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Risk Models for Developing Pancreatic Fistula After Pancreatoduodenectomy

Validation in a Nationwide Prospective Cohort

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Objective: To evaluate the performance of published fistula risk models by external validation, and to identify independent risk factors for postoperative pancreatic fistula (POPF).

Background: Multiple risk models have been developed to predict POPF after pancreatoduodenectomy. External validation in high-quality prospective cohorts is, however, lacking or only performed for individual models.

Methods: A post hoc analysis of data from the stepped-wedge cluster-randomized Care After Pancreatic Resection According to an Algorithm for Early Detection and Minimally Invasive Management of Pancreatic Fistula versus Current Practice (PORSCH) trial was performed. Included were all patients undergoing pancreatoduodenectomy in the Netherlands (January 2018–November 2019). Risk models on POPF were identified by a systematic literature search. Model performance was

evaluated by calculating the area under the receiver operating curves (AUC) and calibration plots. Multivariable logistic regression was performed to identify independent risk factors associated with clinically relevant POPF.

Results: Overall, 1358 patients undergoing pancreatoduodenectomy were included, of whom 341 patients (25%) developed clinically relevant POPF. Fourteen risk models for POPF were evaluated, with AUCs ranging from 0.62 to 0.70. The updated alternative fistula risk score had an AUC of 0.70 (95% confidence intervals [CI]: 0.69–0.72). The alternative fistula risk score demonstrated an AUC of 0.70 (95% CI: 0.689–0.71), whilst an AUC of 0.70 (95% CI: 0.699–0.71) was also found for the model by Petrova and colleagues. Soft pancreatic texture, pathology other than pancreatic ductal adenocarcinoma or chronic pancreatitis, small pancreatic duct diameter, higher body mass index,

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minimally invasive resection and male sex were identified as independent predictors of POPF.

Conclusion: Published risk models predicting clinically relevant POPF after pancreatoduodenectomy have a moderate predictive accuracy. Their clinical applicability to identify high-risk patients and guide treatment strategies is therefore questionable.

Key words: fistula, pancreatic fistula, pancreatic resection, pancreatic surgery, pancreatoduodenectomy, postoperative, risk model

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Pancreatoduodenectomy is a complex surgical procedure associated with a high risk of complications (50%), even in specialized, high-volume centers.^{1,2} A common complication is postoperative pancreatic fistula (POPF), resulting in leakage of enzyme-rich fluid into the abdominal cavity.^{2,3} This can have life-threatening consequences such as bleeding, sepsis, and organ failure.³ As a result, these patients require extensive care with prolonged hospital stays, and increased health care costs.^{4,5} Mortality in patients with clinically relevant POPF [ie, grade B/C according to the 2016 International Study Group on Pancreatic Surgery (ISGPS) definition] is reported to be 12% to 18%.^{2,3,6,7}

Several risk factors associated with the development of POPF have been identified, such as a small pancreatic duct diameter, soft pancreatic parenchyma and a high body mass index (BMI).^{8,9} Over the years, numerous models that aim to predict the risk of POPF have been proposed.^{9–22} The majority of these models was, however, developed in retrospective studies, mostly from single centers. External validation, especially

in large, high-quality prospective cohorts is missing or only performed for single risk models.²³

The recent nationwide stepped-wedge cluster-randomized PORSCH trial showed that the implementation of an algorithm for early recognition and minimally invasive management of complications after pancreatic resection significantly reduces the rate of major complications and 90-day mortality.²⁴ In this trial, all centers delivered usual care (control group) at the start of the study and crossed over to care according to the algorithm (intervention group). Patients treated according to the multi-modality algorithm were strictly monitored, independently of their risk to develop POPF. This potentially may have led to a certain level of overuse of diagnostic tools, which might not be necessary for patients with a low risk of POPF. An accurate risk stratification for the development of POPF in patients undergoing pancreatic resection could therefore be of renewed value. Furthermore, this could be helpful to the longstanding goal of developing specific treatments to prevent POPF in patients with a high preoperatively or perioperatively identified risk of POPF.²⁵

