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BRIEF REPORT

Nationwide validation of the distal fistula risk score (D-FRS)

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Abstract

Purpose Distal pancreatectomy (DP) is associated with a high complication rate of 30–50% with postoperative pancreatic fistula (POPF) as a dominant contributor. Adequate risk estimation for POPF enables surgeons to use a tailor-made approach. Assessment of the risk of POPF prior to DP can lead to the application of preventive strategies. The current study aims to validate the recently published preoperative and intraoperative distal fistula risk score (D-FRS) in a nationwide cohort.

Methods This nationwide retrospective Dutch cohort study included all patients after DP for any indication, all of whom were registered in the Dutch Pancreatic Cancer Audit (DPCA) database between 2013 and 2021. The D-FRS was validated by filling in the probability equations with data from this cohort. The predictive capacity of the models was represented by an area under the receiver operating characteristic (AUROC) curve.

Results A total of 896 patients underwent DP of which 152 (17%) developed POPF of whom 144 grade B (95%) and 8 grade C (5%). The preoperative D-FRS, consisting of the variables pancreatic neck thickness and pancreatic duct diameter, showed an AUROC of 0.73 (95%CI 0.68–0.78). The intraoperative D-FRS, comprising pancreatic neck, duct diameter, BMI, operating time, and soft pancreatic aspect, showed an AUROC of 0.69 (95%CI 0.64–0.74).

Conclusion The current study is the first nationwide validation of the preoperative and intraoperative D-FRS showing acceptable distinguishing capacity for only the preoperative D-FRS for POPF. Therefore, the preoperative score could improve prevention and mitigation strategies such as drain management, which is currently investigated in the multicenter PANDORINA trial.

Keywords Distal fistula risk score · Distal pancreatectomy · Postoperative pancreatic fistula

Introduction

Distal pancreatectomy (DP) is associated with a high complication rate of 30–50% with postoperative pancreatic fistula (POPF) as a dominant contributor, which can also have other severe consequences [1]. Risk factors for POPF after DP include high BMI, low serum albumin level, soft pancreatic texture, prolonged operating time, and excess blood loss [2, 3]. Over the past decades, fistula risk scores (FRS) have only been available for patients undergoing pancreatoduodenectomy [4–6]. Recently, the first three risk models for POPF after distal pancreatectomy have become available. First, the preoperative distal fistula risk score (D-FRS) includes pancreatic duct and pancreatic neck diameter as variables [7]. Second, the intraoperative D-FRS also incorporated BMI, pancreatic texture, and operating time [7]. Third, the DISPAIR FRS included pancreatic transection site (neck versus body/tail), pancreatic thickness at transection site, and presence of diabetes [8]. This third model is left out of the current study since it requires postoperative imaging, operation notes, and pathologist's reports to determine the actual transection site and hence is actually considered a postoperative model [8].

Adequate risk estimation enables surgeons to use a tailor-made approach. Assessment of the risk of POPF prior to DP can lead to the application of preventive strategies such as

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preoperative endoscopic stent placement in the main pancreatic duct or injection of botulinum toxin, application of a polyglycolic acid mesh at the pancreatic remnant, and the perioperative use of somatostatin analogs or hydrocortisone [9–12]. Intraoperative risk estimation could lead to the use of mitigation strategies such as tailored use of abdominal drains or for benchmarking in the postoperative setting to improve outcomes [13, 14].

Studies validating preoperative and intraoperative D-FRS in a nationwide cohort are currently lacking [7].

Methods (Appendix)

This nationwide retrospective Dutch cohort study included all patients after DP for any indication, all of whom were registered in the Dutch Pancreatic Cancer Audit (DPCA) database between 2013 and 2021 with an available CT scan for assessment. In addition to the data from the DPCA, preoperative imaging was assessed to obtain information regarding the variables pancreatic neck thickness and pancreatic duct size and both variables were measured ventral to the confluence of the splenomesenteric veins by a trained observer, which were randomly checked afterwards. Given the observational character of this study, ethical approval was waived by the Medical Ethical Committee of Amsterdam UMC. The study protocol was approved by the scientific committee of the Dutch Pancreatic Cancer Group. The D-FRS was validated by filling in the probability equations with data from this cohort.

