J Hepatobiliary Pancreat Sci (2019) 26:354–359
DOI: 10.1002/jhbp.638

ORIGINAL ARTICLE

Validation of original and alternative fistula risk scores in postoperative pancreatic fistula

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Published online: 1 July 2019

Abstract

Background In 2013, the fistula risk score (FRS) was developed to assess the risk of clinically relevant postoperative pancreatic fistula (CR-POPF). In 2017, the alternative FRS (a-FRS) was proposed. The purpose of this study was to validate the original FRS (o-FRS) and a-FRS for CR-POPF in pancreaticoduodenectomy (PD).

Methods From January 2007 to December 2016, 1,771 patients underwent PD for periampullary cancers. POPF was defined and classified according to the 2016 International Study Group for Pancreatic Fistula. All data were reviewed retrospectively.

Results Pathologic diagnosis other than ductal adenocarcinoma ($P < 0.001$), pancreas duct diameter ($P < 0.001$), and body mass index ($P < 0.001$) were independent risk factors for CR-POPF. Pancreatic texture ($P = 0.534$) and estimated blood loss ($P = 0.827$) were not associated with CR-POPF. The CR-POPF incidence increased with increasing o-FRS score ($P < 0.001$), and also increased statistically significantly with increasing a-FRS in the higher risk group ($P < 0.001$). However, the correlations differed. The area under the curve was 0.629 for o-FRS and 0.622 for a-FRS.

Conclusions Both o-FRS and a-FRS might reflect CR-POPF incidence, but some risk factors had no or low statistical significance. Further research is needed to revise the FRS.

Keywords Fistula risk score · Pancreaticoduodenectomy · Postoperative pancreatic fistula · Risk factor · Validation

Introduction

Postoperative pancreatic fistula (POPF) is the most critical complication after pancreaticoduodenectomy (PD), a procedure that has been used worldwide for many years. As surgeons have accrued experience with PD and improved their surgical skills, the associated risks have decreased, postoperative management has been systematized, and patient burden has decreased [1, 2]. Nevertheless, POPF remains a problem for hepato-pancreato-biliary surgeons because it causes major complications after PD, increases hospital stay, significantly affects morbidity and mortality, and is a major contributor to medical care costs [3, 4].

Many studies have focused on predicting and preventing clinically relevant POPF (CR-POPF), including several analyses that have proposed various CR-POPF risk factors. However, the ability to accurately predict CR-POPF remains controversial (and potentially impossible) because many studies lack statistical validity due to small sample sizes or other design issues [5–7]. A fistula risk score (FRS) was first proposed by Callery et al. in 2013 [8]. Since the original FRS (o-FRS) was presented, many validation studies and studies seeking a new POPF prediction model have been conducted [9–12]. Studies have shown that not all FRS factors are statistically significant, especially volume of intraoperative blood loss (EBL), suggesting that FRS models should be modified [12, 13]. In

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2017, a more reliable FRS was proposed. This alternative FRS (a-FRS) comprises three factors: pancreatic texture, pancreatic duct diameter, and body mass index (BMI) [14].

This study examined the statistical significance of each factor in the o-FRS and a-FRS. Neither the o-FRS nor a-FRS has been validated in a large number of Korean patients. We aimed to validate both FRS methods and determine if the models are useful for Korean patients.

Methods

Patients and surgical methods

Data were reviewed retrospectively from January 2007 to December 2016. This work was approved by our Institutional Review Board (approval number: 2017-07-015-002). Analyses included patients who underwent PD (comprising Whipple's operation, pylorus-preserving PD, and pylorus-resecting PD) by four experienced, skilled surgeons at a single, high-volume center. The study only included patients diagnosed with periampullary cancer (including ampulla of vater cancer, common bile duct cancer, duodenal cancer, and pancreas cancer) by postoperative pathologic diagnosis. Patients who underwent surgery for metastatic cancer or double primary cancer were excluded. Most patients underwent pancreaticojejunostomy (PJ) with the duct-to-mucosa method for pancreatic-intestinal anastomosis.

Risk factor analysis for pancreatic fistula

To study o-FRS and a-FRS, data were collected and analyzed for five factors: pancreatic gland texture, pancreatic duct size, pathological diagnosis, EBL, and BMI. For both o-FRS and a-FRS, pancreatic gland texture was classified as soft or not soft [8, 14] based on operation records. Pancreatic duct size data was also determined from operation records. Pancreatic duct diameter not recorded in the operation record was treated as a missing value. CR-POPF was classified according to the updated International Study Group of Pancreatic Fistula definition published in 2016 [15].

