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Original Research Article

A study on predictive factors for anastomotic leakage in enteropancreatic anastomosis in a tertiary centre in Andhra Pradesh

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ABSTRACT

Background: This study aimed to identify various factors influencing occurrence of post-operative pancreatic fistula.
Methods: Only those patients who underwent standard pancreatojejunostomy anastomosis in duct to mucosa technique using vicryl 4-0 sutures (double layer- interrupted fashion) were included in the study. Patients who had duct size ≤3 mm underwent papillary like main pancreatic duct invaginated technique of pancreaticojejunostomy (fish mouth type).
Results: In 40 patients, 10 patients (25%) developed postoperative pancreatic fistula. 5 (12.5%) patients had grade A pancreatic fistula and 5 patients had CR–POPF [grade B–3(7.5%), grade C–2(5%)]. Pancreatic fistula in relation with duct size has attained statistical significance. When all the four factors were put together and given fistula risk score, it correlated well with the occurrence of fistula. Fistula risk score has high negative predictive value. Of 40 patients, 13 patients fall into low risk zone, out of which 1 patient developed grade A fistula. 26 patients fall into moderate risk zone, out of which 4 patients developed grade A, 3 patients developed grade B and 1 patient developed grade C fistula. One patient fall into high risk zone and developed grade C fistula.
Conclusions: We found in our study that, post-operative pancreatic fistulae could be modestly predicted using fistula risk score. However, the latter had high negative predictive value and thus could be used to prognosticate risk of non-development of fistula than predicting its severity.

Keywords: Pancreatic fistula, Pancreaticojejunostomy, Fistula risk score

INTRODUCTION

Pancreaticoenteric anastomosis (pancreatojejunostomy) is still considered the Achilles heel of pancreatico-duodenectomy (PD). Among high volume centers, while the mortality rates following pancreatic surgery has come down to less than 5%, the morbidity still remains high, ranging from 30-50%.[1]

Traditionally, postoperative pancreatic fistula (POPF) has been regarded as the most frequent major complication following pancreatic resection and reconstruction.

However, a recent study has observed that the incidence of POPF is significantly lower in recent times and ranks third among different complications evaluated in terms of frequency and severity.[2] The significance of POPF lies in the fact that in addition to being a life-threatening

complication, it prolongs the hospital stay and adds on to hospital costs.

Recent literature suggests that many factors influence pancreatic leakage after pancreaticoduodenectomy, including sex, age, jaundice, operation time, intraoperative blood loss, pancreaticojejunal anastomotic technique, texture of the remnant pancreas, pancreatic duct size, use of somatostatin, and surgeon experience. However, no definite factor has yet been identified.

Prompt recognition and proper management of pancreatic fistula when it does occur are important. While many advocate conservative management of pancreatic fistula, some surgeons still favour aggressive surgical intervention.

This study is done to identify predictive factors for anastomotic leakage in enteropancreatic anastomosis and validate the fistula risk score as mentioned by Callery et al.[3] The correlation between the occurrence of pancreatic fistula and chance of morbidity and mortality were studied. By doing so, it can be used to prognosticate patient regarding chance of fistula and plan management accordingly.

Hence current study designed to evaluate the risk factors that predict post-operative pancreatic fistula and management of anastomotic leakage and to compare predictive fistula risk score and actual post-operative pancreatic fistula so as to validate fistula risk score.

METHODS

This is a prospective study conducted in the Department of Surgical Gastroenterology, Narayana Medical College, Nellore from October 2015 to December 2017. Study population was taken from the patients visiting the Department of Surgical Gastroenterology, Narayana Medical College and Hospital. Approval of the study was obtained from the Human Research Ethics Committee (Medical) of the NTR University of health sciences Vijayawada, protocol number SS15540702. All participants were provided with written informed consent.

Study population was taken from the patients who underwent Whipple's procedure in the Department of Surgical Gastroenterology, Narayana Medical College and Hospital for both benign and malignant conditions.

Only those patients who underwent standard pancreatojejunostomy anastomosis in duct to mucosa technique using vicryl 4-0 sutures (double layer-interrupted fashion) were included in the study. Patients who had duct size ≤3 mm underwent papillary –like main pancreatic duct invaginated technique of pancreaticojejunostomy (Fish mouth type)

Inclusion criteria

All the patients who underwent pancreatoduodenectomy within the study period for periampullary malignancy, chronic pancreatitis with head mass, and cystic neoplasms of pancreas.

