Original Article

Clinical validation of scoring systems of postoperative pancreatic fistula after pancreatoduodenectomy: applicability to Eastern cohorts?

Jae Seung Kang[1#], Taesung Park[2#], Youngmin Han[1], Seungyeon Lee[3], Jae Ri Kim[1], Hongbeom Kim[1], Wooil Kwon[1], Sun-Whe Kim[1], Jin Seok Heo[4], Seong Ho Choi[4], Dong Wook Choi[4], Song Cheol Kim[5], Tae Ho Hong[6], Dong Sup Yoon[7], Joon Seong Park[7], Sang Jae Park[8], Sung-Sik Han[8], Sae-Byeol Choi[9], Joo Seop Kim[10], Chang-Sup Lim[11], Jin-Young Jang[1]

[1]Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Department of Statistics and Interdisciplinary Program in Biostatistics, Seoul National University, Seoul, Republic of Korea; [3]Department of Mathematics and Statistics, Sejung University, Seoul, Republic of Korea; [4]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Ulsan University College of Medicine and Asan Medical Center, Seoul, Republic of Korea; [6]Department of Surgery, Seoul St. Mary's Hospital, The Catholic University of Korea, College of Medicine, Seoul, Republic of Korea; [7]Pancreatobiliary Cancer Clinic, Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [8]Center for Liver Cancer, National Cancer Center, Gyeonggido, Republic of Korea; [9]Department of Surgery, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [10]Department of Surgery, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea; [11]Department of Surgery, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Republic of Korea

Contributions: (I) Conception and design: JS Kang, T Park, JY Jang; (II) Administrative support: Y Han, S Lee, JR Kim, H Kim, W Kwon, SW Kim; (III) Provision of study materials or patients: JS Kang, Y Han, DW Choi, SC Kim, TH Hong, JS Park, SJ Park, SB Choi, JS Kim, CS Lim; (IV) Collection and assembly of data: JS Kang, JS Heo, SH Choi, SC Kim, TH Hong, DS Yoon, SS Han, SB Choi, JS Kim, CS Lim; (V) Data analysis and interpretation: JS Kang, T Park, S Lee, JY Jang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jin-Young Jang, MD, PhD. Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, 101 Daehak-ro, Chongno-gu, Seoul 03080, Republic of Korea. Email: jangjy4@snu.ac.kr.

Background: Although several prediction models for the occurrence of postoperative pancreatic fistula (POPF) after pancreatoduodenectomy (PD) exist, all were established using Western cohorts. Large-scale external validation studies in Eastern cohorts that consider demographic variables including lower body mass index (BMI) are scarce. The purpose of this study was to externally validate POPF prediction models using nationwide large-scale Korean cohorts.

Methods: Nine tertiary university hospitals in the Republic of Korea participated. Patients' preoperative characteristics, intraoperative factors, and pathologic findings were evaluated. POPF grades were determined according to the 2016 International Study Group on Pancreatic Surgery definition. Three POPF risk models (Callery, Roberts, and Mungroop) were selected for external validation.

Results: A total of 1,898 PD patients were enrolled. A non-pancreatic disease diagnosis [hazard ratio (HR), 1.856; 95% confidence interval (CI), 1.223–2.817; P=0.004), higher preoperative BMI (HR, 1.069; 95% CI, 1.019–1.121; P=0.006), and soft pancreatic texture (HR, 1.859; 95% CI, 1.264–2.735; P=0.002) were independent risk factors for clinically relevant POPF (CR-POPF). The area under the receiver operating characteristic curve (AUC) values were 0.61, 0.64, and 0.63 on the Callery, Roberts, and Mungroop models, respectively; all were lower than those published in each external validation study.

Conclusions: Western POPF prediction models performed less well when applied to Korean cohorts. Thus, a large-scale Eastern-specific and externally validated POPF prediction model is needed.

Keywords: Pancreatic fistula; pancreatoduodenectomy (PD); predictive score

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Introduction

Postoperative pancreatic fistula (POPF) remains a lethal complication, and is related with increased hospital stays, costs, and surgery-related mortality rates (1-4). The definition of POPF was unified and clarified by The International Study Group for Pancreatic Surgery (ISGPS) in 2005 (5), and revised in 2016 (6).

