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ORIGINAL ARTICLE

Externalized Stents for Pancreatoduodenectomy Provide Value Only in High-Risk Scenarios

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Abstract

Background Evidence suggests externalized trans-anastomotic stents may be beneficial as a fistula mitigation strategy for pancreatoduodenectomy (PD); however, previous studies have not been rigorously risk-adjusted.

Methods From 2001 to 2015, PDs were performed at three institutions, with externalized stents placed at the surgeon's discretion. The Fistula Risk Score (FRS) and the Modified Accordion Severity Grading System were used to analyze occurrence and severity of clinically relevant postoperative pancreatic fistula (CR-POPF) across various risk scenarios.

Results Of 729 PDs, externalized stents were placed during 129 (17.7 %). Overall, CR-POPFs occurred in 77 (10.6 %) patients. The median FRS of patients who received externalized stents was significantly higher compared with patients who did not (6 vs. 3, $p < 0.0001$). Patients with negligible, low, or moderate CR-POPF risk (FRS 0–6) did not demonstrate improved outcomes with externalized stents; however, among high-risk patients (FRS 7–10), stents were associated with significantly reduced rates of CR-POPF (14.0 vs. 36.4 %, $p = 0.031$), severe complications ($p = 0.039$), and hospital stay ($p = 0.014$) compared with no stents. The average complication burden of CR-POPF was significantly lower for patients with externalized stents ($p = 0.035$).

Conclusion This multicenter study, the largest comparative analysis of externalized trans-anastomotic stents versus no stent for PD, demonstrates a risk-stratified benefit to externalized stents.

Keywords Stent · Pancreatectomy · Pancreatic fistula · Pancreatoduodenectomy

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Abbreviations

POPF	Postoperative pancreatic fistula
PD	Pancreatoduodenectomy
CR-POPF	Clinically relevant postoperative pancreatic fistula
RCT	Randomized controlled trial
PDAC	Pancreatic ductal adenocarcinoma
FRS	Fistula Risk Score
ISGPF	International Study Group on Pancreatic Fistula
ACB	Average Complication Burden
SD	Standard deviation
IQR	Interquartile range
OR	Odds ratio

Introduction

Postoperative pancreatic fistula (POPF) is the most common and morbid complication following

pancreatoduodenectomy (PD).[1–4] In the contemporary era, advancements in surgical technique and perioperative care have been associated with a reduction in mortality rates following this procedure; however, clinically relevant pancreatic fistulas (CR-POPF[5]) continue to occur in approximately 15 % of patients.[3] CR-POPFs significantly delay patients' recovery and account for over one third of mortalities.[6,7] Numerous putative mitigation strategies are available to the surgeon for this problem, including the use of somatostatin analogues, drainage, and trans-anastomotic stents.[8–14] Several rationale exist for the placement of trans-anastomotic stents, including the following: (i) the diversion of proteolytic enzymes from the anastomotic site and (ii) decompression of the pancreatic remnant. It has also been suggested that stents facilitate precise suturing of the anastomosis.[1]

Two types of trans-anastomotic stents are commonly used by pancreatic surgeons: internal or externalized.[15] The efficacy of the internal variety has been compared with no stent placement in two randomized controlled trials (RCT).[16,17] Neither RCT found a benefit to the use of internal stents; in fact, one of the studies identified a trend towards higher rates of POPF following internal stent placement in patients with soft pancreatic parenchyma.[16] The use of externalized trans-anastomotic stents for PD has also been studied extensively; in fact, seven RCTs have evaluated their efficacy during the ISGPF era.[8–14] Meta-analyses of these RCTs suggest improved outcomes with externalized stents versus no stents.[18,19]

Despite this scrutiny, these studies suffered from two major limitations. First, comparisons of randomized cohorts were limited to complication occurrence and failed to account for complication severity and burden.[4,20] Second, some of these studies sought to assess the effectiveness of stenting in patients with presumed heightened CR-POPF risk; however, the criteria used to assign this risk was often limited to pancreatic gland texture and/or duct diameter. Consequently, these risk-stratified comparisons failed to account for other risk factors associated with the development of CR-POPF such as high-risk disease pathology (pathologies other than pancreatic ductal adenocarcinoma [PDAC] or pancreatitis) and elevated intraoperative blood loss, which also contribute to the Fistula Risk Score (FRS) (Table 1).[3,21]

The 10-point Fistula Risk Score (FRS) is a predictive tool for CR-POPF formation and has been used extensively for risk-stratified comparisons of CR-POPF mitigation strategies (e.g., drains,[22,23] octreotide,[24] etc.) and surgeon/institutional performance.[3] Using the FRS for risk adjustment, this study sought to compare CR-POPF occurrence between patients who received an externalized stent versus no stent. A secondary analysis aimed to compare complication burden between cohorts.

