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External validation and comparison of the original, alternative and updated-alternative fistula risk scores for the prediction of postoperative pancreatic fistula after pancreatoduodenectomy

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ABSTRACT

Background: Many postoperative pancreatic fistula (POPF) predictions models were developed and validated in western populations. Direct use of these models in the large Indian/Asian population, however, requires proper validation.
Objective: To validate the original, alternative and updated alternative fistula risk score (FRS) models.
Methods: A validation study was performed in consecutive patients undergoing pancreatoduodenectomy (PD) from January 2011 to March 2018. The area under the receiver operating curve (ROC) and calibration plots were used to assess the performance of original-FRS (o-FRS), alternative FRS (a-FRS) and updated alternative FRS (ua-FRS) models.
Results: This cohort consisted of 825 patients of which 66% were males with a median age of 55 years and mean body mass index of 22.6. The majority of tumors (61.8%) were of periampullary origin. Clinically relevant POPF was observed in 16.8% patients. Area under curve (AUC) of ROC for the o-FRS was 0.65, 0.69 for a-FRS and 0.70 for ua-FRS, respectively ($p = 0.006$).
Conclusions: In this large Indian cohort of predominantly periampullary tumors, the ua-FRS performed better than the a-FRS and o-FRS, although differences were small. Since the AUC value of the ua-FRS is at the accepted threshold there might be room for improvement for a FRS.

Introduction

Post-operative pancreatic fistula (POPF) remains the most important cause of perioperative morbidity and mortality after pancreatoduodenectomy (PD) [1–4]. Various risk calculation models have been developed for predicting and calculating risk of POPF [5–9]. The original Fistula Risk Score (o-FRS) is the most commonly used and validated prediction model for this purpose. The o-FRS is based on pancreatic texture, duct diameter, blood loss, and pathology, was designed and validated in US-population [5]. The Alternative FRS (a-FRS) model was based on pancreatic texture, duct diameter and body mass index (BMI), designed in a European population and subsequently validated in Europe and the US. The a-FRS did not include blood loss as this variable was thought to be less reliable [6]. Although both scores were externally validated in western populations, its direct use may not be feasible in the Indian/Asian population due to differences in baseline characteristics and biological features. In the Indian population for example, the proportion of periampullary tumors is higher and these tumors are known to have higher POPF rates as compared to pancreatic head tumors owing to soft texture of pancreas. Recently, an updated version of a-FRS (ua-FRS) was described which added male sex as variable and was validated in a European population, including both patients undergoing minimally invasive and open PD [10]. The Tata Memorial Centre is a high-volume centre for pancreatic surgery performing more than 150 PDs annually, necessitating the need of a validated prediction model, to guide perioperative decisions. Therefore, the aim of this study was to validate and

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Table 1
Baseline characteristics.

