

Pancreatic Duct Occlusion: A Safe and Valid Alternative to Duct Anastomosis After Pancreaticoduodenectomy in a Low Volume Centre

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Abstract

Background: Pancreaticoduodenectomy is the only possible choice of treatment for peri-ampoullar neoplasms. Morbidity in pancreatic surgery is mainly related to the development of a postoperative pancreatic fistula (POPF). According to International Study Group on Pancreatic Fistula it is possible to grade POPF based on clinical variables. Three main different surgical strategies have been proposed to deal with the pancreatic stump following pancreaticoduodenectomy: pancreatojejunostomy, pancreatogastrostomy and pancreatic duct occlusion, but none of them has been clearly demonstrated to be superior to the others. The aim of our study is to evaluate the feasibility of duct occlusion and its correlations with postoperative pancreatic fistula, “brittle diabetes” and overall survival in a low volume centre. We decided to review our previous experience in the light of the recent Covid pandemic where, in our country, it has been forced in many regions to displace treatment of oncological patients in low volume hospitals with limited experience

Methods: We retrospectively reviewed 56 consecutive patients, from a prospective maintained database, who underwent Whipple’s procedure from January 2007 to December 2014 in a tertiary Hepatobiliary Surgery and Liver Transplant Unit with a low volume of pancreatic resections. The mean follow-up was 24.5 months.

Results: The overall incidence of postoperative pancreatic fistula was 66.6%: 15 patients had a Grade A (31.25%), 13 a Grade B fistula (27.03%), and 4 (8.3%) suffered from a life-threatening Grade C fistula. At the last follow-up, 24 of the 28 patients who were alive (85.6%) habitually used substitutive pancreatic enzyme.

Conclusion: Duct occlusion can be a safe alternative to pancreatic anastomosis especially in low volume centres and for those patients (age >75 years, obese, hard pancreatic texture, small pancreatic duct) at higher risk of clinically relevant POPF.

Trial registration: 'retrospectively registered'

Background

Surgical resection is the only possible choice of treatment in several pancreatic disorders including malignancies, adenomas, traumas and severe acute and/or chronic pancreatitis [1]. Radical resection is the single most important factor in determining outcomes in patients with pancreatic adenocarcinoma [1–3].

In experienced hands, the mortality rate following pancreaticoduodenectomy (PD) is 3–5%, however, morbidity rates remain high, ranging from 30–50% [4–7].

Morbidity in pancreatic surgery is mainly related to the development of a postoperative pancreatic fistula (POPF). According to International Study Group on Pancreatic Fistula (ISGPF) [8] it is possible to grade

POPF based on clinical variables. “A grade” fistulas, as called a “biochemical leak” (BL) in update classification, does not need any treatment (currently it is not considered a true pancreatic fistula) and implies no clinical impact. “B grade” fistulas can be managed with medications and only prolong length of hospital stay in association with a clinically relevant condition. “C grade” fistulas need operative treatment and might be life-threatening [7]. In high volume centres for pancreatic surgery the overall POPF incidence is around 20% [7–9].

Intra-abdominal abscesses, delayed gastric emptying, post-pancreatectomy haemorrhage and sepsis represent additional sources of morbidity. In most cases, however, they occur in association or as a consequence of POPF [10, 11].

Advanced age (> 75 years), pancreas texture, pancreatic duct diameter, comorbidities, previous endoscopic retrograde cholangiopancreatography (ERCP), duct obstruction and surgical technique are known risk factors for postoperative morbidity [7–9].

The incidence of postoperative complications has a significant impact on the length of hospital stay, costs, quality of life and chance to start chemotherapy [12–13].

Several different surgical and pharmacological approaches have been proposed to avoid POPF which might be different depending on the experience and preferences at each centre [14].

Three main different surgical strategies have been proposed to deal with the pancreatic stump following PD: pancreatojejunostomy (PJ), pancreatogastrostomy (PG) and pancreatic duct occlusion (DO), but none of them has been clearly demonstrated to be superior to the others [15].

In spite of such detailed reporting of morbidity and mortality following PD, it is still not clear whether is surgeon’s experience or hospital volume to rescue patients when a complication occurs [15]. If PJ is the procedure of choice in medium/high volume centres, DO could be proposed as a safer alternative in medium/low volume centres, in order to reduce the risk of major postoperative complications.

We decided to review our previous experience in the light of the recent Covid pandemic where, in our country, it has been forced in many regions to displace treatment of oncological patients in low volume hospitals with limited experience [16]. The encouraging results of DO in terms of overall survival, POPF and “brittle diabetes” are here presented.