Table 1 Fistula risk score for the prediction of clinically relevant fistula after pancreatoduodenectomy[21]

Risk factor	Parameter	Points
Gland texture	Firm	0
	Soft	2
Pathology	Pancreatic adenocarcinoma or pancreatitis	0
	Ampullary, duodenal, cystic, islet cell, etc.	1
Pancreatic duct diameter	≥5 mm	0
	4 mm	1
	3 mm	2
	2 mm	3
	≤1 mm	4
Intraoperative blood loss	≤400 mL	0
	401–700 mL	1
	701–1000 mL	2
	>1000 mL	3
		Total 0 to 10 points

Materials and Methods

This study was approved by the institutional review board at the University of Pennsylvania. In the overall series, eight pancreatic surgeons contributed PDs for all indications from January 2001 to September 2015 at three high-volume, academic institutions. All anastomoses were reconstructed with end-to-side pancreaticojejunostomy. The use of intraoperative drains, somatostatin analogues (i.e., octreotide), and externalized trans-anastomotic stents were made at the surgeon's discretion. Externalized stents consisted of either 5- or 8-Fr Silastic pediatric feeding tubes (Dow Corning Corporation, Midland, MI); these traversed the anastomosis without fixation and traveled prograde down the pancreaticobiliary limb. They were externalized through the bowel approximately 5 cm past the hepaticojejunostomy and secured with an absorbable, purse-string suture.

Pancreatic Fistula Classification

The primary outcome of interest was CR-POPF, which was graded in accordance with International Study Group of Pancreatic Fistula (ISGPF) standards.[5] Transient, biochemical (i.e., Grade A) leaks were not studied due to their lack of clinical impact on outcomes.[25] Clinically relevant fistulas (i.e., Grades B, C) are clinically impactful and significantly alter the patient's recovery. Grade B POPFs are often treated with therapeutics such as antibiotics, somatostatin analogues (e.g., octreotide), total parenteral nutrition, percutaneous drain placement, or prolonged operative drainage (i.e., beyond 3 weeks). Grade C POPFs are characterized by organ failure, reoperation, or death.[5,7]

Assigning Fistula Risk

Fistula risk was determined using the 10-point FRS (Table 1).[3,21] This risk assessment tool is based on the presence of certain risk factors for the development of CR-POPF: soft/normal pancreatic parenchyma, high-risk disease pathology (all pathologies other than PDAC or pancreatitis), small pancreatic duct diameter, and elevated intraoperative blood loss. Individual scores are derived through the summation of each of the four weighted risk factors. Calculated scores are then discretized and assigned to one of four risk zones: (i) negligible risk, 0 points; (ii) low risk, 1–2 points; (iii) moderate risk, 3–6 points; or (iv) high risk, 7–10 points.

Assignment of Complication Severity Grading

Each postoperative complication was assigned a severity grade (range, 1–6) according to the Modified Accordion Severity Grading System.[20] A Modified Accordion grade of 1 signified the least harmful complications and a 6 indicated death as a direct consequence of the complication. In the absence of any postoperative complication, patients were assigned a grade of zero. Fistula Accordion Severity Grades were assigned in cases of a POPF to qualify the complication severity directly attributable to the sequelae of a fistula. After assessment of severity grades, each POPF was weighted using previously derived utility severity weights (Table 2).[20,26] The Average Complication Burden (ACB) of clinically relevant fistula was calculated by dividing the aggregate sum of individual severity weights of highest graded POPFs by the total number of complication-bearing patients.[4] ACB values offer insight into the average morbidity associated with CR-POPF occurrence.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), while categorical variables are presented as absolute numbers and percentages. Qualitative and quantitative measures for severity of burden were analyzed using the Modified Accordion Severity Grading System and ACB, respectively. For univariate comparisons, χ^2 analysis or Fisher's exact tests were used to evaluate categorical variables; alternatively, continuous variables were analyzed using the Student's t test and Wilcoxon rank-sum test for normally and non-normally distributed data, respectively. Stepwise regression analyses—stratified by FRS risk zone (i.e., negligible, low, moderate, high)—were performed to identify covariates associated with the CR-POPF development ($p \leq 0.05$ for entry; $p > 0.10$ for removal).

Secondary endpoints included mild/moderate complications (Modified Accordion severity grade 1–2[20]), severe complications (Modified Accordion ≥3), any complication (Modified Accordion ≥1), percutaneous drainage for complication management, therapeutic antibiotics, hospital blood transfusion, intensive care unit transfer, and total parenteral nutrition. In congruence with established criteria for CR-POPF follow-up, these were assessed out to 90 days following the index procedure.[6,27] Other outcomes studied were duration of hospital stay, readmission within 30 days of the operation, 90-day reoperation, and 90-day postoperative mortality. p values ≤0.05 were

Table 2 Modified accordion severity grading system specifically for postoperative pancreatic fistula[4]

