickness (PT)/MPD ratio > 4.47 on preoperative computed tomography predicted all POPFs in PD patients (OR: 11.70, $p = 0.001$).

Conclusions: Age and comorbidities had no significant impact on surgical outcomes. PD was associated with higher serious complications and POPF rates. The PT/MPD ratio is a valuable preoperative tool for predicting POPF risk in PD patients.

Key Words: Gastro-enteropancreatic neuroendocrine tumor; Pancreatectomy; Postoperative complications; Pancreatic fistula; Risk factors

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are rare diseases that originate in the pancreas with gradually increasing incidence in recent years [1]. Advancements in imaging diagnostics have led to an increase in the detection of asymptomatic, incidental, and non-functional pancreatic neuroendocrine tumors (NF-PNETs) [2,3]. Surgical resection is the primary treatment option for NF-PNETs. However, recent studies have shown that NF-PNETs < 2 cm tend to have a relatively stable progression, leading to a growing tendency to defer surgical treatment [4-6]. The latest guidelines by the European Neuroendocrine Tu-

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mor Society recommend monitoring progression rather than proceeding with surgical intervention for NF-PNETs < 2 cm [7]. After undergoing pancreatic resection, the quality of life of patients can deteriorate with risks of complications. Therefore, benefits and risks of surgery must be carefully considered for NF-PNETs. Although previous studies have addressed complications in PNET, there is a lack of focused research on postoperative complications in patients with sporadic NF-PNETs [8-11]. Moreover, PNETs are known to have a higher risk of postoperative pancreatic fistula (POPF) owing to a soft texture of the pancreas and a relatively small diameter of the main pancreatic duct (MPD) [12-14]. Risk may differ from those of other pancreatic lesions such as pancreatic ductal adenocarcinoma, necessitating a unique approach to POPF risk assessment. Thus, this study aimed to analyze complications and POPF occurrence patterns according to surgical method for patients with sporadic NF-PNETs and examine previously published risk factors affecting POPF by dividing subjects into subgroups according to surgical method.

MATERIALS AND METHODS

Study population and data collection

This study focused on patients diagnosed with NF-PNETs who underwent surgery at Severance Hospital, Seoul, South Korea between February 2000 and August 2023. The Institutional Review Board of our institution approved this study (approval number: 2023-3327-002). This study followed the STROCSS (strengthening the reporting of cohort studies in surgery) criteria for reporting [15]. Patients exhibiting symptoms or biochemical evidence of hormone overproduction from functional tumors were excluded. Patients with genetic conditions such as Multiple Endocrine Neoplasia type 1 and Von Hippel–Lindau disease were also excluded. To gather information on patients' general characteristics, tumor pathology, perioperative outcomes, surgical procedures, postoperative outcomes, and complications, their medical records, computed tomography (CT) scans, surgical, and pathologic reports were analyzed. Patients with insufficient imaging data or inadequate surgical records were excluded from this study.

Tumor classification and assessment criteria

Tumor grading was based on the World Health Organization 2022 grading system. Tumor location was classified as head, body, or tail based on left borders of the superior mesenteric vein (SMV) and aorta. Tumors crossing these areas were labeled "diffuse." The number and size of tumors were determined based on final pathology reports.

Risk assessment for pancreatic fistula using surgical records and preoperative and postoperative imaging

To evaluate the risk of POPF in patients, risk factors identified in previous studies were analyzed using surgical records and preoperative and postoperative imaging [12,16-20]. Although various criteria exist for assessing pancreatic texture, in this study, we classified pancreatic texture as "soft" or "hard" based on surgeon's notes in the surgical record [20]. We incorporated indicators derived from preoperative and postoperative CT scans in the electronic medical records (EMR) to assess the risk of POPF as described in previous studies [16,17]. Measurement methods varied depending on the surgical technique exemplified in Supplementary Fig. 1. Patients undergoing pylorus-preserving pancreaticoduodenectomy (PD) or Whipple operation, PD, and distal pancreatectomy (DP) had thickness of the pancreas (PT) and diameter of the MPD measured along the resection margin in the last CT scan before surgery. The resection margin was determined on the immediate postoperative CT scan, referencing major structures such as the SMV or aorta. PT and diameter of the MPD at the pancreaticojejunostomy or pancreaticogastrostomy resection margin were measured for patients who underwent central pancreatectomy (CP). For enucleation, duct diameter and pancreatic thickness were measured at the tumor location. The ratio of the pancreatic thickness to the main pancreatic duct diameter (PT/MPD ratio) was also measured. Following previous research studies, cut-off values were set at a pancreatic duct diameter of 3 mm and pancreatic thickness of 13 mm to indicate an increased risk of pancreatic fistula [16,17,19].

