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Pancreatic thickness as a predictor of postoperative pancreatic fistula after laparoscopic or robotic gastrectomy

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Abstract

Background Despite technical advances in minimally invasive gastrectomy for gastric cancer, an increased incidence of postoperative pancreatic fistula (POPF) has been reported. POPF can cause infectious and bleeding complications, which could lead to surgery-related death; therefore, reduction of the post-gastrectomy POPF risk is crucial. This study aimed to investigate the importance of pancreatic anatomy as a predictor of POPF in patients undergoing laparoscopic or robotic gastrectomy.

Methods Data were collected from 331 consecutive patients who underwent laparoscopic or robotic gastrectomy for gastric cancer. The thickness of the pancreas anterior to the most ventral level of the splenic artery (TPS) was measured. The correlation between TPS and POPF incidence was investigated using univariate and multivariate analyses.

Results The cutoff value of TPS was 11.8 mm, which predicted a high drain amylase concentration on postoperative day 1, and patients were categorized into thin (Tn group) and thick TPS groups (Tk group). There was no significant difference in the background characteristics between the two groups, except for sex ($P=0.009$) and body mass index ($P<0.001$). The incidences of POPF grade B or higher (2% vs. 16%, $P<0.001$), all postoperative complications of grade II or higher (12% vs. 28%, $P=0.004$), and postoperative intra-abdominal infections of grade II or higher (4% vs. 17%, $P=0.001$) were significantly higher in the Tk group. Multivariable analysis identified that high TPS was the only independent risk factor for grade B or higher POPF and grade II or higher postoperative intra-abdominal infectious complications.

Conclusions The TPS is a specific predictive factor for POPF and postoperative intra-abdominal infectious complications in patients undergoing laparoscopic or robotic gastrectomy. Careful pancreatic manipulation during suprapancreatic lymphadenectomy is necessary for patients with increased TPS (> 11.8 mm) to avoid postoperative complications.

Keywords Laparoscopic gastrectomy · Robotic gastrectomy · Postoperative pancreatic fistula · Intra-abdominal infectious complications · Pancreatic thickness · Gastric cancer

Gastric cancer was the fifth most common cancer and the fourth leading cause of cancer-related mortality worldwide in 2020 [1]; it has a high incidence, especially in East Asian countries [2]. Minimally invasive surgery, such as laparoscopic (LG) or robotic gastrectomy (RG), is widely used as a curative surgical treatment for gastric cancer. Despite advances in surgical techniques, the incidence of postoperative pancreatic fistula (POPF), one of the most common postoperative complications, has increased significantly [3, 4]. POPF can cause sepsis, bleeding, intra-abdominal infection, and anastomotic leakage, which could lead to surgery-related death; therefore, reduction of the post-gastrectomy POPF risk is crucial. Several factors, including sex, age, body shape, blood reports, cancer progression, and pancreatic anatomy, have been reported as POPF predictors [5–13]. Additionally, POPF is known to occur due to direct physical or thermal pancreatic injury, including compression [14]. Unintentional damage to the pancreas or prolonged duration of pancreatic compression mainly occurs during suprapancreatic lymph node dissection (No.7, 8a, 9, and 11p).