Fistula accordion severity grade	Description	Severity weight
0 (none)	Elevated amylase alone, but no intervention (biochemical POPF)	0.000
1 (mild)	Discharged from hospital with original operatively placed drain, with no other interventions required	0.110
2 (moderate)	Treatment for POPF requires the use of therapeutic (not prophylactic) somatostatin analogues, antibiotics, TPN, or TEN (via pre-existing NG- or J-tubes)	0.260
3 (severe A)	Any operative procedure short of general anesthesia required for POPF management: complex wound management; percutaneous drain placement or aspiration of an amylase-rich collection postoperatively; angiographic procedure for control of a pseudoaneurysm secondary to POPF; or endoscopic procedure for POPF management	0.370
4 (severe B)	Reoperation under general anesthesia for an anastomotic leak from the pancreaticojejunostomy or pancreaticogastrostomy. *or* Single organ failure secondary to the POPF (e.g., renal failure, pulmonary failure, neurologic failure, etc.)	0.600
5 (severe C)	Reoperation under general anesthesia for an anastomotic leak and single organ failure secondary to the POPF event (e.g., renal failure, pulmonary failure, neurologic failure, etc.). *or* Multi-system (2 or more) organ failure secondary to the POPF	0.790
6 (death)	Death attributable to POPF	1.000

J-tube jejunostomy tube, *POPF* postoperative pancreatic fistula, *TPN* total parenteral nutrition, *TEN* total enteral nutrition, *NG* nasogastric

considered statistically significant; all tests were two-sided. All statistical computations were performed using SPSS 22.0 (IBM Corp., Armonk, NY) statistical software.

Results

Characteristics of the Overall Cohort

During the study period, 729 PDs were performed by eight surgeons at three institutions. The median age was 65 (IQR 56–73), and 50.1 % were male (Table 3). Mean body mass index (BMI) was 26.5 ± 5.2 kg/m^3, and the most common BMI classification was normal weight (18.5–24.9 kg/m^2; 39.6 %). The most frequent disease pathology was PDAC, which represented 39.5 % of the cohort. High/risk disease pathology was indicated for 46.9 % of the overall patients.

All pancreatico-enteric anastomoses were end-to-side duct-to-mucosa pancreaticojejunostomies. Octreotide prophylaxis was administered to 230 (31.6 %) patients during the perioperative period. Routine abdominal drainage was practiced for 93.1 % of the cohort. Only Blake drains were used, and the median postoperative day for removal of prophylactic drainage was 7 (IQR 6–8). Externalized trans-anastomotic stents were placed in 129 (10.4 %) patients.

Mean and median intraoperative blood loss were 458.3 ± 673.1 and 300 (IQR 200–500) mL, respectively. The CR-POPF risk factor, soft pancreatic parenchyma, was encountered 52.7 % of the time. The median main pancreatic duct diameter was 4 (IQR 3–5) mm. The mean and median Fistula Risk Scores were 3.3 ± 2.3 and 3 (IQR 1–5), respectively. The distribution of patients across FRS risk zones was as follows: (i) negligible, 13.7 %; (ii) low, 27.3 %; (iii) moderate, 49.1 %; (iv) high, 9.9 %.

Outcomes of the Overall Cohort

In the overall cohort, CR-POPFs developed in 77 (10.6 %) patients, of which 69 and 8 were Grades B and C, respectively. The overall complication rate was 59.3 %; the most common Modified Accordion severity grade for a complication was 2 (N = 199, 27.3 %). Mild/moderate complications (Accordion 1–2) occurred 42.4 % of the time. Severe complications (Accordion ≥3) accounted for 28.5 % of the complications, and they occurred 16.9 % of the overall time.

Therapeutic antibiotics were administered to 223 (30.6 %) patients. Percutaneous drainage was required for complication management in 36 (4.9 %) patients. Intensive care unit transfers were necessary for 50 (6.9 %) patients, with a median duration of 1 (IQR 1–2) day. Total parenteral nutrition was administered to less than one fifth (17.3 %) of the cohort, and 213 (29.2 %) patients received an in-hospital blood transfusion. Reoperations were performed for 34 (4.7 %) patients. The median duration of hospital stay was 8 (IQR 7–10) days, and 16.5 % required readmission within 30 days of the operation. There were 16 (2.2 %) mortalities within 90 days of the index procedure.

Comparison of the Characteristics of the Stent and No Stent Cohorts

There were numerous differences between the externalized stent and no stent cohorts (Table 3). The externalized stent cohort was characterized by elevated BMI (obese/overweight: 67.4 vs. 54.0 %; $p = 0.008$) and less frequent utilization of octreotide prophylaxis (2.3 vs. 37.8 %, $p < 0.001$). In terms of CR-POPF risk factors, intraoperative blood loss was significantly elevated in the externalized stent patients compared with the no stent cohort (median: 400 vs. 300 mL, $p < 0.001$). Externalized stent patients were also more likely to have soft pancreatic parenchyma (87.6 vs. 45.2 %, $p < 0.001$), high-risk disease pathology (81.4 vs. 39.5 %, $p < 0.001$), and smaller pancreatic duct diameters ($p < 0.001$). Comparisons of aggregate CR-POPF risk revealed the externalized stent cohort to have a median Fistula Risk Score two times greater than the no stent patients (6 [IQR 6–7] vs. 3 [IQR 1–4], $p < 0.001$). In fact, externalized stents were placed in none of the negligible risk, 1.5 % of the low risk, 21.2 % of the moderate risk, and 69.4 % of the high-risk patients. Collectively, these data suggest a general bias towards externalized stent placement in scenarios with elevated CR-POPF risk.

