

Original Article

Clinically Significant Post-operative Pancreatic Fistula can be Predicted on First Post-operative Day Following Pancreaticoduodenectomy: A Retrospective Analysis

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ABSTRACT

Background: International Study Group for Pancreatic Fistula (ISGPF) score for pancreaticoduodenectomy (PD) is calculated retrospectively. Ongoing dynamic events are liable to be missed and actual severity of postoperative pancreatic fistula (POPF) is sometimes under estimated and mostly over estimated. In present study we looked for the factors associated with clinically significant POPF following PD.

Methods: Prospectively collected data of all patients who underwent pancreaticoduodenectomy in Apollo Hospitals, Chennai, India from July 2013 to May 2014 was retrospectively analyzed to elicit significance of different risk factors for developing POPF according ISGPF criteria.

Results: Total 35 cases of PD were analysed. First and third postoperative day drain fluid amylase levels varied significantly between clinical POPF and control group ($p=0.013$ & $p=0.022$ respectively) as well as hospital stay ($p=0.056$). Corresponding fluid lipase levels failed to establish such correlation. POPF according to ISGPF criteria was noted in 62.8% of patients in this series, but clinically relevant ones i.e. ISGPF grade B (5.7%) and C (11.4%), occurred in 17.14% of patients.

Conclusion: Day 1 drain fluid amylase > 968 U/L and day 3 drain amylase > 294 U/L were associated with clinically relevant POPF.

KEYWORDS: Pancreaticoduodenectomy, Post-operative Pancreatic Fistula, Drain Fluid Amylase / Lipase.

Introduction

Pancreaticoduodenectomy (PD) is the treatment of choice for benign and malignant tumours located in the periampullary region and head of pancreas. Due to complexity of the anastomosis especially to the pancreas, there is possibility of life threatening complications following the leak which increases the morbidity and mortality. Incidence of postoperative pancreatic fistula (POPF) varies widely in the literature from 2%-27% for PD, which is due to different methods used to define pancreatic fistula^{1,2}. International Study Group for Pancreatic Fistula (ISGPF) was formed in 2004 to frame a uniform definition of POPF as drain output of any measurable volume of fluid on or after day 3 with amylase content greater than 3 times that of normal laboratory serum amylase value after pancreatic resections. Grading of fistula into A, B, C is made depending on the clinical parameters noted post operatively in a retrospective manner^{1,3}. POPF increases delayed gastric emptying (DGE), wound infection, intra abdominal infection, increases length of hospital stay and cost⁴.

ISGPF score is calculated retrospectively. Recently many studies have been conducted to highlight the inherent deficiencies in grading severity⁵. Some surgeons have abandoned the use of drains where as other have begun to remove drains early in the post operative period based on drain volume and amylase content. However little is known about the postoperative dynamics of change in drain amylase, lipase content and amount of drain output towards prediction of post operative pancreatic fistula.

We retrospectively analyzed the factors which are associated with POPF formation following PD. It was proposed in this study to estimate the incidence of POPF according to ISGPF criteria and to study the factors which are associated with formation of POPF.

Materials and Methods

Patient population

This is a retrospective analysis of prospective cohort of patients who have undergone PD for both benign

and malignant lesion of the periampullary and head of pancreas (HOP) from July 2013 to May 2014 in Apollo Hospital, Chennai, India. Study was conducted after approval by the Hospital Scientific and Ethical committee.

Perioperative parameters

Pre-operative hematological, biochemical tests and CECT abdomen were done. Endoscopic biopsy of lesion was done for ampullary and duodenal adenocarcinomas. Pre-operative biliary stenting was done based on the presence of cholangitis. Surgery was performed by 2 surgeons in the department of Surgical Gastroenterology in Apollo Hospital, Chennai, India. Type of anastomosis and technique were in accordance with surgeons' preferences. Use of octreotide during the peri-operative and post-operative period and removal of drains in the post-operative period were also according to the discretion of the operating surgeon. Abdominal drains were placed in all cases on right flank. Blood loss was estimated by adding the suction output to the subtracted weight of dry from wet abdominal pad/gauze. Patients who underwent emergency PD and patients who had ongoing pancreatitis or cholangitis were excluded from the study.