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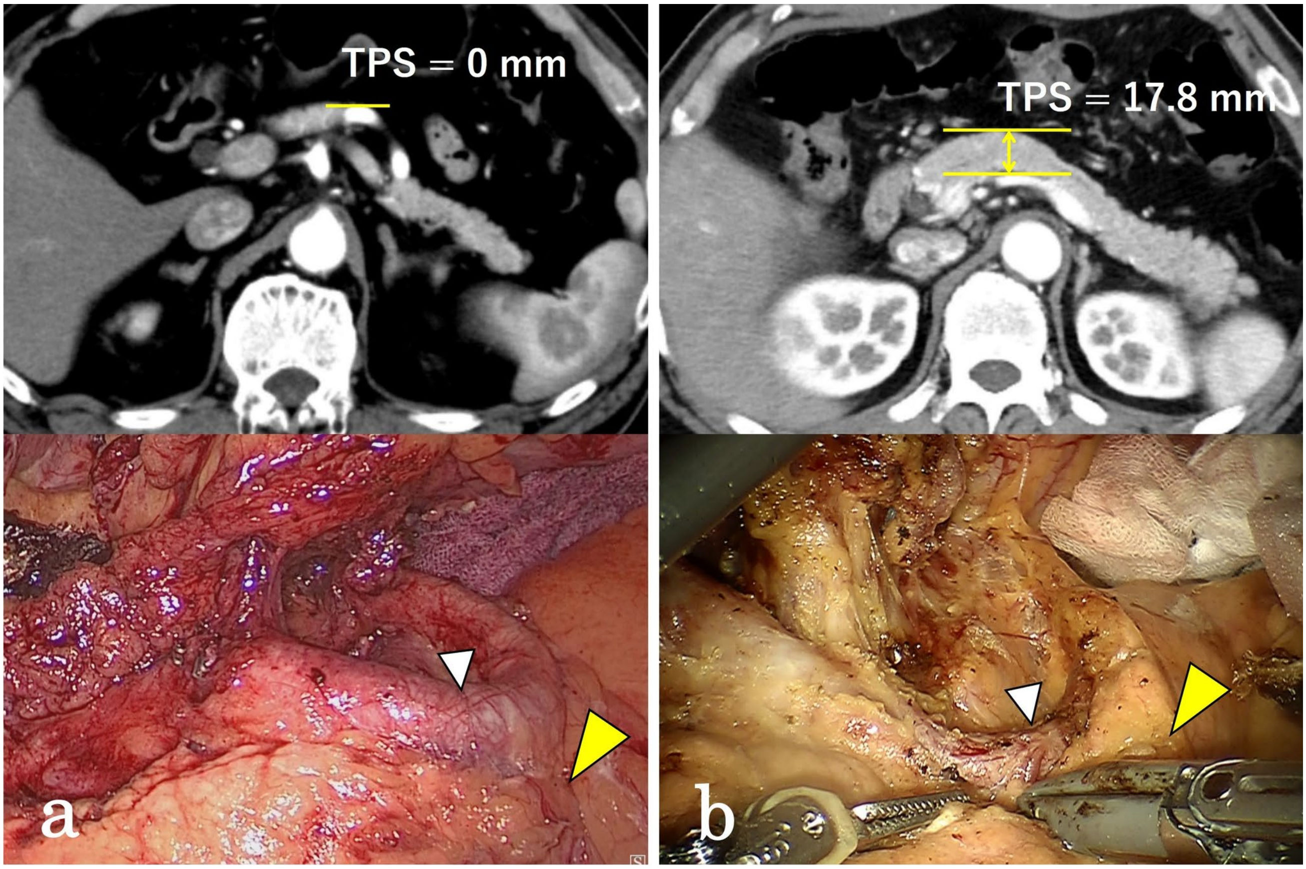

Fig. 1 TPS measurement using CT images. TPS can be measured with axial CT images. The white arrow indicates the splenic artery and yellow, the pancreas anterior to the most ventral level of the splenic artery. **a** a case where TPS is 0 mm, **b** a case where TPS is 17.8 mm. *TPS* thickness of the pancreas anterior to the most ventral level of the splenic artery, *CT* computed tomography

Although pancreatic thickness is reportedly a predictor of POPF risk [10, 12], a thick pancreas, which appears anterior to the most protuberant part of the splenic artery loop, has become an obstacle for suprapancreatic lymphadenectomy. We hypothesized that the thickness of the pancreas in front of the most ventral level of the splenic artery arch after branching from the celiac artery (TPS) is a reliable risk predictor for postoperative complications after gastrectomy. In measuring TPS, we can predict the patients who may develop POPF. Thus, for patients who show a greater TPS, it is possible to perform lymphadenectomy more carefully. Moreover, as TPS is simple and easily measured through thin-slice computed tomography (CT), it can be introduced relatively easily in clinical practice. Therefore, this study aimed to evaluate the importance of pancreatic anatomy as a predictor of POPF in patients undergoing LG or RG.