Exclusion criteria

All those who underwent enteropancreatic anastomoses other than pancreatojejunostomy, patients with chronic pancreatitis who underwent surgery other than Whipple's procedure, patients who underwent trauma Whipple's procedure, and patients who denied consent were excluded.

Based on International Study Group of pancreatic fistula classification, recognized risk factors for CR-POPF (small duct, soft pancreas, high-risk pathology, excessive blood loss) were evaluated during pancreato-duodenectomy.

Each individual FRS score fell into one of four risk zones; negligible risk (0 points). Low risk (l-2 points), moderate risk (3-6 points), and high risk (7-10 points).

Gland texture and diameter of main pancreatic duct were assessed intraoperatively using standard techniques by single chief operating surgeon.

Final pathological diagnosis was arrived after histopathological examination of the operative specimen. Intraoperative blood loss was measured using standard techniques and graded according to fistula risk score.

The fistula risk score was calculated allocating scores for specific variables according to Callery et al[3]. Drain fluid amylase >3 times upper limit of normal serum amylase level or the corresponding serum amylase level, whichever was higher on or after postoperative day 3 is defined as postoperative pancreatic fistula . Individual predictive risk factors and fistula risk scores were compared with actual occurrence of postoperative pancreatic fistula.

Statistical analysis

The statistics in this study were represented by bar and pie diagrams. The statistics in this study were analyzed using SPSS version 17. Categorical variables were expressed as percentage. P value is calculated by Fischer exact test. P value <0.05 is considered significant.

Surgical procedure

Pancreatoduodenectomy uses a midline, or occasionally a transverse, upper abdominal incision. The lesser sac is entered, and the hepatic flexure of the colon is taken

down. The SMV is exposed at the inferior border of the neck of the pancreas, adjacent to the uncinate process.

A Kocher maneuver has been performed by first identifying the inferior vena cava (IVC) at the level of the proximal portion of the transverse segment of the duodenum (D3). Dissection of the porta hepatis begins with identification of the common hepatic artery (CHA) by removal of the large lymph node that commonly sits anterior to this vessel. The CHA is then followed distally to allow identification and ligation and division of the right gastric artery and the gastroduodenal artery (GDA). The portal vein is always identified prior to division of the common hepatic duct (CHD).

The antrum of the stomach is resected with the main specimen by dividing the stomach at the level of the third or fourth transverse vein on the lesser curvature. Transection of the jejunum is followed by ligation and division of its mesentery. The loose attachments of the ligament of Treitz are taken down, and the fourth and third portions of the duodenum are mobilized by dividing their short mesenteric vessels. The pancreatic head and uncinate process are separated from the superior mesenteric-portal vein confluence.

The pancreas has been transected at the level of the portal vein and the pancreatic head is reflected laterally, allowing identification of small venous tributaries from the portal vein and superior mesenteric vein (SMV). Medial retraction of the superior mesenteric-portal vein confluence facilitates dissection of the soft tissues adjacent to the lateral wall of the proximal superior mesenteric artery (SMA); this site represents the SMA margin.

Pancreatic, biliary, and gastrointestinal reconstruction

The pancreatic remnant is mobilized from the retroperitoneum and splenic vein for a distance of 2 to 3 cm. The transected jejunum is brought through a generous incision in the transverse mesocolon to the left of the middle colic vessels. A two-layer, end-to-side, duct-to-mucosa pancreaticojejunostomy is performed. The anastomosis between the pancreatic duct and the small bowel mucosa is completed with 4-0 or 5-0 monofilament sutures. Single-layer biliary anastomosis is performed using interrupted 4-0 absorbable monofilament sutures. An antecolic, end-to-side gastrojejunostomy is constructed in two layers.

Pancreaticojejunostomy

Standardized technique of PJ performed in an end-to-side fashion with a retrocolic jejunal limb (Z'graggen et al, 2002). The anastomosis is performed in two layers with duct-to-mucosa adaptation using vicryl 4-0 sutures in an interrupted double layer fashion.

RESULTS

Over 2 years between October 2015 and December 2017, 40 patients who fulfilled the study criteria were included for the analysis.