Overall baseline characteristics are represented with descriptive statistics. Linear-by-linear association was used to assess the relationships between o-FRS score and CR-POPF occurrence and between o-FRS and a-FRS groups and CR-POPF occurrence. Fisher's exact and Mann–Whitney tests were used to analyze correlations among the five baseline characteristics and CR-POPF occurrence. Logistic regression was calculated with a multivariate analysis of factors and CR-POPF occurrence. Area under the receiver operating curves (AUCs) was calculated to evaluate the efficiency of each FRS model for predicting CR-POPF. IBM SPSS version 23.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

Results

From January 2007 to December 2016, a total of 1,847 patients underwent PD for various periampullary diseases at Samsung Medical Center. The patients were excluded if they lacked a POPF record (n = 5) or if they had a hepato-pancreaticoduodenectomy (n = 21), iatrogenic injury to the pancreas during surgery (n = 1), direct invasion of another organ (n = 14), metastasis from another organ (n = 16), double primary cancer (n = 12), or cancer recurrence (n = 7). A total of 1,771 patients were included in this study. Patient clinical characteristics are described in Table 1. There were included data on 222 CR-POPF patients (12.5%). For pancreatic anastomosis, 10 cases involved pancreaticogastrostomy and other methods, while 1,761 cases (99.5%) used pancreaticojejunostomy. For patients who had the pancreatic anastomosis method recorded, only 12 (0.7%) were performed with an invagination method while 1,731 (99.3%) were performed with a duct-to-mucosa anastomosis. Baseline FRS factors are summarized in Table 2.

The risk factor analysis showed a correlation between FRS factors and the development of CR-POPF in univariate and multivariate analyses (Table 3). Univariate analysis revealed that soft pancreatic texture (P = 0.004),

Table 1 Clinical characteristics of patients included in this study

Variable	N (total n = 1,771) (%)
Age	62.35 (18-92)
Sex	
Male	1,080 (61.0)
Female	691 (39.0)
BMI (kg/m^2)	23.16 (14.4–39.7)
Pancreatic fistula	
No fistula	882 (49.8)
Biochemical leak	667 (37.7)
ISGPF grade B	210 (11.9)
ISGPF grade C	12 (0.7)
Specific treatment	
Use antibiotics	202 (11.4)
Total parenteral nutrition	57 (3.2)
Percutaneous drainage	99 (5.6)

BMI body mass index, *ISGPF* International Study Group of Pancreatic Fistula

Table 2 Baseline characteristics of fistula risk score factors

Variable	*N* (total *n* = 1,771) (%)
Gland texture	
Firm	1,021 (57.7)
Soft	750 (42.4)
Pathology	
PDAC	568 (32.1)
Other[a]	1,203 (67.9)
Pancreatic duct size (median, mm)	3.00 (0.2–35)
FRS diameter distribution	
≥5	456 (25.8)
4	210 (11.9)
3	439 (24.8)
2	445 (25.1)
≤1	175 (9.9)
EBL (median, ml)	400 (25–6,000)
Intraoperative blood loss (ml)	
≤400	1,116 (63.0)
401–700	454 (25.6)
701–1,000	121 (6.8)
≥1,000	80 (4.5)

EBL volume of intraoperative blood loss, *FRS* fistula risk score, *PDAC* pancreatic ductal adenocarcinoma

[a]Ampullary, duodenal, cystic, islet cell

Table 3 Univariate and multivariate analysis of FRS factor and CR-POPF

Risk factor	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Gland texture (soft)	1.52	1.14–2.01	0.004	1.10	0.82–1.48	0.534
Pathology (not PDAC)	3.14	2.13–4.64	<0.001	2.72	1.83–4.03	<0.001
Pancreatic duct size, per mm increase	0.83	0.76–0.91	<0.001	0.87	0.80–0.94	0.001
Estimated volume loss	1.00	1.00–1.00	0.827			
BMI	1.11	1.07–1.16	<0.001	1.09	1.05–1.14	<0.001

BMI body mass index, *CI* confidence interval, *OR* odds ratio, *PDAC* pancreatic ductal adenocarcinoma

pathologic diagnosis other than pancreatic ductal adenocarcinoma (PDAC) ($P < 0.001$), pancreatic duct diameter ($P < 0.001$), and BMI ($P < 0.001$) were statistically significant risk factors associated with CR-POPF. Multivariate analysis revealed that a pathologic diagnosis other than PDAC (odds ratio [OR] 2.72, 95% confidence interval [CI] 1.83–4.03, $P < 0.001$), pancreatic duct diameter per millimeter increase (OR 0.87, 95% CI 0.80–0.94, $P = 0.001$), and BMI (OR 1.09, 95% CI 1.05–1.14, $P < 0.001$) were independent risk factors of CR-POPF. Soft pancreatic texture was not significant in the multivariate analysis. Volume of intraoperative blood loss was not associated with CR-POPF.