Materials and methods

Patients

This retrospective cohort study included data of 331 consecutive patients who underwent LG or RG for gastric cancer at the Department of Gastroenterological Surgery, Ishikawa Prefectural Central Hospital, Ishikawa, Japan, between April 2019 and December 2022. Twelve patients for whom the drain amylase concentration on postoperative day (POD) 1 was not recorded and 48 patients who underwent gastrectomy without suprapancreatic lymph node dissection were excluded. For the 282 patients included, TPS was measured using preoperative CT.

This study was performed in accordance with the World Medical Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, and written informed consent for surgery and the use of clinical data were obtained from all patients included in this study. This study was approved by the ethics committee of Ishikawa Prefectural Central Hospital (approval no. 2042).

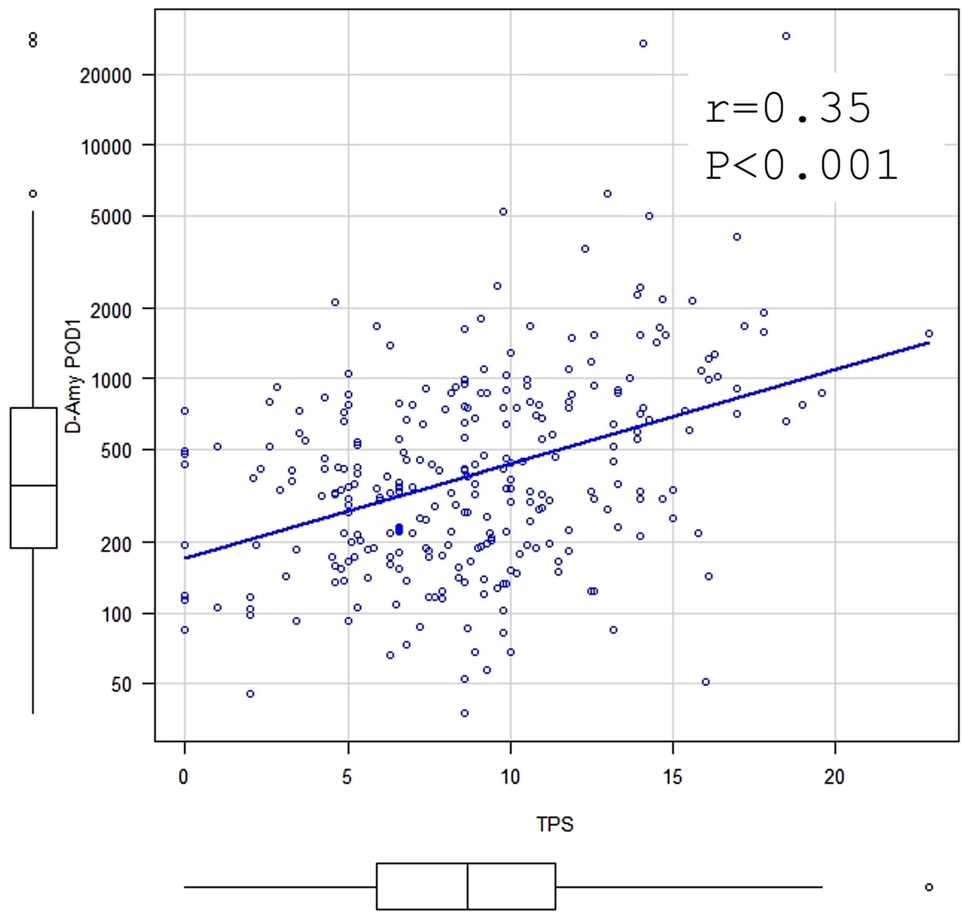

Fig. 2 Correlation between TPS and postoperative drain amylase concentration. The scatterplot of the correlation between TPS and drain amylase concentration on postoperative day 1 is shown. The vertical axis of the plot is scaled logarithmically. There is a weak correlation between the two ($r = 0.35$, $P < 0.001$). *TPS* thickness of the pancreas anterior to the most ventral level of the splenic artery

