ACINAR CELL DENSITY AND FIBROSIS SCORING IN PANCREATICODUODENECTOMY SPECIMEN FOR MALIGNANCIES AND ITS CORRELATION WITH POST-OPERATIVE PANCREATIC EXOCRINE AND ENDOCRINE INSUFFICIENCY -A PROSPECTIVE STUDY

Thesis

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfillment of the requirement for the degree of

MAGISTER OF CHIRURGIAE (MCh)

(SURGICAL GASTROENTEROLOGY)

JULY, 2020

AIIMS, JODHPUR

DR. SHABANA

All India Institute of Medical Sciences, Jodhpur

CERTIFICATE BY HEAD OF THE DEPARTMENT

This is to certify that **Dr. Shabana** has satisfactorily completed her thesis entitled "**ACINAR CELL DENSITY AND FIBROSIS SCORING IN PANCREATICODUODENECTOMY SPECIMEN FOR MALIGNANCIES AND ITS CORRELATION WITH POST-OPERATIVE PANCREATIC EXOCRINE AND ENDOCRINE INSUFFICIENCY-A PROSPECTIVE STUDY**" in partial fulfillment of the requirement for the degree of Magister Chirurgiae (M.Ch.), in Surgical Gastroenterology. She has done the research work under my supervision and guidance. She has fulfilled all the requisites under the regulations laid by the All India Institute of Medical Sciences, Jodhpur and no part of the thesis has been submitted to any other university.

Dr. Naveen Sharma

Professor and Head of Department

Department of General Surgery

All India Institute of Medical Sciences, Jodhpur

All India Institute of Medical Sciences, Jodhpur

CERTIFICATE

This is to certify that the thesis titled "**ACINAR CELL DENSITY AND FIBROSIS SCORING IN PANCREATICODUODENECTOMY SPECIMEN FOR MALIGNANCIES AND ITS CORRELATION WITH POST-OPERATIVE PANCREATIC EXOCRINE AND ENDOCRINE INSUFFICIENCY-A PROSPECTIVE STUDY**" is the bonafide work of **Dr. SHABANA**, carried out in partial fulfilment of the requirement for the degree of Magister Chirurgiae (M.Ch.) in Surgical Gastroenterology under our guidance and supervision, in the Department of Surgical Gastroenterology, All India Institute of Medical Sciences, Jodhpur.

Supervisor
Dr. Subhash Chandra Soni
Associate Professor
Department of Surgical Gastroenterology
All India Institute of Medical Sciences, Jodhpur

Co-Supervisor
Dr. Vaibhav Kumar Varshney
Associate Professor
Department of Surgical Gastroenterology
All India Institute of Medical Sciences, Jodhpur

Co-Supervisor
Prof (Col.) Dr. Ashok Kumar Puranik
Executive Director, AIIMS Guwahati
Ex. Head of Department
Department of General Surgery
All India Institute of Medical Sciences, Jodhpur

Co-Supervisor
Dr Poonam Elhence
Professor and Head of Department
Department of Pathology
All India Institute of Medical Sciences, Jodhpur

Co-Supervisor
Dr Dharmveer Yadav
Additional Professor
Department of Biochemistry
All India Institute of Medical Sciences, Jodhpur

All India Institute of Medical Sciences, Jodhpur

DECLARATION BY THE CANDIDATE

I hereby declare that this thesis entitled "**ACINAR CELL DENSITY AND FIBROSIS SCORING IN PANCREATICODUODENECTOMY SPECIMEN FOR MALIGNANCIES AND ITS CORRELATION WITH POST-OPERATIVE PANCREATIC EXOCRINE AND ENDOCRINE INSUFFICIENCY-A PROSPECTIVE STUDY**" is a bonafide and original research work carried out in partial fulfilment of the requirement for the degree of Magister Chirurgiae (M.Ch.) in Surgical Gastroenterology under supervision and guidance, in the Department of Surgical Gastroenterology, All India Institute of Medical Sciences, Jodhpur.

Dr. Shabana

Department of Surgical Gastroenterology,

All India Institute of Medical Sciences,

Jodhpur.

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ACKNOWLEDGEMENTS

Although it is my name that appears on the cover of this dissertation, a great many people have contributed to its successful fruition, and I take this opportunity toexpress my heartfelt gratitude towards these people.

First and foremost, I would like to thank my guide, ***Dr. Subhash Chandra Soni***, for his support and guidance during this project from its inception to completion, as well as his unwavering patience with me over the past two and a half years.

I am privileged to have had the capable guidance of my co-guides ***Dr Poonam Elhence***, ***Dr Dharmveer Yadav, Dr. Vaibhav Kumar Varshney and Prof (Col.) Dr. Ashok Kumar Puranik***, whose timely inputs and valuable suggestions have been vital to the completion of this project. I wholeheartedly thank them for their encouragement and mentoring during the entire course of my study

I extend my gratitude to other faculty in my department ***Dr. Selvakumar Balakrishnan, Dr. Peeyush Varshney and Dr Lokesh Agarwal*** for their constant support and encouragement.

I also thank the Director and the Dean (Academics) of our institute for having given me the opportunity to do this study.

My colleagues ***Dr Sreeshant K, Dr Sunita Suman, Dr Ashish Swami, Dr Raghav Nayar, Dr Vignesh N, Dr Vishu Jain, Dr Kaushal Rathore, Dr Saikrishnan*** and ***Dr Sanjam*** have been of great help, and I thank them wholeheartedly.

I thank the OPD staff ***Mr. Manoj Katariya, Mr. Ganpat Bishnoi, Mr. Dalip Ram*** and ***Mrs. Annu Kanwar*** for their cooperation and support in ensuring prompt and timely patient follow ups.

I also thank the other ward, OT and ICU staff who help us serve our patients with the utmost care and efficiency.

I thank the Departments of Pathology, Radiodiagnosis and Biochemistry for supporting my study with the relevant investigations.

I wish to convey my gratitude and love for my parents ***Mr. Abdul Jabbar and Mrs. Nafeesa Abdul Jabbar, Mr. Abdul Samad, Mrs. Anita Samad***, my partner ***Nuwaizer Mohamed*** and, my siblings ***Hesham, Nasreena, Shakeel, Niloofer, Chintu, Tariq and Sheza*** for their love

and support.

And last but not the least, I offer sincere thanks to all our patients “who grant us the privilege of practicing our craft,” I sincerely pray for their welfare!

Lastly, I offer my praise and thanks to the Almighty for this great privilege.

Dr. Shabana

SYNOPSIS

Background:

Pancreaticoduodenectomy (PD) is the most common procedure for periampullary cancer with a peri-operative mortality < 5 %. Long term postoperative pancreatic insufficiencies are often underdiagnosed but have significant impact on quality of life, and in the light of improved survival post-surgery there is a need to study their predictive factors. While pancreatic fibrosis has been shown to be associated with postoperative exocrine insufficiency, acinar cell density is reported to have strong correlation with postoperative fistula, which in turn maybe inversely correlated to pancreatic fibrosis. However, there are no studies evaluating correlation between acinar cell density or fibrosis directly with pancreatic endocrine insufficiency. We aimed to correlate these pathological parameters with postoperative pancreatic endocrine and exocrine dysfunctions.

Methodology:

Patients without previous history or radiology suggestive of chronic pancreatitis who underwent PD for malignancies were included and analyzed for acinar cell density and fibrosis score at the pancreatic neck margin of their histopathological specimens which were corelated with preoperative and postoperative exocrine and endocrine functions at 3 and 6 months after surgery, using fecal elastase-1 (FE-1), HbA1c and fasting blood sugar (FBS) profiles.

Results:

20 patients were included, of whom preoperatively 65% had pancreatic exocrine insufficiency (PEI) and 40 % had endocrine insufficiency. On histology 35 % patients had decreased acinar cell density and 85 % had pancreatic fibrosis. The postoperative incidence of PEI was 70 % at 3 months and 90 % at 6 months. In patients with pre-existing exocrine insufficiency there was significant decrease in FE-1 from 86 µg/g before surgery to 31 µg/g at 6 months. In those with normal exocrine function before surgery, new onset PEI was seen

in 87.5 % at 6 months. Post operative endocrine insufficiency decreased to 35 % at 3 months and 20 % at 6 months. New onset endocrine insufficiency was seen in 1 patient at 3 months and in none at 6 months. In patients with pre-existing endocrine insufficiency a significant decrease in FBS and HbA1c values were seen at both 3 and 6 months.

A significant correlation of PEI with fibrosis score was noted at 3 months but none was demonstrated with acinar cell density. Both acinar cell loss and fibrosis were seen to be associated with better glycemic control after surgery which could be attributed to multiple confounders related to glycemic control that were not accounted for in this study.

Conclusion:

The high incidence of preoperative and postoperative PEI indicate that it might be prudent to identify PEI perioperatively and administer pancreatic enzyme replacement therapy (PERT) accordingly to these patients which may have a beneficial role on nutritional parameters and long-term outcome. It would also be worthwhile to include reporting of pancreatic fibrosis in routine histopathology of PD for cancers to risk stratify and educate patients about development of postoperative PEI. The low incidence of postoperative endocrine insufficiency may be attributed to the small period of follow up. Further studies with a longer follow up may be required to estimate the endocrine function after PD and larger samples may be required to further study the association between these histological parameters and endocrine functions after a PD.

ABBREVIATIONS

AJCC- American Joint Committee on Cancer

ACC/AHA- American College of Cardiology/ American Heart Association

ADA- American Diabetes Association

BMI- Body mass index

BP- Blood Pressure

CEA- Carcinoembryonic antigen

CA19-9- Cancer antigen 19-9

CT- Computed Tomography

DGE- Delayed Gastric Emptying

DM- Diabetes Mellitus

ECOG- Eastern Cooperative Oncology Group

FE-1- Fecal Elastase-1

HTN- Hypertension

IQR- Interquartile Range

ISGPS- International Study Group for Pancreatic Surgery

MEN-1- Multiple Endocrine Neoplasia-1

PD- Pancreaticoduodenectomy

PEI- Pancreatic exocrine insufficiency

PERT- Pancreatic enzyme replacement therapy

POPF- Postoperative pancreatic fistula

POPH- Postoperative pancreatic hemorrhage

QOL- Quality of life

SSI- Surgical site infection

TNM- Tumor Node Metastases

USG- Ultrasonography

INTRODUCTION

The indications for pancreatic surgery for both benign and malignant periampullary pathologies have been increasing in the last decade, with pancreaticoduodenectomy (PD) being the most common procedure for pancreatic and periampullary cancer. This rising trend is attributed to the adoption of improved surgical techniques, better selection of patients, and better peri-operative care, which has led to acceptable peri-operative mortality (less than 5 %) and morbidity (45-60 %) in PD.(1–3) Though delayed gastric emptying and pancreatic fistula are the most common short-term complications, (4) there is an increased incidence of long-term survival after PD. Hence, there is a need to study long-term postoperative outcomes such as pancreatic insufficiency, which has a significant and detrimental impact on quality of life.(5)

Postoperative pancreatic endocrine insufficiency causing pancreatogenic diabetes mellitus affects multiple organ systems, which in the long run, can lead to lifelong irreversible complications as well as lifelong insulin dependence. Pancreatic exocrine functions play a significant role in fat absorption, and its insufficiency leads to malabsorption as well as a detrimental quality of life due to malnutrition, steatorrhea and altered bowel consistencies. The incidence of post PD exocrine insufficiency varies widely from 53–73%, and that of endocrine insufficiency is 8- 49%, which includes both long-term and short-term incidences as well as all grades of insufficiencies.(1,6) Mild pancreatic exocrine insufficiency (PEI) with subtle changes on pancreatic function tests has shown no significant clinical symptoms. However, severe PEI, with loss of 90% of pancreatic exocrine function, causes maldigestion of fat and protein leading to dyspepsia and steatorrhea. The clinical impact of PEI stresses the importance of identifying patients at risk for developing postoperative PEI.