Parameter	Published o-FRS cohort [5] (n = 445)	Published a-FRS cohort [6] (n = 1924)	Published ua-FRS cohort [10] (n = 921)	Present study cohort (n = 825)
Age in years (median)	63.1	67	64	55
Sex				
Male	237 (53.3%)	778 (40.4%)	491 (53.4%)	540 (65.5%)
Female	208 (46.7%)	1146 (59.6%)	430 (46.6%)	285 (34.5%)
ASA status				
I		283 (15%)	167 (18%)	444 (53.8%)
II		1273 (67%)	514 (56%)	339 (41.1%)
III	NA	339 (18%)	214 (24%)	42 (5.1%)
Blood loss (median)	NA	NA	NA	900 ml
Body mass index (mean)	NA	25	25	22.6
Pancreatic duct size	(74.6% had duct <5 mm)	Median diameter- 4 mm	Mean diameter-4mm	287 (34.8%)
<3 mm				320 (38.8%)
3–5 mm				218 (26.4%)
>5 mm				
Pancreatic texture				
Soft	209 (49.2%)	970 (54%)	476 (51.7%)	396 (48%)
Firm	–	–	–	334 (40.5%)
Hard	–	–	–	95 (11.5%)
Surgery type				
PPPD	NA	NA	All were minimally invasive	644 (78%)
PPPD + Vascular resection				35 (4.2%)
Classic PD				82 (9.9%)
Classic PD + Vascular resection				06 (0.7%)
Subtotal PD				04 (0.5%)
Multivisceral resection				17 (2.1%)
MIS assisted PPPD				37 (4.5%)
Disease site	NA	NA	NA	
Periampullary				510 (61.8%)
Pancreas				238 (28.8%)
Duodenum				29 (3.5%)
CBD				40 (4.8%)
Colon				5 (0.6%)
Stomach				2 (0.2%)
Retroperitoneum				1 (0.1%)
Pathology	NA		NA	
Adenocarcinoma		1456 (77%)		638 (77.4%)
Neuroendocrine Tumor		104 (5%)		59 (7.1%)
Benign		50 (3%)		57 (6.9%)
Cystic Tumors		128 (7%)		46 (5.6%)
Others		–		25 (3%)
Observed POPF Rate		1692 (88%)	–	
No POPF	352 (79.1%)	232 (12%)	–	601 (72.8%)
POPF A/Biochemical Leak	35 (7.9%)		202 (21%)	85 (10.3%)
POPF B	50 (11.2%)			109 (13.2%)
POPF C	8 (1.8%)			30 (3.6%)

PPPD- Pylorus preserving pancreaticoduodenectomy, *PD*- Pancreaticoduodenectomy, *CBD*- Common bile duct, MIS- Minimally invasive surgery, NA-Not available.

compare the o-FRS, a-FRS and ua-FRS models in an Indian population.

Methods

This was a post-hoc analysis of a prospectively maintained pancreatic surgery database containing preoperative, intra-operative and postoperative information updated during each stage of the treatment. All PD's performed during January 2011 to March 2018 were included. Pancreatico-enteric anastomosis was uniformly done by 4-layer modified duct to mucosa technique pancreatico-jejunostomy (PJ) with 4–0 PDS suture in entire cohort with routine placement of 2 drains (one in Morrison's space and other anterior to PJ). Prophylactic octreotide was used selectively in high-risk anastomoses, starting at transection of pancreas and continued based on drain amylase levels especially in first half of the study period (until 2015) [11,12]. In the second half, octreotide use became less and less frequent. Drain amylase levels were measured on post-operative day 3 and 7. Standardized peri-operative care protocol is followed for all patients. Goal directed fluid therapy is given according to patient weight and requirement. Routinely only 3 doses of broad spectrum antibiotics are given and if the patient develops any signs or symptoms of sepsis, additional antibiotics are given as per bile culture sensitivity. Drain removal is decided based on drain amylase levels and drain color on day 3 and day 7. If there is no delayed gastric emptying (DGE), nasogastric tube is removed and oral feeding is started. Patients with DGE are started on naso-jejunal tube feeding. Routine albumin supplementation is not used at our centre. Necessary variables for calculation of o-FRS, a-FRS, and ua-FRS were retrieved and scores were calculated using online calculator models (www.pancreasclub.com and www.pancreascalculator.com) and compared with our actual fistula rate as defined by 2016 international study group for pancreatic surgery (ISGPS) definition [13]. Grade B/C POPF were collectively referred as clinically relevant POPF (CR-POPF).

Receiver operating curve (ROC) is a well-accepted tool to evaluate the performance of prediction models. The ideal prediction model would have an area under curve (AUC) of 1.00 on ROC, indicating 100% sensitivity and 100% specificity of the model. An AUC of 0.70 is commonly accepted threshold for successful external