Surgical indication and procedures

According to the latest Japanese Gastric Cancer Treatment Guidelines, we performed LG or RG with D1 + or D2 lymph node dissection, according to the cancer stage [15]. Gastric cancer at any stage was considered an indication for LG or RG. The indications for LG and RG did not differ, and we selected either procedure according to patient preference. All LGs and RGs were performed or assisted by a qualified surgeon from the Japanese Society for Endoscopic Surgery, and all RGs were performed using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). During suprapancreatic lymph node dissection, the pancreas was gently compressed with a soft sponge for the shortest required duration. After exposing the splenic artery, nerve fibers were pulled caudally to obtain a good surgical field of view. LG was performed with five ports: one for a scope, two for an operator, and two for a first assistant; however, in cases where the operator forceps unintentionally pressed the pancreas during the suprapancreatic lymph node dissection, we added an additional port to avoid accidental pancreatic compression. A 19 Fr Blake drain was placed in the suprapancreatic region.

Measurement of the pancreatic thickness

Preoperative contrast-enhanced abdominal CT scans of all patients were reviewed. We searched for a slice in which the arch of the splenic artery ran at the ventral level after branching from the celiac artery. The thickness of the axial CT slice was 0.5 or 1 mm. The thickness of the pancreas anterior to the most ventral point of the splenic artery was labeled as the TPS (Fig. 1), which was measured and recorded for all patients.

Definition of outcomes

For all patients, the drain output and serum amylase levels were measured on PODs 1 and 3. We defined a drain amylase concentration > 1000 U/L on POD 1 as a high drain amylase concentration, which has been reported to be an indicator of pancreas-related intra-abdominal abscess [16, 17]. POPF was defined with the International Study Group on Pancreatic Fistula Definition [18]. However, suprapancreatic fluid collection with inflammatory findings detected by CT with high CRP (> 20 on POD 3), without clinical or radiological evidence of anastomotic leakage was also regarded as POPF, despite the low drain amylase concentration. The severity

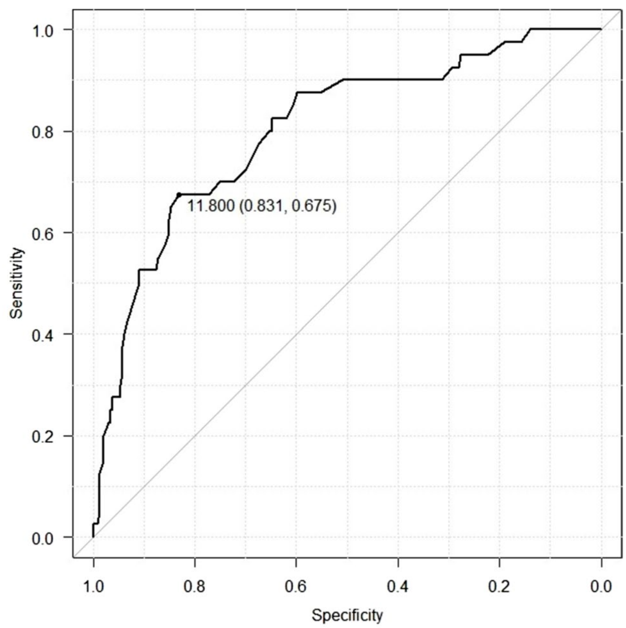

Fig. 3 Optimal TPS value. The receiver operation characteristic curve for predicting high drain amylase concentration over 1000 U/L on postoperative day 1 based on TPS is shown. The cutoff value of TPS is 11.8 mm, which predicts a high drain amylase concentration on postoperative day 1, because the area under the curve is highest. *TPS* thickness of the pancreas anterior to the most ventral level of the splenic artery

of postoperative complications was determined using the Clavien–Dindo (CD) classification [19]. Grade II or higher adverse events that occurred within 30 postoperative days were defined as significant postoperative complications, which included intra-abdominal infectious complications, such as intra-abdominal abscess, pancreatic fistula, and anastomotic leakage. The primary endpoint of this study was the incidence of POPF grade B or higher, and the secondary endpoints were the incidences of POPF and postoperative intra-abdominal infections.