Data collection

Data was collected prospectively in excel sheet format. Patient demographics included age, sex, diagnosis, pathology, pre-operative bilirubin levels, pre-operative stenting, CA 19-9 levels, co-morbidities, albumin levels, peri-operative administration of octreotide. Intra-operative variables like type of surgery either classical PD (CPD) or pylorus preserving PD (PPPD), intra operative octreotide, type of anastomosis either pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ), intra operative blood loss, bile culture, texture of pancreas were also recorded. Postoperative parameters included serum amylase and lipase, drain fluid amylase and lipase on postoperative day 1, 3, 5 and 7. Post-operative day 3 white blood cell (WBC) count and serum C reactive protein (CRP) levels were also recorded. Day of drain removal, imaging in post-operative period if done were recorded. Incidence of DGE, intra abdominal abscess, wound infection, sepsis, hemorrhage, need for reoperation, hospital stay and mortality were also noted.

Control group: Post pancreaticoduodenectomy patients who developed no POPF or grade A POPF according to ISGPF criteria were considered 'control' group in this study.

Clinical group: Patients who developed grade B and grade C POPF according to ISGPF criteria comprised 'clinical' or clinically relevant POPF group.

Statistical methods

The data was entered into an MS-Excel spread sheet and statistical analysis carried out using SPSS version 11. All categorical variables were expressed as either percentage or proportion. All continuous variables were assessed for normality using Shapiro Wilks test and expressed as mean +/- standard deviation. Comparison of normally distributed continuous variables was done by independent 't' test or ANOVA based on number of groups. Comparison of non-normally distributed continuous variables was carried out by Mann Whitney U test or Kruskal wallis H test based on groups. All categorical comparison were performed by either Pearson chi square test or Fisher exact test based on number of observations. An area under the curve (AUC) greater than 0.8 was considered to be of high diagnostic accuracy. Receiver operating curve (ROC) was used to find out the best cut off value at an optimized accuracy with equal weight given to the errors of sensitivity and specificity for drain amylase. p value < 0.05 was considered as statistically significant.

Results

Patient demographics and preoperative parameters

35 cases of PD were performed during the study period. Age of patients ranged from 28 years to 80 years with mean of 52 years, of which males formed 65.7% and females 34.3% in the group. Demographical parameters like age and sex, pathology, co-morbidity, preoperative albumin and bilirubin level and preoperative stenting incidence were not different in clinical POPF and control group (**table 1**). Periampullary tumours constituted 74.2% of cases which were malignant growths arising from distal bile duct, ampulla and duodenum. HOP adenocarcinoma constituted 11.4% of case, ampullary adenoma 3.6%,

pseudopapillary tumour and inflammatory mass of HOP formed 2.9% each. Diabetes mellitus (DM), hypertension and coronary artery disease (CAD) or DM, hypertension and asthma were grouped into three comorbidity groups and they constituted 19 patients (54.3%). Patients who have two comorbidities like DM and hypertension or CAD and DM constituted 3 patients (8.6%) 13 patients (37.1%) had no co morbidity. No preoperative parameters were found to have impact on POPF.

Intraoperative parameters

Clinical POPF incidence was not different between CPD and PPPD but the type of pancreaticoenteric anastomosis. PJ had lower incidence of clinical POPF than PG, though clinically not significant (p = 0.063). Clinical POPF did not vary significantly with pancreatic texture, use of peri-operative octreotide, positive bile culture and peri-operative blood loss (**table 1, 2**).

