Fistula risk score for auditing pancreatoduodenectomy: the auditing-FRS

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Fistula Risk Score for Auditing Pancreatoduodenectomy

The Auditing-FRS

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Objective: To develop a fistula risk score for auditing, to be able to compare postoperative pancreatic fistula (POPF) after pancreatoduodenectomy among hospitals.

Background: For proper comparisons of outcomes in surgical audits, case-mix variation should be accounted for.

Methods: This study included consecutive patients after pancreatoduodenectomy from the mandatory nationwide Dutch Pancreatic Cancer Audit. Derivation of the score was performed with the data from 2014 to 2018 and validation with 2019 to 2020 data. The primary endpoint of the study was POPF (grade B or C). Multivariable logistic regression analysis was performed for case-mix adjustment of known risk factors.

Results: In the derivation cohort, 3271 patients were included, of whom 479 (14.6%) developed POPF. Male sex [odds ratio (OR) = 1.34; 95% confidence interval (CI): 1.09–1.66], higher body mass index (OR = 1.07; 95% CI: 1.05–1.10), a final diagnosis other than pancreatic ductal adenocarcinoma/pancreatitis (OR = 2.41; 95% CI: 1.90–3.06), and a smaller duct diameter (OR = 1.43/mm decrease; 95% CI: 1.32–1.55) were independently associated with POPF. Diabetes mellitus (OR = 0.73; 95% CI: 0.55–0.98) was independently associated with a decreased risk of POPF. Model discrimination was good with a *C*-statistic of 0.73 in the derivation cohort and 0.75 in the validation cohort (n = 913). Hospitals differed in particular in the proportion of pancreatic ductal adenocarcinoma/pancreatitis patients, ranging from 36.0% to 58.1%. The observed POPF risk per center ranged from 2.9% to 25.4%. The expected POPF rate based on the 5 risk factors ranged from 11.6% to 18.0% among hospitals.

Conclusions: The auditing fistula risk score was successful in case-mix adjustment and enables fair comparisons of POPF rates among hospitals.

Keywords: pancreatoduodenectomy, pancreatic fistula, fistula risk score, prediction model, complication

(*Ann Surg* 2023;278:e272–e277)

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The authors report no conflicts of interest.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.

ISSN: 0003-4932/23/27802-e272
DOI: 10.1097/SLA.0000000000005532

Surgical registries have been established to monitor and improve outcomes after pancreatic surgery among hospitals.[1,2] The Dutch Pancreatic Cancer Audit (DPCA) is a mandatory nationwide prospective registry including all Dutch hospitals performing pancreatic resections.[3] An important surgical outcome after pancreatoduodenectomy (PD) is postoperative pancreatic fistula (POPF). POPF is associated with increased length of stay, health care utilization costs, and mortality.[4]

A proper comparison of registry-based outcomes across hospitals requires adjustment for differences in patient and tumor characteristics. A diagnosis other than pancreatic ductal adenocarcinoma (PDAC) or chronic pancreatitis, and higher body mass index (BMI) are examples of known risk factors for POPF.[5–7] These risk factors should be taken into account

because their prevalence differs across hospitals. This applies to median BMI, which is higher in some hospitals in the United States compared with most hospitals in Asia. Referral patterns within a country may lead to differences in diagnosis for which a PD is performed; pancreatic neuroendocrine tumors are frequently centralized in neuroendocrine expert centers.

Several fistula risk scores (FRS) have been developed and validated.[6–15] However, these FRS are less suitable for auditing purposes since unverifiable and subjective factors such as pancreatic texture are included.[6–8,12–15] Inexperienced surgeons would have an excellent *adjusted* POPF rate and rank high in an audit, by classifying every pancreas as soft. Moreover, some FRS include factors that are by themselves a surgical quality indicator, such as intraoperative blood loss.[16] Surgeons with high blood loss would have an excellent *adjusted* POPF rate and rank high in an audit, because of the high blood loss. Existing FRS are particularly useful for intraoperative assessment of the risk of POPF, for example, to determine drain management or the use of somatostatin analogs. They are less suitable for auditing. This study aimed to develop an auditing-FRS for case-mix adjustment after PD.

