Distal Pancreatectomy Fistula Risk Score (D-FRS) development and international validation

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Distal Pancreatectomy Fistula Risk Score (D-FRS)

Development and International Validation

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Objective: To develop 2 distinct preoperative and intraoperative risk scores to predict postoperative pancreatic fistula (POPF) after distal pancreatectomy (DP) to improve preventive and mitigation strategies, respectively.

Background: POPF remains the most common complication after DP. Despite several known risk factors, an adequate risk model has not been developed yet.

Methods: Two prediction risk scores were designed using data of patients undergoing DP in 2 Italian centers (2014–2016) utilizing multivariable logistic regression. The preoperative score (calculated before surgery) aims to facilitate preventive strategies and the intraoperative score (calculated at the end of surgery) aims to facilitate mitigation strategies. Internal validation was achieved using bootstrapping. These data were pooled with data from 5 centers from the United States and the Netherlands (2007–2016) to assess discrimination and calibration in an internal-external validation procedure.

Results: Overall, 1336 patients after DP were included, of whom 291 (22%) developed POPF. The preoperative distal fistula risk score (preoperative D-FRS) included 2 variables: pancreatic neck thickness [odds ratio: 1.14; 95% confidence interval (CI): 1.11–1.17 per mm increase] and pancreatic duct diameter (OR: 1.46; 95% CI: 1.32–1.65 per mm increase). The model performed well with an area under the receiver operating characteristic curve of 0.83 (95% CI: 0.78–0.88) and 0.73 (95% CI: 0.70–0.76) upon internal-external validation. Three risk groups were identified: low risk (< 10%), intermediate risk (10%–25%), and high risk (> 25%) for POPF with 238 (18%), 684 (51%), and 414 (31%) patients, respectively. The intraoperative risk score (intraoperative D-FRS) added body mass index, pancreatic texture, and operative time as variables with an area under the receiver operating characteristic curve of 0.80 (95% CI: 0.74–0.85).

Conclusions: The preoperative and the intraoperative D-FRS are the first validated risk scores for POPF after DP and are readily available at: http://www.pancreascalculator.com. The 3 distinct risk groups allow for personalized treatment and benchmarking.

Keywords: pancreas, pancreatic cancer, distal pancreatectomy, pancreatic fistula, prediction model, postoperative complications

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Distal pancreatectomy (DP) is performed for benign, premalignant, and malignant diseases in the pancreatic body and tail. In recent decades, the mortality of DP has been reduced to below 1% to 2% in high-volume centers.[1] However, the morbidity rate after DP remains high at 35% to 50%, mainly due to postoperative pancreatic fistula (POPF), which accounts for ~50% of all complications after DP.[2–4] Consequences of POPF

after DP could include delayed gastric emptying, infected collections, sepsis, postpancreatectomy hemorrhage, and death.[5] These complications also consume healthcare resources and thereby increase costs.[6]

Previous studies have shown that patient characteristics associated with POPF after DP include body mass index (BMI), advanced age, and diabetes.[7–9] In addition, some evidence indicates that POPF could be associated with anatomic variables such as pancreatic gland texture, pancreatic thickness, duct size, and surgical variables such as level of the pancreatic transection and stump management.[10–12] Ecker et al[13] identified 7 perioperative variables independently associated with POPF in 2026 DP from 10 institutions. However, no accurate POPF risk prediction model has yet been constructed with these or other variables. As a result, currently, no prediction model for POPF after DP is available.

The importance of POPF risk stratification has clearly been demonstrated for pancreatoduodenectomy previously.[14–17] A risk score could be used to employ preventive strategies, such as tailored use of prophylactic abdominal drains and selective medication in high-risk patients.[18] However, if such a score is to be used for deciding on administering preventive therapy, for example, medication only in high-risk patients, including in randomized trials,[19] then this score should be available already before surgery. A more "classical" intraoperative risk score would contain all available variables relating to the surgery itself. Such a score could be used for benchmarking purposes and stratification in trials and clinical protocols on postoperative management (eg, placement of drains). This study aimed to develop and externally validate both a preoperative and an intraoperative risk score for POPF after DP based on predictive variables.

