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Multifactorial mitigation strategy to reduce clinically relevant pancreatic fistula in high-risk pancreatojejunostomy following pancreaticoduodenectomy

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A B S T R A C T

Introduction: Postoperative pancreatic fistula (POPF) is the most dreadful complication of pancreaticoduodenectomy (PD) and previous literature focused on technical modifications of pancreatic remnant reconstruction. We developed a multifactorial mitigation strategy (MS) and the aim of the study is to assess its clinical impact in patients at high-risk of POPF.
Methods: All patients candidate to PD between 2012 and 2018 were considered. Only patients with a high Fistula Risk Score (FRS 7–10) were included. Patients undergoing MS were compared to patients receiving Standard Strategy (SS). Clinical outcomes were compared between the two groups. Multivariate hierarchical logistic regression analyses were performed to detect independent predictors of POPF.
Results: Out of 212 patients, 33 were finally included in MS Group and 29 in SS Group. POPF rate was significantly lower in MS Group (12.1% vs 44.8%, $p = 0.005$). Delayed gastric emptying, postoperative pancreatitis, complications and hospital stay were also significantly lower in MS Group. Hierarchical logistic regression analyses showed that Body Mass Index ($OR = 1.196$, $p = 0.036$) and MS ($OR = 0.187$, $p = 0.032$) were independently associated with POPF.
Conclusion: A multifactorial MS can be helpful to reduce POPF rate in patients with high FRS following PD. Personalized approach for vulnerable patients should be investigated in the future.

Introduction

Pancreaticoduodenectomy (PD) is associated with high morbidity and mortality, and postoperative pancreatic fistula (POPF) is the most dreadful complication. Several types of pancreatic remnant reconstruction as well as strategies to mitigate the risk of POPF have been developed; however, there is no clear evidence to support one technique against the others [1]. The main methodological limitation of the current literature is the lack of stratification for individual risk of POPF and the resulting high heterogeneity between the samples of the different studies. To prevent this bias, Andrianello et al. recently published the first randomized controlled trial comparing two types of pancreatic remnant reconstruction by including 72 patients with high-risk pancreatic anastomosis [2]. The authors evidenced that pancreaticogastrostomy (PG) with external stent was associated with a higher risk of major complications when compared to pancreaticojejunostomy (PJ) with external stent. However, the authors found no significant differences in terms of POPF and fistula-related complications.

Standardized surgical technique, surgeon experience, and centre volume, are certainly important factors to reduce POPF rate [3]. However, providing adequate drainage and minimizing the effects of pancreatic leak remain as key factors, as sepsis and haemorrhage are related to collections of pancreatic exudates and contamination by intestinal or biliary fluid [4]. For this reason, we developed a multifactorial mitigation strategy (MS) for high-risk patients that combined meticulous pancreatic anastomosis, isolation of potential biliary contamination, aggressive prophylactic drains policy and standardized POPF management.

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The aim of this study is to assess the impact of implementing this MS in patients with high-risk pancreatic anastomosis undergoing PD.

Material and methods

This is a longitudinal cohort study comparing two types of strategies in patients who underwent PD in our centre from 2012 to 2018. Following an internal audit on high-risk patients in 2015, we decided to adopt a multifactorial mitigation strategy to improve our results. Therefore, two groups were obtained: MS Group and Standard Strategy (SS) Group. Data were extracted from a prospectively held database.

Surgical techniques

Standard Strategy group: From March 2012 to July 2015, Cattell-Warren PJ was routinely performed as previously described [5]. Continuous or interrupted Polydioxanone suture (PDS) were used for this anastomosis. A posterior row of pancreatic parenchymal sutures (4/0) were followed by a duct to mucosa anastomosis (5/0). Then, a second layer of anastomosis was performed between the seromuscular layer of the jejunum and the capsule of the pancreas. Pancreatic, biliary and gastric anastomoses were performed on a single jejunal loop. Two 14-french Silastic drains were used.