Methods

Study Design

We retrospectively reviewed 56 consecutive patients who underwent Whipple’s procedure from January 2007 to December 2014 in a tertiary Hepatobiliary Surgery and Liver Transplant Unit with a low volume of pancreatic resections.

All data were obtained from a prospective maintained database and analysed retrospectively. For this type of study due to its retrospective nature a formal ethical review was exempt and a formal consent is not required.

Eight patients were lost at follow up so the analysis on morbidity was conducted on the 48 patients available with a mean follow-up of 25.4 months.

In all cases DO was performed with Cyanoacrylate glue injection.

We recorded data about medical history, Body Mass Index (BMI), American Society of Anaesthesiologists' (ASA) score, preoperative CA19.9, survival, mean operative time, incidence of POPF, incidence of sepsis, incidence of post-operative haemorrhage, re-laparotomy rate, hospital stay, incidence of preoperative and postoperative diabetes, 30-day and 90-day postoperative mortality, oncological recurrence and pancreatic exocrine function.

Pancreatic exocrine function was evaluated by personal or telephonic interviews assessing any substitutive pancreatic enzyme therapy (yes/no) related to steatorrhea/diarrhea since surgery.

Pre-operative work up

Our preoperative work up consisted of total body CT and/or MRI scan for oncological staging and for the exact determination of tumor size and resectability. If total bilirubin was higher than 20 mg/dl a biliary drainage was placed via ERCP in patients whose surgery was not scheduled within two weeks.

Surgical technique

We performed a Whipple procedure with an open approach. : gastrectomy was performed using GIA 90 without pylorus preservation.

After pancreatic resection, we performed DO of the Wirsung duct with Cyanoacrylate glue independently from the stump characteristics. In detail, the pancreatic stump was closed with 3/0 polypropylene stiches during glue polymerization while the catheter inserted in the main pancreatic duct for glue injection was simultaneously removed to obtain a complete duct closure.

We finally performed biliary reconstruction with a Roux-en-Y anastomosis.

Two abdominal drainages were placed (one close to the pancreatic remnant and one in the pelvis).

Postoperative care

All patients stayed at least one day in the intensive care unit (range:1-3 days) and then returned to the ward. Amylase and lipase were routinely monitored either in serum and in the drainage starting from postoperative day 3. POPF was defined according to ISGPS [8, 15].

A cephalosporin + metronidazole regimen was always used. Octreotide 0,1 ml was administered subcutaneously three times a day. In absence of POPF patients were allowed oral intake on postoperative day 5.

Complications were graded according to Dindo-Clavien classification [19].

Statistical Analysis

Descriptive statistics were collected and reported as whole number (percentage) and mean or median (range).

The Fisher exact test was used to compare categorical data. Differences were considered to be statistically significant with P values <0.05.

Results

Baseline characteristics of patients are depicted in Table 1.

Table 1
Baseline and preoperative characteristics of the patients

Median age (years)	62 (r.: 34–78)
Gender (M/F)	29/19
Comorbidity (n)	Hypertension 13 (23.2%) Diabetes 6 (10.6%) Chronic obstructive pulmonary disease 5 (8.9%) Atrial fibrillation 2 (3.6%)
BMI (n)	30 (62%)
< 30	18 (38%)
> 30	
ASA score	1 (2%)
I	16 (33%)
II	19 (40%)
III	12 (25%)
IV	
Preoperative Ca19.9 (median)	221.5 U/ml (r.: 1-2734.1)

Median age was 62 (r 34–78) years. The male/female rate was 33/23.

Indication for surgery were as follows: Pancreatic adenocarcinoma in 22 (39.2%), Ampulloma in 20 (35.7%), Biliary duct adenocarcinoma in 6 (10.7%), Cystadenoma in 3 (5.4%), Neuroendocrine tumours in 3 (5.4%), post ERCP severe pancreatitis in 1 (1.8%), and Gastric cancer recurrence in 1 (1.8%).

No patients underwent a pylorus-preserving procedure nor a vascular resection.

Postoperative results are depicted in Table 2.