Several studies have evaluated risk factors leading to the development of post-pancreatectomy pancreatic insufficiency. The risk factors for endocrine insufficiency include previous acute pancreatitis episodes, pre-existing chronic pancreatitis, preoperative glucose

intolerance, pancreatic specimen size, body mass index (BMI) and pancreatic texture, while those for exocrine insufficiency include PD, preoperative endocrine insufficiency, hard pancreatic texture and malignancy. (7)

The majority of subjects with periampullary malignancies undergoing PD have tumors at or near the head of the pancreas, causing pancreatic ductal obstruction, which by itself or in association with chronic pancreatitis leads to pancreatic atrophy or fibrosis.(8) Pancreatic fibrosis is associated with both endocrine and exocrine tissue loss as well as post-PD exocrine insufficiency. (9) But no studies have shown a direct correlation between fibrosis and endocrine insufficiency. The acinar cell density of the parenchyma of the pancreas, a measure of the pancreatic exocrine tissue, has rarely been investigated before as a factor contributing to the malfunction of the pancreatic remnant. It has been shown to have a strong correlation with postoperative fistula in multiple studies (10,11), which in turn is inversely correlated to pancreatic fibrosis. However, no studies evaluate the correlation between acinar cell density and pancreatic endocrine insufficiency. Therefore, we aimed to study the presence and extent of acinar cell loss as well as the extent of fibrosis in the pancreas of patients undergoing PD and correlate them with postoperative pancreatic functions to see if these pathological factors may have a role in these functional changes of the pancreas.

Currently, there are no standard definitions for pancreatic insufficiency. Some studies have used clinical subjective definition. Few other studies used an objective biochemical definition. This study aims to assess pancreatic exocrine and endocrine insufficiency by using biochemical assays- fecal elastase 1, HbA1c, FBS and clinically using a history of diabetes mellitus or need for insulin/ oral hypoglycemic agents.

There is also no standard protocol for postoperative assessment of pancreatic insufficiency. Hence, with this study, baseline data will be available to propose a risk prediction model for post-PD pancreatic endocrine and exocrine insufficiency, which will provide guidelines for early initiation of pancreatic enzyme replacement therapy (PERT) and early diagnosis of

pancreatogenic diabetes, in at risk patients. This may improve the long-term quality of life in these subsets of patients.

REVIEW OF LITERATURE

Pancreaticoduodenectomy- History, overview and outcome

Pancreaticoduodenectomy (PD) is the most common and a standard procedure for most malignant and some benign pancreatic head and periampullary lesions.(12) It entails a combined resection of the duodenum and pancreatic head along with the common bile duct, gall bladder, distal stomach and proximal 15 cm of the jejunum. (13)

The 1st PD for pancreatic cancer was performed in 1898 by Dr Alessandro Codvilla with a gastrojejunostomy and a cholecystojejunostomy albeit without a pancreatic stump drainage or closure. (14) It was modified in 1912 by Dr Walter Kaush as a 2-stage procedure wherein a cholecystoenterostomy for relief of jaundice was performed in the 1st stage. In the 2nd stage, a partial resection of duodenum with pancreatic head and common bile duct was done along with a gastroenterostomy and pancreaticoduodenostomy. (15) Dr Allen Whipple described the first single stage PD in 1940 wherein he included a complete duodenal resection and antrectomy followed by a pancreaticojejunostomy and choledochoenterostomy. (16)

In the 1970s and 1980s PD was associated with a high mortality, as high as 25-30 %. (17) As medical knowledge has advanced; anesthetic and surgical techniques have become refined over the years. These factors combined with implementation of centralization of complex surgeries from low volume or primary care centers to tertiary care centers, adherence to standard post operative care and adoption of enhanced recovery strategies have significantly decreased the mortality associate with this complicated procedure to less than 5 % in high volume tertiary care centers. (18–20)

The most common complications following PD are delayed gastric emptying and post operative pancreatic fistula which are see in the immediate post operative period. (2) The other common complications seen in the early postoperative periods are surgical site infection, pulmonary complications and biliary leak. (3) Over the last 3 decades the advancement in medical literature has paved way for comprehensive understanding of these

complications and their risk factors. This has led to a standardization in their diagnosis and reporting, which has decreased the incidence of these complications over the years. (21–24) However, the morbidity associated with PD is still high at around 45-60 %. (1–3)

While most of the studies surrounding PD are targeted at the above mentioned early post operative complications, despite increased survival over the last few decades, the literature describing long term morbidity and outcome following this surgery are relatively sparse. The long-term complications following a PD include anastomotic stricture of the biliary, gastric and pancreatic drainage procedures, recurrence of the primary malignancy, chronic pancreatitis and a pancreatic insufficiency. However, most studies have focused on benign etiologies as long term follow up is sparse after PD for malignancies. (25,26)

Periampullary malignancies involve the bulk of the indications for PD in malignancies and these include cancers of pancreatic head, ampulla of Vater, distal bile duct and 2nd segment of duodenum. (27) The most common of these is pancreatic cancer which has a poor long-term survival of 20 % at 5 years (27,28) and pancreatic ductal adenocarcinoma, a sub entity of pancreatic cancers, has been reported to have 5 year survival as low as <5 %. (29) The other periampullary entity, distal cholangiocarcinoma has 5 year survival rate of 20-40 %. (27) As a result, prospective studies focusing on long term morbidity after PD for malignancies are lacking.

Though the survival post this surgical procedure, among many other factors is hugely dependent on the site and pathology of the tumor, the decrease in postoperative mortality has led to an increased long term survival. (30) The 2nd most common periampullary malignancy i.e., ampullary cancer has a 5-year survival of 35-60 % and a similarly high survival of 40-55 % at 5 years has been reported in duodenal carcinoma. (27,28) The preoperative prevalence of pancreatic endocrine insufficiency in the form of Diabetes Mellitus has been shown to variedly range from 11- 43 %. (9,31,32) and that of preoperative pancreatic exocrine insufficiency has been reported as 50-65 % (33,34) These preoperative insufficiencies may

have a bearing on the postoperative endocrine and exocrine functions as well and these need to be studied in detail. In this era of increased survival following PD in malignancies, a shift in focus is required to understand the long -term complications, their risk factor associations and their effect on patient survival and quality of life.

Post operative pancreatic insufficiency and their clinical impact

This term included both pancreatic endocrine and exocrine insufficiency, which have been found to significantly impact long-term quality of life.

Pancreatic endocrine insufficiency manifests as glycemic intolerance which can increase risk for stroke, coronary artery disease, and peripheral vascular disease. This burden of DM and its complications maybe reduced by early detection and management and while The American Diabetes Association recommends screening the general population at 3-year intervals beginning at the age of 45 using fasting plasma glucose or hemoglobin A1C, post-pancreatectomy patients should be considered high-risk for the development of DM and screened more frequently. (35) However, in our setting, where patient compliance with follow up is often not satisfactory, a risk assessment guideline that will objectively quantify the risk of postoperative diabetes mellitus, may improve patient compliance.

Pancreatic exocrine insufficiency clinically manifests with steatorrhea, loss of weight and abdominal discomfort which mandates frequent visits to the physician but often remain undiagnosed and untreated. In the long run, these patients are also predisposed to developing malabsorption causing malnutrition as well as micronutrient and fat-soluble vitamin deficiencies. Malnutrition increases the long-term morbidity. These patients also develop secondary complications like mineral bone disease, osteoporosis, bleeding diathesis, night blindness and alopecia. (12,36) Malabsorption can also cause apolipoprotein deficiency. This combined with post PD insulin deficiency and insulin resistance causing peripheral lipolysis and hepatic lipid deposition can lead to increased NAFLD due to PEI after PD. (12)

These symptoms and complications associated with pancreatic insufficiency have significant impact on the patient's quality of life. In a study by Huang et al, the quality of life (QOL) and functional outcome of patients after PD was assessed. It was shown that, though most patients have QOL scores comparable to those of control patients and can function independently in daily activities; many patients reported weight loss and symptoms consistent with pancreatic exocrine and endocrine insufficiency.(1) Similarly, in a study by Fong et al. on functional outcomes in 5-year survivors after PD, around 50 % of the patients required pancreatic enzyme replacement and 11% developed new-onset diabetes. (37)

Malnutrition and weight loss associated with pancreatic insufficiencies decrease the performance state of the patient which delays optimal adjuvant treatment of the primary malignancy. These patients may be deemed unfit for initiation of the adjuvant therapy. Additionally, they are often unable to tolerate the chemotherapy which causes non-compliance to the same. (12)

Pancreatic exocrine insufficiency has also been shown to be associated with decreased survival in pancreatic cancer undergoing PD. A survival benefit of pancreatic enzyme replacement has been seen to be equivalent to surgery or chemotherapy. (12)

An understanding of the pathophysiology of pancreatic endocrine and exocrine insufficiency is crucial for its early diagnosis and for identifying the associated risk factors.

Pancreatic endocrine insufficiency

Pancreatic insufficiencies can be classified as endocrine and exocrine insufficiencies.

Endocrine pancreas is made up of islets of Langerhans, which act as a micro-organ of the pancreas, which form its endocrine functional units. There are five major cell types in each islet of Langerhans: α, β, δ, F, and ε cells.

- α cells: 35% of islet cells, secrete glucagon

- β cells: 55% of islet cells, produce insulin
- δ cells: <10% of islet cells, secrete somatostatin
- F cells: < 5% of islet cells, secrete pancreatic polypeptide (PP)
- ε cells: < 1% of islet cells, secrete human islet cells (38)

While, a larger proportion of α cells are demonstrated within the islets of the body and tail of the pancreas, those in the uncinate process have a larger proportion of F cells. The β cells and δ cells are distributed equally through whole of the pancreas. (38)

Pancreatic endocrine insufficiency presents as glucose intolerance which maybe symptomatic or incidentally detected diabetes mellitus during routine surveillance and the form of diabetes brought on by a pancreatectomy is known as pancreatogenic/ pancreatic diabetes mellitus. It is frequently misdiagnosed as type 2 diabetes which comprises both structural and functional loss of glucose-normalizing insulin production. Type 3c diabetes, which refers to hyperglycemia brought on by overall pancreatic dysfunction, and pancreoprivic diabetes, which describes diabetes in the context of exocrine pancreas pathology, are the more recent terms. Pancreatic diabetes, which encompasses a wide range of etiologies alongside pancreatectomy, is the preferred umbrella term.(39)

Assessment of pancreatic endocrine functions

The evaluation of the endocrine pancreas primary assesses the β-cell function which should include insulin production, β cells response to secretagogue stimuli, and insulin resistance in peripheral tissues. These include:

- Basal/ fasting measurement of the β cell products - insulin, c peptide, insulin/ proinsulin ratio. These tests are not standardized and lack accuracy.
- Intravenous stimulation tests: These tests are cumbersome to perform and are currently used only for research purposes. They do not have a role in clinical application.