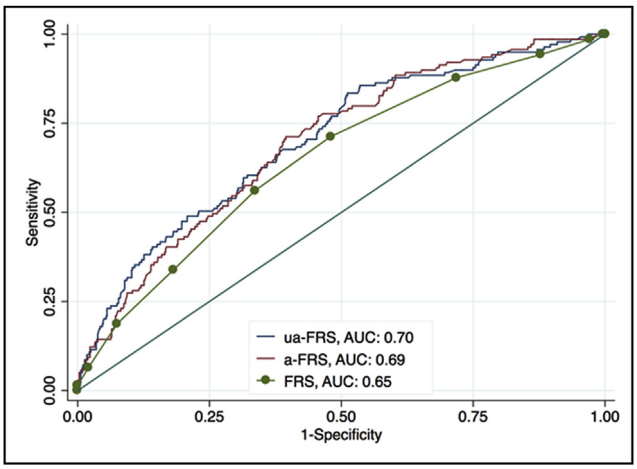

Fig. 1. ROC curves showing discrimination across POPF risk scores.
(1) ua-FRS, updated a-FRS [1]; (2) a-FRS, alternative fistula risk score [2]; (3) FRS, original fistula risk score.
p-value for difference between AUCs: 0.006.
[1]Formula: exp (−2.36+(0.95 * Texture + 0.07 * BMI + 0.64 * Male −0.39 * Duct size)/ 1 + exp (−2.36+(0.95 * Texture + 0.07 * BMI + 0.64 * Male −0.39 * Duct size)
[2] Formula: exp (−3.17 + 0.95 * Texture + 0.07 * BMI - 0.39 * Duct size/1 + exp (−3.17 + 0.95 * Texture + 0.07 * BMI -0.39 * Duct size).

validation. The calibration plot is a curve that measures the model's ability to generate predictions that are close to the observed outcome. A perfectly calibrated model will not show substantial deviation from 45^0 line, which is a perfect bisector [14,15]. Calibration plot was used to represent the predicted risk against observed risk of POPF per decile based on these models. Performance of each model was assessed by ROC and calibration plots.

Statistical analysis

Data entry and statistical analysis was done with Statistical Product and Service Solutions, SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA), and STATA. Nominal data was represented as percentage (%), continuous data as median, mean (range) and p value of <0.05 was considered significant. The DeLong test was used to compare the statistical difference between the AUCs of 3 scores.

Ethics statement

The data in current study was collected in the course of common clinical practice, and accordingly, signed informed consent was obtained from each patient for any surgical and clinical procedure. The study protocol was done in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration. The study was approved by institutional research committee (IEC/0119/3200/001).

Table 3
Comparison of p values for 3 scores.

	a-FRS	ua-FRS
o-FRS	0.003	0.002
a-FRS	–	0.465

o-FRS- *original fistula risk score, ua-FRS*- updated alternative fistula risk score, *a-FRS*- alternative fistula risk score.

Results

Overall, 825 patients undergoing PD during the study period were included. Baseline characteristics of the study population are reported in Table 1. Median age of the study cohort was 55 years and 66% of patients were male. Regarding the American Society of Anesthesiologists (ASA) physical status, 54%, 41% and 5.1% patients were in ASA I, II, and III category respectively. Median blood loss was 900 ml (range, 100–6500 ml). mean body mass index (BMI) was 22.6 (22.6 ± 3.6 SD) and mean pancreatic duct size was 4.5 mm. The majority (61.8%) of tumors were located in periampullary region and 28.8% in the pancreatic head respectively. Intraoperatively, pancreatic texture was reported as soft, firm and hard in 48% (396 out of 825), 40.5% (334 out of 825) and 11.5% (95 out of 825) patients respectively.

Seventy eight percent (644 out of 825) of patients underwent pylorus preserving PD, 4.9% (41 out of 825) underwent a vascular resection and 2.1% (17 out of 825) underwent multivisceral resection. Out of 825 patients, 8 underwent PD for extra-pancreatic pathology (colonic cancer in 5, gastric cancer in 2 and retroperitoneal tumor in 1) to achieve R0 resection. 4.5% (37 out of 825) underwent minimally invasive assisted PD. This minimally invasive cohort consisted of laparoscopy assisted (22 out of 37) and robotic assisted (15 out of 37) PD's, however, reconstruction was done by open approach in majority of these patients. Seventy seven percent (638 out of 825) patients were diagnosed with adenocarcinoma, 7.1% (59 out of 825) were neuroendocrine tumors and 5.6% (46 out of 825) were cystic tumors on final pathology reporting of resected specimen.