METHODS

The multivariable prediction model guidelines of the TRIPOD statement were followed for the design, validation, and reporting of this risk prediction model.[20] Institutional review board approval was waived for this study.

Patients

For model development, data were retrieved from a prospectively maintained database at the Unit of General and Pancreatic Surgery of The Pancreas Institute, Verona University Hospital and Department of Surgery, Poliambulanza Hospital Brescia and pooled to constitute the derivation cohort. Consecutive patients who underwent DP between January 1, 2014, and December 31, 2016, were included. These data were then pooled with that from 5 other centers for validation. Patients were included who underwent DP in 2 United States hospitals (Virginia Mason Medical Center in Seattle, Hospital of the University of Pennsylvania in Philadelphia) and 3 Dutch hospitals (Amsterdam UMC in Amsterdam, Erasmus Medical Center in Rotterdam, and Catharina Hospital in Eindhoven) from January 1, 2007, to December 31, 2016. All of these centers perform at least 20 DPs annually.

In the model derivation cohort from Italy, patients undergoing DP for benign and (pre)malignant lesions of the body and tail of the pancreas, using both open and minimally invasive procedures, were included. Laparoscopic and robot-assisted DPs were carried out as previously described by the Verona group.[21,22] The transection of the pancreas was performed with a triple row stapler reinforced with a PGA felt (NEOVEIL Endo GIA Reinforced Reload with Tri-Staple Technology 45 mm; COVIDIEN, North Haven, CT) using the purple (3 mm) or the black (4 mm) cartridge, according to the surgeon's judgment on the thickness at the pancreatic transection line. The ultrasonic scalpel (HARMONIC; Johnson & Johnson Medical, Ethicon, Tokyo, Japan) was used at the lowest vibration level during pancreatic dissection. In select circumstances, a hand-sewn pancreatic suture closure was performed when the pancreatic tissue was cut sharply without using a stapler.[23] At least 1 silicone drain was placed close to the pancreatic transection margin at the end of the DP; no selective drain policy was adopted. The drain was managed in the postoperative course according to our published institutional protocol.[24] No somatostatin analogs were used in the preoperative or postoperative course. In the validation cohort, both Endo GIA and Echelon staplers were used for pancreatic transection.

Primary Outcome

The primary outcome was clinically relevant (grade B/C) POPF according to the International Study Group of Pancreatic Surgery (ISGPS) 2016 classification.[25] The effect of the potential predictive variables on this primary endpoint was the foundation for the preoperative and intraoperative risk scores.

Definitions

The following preoperatively available variables were analyzed: age (years), sex, BMI (kg/m^2), American Society of Anesthesiologists physical status, diabetes, history of (acute/chronic) pancreatitis, neoadjuvant therapies, age-adjusted Charlson Comorbidity Index score,[26] surgical approach, pancreatic thickness, and pancreatic duct size. The pancreatic thickness and pancreatic duct size were measured on the last preoperative computed tomography or magnetic resonance imaging scan, at the level of the pancreatic neck—meaning at the level of the confluence of the splenomesenteric veins. The pancreatic thickness was measured in a straight anterior-posterior line to simulate the surgical transection plane. The pancreatic duct size was measured along its running course. See Figure 1 for illustration.

Intraoperative variables included multivisceral resections (additional resection, excluding splenectomy), vascular resection (portal vein or superior mesenteric vein), pancreatic texture (soft or nonsoft), intraoperative blood loss (mL), and operating time (minutes).

Statistical Analysis

Statistical analyses were performed using SPSS software, version 22.0 (IBM Corp., Armonk, NY) and STATA software, version 14.2 (StataCorp, College Station, TX). Continuous data were presented as median with interquartile range. Categorical variables were presented as counts and proportions. Group differences were assessed using the χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables. Analyses were stratified by center unless otherwise stated. The statistical analysis was overseen by an expert statistician (E.W.S.).