Mitigation strategy group: From July 2015 to September 2018, PJ was performed by modifying Heidelberg technique [6]. This technique originally described by Büchler and colleagues consists of an end to side duct to mucosa anastomosis and it is performed in four layers with an outer seromuscular and inner full thickness layer. Interrupted 4/0 Polydioxanone suture (PDS) was used for this anastomosis. The original technique was modified by performing a smaller incision on the jejunal loop, similarly to a duct-to-mucosa PJ, and by using U-sutures for the outer layers to allow lesser tension on pancreatic parenchyma while knitting. A separate Roux loop was also created for the end-to-side Hepatico-Jejunostomy (HJ) and the end-to-side antecolic Gastro-Jejunostomy (GJ). Nonabsorbable polymer ligating clips were used for gastroduodenal artery (GDA), and Teres ligament was used to wrap the GDA stump. Three 21-French Silastic drains were used. MS group and SS Group techniques are showed in Figs. 1 and 2.

In both techniques, pancreatic stent was always placed: a 5-French internal stent was used for ≥2 mm Wirsung duct; a 3-French central venous catheter tip was used for smaller ducts. Comparison between the two strategies is showed in Fig. 1. Technical details of Mitigation Strategy are showed in Fig. 2a-b-c.

One specialized pancreatic surgeon (FA) who was trained in high-volume HPB centers, completed the learning curve for PD, and had a personal experience exceeding 200 major pancreatic resections before the study period, performed all the pancreatic reconstructions in high-risk patients. Surgical loupes with 2.5× magnification were always used.

Eligibility criteria

Patients with any indication for elective PD were eligible for inclusion. Only patients with high-risk anastomosis as described by Callery et al. (Fistula Risk Score, FRS, ≥ 7 points) were considered [7]. Wirsung duct size was measured in the remnant pancreas before pancreatic anastomosis using a disposable ruler. Estimated blood loss was calculated as follows: [(Content of the suction canister + weight of surgical swabs) − Total volume of saline used for washing]; (1 g = 1 mL). Daily POPF output volume and number of days up to drain removal were also recorded.

Outcomes

The primary endpoint of the study was the incidence of clinically relevant POPF.

Secondary end points were the rates of Delayed Gastric Emptying (DGE), Post-Pancreatectomy Haemorrhage (PPH), biliary leakage, postoperative acute pancreatitis, 90-day major complications, reoperation, length of hospital stay and hospital readmission.

Ethical approval was obtained for this study by the local Ethics Committee.

Definition of outcome measures

POPF, DGE and PPH, were defined according to updated International Study Group of Pancreatic Surgery (ISGPS) definitions [8–10]. Postoperative bile leakage was defined according to International Study Group of Liver Surgery definition [11], and postoperative acute pancreatitis was defined according to Bannone et al. [12].

Clavien-Dindo classification and CCI (Comprehensive Complication Index) were used to describe postoperative complications at 90 days [13].

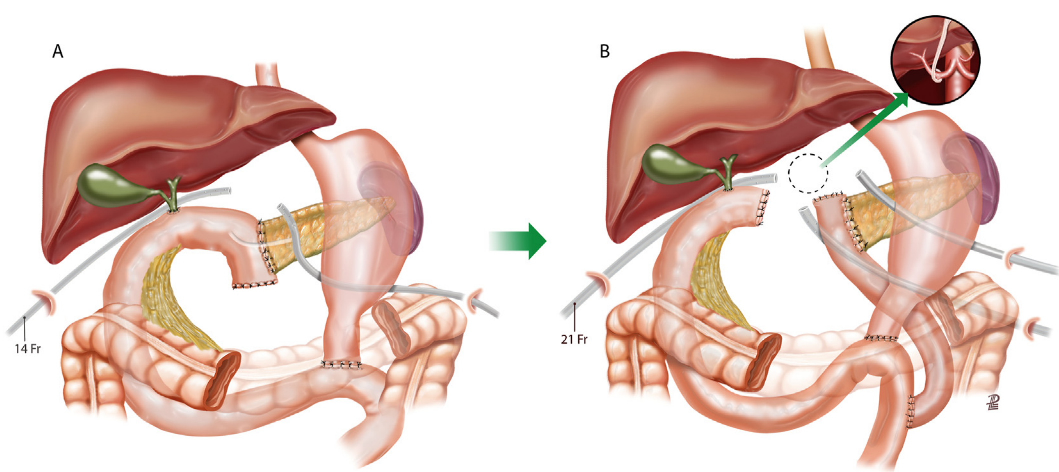

Fig. 1. Comparison between Standard Strategy (A) and Mitigation Strategy (B).