Table 2
postoperative results

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Operative time (mean, minutes)	329 (r.: 221–480)
Postoperative haemorrhage (n)	11 (19.6%)
Morbidity according to Dindo-Clavien	Grade I: 6 (13%) Grade II: 7 (15%) Grade III: 5 (10%) Grade IV: 2 (4.0%) Grade V: 4 (9.0%)
Histology	22 (39.3%)
pancreatic adenocarcinoma	20 (35.7%)
ampulloma	6 (10.7%)
bile duct cancer	8 (14.3%)
other	
Pancreatic texture	46 (82.1%)
- soft	10 (17.9%)
- hard	
Pancreatic duct diameter	34 (70.7%)
- < 3 mm	22 (29.3%)
- > 3 mm	
Reoperation rate	9 (19%)

Eight patients (16.6%) were lost at the follow-up.

The overall incidence of POPF was 66.6%: 15 patients had a Grade A POPF (31.25%), 13 a Grade B fistula (27.03%), and 4 (8.3%) suffered from a life-threatening Grade C fistula.

Mean hospital length of stay was 29 (12–56) days with an overall POPF mortality rate of 8.3%.

Pancreatic duct diameter was < 3 mm in the 70% of cases, our percentage of small wirsung diameter is the highest compared to other authors as depicted in the Table 2.

Our incidence of reoperation was 19.6% (Table 4), it was linked to Grade C POPF in 5 patients (45.4%)

The incidence of POPF according to pancreatic texture is depicted in picture 1.

Thirteen (23.2%) patients developed a Dindo-Clavien Grade I-II complication according to data found in literature [17-19-20-21-22].

Of the four patients with a Grade C fistula, two died, accounting for a mortality rate as high as 50%, whereas postoperative mortality for patients with Grade A and Grade B fistula was 7.1% (2/28) (Table 3).

Table 3
Cause of perioperative death

Mortality	N° of Patients	Cause	POPF
30-days	1	Shock-MOFS	No POPF
	1	MOFS	C grade
	1	Stroke	A grade
90-days	1	Haemorrhage-MOFS	B grade
	1	MOFS	C grade

Table 4
Re-operation rate

Type of operation	N°	POPF	Follow-up
Hemostasis	4 (8.3%)	A	1 dead 7 months po
		NO	1 dead 30 days po
		A	1 alive 78 months
		No	1 alive 12 months
Total pancreatectomies	2	C	1 alive 100 months
		C	1 dead 30 days po
GI Fistula	1	C	1 alive 8 months
Re-anastomosis Bilio-jejunal	1	C	1 alive 27 months
Explorative laparotomy	1	C	1 dead 90 days post-op

Only 5 patients (9%) developed a brittle diabetes, and 13 patients (27.1%) had new onset diabetes after PD.

At the last follow-up, 25.4 months mean after surgery, 24 of the 28 patients who were alive (85.6%) habitually used substitutive pancreatic enzyme.

Overall survival of the 48 remaining patients at the last follow-up as above was 58.3% (Table 3).

Discussion

PD represents the ideal treatment for periampullary lesions. Complications related to pancreatic duct reconstruction are still the leading cause of morbidity and mortality.

Evidences support a strong correlation between surgical outcomes and hospital volume in pancreatic surgery [23–26].

Mortality can be used as an indicator of quality of surgery for PD, but literature lacks an agreed description of the standard of care for such a complex procedure [23].

Surgical outcomes after PD are better in centres performing more than 50 resections per year with a reported overall mortality of less than 5%, compared with a mortality rate of 12.4% in low-volume centres [25, 28]. Centres can be considered for pancreatic surgery accreditation if they meet the requirement of 50 pancreatic procedures (including PD) over 3 years with a mortality rate lower than 50% [28].

In a recent study of Krautz et al., the mortality rates reported in Germany ranged from 6.5% in very high-volume hospital to 11.5% in very low-volume ones [30]. Considering only high-volume centres, mortality rates can be below 2% [31].

Similarly, the overall mortality rate in more than 1500 PD performed in Italy was reported to be as high as 8.1% [25]. The authors classified hospitals according to volume in low-volume, (< 5 PD/year), medium-volume (6–13 PD/year), high-volume (14–51 PD/year) and very high-volume (> 90 PD/year) centres, and found that post-operative mortality rate decreased progressively from 12% (low-volume hospitals) to 2.6% (very high-volume hospitals) [25].

Our results show an overall pancreatic surgery-related mortality, as high as 8.3%, which is lower compared to the observed mortality for low-volume centres [25].

However, in the experience of a high-volume centre, postoperative mortality after PJ seemed to be higher than after DO (6.8% vs 2.4%) [32].