Figure 1 shows the distribution of o-FRS scores, o-FRS groups, and a-FRS groups. As o-FRS score increased, CR-POPF incidence increased significantly ($P < 0.001$) (Fig. 1a). According to o-FRS group classification, 1,311 patients (74.0%) had moderate or high risk (Fig. 1b). CR-POPF incidence was 14.6% in the moderate-risk group and 17% in the high-risk group. CR-POPF incidence increased significantly with increasing o-FRS group ($P < 0.001$) (Fig. 1b, o-FRS group). The a-FRS score is the probability of CR-POPF divided by the group score to show the CR-POPF occurrence rate. A similar number of individuals (1,252 patients, or 70.7%) were in the a-FRS intermediate- and high-risk groups as were in the corresponding o-FRS groups. CR-POPF occurred in 6.7% of patients in the low-risk group, 13.4% in the intermediate-risk group, and 21.6% in the high-risk group. The a-FRS group was significantly associated with CR-POPF ($P < 0.001$).

A receiver operating curve was used to assess the diagnostic value of o-FRS and a-FRS (Fig. 2). The area under the curve (AUC) was similar for the two FRS models. For o-FRS, the AUC was 0.629 (95% CI 0.59–0.67) (Fig. 2a); for a-FRS, the AUC was 0.622 (95% CI 0.59–0.66) (Fig. 2b).

Discussion

Since o-FRS was introduced, several validation studies and modified predictive models have been published [9–12]. Studies focused on o-FRS have been limited by an inability to show statistical significance due to small sample size, inclusion of data from only one institution, and a lack of external validation [16–18]. In contrast, a study of a-FRS included a large number of patients, collected data from 18 centers, and extended external validation internationally [14]. Thus, we chose these two models for validation. In addition, both models were designed for non-Asian patients, leaving their applicability to a Korea sample open to investigation. Many studies and risk factor analyses have been performed for POPF in Korea, but no study has validated FRS in a large number of Korean patients [19, 20]. Therefore, this study is clinically significant for validation both of o-FRS, which is most widely used for predicting POPF, and a-FRS, which is considered the most reliable validation model.

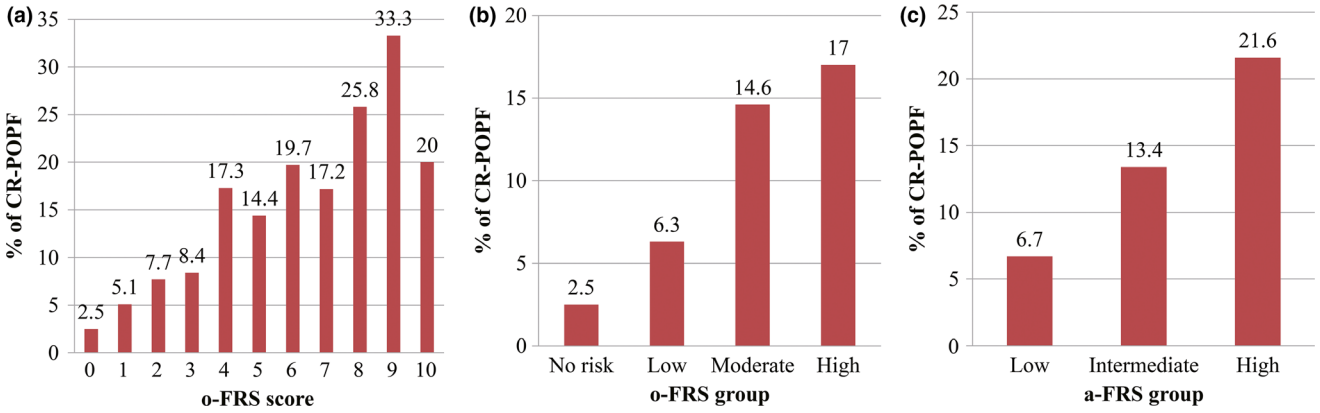

Fig. 1 Occurrence of clinically relevant postoperative pancreatic fistula (CR-POPF) according to the original fistula risk score and alternative fistula risk score. (**a**) CR-POPF occurrence according to the original fistula risk score. (**b**) CR-POPF occurrence according to the original fistula risk score group. (**c**) CR-POPF occurrence according to the alternative fistula risk score group