The utilization of this fistula mitigation strategy also significantly varied among the eight surgeons comprising the study group. Two surgeons frequently employed external stents (37.5 and 56.6 % of career PDs) whereas the six remaining surgeons infrequently employed this mitigation strategy (range, 0.0–2.3 % of career PDs) ($p < 0.001$). Given the association between FRS risk categories and external stent use, the distribution of stent use across surgeons was adjusted for the fistula risk of their individual case volumes. Interestingly, the two surgeons whose practice was characterized by high stent utilization had a greater percentage of high FRS cases (25.9 vs. 2.9 %, $p < 0.001$) and markedly fewer negligible and low FRS cases (24.1 vs. 48.3 %, $p < 0.001$).

Comparison of Outcomes Between the Externalized Stent and No Stent Cohorts

Non-risk-stratified comparisons of outcomes between cohorts demonstrated higher rates of CR-POPF with externalized stent placement (17.1 vs. 9.2 %, $p = 0.008$), but no significant differences were observed for every other major postoperative outcome (Table 4). Since there were significant discrepancies in individual and aggregate CR-POPF risk between cohorts (Table 3), CR-POPF rates were then compared when stratified by FRS variables. When patients were stratified by FRS risk

Table 3 Comparison of demographics, operative/pathologic factors, and pancreatic fistula risk between no stent and externalized stent cohorts

Variable, *N* (%) or median (IQR)	Overall	Cohort		*p* value
		Externalized stent	No stent	
Patients	729	129 (17.7)	600 (82.3)	–
Demographics				
Age, years (median)	65 (56–73)	65 (57.5–72)	65 (55–73)	0.844
BMI, kg/m^2				
<25.0 (normal weight/underweight)	304 (41.7)	42 (32.6)	262 (43.7)	0.008
≥25 (overweight/obese)	411 (56.4)	87 (67.4)	324 (54.0)	
Unknown	14 (1.9)	0 (0)	14 (2.3)	
Gender				
Male	365 (50.1)	64 (49.6)	301 (50.2)	0.909
Female	364 (49.9)	65 (50.4)	299 (49.8)	
Operative and pathologic factors				
Anastomotic technique				
PJ, end-to-side, duct-to-mucosa	729 (100)	129 (10.4)	600 (48.4)	–
Intraoperative drain placement				
No (FRS 0–2)	38 (5.2)	0 (0)	38 (6.3)	<0.0001
No (FRS 3–10)	12 (1.6)	0 (0)	12 (2.0)	
Yes (FRS 0–2)	261 (35.8)	3 (2.3)	258 (43.0)	
Yes (FRS 3–10)	418 (57.3)	126 (97.7)	292 (48.7)	
Intraoperative blood loss, mL (median)	300 (200–500)	400 (250–675)	300 (200–500)	0.000
Prophylactic octreotide administered				
No	499 (68.4)	126 (97.7)	373 (62.2)	<0.0001
Yes	230 (31.6)	3 (2.3)	227 (37.8)	
Disease pathology				
PDAC	288 (39.5)	12 (9.3)	276 (46.0)	<0.0001
Ampullary cancer	86 (11.8)	15 (11.6)	71 (11.8)	
Cholangiocarcinoma	34 (4.7)	10 (7.8)	24 (4.0)	
Duodenal cancer	27 (3.7)	12 (9.3)	15 (2.5)	
Pancreatitis	81 (11.1)	13 (10.1)	68 (11.3)	
Cystic neoplasm	101 (13.9)	32 (24.8)	69 (11.5)	
Benign lesion	50 (6.9)	16 (12.4)	34 (5.7)	
Islet cell	33 (4.5)	12 (9.3)	21 (3.5)	
Metastatic lesion	9 (1.2)	1 (0.8)	8 (1.3)	
Other lesions	20 (2.7)	6 (4.7)	14 (2.3)	
Fistula risk				
Pancreatic gland texture				
Hard	345 (47.3)	16 (12.4)	329 (54.8)	<0.0001
Soft	384 (52.7)	113 (87.6)	271 (45.2)	
High-risk pathology				
No (PDAC or pancreatitis)	387 (53.1)	24 (18.6)	363 (60.5)	<0.0001
Yes (other pathology)	342 (46.9)	105 (81.4)	237 (39.5)	
Pancreatic duct diameter, mm				
≥5	283 (38.8)	2 (1.6)	281 (46.8)	<0.0001
4	169 (23.2)	3 (2.3)	166 (27.7)	
3	121 (16.6)	27 (20.9)	94 (15.7)	
2	115 (15.8)	77 (59.7)	38 (6.3)	
≤1	41 (5.6)	20 (15.5)	21 (3.5)	
Intraoperative blood loss, mL				
≤400	488 (66.9)	71 (55.0)	417 (69.5)	0.001
401–700	150 (20.6)	30 (23.3)	120 (20.0)	