METHODS

The study protocol has been discussed and approved at the scientific meeting of the Dutch Pancreatic Cancer Group before initiation of the study.[17] This study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18]

Study Design

This study was an observational, retrospective analysis of the DPCA including all consecutive pancreatoduodenectomies from pancreatic surgery centers in The Netherlands from January 2014 to December 2020. The cohort was divided in a derivation cohort (2014–2018) and validation cohort (2019–2020). The DPCA is a mandatory, prospective registry for all pancreatic surgery centers in The Netherlands. All participating centers perform a minimum of 20 pancreatoduodenectomies annually.[19] The validation cohort included 2 centers fewer due to the further centralization of pancreatic surgery care in The Netherlands. Patients were excluded if they underwent a total or subtotal pancreatectomy without a pancreaticoenteric anastomosis, or if the primary outcome was not registered. Patients were also excluded if they were enrolled in the intervention arm of the PORSCH trial because of the influence on the incidence of grade B/C POPF due to the nature of the study.[20] From February 2018 to December 2019 all Dutch pancreatic cancer centers participated in the nationwide stepped-wedge randomized controlled PORSCH trial. The PORSCH trial investigated the effect of early postoperative intervention in case of suspicion of POPF on severe morbidity and mortality (NCT03400280).

Extracted Data and Definitions

For this study, we only considered unambiguous patient and tumor characteristics. Parameters that were not verifiable (eg, pancreatic texture), were not considered for the auditing-FRS. Also, surrogate outcomes related to surgical quality were not included (ie, intraoperative blood loss). Diabetes mellitus was defined as dysregulation of blood glucose levels requiring oral medication or insulin.

The primary endpoint was grade B/C POPF as defined by the International Study Group for Pancreatic Fistula Study Group,[21] which is a compulsory registration item in the DPCA. Other complications included postpancreatectomy hemorrhage,[22] delayed gastric emptying,[23] bile leakage,[24] and major complications ($\geq$ grade 3a according to Clavien-Dindo).[25]

Statistical Analysis

Continuous variables were presented using mean with SD or median with interquartile range, depending on the distribution. Categorical variables were presented as count, with the corresponding percentage. For univariable analysis, continuous variables were compared using t test (parametric) or Wilcoxon rank-sum test (nonparametric). Categorical variables were compared using the Fisher exact test. Violin plots were constructed to display the (interquartile) range, median, and density of proportions of baseline characteristics across centers.[26]

A logistic regression derivation model was constructed based on patients who underwent PD from January 2014 to December 2018. Linearity assumption was checked for continuous variables. Variables with a P value <0.2 in univariable analysis were included in the multivariable analysis, and the variables significant at P value < 0.05 were retained in the final multivariable model. Model performance was assessed using the area under the receiver operating characteristics curve (AUC) and calibration plots. The model was validated in a subsequent cohort of patients who underwent PD from January 2019 to December 2020. This was done according to a previously published guideline.[27]

Case-mix adjusted analysis was performed using the auditing-FRS for each center to calculate an observed-versus-expected (O-E) POPF rate. A funnel plot was constructed to visualize the O-E POPF rate for each center.[28]

P values <0.05 were considered statistically significant. All statistical analyses were performed using R statistical software (version 4.0.4). Missing values were imputed with multiple imputation using the *mice* package.

RESULTS

Patients

In total, 3271 patients who underwent a PD were included in the derivation cohort. Baseline characteristics are presented in Table 1. The median age was 68 years (interquartile range: 60–74 years) and 55.7% were male. The final diagnosis showed PDAC or chronic pancreatitis in 1503 patients (46.4%). The validation cohort included 913 patients who underwent PD.

The variation of baseline characteristics among centers in the derivation cohort is presented in Supplementary Figure 1 (Supplemental Digital Content 1, http://links.lww.com/SLA/D887). Large variation exists among the centers in patients' baseline characteristics. For example, the proportion of patients per center with BMI >30 kg/m^2 ranged from 12.5% to 40.0% and the proportion of a final diagnosis of PDAC/chronic pancreatitis ranged from 36.0% to 58.1%.