Perioperative and postoperative data analysis

In this study, we collected body mass index (BMI) and American Society of Anesthesiology (ASA) scores from patients' preoperative weight and height measurements and anesthesia records [21]. Type of surgery (open or minimally invasive) was determined from surgical records. Open surgeries included both initially planned open procedures and conversions from minimally invasive surgery (MIS), while MIS encompassed both laparoscopic and robotic approaches. Intraoperative data including total surgery time, estimated blood loss, and transfusion requirements were collected. Postoperative outcomes and complications were gathered from postoperative records and test results, classified, and collected according to the Clavien–Dindo classification [21]. To understand the overall burden of postoperative complications, we used the comprehensive complication index (CCI) [22]. Severe complications were defined as those above grade IIIA in the Clavien–Dindo classification. Delayed gastric emptying, POPF, chyle leakage, and postpancreatectomy hemorrhage were classified and defined according to the International Study Group for Pancreatic Surgery criteria [23-26]. For POPF risk analysis, "clinically relevant POPF (CR-POPF)" was defined as grades B and C POPF, whereas "all POPF" included CR-POPF and biochemical leaks. Biochemical leaks were excluded from the definition of POPF as they were clinically insignificant without affecting patient outcomes [23]. However, the objective of this study was to investigate parameters that could influence the risk, including subclinical occur-

rences of POPF. Therefore, biochemical leaks were included in the analysis as part of the POPF definition.

Statistical analysis

Continuous variables were tested for normality and expressed as mean and standard deviation or median and interquartile range (IQR). Continuous variables were analyzed using one-way analysis of variance or the Kruskal–Wallis test after normal distribution testing to compare perioperative and postoperative outcomes across different types of surgeries. Categorical variables were examined using Pearson's chi-square or Fisher's exact test. Risk factors for severe complications and POPF were analyzed using logistic regression. Variables included in the multiple regression were selected through stepwise regression from those with a p-value < 0.2 in univariate analysis. For continuous variables requiring a cut-off value in this risk factor analysis, the cut-off value was determined using a receiver operating characteristic (ROC) curve. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS version 24 (IBM Corp.) and R version 4.3.2.

RESULTS

Clinicopathologic characteristics of patients

Of patients diagnosed with sporadic NF-PNETs who underwent surgery, 166 were included in this study after excluding four patients with insufficient imaging data in the EMR as shown in Supplementary Fig. 2. General characteristics of patients are summarized in Table 1. Number of patients according to the type of surgery was as follows: enucleation, 23 (13.9%); DP, 83 (50.0%); CP, 8 (4.8%); PD, 44 (26.5%); and total pancreatectomy (TP), 8 (4.8%). Among these, 99 (59.6%) underwent MIS. Variables known to be risk factors for POPF were investigated for all patients except for those who underwent TP.

According to surgical records, the pancreatic texture was classified as soft in 146 (93.0%) patients. The MPD diameter measured at the resection margin or tumor location had a median of 2.0 mm with an IQR of 1.6–2.5 mm. Seventy-seven (48.7%) patients had an MPD diameter ≤ 2 mm, 63 (39.9%) had a diameter > 2 mm but ≤ 3 mm, and 18 (11.4%) had a diameter > 3 mm. The median of pancreatic thickness was 13.2 mm with an IQR of 10.8–16.0 mm. The median of the PT/MPD ratio was 6.3 with an IQR of 4.8–8.3.

Perioperative outcomes based on surgical types

Results of comparing perioperative and postoperative outcomes according to surgery type are presented in Table 2. Operative time, estimated blood loss, and length of hospital stay were higher in PD and TP groups than in enucleation and DP groups. In the TP group, the rate of severe complications was 20/166 (12.05%). However, no mortalities occurred within 90 days of surgery. Rates of severe complications for each type of surgery were as follows: enucleation, 8.7%; DP, 3.6%; CP, 25.0%;

Table 1. Baseline characteristics of patients

Variable	Value (n = 166)
Age (yr)	56.0 [46.0–62.0]
Sex	
Male	82 (49.4)
Female	84 (50.6)
BMI (kg/m^2)	24.1 ± 3.1
ASA classification	
ASA I	37 (22.3)
ASA II	97 (58.4)
ASA III	32 (19.3)
Tumor location	
Head	59 (35.5)
Body	45 (27.1)
Tail	54 (32.5)
Diffuse	8 (4.8)
Type of surgery	
Enucleation	23 (13.9)
Distal pancreatectomy	83 (50.0)
Central pancreatectomy	8 (4.8)
Pancreaticoduodenectomy	44 (26.5)
Total pancreatectomy	8 (4.8)
Surgical approach	
Open	67 (40.4)
Minimally invasive approach	99 (59.6)
WHO grading system	
Grade 1	129 (77.7)
Grade 2	35 (21.1)
Grade 3	2 (1.2)
Largest tumor size (mm)	1.9 [1.3–3.2]
Number of tumors	
Unifocal	158 (95.2)
Multifocal	8 (4.8)
Variables associated with POPF (except patients who underwent TP)	(n=158)
Pancreatic texture	
Soft	146 (93.0)
Hard	11 (7.0)
Pancreas thickness (mm)	13.2 [10.8–16.0]
Diameter of MPD (mm)	2.0 [1.6–2.5]
MPD diameter ≤ 2 mm	77 (48.7)
2 mm < MPD diameter ≤ 3 mm	63 (39.9)
3 mm < MPD diameter	18 (11.4)
PT/MPD ratio	6.3 [4.8–8.3]