Of 40 patients, 21 (52.5%) were male, and 19 (47.5%) were female.

Of 40 patients, 13 patients were in between 41-50 years, 16 patients were in 51-60 years and 11 patients were in 61-70 years. The mean age of these patients is 55.78 years. Of 40 patients, 32 (80%) patients had pancreatic ductal adenocarcinoma and chronic calcific pancreatitis. 8 patients had mucinous cystic neoplasms, ampullary cancer, and duodenal cancer.

Table 1: Fistula risk score.

Fistula risk score	Number	%
1	2	5
2	11	27.5
3	12	30
4	8	20
5	6	15
6	0	0
7	1	2.5
	40	100

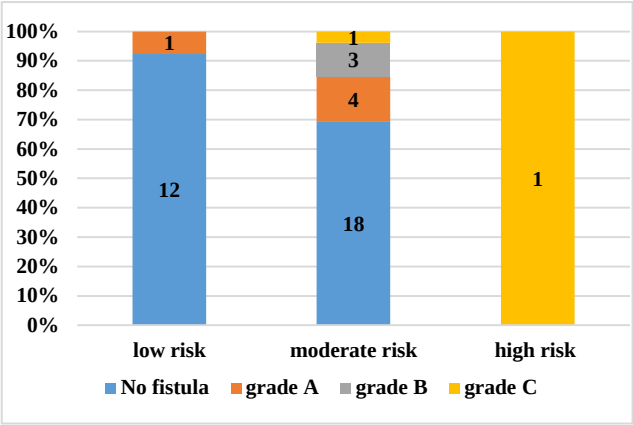

Figure 1: Occurrence of fistula vs. fistula risk.

Hemoglobin

Many of the patients in this study were anemic preoperatively and received multiple transfusions peri operatively. Those who developed postoperative pancreatic fistula also were anemic preoperatively and received multiple blood transfusions.

Albumin

Patients who developed grade B and C fistula had albumin <2.5 g/dl preoperatively. Two patients who underwent ERCP stenting had slight improvement in

albumin from 2.2 g/dl to 3 g/dl. Two of the patients who developed grade A fistula also had albumin <2.5 g/dl. All the patients who did not develop postoperative pancreatic fistula had albumin >2.5 g/dl

Jaundice and preoperative biliary drainage

Preoperative biliary drainage is not routinely done in our unit. 6 patients underwent pre op biliary drainage indications being cholangitis and poor performance status. All these patients were taken for surgery after 4 weeks. Out of 6 patients, 4 developed pancreatic fistula, out of which 2 died. Both the patients who died postoperatively had cholangitis preoperatively for which ERCP stenting was done.

Table 2: Texture vs. fistula.

Texture	Fistula		Total	P value*
	Present	Absent		
Firm	3	4	7	0.337
Soft	7	26	33	
Total	10	30	40	

*By Fisher exact test, where p<0.05 is significant.

Table 3: Duct size vs fistula.

Duct size (mm)	Fistula		Total	P value*
	Present	Absent		
3	4	1	5	0.007
4	3	8	11	
≥5	3	21	24	
Total	10	30	40	

*p<0.05 is significant.

Table 4: Pathological risk vs fistula.

Pathological risk	Fistula		Total	P value
	Present	Absent		
High	4	4	8	0.08
Low	6	26	32	
Total	10	30	40	

Table 5: Blood loss vs. fistula.

Blood loss (ml)	Fistula		Total	P value
	Present	Absent		
≤400	1	8	9	0.53
401-700	7	19	26	
701-1,000	2	3	5	
Total	10	30	40	

Of 40 patients, 33 (82.5%) had soft texture of pancreas. 7 (17.5%) had firm texture.

Of 40 patients, 24 patients had duct size greater than or equal to 5 mm. Five patients had duct size equal to 3 mm.

Of 40 patients, 26 patients had blood loss equal to 401-700 ml. No patient had blood loss more than 1000 ml.

Table 6: FRS score vs. fistula.

FRS score	Fistula		Total	P value
	Present	Absent		
Low risk	1	12	13	0.05*
Moderate risk	8	18	26	
High risk	1	0	1	
Total	10	30	40	

*p<0.05 is significant.