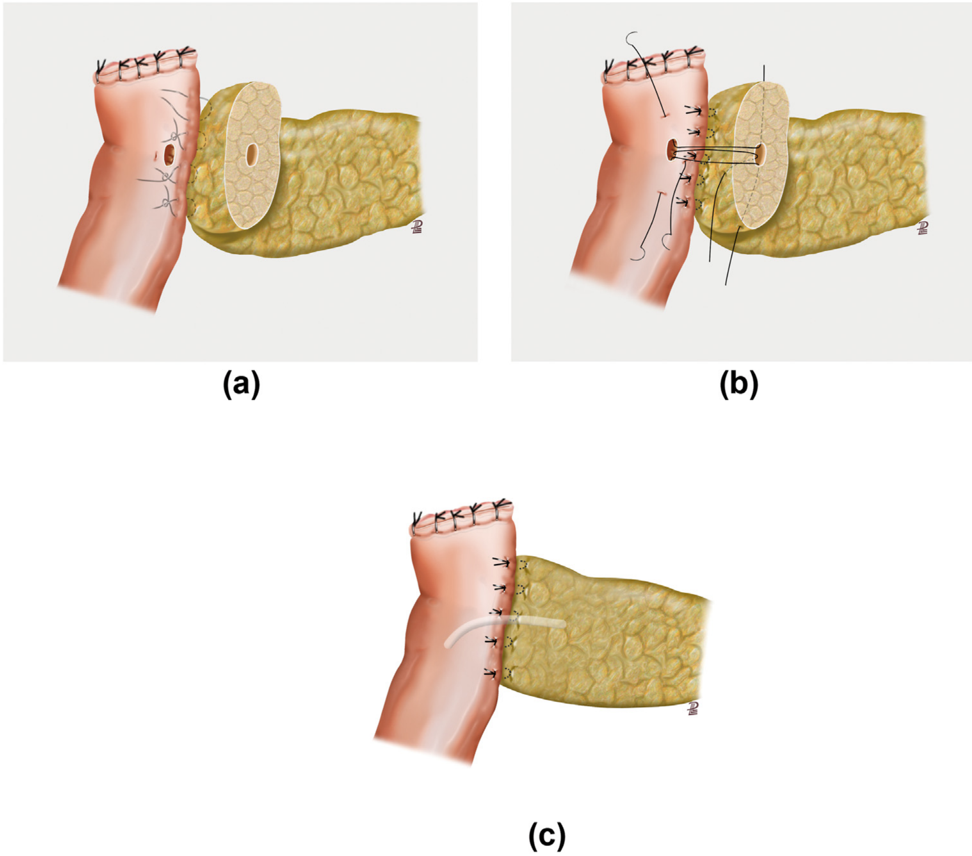

Fig. 2. Technical details of pancreatic anastomosis in Mitigation Strategy group: posterior outer layer with interrupted U sutures (2a); inner layer with full-thickness sutures (2b); anterior outer layer with interrupted U sutures, final aspect of the anastomosis (2c).

Perioperative management

Perioperative management was similar between the study periods. Preoperative endoscopic biliary drainage was indicated in case of suspected preoperative cholangitis or expected preoperative bilirubin >20 mg/dL. All patients received preoperative single-dose antibiotic prophylaxis with Piperacillin-Tazobactam. Prophylactic octreotide was never used. Standard lymphadenectomy was performed in all patients according to ISGPS criteria [14]. Drain fluid amylase was measured on postoperative day 3 and 5. Fluid from each drain was analyzed separately and level more than three times the normal serum amylase was considered significant. Drainages were removed in absence of concern for clinical POPF on day 5. Nasogastric tube was removed at postoperative day 3 in absence of clinical concerns for delayed gastric emptying, pancreatic leakage, or other intra-abdominal complications. CT-scan of the abdomen with arterial and venous phases was performed in all patients with suspected POPF. Total parenteral nutrition (TPN) was used only in patients unable to tolerate oral feeding during >5 days. Wide spectrum antibiotics were administered in all patients with B and C POPF, and final antibiotic treatment was decided based on the results of blood and drain fluid cultures. Octreotide was used to treat POPF in SS Group only. In case of POPF, drains were gradually mobilized before complete removal. Main differences between MS and SS Group are showed in Table 1.