Pedrazzoli in a large systematic review on Pancreaticoduodenectomy and pancreatic fistula analysed 162 articles involving 54,232 patients. The review shows 4813 Grade A (8.9%), 4830 Grade B (8.9%), and 1872 Grade C (3.5%) POPFs with a mean overall fistula rate of 21.3%. A huge variability of Grades A and B POPFs varied from less than 2% to more than 20% with a minimum of 0% and a maximum of 42.5% for Grade A and a minimum of 0.7% and a maximum of 33.3% for Grade B POPF. Grade C POPFs arises from 1% to more than 9% with a maximum of 13.6% [21].

It has been suggested that avoiding an anastomosis of the pancreatic duct by means of duct occlusion could minimize anastomosis-related morbidity, especially in low-volume centres [17, 18, 32, 3]. The aim

was to obtain a “*pure*” pancreatic fistula with no activation by bile and/or enteric juice, thereby reducing the risk of life-threatening complications.

Di Carlo et al showed that DO procedure was feasible and less time-consuming than PJ, although it could be associated with higher fistula rates. However, POPF could not be clinically relevant probably due to the absence of a pancreatic enzymes activation [33].

In our experience the overall incidence of POPF was 66.6%. This observation is consistent with the experience of Tersigni et al, who observed a higher rate of POPF after DO (45.4%) compared to end-to-end PJ anastomosis (15.6%) and to end-to-side PJ anastomosis (11.3%), with a similar incidence of Grade C fistula in all the groups (3.1% after end-to-end PJ anastomosis, 2.3 after end-to-side anastomosis and 3.0% after DO) [32]. In our hands only 4 patients (8.3%) had a life-threatening POPF. In a recent study comparing 54 patients operated on in a high-volume centre with 44 patients operated on in a low-volume centre over five years, there were no statistical differences in the incidence of POPF between the two groups (30% vs 27%, $P = 0.826$) [18]. All patients in this study had a PJ after PD. Interestingly, the rates of Grade C fistula were 25% in the high-volume centres and 17% in the low-volume centre. These figures are slightly higher than those observed in our centre with DO. Others have reported that DO has higher postoperative morbidity and mortality, even if not statically significant [17].

Consistent with other reports, in our patients a soft pancreatic texture was associated with a significantly higher incidence of POPF (overall 27.1% of POPF with soft pancreas vs. 6.25% of POPF with fibrotic pancreas, $P = 0.0068$).

Moreover, when considering only clinically relevant POPF, we had only 2 POPF (4.2%) with fibrotic pancreas versus 15 POPF (31.4%) with soft pancreas ($P < 0.005$).

In a recent prospective randomised control study [21] compared POPF following PO in high risk patients for pancreatic fistula vs PJ after PD for low risk patients for pancreatic fistula, mortality after PO was 5.9% and 2.0% after PJ anastomosis, in our serie 90-day mortality related to significant POPF was (3/48) 6%, so mortality might be considered superimposable with other authors who performed DO (Table4) .

He et al. analysed RCTs and OCSs, where were related different treatment of pancreatic stump and maojor outcomes after PD or pylorus-preserving PD for malignant or benign pancreatic tumor, chronic pancreatitis, or extra- pancreatic tumors (periampullary, biliary or duodenal)

The objective of the metanalysis was a comparison between PJ and PG using quantitative data on PF and overall complications. PD without anastomosis, or duodenum-preserving pancreatectomy was excluded. (He et. al) [24] We shall underline metanalysis by He et al. reported a lower mortality index performing PG and PJ, but these data were published by high volume and referral centres for pancreatic surgery [28], the same paper reported data by Duffas et al. showing in their experience an incidence of death after PG 10 (12%) and PJ 7 (10%). A summary of these findings is depicted in Table 5.

Our incidence of reoperation was quite high 19.6% (Table 4), it was linked to Grade C POPF in 5 patients (45.4% of C grade fistula patients) our incidence is similar to what other authors reported in literature either after DO either after PA [20-21-23-27], but as depicted in the Table 5, high volume referral centre showed lower rate of reoperations.

In our opinion, in patients with a higher risk for POPF (soft pancreas, dilated pancreatic duct) DO can be a safer option, ideally suitable in low-volume centres.

Four of our patients (8.3%) had postoperative haemorrhage, and all of them needed return to operative room. Interestingly, in only two patients (50%) haemorrhage was a consequence of POPF (all grade A). In the other two cases the bleeding originated from a small vessel from the portal vein and the gastroepiploic artery. The overall incidence of POPF-related bleeding was 4.2%, which is in line with other experiences [15].