Postoperative parameters

Pancreatic fistula according to ISGPF criteria was noted in 22 (62.8%) of patients in this series, but clinically relevant POPF i.e. ISGPF grade B (n = 2, 5.7%) and C (n = 4, 11.4%) occurred in 17.14% of patients. Morbidity and mortality rate in this series were 45.9% (n = 16) and 5.7% (n = 2) respectively. Day 1 drain fluid amylase (median: 485 U/L, range: 63-1200 U/L) varied significantly between clinical POPF and control groups (p = 0.013). Day 3 drain amylase level (median: 157.3 U/L, range 22-400 U/L, p = 0.022) revealed similar difference (**table 3**). Receiver operating curve (ROC) for day 1 drain amylase verified a cut off value of 968 U/L with 100% sensitivity and 79.3% specificity in predicting POPF (**figure 1**). At the same time day 3 drain amylase level >294 U/L had sensitivity of 83% and specificity of 75% in predicting POPF (**figure 2**). Drain fluid lipase and serum CRP levels failed to correlate with POPF (**table 3**). Peak raise in drain fluid amylase level was noted on the first day following surgery with maximum of 8180 U/L and a mean value of 1190 U/L. Maximum third day drain amylase level recorded was 7072 U/L and the mean value decreased to 591.4 U/L. Fifth day showed a significant decrease in the drain amylase level with maximum of 450 U/L and a mean value of 59.5 U/L (**figure 3**).

Clinical POPF was significantly associated with DGE, intra abdominal abscess, wound infection, sepsis, hemorrhage, need for reoperation, extended hospital stay and mortality (**table 2**, $p = 0.0001$). Two patients died and they all had clinical POPF.

Discussion

Risk factors for POPF are 1) patient-related risk factors like age, gender, jaundice, pre-operative biliary drainage and malnutrition; 2) disease-related risk factors like pancreatic pathology, pancreatic texture, pancreatic duct size, pancreatic juice output; 3) procedure related risk factors like operation time, resection type, anastomotic technique, intraoperative blood loss and other factors like surgeons' experience, prophylactic use of octreotide and pre-operative stenting.

Patient-related risk factors

Patient characteristics are considered as predictive factors for POPF and include male sex, advanced age > 70 yrs,

identifiable jaundice and low creatinine clearance (CCI)⁶. Age > 70 years had been found to have poor anastomotic healing and higher association of coronary artery and atherosclerotic diseases impairing visceral perfusion, ultimately leading to POPF⁶. Age and sex of the patients did not significantly affect the outcome in the present study ($p = 0.563$ and $p = 0.64$ respectively). Jaundice rather than CCI has been previously reported to be significant patient-related risk factor predisposing to POPF. Pre-operative serum bilirubin level had no significant impact on fistula development in present study similar to the observation by Yeh T.S *et al* who pointed duration of jaundice rather than the extent of jaundice to be of more importance⁷. Pre-operative biliary decompression as well had no impact on POPF ($p = 0.352$, **table 1**). Lower CCI is known to precipitate acute renal failure, intra-abdominal bleeding, sepsis and subsequent POPF particularly in those with obstructive jaundice. Fortunately no patient operated in this study had high preoperative creatinine value and was therefore investigated for CCI. Interestingly DM and neoadjuvant chemoradiotherapy have been shown to

Table 1: Distribution of pre-operative characteristics among clinical and control group. Age, sex, diagnosis, pre-operative stenting, pre-operative serum albumin and bilirubin level, and pre-operative use of octreotide do not have any significant difference among clinical and control groups.

Clinical Variables		Clinical POPF	Control	p value
Age (years)		52.8±9.8	52.1±12.9	0.902
Sex	Male	5	18	0.640
	Female	1	11	
Diagnosis	Pancreatic ductal adenocarcinoma	0	4	0.749
	Periampullary carcinoma	5	21	
	Ampullary adenoma	1	2	
	Inflammatory head mass	0	1	
	Pseudopapillary tumour	0	1	
Co morbidity	Three co-morbidity	2	17	0.982
	Two co-morbidity	1	2	
	No morbidity	3	10	
Pre-operative stenting	No	3	21	0.352
	Yes	3	8	
Pre-operative Octreotide	Not given	4	26	0.195
	Given	2	3	
Pre-operative serum albumin level (gm/dl)		3.6±0.47	4.03±0.61	0.093
Pre-operative serum bilirubin level (mg/dl)		9.8 (2.4-14.9)	6.3 (2.6-10.3)	0.511

offer a protective benefit against pancreatic fistula, with the latter presumably causing a decrease in pancreatic exocrine secretion. Increase in number of co-morbidities has an additive effect in studies by Pratt *et al*⁸ but this study failed to show association with clinically relevant POPF (P=0.982). No patient received neoadjuvant treatment.