Table 1
Main differences between MS and Standard Strategy Group. GDA: gastro-duodenal artery; POPF: post-operative pancreatic fistula; CT: computed tomography; TPN: total parenteral nutrition.

	Mitigation Strategy	Standard Strategy
Anastomotic technique (PJ)	Modified Heidelberg	Cattel-Warren
PJ reconstruction	Isolated jejunal loop	Common jejunal loop
N. of drainages	3 (21 Fr)	2 (14 Fr)
Pancreatic Stent	Internal	Internal
GDA wrapping with Teres ligament	Yes	No
Prophylactic Octreotide	No	No
Management of POPF	Abdominal CT + TPN (B2-C) + antibiotics	

Statistical analysis

All categorical data are presented as the number of cases and percentages. Chi-square and Fisher's exact tests, when appropriate, were used to compare proportional data between patients underwent each type of reconstruction. Continuous nonparametric data were expressed as the median with interquartile range (IQR), while parametric data were expressed as the mean with standard deviation (SD). The Mann-Whitney *U* test was used for comparing nonparametric variables, and the *t*-test was used for parametric continuous variables. To elucidate the independent predictors of clinical POPF, all potential relevant factors were divided according to the hierarchical order in which they were expected to occur (i.e., preoperative and intraoperative). Multivariate hierarchical logistic regression analyses were run to adjust for covariates and to obtain the odds ratio (OR) and parameter estimates. The models were set entering the groups of variables in the previous order, controlling for the effects of variables retained from the first input. The improvement in performance was established by calculating the p values from the change in chi-square resulting from each inclusion.

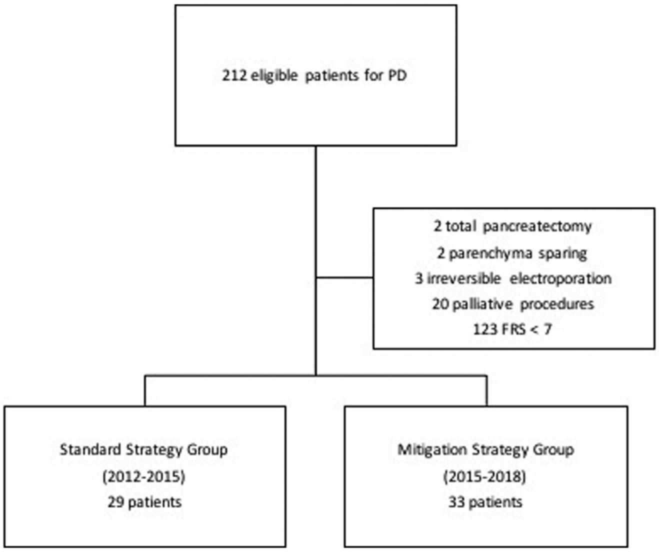

Fig. 3. Flowchart of patients included in our study. PD: pancreaticoduodenectomy; FRS: fistula risk-score.

All the tests were 2-sided, and the threshold of significance was set at $p < 0.05$. Statistical analyses were performed using Statistical Package for Social Sciences software (IBM SPSS Statistics, Version 25 for Macintosh; IBM Corp., Armonk, NY, USA).

Results

Out of 212 patients assessed for eligibility, a total of 62 PD patients with high FRS score were included in the present study. Flowchart listing reasons for exclusion is showed in Fig. 3.

Preoperative baseline characteristics and intraoperative features are showed in Table 2. There were no patients with previous neoadjuvant treatment (FRS < 7). All patients showed soft pancreatic texture. Wirsung duct size was either 1 mm (61.3%) or 2 mm (38.7%). There were no patients with chronic pancreatitis. According to FRS, 56 (90%) patients scored 7 points, 2 patients scored 8 points and 4 patients scored 9 points.

Baseline comparison between groups showed significantly higher operative time for MS Group (280 vs 250 min, $p = 0.018$). No other significant differences were detected.