This study aims to evaluate the performance of published risk models and to identify independent predictors of POPF using the unselected nationwide prospective cohort of patients undergoing pancreatoduodenectomy in the randomized PORSCH trial.²⁶

METHODS

Study Selection

A systematic literature search was performed in PubMed, EMBASE, and the Cochrane Library up to December 2021 to

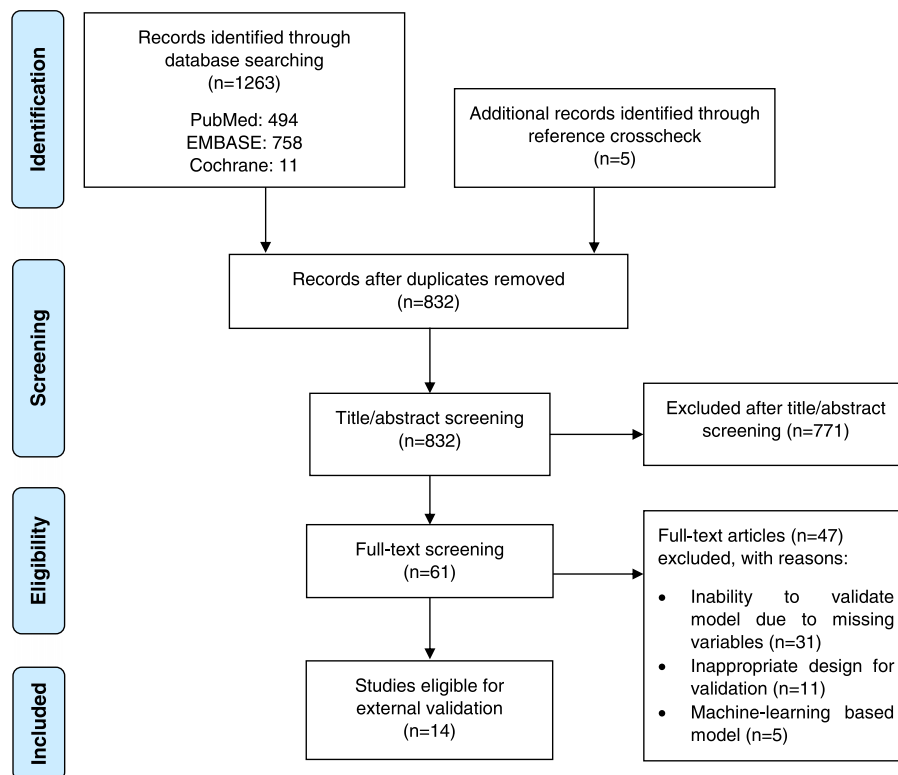


FIGURE 1. Flow chart of identified risk models eligible for external validation.

TABLE 1. Overview of Evaluated Risk Models for Development of Postoperative Pancreatic Fistula After Pancreatoduodenectomy