Variables found to be a value of <0.05 on univariable analysis were subjected to multivariable analysis, and a prediction model was developed using multivariable logistic regression modeling. The Akaike information criterion was used to optimize the number of covariates in the model.[27] This implies the model with the smallest difference in predictive capacity is selected if this only leads to marginal loss of predictive value compared with a more complex model. The model's discriminative ability was assessed using area under the receiver operating characteristic curve (AUC, or concordance statistic, c).[28] The goodness-of-fit was assessed using a calibration plot characterized by an intercept (ideal value: 0) and slope

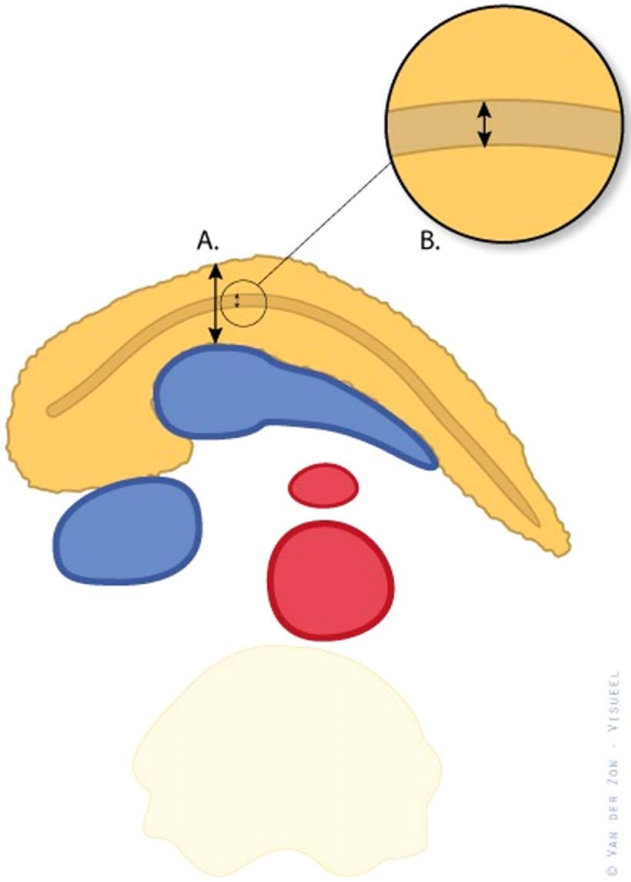

FIGURE 1. Measurement of the pancreatic neck thickness and pancreatic duct size on the preoperative computed tomography scan. Pancreatic neck thickness (line A, in the A-P direction) and pancreatic duct size (line B), both at the level of the confluence of the splenomesenteric veins. Blue structures represented the splenomesenteric confluence and the inferior cava vein. Red structures represented the superior mesenteric artery and aorta. The white structure is the lumbar vertebra.

(ideal value: 1).[29] Discrimination and calibration were assessed in an internal-external validation procedure according to current recommendations.[30] This implied that each center was left out once for validation of a model based on the data of the remaining cohorts. Smaller centers were grouped for this cross-validation procedure.[30] The preoperative model is based on the complete dataset, which we label an "internally-externally validated model." An internal-external validation design is advised to combine the strength of external validation with the strength of prediction model development on all available data. Intercept (*a*), slope (*b*), and discriminative ability (*c*) were plotted in a forest plot, with a pooled estimate obtained from a random-effects model.[30] In addition, a more "classical" intraoperative risk model was designed including intraoperative variables that have traditionally been regarded as relevant for the risk of POPF after DP. All analyses for the prediction model(s) and score were overseen by an expert statistician in risk modeling (E.W.S.).