Statistical analysis

All categorical variables are expressed as numbers (percentages) and continuous variables as medians (ranges). A scatterplot was used to analyze correlations, and Spearman's rank correlation coefficient was used to assess the strength of the correlation. To determine the optimal cutoff values of TPS as a predictor of POPF, receiver operating characteristic (ROC) curves were calculated. To evaluate the differences in categorical and continuous variables, Fisher's exact, Chi-squared, and Mann–Whitney U tests were used, as appropriate. If there were more than eight events per cofounder for multivariable analysis, logistic regression analysis was adopted, not propensity scores [20]. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the EZR statistical software (Easy R, Saitama Medical Center, Jichi Medical University, Japan) [21] based on R and R commander.

Results

This study included 282 patients. Spearman's rank correlation coefficient was 0.35 ($P < 0.001$); therefore, there was a weak correlation between TPS and drain amylase concentration on POD 1 on the scatterplot (Fig. 2). The ROC curve indicated that the area under the curve was highest when the TPS was 11.8 mm (Fig. 3), which was considered as the optimal TPS cutoff value. We categorized the patients into thin (Tn group, $n = 215$) and thick (Tk group, $n = 67$) TPS groups. Patient characteristics and surgical details of the two groups are described in Table 1. There were significant differences in sex ($P = 0.009$) and body mass index (BMI) ($P < 0.001$) between the two groups. Surgical outcomes of the two groups are shown in Table 2. Amylase level in the drained fluid (D-Amy) on POD 1 ($P < 0.001$), the incidence of grade II or higher complications ($P = 0.004$), all POPF ($P = 0.004$), POPF grade B ($P < 0.001$), and grade II or higher intra-abdominal infectious complications ($P = 0.001$) were significantly higher in the Tk group. In the multivariable logistic regression analysis, TPS was identified as the only independent risk factor for all POPF (odds ratio [OR] 2.55, 95% confidence interval [CI] 1.42–4.98, $P = 0.009$) (Table 3), grade B or higher POPF (OR 7.52, 95% CI 2.46–23.0, $P < 0.001$) (Table 4), and intra-abdominal infection (OR 4.89, 95% CI 1.91–12.6, $P < 0.001$) (Table 5).

Discussion

The primary endpoint that TPS predicts POPF of grade B or higher was achieved with a high OR of 7.59. The secondary endpoints were also achieved, except for postoperative complications of CD grade II or higher. Although a high BMI, male sex, advanced cancer stage, and extended lymphadenectomy have been reported to be associated with POPF or postoperative complications, they were not regarded as independent predictors of postoperative complications [5–9].

The POPF occurrence rate after LG is 1.7–7.2% [5, 22–25], which is higher than that after an open gastrectomy (OG) [22, 26, 27]. Pancreatic juice leakage occurs not only after pancreatic parenchymal injury but also following pancreatic compression [14]. Regarding surgical procedures, Itamoto et al. reported that a longer time of pancreas compression during minimally invasive gastrectomy was associated with a higher incidence of postoperative complications [28]. However, pancreatic compression is required during suprapancreatic lymphadenectomy to identify the dissection line between the lymph nodes to be dissected and the