References	Country	Design	N	Usage	Risk Factors													
					Pancreatic texture	PD diameter	Pathology	Operative blood loss	BMI	Sex	Age	Neoadjuvant treatment	Vascular resection	Preoperative bilirubin	Drain AMYLASE	Operative time	WBC POD4	CRP POD4
Callery et al ⁹	USA	RC	445	Intra	Soft	≤ 4 mm	Other than PDAC or pancreatitis	> 400 mL	—	—	—	—	—	—	—	—	—	—
Kim et al ¹⁰	Korea	RC	100	Intra	Soft	≤ 3 mm	—	—	—	—	—	—	—	SMV/PV	—	—	—	—
Kosaka et al ¹¹	Japan	RC	100	Post	—	—	—	—	—	—	—	—	—	—	POD4 > 647 U/L	—	> 73.6 ×10 ² /μl	> 93 mg/L
Roberts et al ¹²	UK	RC	325	Pre	—	Continuous	—	—	Continuous	—	—	—	—	—	—	—	—	—
Chen et al ¹³	China	RC	921	Intra	Soft	≤ 4 mm	—	Difference BL and transfusion ≥ 800 mL	≥ 28	—	—	—	—	—	—	—	—	—
Casadei et al ¹⁴	Italy	PC	84	Pre	—	≤ 3 mm	Other than PDAC or pancreatitis	—	> 24	—	—	—	—	—	—	—	—	—
Kantor et al ¹⁵	North America	RC	1731	Intra	Soft	≤ 5 mm	—	—	≥ 25	Male	—	—	—	< 2 mg/dL	—	—	—	—
Mungroop et al ¹⁶	Multiple	PC	2850	Intra	Soft	Continuous	—	—	Continuous	—	—	—	—	—	—	—	—	—
Petrova et al ¹⁷	Germany	RC	2488	Intra	Soft	—	Other than PDAC	—	Continuous	—	—	—	—	—	—	Continuous	—	—
Tabchouri et al ¹⁸	France	RC	661	Intra	Soft	Continuous	—	—	—	Continuous	—	Radiation therapy	—	—	—	—	—	—
Huang et al ¹⁹	China	RC	1182	Pre	—	< 3 mm	—	—	≥ 24	—	—	—	—	—	POD1 ≥ 2484 U/L	—	—	—
Mungroop et al ²⁰	Multiple	PC	952	Intra	Soft	Continuous	—	—	Continuous	Male	—	—	—	—	—	—	—	—
Schuh et al ²¹	Multiple	RC	5533	Intra	Soft	≤ 3 mm	—	—	—	—	—	—	—	—	—	—	—	—
Perri et al ²²	Italy	PC	566	Pre	—	< 5 mm	—	—	≥ 25	—	—	—	—	—	—	—	—	—

Other indicates ampullary/cystic/duodenal/islet cell; BL, blood loss; BMI, body mass index; CRP, C-reactive protein; FRS, fistula risk score; intra, intraoperative; ISGPS, International Study Group on Pancreatic Surgery; PC, prospective cohort; PD, pancreatic duct; PDAC, pancreatic ductal adenocarcinoma; POD, postoperative day; POPF, postoperative pancreatic fistula; post, postoperative; pre, preoperative; PV, portal vein; RC, retrospective cohort; SMV, superior mesenteric vein; WBC, white blood cell count.

TABLE 2. Baseline Characteristics of 1358 Patients Undergoing Pancreatoduodenectomy (After Multiple Imputation)

Characteristic	No POPF* (N = 1017), n (%)	POPF* (N = 341), n (%)	P
Male sex	516 (51)	197 (58)	0.029
Age in years, mean ± SD	67.0 ± 10.4	66.4 ± 10.2	0.040
BMI, median (IQR)	24.4 (22.0–27.1)	25.5 (23.2–28.7)	<0.001
Charlson comorbidity index			0.88
< 2	792 (78)	268 (79)	
≥ 2	225 (22)	73 (21)	
ASA classification			0.71
I	68 (7)	27 (8)	
II	629 (62)	211 (62)	
III–IV	320 (31)	103 (30)	
ECOG performance score at diagnosis			0.58
0–1	938 (92)	318 (93)	
2–3	79 (8)	23 (7)	
Neoadjuvant treatment	117 (12)	20 (6)	0.004
Diabetes	280 (27)	71 (21)	0.017
Laparoscopic or robotic-assisted resection	170 (17)	95 (28)	<0.001
Soft pancreatic gland texture	579 (57)	276 (81)	<0.001
Pancreatic duct diameter, mm, median (IQR)	4 (3–5)	3 (2–4)	<0.001
Vascular resection	177 (17)	27 (8)	<0.001
Perioperative blood loss, ml, median (IQR)	450 (211–900)	450 (200–850)	0.001
Definitive postoperative pathology			<0.001
Pancreatic ductal adenocarcinoma	467 (46)	68 (20)	
Ampullary carcinoma	128 (13)	64 (19)	
Cholangiocarcinoma	124 (12)	57 (17)	
IPMN	70 (7)	25 (7)	
pNET	33 (3)	25 (7)	
Chronic pancreatitis	34 (3)	10 (3)	
Other	161 (16)	92 (27)	

*According to the International Study Group on Pancreatic Surgery definition (2016). Only grade B/C complications were considered.