RESULTS

Overall, 1336 patients after DP from 7 centers in 3 countries were evaluated, of whom 291 (22%) developed POPF. In the model design cohort, 339 consecutive patients underwent DP of whom 78 (23%) developed POPF. See Table 1 for baseline characteristics of all cohorts and in Table 2 for the design cohort.

Selection of Risk Factors

The univariable analysis revealed 3 preoperative and 2 intraoperative variables (Table 2) which were significantly related to the development of POPF. Multivariable analysis was performed on 5 variables.

Preoperative Distal Fistula Risk Score (D-FRS)

The preoperative D-FRS included pancreatic neck thickness [odds ratio (OR): 1.14; 95% confidence interval (CI): 1.11–1.17 per mm increase] and pancreatic duct diameter (OR: 1.46; 95% CI: 1.32–1.65 per mm increase). BMI was not a statistically significant predictive variable, $P = 0.234$, and, consequently, excluded from the final score (Table 3). The regression equation of the preoperative D-FRS is:

$$P = \frac{\exp(-4.211 + 0.388\,[\textit{pancreatic duct size}] + 0.131\,[\textit{pancreatic thickness}])}{1 + \exp(-4.211 + 0.388\,[\textit{pancreatic duct size}] + 0.131\,[\textit{pancreatic thickness}])}.$$

TABLE 1. Characteristics of the Design and External Validation Cohorts

	n (%)				
	Design Cohort (N = 339)	Dutch Cohort (N = 312)	Pennsylvania Cohort (N = 299)	Virginia Mason Cohort (N = 386)	Total
Female	199 (59)	191 (61)	183 (61)	230 (60)	803 (60)
Age [median (IQR)] (y)	61 (49–70)	61 (48–69)	62 (53–70)	61 (49–69)	61 (50–69)
BMI [median (IQR)] (kg/m^2)	25 (22–28)	25 (22–28)	27 (24–33)	27 (23–31)	26 (23–30)
ASA					
I	29 (9)	88 (28)	59 (20)	8 (2)	184 (14)
II	256 (75)	184 (59)	52 (17)	271 (70)	763 (57)
III/IV	54 (16)	39 (13)	188 (63)	107 (28)	389 (29)
Pancreas thickness [median (range)] (mm)	15 (13–20)	13 (11–16)	12 (9–16)	12 (10–15)	13 (10–17)
Pancreatic duct size [median (range)] (mm)	2 (1–10)	2 (1–13)	2 (1–6)	3 (1–16)	2 (1–16)
POPF (ISGPS grade B/C)	78 (23)	88 (28)	39 (13)	104 (27)	291 (22)

ASA indicates American Society of Anesthesiology; ISGPS, International Study Group of Pancreatic Surgery.

TABLE 2. Descriptive data of the Design Cohort

	n (%)		
	No POPF (N = 263)	**POPF (N = 78)**	***P***
Female	160 (61)	38 (51)	0.132
Age [median (IQR)] (y)	62 (61–64)	58 (56–65)	0.190
BMI [median (IQR)] (kg/m^2)	24.5 (23.6–24.9)	26.4 (25.3–26.9)	**< 0.001**
ASA	—	—	0.732
I	25 (10)	5 (6)	—
II	197 (75)	60 (77)	—
III/IV	41 (16)	13 (17)	—
History acute pancreatitis	27 (10)	5 (6)	0.280
History chronic pancreatitis	10 (4)	2 (3)	0.384
History diabetes mellitus	43 (16)	8 (10)	0.185
CCI ≥ 5	94 (36)	26 (33)	0.797
Neoadjuvant therapy	41 (16)	9 (12)	0.464
Laparoscopic approach	92 (35)	38 (49)	0.156
Pancreas thickness [median (IQR)] (mm)	15 (12–18)	20 (16–23)	**< 0.001**
Pancreatic duct size [median (IQR)] (mm)	2 (1–10)	3 (1–16)	**< 0.001**
Pancreatic length [median (IQR)] (mm)	32 (25–38)	30 (28–38)	0.283
Soft texture	181 (69)	68 (88)	**< 0.001**
EBL [median (IQR)] (mL)	150 (150–200)	200 (150–250)	0.243
OT [median (IQR)] (min)	230 (225–245)	278 (250–300)	**< 0.001**
Vascular resection	20 (8)	7 (9)	0.715

Bold values indicate statistical significance ($P < 0.05$).