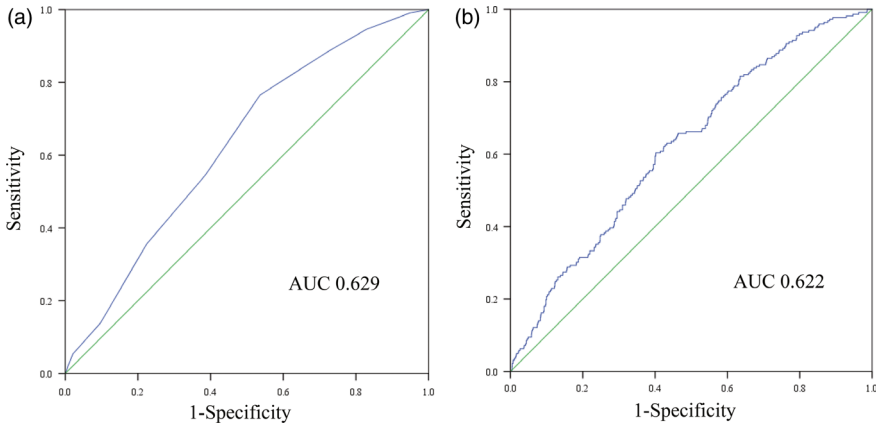

Fig. 2 Receiver operating curve (ROC) and the area under the curve (AUC) of the original fistula risk score and alternative fistula risk score. (**a**) ROC of the original fistula risk score. (**b**) ROC of the alternative fistula risk score

While accurately measuring EBL and ensuring objectivity are difficult, we showed that EBL, which is a factor in o-FRS but not a-FRS, was not a risk factor for CR-POPF. Other studies have also shown that EBL is not a prognostic factor of POPF [12, 13]. For example, a recent multicenter study in Korea showed that EBL was not a risk factor for POPF but was related to intraoperative fluid volume. Excess fluid can induce edema of the jejunum, causing anastomosis tension of pancreaticojejunostomy and POPF [21]. These findings suggest that EBL itself is not a POPF risk factor, and further studies should be conducted to assess intraoperative fluid volume.

In previous studies, soft pancreatic texture was a risk factor of CR-POPF. Some models include soft pancreatic texture in predicting CR-POPF [18, 22]. This study demonstrated an association between soft pancreatic texture and CR-POPF. In univariate analysis, soft pancreatic texture was a risk factor of CR-POPF. However, in the multivariate analysis, soft pancreatic texture was not an independent prognostic factor of CR-POPF. This difference between the univariate and multivariate analyses can be explained several ways. Our study was retrospective, so the assessments are subjective because surgeons had different criteria for judging pancreatic texture. A meta-analysis showed that soft pancreatic texture is not a risk factor of CR-POPF [16]. Patients with pancreas head cancer are susceptible to obstructive pancreatitis, which can cause pancreatic fibrosis [23]. Thus, pancreas pathology and pancreatic texture are related through inflammation. Finally, this center performs an extremely high number of PDs, averaging 200 or more per year. High-volume centers have standardized procedures, a number of experienced surgeons, and relatively low complication rates [24].

This study indicates that, for a-FRS, BMI is an independent risk factor for CR-POPF. Previous studies have also shown that BMI is a risk factor for CR-POPF [25, 26]. Studies show that visceral fat distribution is important for CR-POPF development. Many studies have reported the effects of sarcopenia or sarcopenic obesity on PD [27–29]. BMI, sarcopenia, and sarcopenic obesity are considered to be related factors. Therefore, to better understand the correlation of these factors, a risk factor analysis should be performed with BMI and sarcopenia or sarcopenic obesity.

The pancreatic duct diameter is a well-known factor for CR-POPF development. This finding has been demonstrated not only in o-FRS and a-FRS, but in many other validation studies [9, 10, 12, 13, 22]. In this study, pancreatic duct diameter was an independent prognostic factor for CR-POPF incidence in univariate and multivariate analyses. Our results agree with several previous studies, and they have a larger sample size. Therefore, pancreatic duct diameter remains an important risk factor for CR-POPF.

In this validation, the AUC was 0.629 for o-FRS and 0.622 for a-FRS (Fig. 2). This result indicates that, although the factors in both FRS models were significant risk factors, both models have questionable predictive value for CR-POPF [30]. Considering the results of previous studies [5–7, 9–12], the similarity of the two model AUC values in this study, despite the different correlation of each risk factor with occurrence of POPF, suggests that additional factors affecting the occurrence of POPF should be considered. This study confirmed that o-FRS and a-FRS require a supplementary factor, and a nomogram was created to predict POPF.

This research has several limitations. We used retrospective data, which could have led to selection bias. This study only included data from a single center, which decreases the strength of statistical analyses. A disadvantage of single-center studies is that the sample does not represent the entire patient population. These results, therefore, may not reflect nationwide data. However, by using data from one center, the surgical technique was consistent for all patients. Despite the limitations listed here, we included a large number of patients.

Conclusion

Both o-FRS and a-FRS significantly predicted POPF. However, neither EBL nor soft pancreatic texture, which are included in both FRS models, were significant in our analyses. Neither model had sufficient diagnostic value. Therefore, to more accurately predict CR-POPF, further research is needed to revise these models.

Acknowledgments This study was supported by Samsung Medical Center grant (grant number: SMX1180101). The authors would like to thank Hyemin Kim (data manager, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine) for help with data collection.

Conflict of interest None declared.

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