ASA indicates American Society of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IPMN, Intraductal Papillary Mucinous Neoplasm; IQR, interquartile range; pNET, Pancreatic neuroendocrine tumor; POPF, postoperative pancreatic fistula.

Significant *P* values < 0.05 are depicted in bold.

Sensitivity Analysis

A total of 643 of 1358 patients (47%) after pancreatoduodenectomy was assigned to the intervention group of the PORSC trial. In this subgroup, POPF occurred in 186 of 643 patients (29%), whilst this occurred in 21% of patients allocated in the control group. All risk models displayed a higher predictive accuracy, with AUCs ranging from 0.66 to 0.74 (Supplemental Digital Content 3, <http://links.lww.com/SLA/E447>). The models with the highest performance were the a-FRS (AUC: 0.74, 95% CI: 0.72–0.76), and a-FRS (AUC: 0.74, 95% CI: 0.72–0.76).

Predictors of POPF

Univariate and multivariable logistic regression analyses are presented in Table 4. Multivariable logistic regression analysis identified soft pancreatic texture (OR: 1.93, 95% CI:

TABLE 3. Area Under the Curves of Risk Models for Postoperative pancreatic Fistula After Pancreatoduodenectomy

References	AUC (originally reported)	AUC with corresponding 95% CI (external validation)
Callery et al ⁹	0.94	0.65 (0.63–0.66)
Kim et al ¹⁰	0.73	0.62 (0.61–0.64)
Kosaka et al ¹¹	0.95	0.63 (0.61–0.63)
Roberts et al ¹²	0.83	0.66 (0.65–0.68)
Chen et al ¹³	0.81	0.64 (0.63–0.65)
Casadei et al ¹⁴	0.66	0.64 (0.63–0.65)
Kantor et al ¹⁵	0.70	0.65 (0.63–0.66)
Mungroop et al ¹⁶	0.75	0.70 (0.68–0.71)
Petrova et al ¹⁷	0.70	0.70 (0.69–0.71)
Tabchouri et al ¹⁸	0.73	0.66 (0.65–0.68)
Huang et al ¹⁹	0.74	0.67 (0.66–0.69)
Mungroop et al ²⁰	0.75	0.70 (0.69–0.72)
Schuh et al ²¹	NA	0.68 (0.66–0.69)
Perri et al ²²	0.65	0.63 (0.62–0.65)

AUC indicates area under the receiver operating curve; FRS, fistula risk score; ISGPS, International Study Group on Pancreatic Surgery; NA, not assessed.

1.38–2.70; *P* < 0.001) as an independent predictor for POPF in the validation cohort. Postoperative pathology other than pancreatic adenocarcinoma or pancreatitis was also independently associated with POPF (OR: 1.97, 95% CI: 1.29–3.00; *P* = 0.002). Other independent risk factors for POPF were small pancreatic duct size (OR: 1.38/mm decrease, 95% CI: 1.22–1.56; *P* < 0.001), laparoscopic or robotic-assisted resection (OR: 1.60, 95% CI: 1.16–2.21; *P* = 0.004), higher BMI (OR: 1.04 per increasing kg/m², 95% CI: 1.01–1.06; *P* = 0.012), and male sex (OR: 1.34, 95% CI: 1.02–1.76; *P* = 0.034).