Outcomes

Surgical outcomes in the derivation cohort are displayed in Supplementary Table 1 (Supplemental Digital Content 2, http://links.lww.com/SLA/D888). After PD, 479 patients (14.6%) developed POPF. The proportion of POPF ranged from 2.9% to 24.6% across the centers. Major complications occurred in 1029 patients (31.5%) and in-hospital mortality was 3.6%.

Patients who developed POPF had a higher risk of major complications (83.9% vs 22.5%; $P < 0.001$) and mortality (8.6%

TABLE 1. Baseline Characteristics of the Derivation and Validation Cohorts

Characteristics	n (%) Derivation Cohort* (N = 3271)	Validation Cohort† (N = 913)
Age [median (IQR)] (y)	68.0 (60.0–74.0)	69.0 (61.0–75.0)
Sex		
Female	1450 (44)	393 (43)
Male	1821 (56)	520 (57)
ASA status		
ASA 1–2	2473 (77)	559 (63)
ASA 3–4	758 (23)	332 (37)
BMI [median (IQR)]	24.7 (22.5–27.5)	24.8 (22.4–27.7)
Diabetes mellitus	642 (20)	197 (22)
Final pathology		
PDAC/pancreatitis	1503 (46)	416 (46)
Other	1737 (54)	495 (54)
Pancreatic duct diameter [median (IQR)]	4.0 (2.0–6.0)	3.0 (2.0–5.0)

*Missing data: ASA status in 40 patients (1.2%), BMI in 133 patients (4.1%), final pathology in 31 patients (0.9%), and pancreatic duct diameter in 1241 patients (37.9%).

†Missing data: ASA status in 22 patients (2.4%), BMI in 8 patients (0.9%), final pathology in 2 patients (0.2%), and pancreatic duct diameter in 111 patients (12.2%).

ASA indicates American Society of Anesthesiologists; IQR, interquartile range

vs 2.8%; $P < 0.001$). In addition, other pancreas surgery-specific complications occurred more frequently in patients who developed POPF, such as postpancreatectomy hemorrhage (22.6% vs 5.8%; $P < 0.001$), bile leak (12.7% vs 4.1%; $P < 0.001$) and delayed gastric emptying (46.4% vs 14.6%; $P < 0.001$), as well as reoperation (22.9% vs 6.4%; $P < 0.001$). Length of hospital stay was increased in patients with POPF (11 vs 24 days; $P < 0.001$) as well as readmission within 30 days (30.7% vs 15.3%; $P < 0.001$).

Univariable Logistic Regression in the Derivation Cohort

Univariate risk factors for POPF were male sex [odds ratio (OR) = 1.25; 95% confidence interval (CI): 1.03–1.52], increased BMI (OR = 1.09/1 kg/m^2 increase; 95% CI: 1.07–1.11), smaller pancreatic duct diameter (OR = 1.55/mm decrease starting at ≥ 5 mm, 95% CI: 1.44–1.68; starting at 5 mm), and a final diagnosis other than PDAC or pancreatitis (OR = 3.26; 95% CI: 2.61–4.08) (Table 2). Diabetes mellitus (OR = 0.72; 95% CI: 0.55–0.93) was associated with a decreased risk of POPF.

Multivariable Logistic Regression in the Derivation Cohort

Male sex (OR = 1.34; 95% CI: 1.09–1.66), higher BMI (OR = 1.07; 95% CI: 1.05–1.10), a final diagnosis other than PDAC/pancreatitis (OR = 2.41; 95% CI: 1.90–3.06), and a smaller duct diameter (OR = 1.43/mm decrease starting at ≥ 5 mm, 95% CI: 1.32–1.55) were independently associated with POPF. Diabetes mellitus (OR = 0.73; 95% CI: 0.55–0.98) was associated with a decreased risk (Table 2). The equation for the auditing-FRS including these independent risk factors is found in Supplementary Table 2 (Supplemental Digital Content 3, http://links.lww.com/SLA/D889). A web-based calculator is available at: http://www.pancreascalculator.nl.