Postoperative outcomes within 90 days are showed in Table 3. Clinically relevant POPF occurred in 17 (27.4%) patients. However, a higher FRS was not associated with POPF development (7 points = 28.6%; 8 points = 50%; 9 points = 0).

MS Group showed significantly lower incidence of POPF B/C (12.1% vs 44.8%, $p = 0.005$). DGE (15% vs 55.2%), postoperative pancreatitis (21.2% vs 69%), and hospital stay (13 vs 21 days) were also significantly lower in MS Group ($p = 0.001$, $p = 0.001$ and $p < 0.001$, respectively). There was no type C POPF in this group. Although major complications (Clavien-Dindo 3–4) were not statistically different (18.2% vs 37.9%, $p = 0.082$), CCI score was significantly lower in MS (20.9 vs 34.6, $p < 0.001$). There was no 90-day mortality in this series.

Hierarchical logistic regression analyses were run including all relevant variables. Addition of the intraoperative variables to the prediction of POPF led to a statistically significant increase in R2 of 0.149 (X2 $p = 0.006$). In the final model, two variables were found to be independent predictors for clinically relevant POPF: BMI (OR = 1.196, 95% CI: 1.012–1.415; $p = 0.036$) and the Mitigation Strategy (OR = 0.187, 95% CI: 0.040–0.869; $p = 0.032$) (Table 4).

Discussion

In this study, we demonstrated that a multifactorial MS can reduce the incidence of clinically relevant POPF after PD in high-risk patients (FRS 7–10). This strategy includes a meticulous pancreatic anastomosis, isolation of pancreatic leak from biliary content and an aggressive prophylactic drain policy.

Pancreatic fistula represents the Achille's heel of pancreatic surgery and most of the literature has focused on the difference between PJ and PG. The most recent meta-analysis using the 2016 updated definition of POPF showed no difference between the 2 techniques [15].

We believe that POPF is not only related to a single technical

Table 2
Preoperative baseline characteristics and intraoperative features (n = 62). BMI: Body Mass Index; ASA: American Society of Anaesthesiology; POPF: post-operative pancreatic fistula.

	Mitigation Strategy (n = 33)	Standard Strategy (n = 29)	Total (n = 62)	p value^{test}
Preoperative baseline				
Age *[median (IQR)]*	67 (17)	69 (12)	68.5 (14)	0.882^{u}
Male gender *[n (%)]*	19 (57.6%)	18 (62.1%)	37 (59.7%)	0.719^{c}
Charlson score *[median (IQR)]*	7 (3)	6 (3)	7 (3)	0.769^{u}
BMI *[median (IQR)]*	25 (5.52)	26.2 (6.7)	26 (6.17)	0.259^{u}
Albumin *[median (IQR)]*	3.9 (1.07)	3.9 (0.85)	3.9 (0.74)	0.425^{u}
Biliary drainage *[n (%)]*	2 (6.1%)	4 (13.8%)	6 (9.7%)	0.405^{f}
Previous abdominal surgery *[n (%)]*	2 (6.1%)	3 (10.3%)	5 (8.1%)	0.658^{f}
ASA score *[n (%)]*				0.356^{c}
2	12 (36.4%)	7 (24.1%)	19 (30.6%)	
3	21 (63.6%)	21 (72.4%)	42 (67.7%)	
4	0 (0%)	1 (3.4%)	1 (1.6%)	
Intraoperative				
Vascular resection *[n (%)]*	3 (9.1%)	3 (10.3%)	6 (9.7%)	1^{f}
Score POPF *[n (%)]*				0.616^{f}
- **7–8**	30 (90.9%)	28 (96.6%)	58 (93.5%)	
- **9–10**	3 (9.1%)	1 (3.4%)	4 (6.5%)	
• 701–1000 ml Bleeding	3 (9.1%)	2 (6.9%)	5 (8.1%)	1^{f}
• Soft Texture	33 (100%)	29 (100%)	62 (100%)	
• Pathology other than PDAC	26 (78.8%)	23 (79.3%)	49 (79%)	0.960^{c}
• Duct Diameter (1 mm)	19 (57.6%)	19 (65.5%)	38 (61.3%)	0.522^{c}
Operative time *[median (IQR)]*	280 (50)	250 (53)	270 (60)	0.018^{u}

Table 3
Postoperative outcomes within 90 days (n = 62). POPF: post-operative pancreatic fistula; PPH: Post-Pancreatectomy Haemorrhage; DGE; delayed Gastric Emptying, C-D: Clavien-Dindo score; CCI: Comprehensive Complication index.