The availability of a prediction model is required for the development of individualized programs for the postoperative management of POPF. Such models can also decrease unnecessary postoperative interventions and hospital costs in low-risk patients, enable appropriate evaluations and treatments, and decrease life-threatening events and mortality in high-risk patients (7). Callery *et al.* reported that pancreatic texture, pathologic diagnosis, main pancreatic duct (MPD) diameter, and intraoperative estimated blood loss (EBL) were associated with the development of POPF after pancreatoduodenectomy (PD) and subsequently established the Callery score of POPF prediction based on these four factors (2). The Callery score has been widely used and demonstrated reliable validity in some studies (8-10). Simpler risk prediction models of POPF were recently developed and reported in the United Kingdom (UK) and The Netherlands (11,12). The UK group proposed body mass index (BMI) and MPD diameter as POPF risk factors, while The Netherlands group reported pancreatic texture, BMI and MPD diameter. These two models performed moderately well in external validation studies (11,13).

However, these POPF prediction models were established using Western cohorts. Baseline patient characteristics, surgical techniques, and postoperative managements differ different between Eastern and Western countries, and large-scale external validation studies of Eastern cohorts are scarce. This study aimed to externally validate several POPF prediction models using large-scale nationwide Korean cohorts.

Methods

Patients

This retrospective cohort study examined data from a prospectively collected medical database. Nine tertiary university hospitals in the Republic of Korea participated in this study: Seoul National University Hospital, Samsung Medical Center, Asan Medical Center, Catholic Medical Center, Gangnam Severance Hospital, National Cancer Center in Korea, Korea University Guro Hospital, Hallym University Sacred Heart Hospital, and Seoul Metropolitan Government Seoul National University Boramae Hospital. The surgeons in each of these nine hospitals performed a minimum of 20 cases of PD annually. Patients who underwent PD or pylorus-preserving pancreatoduodenectomy (PPPD) due to periampullary disease were enrolled. Patients who did not undergo pancreatico-enteric anastomosis, who underwent combined other organ resections, who had a previous history of abdominal surgery before PD, and for whom insufficient medical data were available to investigate POPF were excluded.

This study was approved by our hospital's institutional review board (C-1806-129-954).

Data collection and definition of POPF

Preoperative patient characteristics were investigated, including age, sex, BMI, preoperative co-morbidities, preoperative lab data, and MPD diameter on a cross-sectional view of a preoperative computed tomography (CT) image. Intraoperative factors included operation type, combined vascular resection, pancreatico-enteric anastomosis site (pancreaticojejunostomy or pancreaticogastrostomy), pancreatico-enteric anastomosis type (invagination or duct-to-mucosa), operation time, intraoperative EBL, and pancreatic texture. Postoperative data included pathologic diagnosis, drain amylase concentration on postoperative day 3, and complications with a Clavian-Dindo classification > grade II. Pancreatic cancer and pancreatitis were categorized as pancreatic disease, and the other pancreatic disease such as benign pancreatic cystic neoplasm, or neuroendocrine tumors were categorized in other periampullary disease of non-pancreatic disease (2).

POPF was determined based on the 2016 ISGPS guideline, while clinically relevant POPF (CR-POPF) was

Table 1 Demographic and pathologic findings of modeling cohorts in four studies

Variables	Callery *et al.* (2)	Roberts *et al.* (11)	Mungroop *et al.* (12)	Present study
Modeling cohorts (No.)	233	217	1,924	1,898
Age, year, median (IQR)	–	67 [60–73]	67 [60–74]	64 [56–70]
Male sex (%)	–	120 (55.8)	778 (57.0)	1,116 (58.8)
Diagnosis (%)				
Pancreatic ductal adenocarcinoma	145 (62.2)	88 (40.6)	816 (43.0)	669 (35.2)
Pancreatitis		–	50 (3.0)	22 (1.2)
Common bile duct cancer	88 (37.8)	33 (15.2)	265 (14.0)	407 (21.4)
Ampulla of Vater cancer		40 (18.4)	265 (14.0)	365 (19.2)
Duodenal cancer		11 (5.1)	110 (6.0)	39 (2.1)
Others		45 (20.7)	453 (20.0)	396 (20.9)
Preoperative BMI, kg/m^2, median (IQR)	–	25.0 (22.5–27.8)	25 [22–28]	22.9 (20.8–24.9)
Preoperative diabetes mellitus (%)	–	31 (14.3)	403 (26.0)	467 (24.6)
Preoperative MPD diameter, mm, median (IQR)	–	–	4 [2–5]	3 [2–5]
Anastomotic site (%)				
Pancreaticojejunostomy	–	117 (53.9)	–	1,767 (93.1)
Pancreaticogastrostomy	–	100 (46.1)	–	131 (6.9)
Estimated blood loss (≥1,000 mL) (%)	13 (5.6)	–	–	236 (15.9)
Soft pancreatic texture (%)	110 (47.2)	–	970 (54.0)	1,091 (57.5)
Overall POPF (%)	60 (25.8)	48 (22.1)	–	752 (39.6)
Clinically relevant POPF (%)	31 (13.3)	27 (12.4)	232 (12.0)	275 (14.5)

BMI, body mass index; MPD, main pancreatic duct; POPF, postoperative pancreatic fistula.

defined as grade B or C (6).