The predictive capacity of the models was represented by an area under the receiver operating characteristic (AUROC) curve. The goodness-of-fit was assessed using a calibration plot characterized by an intercept (ideal value, 0) and slope (ideal value, 1) [15, 16].

Results

Baseline characteristics

During the study period, a total of 1113 patients underwent DP in one of the 15 centers in the Netherlands. A total of 217 patients were excluded because the preoperative scan was not available for assessment. Of these 896 patients, 152 (17%) developed POPF of whom 144 grade B (95%) and 8 grade C (5%). Baseline characteristics and perioperative details of all patients are shown in Table S1. Table 1 summarizes the characteristics per group (POPF vs no POPF). In the POPF group,

Table 1 Preoperative and intraoperative characteristics, no POPF vs POPF group

	No POPF ($n = 744$)	POPF ($n = 152$)	p-value
Female, $n°$ (%)	405 (55.3)	79 (52.3)	0.510
Age, year, median (IQR)	65 (55–72)	64 (50–70)	0.078
ASA > 2, $n°$ (%)	202 (28)	48 (31.6)	0.378
BMI, kg/m^2, median (IQR)	25.5 (22.9–28.7)	26.2 (23.3–29.4)	0.478
History of diabetes mellitus, $n°$ (%)	178 (23.9)	24 (15.8)	**0.030**
History of pancreatitis, $n°$ (%)	111 (15.1)	19 (12.5)	0.417
Neoadjuvant therapy, $n°$ (%)	59 (8.1)	7 (4.8)	0.167
Preoperative diagnosis, $n°$ (%)			0.626
PDAC	313 (44.3)	47 (32.6)	**0.011**
PNET	101 (14.3)	41 (28.5)	**<0.001**
IPMN	136 (19.2)	27 (18.8)	0.880
MCN	71 (10)	19 (13.2)	0.271
Pancreatitis	36 (5.1)	4 (2.8)	0.417
Pancreatic neck thickness in mm, median (IQR)	12 (9–16)	15 (12–19)	**<0.001**
Pancreatic duct size in mm, median (IQR)	2 (1–2)	3 (3–4)	**<0.001**
Minimally invasive, $n°$ (%)	351 (48.5)	106 (70.2)	**<0.001**
Soft texture, $n°$ (%)	345 (46.4)	78 (51.3)	0.266
EBL in mL median (IQR)	300 (100–800)	300 (100–500)	**0.040**
OT in min median (IQR)	220 (159-300)	207 (150-278)	0.058
Venous resection, $n°$ (%)	40 (5.4)	2 (1.3)	**0.045**
Splenectomy, $n°$ (%)	456 (61.3)	87 (57.2)	0.352
Somatostatin analog, $n°$ (%)	318 (42.7)	64 (42.1)	0.885

BMI body mass index, *ASA* American Society of Anesthesiology, *OT* operation time, *EBL* estimated blood loss

Percentages may not add up due to rounding and missing data. p-value of <0.05 is considered as statistically significant

Table 2 Validation of the preoperative and intraoperative D-FRS

	Preoperative	Intraoperative
Area under curve (AUC [95%CI])	0.731, 0.684–0.777	0.689, 0.635–0.743

both the pancreatic neck and main pancreatic duct diameter were larger; there were fewer patients with diabetes, less often malignancy, and more often neuroendocrine tumor as the suspected preoperative diagnosis, and more patients in whom minimally invasive surgery was performed (70.2% POPF vs. 48.5% no POPF). Finally, blood loss was less and the number of venous resections was lower in the POPF group.