Of 40 patients, 10 patients (25%) developed postoperative pancreatic fistula. 5 (12.5%) patients had grade A pancreatic fistula and 5 patients had CR–POPF [grade B– 3 (7.5%), grade C– 2 (5%)].

Of 40 patients, 11 patients had fistula risk score of 2.12 patients had FRS of 3. Only 1 patient had FRS of 7.

Fistula risk

Of 40 patients, 26 patients had moderate risk and 13 patients had low risk. Only 1 patient had high risk.

Of 40 patients, 13 patients fall into low risk zone, out of which 1 patient developed grade A fistula. 26 patients fall into moderate risk zone, out of which 4 patients developed grade A, 3 patients developed grade B and 1 patient developed grade C fistula. 1 patient fall into high risk zone and developed grade C fistula.

Patient who died with grade C fistula had duodenal malignancy and underwent Whipple's procedure. Intraoperatively, patient had soft pancreas and undilated duct. Postoperative pancreatic fistula was confirmed by drain fluid amylase levels on day 3. Patient was treated conservatively initially and serial ultrasound scans were taken to look for intraabdominal collection. Parenteral nutrition was started, but there was no improvement in the general condition of the patient and so planned for surgery. But the patient expired on postoperative day 8.

The other patient who developed grade B fistula had pancreatic ductal cancer and also expired due to cardiac arrest on postoperative day 6.

P value calculated by Fisher exact test

When each risk factor is compared with fistula risk rate, duct size had significant P value. Other risk factors like pathology, texture and intraoperative blood loss did not have significant P value. But when all the risk factors were put together and calculated fistula risk score, it carried a significant P value with the development of pancreatic fistula.

DISCUSSION

Pancreatic fistula remains the most troublesome complication after pancreaticoduodenectomy. These problems lead to increased clinical and financial burden on the patient and the medical systems overseeing their convalescence by adding to postoperative complication severity, overall duration of stay, readmissions, reoperations, and even demise. Despite the best efforts of surgeons and even with the improved consensus definition of POPF, clinically relevant fistula rates have thus far remained constant at around 15% after pancreaticoduodenectomies.

The influence of age and sex of patient undergoing Whipple's procedure on development of postoperative pancreatic fistula is controversial.

According to Gupta et al, Whipple's procedure yesterday and today, age group of patients undergoing this surgery is most commonly 60–70 years. Pancreatic leak was seen in 19.1% of patients.[4]

Matsusue et al, found that advanced age (>70 years) was an adverse factor for pancreatic leakage.[5]

According to Kazanjian et al, management of pancreatic fistulas after xancreaticoduodenectomy. The mean age of patients with PF (n=55) was 65.2 years, and of those without PF (n=382), 62.9 years (p=0.20). Thirty-four (61.8%) of the patients with PF were male and 21 (38.2%) were female; 189 (49.5%) of the patients without PF were male and 193 (50.5%) were female (p=0.09).[6]

According to De Oliveira et al, assessment of complications after pancreatic surgery, there were 340 male (54.0%) and 293 female (46.0%) patients with a median age of 65 years (range, 46–80 years).[7]

The mean age of the patients in this study is 55.75 years and 47.5% of the patients were females. The mean age of the patients developing pancreatic fistula is 54.6 years. Among these, the mean age of male patients developing pancreatic fistula is 54.6 years and mean age of female patients developing pancreatic fistula is 53.4 years.

In this study, male and female were equally affected with pancreatic fistula.

In a study by Marcus et al, male sex was found to be a significant factor predisposing pancreatic fistula.[8]

Pathology

Out of 40 patients, 32 patients had pancreatic ductal cancer and chronic calcific pancreatitis. Rest 8 patients had duodenal, ampullary and mucinous cystic neoplasm of pancreas. Incidence of CR-POPF was more common in duodenal and ampullary cancer (3 patients with duodenal and ampullary cancer, 2 patients with pancreatic ductal cancer).

According to Lin et al, Fistula rates were lowest among patients with pancreatic adenocarcinoma, at only 4.9%.[9] Fistula rates were higher for the other periampullary cancers: distal cholangiocarcinoma, 15.8% (29 of 183); duodenal carcinoma, 15.4% (12 of 78); and ampullary carcinoma, 18.4% (41 of 223). Patients with chronic pancreatitis developed postoperative pancreatico-cutaneous fistulas in 10.1% of cases.