ASA indicates American Society of Anesthesiology; CCI, Charlson Comorbidity Index[31]; EBL, estimated blood loss; OT, operation time.

Internal-External Validation and Preoperative Model Performance

After internal-external validation, the D-FRS still performed well with an AUC of 0.73 (0.70–0.76) (Tables 3, 4). Calibration of the model was ideal with an intercept of 0 and a slope of 1, as shown in Table 4 and Supplementary Figure 1 (Supplemental Digital Content 1, http://links.lww.com/SLA/D943). The absolute preoperative risk for POPF was assessed using the model and identified 3 risk groups: low risk (< 10%), intermediate risk (10%–25%), and high risk (> 25%) of POPF. In the entire study population, 238 (17.8%) patients had a low risk to develop POPF, 684 (51.2%) had an intermediate risk, and 414 (31.0%) had a high risk, as displayed in Table 4. The risk distribution per cohort is shown in Table 5.

Intraoperative D-FRS

The intraoperative D-FRS is shown in Table 6 and consists of pancreatic neck thickness (OR: 1.22; 95% CI:1.13–1.31 per mm increase) and pancreatic duct diameter (OR: 2.24; 95% CI: 1.52–1.2.78 per mm increase), BMI (OR: 1.11; 95% CI: 1.03–1.21 per kg/m^2 increase), soft pancreas texture (OR: 4.92; 95% CI: 1.11–21.80), and operative time (OR: 1.01; 95% CI:1.01–1.10 per min increase). The regression equation of the intraoperative model is:

$$P = \frac{\exp(-11.923 + 0.783\ [pancreatic\ \ duct\ size] + 0.199\ [pancreatic\ thickness] + 0.107\ [\mathrm{BMI}] + 1.592\ [soft\ \ pancreas\ texture] + 0.005\ [operating\ time])}{1 + \exp(-11.923 + 0.783\ [pancreatic\ duct\ size] + 0.199\ [pancreatic\ \ thickness] + 0.107\ [\mathrm{BMI}] + 1.592\ [soft\ pancreas\ texture] + 0.005\ [operating\ time])}.$$

The AUC for the intraoperative D-FRS was 0.85 (95% CI: 0.80–0.90) (Table 3). For the intraoperative D-FRS, no external validation was available since data on operative time and pancreatic texture was lacking in the majority of patients of the validation cohort.

DISCUSSION

The preoperative and intraoperative D-FRS are the first internationally validated scores to predict the risk of POPF after DP. The risk models are objective and easy to use. The D-FRS can be used to estimate both the absolute risk and determine the risk category (0% to <10%, 10%–25%, and > 25%) for POPF after DP.

Since this is the first study including risk scores for POPF after DP, these findings cannot be compared with other studies. Prospective studies should now confirm the value of both these scores. Such studies could include assessing a risk-stratified approach versus a "one size fits all" approach. Indeed, the proposal of 2 different risk scores could be justified by the difference in timing. The preoperative assessment could lead to an improvement of the preventive strategies to reduce the POPF. While the intraoperative could be used to increase the results of the mitigation strategies or for benchmarking in the postoperative setting which occur at the end of the surgical procedure or in the early postoperative days. Some may consider the intraoperative D-FRS more "reliable" since it contains the more "classical" variables as compared with the preoperative D-FRS which contains only pancreatic neck thickness and duct diameter. However, both performed almost equally well in our statistician expert-supervised internal-external validation process. Important to realize that this approach was performed to the most recent recommendations whereas many may be more familiar with the former advice of fully external validation.[32]