Validation

Results of the validation of the D-FRS are displayed in Table 2. The preoperative D-FRS, consisting of the variables pancreatic neck thickness and pancreatic duct diameter, showed an AUROC of 0.73 (95% CI 0.68–0.78) (Fig. S1a). The intraoperative D-FRS, comprising again of both pancreatic neck and duct diameter and in addition BMI, operating time, and soft pancreatic aspect, showed an AUROC of 0.69 (95% CI 0.64–0.74) (Fig. S1b).

Discussion

This first nationwide validation of the D-FRS found only the preoperative D-FRS to have an acceptable discriminative value for POPF after distal pancreatectomy with an AUROC of 0.73 which is consistent with the initial external validation of this model. The intraoperative risk score had a poor discriminative value with an AUROC of 0.69.

The univariable analysis confirmed that larger pancreatic duct and neck diameter were risk factors for the development of POPF. However, BMI, soft pancreatic texture, and prolonged operating time were not significant risk factors. This is mainly due to the operating time, which is subjected to confounders. In the current cohort, operation time was found to be shorter in the POPF group. That soft texture is not a risk factor can also be attributed to the overrepresentation of minimally invasive surgery of the POPF group, as it makes assessment of pancreatic texture more difficult and less reliable since this was assessed by sight and tactile feedback. Ideally, a predictive model only consists of objective and measurable variables such as in the preoperative D-FRS. This can be used to selectively drain patients and manage mitigation strategies, including optimal application of various transection techniques, sealants, or tissue patches. Besides, by risk group identification, surgeons can inform their patients about the risks, tailor-made per patient.

In the current study, validation of the DISPAIR FRS was considered not possible because of missing data on the location of pancreatic transection. The DISPAIR study group determined the transection location by postoperative CT images, operation notes, and pathologist's reports which do not correspond well with a preoperative model and may therefore decrease its clinical relevance. Moreover, transection site was reported as a dichotomous variable with the option neck or body/tail, leading to a less accurate measurement at the transection site.

The current validation should be interpreted in light of some limitations. First, the minimally invasive approach was overrepresented in the POPF group which has been reported as a risk factor of POPF, but was not taken into the original model, which is plausible, since minimally invasive DP has become the routine approach in recent years and not taken into account in the D-FRS [17]. Second, measurement of the pancreatic duct and neck diameter on preoperative imaging was not done by experienced radiologists but done by four observers, trained by experienced radiologists. Afterwards, cases were randomly checked, and no significant inter-observer bias was found. Third, heterogeneity may have arisen from different types of transection and stump closure. However, there are no studies to date showing superiority in terms of type of stump closure regarding POPF rate following DP [18]. Fourth, the current study could not predict CR-POPF postoperatively, which has a great role in postoperative management and mitigation of CR-POPF, as Pecorelli et al. showed by predicting CR-POPF based on drain amylase, serum amylase, and CRP [19].

In conclusion, the current study is the first nationwide validation of the preoperative and intraoperative D-FRS showing acceptable distinguishing capacity for only the preoperative D-FRS for POPF. Therefore, the preoperative score could improve prevention and mitigation strategies such as drain management, which is currently investigated in the multicenter PANDORINA trial [20]. To prove the predictive accuracy and to develop a broadly applicable model, more nationwide validations and prospective studies are warranted.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00423-023-03192-w.

Author contribution EvB and FdH did the analyses and wrote the main manuscript. All authors supervised the statistical process and critically reviewed the manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Bassi C, Marchegiani G, Dervenis C et al (2017) The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 161(3):584–591. https://doi.org/10.1016/j.surg.2016.11.014