According to Kazanjian et al, fifty-five patients (12.6%) developed a PF, which was most common after resections for ampullary tumors (21.1%) and cystic neoplasms (31.3%), and uncommon after resection for pancreatic cancer (6.5%). Patients with pancreatic adenocarcinoma had a lower chance of the development of PF (p<0.03).[3]

Texture of the pancreas

The tendency of gland to retain sutures varies with its consistency, with firm pancreas holding better.

Out of 40 patients, 33 patients had soft texture and 7 patients had firm texture. Three out of seven patients who had firm texture had pancreatic fistula.

According to Lin et al, among patients with a soft gland, 22.6% developed a fistula. No patient with a firm gland developed a postoperative pancreatic fistula. Compared with patients with a moderate or firm gland, patients with a soft gland were 20.4-fold more likely to develop a fistula (odds ratio 20.4; 95% confidence interval (CI, 4.7–90.9).

Yeo et al, found that there was a strong association between the pancreatic texture and pancreatic leakage.[10] None of the 53 patients with hard pancreatic remnants developed pancreatic leakage, whereas 25% (19/75) of patients with soft pancreatic texture were complicated by pancreatic leakage.

The pancreatic leakage rate was 2.94% in patients with a hard pancreas, and was 32.1% in those with a soft pancreas (p=0.004). Both pancreatic duct size and texture of the remnant pancreas were demonstrated to be independent risk factors.[11]

Pancreatic duct size

Hosotani et al, reviewed 161 patients who had undergone PD and reported a fistula rate of 11% (17/161), finding that pancreaticojejunostomy anastomotic technique, pancreatic texture and pancreatic duct size were substantial risk factors for pancreatic leakage after PD.[12]

According to Yang et al, the incidence of pancreatic leakage was 4.88% in patients with a pancreatic duct size greater than or equal to 3 mm, and was 38.1% in those with ducts smaller than 3 mm (p=0.002). In this study, all the patients who developed grade B and C pancreatic fistula had duct diameter <5 mm.Some of those who had grade A fistula had duct diameter >5 mm.

Intraoperative blood loss

According to Kazanjian et al, the mean operative blood loss was 493±29 ml for the no-PF group and 492±47 ml for the PF group.

In the study conducted by Yeh et al, the pancreatic fistula group suffered significantly greater blood loss than their no fistula counterparts: 1584±862 ml versus 794±387 ml (p=0.0005).[13] The investigators proposed that patients with intraoperative blood loss exceeding 1,500 ml are at higher risk of fistula development. Their results also indicate that this scenario is associated with more advanced stages of disease (i.e., portal or superior mesenteric vein invasion), adhesions due to prior operations, patient obesity, jaundice-associated coagulopathy, and concurrent pancreatitis.

In the study conducted by Lin et al, estimated blood loss (ml) in patients developing fistula 1150±87 ml, patients without fistula 914±26 ml.

Anastomotic technique

All the patients in our series underwent duct to mucosa type pancreatico jejenostomy anastomosis irrespective of the duct size. Patients who underwent other type of anastomosis were not included in the study.

Poon et al found that duct-to-mucosa anastomosis was a safer technique than invagination anastomosis.[14]

Pancreatic fistula

According to Callery et al, after analyzing and comparing the clinical and economic effects of pancreatic fistulae among patients undergoing pancreaticoduodenectomy, distal and central pancreatectomy, incidence of clinically relevant fistulae (Grades B and C, according to the ISGPF grading system) was 16% for pancreatico-duodenectomy, 13% for distal pancreatectomy, and 83% for central pancreatectomy.[3]

In a study conducted by Yeh et al, frequency of PJ leak following PD was 16% (21 of 131 patients).

In a study conducted by Yang et al, of the 62 patients, 10 (16.1%) were identified as having pancreatic leakage after operation. Patient age, gender, history of jaundice, preoperative nutrition, pathological diagnosis and the length of postoperative stay were similar in the two groups.

In a study conducted by Callery et al, over 11 years out of 594 patients, 142 patients developed any sort of POPF (23.9%), of which, 68 were clinically relevant (11.4% overall; 8.9% grade B, 2.5 % grade C).