Pancreas and disease-related factors

The most widely recognized risk factors for pancreatic fistula are directly linked to state and disease of the pancreas and periampullary region. Principal among them is a soft pancreatic parenchyma. In a series of nearly 2000 PD, it is noted that a soft pancreas is associated with 22.6% fistula rate and lead to a 10-fold increased risk of POPF versus an intermediate or hard gland^{6,9}.

That a fibrotic pancreatic remnant facilitates anastomotic integrity is also well accepted¹⁰. This study failed to show any impact of pancreatic texture on POPF development following PD. Also it did not reveal any association of POPF with pancreatic disease contrary to the finding of its higher incidence in duodenal adenocarcinoma, ampullary lesions, cystic lesions of pancreas in some studies¹¹.

Operative risk factors

In past two decades, various technical aspects have been scrutinized to identify operative factors associated with increased fistula rate. Various techniques for managing the pancreatic remnant have been compared including PG vs. PJ, the duct to mucosa vs. invagination pancreaticojejunal anastomosis, stent vs. no stent across

Table 2: Distribution of intra-operative and postoperative characteristics among clinical and control group. Post-operative complications are significantly higher in clinical POPF group.

Clinical Variables		Clinical POPF	Control	p value
Intra operative octreotide	Not given	5	26	0.546
	Given	1	3	
Texture of pancreas	Soft	1	9	0.649
	Firm	5	20	
Type of surgery	Classical	5	26	0.546
	Pylorus preserving	1	3	
Pancreatic nastomosis	Pancreaticogastrostomy	2	6	0.063
	Pancreaticojejunostomy	4	23	
Blood loss	< 500 ml	2	14	0.123
	501-1000 ml	2	13	
	1001-1500 ml	1	2	
	>1500 ml	1	0	
Post operative octreotide	< 5 day	1	13	0.210
	5-10 days	3	6	
	11-20 days	1	1	
	Not given	1	9	
Bile culture	No Growth	3	19	0.648
	Growth	3	10	
Complications	No	0	19	0.0001
	Delayed Gastric Emptying	0	8	
	Hemorrhage with Pancreatic	4	0	
	Biliary with Pancreatic Fistula	1	0	
	Other Complications	1	2	
Postoperative period of stay in days		19.5(10-34)	10(8-12)	0.056

Table 3: Distribution of relevant blood and drain fluid investigation related parameters across clinical and control group. Drain fluid amylase level on day 1 and day 3 are significantly higher in clinical POPF group compared to control group.

Clinical Variables	POPF [Median (IQR)†]	Control [Median (IQR)]	p value
Day 1 serum amylase (U/L)	204 (126-323)	122(46-198)	0.105
Day 1 serum lipase (U/L)	101(57-220)	61(34-160)	0.314
Day 1 drain amount (mL)	100(75-400)	100(50-160)	0.710
Day 1 drain amylase (U/L)	1357(1120-1541)	456(53-936)	0.013
Day 1 drain lipase (U/L)	1926(823-2828)	450(100-1886)	0.137
Day 3 serum amylase (U/L)	55.5(25-105)	34(18-62)	0.303
Day 3 serum lipase (U/L)	46.5(25-50)	29(20-34)	0.254
Day 3 drain amount (mL)	165(125-360)	200(100-320)	0.965
Day 3 drain amylase (U/L)	501.5(333-561)	120(16-294)	0.022
Day 3 drain lipase (U/L)	281(200-995)	150(18-597)	0.204
Day 3 C reactive protein	157(126-289)	116(62-156)	0.084
Day3 White cell count	11375(11200-12920)	12350(8520-15840)	0.599
Day 5 serum amylase (U/L)	49.5(24-79)	38(30-50)	0.599
Day 5 serum lipase (U/L)	45(32-62)	32(21-40)	0.105
Day 5 drain amount (mL)	175(100-430)	200(30-350)	0.569
Day 5 drain amylase (U/L)	91(11-116)	30(16-53)	0.264
Day 5 drain lipase (U/L)	84(14-250)	27(21-43)	0.293
Day 5 C reactive protein	138(83.5-198)	68.8(51.7-131)	0.548
Day 7 drain amount (mL)	450(450-500)	200(100-420)	0.293
Day 7 drain amylase (U/L)	48(27-11379)	32.5(23-57)	0.606
Day 7 drain lipase (U/L)	5797(46-11548)	15.5(10-40.5)	0.165

† IQR – Interquartile range.