Validation

The model showed good discrimination with an AUC of 0.73 in the derivation cohort. Model calibration was good with a slope of 0.986 (Fig. 1A). In the validation cohort, discrimination was also good with an AUC of 0.75. With a slope of 1.20, risk estimates were a bit underestimated in the validation cohort (Fig. 1B).

Funnel Plot

The observed POPF rate per center ranged from 2.9% to 25.4%. The funnel plot of the O:E ratio for POPF is displayed in Figure 2. The expected POPF rate ranged from 11.6% to 18.0%. Three hospitals performed better and 1 worse than expected. The funnel plot in the validation data is displayed in Supplementary Figure 2 (Supplemental Digital Content 4, http://links.lww.com/SLA/D890).

DISCUSSION

The auditing-FRS was developed to predict POPF based on >3000 patients who underwent a PD and were prospectively registered in the Dutch Pancreatic Cancer Audit. It includes only risk factors that are unambiguous and verifiable; male sex, high BMI, final diagnosis other than PDAC or chronic pancreatitis,

TABLE 2. Univariable and Multivariable Logistic Regression in the Derivation Cohort for Predicting POPF (N = 3271)

Characteristics	Univariable OR	95% CI	*P*	Multivariable OR	95% CI	*P*
Age per decade	0.99	0.90–1.09	0.865			
Sex						
Female	—	—	—	—		
Male	1.25	1.03–1.52	0.026	1.34	1.09–1.66	0.006
ASA status						
1–2	—	—	—	—		
3–4	1.12	0.89–1.41	0.317			
BMI (per kg/m^2 increase)	1.09	1.07–1.11	< 0.001	1.07	1.05–1.10	< 0.001
Diabetes mellitus	0.72	0.55–0.93	0.013	0.73	0.55–0.98	0.033
Final pathology						
PDAC/pancreatitis	—	—	—	—		
Other	3.26	2.61–4.08	< 0.001	2.41	1.90–3.06	< 0.001
Pancreatic duct diameter*	1.55	1.44–1.68	< 0.001	1.43	1.32–1.55	< 0.001

*Pancreatic duct diameter per diameter decrease starting at a diameter ≥ 5 mm. Up to 5 mm the diameter of the pancreatic duct was inversely linear to the log odds of POPF, after 5 mm the log odds were stable.