Table 1 Patient characteristics and surgical data

Variables	Tn group *N*=215	Tk group *N*=67	*P* value
Age (years)	71 (35–91)	69 (36–89)	0.24
Sex			**0.009**
Male	116 (54)	50 (75)	
Female	99 (46)	17 (25)	
BMI	22.1 (14.3–32.8)	24.3 (14.8–33.7)	**<0.001**
ASA-PS			0.92
1	41 (21)	11 (16)	
2	147 (68)	48 (72)	
3	27 (12)	8 (12)	
NAC	4 (2)	1 (1)	1
Pancreatic thickness	7.5 (0–11.5)	14.0 (11.8–22.9)	**<0.001**
Clinical T category			0.71
1a	19 (9)	5 (7)	
1b	106 (49)	32 (47)	
2	35 (16)	11 (17)	
3	22 (10)	11 (17)	
4a	33 (15)	8 (12)	
Clinical N category			0.62
0	164 (76)	49 (73)	
+	51 (23)	18 (27)	
Clinical M category			1
0	214 (99)	67 (100)	
+	1 (1)	0 (0)	
Clinical stage			0.87
I	142 (66)	44 (66)	
IIA	17 (8)	5 (7)	
IIB	19 (9)	4 (6)	
III	36 (16)	14 (20)	
>IV	1 (1)	0 (0)	
Approach			0.57
Laparoscopy	94 (44)	32 (48)	
Robot	121 (56)	35 (52)	
Procedure			0.97
Distal	145 (68)	46 (68)	
Proximal	22 (10)	7 (10)	
Total	48 (22)	14 (22)	
Extent of lymph node dissection			0.77
D1+	139 (65)	42 (23)	
D2	76 (35)	25 (36)	

Bold values indicate statistically significant $p < 0.05$

ASA-PS The American Society of Anesthesiologists physical status, *NAC* neoadjuvant chemotherapy

pancreas or artery. Therefore, a thick or protruding pancreas that impedes lymphadenectomy is expected to be a risk factor for increasing the outflow of pancreatic juice. A novel procedure for pancreas-compressionless lymphadenectomy was reported by Tsujiura et al.; however, minimal pancreatic compression by an assistant's forceps may be required according to the pancreatic anatomy to obtain a good surgical view or to avoid lateral thermal injuries by surgical instruments [29]. Previous studies have reported the impact of anatomical features of the pancreas on POPF: Kobayashi et al. reported that the process of the pancreatic head is a risk factor for POPF after LG for gastric cancer; Migita et al. reported that the length between the levels of the pancreatic body surface and root of the common hepatic artery is a predictor of POPF; Kumagai et al. reported that the length of the vertical line between the pancreas and aorta, and angle

Table 2 Surgical outcomes of both groups divided by the TPS cutoff value

	Tn group *N*=215	Tk group *N*=67	*P* value
Bleeding (ml)	10 (0–400)	10 (0–690)	0.69
D-Amy on POD 1 (U/L)	314 (37–5176)	851 (51–27350)	**<0.001**
Harvested LNs	37 (4–112)	37 (17–126)	0.98
Postoperative hospitalization (days)	11 (7–63)	11 (7–62)	0.21
Complications ≧ CD Grade II	26 (12%)	19 (28%)	**0.004**
All pancreatic fistula	38 (20%)	24 (36%)	**0.004**
Pancreatic fistula Grade B	5 (2%)	11 (16%)	**<0.001**
Pancreatic fistula Grade C	0 (0)	0 (0)	
Intra-abdominal infectious complications ≧ CD Grade II	9 (4%)	12 (17%)	**0.001**

Bold values indicate statistically significant $p < 0.05$

TPS thickness of the pancreas anterior to the most ventral level of the splenic artery, *D-Amy* Amylase level in the drained fluid, *CD* Clavien-Dindo

Table 3 Risk factors for all postoperative pancreatic fistulas

All POPF	Univariable			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
TPS (mm)						
≥ 11.8	2.58	1.33–4.97	**0.003**	2.66	1.42–4.98	**0.002**
< 11.8	1			1		
Age (years)						
≥ 75	0.54	0.25–1.10	0.08	0.62	0.30–1.29	0.2
< 75	1			1		
Sex						
Male	1.13	0.61–2.12	0.77			
Female	1					
BMI (kg/m^2)						
≥ 25	1.01	0.49–2.00	1			
< 25	1					
ASA-PS						
2.3	0.55	0.27–1.16	0.09	0.63	0.30–1.35	0.23
1	1			1		
cStage						
> I	1.41	0.75–2.63	0.28	0.97	0.45–2.11	0.95
I	1			1		
Approach						
Laparoscopic	0.73	0.39–1.34	0.31	1.03	0.52–2.02	0.93
Robotic	1			1		
Extent of LD						
D2	2.13	1.15–3.95	0.01	2.03	0.94–4.38	0.07
D1+	1			1		