- Oral stimulation tests: These include mixed meal tolerance test and oral glucose tolerance test, of which the latter is the most used test. (38)

The American Diabetic Association (ADA) guidelines which are used worldwide to define diabetes mellitus (DM) are also applied to characterize the pancreatic endocrine insufficiency manifesting as β cell dysfunction and included the following:

1. Fasting plasma glucose ≥ 126 mg/dL (with fasting defined as no caloric intake for >/= 8 hours
2. Oral glucose tolerance test (with 75 g anhydrous glucose dissolved in water) showing a 2-hour post glucose plasma glucose ≥ 200 mg/dL
3. HbA1c (glycated hemoglobin/ hemoglobin A1c) ≥ 6.5 %
4. Fasting plasma glucose ≥ 200 mg/dL with classic symptoms of hyperglycemia (39)

Incidence of postoperative pancreatic endocrine insufficiency

The incidence of post pancreatectomy diabetes rates range widely from 3 to 50 percent in literature and depends on the surgical procedure used to resect the pancreas as well as the underlying conditions. (40,41) The prevalence of type 3c diabetes among all diabetic individuals is estimated to be 5% to 10%. Because of the varied pathophysiology of type 3c diabetes, its clinical symptoms differ from those of type 1 and type 2 diabetes. (40) Pancreatic DM, like any other kinds of DM, can impair patients' long-term quality of life since if left unrecognized it can lead to undiagnosed long term secondary complications such as nephropathy, neuropathy, and retinopathy. Additionally pancreatogenic DM is commonly linked with iatrogenic hypoglycemia caused by enhanced peripheral sensitivity to insulin; hence, it is difficult to treat with medication. (42)

There is a theoretical reduction in the islet cells number after any pancreatic resection which could explain the post pancreatectomy glycemic intolerance. In spite of the common thought that removal of 80% of the pancreas is required to cause a pancreatic insufficiency, even post

PD wherein there is a removal of approximately 30-50% of the pancreatic volume, new-onset diabetes has been reported in 20-50% of patients. (42)

Ferraro et al (2012) retrospectively analyzed 544 patients who had undergone PD from 2004 to 2010 and their need for pharmacological treatment for hyperglycemia in the immediate postoperative period defined as in the first month following surgery. He reported a 4% incidence of new onset post operative DM in these patients. The large sample size, short-term (30 day) follow-up design, and fewer patients with chronic pancreatitis, may account for the lower incidence of post resection DM in this study. (43)

Wu et al (2015) in a retrospective analysis of 3914 patients who underwent PD over a period of 10 years, reported an incidence of post PD DM in 16% of the patients. The mean follow-up duration was 1500 days and patients who had a year or more of follow up were included. They also found that PD when done for periampullary cancer was less often associated with DM than for other malignancies. (40)

Kusakabe et al (2019) conducted a retrospective analysis of 1,717 patients who underwent pancreatectomy and reported that 20% of patients developed postoperative endocrine insufficiency at a mean time to onset of 20 months. This study analyzed both distal pancreatectomy as well as PD, and distal pancreatectomy was more significantly associated with endocrine insufficiency than PD. The greater frequency of endocrine insufficiency following DP may be partially accounted for by the islet distribution's variability, which is illustrated by the increased islet volume density in the pancreas' tail compared to its head and body. (41)

A retrospective analysis by Cai et al (2020), in 168 patients undergoing PD, a 36 % incidence of pancreatic endocrine insufficiency was seen at a follow up of 6 months and noted male gender and metabolic syndrome to be the independent risk factors for the same. (44)

Risk factors for post PD DM

The etiology of endocrine dysfunction following resection is multifactorial. In addition to the pancreatic parenchymal loss and altered neurohormonal responses following resection, other contributing factors may include the development or progression of the underlying pancreatic disease, the progressive atrophy of glands, weight loss or weight gain, high body mass index (BMI), old age, type of pancreatic resection, resected pancreatic volume as well as administration of adjuvant chemo- or radio-therapies.

In a study by Tran et al (2008) of 74 patients undergoing PD, 26% developed DM post operatively and a significant correlation between preoperative fibrosis score and endocrine tissue loss was also demonstrated. (9)

The study by Ferrara et al (2012) used only first 30 days post-surgery to prevent confounding variables other than resection which offered an opportunity to try to determine the separate effect of pancreatic parenchymal loss and physiological alterations caused by pancreatic resection. Impaired glucose tolerance, FBG 126 mg/dl, and increased specimen length were found as three variables predictive of DM. In patients with normal pre-operative FBG levels, the incidence of iPRDM is only 1%; this knowledge is useful for surgeons and their patients when contemplating PD as a therapeutic option for pancreatic illness. (43)

The loss of the gastrin and cholecystokinin induced by excision of the duodenum and, in certain circumstances, the distal stomach, or a blockage of the pancreatic duct produced by stenosis of the pancreatico-enteric anastomosis maybe responsible for the ongoing atrophy of the pancreatic remnant which in turn may account for the postoperative DM.(31)

Oh et al (2012) retrospectively analyzed the incidence of as well as risk factors associated with post PD in 98 patients who underwent surgery from 2003 to 2009. The postoperative DM was analyzed by OGTT done at 1 year of follow up and it was seen that 17% patients developed post PD DM. A comparative analysis of variables between patients who developed and did not develop postoperative DM revealed that postoperative pancreatic atrophy was the

only factor positively and significantly associated with the same. It was defined as a decrease in the pancreatic parenchymal thickness by more than 50% of the preoperative value on a CECT at 1 year follow up. (42)

Kwon et al (2015) prospectively collected data of 229 patients who underwent various types of pancreatic resections for benign pathologies and retrospectively analyzed the occurrence of glycemic intolerance in these patients postoperatively. They also did risk factor analysis for the same and found that a high BMI, old age and the type of resection specifically distal pancreatectomy were the only factors with significant risk of developing post operative DM. In this study pancreatectomy for malignant etiologies were excluded in view of association of pancreatic cancer with DM which could become a confounding factor.(35)

Pancreatic exocrine insufficiency - definition and pathophysiology

Exocrine pancreas is composed of the pancreatic acini containing the acinar cells and the pancreatic ductal network lined by ductal epithelial cells. While the ductal cells secret a water and bicarbonate rich fluid, the acinar cells are primarily responsible for synthesis and secretion of the pancreatic enzymes. These enzymes are composed of lipase, amylase and peptidases in an inactive form and get activated within the small bowel. The primary function of the bicarbonate ions is to buffer the acidic pH of the gastric secretion that enters the duodenum so that a suitable pH is available for the activation of the pancreatic enzymes. Pancreatic exocrine secretion occurs in three main phases- cephalic, gastric and intestinal and the stimuli for the same is provided by a multitude of factors including the presence of components of ingestion in the duodenum via hormones like secretin and cholecystokinin. (38)

Pancreatic exocrine insufficiency (PEI) is a disorder characterized by inadequacy of pancreatic enzymes in the background of complete or partial, structural, or functional loss of pancreatic glands. It typically manifests with clinical symptoms of steatorrhea, abdominal discomfort, and bloating. It might be related to reduced parenchymal mass following

pancreatic surgery and could worsen further due to continued pancreatic residual atrophy.

Diagnosis of PEI

There are multiple modalities to assess pancreatic exocrine insufficiency. It is often diagnosed by physicians using a clinical history of steatorrhea- defined as new onset of steatorrhea at least three times a day, three days a week, with weight loss or malabsorption signs, excluding others causes or a pharmacological requirement of pancreatic enzymes that persisted beyond discharge after initial surgery. (45) Patients are often empirically administered a trial of pancreatic enzyme replacement and the diagnosis of PEI is confirmed if there is decrease in steatorrhea reported by the patients. However, this is not optimal due to the availability of various enzyme replacement formulations, drug costs, and patient compliance. Moreover, owing to the significant functional reserve of the human pancreas, steatorrhea is manifested usually after a loss of at least 90% of the pancreatic parenchymal function. (38)Hence steatorrhea is not a reliable indicator of exocrine insufficiency in the early stages of the disease. As a result, identifying precise indicators of the disease activity is a top objective and this can be achieved by the various pancreatic function test.

Pancreatic function tests include indirect and direct tests. The indirect tests non-invasively evaluate the consequences of decreased pancreatic exocrine secretions. These include a quantitative (72-hr) fecal fat estimation test which is considered the gold standard indirect tests. Following consumption of 100g fat per day for 5 days, fecal collection is done for 72 hours and pancreatic exocrine insufficiency is defined as fecal fat of >7g/ day. This test measures global fat malabsorption, of which pancreatic exocrine insufficiency is one cause. Moreover, it is a cumbersome test and cause significant burden on the health personnel due to handling of large amounts of fecal sample. (36,38)Another indirect test is the 13C–mixed triglyceride breath test which is a measure of triglyceride degradation, the most clinically significant end-effect of exocrine pancreatic function. It involves administration of ^{13}C–mixed triglyceride breath test that gets hydrolyzed by lipase into $^{13}CO2$ which is then

quantified by infrared assay or mass spectrometry. Both these tests are non-invasive and tolerated well by patients and the latter has a high sensitivity (90-100%) and specificity (80-90%) for severe exocrine insufficiency. (46) However, they are both cumbersome to perform and have poor sensitivity in the early stages of the disease. They are better reliable in the advances phase of pancreatic exocrine insufficiency. (38)

The direct pancreatic function tests include both invasive and non-invasive tests. The gold standard for determination of pancreatic exocrine insufficiency are the invasive hormone-stimulated pancreas function tests. (47) These include secretin, cholecystokinin (CCK) or combined secretin-CCK stimulations tests. wherein following the intravenous administration of these agents, using an orally placed gastro duodenal tube, periodic collection of pancreatic secretions is done. A secretin stimulation test is a measure of the ductal cells and is performed by intravenous administration of secretin at a bolus dose of 0.2 mcg/kg following which duodenal fluid is continuously collected in 4 aliquots of 15-minute intervals each. A bicarbonate concentration in each aliquot of <80 mEq/L is diagnostic of PEI and a value <50 mEq/L is considered as severe PEI. CCK stimulation test measures the lipase in duodenal fluid collected over a continuous 80-minute period and a value >780 IU/L is indicative of acinar cell dysfunction causing PEI. A combined secretin-CCK stimulation test measures both acinar and ductal cell functions and has a higher sensitivity. However, the large amount of pancreatic fluid secreted compounded by the additional fluid secreted from gall bladder due to CCK stimulation may dilute the pancreatic secretions in the duodenal fluid and hence contribute to high false positive values. (38) These tests are not only invasive and uncomfortable for the patients, but also cumbersome and less easily available. Endoscopic secretin pancreatic function test is a simplified version of the same, however it is similarly invasive, uncomfortable and its diagnostic value for EPI has also not been proven. (47) Hormonal stimulation have also been combined with magnetic resonance imaging (secretin-enhanced MRI) to demonstrate change in pancreatic capillary blood flow or pancreatic

secretion as well as with magnetic resonance cholangiopancreatography (secretin- enhanced MRCP) to measure the pancreatic function in terms of duodenal filling. These tests have not been standardized and are not widely used in clinical application. (36,38)