Overall 139 of 825 (16.8%) patients developed CR-POPF (Table 1). The AUC of the three models were 0.65 for o-FRS, 0.69 for a-FRS, and 0.70 for ua-FRS (Fig. 1). Table 2 elaborates the risk group allocation of study cohort using all three models. Interestingly, CR-POPF was observed in 6%, 14.1% and 31.1% of the low, intermediate and high-risk groups according to ua-FRS model, however, these figures were different for the a-FRS model. The difference between the AUCs of models was statistically significant (p = 0.006). The difference in AUCs on one to one comparison of these models is depicted in Table 3. Fig. 2 depicts the calibration plots for 3 models and ua-FRS model exhibited adequate calibration than the other two. A multivariate logistic regression was performed to ascertain the predictors of POPF in our cohort. Interestingly only BMI, pancreatic texture, pancreatic duct diameter and

Table 2
Observed POPF rates amongst various risk groups in 3 prediction models.

Variable	o-FRS groups				a-FRS groups			ua-FRS groups		
	Negligible	Low	Moderate	High	Low	Inter-mediate	High	Low	Inter-mediate	High
No of Patients (n = 825)	3 (0.4%)	89 (10.8%)	562 (68.1%)	171 (20.7%)	339 (41.1%)	451 (54.7%)	35 (4.2%)	133 (16.1%)	496 (60.1%)	196 (23.8%)
Overall POPF	0	12 (13.5%)	137 (24.8%)	75 (43.8%)	51 (15%)	151 (33.5%)	22 (62.8%)	13 (9.7%)	120 (24.2%)	91 (46.4%)
CR-POPF	0	8 (9%)	84 (15%)	47 (27.5%)	29 (8.5%)	94 (20.8%)	16 (45.7%)	8 (6%)	70 (14.1%)	61 (31.1%)

o-FRS- original fistula risk score, *a-FRS*- alternative fistula risk score, *ua-FRS*- updated alternative fistula risk score, *POPF*- postoperative pancreatic fistula, *CR-POPF*- clinically relevant POPF.