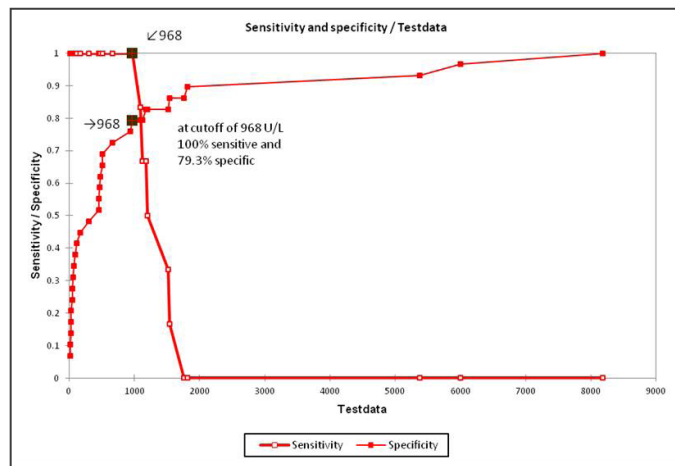


Figure 1: Receiver operating curve (ROC) for day 1 drain amylase. AUROC was 0.825 with p = 0.013. The optimal cut off value was 968 U/L which was 100% sensitive and 79.3% specific.

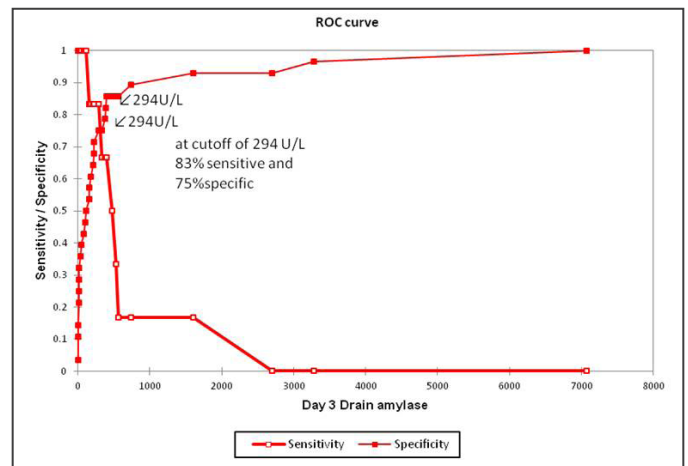


Figure 2: Receiver operating curve for day 3 drain amylase. AUROC was 0.802 with p= 0.022. The optimal cut off value was 294 U/L with sensitivity of 83% and specificity of 75%.

the pancreatocenteric anastomosis, single vs. double Roux-en-Y loop reconstruction and the use of octreotide and fibrin sealants 10. Increased intra-operative blood loss is an important risk factor for developing POPF. Yeh *et al* group noticed in their study that POPF group significantly suffered greater blood loss, rather than their no fistula counter parts (1584±862 mL versus 794±387 ml, p = 0.0005)⁷. They proposed that blood loss ≥ 1,500 ml to be at higher risk of fistula development. Increased blood loss is likely to be associated with other factors including more advanced stages of disease, i.e. portal or superior mesenteric vein invasion, obesity, jaundice-associated coagulopathy and concurrent pancreatitis. Lai *et al.* found intra-operative blood loss ≥ 1000 ml be significantly associated with POPF¹². Only 4 patients in present study had ≥ 1000 ml blood loss during surgery and thus failed to appreciate any significance in developing POPF (p = 0.123).