Statistical analysis

Nominal data were compared using χ^2 tests, while continuous variables were examined using Student's *t*-test. Only variables statistically significant on univariate analysis were included in the multivariate analysis. To calculate the performance of each model, the area under the receiver operating characteristic curve (AUC) was calculated. All statistical analyses were performed using R version 3.3.0 (R Foundation, Vienna, Austria), and two-sided P values <0.05 were considered statistically significant.

Results

Patient demographics

Between 2007 and 2014, a total of 1,898 patients from the nine tertiary pancreaticobiliary centers in Korea were enrolled in this study (*Table 1*). The mean patient age was 62.6 years; 1,116 patients (58.8%) were male; and 669 (35.2%) were diagnosed with pancreatic ductal adenocarcinoma, 407 (21.4%) with extrahepatic common bile duct cancer, 365 (19.2%) with ampulla of Vater cancer, 39 (2.1%) with duodenal cancer, and 396 (20.9%) with other periampullary diseases (*Table 1*). The mean patient BMI was 23.0. Of the cohort, 1,767 patients (93.1%) underwent pancreaticojejunostomy anastomosis and 1,630 (85.9%) underwent duct-to-mucosa anastomosis. A soft pancreatic texture was seen in 57.5% of cases. Overall, POPF occurred in 752 patients (39.6%), while CR-POPF (grade B or C) occurred in 275 (14.5%).

Predictive factors for CR-POPF after PD

In the univariate analysis, male sex, non-pancreatic disease

Table 2 Predictive factors for postoperative pancreatic fistula in univariate and multivariate analysis

Predictive factors	Total (N=1,898)	Univariate analysis			Multivariate analysis		
		CR-POPF (–) (N=1,623)	CR-POPF (+) (N=275)	P value	HR	95% CI	P value
Age (year, mean ± SD)	62.6±10.7	62.5±10.9	63.2±9.8	0.280	–	–	–
Gender (%)							
Male	1,116 (58.8)	934 (83.7)	182 (16.3)	0.008	1.334	0.970–1.835	0.077
Female	782 (41.2)	689 (88.1)	93 (11.9)				
Diagnosis (%)							
Others	1,198 (63.1)	975 (81.4)	223 (18.6)	<0.001	1.856	1.223–2.817	0.004
Pancreatic	693 (36.5)	641 (92.5)	52 (7.5)				
Preoperative BMI (kg/m^2, mean ± SD)	23.0±3.2	22.9±3.3	23.7±2.9	<0.001	1.069	1.019–1.121	0.006
Preoperative DM (%)	467 (24.6)	413 (25.4)	54 (19.6)	0.041	1.124	0.765–1.653	0.552
Preoperative MPD diameter (mm, mean ± SD)	3.6±2.2	3.7±2.3	3.2±1.6	<0.001	0.936	0.855–1.025	0.153
Operation type (%)							
PPPD	1,558 (82.1)	1,314 (84.3)	244 (15.7)	0.002	1.231	0.750–2.019	0.411
Whipple's operation	340 (17.9)	309 (90.9)	31 (9.1)				
Vessel resection (%)							
No	1,754 (92.4)	1,486 (84.7)	268 (15.3)	0.001	1.623	0.657–4.009	0.294
Yes	144 (7.6)	137 (95.1)	7 (4.9)				
Anastomotic site (%)							
Pancreaticojejunostomy	1,767 (93.1)	1,503 (85.1)	264 (14.9)	0.052	–	–	–
Pancreaticogastrostomy	131 (6.9)	120 (91.6)	11 (8.4)				
Anastomotic method (%)							
Duct-to-mucosa	1,630 (85.9)	1,372 (84.2)	258 (15.8)	<0.001	1.293	0.428–3.904	0.648
Invagination	145 (7.6)	138 (95.2)	7 (4.8)		0.845	0.074–9.643	0.893
Others	123 (6.5)	113 (91.9)	10 (8.1)				
Operation time (minute, mean ± SD)	369.3±116.7	373.1±117.9	347.1±106.9	<0.001	1.000	0.998–1.002	0.996
Intraoperative blood loss (mL, mean ± SD)	593.0±653.8	607.3±677.0	521.8±517.7	0.026	1.000	1.000–1.000	0.688
Pancreatic texture (%)							
Soft	1,091 (57.5)	891 (81.7)	200 (18.3)	<0.001	1.859	1.264–2.735	0.002
Hard	716 (37.7)	654 (91.3)	62 (8.7)				
Malignancy (%)							
Yes	1,603 (84.5)	1,362 (85.0)	241 (15.0)	0.126	–	–	–
No	295 (15.5)	261 (88.5)	34 (11.5)				