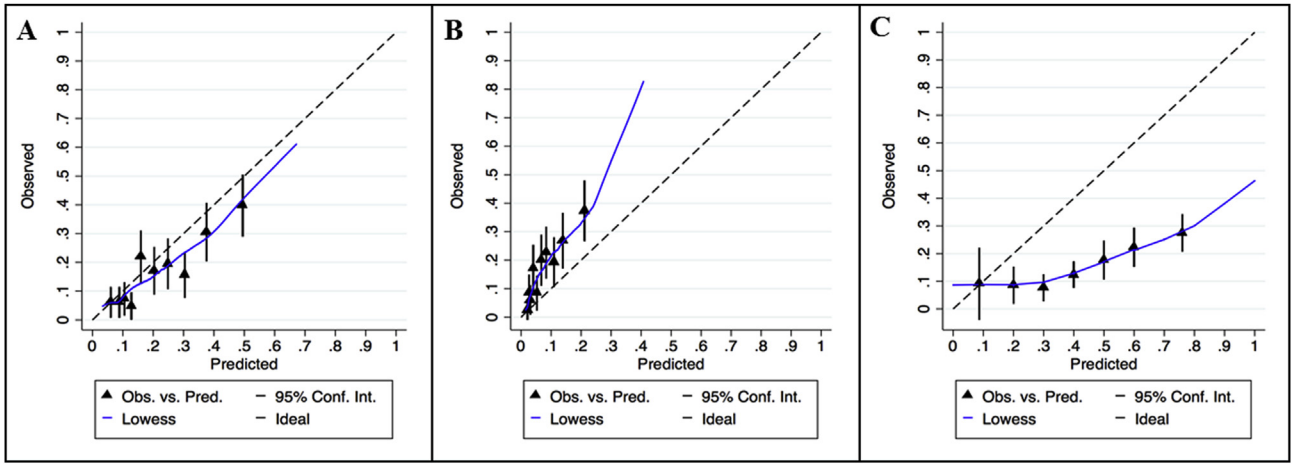

Fig. 2. Calibration plots for ua-FRS (A), a-FRS (B) and FRS (C).
*This LOESS curve is a locally weighted polynomial regression. The triangle indicates the observed frequencies by deciles of predicted probabilities.

Table 4
Univariate and Multivariate analysis for predictors of POPF.

Variables	Demographics	Univariate Analysis			Multivariate Analysis		
		Odds Ratio	CI	p Value	Odds Ratio	CI	p Value
Age [Median]	55 years	1.00	0.99–1.01	0.93			
Blood Loss [Median]	900 ml	1.00	1.00–1.00	0.98			
BMI [Mean]	22.6	1.10	1.05–1.15	0.00	1.09	1.04–1.14	0.00
	n (%)						
ASA status		0.73	0.53–1.01	0.06			
ASA 1 (Ref)	444 (53.8)	0.73	0.35–1.53	0.41			
ASA 2	339 (41.1)						
ASA 3	42 (5.1)						
Pancreatic Texture		0.39	0.28–0.55	0.00	0.44	0.31–0.63	0.00
Soft (Ref)	396 (48)	0.19	0.10–0.38	0.00	0.23	0.11–0.46	0.00
Firm	334 (40.5)						
Hard	95 (11.5)						
PD Size		0.52	0.37–0.74	0.00	0.65	0.45–0.94	0.02
<3 mm (Ref.)	287 (34.8)	0.32	0.21–0.49	0.00	0.46	0.29–0.72	0.00
4–5 mm	320 (38.8)						
>5 mm	218 (26.4)						
PD Location		3.01	0.95–9.52	0.06			
Central (Ref)	449 (54.4)	1.32	0.96–1.81	0.09			
Anterior	12 (1.5)						
Posterior	325 (39.4)						
Tumor Location		1.53	0.67–3.46	0.31			
Pancreas	238 (28.8)	1.10	0.52–2.34	0.80			
Duodenum	29 (3.5)	1.10	0.77–1.56	0.60			
Bile duct	40 (4.8)	0.00	0.00	1.00			
Periampullary	510 (61.8)						
Others	8 (0.9)						
Pathology		1.43	0.81–2.54	0.22	2.05	1.08–3.89	0.03
Adeno (Ref.)	634 (76.8)	1.97	1.08–3.62	0.03	1.62	0.90–2.94	0.11
NET	59 (7.2)	1.76	1.00–3.10	0.05			
Cystic Tumors	48 (5.8)	1.05	0.44–2.54	0.91			
Benign	57 (6.9)						
Others	27 (3.3)						

POPF: Postoperative pancreatic fistula, CI: Confidence interval, PD: Pancreatic duct.

cystic tumor pathology were significant factors on univariate and multivariate analysis for predictors of POPF in our cohort (Table 4).

Discussion

Our study reports the first external validation and direct comparison of three FRS models in an Indian population, using a large cohort of 825 consecutive patients undergoing PD with distinct baseline differences from a Western population. The ua-FRS (available via www.pancreascalculator.com) had the best predictive score for POPF (AUC 0.70; vs 0.69 for a-FRS and 0.65 for o-FRS, p = 0.006).

Of the numerous POPF risk factors already described in literature (male sex, BMI>25, soft pancreas, pancreatic duct <3 mm, diabetes, single layer versus double layer PJ) [16,17], our cohort had significant number of these predisposing factors (65.5% male, 48% soft pancreas, 34.8% pancreatic duct size <3 mm, 61.8% periampullary location, 22.6% non-adenocarcinoma pathology and 26.2% patients with BMI>25). These findings render this study cohort distinct from the previous western cohorts, in which these

models were designed and validated. CR-POPF was observed in 16.8% patients, however, the o-FRS, a-FRS and ua-FRS model predicted a high-risk for POPF in 20.7%, 4.2% and 23.8% patients respectively.