Waugh and Clagett first performed PG in clinical practice in 1946¹³. PG has recently gained favor as a possible mean of reducing the incidence of POPF by several factors like acidic inactivation of pancreatic juice, absence of enterokinase in stomach, which is required for conversion of trypsinogen to trypsin and subsequent activation of proteolytic enzymes. A lack of enzyme activation may help in preventing autodigestion of the anastomosis. Furthermore the proximity of the pancreas to the posterior gastric wall allows potentially less tension on the anastomosis. The excellent blood supply of stomach favors anastomotic healing and the thickness of the stomach holds the sutures well¹⁰.

On the other hand PJ has been the most commonly used method of pancreatocenteric anastomosis after PD. The jejunum is a logical choice for a pancreatocenteric anastomosis due to its generous blood supply and mobile mesentery. Yet during the past 30 years, this technique has consistently been reported to yield on an average a 10% fistula rate (range 2%-19%)¹⁰. Apart from the different positions of the jejunal loop (antecolic, retrocolic, or retromesenteric) and other variations, such as isolated Roux Loop PJ, the anastomosis can be performed as an end-to-end anastomosis with invagination of the pancreatic stump in the jejunum or as end to side anastomosis with

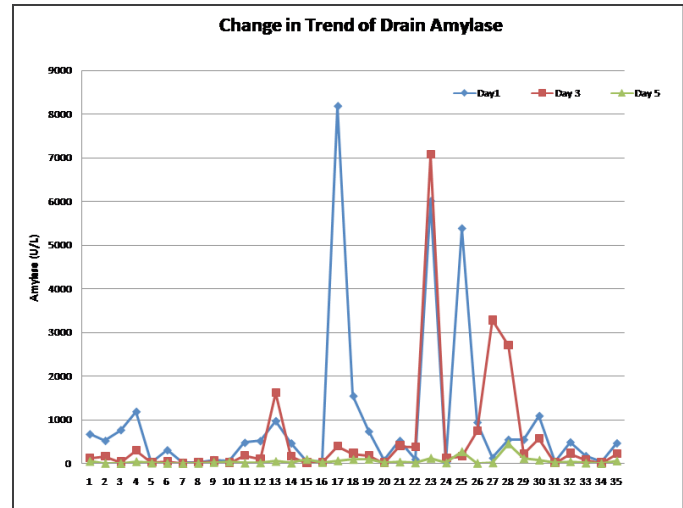


Figure 3: Trends of drain amylase on 1st, 3rd & 5th day. Peak raise in amylase levels was noted on the first day following surgery with maximum of 8180 U/L and a mean value of 1190 U/L. Maximum 3rd day drain amylase levels recorded was 7072 U/L and the mean value decreased to 591.4 U/L. Fifth day value showed a significant decrease in the drain amylase levels with maximum of 450 U/L and a mean value of 59.5 U/L.

or without duct to mucosa suturing. In addition to these, there are some more variations of these anastomotic techniques. Duct to mucosa pancreaticojejunal anastomosis is theoretically more rational technique to avoid POPF for its direct contact of the pancreatic duct with jejunal mucosa, preventing direct contact of the pancreatic juice with the cut end of the pancreas. Though it seems difficult in undilated ducts, in recent years this technique has been preferred regardless of the diameter of the pancreatic duct¹². Suzuki *et al.* selected various PJ techniques according to the pancreatic texture and duct size and obtained an overall pancreatic leakage rate of 8%¹⁴.

Several meta-analyses comparing PG and PJ found less POPF with PG but similar overall complications including mortality in both groups¹⁵⁻¹⁸. Grendar J *et al* in a recent randomized controlled trial (RCT) found no superiority of PG over PJ¹⁹. In another RCT comparing PG with PJ, Yeo *et al* found similar fistula rates of 12% in both groups but more clinically relevant POPF in the PG group (4 out of 10, p = 0.043)²⁰. In present study PG has been found not to be significantly associated with clinical

POPF compared to PJ. Also type of surgery either CPD or PPPD did not have any significance in developing POPF ($p = 0.546$).