CR-POPF, clinically-relevant postoperative pancreatic fistula; BMI, body mass index; DM, diabetes mellitus; MPD, main pancreatic duct; PPPD, pylorus-preserving pancreatoduodenectomy; HR, hazard ratio; CI, confidence interval.

Table 3 Comparisons of the scoring system of postoperative pancreatic fistula after pancreatoduodenectomy

POPF model	Modeling cohorts (n)	POPF (2005 grade)	Predictive factors	AUC (internal)	External validation studies	
					Validation cohorts (n)	AUC
Callery *et al.* (2)	233	B, C	Pancreatic texture; MPD diameter; diagnosis; EBL	0.94	594 [9]; 444 [8]; 1,898†	0.72; 0.72; 0.61
Roberts *et al.* (11)	217	A, B, C	MPD diameter; BMI	0.75	630 [13]; 1,898†	0.77; 0.64
Mungroop *et al.* (12)	1,924	B, C	Pancreatic texture; MPD diameter; BMI	0.75	924 [12]; 1,898†	0.78; 0.63

†, the present study. POPF, postoperative pancreatic fistula; AUC, area under the receiver operating curve; MPD, main pancreatic duct; EBL, estimated blood loss; BMI, body mass index; Internal, indicates internal validation study.

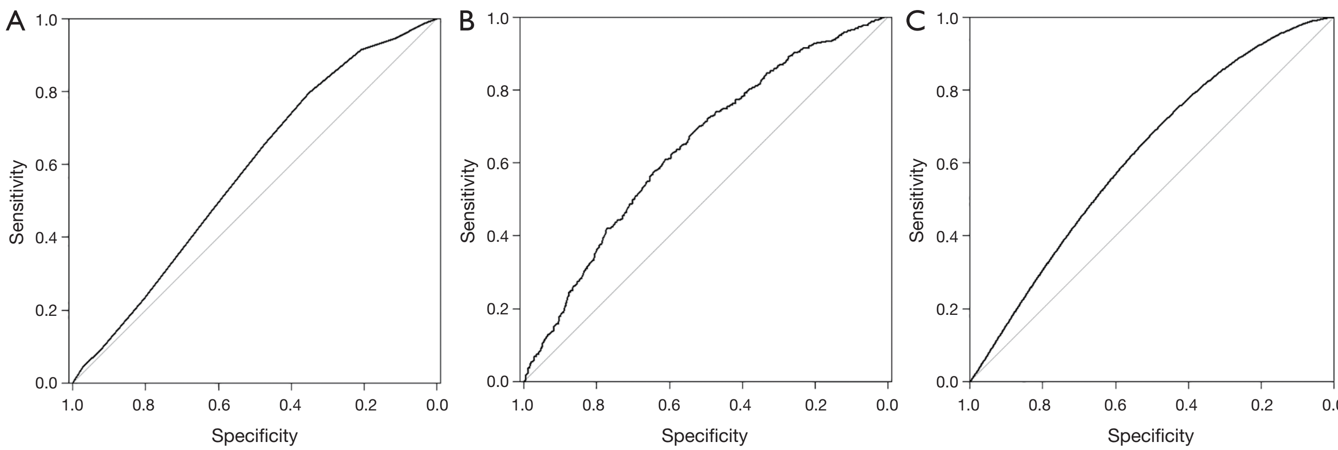

Figure 1 The receiver operating curves of the Korean cohorts based on the three models. (A) Callery model (2); (B) Roberts model (11); (C) Mungroop model (12).

diagnosis, preoperative BMI, preoperative DM, MPD diameter on preoperative CT images, operation type, absence of vessel resection, duct-to-mucosa anastomosis, operation time, intraoperative blood loss, and soft pancreatic texture were associated with CR-POPF (*Table 2*). In the multivariate analysis, a non-pancreatic disease diagnosis [hazard ratio (HR), 1.856; 95% confidence interval (CI), 1.223–2.817; P=0.004), higher preoperative BMI (HR, 1.069; 95% CI, 1.019–1.121; P=0.006), and soft pancreatic texture (HR, 1.859; 95% CI, 1.264–2.735; P=0.002) were the independent risk factors for CR-POPF after PD.