The 2 variables included in the preoperative D-FRS are pancreatic thickness and duct diameter. Pancreatic thickness has previously been identified as a predictor for POPF after DP.[33,34] Several studies have reported a lower risk in patients with an atrophic pancreas.[35–37] Furthermore, unsatisfactory closure of the pancreatic remnant in patients with a thicker pancreatic gland has been identified as a risk factor for POPF, especially when using staplers.[7,38] It is well known that fat and thick pancreas is more prone to rupture when compressed by a surgical stapler.[39] A graded compression technique during several

TABLE 3. D-FRS Model After Internal-External Validation

	D-FRS Model			
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
AUC (95% CI)	0.733 (0.70–0.76)		0.731 (0.70–0.76)	
BMI	1.015 (0.990–1.041)	**0.234**		
Pancreatic duct size (per mm)	1.137 (1.103–1.171)	< 0.001	1.140 (1.107–1.174)	< 0.001
Pancreatic neck thickness (per mm)	1.470 (1.317–1.641)	< 0.001	1.474 (1.321–1.645)	< 0.001

Bold values indicate statistical significance ($p < 0.05$).

TABLE 4. AUC Internal-External Validation Procedure for the D-FRS

Left Out Cohort	Design Cohort (n = 339)	Dutch Cohort (n = 312)	Pennsylvania Cohort (n = 299)	Virginia Mason Cohort (n = 386)	Total (N = 1336)
AUC (95% CI)	0.713 (0.675–0.752)	0.702 (0.662–0.743)	0.719 (0.675–0.763)	0.768 (0.729–0.806)	0.731 (0.698–0.764)
Intercept calibration plot	0.0	0.0	0.0	0.0	0.0
Slope calibration plot	1.0	1.0	1.0	1.0	1.0

Design cohort: Verona and Brescia. Dutch cohort: Amsterdam UMC, Erasmus Medical Center, and Catharina Hospital Eindhoven.

minutes has been described by Asbun and colleagues[40,41] to avoid such damage and subsequent fistula development. A wide main pancreatic duct seen on preoperative diagnostic imaging is also a known risk factor for POPF.[38,42] This could be explained by downstream outflow obstruction of the main pancreatic duct leading to increased ductal pressure and, subsequently, a higher risk of disruption of the duct at the level of transection. This study also confirmed soft pancreatic texture as a predictor for POPF after DP. However, since the pancreatic texture is not available preoperatively, it cannot be used to predict the risk of POPF before surgery.

The preoperative D-FRS could be used for the assessment of several prevention strategies in high-risk patients. As for prevention strategies, a preoperative decrease of Sphincter of Oddi pressure by endoscopic injection of botulinum toxin (BOTOX) could potentially decrease intraductal pressure, similar to preoperative stenting of the pancreatic duct, but without the associated risks of endoscopic retrograde cholangiopancreatography and infectious complications.[43] In addition, novel somatostatin analogs have been associated in a randomized controlled trial with a significant reduction of POPF incidence and therefore could be applied to high-risk patients preoperatively.[19,44,45] However, other authors have argued against the administration of somatostatin analogs in pancreatic surgery, particularly Pasireotide, as it is not widely available, and its efficacy has not been universally recapitulated.[46] Perioperative hydrocortisone decreases inflammation and edema in the pancreatic tissue which lowers the pressure in the pancreatic duct and might prevent the formation of a fistula. This was confirmed by a randomized trial where hydrocortisone was applied as an intervention, given in 9 doses every 8 hours after DP.[19] The preoperative stratification of fistula risk can further improve the future trial design by stratification and prospective studies examining prophylactic invasive procedures or costly medications that purportedly might decrease fistula development.[44,45]

The intraoperative D-FRS might form a basis of performance assessment as well.[31] The proposed score could be used to plan prospective studies of risk-stratified, selective drain placement, and management regarding other mitigation strategies, including the optimal application of various transection techniques, sealants, or tissue patches. The intraoperative model could be used to compare data between published series, objectify the results of various surgical techniques, and provide risk-adjusted comparisons of surgical and postoperative outcomes.[31] Knowing the risk of fistula development may also offer an opportunity for tailored postoperative management (eg, lower threshold for imaging, early drain removal, or delayed discharge).[47,48] Both the preoperative and intraoperative D-FRS are readily available via the online calculator (http://www.pancreascalculator.com).