Values are presented as median [range], number (%), or mean ± standard deviation.
BMI, body mass index; ASA, American Society of Anesthesiology; WHO, World Health Organization; POPF, postoperative pancreatic fistula; TP, total pancreatectomy; MPD, main pancreatic duct; PT/MPD ratio, the ratio of pancreatic thickness/main pancreatic duct diameter.

Table 2. Comparison of surgical types: perioperative outcomes and complications

Variable	Enucleation (n = 23)	Distal pancreatectomy (n = 83)	Central pancreatectomy (n = 8)	PPPD or Whipple operation (n = 44)	Total pancreatectomy (n = 8)	*p*-value
Age (yr)	55.0 [49.0–58.0]	54.0 [45.0–62.0]	56.5 [50.0–59.5]	57.5 [45.5–65.0]	58.0 [53.0–64.5]	0.801
Male : female	9 : 14 (39.1% : 60.9%)	47 : 36 (56.6% : 43.4%)	3 : 5 (37.5% : 62.5%)	18 : 26 (40.9% : 59.1%)	5 : 3 (62.5% : 37.5%)	0.293
BMI (kg/m^2)	23.8 ± 2.9	24.6 ± 3.1	22.6 ± 1.6	23.9 ± 3.3	22.8 ± 3.0	0.203
ASA classification						0.002
ASA I	13 (56.5)	16 (19.3)	1 (12.5)	5 (11.4)	2 (25.0)	
ASA II	5 (21.7)	51 (61.4)	7 (87.5)	30 (68.2)	4 (50.0)	
ASA III	5 (21.7)	16 (19.3)	0 (0.0)	9 (20.5)	2 (25.0)	
Open : MIS	13 : 10 (56.5% : 43.5%)	19 : 64 (22.9% : 77.1%)	3 : 5 (37.5% : 62.5%)	27 : 17 (61.4% : 38.6%)	5 : 3 (62.5% : 37.5%)	< 0.001
Operation time (min)	154.0 [90.0–190.0]	194.0 [152.0–250.0]	329.5 [267.5–429.5]	383.0 [326.5–499.5]	401.5 [343.5–473.5]	< 0.001
Blood loss (mL)	50.0 [20.0–100.0]	100.0 [30.0–250.0]	100.0 [50.0–350.0]	275.0 [100.0–550.0]	750.0 [275.0–1,300.0]	< 0.001
Transfusion	2 (8.7)	2 (2.4)	0 (0.0)	2 (4.5)	5 (62.5)	< 0.001
Hospital stay (day)	9.0 [7.5–13.0]	9.0 [8.0–12.0]	24.5 [9.0–33.0]	14.0 [11.5–26.0]	23.0 [15.0–31.5]	< 0.001
Clavien–Dindo classification						
Grade I	12 (52.2)	31 (37.3)	2 (25.0)	12 (27.3)	1 (12.5)	
Grade II	0 (0.0)	16 (19.3)	2 (25.0)	10 (22.7)	2 (25.0)	
Grade IIIA	2 (8.7)	3 (3.6)	1 (12.5)	7 (15.9)	0 (0.0)	
Grade IIIB	0 (0.0)	0 (0.0)	1 (12.5)	2 (4.5)	0 (0.0)	
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.8)	1 (12.5)	
CCI	8.7 [0.0–8.7]	8.7 [0.0–8.7]	14.8 [4.3–27.2]	14.8 [8.7–26.2]	4.3 [0.0–20.9]	0.007
POPF						< 0.001
Biochemical leak	9 (39.1)	39 (47.0)	4 (50.0)	23 (52.3)	0 (0.0)	
Grade B	2 (8.7)	2 (2.4)	1 (12.5)	7 (15.9)	0 (0.0)	
Grade C	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	
CR POPF (Grade B or C)	2 (8.7)	2 (2.4)	2 (25.0)	7 (15.9)	0 (0.0)	0.023
Bile leakage						0.013
Grade A	0 (0.0)	0 (0.0)	0 (0.0)	5 (11.4)	0 (0.0)	
Grade B	1 (4.3)	0 (0.0)	0 (0.0)	2 (4.5)	0 (0.0)	
Delayed gastric emptying						0.001
Grade A	1 (4.3)	2 (2.4)	3 (37.5)	9 (20.5)	1 (12.5)	
Grade B	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	
Chyle leakage (Grade A)	0 (0.0)	4 (4.8)	0 (0.0)	2 (4.5)	2 (25.0)	0.154
Post-pancreatectomy hemorrhage						
Grade A	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0.189
Grade B	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (12.5)	
Grade C	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	