DISCUSSION

This study shows that 14 risk models on POPF after pancreatoduodenectomy demonstrated a moderate predictive accuracy.^{9–22} The highest discrimination at validation was found for the a-FRS, model by Petrova and colleagues and the a-FRS.^{16,17,20}

Most of the identified risk models that were developed in recent years use the same key risk factors, but with different cutoff values. This leads to confusion on which risk model should be applied in clinical practice.^{23,30} To investigate the true predictive accuracy and generalizability, external validation of risk model performance is warranted, preferably using data from multicenter cohorts.³¹ The current study showed that none of the currently published fistula risk models appear to perform well in a large, nationwide, unselected prospective patient cohort with complete enumeration, as the highest observed AUC was 0.70. This was lower than reported by the original studies and is in line with results from previous retrospective validation studies.^{23,32–36} The reduced performance is most likely explained due to predictive accuracy generally being more impressive after internal validation, as models tend to fit above average to data they were built upon.³¹

Consistent with previous studies, pancreatic texture, pancreatic duct diameter, and pathology diagnosis were strong predictors of POPF after pancreatoduodenectomy in our dataset.^{9,16,37} Soft, friable pancreatic tissue complicates construction of the pancreatic anastomosis, and is associated with increased excretion of pancreatic enzymes.³⁸ In contrast, a wider

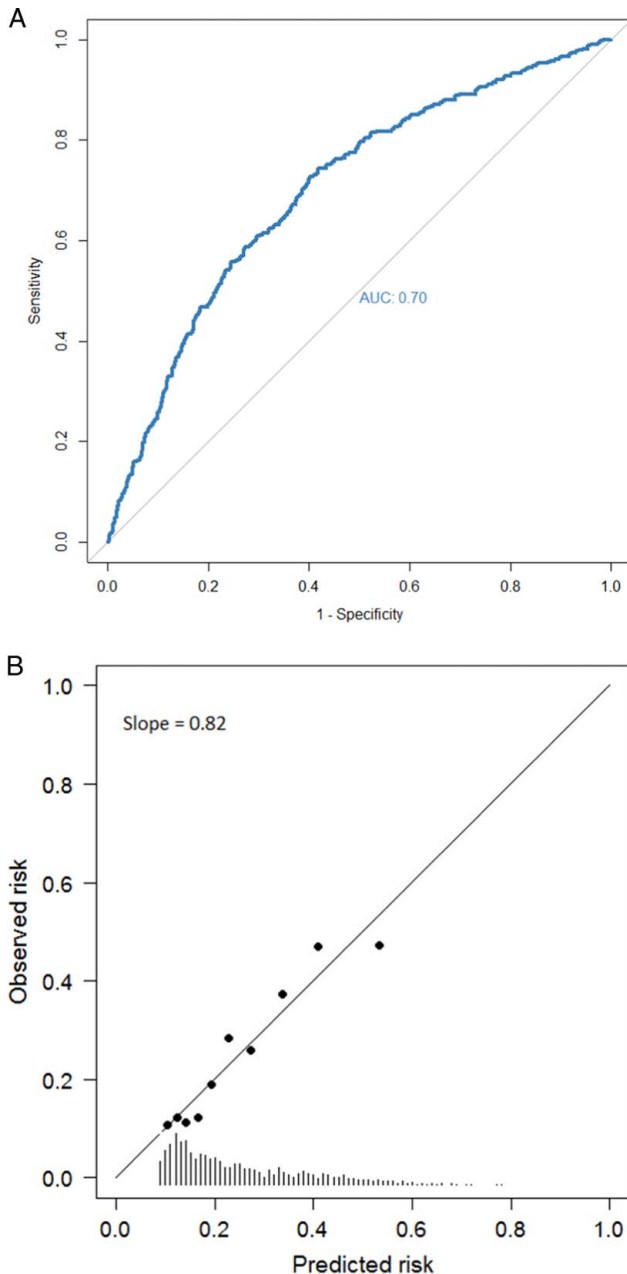


FIGURE 2. Area under the receiver operating curve plot (A) and calibration plot (B) of the updated alternative fistula risk score. AUC indicates area under the curve.