Comparisons of discrimination ability and relationship between score severity and actual occurrence rates of POPF

Of the published POPF prediction models, we selected those with proven validity in clinical circumstances in both internal and large-scale external validation studies. The models of Callery *et al.*, Roberts *et al.*, and Mungroop *et al.* were selected and investigated (2,11,12). *Table 3* shows the summarization of these three-scoring system and the comparisons of the AUC values. The three western models showed moderate discrimination ability that the AUC values were more than 0.7. *Figure 1* shows the ROCs of the Korean cohorts based on the three-scoring system (*Figure 1A*, Callery model; *Figure 1B* Roberts model; *Figure 1C*, Mungroop model). The AUC values were calculated based on these ROCs that these models performed less well when the Korean cohorts were applied that the AUC values were between 0.61 and 0.64.

Figure 2 shows the relationship between score severity and actual POPF occurrence rates of Korean cohorts for each scoring system. The higher the score, the more frequent the occurrence of POPF in each model. However, the actual CR-POPF rate in the high-risk group was lower in this Korean cohort than in the reported validation studies.

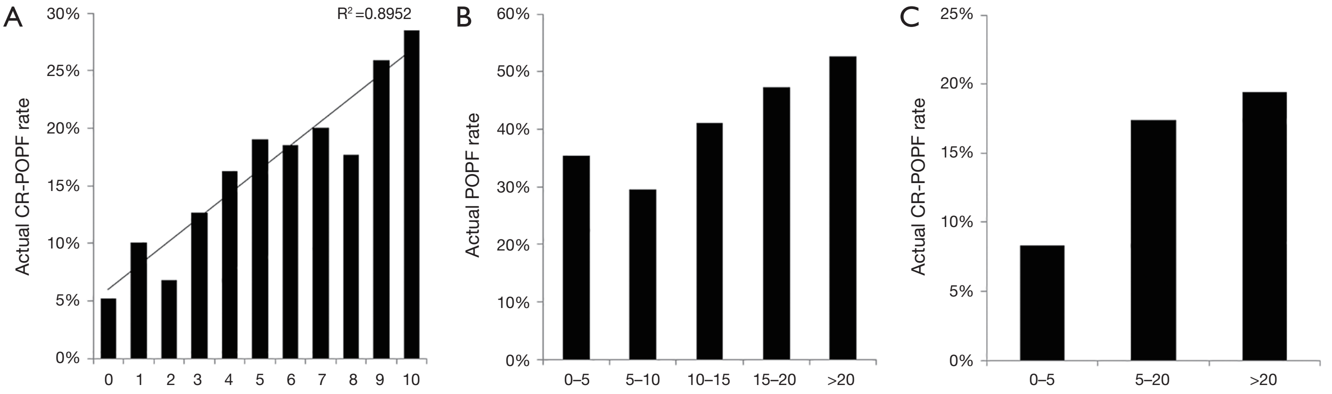

Figure 2 Relationship between score severity and actual POPF rate of Korean cohorts. (A) Callery model; (B) Roberts model; (C) Mungroop model. POPF, postoperative pancreatic fistula; CR-POPF, clinically-relevant POPF.

Regarding Callery score, the actual rate of CR-POPF in the high-risk group (Callery score 7–10) was 20.3% in the Korean cohort (*Figure 2A*) versus 28.6% in one external validation study (9) and 42.3% in another study (8). Regarding Mungroop score, the actual CR-POPF rate was 19.3% in the Korean cohort (*Figure 2C*) versus 31.0% in an external validation study (11).

Discussion

Predicting POPF is important because it enables the development of individualized treatment plans for affected patients. Numerous risk factors for POPF have been identified, while several POPF prediction models have been subsequently developed (2,11,12,14-16). However, most have not been externally validated. Furthermore, there have been few large-scale external validation studies of POPF in Eastern cohorts. The present study identified three large-scale validated models and investigated their applicability to a large-scale Korean cohort.