Values are presented as median [range], mean ± standard deviation, or number (%).
PPPD, pylorus-preserving pancreaticoduodenectomy; BMI, body mass index; ASA, American Society of Anesthesiology; MIS, minimally invasive surgery; CCI, comprehensive complication index; POPF, postoperative pancreatic fistula; CR POPF, clinically relevant POPF.

PD, 27.3%; and TP, 12.5% (p = 0.002). Differences of CCI for each type of surgery are shown in Supplementary Fig. 3. The median CCI was higher in PD or CP group than in DP or enucleation group. The median CCI of the TP group was less than that of the PD or CP group.

Risk factors for severe complications in patients with sporadic NF-PNETs undergoing pancreatic resection

Results of logistic regression analysis of risk factors for severe complications are shown in Table 3. Sex, age, BMI, and preoperative ASA scores were not significantly associated with severe complications. Severe complications showed no significant differences between open and minimally invasive surgeries either.

Table 3. Risk factors for a severe complications (Grade IIIA or higher)

	Univariable analysis		Multiple regression	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Male (ref: female)	1.29 (0.50–3.38)	0.594		
Age > 65 years (ref: age ≤ 65 years)	1.10 (0.30–3.29)	0.871		
BMI ≥ 25.0 kg/m^2 (ref: BMI < 25 kg/m^2)	0.54 (0.17–1.47)	0.251		
ASA Grade 3 or 4 (ref: Grade 1 or 2)	1.47 (0.45–4.17)	0.491		
MIS (ref: open laparotomy)	0.51 (0.19–1.31)	0.16		
Type of surgery				
Enucleation	ref	ref	ref	ref
DP	0.39 (0.06–3.13)	0.324	0.39 (0.06–3.13)	0.324
PD	3.94 (0.95–26.97)	0.092	3.94 (0.95–26.97)	0.092
TP or others	2.42 (0.36–20.33)	0.366	2.42 (0.36–20.33)	0.366
WHO grade 2 or 3 (ref: Grade 1)	1.59 (0.53–4.32)	0.38		
Tumor size > 2 cm (ref: Size ≤ 2 cm)	0.80 (0.30–2.04)	0.634		
LN metastasis (ref: no LN metastasis)	2.36 (0.61–7.55)	0.171		

OR, odds ratio; CI, confidence interval; ref, reference; BMI, body mass index; ASA, American Society of Anesthesiology; MIS, minimally invasive surgery; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; TP, total pancreatectomy; WHO, world health organization; LN, lymph node.

Through stepwise regression, the multiple regression analysis included only type of surgery. Patients who underwent PD showed a tendency towards more severe complications compared to those who had enucleation (odds ratio [OR]: 3.94, 95% confidential interval [CI]: 0.95–26.97, $p = 0.092$).

Risk factors for POPF in patients with sporadic NF-PNETs undergoing pancreatic resection

Results of the logistic regression analysis of risk factors for all POPFs in patients, excluding those who underwent TP, are shown in Table 4. Pancreatic texture, thickness of pancreas measured by CT at the resection margin or tumor location, and PT/MPD ratio were not significantly associated with the risk

Table 4. Risk factors for POPF in patients with non-functional pancreatic neuroendocrine tumors who underwent pancreatic resection except total pancreatectomy

All POPF	Univariable analysis		Multiple regression	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Male (ref: female)	0.91 (0.49–1.71)	0.776		
Age > 65 years (ref: age ≤ 65 years)	0.58 (0.26–1.31)	0.195	0.51 (0.21–1.21)	0.129
BMI ≥ 25.0 kg/m^2 (ref: BMI < 25.0 kg/m^2)	0.91 (0.48–1.75)	0.776		
MIS (ref: open laparotomy)	0.85 (0.45–1.62)	0.63		
Pancreatic texture: Hard (ref: soft)	0.95 (0.27–3.43)	0.937		
Type of surgery				
Enucleation	ref	ref	ref	ref
DP	1.06 (0.42–2.72)	0.894	1.22 (0.46–3.24)	0.685
CP	3.27 (0.60–25.70)	0.196	3.04 (0.55–24.30)	0.232
PD	2.34 (0.83–6.71)	0.108	3.70 (1.22–11.74)	0.022
MPD diameter > 3 mm (ref: diameter ≤ 3 mm)	0.32 (0.11–0.86)	0.03	0.22 (0.07–0.63)	0.008
Pancreas thickness > 13 mm (ref: thickness ≤ 13 mm)	1.08 (0.58–2.03)	0.804		
PT/MPD ratio (continuous)	1.06 (0.95–1.19)	0.315		
WHO grade 2 or 3 (ref: Grade 1)	0.55 (0.25–1.18)	0.128	0.52 (0.22–1.17)	0.116
Tumor size > 2 cm (ref: size ≤ 2 cm)	0.79 (0.42–1.48)	0.456		
EBL > 180 mL (ref: EBL ≤ 180 mL)	0.88 (0.45–1.69)	0.69		