Noninvasive direct pancreatic function tests include serum trypsinogen, fecal chymotrypsin and fecal elastase assays. These tests are easy to perform and due to their non-invasive nature, well tolerated by the patients. Serum trypsinogen with a cut off value of less than 20 ng/ml has high sensitivity and specificity for diagnosis of advanced PEI. However, its accuracy is low for early stages of the deficiency. (38) Fecal chymotrypsin assay involves a photometric measurement of the enzyme in 3 consecutive fecal samples. The normal chymotrypsin activity in stool is >6 U/g. (48) It requires discontinuation of pancreatic enzyme replacement therapy (PERT) for 2-5 days prior to the test as it is not possible to differentiate human chymotrypsin from the exogenous form. (38,48) A limitation of this assay is its high false positivity rate due to the susceptibility of chymotrypsin to proteolytic degradation during intestinal transit and its dilution in the presence of diarrhea. (38) It also has a low accuracy in patients with mild or moderate PEI. (48)

Fecal elastase 1 assay

The fecal elastase-1 (FE-1) assay is an enzyme-linked immunosorbent assay (ELISA) that specifically measures the stool concentration of pancreatic protease elastase-1. This enzyme is 6 times more concentrated in stool than in pancreatic juice and hence, FE-1 is a reliable indicator of pancreatic secretory function. Moreover, the test requires only a spot stool sample making it a simple and fast test. (49) Pancreatic elastase additionally, is a highly stable pancreatic enzyme that is resistant to the proteolytic degradation during intestinal tract. As the ELISA test uses specific antibody against the enzyme, FE-1 test is unaffected by simultaneous enzyme supplementation, which are porcine derived. (36,38,48)

The FE-1 immunoassay is a reasonably affordable test and requires less than 1 gram of spot stool sample, which may be collected in a fasting or post prandial state. The sample should be

in a semi solid or solid form and, runny or diluted samples should be avoided to decrease false positivity rate for PEI. It can be stored at room temperature for up to a week (49) and at 4–8°C for 72 hours. When refrigerated at −20°C, the elastase within these samples remain stable for up to one year. (47) Normal concentration of fecal elastase-1 exceeds 200 μg/g stool, and a concentration 100-200 μg/g stool is diagnostic of mild-moderate PEI while that of 100 μg/g stool denotes severe PEI. (49,50) In pancreatic adenocarcinoma patients undergoing curative resection FE-1 has also been shown to be a marker of prognosis with normal FE-1 predicting a better disease-free survival. (33)

FE-1 tests are known to exhibit assay variability, which might affect the test's diagnostic accuracy and despite its extensive usage in chronic pancreatitis and PEI screening, the diagnostic accuracy of FE-1 is unknown. It is known to have 60-85% sensitivity for the detection of moderate to severe chronic pancreatitis while its sensitivity for mild to moderate early chronic pancreatitis remains low at 25-75 % which limits its diagnostic use in chronic pancreatitis (50). FE-1 has a high negative predictive value of 99% and a positive predictive value of 88% for PEI at a cut-off of 100mcg/g. (51) The diagnostic efficiency of pancreatic elastase-1 determination in stool has been evaluated in many clinical studies and in a study by Loser et al. FE-1 was reported to have sensitivity and specificity of 93% for the diagnosis of PEI. (52) FE-1 at a cut off of 201μg/g, has been shown to have an accuracy, sensitivity, and specificity of 78.8%, 67.7%, and 82.5%, respectively for the diagnosis of PEI in chronic pancreatitis. (53) In a systematic review and meta-analysis, when compared with secretin stimulation test, FE-1 has demonstrated a diagnostic accuracy of 23%, and a pooled sensitivity and specificity of 77% and 88%, respectively. The sensitivity of FE-1 for PEI when compared with fecal estimation test was 96% and its sensitivity to diagnose mild-moderate PEI was low at 45-67%. (47)

Prevalence of post operative PEI

Currently there are no standard definitions for post PD pancreatic exocrine insufficiency.

Studies have used varying combinations of the above-described methods including history of steatorrhea, fecal pancreatic enzymatic assays as well as invasive hormonal stimulation tests to evaluate PEI post pancreatic surgeries. In a general population based study by Rothenbacher et al using FE-1 measurements, the prevalence of PEI in 914 subjects was 11.5% and 5.1% of subjected had a severe PEI. (50) The incidence of post PD PEI has been reported to widely range from as low as 30% to as high as 100%. This wide range may be accounted for the lack of a uniform consensus regarding definition of this entity. Different studies have used different modalities to test for PEI as well as there is no uniformity regarding the time post operatively when the diagnosis has been done.

In an observational study by Matsumoto et al (2006) a reduced FE-1 indicative of PEI was noted in 33% of 132 patients undergoing PD. They also found a significant decrease in FE-1 post pancreatic resection which was most pronounced at 1 year. (49) Nordback et al (2007) demonstrated highest median FE-1 at a median duration of of 52 months after PD in patients who had a patent pancreatico-enteric anastomosis. (54) Tran et al (2008) et al demonstrated a severe pancreatic exocrine in 76% using FE-1 in 74 patients undergoing PD. 12% of the patients developed a moderate PEI and 12 % had a normal fecal elastase-1 value. (9)

Kusakabe et al in a retrospective analysis of 1,717 patients who underwent pancreatectomy reported exocrine insufficiency in 36% patients at around 14 months. This study analyzed both distal pancreatectomy as well as PD. While distal pancreatectomy was more significantly associated with endocrine insufficiency than PD, the reverse was noted for exocrine insufficiency. The diagnoses of exocrine insufficiencies were based on clinical diagnoses of pancreatic insufficiencies and may be understated, particularly in the case of exocrine insufficiency, where mild to moderate symptoms frequently go unnoticed and untreated.(41)

Hartman et al. (2019) conducted a retrospective study of patients who underwent pylorus preserving PD. Exocrine insufficiency was measured in 37 patients using 13C labeled mixed

triglyceride (MTG) breath test at a mean interval postoperatively at 3.4 months and found that after resection, exocrine function deteriorated in 54 % patients while it improved in 5.4 % of them. 28 patients were analyzed with OGTT post PD at around 3.4 months and postoperative DM was present in 29% of them. (31)

In a systematic review of 34 articles by Pathanki et al (2020), the reported incidences of post PD exocrine insufficiency ranged from 38-93%.(12) In the retrospective study by Cai et al. (2020) a 42.50% incidence of post PD exocrine insufficiency was seen. (44) In a prospective study by Kumar et al 2021**,** a 100% incidence of PEI after 3 months was seen in 30 patients who underwent PD for periampullary malignancies. While 33% patients had a moderately decreased FE-1 67% of them had a severely decreased FE-1. (55)

Risk factors for post operative PEI

Several studies have looked at the risk factors for postoperative pancreatic insufficiency.

Nordback et al (2007) hypothesized that obstruction of the pancreatogastrostomy or pancreatojejunostomy may have an association with the development of delayed post PD PEI. (54) In the retrospective study by Tran et al (2009) a strong correlation was also seen between the post PD PEI and preoperative pancreatic fibrosis score. Pancreatic atrophy and associated fibrosis might explain the loss of exocrine function. The parenchymal fibrosis might be caused by tumor-induced duct blockage, chronic inflammation coexisting with tumor, or just chronic pancreatitis. (9) A significant correlation between post operative zinc deficiency and pancreatic exocrine insufficiency was shown by Yu et (2011) in 48 patients who underwent a PD for periampullary cancers. (56)

The retrospective study by Hartman et al (2019) also aimed to see if pancreatic volumetric evaluation might predict exocrine and endocrine insufficiency following PD. The preoperative and postoperative pancreatic volumetry were determined based on available imaging at 2-6 months following surgery. The study found limited predictive value of post PD, pancreatic volumetry for exocrine insufficiency. They also found no correlation of the

same with postoperative diabetes. (31)

A BMI 18.5 kg/m^2, chronic pancreatitis, and total bilirubin 171 mol/L were found to be independent risk factors for post PD PEI on a multivariate analysis in the retrospective study by Cai et al. (44) A meta-analysis of 20 studies involving 4131 patients by Budipramana et al (2022), demonstrated PD, preoperative dilatation of main pancreatic duct (>3mm diameter), pancreatogastrostomy anastomosis, hard texture of the pancreas and adjuvant chemotherapy as being significant risk factors for development of PEI after pancreatic surgery were found to be. They also found that pylorus preserving PD, gender, endocrine insufficiency or underlying disease were not risk factors for PEI. (57) However, the systemic review by Pathanki et al (2020) noted that there was no difference between a classical Whipple's procedure or pylorus preserving PD on development of PEI. There was conflicting evidence regarding the influence of the type of pancreatoenteric anastomosis on post PD PEI. (12) Neophytou et al. evaluated the risk factors of exocrine insufficiency after pancreatic resections with PEI defined by the onset of steatorrhea associated with weight loss. The risks factors for the occurrence of PEI were a BMI < 18.5 kg/m2, tumors located in the pancreatic head, preoperative chronic pancreatitis, fibrotic pancreas and biological markers of chronic obstruction. (6)

Histopathology of pancreatic parenchyma

Because pancreatic function can be altered during chronic pancreatitis, fibrosis and loss of functional acinar tissue may have a leading role in pancreatic insufficiency. Exocrine pancreatic structural and functional alterations have been seen in diabetes individuals. Diabetes mellitus can predispose to PEI, and chronic PEI can be associated with diabetes. (58,59)

Insulin-acinar axis

Topographical association and functional interactions between the pancreatic acinar and islet cellular components have been described in the adult human pancreas and the term islet-

acinar axis has been used to describe this complex endocrine-exocrine link within the pancreas, in which the different cell types interact vascularly and physiologically. The islet hormone insulin has been shown to reach the acinar cells via an acinar portal system and a high concentration of the same has also been seen in the venous supply from acini to the pancreatic duct. As such the islet hormones have a role in regulation of the exocrine function. This insulin-acinar axis also regulates the differentiation and functional development of endocrine cell. (60,61)

In chronic pancreatitis and fibro-calculous pancreatic disease, stagnation of pancreatic enzymes, increased intraductal pressure and ductal calculi cause atrophic damage to the acini and fibrosis of pancreatic parenchyma, which in turn cause, exocrine insufficiency. It has also been seen that the increased viscosity of the pancreatic secretions coupled with increased intraductal pressure can cause metaplasia of ductal cells impairing the neogenesis of beta cells from the ductal progenitor cells. Additionally, the acinar cell damage associated with surrounding parenchyma fibrosis can lead to endocrine tissue damage. Thirdly the fibrosis can impair the intrapancreatic circulating of insulin. These factors combinedly lead to an endocrine dysfunction. (62)

Role of acinar cell density and pancreatic fibrosis

The role of acinar cell density in post pancreatectomy pancreatic fistula (POPF) as well as pancreatitis is documented. Nahm et al correlated with the acinar cell density of the pancreatic neck resection margin of 65 patients undergoing PD with postoperative pancreatitis and POPF and a significant correlation between these were demonstrated. (11) Partelli et al demonstrated an association between increased acinar content at the pancreatic neck margin with clinically relevant postoperative pancreatic fistula and post operative acute pancreatitis in 388 patients who underwent PD. (10)

However, both acinar cell density as well as fibrosis of the parenchyma of the pancreas have been less investigated before as factors associating with the malfunction of post PD

pancreatic remnant.