The calibration curves of the three models and the slope of the calibration curve for FRS model was far from ideal and over predicted the risk of POPF risk across all categories in this population. The a-FRS model did fairly well for the low risk and intermediate risk categories but the calibration plot deviates away as we move across the high-risk group, thereby underestimating the fistula risk in this high-risk category. The ua-FRS model showed the best calibration among the three, with its slope close to the perfect bisector (45^0 slope), with increasing predictive ability in high-risk group. The ua-FRS model was the only one primarily designed and validated in both minimally invasive and open PD. The proportion of minimally invasive PD was only 4.5% in our cohort.

A number of POPF prediction models have been reported in literature and abdominal fat distribution (or BMI), pancreatic duct diameter and pancreatic gland texture are the most consistently used parameters, apart from many other independent variables like blood loss and pathology [18]. However, the majority of these have either never been externally validated and few have considered post-operatively available variables, such as drain amylase in their risk prediction models which limit their applicability in guiding treatment decision early in the post-operative course [5].

The o-FRS was designed by Callery et al. in a cohort of 445 patients [5], is a simple 10-point score based on intraoperative findings and concordance index of 0.94. Based on the score, it classifies patients into negligible, low, intermediate and high-risk category. Miller et al. [19], performed a multi-institutional external validation of this model in a cohort of 594 patients with a concordance index of 0.716. Similarly, Grendar et al. [20], also a reported multi-institutional external validation in a cohort of 444 patients with similar findings and concordance index of 0.719.

Mungroop et al. [6], reported the design and external validation of a-FRS model, which did not include blood loss as a variable, in a cohort of 926 patients using ROC as a model assessment tool and found a marginally better performance with a-FRS model over o-FRS model (AUCs of 0.72 versus 0.70, $p = 0.05$). Mungroop et al. [10], also reported the ua-FRS model, which added male sex and could also be used for minimally invasive PD, in a cohort of 952 patients with better discrimination than a-FRS on ROC and adequate calibration.

Recently Kang JS et al [21] reported external validation of 3 risk scores in Korean population. In the cohort of 1898 PD patients, AUC values were 0.61, 0.64, and 0.63 for Callery [5], Roberts [8] and Mungroop [6] models respectively; all were lower than those published in each external validation study. However, Korean cohort and our cohort had many differences (median age-64 versus 55yrs, male gender-58.8% versus 65.5%, periampullary location-19.2% versus 61.8% in Korean and Indian cohort respectively). Overall POPF rate was 39.6% (versus 27.1%) and 6.9% patients had undergone pancreato-gastrostomy in Korean cohort. These observations seem to suggest that the Indian population characteristics are perhaps juxtaposed between the western and far eastern populations.

This study has several limitations which should be taken into account. First, the retrospective nature of the data, despite the prospectively maintained database. Second, this is a single centre study from a single country which may increase reflect the heterogeneity around the Asian subcontinent. Thirdly, on multivariate analysis in our cohort, BMI, pancreatic texture, PD size, and pathology were the independent factors and the combination of these four factors could be a new predicting model which was different from any other previous models. The main strengths of this study include the assessment and external validation of these three models in a new geographical area. Also, this was a large cohort from a single centre with a uniform clinical practice [11,22,23] as compared to previously reported studies using these models [5,6,10]. We believe that, future studies should be focused towards change in routine clinical practice like use of somatostatin analogue, steroids and (number of) drains based on the predicted risk of such prediction models.

To conclude, in this external validation of three FRS models in an Indian cohort of predominantly periampullary tumors, the ua-FRS performed better than the a-FRS and o-FRS, although differences were small. AUC values may still be further improved indicating the need for development of novel FRS model in this subset of patients.

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None.

Declaration of competing interest

None.

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