POPF, postoperative pancreatic fistula; OR, odds ratio; CI, confidence interval; ref, reference; BMI, body mass index; MIS, minimally invasive surgery; DP, distal pancreatectomy; CP, central pancreatectomy; PD, pancreaticoduodenectomy; MPD, main pancreatic duct; PT/MPD ratio, the ratio of pancreatic thickness/main pancreatic duct diameter; WHO, world health organization; EBL, estimated blood loss.

of POPF (pancreatic texture, OR: 0.95, 95% CI: 0.27–3.43, p = 0.937; pancreatic thickness > 13 mm [reference: < 13 mm], OR: 1.08, 95% CI: 0.58–2.03, p = 0.804; PT/MPD ratio [continuous], OR: 1.06, 95% CI: 0.95–1.19, p = 0.315). In the multiple regression analysis, undergoing PD and MPD diameter > 3 mm were significant risk factors for POPF (PD vs. enucleation: adjusted OR: 3.70, 95% CI: 1.22–11.74, p = 0.022; MPD diameter > 3 mm [ref ≤ 3 mm]: adjusted OR: 0.22, 95% CI: 0.07–0.63, p = 0.008). Results of logistic regression analysis for CR-POPF are detailed in Supplementary Table 1, showing no statistically significant risk factors.

Subgroup analysis of risk factors for POPF in patients with sporadic NF-PNETs based on surgical types

Results of logistic regression analysis for risk factors of all POPFs in patients undergoing PD are presented in Table 5. Both MPD diameter and PT/MPD ratio showed statistically significant associations with all POPFs. For MPD diameter > 3 mm (ref: ≤ 3 mm), the OR was 0.11 (95% CI: 0.02–0.50, p = 0.007). For PT/MPD ratio (continuous), OR was 1.80 (95% CI: 1.23–2.96, p = 0.007). Results of ROC curve analysis to determine the cut-off value for the PT/MPD ratio in risk of all POPFs are shown in Supplementary Fig. 4. The ROC curve for the MPD diameter is also shown in Supplementary Fig. 4. Area under the curve (AUC) of the MPD diameter was 0.748 (95% CI: 0.58–0.915, p < 0.001). A PT/MPD ratio cut-off of 4.47 had a sensitivity of 86.2%, a specificity of 64.3%, a positive predictive value of 83.3%, and a negative predictive value of 69.2% with an AUC of 0.786 (95% CI: 0.626–0.945, p < 0.001). Patients with a PT/MPD ratio > 4.47 had an OR of 11.70 (95% CI: 2.76–60.08, p = 0.001) for risk of all POPFs compared to those with a ratio ≤ 4.47. In the multiple regression analysis, only the variable of PT/MPD ratio divided at a 4.47 cut-off was included. On the other hand, the only factor that significantly increased the risk of CR-POPF in patients who underwent PD was the PT/MPD ratio (PT/MPD ratio, OR: 1.57, 95% CI: 1.09–2.48, p = 0.024, Supplementary Table 2).

Results of logistic regression analysis for risk factors of all POPFs and CR-POPF in patients who underwent DP are presented in Supplementary Table 3. It was found that variables such as pancreatic texture, MPD diameter, pancreatic thickness, and PT/MPD ratio did not show statistically significant differences with respect to POPF.

DISCUSSION

In this study, we comprehensively analyzed complications that occurred in patients undergoing surgery for sporadic non-functional neuroendocrine tumors. To the best of our knowledge, this is the first study focusing exclusively on postoperative complications of sporadic NF-PNETs. In a previous study that included functional and hereditary PNETs, the rate of severe complications (Grade 3 or above) was approximately 41.5% (51/123) [8]. However, a lower rate of 12.05% (20/166) was found in our study. Both our study and the previous study showed no statistically significant differences in severe complications among patients ≥ 65 years or those with higher ASA grades [8]. This finding indicated that age and existing morbidities might not necessarily preclude surgery in eligible patients. Additionally, there was no significant difference in complication rate between open and minimally invasive approaches, although patients who underwent PD had a higher rate of severe