The association of pancreatic fibrosis with post operative exocrine function was demonstrated by Tran et al. (9)

Yuasa et al (2012) investigated the relationship between acinar cell density of the pancreatic stump and postoperative pancreatic exocrine function in patients who underwent pancreatoduodenectomy (PD) and distal pancreatectomy (DP). The exocrine pancreatic function was evaluated by 13C-labeled mixed triglyceride breath test. It was noted that acinar cell density of patients undergoing PD was significantly less than that of patients undergoing DP. The extent of pancreatic exocrine insufficiency in PD was higher than in DP. There was also a significant correlation between acinar cell density of the pancreatic stump and the postoperative pancreatic exocrine function. (63)

These data underline the need for further prospective studies regarding the association between pancreatic histological findings and post PD endocrine and exocrine insufficiency.

AIMS AND OBJECTIVES

Aim

To evaluate the correlation between acinar cell density and fibrosis score in post pancreaticodudoenectomy specimens with postoperative pancreatic endocrine and exocrine insufficiency.

Objectives:

Primary objective:

To study the pancreatic fibrosis score and acinar cell density in the postoperative specimens of patients who undergo pancreaticoduodenectomy for malignancies and correlate these with postoperative pancreatic exocrine and endocrine insufficiency.

Secondary objective:

1. To study the incidence of post pancreaticoduodenectomy endocrine and exocrine insufficiency.
2. To study the incidence of post pancreaticoduodenectomy complications

MATERIALS AND METHODS

Study design

It is a single-center prospective, observational study conducted on patients undergoing pancreaticoduodenectomy, for malignancies, under the Department of Surgical Gastroenterology, in collaboration with the Department of Pathology and Department of Biochemistry, at the All India Institute of Medical Sciences (AIIMS), Jodhpur. All the patients included in the study were registered in the CPMS of the hospital.

Study setting

All the patients who underwent PD for malignancies and met the inclusion criteria were recruited from the Department of Surgical Gastroenterology, AIIMS, Jodhpur.

Duration of study

From 1st January 2021 to 30th November 2022

Study population

There is no study in published literature analyzing the correlation between acinar cell density and post PD pancreatic endocrine insufficiency. Hence no sample size was calculated. All patients who underwent PD in the Department of Surgical Gastroenterology, AIIMS, Jodhpur during the study period were evaluated for inclusion and exclusion criteria, and a total of 20 patients were recruited in the study.

Ethics Approval

Ethical approval for this study was obtained from the AIIMS Ethics committee with reference no AIIMS/IEC/2021/3473.

Ethical considerations

All the patients enrolled in the study received standard care management, and participation in the study did not lead to any change in their usual diagnostic workup, follow-up, or management. All personal data collected during the study were kept strictly confidential.

Inclusion Criteria:

a) All patients who underwent PD for malignancies that were confirmed by histopathology
b) Aged 18-80 years

Exclusion Criteria:

a) Patients who refused consent
b) Who do not fulfill the inclusion criteria
c) Who are lost to follow up
d) Who are pre-operatively diagnosed with chronic pancreatitis
e) Who are postoperatively diagnosed to have benign etiology on HPE

Methodology

Consent and counselling

All patients were provided with a patient information leaflet and were counseled regarding the following:

- Benefits and procedure-related details of pancreatoduodenectomy
- The concept of pancreatic endocrine and exocrine insufficiency
- Benefits of timely detection of endocrine and exocrine insufficiency

The patients were explained the purpose of the study. A detailed written informed consent was taken.

History, examination and investigations

Patients planned for PD underwent a detailed history and clinical examination. The history of presenting complaints like jaundice, abdominal pain, fever, gastrointestinal bleeding and vomiting were noted. History of preoperative biliary drainage and associated symptoms like anorexia, weight loss and steatorrhea were evaluated. The patient's demography and

comorbidities, and addictions were noted, and the ECOG statuses were also evaluated. Physical examination included routine abdominal examination and measurement of BMI. All patients underwent the following investigations

A. Laboratory investigations

- Complete blood count
- Liver function tests
- Renal function tests
- Serum electrolyte
- Prothrombin time/INR
- Tumor markers (CA19-9 and CEA)

B. Imaging

- Chest radiograph as a part of a pre-anesthesia check-up.
- Pancreatic protocol CT for assessment of tumor morphology, local extent, vascular anatomy and involvement, lymph node involvement, distant metastasis, common bile duct diameter, pancreatic duct diameter, tumor size and pancreatic atrophy.

All patients underwent a comprehensive multi-disciplinary evaluation, which included-

- Radiologist evaluation – A pancreatic protocol CT examination.
    - Pre-operative anesthesia evaluation– To rule out associated risk factors and immediate /delayed morbidity.
    - Medical gastroenterology evaluation: For side-viewing endoscopy ± biopsy of tumor and ERCP and CBD stent placement for jaundice (optional).
    - Pathology – Pre-operative assessment of biopsy (if done).

All patients underwent a pre-operative baseline pancreatic exocrine and endocrine function assessment.

Surgical procedure:

Perioperative antibiotic prophylaxis was given in the form of Inj. Cefoperazone - Sulbactam 1.5gm half an hour before surgery and then continued for three days till patient allowed oral soft diet. A team of five skilled pancreaticobiliary surgeons performed PD as per standardized protocol in the Department of Surgical Gastroenterology, AIIMS Jodhpur.

After excluding distant metastasis and local irresectability, all patients underwent a pylorus resecting pancreatoduodenectomy. (Figure 1) End-to-side double-layer duct-to-mucosa pancreatojejunostomy was made according to the standard technique. Subsequently, a single-layer end-to-side hepaticojejunostomy was performed. Finally, antecolic end-to-side anastomosis was made between the gastric remnant and the proximal jejunum. Feeding access was established either via a feeding jejunostomy (FJ) or a nasojejunal (NJ) tube. Two abdominal drains were placed for all the patients.

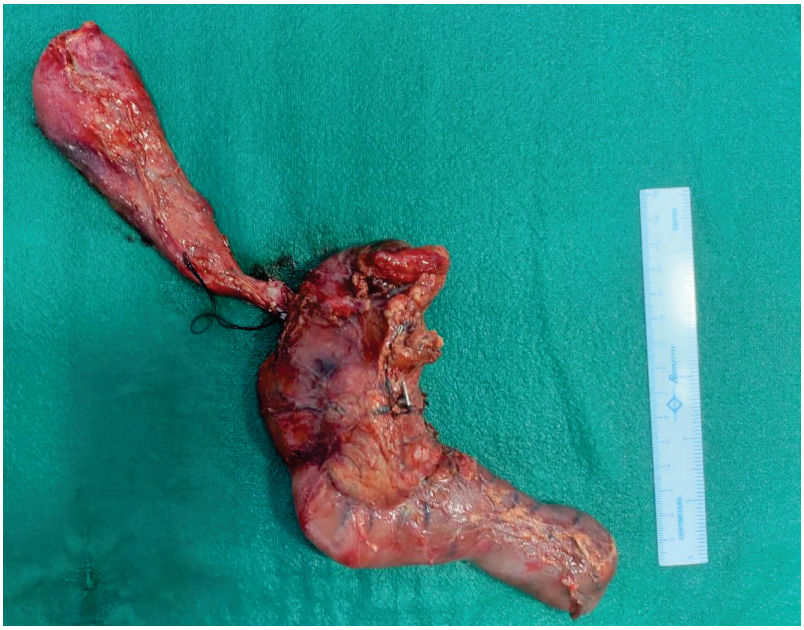


Figure 1: Operative specimen of pylorus resecting pancreaticoduodenectomy

Postoperative management and follow-up:

The standard pathway for recovery was followed in all patients. In the immediate postoperative period, patients were shifted to the intensive care unit if not extubated and to a high dependency unit if extubated. After proper evaluation and clearance from anesthetist, the patients were shifted to the ward. Enteric feeding via the NJ or FJ tube was initiated on post operative day 1. They were administered on oral liquids on post operative day 2 or 3 and subsequently introduced to semi-solid and solid foods. Patients were managed actively in the ward for any surgical complication as per standardized protocols. On discharge, all patients were prescribed oral medications after full recovery.

The patients were followed up as per standard protocol with clinical assessment every 3 months in the outpatient clinic. At the 3^{rd} and 6^{th} months, they were assessed for pancreatic exocrine and endocrine insufficiency.

Pancreatic exocrine function assessment

The fecal elastase 1 test was done preoperatively and at 3^{rd} and 6^{th} months following the surgery. A single spot feces sample was at each time and till the time of analysis, it was stored at sub-zero temperatures. The elastase-1 concentration was measured with a commercially available ELISA kit (IDK, Pancreatic Elastase ELISA, Immunodiagnostik, Germany) according to the manufacturer's instructions. The pancreatic function was considered normal when fecal elastase-1 concentration exceeded 200 µg/g feces, moderately insufficient when it was between 100 and 200 µg/g feces and severely insufficient when it was less than 100 µg/g feces. None of the patients received PERT pre or post operatively.

Pancreatic endocrine function assessment

The endocrine insufficiency will be assessed by fasting blood glucose and HbA1c levels, as well as a history of postoperative new-onset diabetes mellitus requiring treatment in the form of dietary modifications, oral hypoglycemic agents and/ or insulin. This was done preoperatively and at the 3rd and 6th months of follow-up. History was also taken at follow regarding the continued need for oral hypoglycemic agents or insulin injections.

Histopathological analysis:

All operative specimens underwent routine histopathological analysis as per standard guidelines in the Department of Pathology.

The acinar cell density and fibrosis score were assessed for this study by an experienced individual pathologist who was blinded about the clinical course of patients. Archived hematoxylin and eosin (H&E) stained sections of the paraffin-embedded pancreatic neck resection margin were retrieved for all patients. Masson trichrome staining was done to accurately estimate the degree of fibrosis. These slides were assessed under light microscopy (Figures 2 and 3), and semi-quantitative subjective analysis was used to assess the extent of fibrosis and acinar cell loss in the pancreatic parenchyma, and they were graded as follows.