Table 3 (continued)

Variable, *N* (%) or median (IQR)	Overall	Cohort		*p* value
		Externalized stent	No stent	
701–1000	51 (7.0)	18 (14.0)	33 (5.5)	
>1000	40 (5.5)	10 (7.8)	30 (5.0)	
Fistula risk score, median	3 (1–5)	6 (6–7)	3 (1–4)	<0.0001
FRS risk zone				
Negligible	100 (13.7)	0 (0)	100 (16.7)	<0.0001
Low	199 (27.3)	3 (2.3)	196 (32.7)	
Moderate	358 (49.1)	76 (58.9)	282 (47.0)	
High	72 (9.9)	50 (38.8)	22 (3.7)	

IQR interquartile range, *BMI* body mass index, *PJ* pancreaticojejunostomy, *FRS* Fistula Risk Score, *PDAC* pancreatic ductal adenocarcinoma

zone, externalized stent and no stent cohorts had similar outcomes for negligible, low, and moderate risk; however, externalized stents patients with high FRS risk demonstrated markedly lower rates of CR-POPF (14.0 vs. 36.4 %, $p = 0.031$, Fig. 1) and severe complications (18.0 vs. 40.9 %, $p = 0.039$) (Table 4). High FRS risk patients also experienced reduced hospital stay when externalized stents were placed (median: 9 [IQR 7–12.3] vs. 12.5 [IQR 8.8–23.5], $p = 0.014$). When stratifying comparisons by individual glandular risk factors in isolation, however, there were no significant differences in rates of CR-POPF in the setting of the following: soft gland (17.7 vs. 15.5 %, $p = 0.593$); high-risk pathology (18.1 vs. 16.9 %, $p = 0.783$); or small (≤3 mm) duct size (15.4 vs. 15.1 %, $p = 0.942$)—suggesting that the benefit of external stents may be in the cohort of compounded risk identified by multiple FRS factors rather than individual risk factors in isolation.

A secondary analysis was performed after stratifying the patients between the high- and low-stent utilization surgeons. A total of 220 PDs were performed by the high stent use surgeons, with an observed CR-POPF rate of 13.2 %. There was no association between stent use and CR-POPF occurrence in the negligible (0.0 vs. 0.0 %, $p = 1.000$), low (0.0 vs. 2.2 %, $p = 0.831$), or moderate (19.2 vs. 8.1 %, $p = 0.129$) FRS risk zones. Externalized stent use was associated with fewer CR-POPFs in the high FRS risk patients (14.6 vs. 44.4 %, $p = 0.037$). A total of 509 PDs were performed by the low stent use surgeons, with an observed CR-POPF rate of 9.4 %. There was no association between stent use and CR-POPF occurrence at any FRS risk zone: negligible (0.0 vs. 0.0 %, $p = 0.100$), low (0.0 vs. 3.3 %, $p = 0.853$), moderate (33.3 vs. 15.5 %, $p = 0.399$), or high (0.0 vs. 30.8 %, $p = 0.360$). Notably, there were 57 high FRS risk patients in the high stent use surgeon cohort, yet only 15 such risk patients in the low stent use surgeon cohort—which may have limited the statistical power of this subset analysis.

Comparing Complication Burden Between Externalized Stent and No Stent Cohorts

The ACB of CR-POPF was significantly greater in the no stent cohort compared with the externalized stent cohort (0.394 ± 0.232 vs. 0.252 ± 0.146, $p = 0.035$), implying that stents may reduce the complication burden of fistula from severe to moderate grade. The ACB for non-fistulous complications was nearly identical between the externalized stent and no stent patients (0.302 ± 0.161 vs. 0.301 ± 0.193, $p = 0.968$). When stratified by FRS risk categories, patients with externalized stents trended to reduced fistula severity in both the high FRS (0.410 ± 0.203 vs. 0.250 ± 0.107, $p = 0.201$) and moderate FRS (0.409 ± 0.246 vs. 0.253 ± 0.162, $p = 0.065$) patients.