Table 5. Risk factors for POPF in patients with non-functional pancreatic neuroendocrine tumors who underwent pancreaticoduodenectomy

All POPF	Univariable analysis		Multiple regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Male (ref: female)	1.38 (0.38–5.41)	0.633		
Age > 65 years	1.12 (0.25–5.94)	0.888		
BMI ≥ 25.0 kg/m^2	2.44 (0.61–12.50)	0.234		
MIS (ref: open laparotomy)	3.21 (0.81–16.36)	0.119		
Pancreatic texture: Hard	0.67 (0.10–5.56)	0.678		
MPD diameter > 3 mm	0.11 (0.02–0.50)	0.007		
Pancreas thickness > 13 mm	1.04 (0.28–4.12)	0.951		
PT/MPD ratio (continuous)	1.80 (1.23–2.96)	0.007		
PT/MPD ratio > 4.47[a)]	11.70 (2.76–60.08)	0.001	11.70 (2.76–60.08)	0.001
WHO grade 2 or 3	0.62 (0.14–2.89)	0.529		
Tumor size > 2 cm	0.96 (0.24–3.55)	0.951		
EBL > 180 mL (ref: EBL ≤ 180 mL)	0.73 (0.18–2.64)	0.633		

POPF, postoperative pancreatic fistula; OR, odds ratio; CI, confidence interval; ref, reference; BMI, body mass index; MIS, minimally invasive surgery; MPD, main pancreatic duct; PT/MPD ratio, the ratio of pancreatic thickness/main pancreatic duct diameter; WHO, world health organization; EBL, estimated blood loss.

[a)]Cut-off value of PT/MPD ratio was calculated using Receiver Operating Characteristic curve analysis on POPF.

complications than those who underwent enucleation alone. In addition, patients who underwent TP tended to have a lower CCI than those who underwent PD or CP. This might be related to the occurrence of POPF following reconstruction of the remnant pancreas.

In the context of PNETs, which generally have a favorable prognosis, predicting the risk of POPF is of significant clinical importance. PNETs have previously been shown to have a higher tendency for POPF than other types of cancers [12-14]. In our study, the rate of POPF was 53.0% (88/166) and that of CR-POPF was 7.8% (13/166). Postoperative incidence of CR-POPF in patients with NF-PNET who underwent surgery in this study was comparable to results reported by other institutions in South Korea (12/94, 12.8% [27]; right-side NF-PNETs: 9.7%, left-side NF-PNETs: 6.5% [28]; 31/404, 7.7% [29]). A previous study from the American College of Surgeons National Surgical Quality Improvement Program database (NSQIP) reported a POPF rate of 24.8% and a CR-POPF rate of 10% [12]. A single-center retrospective study in the Netherlands reported a CR-POPF rate of 22.7% [14]. In our study, the median diameter of the MPD was 2 mm, with > 90% of patients having a soft pancreatic texture. Additionally, 80.72% (134/166) of patients with PNETs in our study had known independent high-risk factors for POPF: a soft pancreatic texture and an MPD diameter ≤ 3 mm. Previous research from the NSQIP focusing solely on patients with PNETs has identified MPD diameter, pancreatic texture, male sex, and PD as risk factors for POPF [12]. Our study also found that MPD diameter and PD were risk factors for POPF after excluding patients who underwent TP, consistent with previous findings. Therefore, special attention should be paid to POPF when performing PD in patients with PNETs.

In patients undergoing PD, both PT/MPD ratio and diameter of the MPD were found to be significant predictors of POPF risk. PT/MPD ratio derived from preoperative CT scans has been established as a valuable clinical tool for assessing POPF risk. It has been consistently validated in prior studies following PD [30,31]. By anticipating the resection plane preoperatively and assessing PT and MPD diameter at that plane on CT scans, surgeons can effectively evaluate the risk of POPF. Notably, our study identified a specific cut-off value of PT/MPD (4.77) from the ROC curve, aiding surgeons in preoperative risk assessment for POPF.

When analyzing the 83 patients who underwent DP, previously known risk factors did not show statistically significant differences. This might be due to an insufficient number of patients. However, this could also be attributed to homogeneity of patients with PNET compared to other pathologies of the pancreas, suggesting that existing POPF risk-scoring models might not be directly applicable [19,32,33]. Further multicenter studies focusing specifically on NET patients are warranted to develop a more accurate POPF risk model.