The results of this study have to be interpreted in light of some limitations. First, some may consider the need for radiological measurement of the pancreatic neck thickness (in the A-P direction) and duct size (perpendicular to the pancreatic duct) a limitation of this study. However, with the current widespread availability of "picture archiving and communication systems" (PACS) with integrated tools to measure distances, these variables are easily determined, even by nonradiologists. Second, this model has not been externally validated outside of Europe and the United States. Using the online calculator, however, such validation is easily done. Third, intraoperative differences in pancreatic transection and stump management between centers will have introduced clinical heterogeneity. However, recent randomized trials found no differences in the rate of POPF after DP based on the methods of transection and stump management.[49–51] Fourth, the model works only if POPF events actually occur. The prediction and risk stratification of the POPF might be suboptimal or less relevant in practices with an extremely low POPF rate (eg <10%). Fifth, some may consider the need for 2 different scores a limitation. However, this approach stems from the different timing of interventions. The preoperative assessment could lead to an improvement of the preventive strategies to reduce the POPF. While the intraoperative assessment could be used to increase the results of the mitigation strategies or for benchmarking in the postoperative setting which occurs at the end of the surgical procedure or in the early postoperative days. The use of the models should be calibrated on the timing of the intervention. Clearly, further studies are needed to confirm this hypothesis, especially regarding diverging outcomes.

Strengths of this study include the development of 2 distinct models with different potential applications of their risk

TABLE 5. Risk Distribution Per Cohort

	n (%)					
	Total (N = 1336)	Design Cohort D-FRS (n = 339)	Design Cohort Intraoperative D-FRS (n = 339)	Dutch Cohort (n = 312)	Pennsylvania Cohort (n = 299)	Virginia Mason Cohort (n = 386)
Low risk (< 10%)	238 (18)	37 (11)	114 (34)	76 (24)	94 (31)	31 (8)
Intermediate risk (10%–25%)	684 (51)	158 (47)	115 (34)	153 (49)	152 (51)	221 (57)
High risk (> 25%)	414 (31)	144 (42)	109 (32)	83 (27)	53 (18)	134 (35)

Design cohort: Verona and Brescia. Dutch cohort: Amsterdam UMC, Erasmus Medical Center, and Catharina Hospital Eindhoven.

TABLE 6. Intraoperative D-FRS Design Cohort

	Intraoperative D-FRS	
	OR (95% CI)	*P*
AUC (95% CI)	0.851 (0.80–0.90)	
Pancreatic duct size (per mm)	2.244 (1.523–2.779)	< 0.001
Pancreatic neck thickness (per mm)	1.217 (1.133–1.307)	< 0.001
BMI (per kg/m^2)	1.113 (1.026–1.206)	0.009
Soft pancreas texture	4.915 (1.108–21.800)	0.036
Operating time (per min)	1.005 (1.000–1.009)	0.036

stratification, similarly to what previously has been done for pancreatoduodenectomy.[14,15] The prediction of the occurrence of POPF after DP is challenging due to the multifactorial nature of this event.[13] Although the proposed D-FRS score is internally-externally validated, future studies should be performed to confirm the applicability of this model and the impact on surgical outcomes and cost-effectiveness of different fistula prevention and mitigation strategies.

CONCLUSIONS

The proposed preoperative D-FRS and intraoperative D-FRS are the first international, validated risk scores for the risk of POPF after DP. The proposal of 2 different risk scores could be justified by the different timing approach, improving the prevention and mitigation strategies of the reduction of POPF. The segregation of 3 distinct risk groups may facilitate personalized and optimized treatment. Further independent and prospective validation is warranted to prove their predictive accuracy.

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