	Mitigation Strategy (n = 33)	Control (n = 29)	Total (n = 62)	p value[test]
POPF *[n (%)]*	4 (12.1%)	13 (44.8%)	17 (27.4%)	0.005[f] 0.519[f]
Type B	4 (100%)	9 (69.2%)	13 (76.5%)	
(B1/B2/B3)	(0/4/0)	(0/7/2)	(0/11/2)	
Type C	0 (0%)	4 (30.8%)	4 (23.5%)	
POPF duration (days) *[median (IQR)]*	23 (9)	34 (29)	27 (23)	0.245
POPF max. vol/day *[median (IQR)]*	260 (170)	300 (300)	300 (150)	0.703
Pancreatitis *[n (%)]*	7 (21.2%)	20 (69%)	27 (43.5%)	<0.001[c]
PPH *[n (%)]*	2 (6.1%)	6 (20.7%)	8 (12.9%)	0.131[f] 0.429[f]
Type B	2 (100%)	2 (33.3%)	4 (50%)	
Type C	0 (0.0%)	4 (66.7%)	4 (60%)	
DGE *[n (%)]*	5 (15.2%)	16 (55.2%)	21 (33.9%)	0.001[c] 0.522 [f]
Type B	3 (100%)	10 (66.7%)	13 (72.2%)	
Type C	0 (0%)	5 (33.3%)	5 (27.8%)	
Bile leakage *[n (%)]*	0 (0%)	1 (3.4%)	1 (1.6%)	0.468[f]
Relaparotomy *[n (%)]*	0 (0%)	4 (13.8%)	4 (13.8%)	0.304[f]
Blood transfusion *[n (%)]*	1 (3%)	4 (13.8%)	5 (8.1%)	0.176[f]
Complications C-D ≥ 3 *[n (%)]*	6 (18.2%)	11 (37.9%)	17 (27.4%)	0.082[c]
CCI *[median (IQR)]*	20.9 (28)	34.6 (21)	23.4 (31)	<0.001[u]
Hospital stay *[median (IQR)]*	13 (10)	21 (18)	18 (12)	<0.001[u]
Readmission *[n (%)]*	2 (6.1%)	4 (13.8%)	6 (9.7%)	0.405[f]

Table 4
Results from hierarchical logistic regression analyses on the association between the variables of interest and POPF grades B-C (n = 62). BMI: Body Mass Index.

	Odds Ratio	(95%CI)	p value	Nagelkerke R^2 (H-L test p value)	R^2 change X^2 (p value)
Preoperative variables				*0.151 (0.251)*	*0.151 6.837 (0.009)*
Age (years)	1.011	0.946–1.079	0.752		
Male Gender	1.633	0.321–8.317	0.555		
Charlson score	0.919	0.628–1.345	0.664		
BMI (kg/m2)	**1.196**	**1.012–1.415**	**0.036**		
Albumin (mg/dL)	2.119	0.659–6.806	0.207		
Operative variables				*0.300 (0.680)*	*0.149 7.591 (0.006)*
Mitigation Strategy	**0.187**	**0.040–0.869**	**0.032**		
Operative time (min)	0.995	0.973–1.019	0.693		
Blood loss (701–1000 ml)	1.152	0.078–17.101	0.918		
Absence of PDAC	1.301	0.219–7.734	0.772		
Duct diameter (1 mm)	1.522	0.351–6.597	0.574		

factor: for this reason, in 2015, following an internal audit we decided to modify our approach to patients in high-risk zone (FRS 7–10) introducing a Multifactorial Mitigation strategy:

- *Anastomotic technique*: our decision to adopt Heidelberg anastomosis was based on the published data that showed almost nil fistula-related mortality in large series [16]. The original anastomotic technique was modified as explained in the Methods paragraph by performing a smaller incision on the jejunal loop similarly to a duct-to-mucosa anastomosis and using U-sutures for outer layers to avoid tension on soft pancreatic parenchyma.
- *Internal stent*: there is no clear evidence that either internal or external pancreatic stenting can reduce pancreatic leak rate [17]. Encouraging data have been published about the use of externalized stent to mitigate POPF in high-risk patients [18]. However, the malfunctioning rate in case of such small stents could be very high, as recently reported by Andrianello et al. (36% of high FRS patients, with a 65% POPF rate within this group) [2]. Moreover, a 3-French stent with sufficient length to be externalized is not available. In our normal practice, we never place a 5 French stent into a ≤1 mm duct because we believe it could increase the risk of postoperative pancreatitis.
- *Isolated jejunal loop PJ*: this technique was previously described, and similar POPF rate compared to other reconstructions have been reported [19]. It has been hypothesized that isolating pancreatic anastomosis is associated with absence of contamination by biliary content or oral feeding even in case of POPF [20,21], as also recently demonstrated by the Heidelberg group [22].
- *The use of Teres ligament* to prevent bleeding caused by POPF was previously described, and several cohort studies have demonstrated lower bleeding rate following GDA wrapping [23].
- *Aggressive prophylactic drains policy:* routine drainage following PD seems to be slightly associated with a 90-day mortality reduction [24]. Although the use of drains is questionable in low FRS patients, we believe it is mandatory in patients with high FRS, as expected POPF rates could rise up to 50% [3].We also decided to increase number of drains and upsize caliber as if we were treating complicated acute pancreatitis [25]. In our series, adequate drainage could have contributed to avoid reoperations and type C POPF in MS Group.
- Finally, *standardization of perioperative management* is crucial [26], and we believe that teamwork is of the utmost importance to achieve good results.

Our multifactorial MS combines techniques or strategies that were previously described. We think the novelty of our study is the simultaneous adoption of these changes, which has not been previously described. We believe postoperative pancreatitis is the trigger for POPF in most cases, and we managed to reduce in the first instance the occurrence of this complications: Heidelberg technique seems less traumatic on pancreatic stump compared to other pancreaticojejunal anastomoses, avoiding both tearing of pancreatic surface and compression on pancreatic duct. Also, we used a 3-Frech pancreatic stent which has not been previously described: we think that in case of 1-mm duct using a larger stent might cause pancreatic injury (5-French = 1,67 mm). All the other measures we adopted in our strategy aimed to reduce the complications caused by pancreatic juice, such as infection and bleeding. We were unable to identify the weight of each factor on POPF development, although we feel that analysing each technique individually would require a study with a complex design and a much larger population.

Because of the introduction of this multifactorial approach, the rate of clinically-relevant POPF was reduced from 44.8% to 12.1% in high-risk pancreatic anastomosis. In this setting, the MS was significantly associated with 5 times lower odds of POPF. Few studies have previously focused on high FRS patients [26,27]. Ecker et al. analyzed the outcome of 522 high FRS patients in a multinational study showing that use of external stents and omission of prophylactic octreotide were independently associated with decreased POPF in PJ setting [18]. However, no deep technical details on anastomotic technique, strategy of reconstruction and perioperative management were provided. In this series, BMI was independently associated with clinically relevant POPF. This is consistent with the findings of a recent multicentric study validating an alternative FRS based on pancreatic texture, duct diameter and BMI [28].

Limitations

The retrospective nature and the relatively small sample size are potential limitations of this study. However, data were extracted from a prospectively held database including consecutive patients from a single surgeon/institution, thus mitigating the risk of bias. Also, the ISGPS definition of POPF changed in 2016, and classification of subtype of Grade B might not be accurate. The Groups belong to different time periods and it could be argued that the results have improved over time with the growing experience. Although this bias cannot be completely ruled out, the senior surgeon who performed all the high-FRS procedures had completed his learning curve before the start of the study period. Additionally, the observed rate of POPF in the SS Group was 44.8%, which was similar to the rate reported by very high-volume centers (44.4% in highest fistula risk zone) [3].

Conclusion

POPF is an inevitable complication for high FRS patients. However, the incidence and the impact of clinically relevant POPF could be diminished by the adoption of a multifactorial mitigation strategy. Personalized approach for vulnerable patients should be explored in the future.

Declaration of competing interest

Authors declare no conflict of interest for this article.

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