pancreatic duct and parenchymal fibrosis, which are more common in patients with pancreatic adenocarcinoma or chronic pancreatitis, allow for a less risky pancreatic anastomosis, and hence a decreased risk of POPF.³⁹ Also, minimally invasive surgery was found to be a risk factor for POPF, although its feasibility and safety have recently been demonstrated in a multicenter training program.⁴⁰ Possibly, the demonstrated relation in our study was due to its nationwide design with complete enumeration, and surgeons still being in their learning curve. The association of these risk factors with POPF after

pancreatoduodenectomy is reflected in the higher performance of risk models that incorporated these parameters.

Risk models can be used to stratify for comparison of outcomes across different populations and studies. In addition, they can be helpful in daily clinical practice to identify low-risk and high-risk patients, allowing for guidance of treatment strategies.⁴¹ However, this is only useful if a patient's risk for POPF can be determined accurately. Intensive monitoring might be indicated for high-risk patients, whereas low-risk patients may not need daily biochemical evaluation for instance. Also, early removal or omission of abdominal drains may be warranted in patients at low risk of POPF.⁴² In contrast, misclassification of these patients' risk can lead to delayed detection and treatment of POPF, which may have life-threatening consequences like severe bleeding, organ failure, and eventually death. Furthermore, delayed recovery due to major complications influences the patient's eligibility to receive or complete adjuvant chemotherapy, which is known to significantly improve survival.⁴³ In this study, only moderate predictive accuracy was found for all risk models after pancreatoduodenectomy, suggesting that clinical application of these models may result in miscalculation of patients' risks. Therefore, determining treatment strategies based on probability estimates of these risk scores might be doubtful.

Currently, there are few treatment options to prevent the occurrence and severity of POPF.^{2,44} Perioperative application of somatostatin analogs can be considered in high-risk patients.⁴⁵ Their effectiveness on preventing fistula is, however, still a point of debate.^{46,47} Total pancreatectomy, as an alternative to pancreatoduodenectomy, in patients at high risk of POPF has also been suggested.⁴⁸ Since the effectiveness of preventive measures on POPF remains controversial, new postoperative treatment strategies have emerged. Recently, the nationwide stepped-wedge cluster-randomized PORSCH trial was conducted in the Netherlands.^{24,26} In this trial, implementation of a multimodal algorithm for early recognition and minimally invasive treatment of postoperative complications after pancreatic surgery substantially reduced the incidence of the most severe complications.²⁴ In patients with POPF treated according to the algorithm, the composite endpoint of severe bleeding, organ failure, and 90-day mortality was significantly reduced (from 14% to 8%). Since these patients were more closely monitored during their postoperative course, there was an increase in CT imaging, antibiotics use and radiologic drainage procedures, irrespective of their preoperatively estimated risk of postoperative complications. Ideally, the intensity of postoperative monitoring, as suggested in the PORSCH trial, could be adjusted to the patient's individual risk of developing POPF. This may lead to more efficient health care utilization and costs reduction, while preserving the clinical impact of the algorithm. However, stratification using the currently available risk models is debatable, given the moderate performance.

An upcoming technique to develop novel prediction models is machine learning modeling using artificial intelligence.⁴⁹ Machine learning can identify latent variables deduced from known variables related to pancreatic fistula.⁵⁰ It can be a valuable addition with regard to pattern recognition, such as potential identification of yet unknown features on imaging that may influence the development of POPF.⁵¹ Models that incorporated these so-called radiomic features from preoperative CT scans have displayed good internal performance.^{52,53} Future research should investigate the use of machine learning techniques in risk assessment of POPF after pancreatic resection.