Multivariable Analysis

To control for potential confounders not encompassed by the FRS, logistic regression analyses—stratified by FRS risk zone—were performed to identify factors associated with CR-POPF development. Patient demographics (i.e., age, gender, overweight/obese), surgeon characteristics (i.e., surgeon ID, career PD volume, stent utilization rate), and select mitigation strategies (i.e., prophylactic octreotide, externalized stent, and intraperitoneal drain use) were entered into a stepwise regression model. The absence of CR-POPF among negligible risk patients precluded an assessment of this patient subgroup. Among low FRS risk patients, multivariable analysis was unable to identify any variables associated with CR-POPF incidence (Table 5). Notably, externalized stent placement was associated with an increased risk of CR-POPF in the moderate FRS risk patients (OR 2.52, $p = 0.025$), yet was associated with a *decreased* risk of CR-POPF in the high FRS risk patients (OR 0.29, $p = 0.037$).

Table 4 Comparison of outcomes between externalized stent and no stent cohorts stratified by Fistula Risk Score (FRS) risk zone

Variable, *N* (%)	Externalized stent (*N* = 129)	No stent (*N* = 600)	*p* value
Clinically relevant pancreatic fistula			
Overall (FRS 0–10)	22 (17.1)	55 (9.2)	0.008
Negligible (FRS 0)	–	0 (0)	–
Low (FRS 1–2)	0 (0)	6 (3.1)	1.000
Moderate (FRS 3–6)	15 (19.7)	41 (14.5)	0.268
High (FRS 7–10)	7 (14.0)	8 (36.4)	0.031
Any complication (Accordion ≥1)			
Overall (FRS 0–10)	86 (66.7)	346 (57.7)	0.059
Negligible (FRS 0)	–	56 (56.0)	–
Low (FRS 1–2)	1 (33.3)	101 (51.5)	0.614
Moderate (FRS 3–6)	49 (64.5)	170 (60.3)	0.506
High (FRS 7–10)	36 (72.0)	19 (86.4)	0.186
Severe complication (Accordion ≥3)			
Overall (FRS 0–10)	24 (18.6)	99 (16.5)	0.563
Negligible (FRS 0)	–	13 (13.0)	–
Low (FRS 1–2)	0 (0)	24 (12.2)	1.000
Moderate (FRS 3–6)	15 (19.7)	53 (18.8)	0.853
High (FRS 7–10)	9 (18.0)	9 (40.9)	0.039
Median (IQR) duration of hospital stay			
Overall (FRS 0–10)	8 (7–12.5)	8 (7–10)	0.234
Negligible (FRS 0)	–	8 (7–9)	–
Low (FRS 1–2)	7 (6-not available)	8 (7–9)	0.179
Moderate (FRS 3–6)	8 (7–13)	8 (7–11)	0.988
High (FRS 7–10)	9 (7–12.3)	12.50 (8.8–23.5)	0.014
Percutaneous drainage			
Overall (FRS 0–10)	8 (6.2)	28 (4.7)	0.465
Negligible (FRS 0)	–	3 (3.0)	–
Low (FRS 1–2)	0 (0)	5 (2.6)	1.000
Moderate (FRS 3–6)	3 (3.9)	19 (6.7)	0.590
High (FRS 7–10)	5 (10.0)	1 (4.5)	0.660
Therapeutic antibiotics			
Overall (FRS 0–10)	39 (30.2)	184 (30.7)	0.923
Negligible (FRS 0)	–	30 (30.0)	–
Low (FRS 1–2)	0 (0)	42 (21.4)	1.000
Moderate (FRS 3–6)	19 (25.0)	98 (34.8)	0.108
High (FRS 7–10)	20 (40.0)	14 (63.6)	0.064
Reoperation			
Overall (FRS 0–10)	5 (3.9)	29 (4.8)	0.640
Negligible (FRS 0)	–	3 (3.0)	–
Low (FRS 1–2)	0 (0)	3 (1.5)	1.000
Moderate (FRS 3–6)	3 (3.9)	20 (7.1)	0.434
High (FRS 7–10)	2 (4.0)	3 (13.6)	0.163
Readmission (30D)			
Overall (FRS 0–10)	21 (16.3)	99 (16.5)	0.951
Negligible (FRS 0)	–	16 (16.0)	–
Low (FRS 1–2)	2 (66.7)	26 (13.3)	0.052
Moderate (FRS 3–6)	11 (14.5)	53 (18.8)	0.383
High (FRS 7–10)	8 (16.0)	4 (18.2)	1.000

Table 4 (continued)

Variable, *N* (%)	Externalized stent (*N* = 129)	No stent (*N* = 600)	*p* value
Mortality (90D)			
Overall (FRS 0–10)	3 (2.3)	13 (2.2)	1.000
Negligible (FRS 0)	–	1 (1.0)	–
Low (FRS 1–2)	0 (0)	5 (2.6)	1.000
Moderate (FRS 3–6)	1 (1.3)	6 (2.1)	1.000
High (FRS 7–10)	2 (4.0)	1 (4.5)	1.000

Discussion

This study demonstrates that externalized stent placement is a fistula mitigation strategy with an efficacy that varies by degree of fistula risk. Externalized stents were associated with reduced CR-POPF risk for patients with high FRS risk; however, they are not valuable, and even may be detrimental, in patients of lesser risk. Furthermore, externalized stents for high FRS risk patients are associated with significantly reduced rates of severe complications and shorter hospital stay. In addition, the burden of CR-POPF was significantly lower following externalized stent placement. These data suggest that the decision to place externalized stents should depend upon the aggregate fistula risk profile of individual patients.