Fibrosis score	Acinar cell density
• 0: no fibrosis	• No loss
• 1+: mild periductal/focal	• 1+ loss
• 2+: moderate fibrosis	• 2+ loss
• 3+: marked fibrosis	• 3+ loss

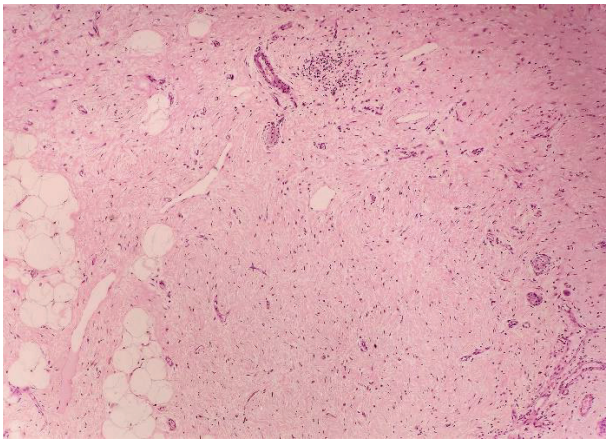


Figure 2. Hematoxylin & Eosin stain showing marked fibrosis, fat infiltration and marked acinar loss, 200X

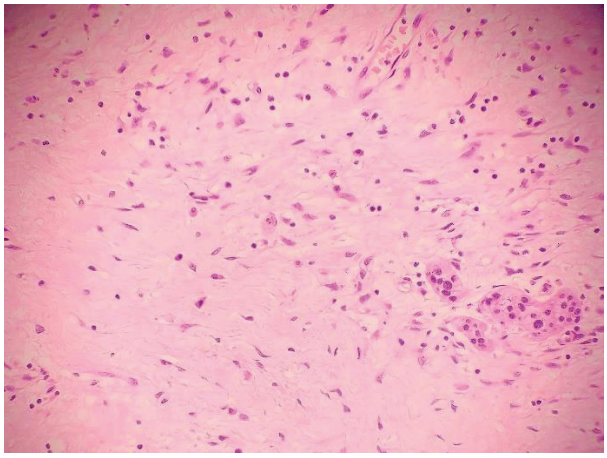


Figure 3. Hematoxylin & Eosin stain showing marked fibrosis, moderate chronic inflammation and prominent acinar loss with few islets seen, 400X

Statistical analysis

All data was acquired in a predetermined proforma and entered in Microsoft Excel sheets (Annexures- Masterchart). The Statistical softwares SPSS version 23.0 was used to analyse the data. Tables and figures were generated using Microsoft Word. Continuous data are presented as median with interquartile range (IQR) at the 25th and 75th percentiles or as percentages. These variables were analyzed for normality using the Shapiro-Wilk test. And all variables were found to have a non-parametric distribution The comparison of continuous variables was accomplished with the nonparametric Wilcoxon matched-pairs signed rank test

or McNemar's test. The correlation was analyzed using Pearson's correlation coefficient for continuous variables and Spearman correlation coefficient for ordinal variables. Statistical significance was achieved with a p value < 0.05.

Definitions

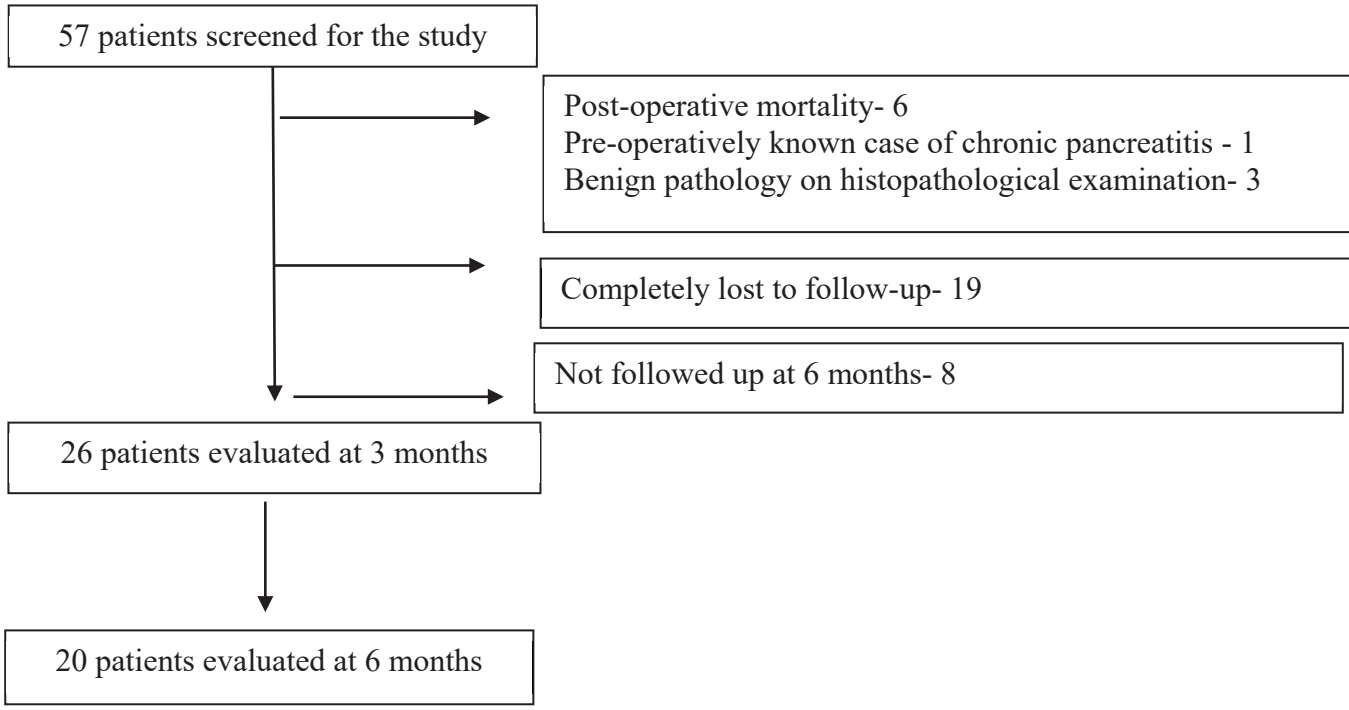
Significant weight loss was defined as a loss of more than 10 % weight from the baseline over a period of 6 months, more than 5 % loss over 1 month or noticeable loosening of clothes

Hypertension was defined in those subjects who had previously been diagnosed with hypertension prior to admission or those diagnosed post admission. 2 blood pressure (BP) readings were measured 6 hours apart in the left arm in sitting position and a HTN was diagnosed when systolic BP was >/= 140 mmHg and diastolic BP was >/= 90 mmHg according to the 2017 ACC/AHA guidelines. (65)

Diabetes mellitus was defined in subjects who had previously been diagnosed with DM prior to admission or those diagnosed post admission with FBS and HbA1c values according to ADA guidelines. (39)

RESULTS

A total of 57 patients underwent a PD for malignancies in the Department of Surgical Gastroenterology during the duration of this study, from January 2021 to June 2022. While all the patients underwent a preoperative pancreatic endocrine and exocrine function assessment, a total of 20 patients who had a postoperative diagnosis of malignancies and who completed both 3 monthly and 6 monthly follow ups were included in this study. The rest 32 were excluded for reasons mentioned below.



The age and gender distribution of the study population is depicted in the Tables 1, and figures 1 and 2. The mean age was 52 +/- 11.9 (32-80) years. Most of the patients were in the 5^{th} or 6^{th} decade. The youngest patient was 33 years of age and the oldest was 80 years of age. Most patients were males (75%) and the male to female ratio was 3:1.

Figure 1: Distribution of gender (n =20)

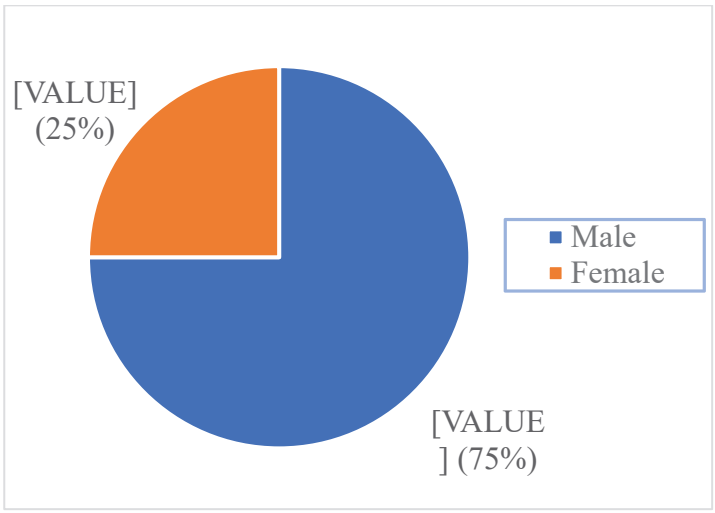


Figure 2: Distribution of age (n =20)

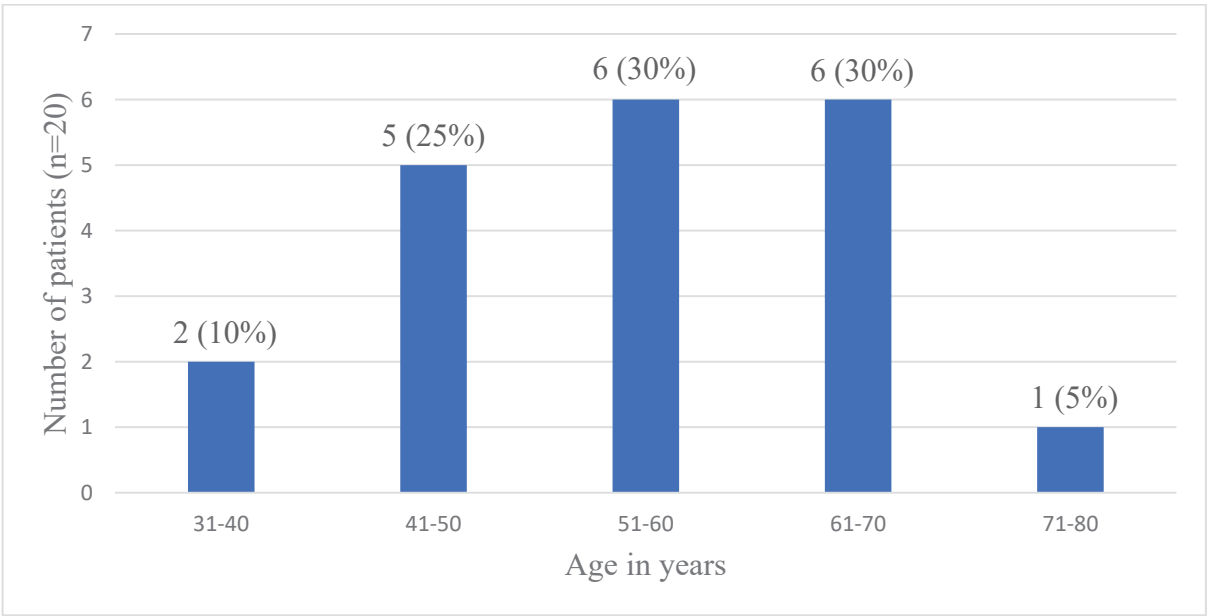


Table 1: Distribution of age and gender (n =20)

Age in years	Number of patients, n=20 (%)	Males, n=15 (%)	Females, n=5 (%)
31-40	2 (10)	2 (13.3)	0
41-50	5 (25)	5 (33.3)	0
51-60	6 (30)	4 (26.7)	2 (40)
61-70	6 (30)	3 (20)	3 (60)
71-80	1 (5)	1 (6.7)	0

The baseline demographic and clinical characteristics of the patients are presented in Table 2. The most common presenting complaint was abdominal pain which was reported by 16 (80%) patients, followed by jaundice which was reported by 14 patients (75%). 16 (80%) patients reported a loss of appetite, and a similar proportion of patients had a history of significant weight loss (85%). 4 patients (20%) had a history of fever suggestive of cholangitis, and 11 (55 %) patients had a history of pre-operative biliary drainage.

Eight (40%) patients had pre-operatively diagnosed DM, while only 1 patient had a history of HTN. Two (10%) patients were recently diagnosed with HBV-related chronic viral hepatitis and 1 patient was diagnosed with MEN-1 syndrome. Two (10%) patients had a history of chronic tobacco smoking, and 2 (10%) patients were chronic alcoholics.

Body mass index (BMI) was calculated based on the standard formula. The WHO guidelines for the Asian population were used to classify the BMI. (Appendix) The median Body mass index (BMI) of the study population was 20.9 (IQR: 18.2- 23.9) kg/m^2. While a majority (35 %) of the patients were within the normal range of BMI, a similar proportion (30 %) were underweight. All the patients had a good ECOG performance score of 0-1, and a majority (65 %) had an ECOG 1 performance score.