Our length of stay was 28 days, higher than those observed in other experiences [7, 18]. Of note, availability of post-discharge opportunities, financial problems, low human resources and patients wish could affect this figure.

More than 80% of patients needed pancreatic enzymes supplementation due to postoperative pancreatic insufficiency. This facet is consistent with others [15–17] however, Tran et al reported that the need for enzyme supplementation one year after surgery was not related to the type of reconstruction [17] Probably, pancreatic exocrine insufficiency is more related to the pancreatic atrophy/fibrosis and preoperative texture than to DO or PJ [15–17].

In our series, 9% of patients developed brittle diabetes, with only 13 patients (27.1%) developing new onset diabetes. This might confirm that DO has higher risk of new onset diabetes, even if only few patients suffer from an uncontrolled diabetes [15–17].

According to Tran et al., the incidence of endocrine insufficiency is significantly higher after DO compared with PJ at 3- and 12-month follow-up after surgery ($P = 0.001$ for both) [17].

It is clear that the outcome of complex surgical procedures may not only rely on technical aspects of surgery, but it is also affected by resource availability. However, some technical aspects can be modified and reduce the risk of life-threatening postoperative complications even in low/medium volume centres.

PD can be safely performed in low-volume centres if amenities and processes typical of high-volume centres can be replicated in specialized units [34–35].

The ideal concept of reserving pancreatic surgery only to high specialized centres is probably *utopian*. Geographical limitations, elevated costs for the patients and their relatives, political issues, different regional health-care systems, and the opposition by medical and surgical staff determine the need to perform this surgery even in academic or tertiary referral hospitals with a limited experience in pancreatic surgery [19] but with all the amenities required for very complex surgery.

According to Diaz et al. although most patients who need PD bypass the nearest providing hospital to seek care at a higher-volume hospital, nearly 25% of the patients still underwent PD at a low-volume centre [36].

So, considering criteria published in literature [23–26], pancreatic surgery should be centralized, this implies unavoidably an increase of interregional mobility and related health care costs, especially for patients from region of southern Italy.

During Covid-19 pandemic, as we know from the survey written by Aldrighetti et al. on HPB surgery in Italy [16], 72.8% of HPB centers showed a reduction of routine elective operations $\geq 50\%$, if we combine effects of centralization to the effects of Covid-19 pandemic we understand how difficult would be for patients to undergo pancreatic surgery in a quite fast, safe and effective way. In this situation we decided to analyze our outcomes from a low volume center for pancreatic surgery to overcome the impossibility to send patients to pancreatic surgery referral centers, considering their overload, ensuring to patients a high-quality service at the same time. Our approach led us to guarantee effective treatment and safety procedures during the critical pandemic period.

Probably, a surgical alternative such as DO during the phase of PD at higher risk of complications, i.e. the pancreatic anastomosis, can reduce the rates of subsequent morbidity and mortality with similar oncological results.

Conclusions

Despite of we understand that our study is a retrospective, single-centre analysis, we considered consecutive patients who underwent PD and were registered in a prospectively maintained database. We can consider our centre as low volume due to the number of PD per year, but we can be supported by high-volume centre facilities, including a) being a referral centre for hepatobiliary surgery, liver transplantation, advanced colorectal surgery, b) having a dedicated intensive care unit, and c) having interventional radiology and endoscopy available 24 h.

A comparison of DO with other types of pancreatic duct reconstructions should be advisable in order to draw definitive conclusions, ideally by means of an adequately designed randomized controlled trial (RCT). Given the lack of such high quality evidence, our study has some merits. Our aim was to give an overview of current clinical practice in a “real life” setting, considering that not always a RCT can be performed with a sufficient power and that observational studies can be properly used with prospectively maintained series to assess feasibility of a surgical procedures.

In conclusion, DO can be a safe alternative to pancreatic anastomosis especially in low/medium volume centres and for those patients (age > 75 years, obese, hard pancreatic texture, small pancreatic duct) at higher risk of clinically relevant POPF.

Abbreviations

COVID-19: Coronavirus disease 2019

PD: Pancreaticoduodenectomy

POPF: postoperative pancreatic fistula

ISGPF: International Study Group on Pancreatic Fistula

BL: biochemical leak

ERCP: cholangiopancreatography

PJ: pancreatojejunostomy

PG: pancreatogastrostomy

DO: duct occlusion

BMI: Body Mass Index

ASA: American Society of Anaesthesiologists'

Declarations

- Ethics approval and consent to participate:

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study

Trial registration: 'retrospectively registered'

- Consent to publish

Not applicable.

- Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- Competing interests

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

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- Authors' Contributions

- AG, AR, FC: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting, editing and writing of the manuscript. These authors equally contributed to the paper. ALS: extracted all data. MC, GDN, CL , AB , MLI , MP: Participated in execution of the study and in the analysis and interpretation of data KK: Participated in the analysis and interpretation of data. BA: contributed to write the paper. All authors contributed to and revised the final manuscript. The author(s) read and approved the final manuscript.

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Figures

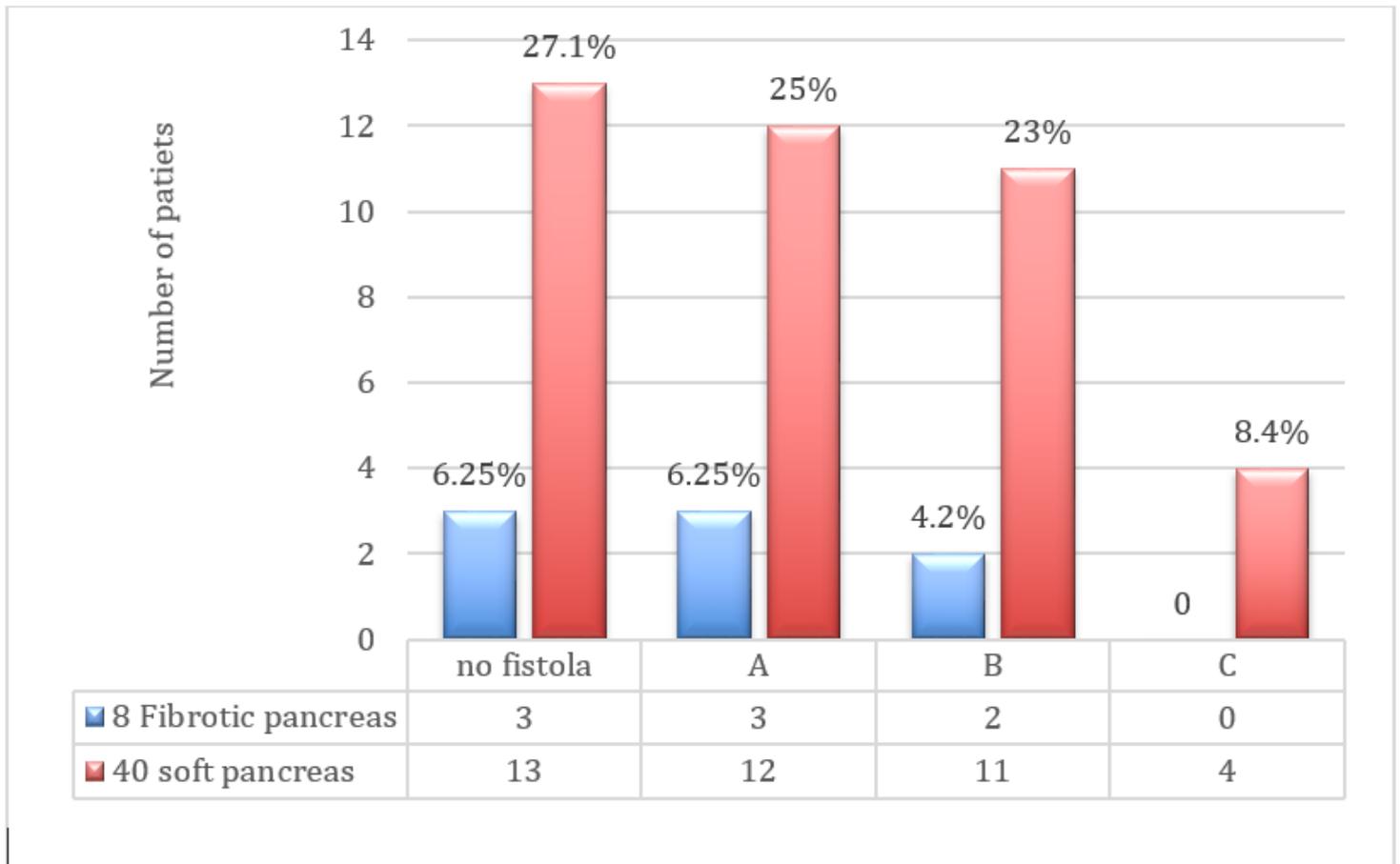


Figure 1

Picture 1: POPF according to pancreatic texture