TABLE 4. Logistic Regression Analysis of Risk Factors for Predicting Postoperative Pancreatic Fistula After Pancreatoduodenectomy*

Preoperative and perioperative risk factors	Univariate			Multivariable		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Sex (male vs. female)	1.33	(1.04–1.70)	0.024	1.34	(1.02–1.76)	0.034
BMI (continuous, per increasing kg/m ²)	1.04	(1.02–1.06)	0.001	1.04	(1.01–1.06)	0.012
Neoadjuvant treatment (yes vs. no)	0.48	(0.29–0.78)	0.003	0.86	(0.50–1.48)	0.60
Diabetes (yes vs. no)	0.69	(0.51–0.93)	0.016	0.82	(0.59–1.13)	0.26
Laparoscopic or robotic-assisted resection (yes vs. no)	1.92	(1.44–2.57)	<0.001	1.60	(1.16–2.21)	0.004
Tumor origin (nonpancreas vs. pancreas)	2.53	(1.97–3.26)	<0.001	1.19	(0.82–1.72)	0.37
Perioperative blood loss (>400 mL vs. ≤400 mL)	0.94	(0.73–1.21)	0.64	1.08	(0.81–1.43)	0.60
Decreasing pancreatic duct diameter (continuous, per mm decrease and truncated at 5 mm)	1.54	(1.38–1.74)	<0.001	1.38	(1.22–1.56)	<0.001
Soft pancreatic gland texture (yes vs. no)	3.21	(2.37–4.34)	<0.001	1.93	(1.38–2.70)	<0.001
Vascular resection (yes vs. no)	0.41	(0.26–0.63)	<0.001	0.80	(0.49–1.31)	0.38
Definitive postoperative pathology (others vs. PDAC or chronic pancreatitis)	3.27	(2.47–4.34)	<0.001	1.97	(1.29–3.00)	0.002

*According to the International Study Group on Pancreatic Surgery definition (2016). Only grade B/C complications were considered.
 BMI indicates body mass index; PDAC, pancreatic ductal adenocarcinoma.
 Significant P values < 0.05 are depicted in bold.

This study has some limitations. First, we could not evaluate all published risk models identified by our literature search due to missing parameters in our database. This included the models that used intra-abdominal thickness on CT imaging, or those that used the presence of a fatty pancreas at histopathologic examination.^{54,55} Nevertheless, implementation of these scores in clinical practice can be challenging, as specialized measurements are required which can be time consuming. Second, postoperative pathology reports were used to determine the underlying disease in case of a malignancy. Preferably, risk models should be based on preoperative and perioperative factors, resulting in timely identification of high-risk patients. Suspicion of a malignancy was, however, often based on imaging results and therefore preoperative pathology was not always obtained. Besides, a recent study demonstrated that 16% of patients with presumed pancreatic cancer scheduled for pancreatic resection was misdiagnosed preoperatively as periampullary cancer, and vice versa.⁵⁶ This makes the demonstrated association between pathology and POPF possibly less usable in real-life clinical practice.

In future comprehensive analyses, exploring for novel strong predictors for POPF could be considered when designing prediction models, since the current models based on preoperative and perioperative risk factors appeared to either underperform or be impractical. It must be noted, however, that uncertainty regarding prediction will remain due to the stochastic nature of POPF.⁵⁷ Nevertheless, we found an increase of model performance in patients who were treated according to an intensive postoperative monitoring strategy (i.e., the intervention group of the PORSCH trial), irrespective of a low or high fistula rate that was reported in the original study. Therefore, combining novel risk factors within a closely monitored population might increase the predictive accuracy of newly created models, herewith potentially allowing fistula risk prediction tools to safely guide patient-tailored treatment strategies in the future.

In conclusion, external validation of published FRSs for POPF after pancreatoduodenectomy in a large prospective, nationwide patient cohort shows that all risk models perform only moderately, at best. The ability of these models to better stratify patients into low or high-risk categories to guide monitoring and preventive strategies or for comparison of results between institutions in clinical research is therefore questionable.

Consequently, we recommend clinicians to focus on early signs and timely treatment of POPF in all patients after pancreatoduodenectomy, irrespective of their predicted risk on POPF.

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