Table 2. Baseline demographic and clinical characteristics (n=20)

Demographic Characteristics	
Age, median (IQR) (years)	54.5 (45.7- 62.7)
Sex, n (%)	
• Male	15 (75)
• Female	5 (25)
Clinical Characteristics	n (%)
Presenting complaints	
• Abdominal pain	16 (80)
• Vomiting	5 (25)
• Jaundice	14 (70)
• Fever	4 (20)
Associated history	
• Anorexia	16 (80)
• Weight loss	17 (85)
• GI bleed	0 (0)
• Preoperative biliary drainage	11 (55%)
• Steatorrhea	0 (0)
Comorbidities	
• DM	8 (40)
• HTN	1 (5)
• Chronic viral hepatitis (HBV)	2 (10)
• MEN-1	1 (5)

Addictions	
• Tobacco	2 (10)
• Alcohol	2 (10)
BMI, median (IQR)(kg/m^2)	20.9 (18.2- 23.9)
• Underweight, <18.5	6 (30)
• Normal, 18.5-22.9	7 (35)
• Overweight, 23-24.9	4 (20)
• Obese, >/= 25	3 (15)
ECOG	
• 0	7 (35)
• 1	13 (65)
• 2-4	0 (0)

IQR- Interquartile range, *DM*- Diabetes Mellitus, *HTN*- hypertension, *HBV*- Hepatitis B Virus, *BMI*- Body mass index, *ECOG*- Eastern cooperative oncology group

The pre-operative hematological, biochemical, and radiological profile of the patients are described in table 3. The median hemoglobin of study population was 11.7 (IQR, 11-12.8) gm% and the median total leukocyte count was 8.6 (IQR, 6.1-10.8) x 10^3 cells/mm^3. The median total bilirubin, direct bilirubin and alkaline phosphatase levels were 3.1 (IQR, 0.9-7.9) mg %, 1.5 (IQR, 0.2-4.6) mg % and 209 (IQR, 105.2-519.5) IU/L respectively. The median serum albumin was 3.4 (IQR, 3.1-3.9) gm % and the tumor marker analysis showed a median CA 19-9 and CEA levels of 72.5 (IQR, 23-456) IU/ml and 2.0 (IQR, 1.3-2.9) ng/ml, respectively.

A pre-operative imaging with pancreatic protocol computed tomography (CT) was performed for all the patients which revealed a median CBD and MPD diameters to be 15.4 (IQR, 8.5-18.8) mm and 3.5 (IQR, 2-6) mm. The median maximum diameter of tumor was 2 (IQR, 1.5-

2.6) cm. Only 2 patients had evidence of pancreatic atrophy on the pre-operative CT.

Table 3. Pre-operative hematological, biochemical, and radiological findings (n=20)

Laboratory investigations	**Median (IQR); n (%)**
• Hemoglobin (gm %)	11.7 (11-12.8)
• Total leukocyte count (x 10^3 cells/ mm^3)	8.6 (6.1-10.8)
• Total bilirubin (mg %)	3.1 (0.9-7.9)
• Direct bilirubin (mg %)	1.5 (0.2-4.6)
• Alkaline phosphatase (IU/L)	209 (105.2-519.5)
• Albumin (gm%)	3.4 (3.1-3.9)
• CA 19-9 (IU/ml)	72.5 (23-456)
• CEA (ng/ml)	2.0 (1.3-2.9)
Radiological findings	**Median (IQR); n (%)**
• CBD diameter (mm)	15.4 (8.5-18.8)
• MPD diameter (mm)	3.5 (2-6)
• Maximum tumor diameter (cm)	2 (1.5-2.6)
• Pancreatic atrophy	2 (10%)

IQR-Interquartile range, *CEA*- Carcinoembryonic antigen, *CA19-9*- Carbohydrate antigen 19-9, *CBD*- Common bile duct, *MPD*- Main pancreatic duct

The pathological characteristics of the operative specimen of PD have been described in table 4. The most common pathology was an ampullary adenocarcinoma (70%). 2 patients had a distal cholangiocarcinoma while pancreatic ductal carcinoma, duodenal adenocarcinoma, and pancreatic neuroendocrine tumor (NET) were found only in 1 patient each. One patient had a rare case of pancreatic MiNEN. Many of the patients had a pT2 (40%) and pN1 (50%) stage

of the disease. AJCC 8th edition was used for all the pathological staging. (67–69) (Appendix)

Table 4. Histopathological characteristics of the tumor specimen

	n (%)
Pathology	
• Ampullary carcinoma	14 (70)
• Distal cholangiocarcinoma	2 (10)
• Pancreatic ductal adenocarcinoma	1 (5)
• Duodenal adenocarcinoma	1 (5)
• Pancreatic NET	1 (5)
• Pancreatic MiNEN	1 (5)
pT Staging	
• T1	4 (20)
• T2	8 (40)
• T3	7 (35)
• T4	1 (5)
pN staging *	
• N0	6 (30)
• N1	10 (50)
• N2	4 (20)

NET- Neuroendocrine tumor, *MiNEN*- Mixed neuro endocrine neoplasm

*pN staging: N1: 1-2 nodes, N2: 3 or more nodes

All patients underwent an analysis of the acinar density and fibrosis score at the pancreatic neck resection margin of the PD specimen. (Table 5) While a majority (65%) of the patients had a normal acinar cell density, a mild loss of acinar cells was seen in 7 patients (35%). On the other hand, most of the patients (85%) demonstrated fibrosis at the pancreatic neck margin. Of these 45% patients had a mild focal or periductal fibrosis while 40% had a moderate fibrosis. A significant correlation was seen between acinar cell loss and fibrosis score ($p < 0.001$)

Table 5. Acinar cell density and fibrosis score at pancreatic neck resection margin

	n (%)
Acinar cell density	
• Normal	13 (65)
• Mild loss of acinar cells	7 (35)
Fibrosis score	
• No fibrosis	3 (15)
• Mild fibrosis	9 (45)
• Moderate fibrosis	8 (40)

Table 6 shows the distribution of fibrosis and acinar cell loss between the different sites of malignancy. Out of 3 patients with pancreatic malignancies, 2 (66.7 %) had moderate fibrosis and 1 (33.3 %) had a mild fibrosis. Of the 14 patients who had ampullary malignancies, 50 % had a mild fibrosis, 35.7% had moderate fibrosis and the remaining 14.3% had no fibrosis. Of the 2 patients with bile duct malignancy, only 1 (50 %) had fibrosis and it was mild. The only patient with duodenal cancer in this study showed a mild pancreatic fibrosis (100%). There was no significant difference in the distribution of extent of fibrosis between these groups. ($p = 0.56$).

While 2 of the 3 patients with pancreatic malignancies showed mild loss of acinar cells, most of the patients with ampullary cancers (9/14, 64.3 %) showed normal acinar cell density. No acinar cell loss was seen in patients with duodenal or biliary malignancies. The difference in acinar cell density between these groups was insignificant ($p = 0.401$)

Table 6. Distribution of histological changes in different sites of malignancy

Site	Fibrosis n (%)		
	Nil	Mild	Moderate
Pancreatic (n=3)	0	1 (33.3)	2 (66.7)
Ampullary (n=14)	2 (14.3)	7 (50.0)	5 (35.7%)
Bile duct (n=2)	1 (50)	1 (50)	0
Duodenal (n=1)	0	1 (100)	0

Site	Acinar cell density	
	Normal n (%)	Mild acinar cell loss n (%)
Pancreatic (n=3)	1 (33.3)	2 (66.7)
Ampullary (n=14)	9 (64.3)	5 (35.7)
Duodenal (n=2)	2 (100)	0 (0)
Bile duct (n=1)	1 (100)	0 (0)

One of the secondary outcomes of the study was to determine the incidence pancreatic exocrine and endocrine insufficiency after PD. Table 6 demonstrates the preoperative as well as post operative pancreatic function analysis in the study subjects.

Pancreatic exocrine function: The median FE-1 preoperatively was 160 (IQR, 58-76) µg/g and most of the patients (65%) had an FE-1 <200 µg/g suggestive of pancreatic exocrine insufficiency preoperatively. While it was moderately decreased (100-200 µg/g) in 5 patients (25%), 8 (40 %) patients had a severely decreased FE-1 (<100 µg/g). The preoperative elastase levels showed no significant correlation with preoperative weight loss, BMI, hemoglobin, albumin or ECOG status.

At 3 months after a PD, the median FE-1 decreased to 47 (IQR, 25-212) µg/g and 70 % patients had PEI with 10 % patients having a moderate PEI and 60 % patients having a severe

PEI. The median FE-1 further decreased to 26 (IQR, 24-45) μg/g at 6 months after surgery, at which point, 90 % patients had a PEI and all them had a severely decreased FE-1.

A Wilcoxon signed rank test was used to analyze the difference in the FE-1 values and it was seen that there was no significant difference in the elastase value between the preoperative period and 3 monthly follow up. However, the decrease in FE-1 from before surgery to 6 months post operatively was significant (p = 0.001). The increase in exocrine insufficiency post operatively at 3rd and 6th month of follow ups were not found to be significant.

Pancreatic endocrine function: The baseline preoperative median HbA1c was 5.8 (IQR, 5.1-7.9) % and the median fasting blood sugar was 106 (IQR, 93-204) g %. 8 (40 %) of the 20 patients were preoperatively diagnosed with DM or pancreatic endocrine insufficiency. The median HbA1c post operatively was 5.6 (IQR, 5-6.5) % at 3 months and 5.7 (IQR, 5.1-6.3) at 6 months of follow up. The median FBS at 3 months was 96 (IQR, 93-103) g % and 98 (IQR, 93-103) g % at 6 months. The number of patients with DM saw a decline postoperatively to 7 (35 %) at 3 months and 4 (20 %) at 6 months.

A Wilcoxon signed rank test showed that the change in HbA1c over a 3 month follow up was not significant but a significant decrease was seen in the HbA1c from preoperative to 6 months post operative- follow up (p = 0.04).

The decrease in FBS over 3 months as well as 6 months follow up were noted to be significant (p = 0.08 and 0.04 respectively) by a Wilcoxon signed rank test. However, the differences in the number of patients with endocrine insufficiency before and after the surgery at both the 3rd and 6th month of follow up, were not significant on analysis by McNemar test.

Table 6. Pre-operative and postoperative pancreatic endocrine and exocrine function assessment

	Preoperative	**Postoperative 3 months**	**Postoperative 6 months**
FE-1 (Median, IQR) (g/g)	160 (58-376)	47 (25-212)	26 (24-45)
Exocrine insufficiency			
• Nil	7 (35)	6 (30)	2 (10)
• Moderate	5 (25)	2 (10)	0 (0)
• Severe	8 (40)	12 (60)	18 (90)
HbA1c (Median, IQR), %	5.8 (5.1-7.9)	5.6 (5-6.5)	5.7 (5.1-6.3)
FBS (Median, IQR), g %	106 (93-204)	96 (93-103)	98 (93-103)
Endocrine insufficiency, n (%)	8 (40)	7 (35)	4 (20)

FE-1- Fecal elastase-1, *HbA1c*- Glycated hemoglobin A1C, *FBS*- Fasting blood sugar, *IQR*- Interquartile range

The primary outcome of this study was to correlate the pancreatic acinar cell density and fibrosis score with post PD pancreatic insufficiency.