In the ISGPF era (i.e., 2005 to the present), three randomized controlled trials have conducted risk-stratified comparisons of externalized stents versus no stent.[11–13] The first, by Pessaux and colleagues, was a multi-center RCT that focused exclusively on patients with soft glands and pancreatic ducts <3 mm (i.e., patients with presumed elevated CR-POPF risk).[11] That study reported reduced rates of CR-POPF when externalized stents were placed (24.7 vs. 35.8 %). These findings were supported by another recent RCT, which stratified

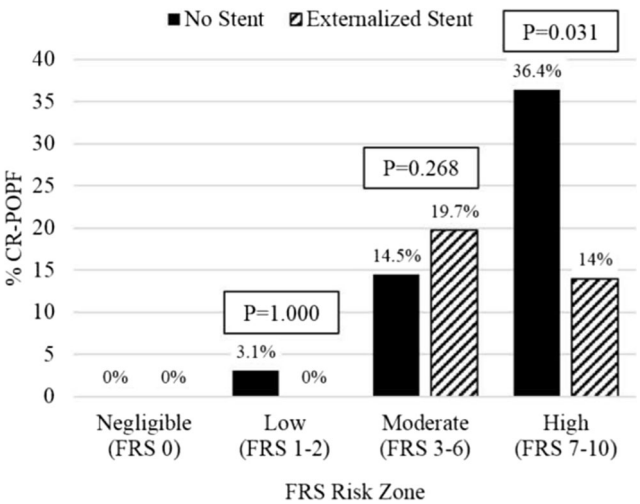

Fig. 1 Comparison of clinically relevant pancreatic fistula incidence between externalized stent and no stent cohorts, stratified by Fistula Risk Score (FRS) risk zone

CR-POPF risk based upon duct diameter, and demonstrated that patients with dilated ducts (>3 mm) did not benefit from externalized stent placement (3.8 vs. 7.7 %, $p = 1.000$); however, patients with non-dilated ducts (≤3 mm) had significantly lower CR-POPF rates when externalized stents were placed (9.5 vs. 40.0 %, $p = 0.033$).[13]

Although both Pessaux and Motoi attempted to stratify comparisons based upon CR-POPF risk, they failed to consider two important risk factors for CR-POPF: disease pathology and intraoperative blood loss.[1,3,21] In the present study, comprehensively controlling for CR-POPF risk using the FRS showed that only patients with high FRS benefit from externalized stent placement. It is possible that a substantial subset of patients in both RCTs had high FRS risk, but it is also possible that some had low (FRS 1–2) or moderate (FRS 3–6) CR-POPF risk, and these patients might not have benefitted from externalized stent utilization.

Only one contemporary risk-stratified RCT of externalized stent placement has demonstrated a non-significant improvement in CR-POPF rates following externalized stent placement.[12] The study had two major shortcomings, however, including a small sample size ($N = 45$) and their study inclusion criteria was limited to patients with so-called non-fibrotic glands—based upon MRI assessment. This minimal degree of risk stratification only considered gland texture—two of 10 possible FRS points—since patients with non-fibrotic glands have normal/soft pancreatic parenchyma.

In addition to reduced rates of CR-POPF, high FRS risk patients also had shorter hospital stays and fewer severe complications following externalized stent placement. Meta-analyses of RCTs comparing externalized stents versus no stent have supported this finding, as they have shown that externalized stents are associated with reduced overall morbidity and hospital stay.[18,19] Since pancreatic fistula is the major driver of morbidity following PD, it is logical that a decrease in CR-POPF would also be accompanied by a reduction in overall complication incidence and duration of hospital stay. These findings underscore the value of advancing efforts to decrease the incidence of this highly morbid complication.

Seemingly paradoxical is the increased risk of CR-POPF associated with the use of externalized stents for moderate risk patients. Such findings are reflected in the absolute fistula

Table 5 Logistic regression analysis, stratified by FRS risk zone, identifying variables associated with CR-POPF development. Patients with negligible FRS risk were not evaluated, since no patients matching that risk profile developed a CR-POPF