Our study has several important limitations. First, as a single-center study, the relatively small number of patients limited the validity of creating a robust risk model or logistic regression analysis for serious complications or POPF. Additionally, over a relatively long study period (2000–2023), changes in surgical techniques and indications might not have been fully accounted for in this study. Second, while biochemical leaks are clinically insignificant and not typically considered POPF, our small sample size limited the evaluation of CR-POPF risk as indicated in Supplementary Table 1–3. Therefore, indicators showing significant associations with the risk of all POPF, including biochemical leaks, in this study might not be strongly linked to actual clinical outcomes. To address this limitation, future multicenter studies with a larger patient population are needed to develop a POPF risk prediction model that is clinically meaningful and applicable. Finally, although many studies have investigated risk factors for POPF, another significant limitation of our study was the inability to incorporate all these variables into our analysis.

In conclusion, this study revealed that in patients with NETs undergoing surgery, the rate of severe complications did not differ significantly between older adults and comorbid patients. It also revealed that a higher rate of POPF in patients with PNETs might be attributable to factors such as small pancreatic ducts and soft texture. Notably, for patients undergoing PD, pancreatic duct thickness and its ratio to pancreatic thickness measured using preoperative CT were key predictors of surgical outcomes. These insights are crucial for evaluating surgical risks in the treatment of NF-PNET.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.14701/ahbps.24-215.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Liu X, Chen B, Chen J, Su Z, Sun S. The incidence, prevalence, and survival analysis of pancreatic neuroendocrine tumors in the United States. J Endocrinol Invest 2023;46:1373-1384.
2. Gorelik M, Ahmad M, Grossman D, Grossman M, Cooperman AM. Nonfunctioning incidental pancreatic neuroendocrine tumors: who, when, and how to treat? Surg Clin North Am 2018;98:157-167.
3. Park SM, Jang JY, Kang MJ, Yoon YS, Han HS, Cho JY, et al. Clinicopathologic characteristics and prognostic factors of nonfunctioning endocrine tumor of the pancreas. Korean J Hepatobiliary Pancreat Surg 2011;15:50-57.
4. Heidsma CM, Engelsman AF, van Dieren S, Stommel MWJ, de Hingh I, Vriens M, et al. Watchful waiting for small non-functional pancreatic neuroendocrine tumours: nationwide prospective cohort study (PANDORA). Br J Surg 2021;108:888-891.
5. Partelli S, Massironi S, Zerbi A, Niccoli P, Kwon W, Landoni L, et al. Management of asymptomatic sporadic non-functioning pancreatic neuroendocrine neoplasms no larger than 2 cm: interim analysis of prospective ASPEN trial. Br J Surg 2022;109:1186-1190.
6. Lee YH, Sohn JH, Yun HJ, Kwon HJ, Chun JM, Kim SM, et al. Clinical features and long term survival of pancreatic neuroendocrine tumors according to the WHO classification. Korean J Hepatobiliary Pancreat Surg 2010;14:199-206.
7. Kos-Kudła B, Castaño JP, Denecke T, Grande E, Kjaer A, Koumarianou A, et al. European Neuroendocrine Tumour Society (ENETS) 2023 guidance paper for nonfunctioning pancreatic neuroendocrine tumours. J Neuroendocrinol 2023;35:e13343.
8. van Beek DJ, Takkenkamp TJ, Wong-Lun-Hing EM, de Kleine RHJ, Walenkamp AME, Klaase JM, et al. Risk factors for complications after surgery for pancreatic neuroendocrine tumors. Surgery 2022;172:127-136.
9. Smith JK, Ng SC, Hill JS, Simons JP, Arous EJ, Shah SA, et al. Complications after pancreatectomy for neuroendocrine tumors: a national study. J Surg Res 2010;163:63-68.
10. Jilesen AP, van Eijck CH, in't Hof KH, van Dieren S, Gouma DJ, van Dijkum EJ. Postoperative complications, in-hospital mortality and 5-year survival after surgical resection for patients with a pancreatic neuroendocrine tumor: a systematic review. World J Surg 2016;40:729-748.
11. Jilesen AP, van Eijck CH, Busch OR, van Gulik TM, Gouma DJ, van Dijkum EJ. Postoperative outcomes of enucleation and standard resections in patients with a pancreatic neuroendocrine tumor. World J Surg 2016;40:715-728.
12. Hedges EA, Khan TM, Babic B, Nilubol N. Predictors of post-operative pancreatic fistula formation in pancreatic neuroendocrine tumors: a national surgical quality improvement program analysis. Am J Surg 2022;224:1256-1261.
13. Partelli S, Tamburrino D, Cherif R, Muffatti F, Moggia E, Gaujoux S, et al. Risk and predictors of postoperative morbidity and mortality after pancreaticoduodenectomy for pancreatic neuroendocrine neoplasms: a comparative study with pancreatic ductal adenocarcinoma. Pancreas 2019;48:504-509.
14. Atema JJ, Jilesen AP, Busch OR, van Gulik TM, Gouma DJ, Nieveen van Dijkum EJ. Pancreatic fistulae after pancreatic resections for neuroendocrine tumours compared with resections for other lesions. HPB (Oxford). 2015;17:38-45.
15. Mathew G, Agha R, Albrecht J, Goel P, Mukherjee I, Pai P, et al.; STROCSS Group. STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg 2021;96:106165.
16. Bag YM, Topel C, Ozdemir E, Saglam K, Sumer F, Kayaalp C. A novel radiological predictor for postoperative pancreatic fistula after stapled distal pancreatectomy. Am Surg 2021;87:725-731.
17. Sugimoto M, Kendrick ML, Farnell MB, Nomura S, Takahashi N, Kobayashi T, et al. Relationship between pancreatic thickness and staple height is relevant to the occurrence of pancreatic fistula after distal pancreatectomy. HPB (Oxford) 2020;22:398-404.
18. Kamarajah SK, Bundred JR, Lin A, Halle-Smith J, Pande R, Sutcliffe R, et al.; PARANOIA Study Group. Systematic review and meta-analysis of factors associated with post-operative pancreatic fistula following pancreatoduodenectomy. ANZ J Surg 2021;91:810-821.
19. De Pastena M, van Bodegraven EA, Mungroop TH, Vissers FL, Jones LR, Marchegiani G, et al. Distal Pancreatectomy Fistula Risk Score (D-FRS): development and international validation. Ann Surg 2023;277:e1099-e1105.
20. Mungroop TH, van Rijssen LB, van Klaveren D, Smits FJ, van Woerden V, Linnemann RJ, et al.; Dutch Pancreatic Cancer Group. Alternative fistula risk score for pancreatoduodenectomy (a-FRS): design and international external validation. Ann Surg 2019;269:937-943.
21. Doyle DJ, Hendrix JM, Garmon EH. American Society of Anesthesiologists Classification. StatPearls Publishing, 2017.
22. Kim SH, Hwang HK, Lee WJ, Kang CM. Comprehensive complication index or Clavien-Dindo classification: which is better for evaluating the severity of postoperative complications following pancreatectomy? World J Surg 2021;45:849-856.
23. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al.; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery 2017;161:584-591.
24. Malleo G, Crippa S, Butturini G, Salvia R, Partelli S, Rossini R, et al. Delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy: validation of International Study Group of Pancreatic Surgery classification and analysis of risk factors. HPB (Oxford) 2010;12:610-618.
25. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M, et al.; International Study Group on Pancreatic Surgery. Definition and classification of chyle leak after pancreatic operation: a consensus statement by the International Study Group on Pancreatic Surgery. Surgery 2017;161:365-372.
26. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al Postpancreatectomy hemorrhage (PPH): an International Study

Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20-25.
27. Han SH, Han IW, Heo JS, Choi SH, Choi DW, Han S, et al. Laparoscopic versus open distal pancreatectomy for nonfunctioning pancreatic neuroendocrine tumors: a large single-center study. Surg Endosc 2018;32:443-449.
28. Hwang HK, Song KB, Park M, Kwon W, Jang JY, Heo JS, et al.; Korean Pancreas Surgery Club. Minimally invasive versus open pancreatectomy for right-sided and left-sided G1/G2 nonfunctioning pancreatic neuroendocrine tumors: a multicenter matched analysis with an inverse probability of treatment-weighting method. Ann Surg Oncol 2021;28:7742-7758.
29. Ha S, Song KB, Hong S, Shin D, Park Y, Kwon J, et al. The clinicopathologic and operative characteristics of patients with small nonfunctioning pancreatic neuroendocrine tumors. ANZ J Surg 2021;91:E484-E492.
30. Akamatsu N, Sugawara Y, Komagome M, Shin N, Cho N, Ishida T, et al. Risk factors for postoperative pancreatic fistula after pancreaticoduodenectomy: the significance of the ratio of the main pancreatic duct to the pancreas body as a predictor of leakage. J Hepatobiliary Pancreat Sci 2010;17:322-328.
31. Barbier L, Mège D, Reyre A, Moutardier VM, Ewald JA, Delpero JR. Predict pancreatic fistula after pancreaticoduodenectomy: ratio body thickness/main duct. ANZ J Surg 2018;88:E451-E455.
32. Chong E, Ratnayake B, Lee S, French JJ, Wilson C, Roberts KJ, et al. Systematic review and meta-analysis of risk factors of postoperative pancreatic fistula after distal pancreatectomy in the era of 2016 International Study Group pancreatic fistula definition. HPB (Oxford) 2021;23:1139-1151.
33. Peng YP, Zhu XL, Yin LD, Zhu Y, Wei JS, Wu JL, et al. Risk factors of postoperative pancreatic fistula in patients after distal pancreatectomy: a systematic review and meta-analysis. Sci Rep 2017;7:185.