Bold values indicate statistically significant $p < 0.05$

TPS thickness of the pancreas anterior to the most ventral level of the splenic artery, *ASA-PS* The American Society of Anesthesiologists physical status, *LD* lymphadenectomy

Table 4 Risk factors for postoperative pancreatic fistula over grade A

POPF ≥ GradeB	Univariable			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
TPS (mm)						
≥ 11.8	8.16	2.49–31.2	**<0.001**	7.53	2.46–23.0	**<0.001**
< 11.8	1			1		
Age (years)						
≥ 75	0.76	0.17–2.61	0.78			
< 75	1					
Sex						
Male	2.17	0.63–9.50	0.2			
Female	1					
BMI (kg/m^2)						
≥ 25	2.39	0.72–7.55	0.13	1.62	0.54–4.76	0.38
< 25	1			1		
ASA-PS						
2.3	1.6	0.34–14.9	0.74			
1	1					
cStage						
> I	1.17	0.33–3.69	0.78			
I	1					
Approach						
Laparoscopic	0.73	0.21–2.29	0.61			
Robotic	1					
Extent of LD						
D2	1.85	0.58–5.87	0.28			
D1+	1					

Bold values indicate statistically significant $p < 0.05$

TPS thickness of the pancreas anterior to the most ventral level of the splenic artery, *ASA-PS* The American Society of Anesthesiologists physical status, *LD* lymphadenectomy

between a line drawn from the upper border of the pancreas to the root of the celiac artery and aorta are independent predictors of pancreatic fistula and/or postoperative complications and correlate with drain amylase concentration after LG for gastric cancer; and Kinoshita et al. reported that the maximum vertical length between the upper border of the pancreas and root of the left gastric artery on a preoperative sagittal CT is a specific and independent predictor of POPF in LG [10–13]. However, the splenic artery is known for its tortuosity after branching from the celiac trunk [30, 31]. We hypothesized that a thick pancreas, anterior to the most protuberant section of the splenic artery loop, could be a more precise predictor of the part of the pancreas that needs to be compressed during suprapancreatic lymphadenectomy and POPF. Our study concluded that a TPS ≥ 11.8 mm is an independent risk factor of POPF of grade B or higher, with a higher OR (7.53) than those of previously reported predictors.

Additionally, a previous study reported a significant positive correlation between BMI and pancreatic volume [32]; BMI and TPS positively correlated in our study. However, since BMI was not a significant indicator of POPF and intra-abdominal infectious complications in the univariable and multivariable analyses, TPS is not an indicator of pancreatic thickness or volume; instead, it indicates the part of the pancreas that can hinder suprapancreatic lymphadenectomy.

To ensure safe and effective suprapancreatic lymphadenectomy, we used the outermost layer-oriented medial approach [33–35]. In this technique, the thin loose connective tissue layer between the autonomic nerve sheaths of the arteries and adipose tissue, including lymph nodes, is dissected [33–35]. After exposing the autonomic nerve sheath, we pulled the nerve sheath caudally to identify the No. 11p lymph nodes instead of compressing the pancreatic body. We presumed that the use of this technique led to our finding that there was no significant difference in the POPF occurrence between D1 + and D2 lymph node dissections, although D2 lymphadenectomy is reportedly a risk factor for POPF [9].