		Low (FRS 1–2)		Moderate (FRS 3–6)		High FRS (7–10)	
		OR (95 % CI)	*p* value	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Age, years			0.313	1.04 (1.02–1.07)	0.002		0.891
Gender, male			0.116		0.099		0.829
BMI, kg/m^3	<25.0 ≥25		0.882		0.426		0.409
Surgeon (identification #)			0.055		0.571		0.931
Surgeon career PD volume	1–50 51–199		0.305		0.865		0.427
	≥200						
Surgeon stent use	High Low		0.684		0.546		0.405
Intraoperative drain placement	No Yes		0.584	REF 0.24 (0.06–0.94)	– 0.040		0.176
Prophylactic octreotide	No Yes		0.592	REF 2.30 (1.13–4.70)	– 0.022		0.512
Externalized stent	No		0.758	REF	–	REF	–
	Yes			2.52 (1.13–5.62)	0.025	0.29 (0.09–0.93)	0.037

BMI body mass index, *PD* pancreaticoduodenectomy, *FRS* Fistula Risk Score

rates even when stratified by surgeon and their stent utilization practices. Both the high stent use and low stent use surgeons evidenced absolute improvements in the CR-POPF rate in high FRS patients yet higher rates of CR-POPF for moderate FRS patients. A possible explanation involves competing factors between the benefits of an externalized stent in facilitating precise suturing of the anastomosis and the possible detrimental effects of a foreign body reaction. In cases of lesser risk, the potential benefits of an externalized stent may be outweighed by the influence of a non-organic material at the anastomosis. It is speculative that a similar effect could underlie the trend towards higher rates of POPF with internal stents.[16,17,28–30]

Additional hazards associated with externalized stents include accidental removal, kinking of the stent, and peritonitis; furthermore, removal of an externalized stent can cause pancreatitis or late-onset stenosis.[14,29] Other concerns include quality of life issues such as discomfort, the inconvenience of maintenance over extended periods of time (up to 6 weeks), and the need for pancreatic enzyme supplementation with externalized pancreatic fluid loss. Taken together, these underscore the importance of selectively placing externalized stents based upon a patient's aggregate CR-POPF risk; only patients with high FRS risk appear to benefit from their use.

A unique aspect of the current study was the comparison of complication burden between cohorts. Interestingly, CR-POPFs incurred significantly reduced complication burden in externalized stent patients compared with no stent patients (0.252 vs. 0.394, $p = 0.035$). In fact, the difference in CR-POPF ACB between groups was equivalent to greater than an entire level of utility-weighted severity. For example, a patient with a CR-POPF following externalized stent placement can expect treatment with therapeutic somatostatin analogues, antibiotics, TPN, or TEN—corresponding to a Modified Accordion Grade 2 weight of 0.260. In contrast, the average patient developing a CR-POPF without stent placement can expect an operative procedure short of general anesthesia such as complex wound management or percutaneous drain placement; put another way, these characterize a Modified Accordion Grade 3 severity weight of 0.370.

Several limitations of this study warrant further discussion. First, the study is retrospective, so there was no randomization process for placement of externalized stents, which were utilized at the surgeon's discretion. This led to a selection bias where they were typically utilized by surgeons for perceived higher risk patients; however, this limitation was addressed by using the FRS to compare patients with similar comprehensive risk profiles for CR-POPF development. Moreover, to minimize this potential source of bias, the current study used risk-stratified multivariable analyses that considered other potential confounding factors for CR-POPF development such as age, gender, BMI, drain placement, and the administration of octreotide prophylaxis. One potential approach for minimizing bias from non-randomized treatment assignment involves propensity score-matching; the present study was unable to utilize this approach due to cohort heterogeneity, which substantially limited the number of patients available for such an analysis. Another limitation regards the relative homogeneity of the institutions studied—all are high-volume,

academic centers; therefore, our findings may not be generalizable to lower-volume, nonacademic centers. Lastly, despite the collective effort of several high-volume institutions, the rare occurrence of high FRS scenarios may have limited the statistical power of certain analyses. Both type I (in the case of stent high-use surgeons) and type II (in the case of stent low-use surgeons) errors remain possibilities.

Lastly, improvement in surgical outcomes is predicated on recognition of effective and ineffective approaches and subsequent, willful adaptation. While the findings of this study are still too recent to determine whether practice has been altered, the surgeons who contributed to this series were polled regarding the potential impact the results of this study might have on their management of patients. Four out of five of the low frequency stent users profess that they are already, or will consider, applying external stents in high-risk scenarios. Both high-frequency users expressed recognition of the potential detrimental effects associated with stents in lesser-risk scenarios and indicate they will consider more discretionary use going forward. Furthermore all of the study authors offered that the development of the FRS, and its subsequent use in risk-adjusted analyses[3,22–24,30], has impacted on their perceptions of operative risk and strategies for mitigation.

Conclusion

This multicenter study is the largest comparative analysis of externalized trans-anastomotic stents versus no stent for PD. It demonstrates that the value of externalized stents as a CR-POPF mitigation strategy may vary by risk—as judged by the comprehensive Fistula Risk Score. Additionally, the complication burden of postoperative fistula may be influenced by the presence of an externalized stents. Lastly, this study demonstrates how a patient's overall CR-POPF risk—rather than individual risk factors—should be used when evaluating the efficacy of fistula mitigation strategies.

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