Clinical course

ISGPF criteria is useful for reporting and comparing the incidence and severity of POPF uniformly among different canters, but its retrospective character does not help predicting the clinical course and clinical decision making in managing the POPF²¹. In this study Grade A fistulas constituted 45.7% of patients. The critical question in managing these patients is to know, how to identify patients who may develop complications requiring interventions and who can be managed without complications. Very little data are available to predict factors that allow identification of patients, at the time of onset of fistula, as having “high risk” or “low risk” fistula. To identify factors which are associated with high risk fistula, variables studied, were day 1 drain fluid amylase, lipase; day 3 drain fluid amylase, lipase, CRP levels, WBC count; day 5 drain fluid amylase, lipase, CRP levels and day 7 drain fluid amylase and lipase.

Day 1 drain fluid amylase level was found to be significant in predicting high risk fistula in this study with a cut off value of 968 U/L as compared to higher cut off value of 5000 U/L in Molinari E *et al* series²². Similarly other studies by Sutcliffe *et al* showed cut off value of day 1 drain fluid amylase concentration 350 U/L and by Kawai *et al* and El Nakeeb *et al*, 4000 U/L each, predicting clinically significant POPF^{8, 23-25}. Whereas Moskovic *et al* found no usefulness of day 1 drain fluid amylase level in predicting clinical POPF²⁶. Pratt *et al* observed latent development of POPF in 26.4% and clinically relevant POPF in 36% of patients, who had normal drain fluid amylase levels and this group of patients faced worst outcome²⁷. Though the mean value of day 1 drain lipase levels was 2122.5 U/L which was comparatively higher than the mean value of day 1 amylase 1190 U/L, it was not associated with clinically significant POPF formation.

Day 3 drain amylase level was found to be significantly associated with predicting high risk POPF formation with cut off value of 294 U/L in our study. Day 3 CRP level was not associated with clinical POPF in this

study contrary to Ansoorge *et al* who found day 1 drain amylase, day 2 drain amylase and day 3 CRP levels to be significant for predicting clinically relevant POPF²⁸. A study found increased CRP level in patients requiring reoperation and in patients with in hospital mortality⁵. Day 3 drain fluid lipase level (median: 174 U/L, range: 28-825 U/L, $p = 0.2$) was not found to be associated with clinically relevant POPF in this study as compared to another study which found lipase levels > 1000 U/L to be highly sensitive and specific for diagnosis of clinical relevant POPF²².

Pre-operative, intra operative or post-operative octreotide did not confer benefit for preventing POPF in our series (**table 1,2**). There are 11 RCTs involving 2023 patients in whom the somatostatin analogue was examined. Five RCTs from Europe and 1 RCT from Asia showed the benefit of perioperative use of somatostatin analogues to decrease the postoperative complication rate. On the other hand, 2 recent RCTs from Europe and 3 RCTs from USA failed to show benefit^{6,10}. Connor *et al*. analyzed 10 studies and showed that somatostatin and its analogues reduced rate of biochemical fistula but not the incidence of anastomotic disruption²⁹. Hence the prophylactic use of perioperative somatostatin and its analogues to prevent POPF after pancreatic surgery remains controversial. It does not result in reduction of mortality. However the efficacy of prophylactic octreotide is reported in selective administration in the setting of high risk glands, including patients with either soft glands or small pancreatic duct, in those harbouring ampullary, duodenal cystic or islet lesions, or in cases where intraoperative blood loss is excessive. Prophylactic octreotide did not influence clinically relevant fistula rates among low-risk glands.

Prevalence of PPH in this study was 14.2% which is higher compared to Yekebas *et al* (5.4%)³⁰. Mortality due to PPH in this study is 2% as compared to higher mortality of 16% in Yekebas. *et al* series. PPH and other complications, particularly DGE (22.9%), ileus, wound infection, intra-abdominal abscess, pancreatitis, haemorrhage, and sepsis were significantly associated with POPF in this study ($p = 0.0001$). Nearly all the patients who developed late PPH (3 of the 4 patients) had POPF. Hospital costs, rate of reoperation, hospital stay and readmission were significantly increased.

Conclusion

Post-operative day 1 and day 3 drain fluid amylase >968 U/L and >294 U/L respectively were associated with clinically relevant POPF. This study was limited by small sample size; nevertheless it established the possibility of predicting clinically significant POPF on first postoperative day from simple drain fluid amylase estimation.

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