POPF occurs more frequently after LG compared with OG [22, 27, 36, 37]. A Japanese nationwide prospective cohort study using the National Clinical Database reported

Table 5 Risk factors for intra-abdominal infection over CD grade I

Intra-abdominal Infection (≥ CD grade II)	Univariable			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
TPS (mm)						
≥ 11.8	4.95	1.8–14.0	**<0.001**	4.89	1.91–12.6	**<0.001**
< 11.8	1			1		
Age (years)						
≥ 75	1.17	0.38–3.24	0.8			
< 75	1					
Sex						
Male	1.81	0.64–5.90	0.25			
Female	1					
BMI (kg/m^2)						
≥ 25	1.5	0.49–4.19	0.43	1.14	0.41–3.13	0.79
< 25	1			1		
ASA-PS						
2.3	1.39	0.37–7.54	0.77			
1	1					
cStage						
> I	0.43	0.10–1.38	0.15	0.13	0.41–1.29	0.12
I	1			1		
Approach						
Laparoscopic	1.39	0.51–3.86	0.49			
Robotic	1					
Extent of LD						
D2	0.69	0.21–1.98	0.63			
D1+	1					

Bold values indicate statistically significant $p < 0.05$

TPS thickness of the pancreas anterior to the most ventral level of the splenic artery, *ASA-PS* The American Society of Anesthesiologists physical status, *LD* lymphadenectomy

a higher incidence of POPF after LG than after an open procedure. Kinoshita et al. reported that the anatomical location of the pancreas was one of the reasons for the high POPF incidence after LG, because limited forceps mobility and unintentionally strong compression may have led to pancreatic trauma [10]. In the present study, we examined LG and RG during the same period, at the same institution, and with the same surgical indication. Although RG is expected to decrease the incidence of POPF with the use of articulated forceps, which reduce unintentional pancreatic compression, and laparoscopic coagulating shears, which are frequently used in LG, to decrease lateral thermal injuries, the impact of the robotic approach on POPF reduction remains controversial [38–40]. Similarly, our study did not detect statistically significant differences between the impacts of the laparoscopic and robotic approaches on the incidences of POPF grade B or higher ($P=0.61$), all POPF ($P=0.31$), and intra-abdominal infectious complications ($P=0.49$). This may be because pancreatic compression, conducted to provide a good surgical view, is mainly performed laparoscopically using the assistant's forceps. Therefore, direct laparoscopic pancreatic compression should be avoided as much as possible to decrease the incidence of POPF.

As we reported, TPS is an independent predictor not only for POPF grade B or higher, but also for all POPF and intra-abdominal infectious complications. Measuring TPS is simple and does not require any specific device. Therefore, we believe that the TPS is a good predictor of postoperative complications after minimally invasive gastrectomy. For patients with increased TPS over 11.8 mm, careful pancreatic manipulation is required. When performing the pancreas-contactless technique, the operator themself should gently perform the minimal number of necessary pancreatic compressions instead of an assistant to pay more awareness to the procedure [41].

This study had some limitations. First, it was conducted retrospectively at a single institution. Pancreatic compression time should be investigated to verify its positive relationship with TPS; however, it was difficult to check this because several surgical videos were unavailable. Furthermore, because the incidence of grade B or higher POPF and grade II or higher intra-abdominal infectious complications were low, only a few explanatory variables were included in the multivariable analysis to maintain statistical quality, and a larger sample size will strengthen the conclusion. Additionally, different operating platforms were included in this study and there was weakness in the analysis performance. Prospective studies with a larger sample size and that investigate the relationships between TPS and pancreatic compression time are necessary to strengthen the power of this study.

In conclusion, TPS is a specific predictive factor for POPF and postoperative intra-abdominal infections in patients undergoing LG and RG. By measuring TPS, patients at a high risk of developing POPF and postoperative intra-abdominal infections can be identified preoperatively. Additionally, careful pancreatic manipulation during suprapancreatic lymphadenectomy is necessary for patients with increased TPS (> 11.8 mm) to avoid postoperative complications.

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Declarations

Disclosures Kengo Hayashi, Noriyuki Inaki, Yusuke Sakimura, Takahisa Yamaguchi, Yoshinao Obatake, Shiro Terai, Hirotaka Kitamura, Shinichi Kadoya, and Hiroyuki Bando have no conflicts of interest to disclose.

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