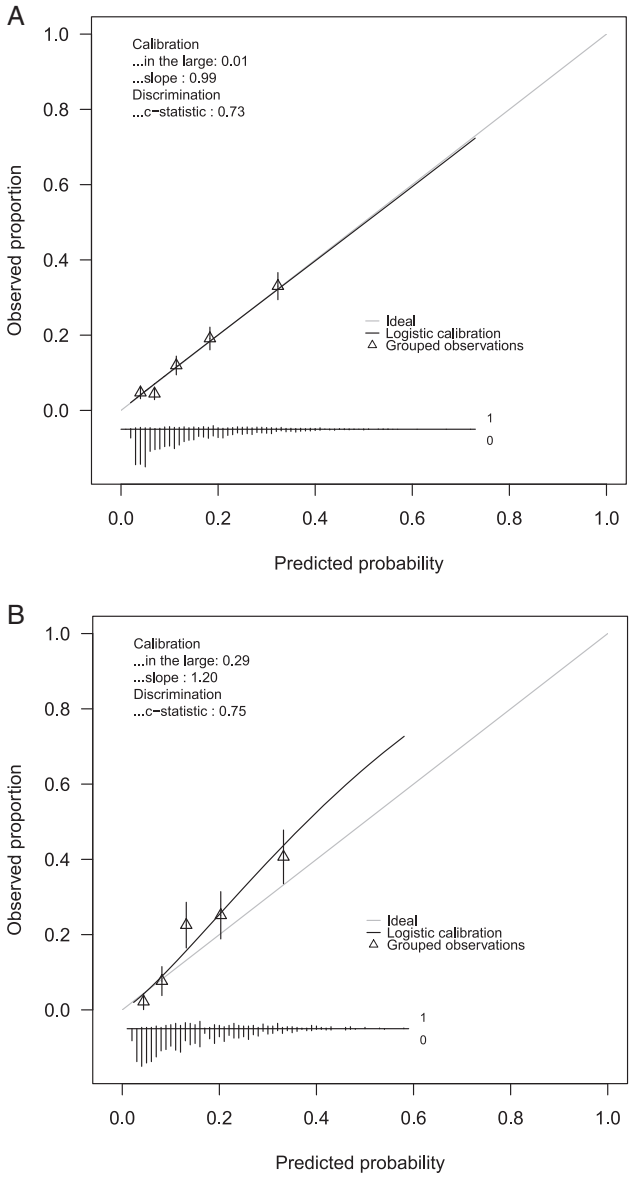

FIGURE 1. A, Calibration plot of the auditing-FRS model of derivation cohort (n = 3271). B, Calibration plot of the auditing-FRS model of validation cohort (n = 913).

small pancreatic duct diameter, and absence of diabetes mellitus in the past medical history. This model can be used to adjust for case-mix and allow for proper comparison of POPF rates across hospitals and surgeons. The auditing-FRS had an acceptable discriminatory value in both the derivation and validation cohorts (AUC: 0.73 and 0.75, respectively).

Several FRS's have been developed to identify patients with an increased risk of POPF (Table 3).[6,7,13,14] These FRS were developed to guide early intraoperative or postoperative interventions, such as the intraoperative placement of drains or postoperative administration of somatostatin analogs. A study of McMillan and colleagues found that the POPF risk varied considerably across hospitals and surgeons. They applied the original FRS to compare risk-adjusted performance.[29] The auditing-FRS has some advantages when comparing the POPF

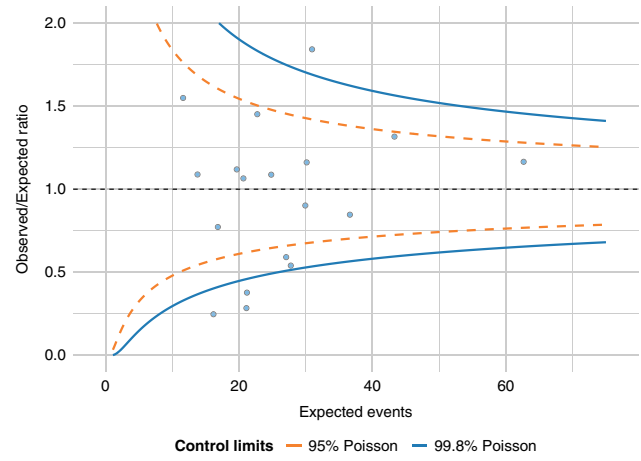

FIGURE 2. Funnel plot of POPF after PD in the derivation cohort.

rate across hospitals. The auditing-FRS is the only FRS that does not include pancreatic texture, which is ambiguous and unverifiable. Moreover, the auditing-FRS does not include blood loss, which is a surgical quality indicator itself. A surgeon with higher-than-average blood loss and a POPF rate of 20%, may see his or her *adjusted* POPF rate drop below 10% when using the original FRS, because of the high blood loss. The high blood loss may be entirely explained by lack of training or experience, but the original FRS will attribute the high POPF rate entirely to the difficulty of the procedure rather than the surgeon's inexperience. The discriminatory value of the auditing-FRS was comparable to the other FRS. External validation of the original FRS found discriminatory values (AUC: 0.62–0.72) that are comparable to the auditing-FRS.[6,10,11]

All factors included in the auditing-FRS are well-known risk factors for POPF. First, high BMI may result in more POPF through a more fatty, soft pancreas that is more prone to leakage.[30,31] Second, diabetes mellitus and PDAC/chronic pancreatitis are associated with a more fibrotic pancreas.[32] The final diagnosis is typically only available about 1 week after surgery. A recent study found that in about 16% of patients, the final diagnosis differs from the preoperative diagnosis.[33] In particular, distal cholangiocarcinoma and PDAC are frequently misclassified. While this is a drawback to inform intraoperative and immediate postoperative decisions (eg, drain placement and somatostatin analogs), the final diagnosis is an appropriate risk factor for auditing, because it is verifiable. Third, a smaller pancreatic duct diameter increases the technical difficulty of the pancreatic-enteric anastomosis and the risk of POPF. Previous studies demonstrated the relationship between duct diameter and the log odds of POPF to be inversely linear up to a diameter of 5 mm, which was also found in the present dataset.[6,34] Therefore, it was added as a continuous variable in the auditing-FRS with a cutoff at 5 mm. The diameter of the pancreatic duct should be measured on preoperative imaging at the neck of the pancreas on an axial slide. The measurement of the diameter of the pancreatic duct is also verifiable, and therefore could be included in the model.