Out of 161 patients, 60 patients had a fistula for an overall POPF incidence 37.3%; 23 patients had POPF grade A (14.3%), 29 had POPF grade B (18.0%), and 8 had POPF grade C (5%). The 30-day mortality rate was 1.2% (2 patients); overall in-hospital mortality rate was 3.7% (6 patients).

In this study, 10 (25%) patients developed pancreatic fistula of which 5 patients had grade A, 3 patients had grade B and 2 patients had grade C.

Out of 10 patients who developed pancreatic fistula, 5 patients had CR-POPF.

Table 7: Comparison table with other studies

Variable	Original study by Callery et al[3]	External validation by Miller et al[15]	Our study
Total patients	445	594	40
Age, mean (years)	63.1	62.2	55.775
Gender (male), n (%)	237 (53.3)	292 (49.2)	21 (52.5)
Pancreatic fistula occurrence, n (%)			
No fistula	352 (79.1)	452 (76.1)	30 (75)
Patients with POPF	93 (20.9)	142 (23.9)	10 (25)
ISGPF grade A	35 (7.9)	74 (12.5)	5 (12.5)
Patients with CR POPF	58 (13)	68 (11.4)	5 (12.5)
ISGPF grade B	50 (11.2)	53 (8.9)	3 (7.5)
ISGPF grade C	8 (1.8)	15 (2.5)	2 (5)
Risk factors, n%			
Soft gland texture	219 (49.2)	304 (51.2)	33 (82.5)
High risk pathology	297 (66.7)	279 (47)	8 (20)
Pancreatic duct diameter (<5 mm)	332 (74.6)	430 (72.4)	16 (40)
Estimated blood loss (>400 ml)	163 (36.6)	216 (36.4)	31 (77.5)
Fistula risk score			
Mean	2.68	3.54	3.22
Median	3	3	3
Mode	0	2	3

Fistula risk score

When fistula risk score is calculated as proposed by Callery, 11 patients had FRS 2 and 12 patients had FRS 3. The highest score observed was 7, it was seen in 1 patient.

Out of 40 patients, 26 patients had moderate risk. Out of 10 pancreatic fistulas occurred, 8 occurred in moderate risk zone and 1 occurred in low risk and 1 occurred in high risk zone.

The mean, median, mode of the FRS were 3.22, 3 and 3 respectively, indicating that most patients harbor a relatively modest level of risk for CR-POPF development. Increasing scores correlated well with CR-POPF development. When segregated by defined FRS risk groups, CR-POPFs occurred in 4 moderate risk patients (15%) and 1 high risk patient. There were no patients in negligible risk in our series. Grade A fistulas constitute 7.6% of low risk patients and 15.4% of moderate risk patients.

According to Callery et al, the most commonly encountered Fistula Risk Score was 2 (14.1%), while the least frequent score was I0 (only a single patient). Most patients in the series segregated into the moderate-risk group n=302 (51%). The mean, median, and mode of the FRS were 3.54, 3, and 2, respectively, for this series indicating that most patients harbor a relatively modest level of risk for CR-POPF development.

When a CR-POPF occurred, antibiotics were used in 9% of patients while supplemental nutrition and interventionally placed percutaneous catheters were each required 5% of the time. A total of 1 out of 2 overall deaths (2.5% overall 90 day mortality) were directly attributable to pancreatic fistula. The other patient died due to cardiac arrest.

The most important finding in this study is that as the FRS score increases, chance of developing a pancreatic fistula increases. Using the information provided by the FRS, a surgeon can perhaps alter intraoperative techniques, such as type of anastomotic reconstruction, application of octreotide, drain usage, or other prophylactic techniques. This knowledge may also assist the surgeon's decision making in the postoperative recovery period. For instance, the timing of drain removal may be influenced; higher FRS scores could perhaps warrant a more cautious management approach, realizing they are more likely to incur a CR-POPF.

Although grade A (biochemical) fistulas have historically been considered innocuous, Miller et al have shown that they are not as harmless as originally believed.[15]

CONCLUSION

We found in our study that, post-operative pancreatic fistulae could be modestly predicted using fistula risk score. However, the latter had high negative predictive value and thus could be used to prognosticate risk of non-development of fistula than predicting its severity.

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