2. Diener MK, Seiler CM, Rossion I et al (2011) Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet 377(9776):1514–1522. https://doi.org/10.1016/s0140-6736(11)60237-7
3. Van Buren G 2nd, Bloomston M, Schmidt CR et al (2017) A prospective randomized multicenter trial of distal pancreatectomy with and without routine intraperitoneal drainage. Ann Surg 266(3):421–431. https://doi.org/10.1097/sla.0000000000002375
4. McMillan MT, Malleo G, Bassi C et al (2017) Multicenter, prospective trial of selective drain management for pancreatoduodenectomy using risk stratification. Ann Surg 265(6):1209–1218. https://doi.org/10.1097/SLA.0000000000001832
5. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr (2013) A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg 216(1):1–14. https://doi.org/10.1016/j.jamcollsurg.2012.09.002
6. Mungroop TH, van Rijssen LB, van Klaveren D et al (2019) Alternative fistula risk score for pancreatoduodenectomy (a-FRS): design and international external validation. Ann Surg 269(5):937–943. https://doi.org/10.1097/SLA.0000000000002620
7. De Pastena M, van Bodegraven EA, Mungroop TH et al (2022) Distal pancreatectomy fistula risk score (D-FRS): development and international validation. Ann Surg. https://doi.org/10.1097/SLA.0000000000005497
8. Bonsdorff A, Ghorbani P, Helantera I et al (2022) Development and external validation of DISPAIR fistula risk score for clinically relevant postoperative pancreatic fistula risk after distal pancreatectomy. Br J Surg 109(11):1131–1139. https://doi.org/10.1093/bjs/znac266
9. Hackert T, Klaiber U, Hinz U et al (2017) Sphincter of Oddi botulinum toxin injection to prevent pancreatic fistula after distal pancreatectomy. Surgery. 161(5):1444–1450. https://doi.org/10.1016/j.surg.2016.09.005
10. Jang JY, Shin YC, Han Y et al (2017) Effect of polyglycolic acid mesh for prevention of pancreatic fistula following distal pancreatectomy: a randomized clinical trial. JAMA Surg 152(2):150–155. https://doi.org/10.1001/jamasurg.2016.3644
11. Allen PJ, Gonen M, Brennan MF et al (2014) Pasireotide for postoperative pancreatic fistula. N Engl J Med 370(21):2014–2022. https://doi.org/10.1056/NEJMoa1313688
12. Antila A, Siiki A, Sand J, Laukkarinen J (2019) Perioperative hydrocortisone treatment reduces postoperative pancreatic fistula rate after open distal pancreatectomy. A randomized placebo-controlled trial. Pancreatology. 19(5):786–792. https://doi.org/10.1016/j.pan.2019.05.457
13. van Bodegraven EA, van Ramshorst TME, Balduzzi A et al (2022) Routine abdominal drainage after distal pancreatectomy: meta-analysis. Br J Surg. https://doi.org/10.1093/bjs/znac042
14. Giani A, van Ramshorst T, Mazzola M et al (2022) Benchmarking of minimally invasive distal pancreatectomy with splenectomy: European multicentre study. Br J Surg. https://doi.org/10.1093/bjs/znac204
15. Steyerberg E (ed) (2009) Clinical prediction models: a practical approach to development, validation, and updating. Springer
16. Steyerberg EW, Vickers AJ, Cook NR et al (2010) Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology. 21(1):128–138. https://doi.org/10.1097/EDE.0b013e3181c30fb2
17. van Hilst J, de Rooij T, Abu Hilal M et al (2017) Worldwide survey on opinions and use of minimally invasive pancreatic resection. HPB (Oxford) 19(3):190–204. https://doi.org/10.1016/j.hpb.2017.01.011
18. Landoni L, De Pastena M, Fontana M et al (2022) A randomized controlled trial of stapled versus ultrasonic transection in distal pancreatectomy. Surg Endosc 36(6):4033–4041. https://doi.org/10.1007/s00464-021-08724-3
19. Pecorelli N, Guarneri G, Palucci M et al (2022) Early biochemical predictors of clinically relevant pancreatic fistula after distal pancreatectomy: a role for serum amylase and C-reactive protein. Surg Endosc 36(7):5431–5441. https://doi.org/10.1007/s00464-021-08883-3
20. Vissers FL, Balduzzi A, van Bodegraven EA et al (2022) Prophylactic abdominal drainage or no drainage after distal pancreatectomy (PANDORINA): a binational multicenter randomized controlled trial. Trials. 23(1):809. https://doi.org/10.1186/s13063-022-06736-5

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