To allow for comparisons across hospitals the concept of benchmarking has been under increasing interest over the last years. Benchmark criteria and outcomes have been developed for PD in low-risk patients.[35–37] Differences across hospitals, however, are probably more pronounced for high-risk patients. In addition, the proportion of benchmark cases varies considerably

TABLE 3. Overview of Previously Published FRS

	Original FRS[7]	Alternative FRS[6]	Updated Alternative FRS[14]	NSQIP FRS[13]	Auditing-FRS (This Study)
Soft/normal pancreatic texture	x	x	x	x	
Diameter pancreatic duct	x	x	x	x	x
Blood loss	x				
BMI		x	x	x	x
High-risk pathology*	x				x
Male sex			x	x	x
Diabetes mellitus					x
Preoperative total bilirubin				x	
AUC	Derivation: 0.94 External validation: —	Derivation: 0.75 External validation: 0.72	Derivation: 0.76 External validation: 0.76	Derivation: 0.70 External validation: 0.62	Derivation: 0.73 External validation: 0.75
POPF definition	2005 ISGPF definition	2016 ISGPF definition	2016 ISGPF definition	2005 ISGPF definition	2016 ISGPF definition
Clinical use	Intraoperative/postoperative† decision-making	Intraoperative/postoperative decision-making	Intraoperative/postoperative decision-making	Intra Intraoperative/postoperative decision-making	Auditing

*High-risk pathology is defined as any other pathological diagnosis than pancreatic cancer or chronic pancreatitis.
†Intraoperative decision-making not possible if pathology only known after postoperative assessment of the resected specimen by the pathologist.
x signifies the presence of the variables in the different fistula risk scores listed in the columns.
ISGPS indicates International Study. Group on Pancreatic Surgery; NSQIP, National Surgical Quality Improvement Program.

across centers.[35] The auditing-FRS allows for comparison of hospitals, adjusted for case-mix.

Dutch hospitals differed in case-mix factors, which resulted in substantial differences between observed and expected POPF proportions. The observed variation in the proportion of POPF across centers ranged from 2.9% to 24.6%. After adjustment for case-mix with the auditing-FRS, the expected variation found a narrower range from 11.6% to 18.0%. Case-mix factors differed across centers because of referral patterns, patient selection for surgery, and random chance. Adjustment for case-mix reduced the variation of the proportion of POPF across centers. Thus, case-mix explained some of the variation in the risk of POPF across Dutch pancreatic surgery centers.

The present study includes a large cohort with high-quality data from a nationwide surgical audit.[3] This study has several limitations. The data in the DPCA were self-reported by each center. Centers may differ in their interpretation of the POPF definition and in the measurement of some of the risk factors (eg, pancreatic ductal diameter). However, a previous study of data verification showed excellent consistency (97.2%) between the self-reported and the validated data.[3] Moreover, centers may differ in other risk factors that were not accounted for in the auditing-FRS. Strong risk factors may not end up in risk scores if they are rare. Furthermore, hospitals with a low volume had an imprecise estimate of the expected proportion of POPF as reflected by the wide confidence intervals in Figure 2. It remains uncertain whether clinically relevant differences in POPF rate are due to differences in the quality of care, for example, the local policy regarding fluid collections nearby the pancreatic-enteric anastomosis (wait-and-see attitude or early drainage), or due to chance. Finally, this model should be externally validated using a geographical validation cohort [eg, National Surgical Quality Improvement Program (NSQIP) or Swedish National Pancreatic and Periampullary Registry]. Since local (post)operative practice might differ and could influence the generalizability of the model.

In conclusion, the auditing-FRS including sex, BMI, final diagnosis, pancreatic duct diameter, and diabetes mellitus, allows for objective case-mix adjustment after PD.

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