AUC values, a discriminatory index for the prediction models, range from 0.5 (no discrimination ability) to 1.0 (perfect discrimination) (17,18). One study categorized the discriminatory ability of AUC values of 0.5–0.7 as poor, 0.7–0.9 as reasonable, and 0.9–1.0 as very good (19). *Table 2* summarized the outcomes of internal and external validation studies for Callery, Roberts, and Mungroop scores. An internal validation revealed an AUC of the Callery score of 0.94 (2). However, the predictability of internal validation could be overestimated because establishing the prediction model was based on the multivariate logistic regression analysis of the study modeling cohorts. Miller *et al.* performed an external validation using the data of 594 PD patients who underwent pancreaticojejunostomy anastomosis and reported an AUC of 0.72 (9). Grendar *et al.* reported an AUC of 0.71 (8). Regarding Roberts and Mungroop scoring, the AUC in the external validation study was 0.77 and 0.78, respectively (*Table 2*) (11,13). These values indicated that these three models demonstrated reasonable performance for predicting POPF or CR-POPF when applied to Western cohorts.

Miller *et al.* insisted that the variations in predictability among the validation studies might have been caused by differences in patient characteristics, POPF rates in the high-risk groups, and perioperative managements (9). The present study performed external validation of the three methods using the data of 1,898 consecutive Korean PD patients from nine tertiary hospitals. The incidence of POPF in this Korean cohort increased as score severity increased (*Figure 2*). However, the AUC values were 0.61–0.64, meaning that these Western POPF scoring models had poor discriminatory ability when applied to our Korean cohort (*Table 3*). This might have been due to differences in demographics such as BMI and the proportion of patients with non-pancreatic diseases (*Table 1*). In addition, in our high-risk group of our cohorts, the actual CR-POPF rates were <30% for Callery scoring (*Figure 2A*) and 20% for Mungroop scoring (*Figure 2C*). Therefore, these Western models must be revised to increase their applicability to Korean cohorts.

Pancreatic texture and pathologic diagnosis were the risk factors proposed by Callery *et al.* (2). Preoperative BMI was recently included in two prediction models (11,12). EBL was also a risk factor proposed by Callery *et al.* proposed, but two recent external validation studies refuted this claim (8,10). Furthermore, due to the advent of minimally invasive surgery, reported intraoperative blood loss volumes became lower than those of studies of the period when Callery scoring was developed (20-22). In the present study, preoperative valuables including a non-pancreatic disease diagnosis (HR, 1.856; 95% CI, 1.223–2.817; P=0.004), higher preoperative BMI (HR, 1.069; 95% CI, 1.019–1.121; P=0.006), and soft pancreatic texture (HR, 1.859; 95% CI, 1.264–2.735; P=0.002) were the independent risk factors for CR-POPF in the multivariate analysis (*Table 2*), and one study suggested the exact same risk factors (23). Because patient characteristics, surgical skills, and perioperative management methods differ among countries, the statistically significant factors and hazard ratios could be different. Therefore, it is necessary to establish new models that reflect the factors and hazard ratios of each cohort. To consider such differences, pathologic diagnoses, preoperative BMI, and pancreatic texture should be included in the new model.

The previous three scoring system mentioned MPD size as one of the risk factors (2,11,12). However, it was not consistent with the present study that the MPD size was not statistically associated with CR-POPF (HR 0.936; 95% CI, 0.855–1.025, P=0.153, *Table 2*). This was probably because the anastomotic method (duct-to-mucosa or invagination), or pancreatic duct stenting method were not unified around nine institutions. In addition, different surgeons investigated MPD size in the preoperative CT image. In order to overcome this limitation, prospective study design and unified method to evaluate the MPD size would be needed.

The present study has some limitations. First, surgical techniques and perioperative management methods were not unified among the nine hospitals. Thus, surgeon preference was a potential confounding factor. Second, data missing from the surgical and pathologic reports could not be controlled for in this retrospective study. To ensure high-quality collaboration studies, centralization of the electric medical database and regular monitoring are needed. Despite these limitations, this was the largest external validation study of Western POPF prediction models in an Eastern cohort.

In conclusion, Western POPF prediction models performed less well when applied to Korean cohorts. Risk factors for POPF in Eastern model were a higher BMI, soft pancreatic texture, and non-pancreatic disease diagnosis. Thus, the development of a large-scale externally validated Eastern-specific POPF prediction model using Eastern cohorts is needed.

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Footnote

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

Ethical Statement: This study was approved by the institutional review board of Seoul National University Hospital (C-1806-129-954).

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