Acinar cell density:

There was no significant correlation between the acinar cell density of the operative specimen and the fecal elastase-1 values or the pancreatic exocrine insufficiency, preoperatively or post operatively. A significant correlation was not seen between the acinar cell density of the operative specimen and the preoperative and postoperative Hba1c and FBS values, as well as with endocrine insufficiency preoperatively and postoperatively.

Fibrosis score:

There was no significant correlation between the fibrosis score of the pancreatic neck margin and the FE-1 values or pancreatic exocrine insufficiency preoperatively. An increased fibrosis score was seen to be inversely and significantly correlated to FE-1 values post 3 months of surgery (Pearson's correlation coefficient -0.498, p = 0.025). A significant correlation was demonstrated between the fibrosis score and the pancreatic exocrine insufficiency at 3 months postoperatively. (Spearman's correlation coefficient 0.461, p = 0.041). No significant correlation was seen between pancreatic fibrosis and FE-1 or pancreatic exocrine insufficiency at 6 months post operatively

The fibrosis score showed no correlation with HbA1c and FBS values as well as with the pancreatic endocrine insufficiency at all 3 time points- preoperatively, 3 months post operatively and 6 months post operatively.

SUBGROUP ANALYSIS

New onset exocrine insufficiency

Seven patients had a normal preoperative exocrine function with a preoperative median FE-1 of 520 (IQR, 376-907) µg/g which decreased to 28 (IQR, 22-145) µg/g at 3 months and 25 (IQR, 24-28) µg/g at 6 months. 6 of the 7 patients (85.7 %) had post operative exocrine insufficiency at 3 months with a majority (57.1 %) of them having a severe insufficiency, and at 6 months while the net proportion of patients with PEI was same, all 87.5 % had a severe grade of PEI. (Table 7)

The difference in FE-1 from preoperative to postoperative values at both the 3rd and 6th months was significant as analyzed by Wilcoxon signed rank test (p= 0.028 and 0.018, respectively).

Three of the patients (42.9 %) had mildly decreased acinar cell density, and all patients had pancreatic fibrosis of which a majority (4/7, 57.1 %) had mild fibrosis, and the rest 3/7 (42.9 %) had moderate fibrosis. (Table 8)

Further analysis demonstrated no significant correlation between these histopathological parameters and the post operative fecal elastase values.

Table 7. Pre-operative and postoperative pancreatic exocrine function assessment of patients with normal preoperative exocrine function (n=7)

	Preoperative	**Postoperative 3 months**	**Postoperative 6 months**
FE-1 (Median, IQR) (µg/g)	520 (376-907)	28 (22-145)	25 (24-28)
Exocrine insufficiency			
• Nil	7 (100)	1 (14.3)	1 (14.3)
• Moderate	0	2 (28.6)	0 (0)
• Severe	0	4 (57.1)	6 (85.7)

FE-1- Fecal elastase-1, *IQR*- Interquartile range

Table 8. Acinar cell density and fibrosis score in patients with normal preoperative exocrine function (n=7)

	n (%)
Acinar cell density	
• Normal	4 (57.1)
• Mild loss of acinar cells	3 (42.9)
Fibrosis score	
• No fibrosis	0 (0)
• Mild fibrosis	4 (57.1)
• Moderate fibrosis	3 (42.9)

Trend in pre-existing exocrine insufficiency

Thirteen patients had deranged preoperative exocrine function with a preoperative median FE-1 of 86 (38.5-125) µg/g. The median FE-1 decreased to 47 (25.5-266.5) µg/g at 3 months and 31 (24-45.5) µg/g at 6 months.

A majority of them (61.5 %) had severe exocrine insufficiency preoperatively. At three months post operatively, while there was a resolution of exocrine insufficiency in 5 patients (38.5 %), the proportion of patients with severe insufficiency was the same at 61.5 %. However, at 6 months, all but 1 patient (12/13, 92.3 %) had a severe exocrine insufficiency. None of the patients had moderate PEI at either 3 or 6 months. (Table 9) The difference in FE-1 from preoperative to postoperative values was insignificant at 3rd month, but a significant decrease was noted in the 6th month as analyzed by Wilcoxon signed rank test (p= 0.65 and 0.033, respectively).

4 of the 13 patients (30.8 %) had mildly decreased acinar cell density, and most of the patients (76.2 %) had pancreatic fibrosis, of which 46.2 % had mild fibrosis and 30.8 % had moderate fibrosis. (Table 10)

Further analysis showed no significant correlation between these histopathological parameters and the post operative fecal elastase values.

Table 9. Pre-operative and postoperative pancreatic exocrine function assessment of patients with deranged preoperative exocrine function (n=13)

	Preoperative	**Postoperative 3 months**	**Postoperative 6 months**
FE-1 (Median, IQR) (µg/g)	86 (38.5-125)	47 (25.5-266.5)	31 (24-45.5)
Exocrine insufficiency			
• Nil	0	5 (38.5)	1 (7.7)
• Moderate	5 (38.5)	0 (0)	0 (0)
• Severe	8 (61.5)	8 (61.5)	12 (92.3)

FE-1- Fecal elastase-1, *IQR*- Interquartile range

Table 10. Acinar cell density and fibrosis score in patients with deranged preoperative exocrine function (n=13)

	n (%)
Acinar cell density	
• Normal	9 (69.2)
• Mild loss of acinar cells	4 (30.8)
Fibrosis score	
• No fibrosis	3 (23.1)
• Mild fibrosis	6 (46.2)
• Moderate fibrosis	4 (30.8)

New onset endocrine insufficiency

12 patients had a normal preoperative endocrine function with a preoperative median HbA1c of 5.1 (IQR, 5.1-5.6) % and post operative median HbA1c of 5.3 (IQR, 5-5.8) % at 3 months and 5.2 (IQR,4.9-5.7) % at 6 months. The median FBS preoperatively was 97 (IQR, 92-102) g% and postoperatively it was 94.5 (IQR, 90-97.5) g% and 97 (IQR, 89.2-101) g% at 3rd and 6th months, respectively. While only one patient (8.3 %) had an endocrine insufficiency at 3 months, none of them had it at 6 months. (Table 11) The difference in the endocrine functions from preoperative to postoperative values were insignificant at both 3rd and 6th months.

3 of the patients (25 %) had mildly decreased acinar cell density, and most of the patients (83.3 %) had pancreatic fibrosis of which a majority (50 %) had a mild fibrosis and the rest (33.3 %) had moderate fibrosis. (Table 12)

Further analysis demonstrated a significant inverse correlation between acinar cell loss and the HbA1c values at 3 months (Pearson correlation coefficient: -0.62, p = 0.029), this was not demonstrated at 6 months. However, while there was a significant inverse correlation seen between the fibrosis score and the HbA1c values at 6 months (Pearson correlation coefficient: -0.70, p = 0.011)., similar findings were not seen at 3 months. There was no significant correlation between histopathological parameters and the FBS values at 3rd and 6th months.

Table 11. Pre-operative and postoperative endocrine function assessment of patients with normal preoperative endocrine function (n=12)

	Preoperative	**Postoperative 3 months**	**Postoperative 6 months**
HbA1c (Median, IQR), %	5.1 (5.1-5.6)	5.3 (5-5.8)	5.2 (4.9-5.7)
FBS (Median, IQR), g %	97 (92-102)	94.5 (90-97.5)	97 (89.2-101)
Endocrine insufficiency, n (%)	0	1 (8.3)	0 (0)

HbA1c- Glycated hemoglobin A1c, *FBS*- Fasting blood sugar, *IQR*- Interquartile range

Table 12. Acinar cell density and fibrosis score in patients with normal preoperative endocrine function (n=12)

	n (%)
Acinar cell density	
• Normal	9 (75)
• Mild loss of acinar cells	3 (25)
Fibrosis score	
• No fibrosis	2 (16.7)
• Mild fibrosis	6 (50)
• Moderate fibrosis	4 (33.3)

Trend in pre-existing endocrine insufficiency

8 patients were preoperatively diagnosed with endocrine dysfunction. They had a preoperative median HbA1c of 8.7 (7.1-11.1) % and post operative median HbA1c of 6.6 (IQR, 5.8-7.0) % at 3 months and 6.5 (IQR, 5.9-6.9) % at 6 months. The median FBS preoperatively was 225 (IQR, 155-261) g% and postoperatively it was 103.5 (IQR, 93.7-188) g% and 100 (IQR, 94.2-128.7) g% at 3^{rd} and 6^{th} months, respectively. 2 patients (25 %) had normalization of the endocrine functions at 3 months and the same was noted in a total of 4 patients (50 %) at 6 months. (Table 13)

A significant decrease in HbA1c between preoperative and postoperative values at both 3 and 6 months were seen on analysis. (Wilcoxon signed rank test, p = 0.025 and 0.012, respectively) A significant decrease was also seen in the between preoperative and postoperative FBS values at both 3 and 6 months. (Wilcoxon signed rank test, p = 0.017 and 0.012, respectively)

50 % of the patients had mildly decreased acinar cell density and most of the patients (87.5 %) had pancreatic fibrosis of which a majority (50 %) had a mild fibrosis and the rest (37.5

%) had moderate fibrosis. (Table 14)

Further analysis demonstrated a significant inverse correlation between acinar cell loss and the HbA1c values at 3 months (Pearson correlation coefficient: -0.62, p = 0.029). No significant correlation was seen between fibrosis score and the HbA1c values at 3 months. There was also no significant correlation between histopathological parameters and the post operative HbA1c values at 6 months or the FBS values at 3rd and 6th months.

Table 13. Pre-operative and postoperative endocrine function assessment of patients with deranged preoperative endocrine function (n=8)

	Preoperative	**Postoperative 3 months**	**Postoperative 6 months**
HbA1c (Median, IQR), %	8.7 (7.1-11.1)	6.6 (5.8-7.0)	6.5 (5.9-6.9)
FBS (Median, IQR), g %	225 (155-261)	103.5 (93.7-188)	100 (94.2-128.7)
Endocrine insufficiency, n (%)	8 (100%)	6 (75)	4 (50)

HbA1c- Glycated hemoglobin A1c, *FBS*- Fasting blood sugar, *IQR*- Interquartile range

Table 14. Acinar cell density and fibrosis score in patients with deranged preoperative endocrine function (n=8)

	n (%)
Acinar cell density	
• Normal	4 (50)
• Mild loss of acinar cells	4 (50)
Fibrosis score	
• No fibrosis	1 (12.5)
• Mild fibrosis	4 (50)
• Moderate fibrosis	3 (37.5)

The other secondary outcome of the study was to demonstrate the incidence of post PD complications which have been described in table 7. 4 (20%) patients had no postoperative complications. The Clavien-Dindo classification was used to grade the complications in the remaining 16 patients (80 %). (70) (Appendix)

Of the 16 (80%) who had one or more postoperative complications, a majority (12 patients, 60 %) had a minor Clavien-Dindo score and only 4 patients (20%) had major complications. 2 patients underwent an ultrasound guided per cutaneous drain placement, one for grade B post operative pancreatic fistula (POPF) with sepsis and in the other patient, for grade B post operative pancreatic hemorrhage with sepsis. One patient underwent re-exploratory laparotomy for grade C PPH and one patient developed worsening of cholangitis after surgery, leading to sepsis and acute kidney injury.

The ISGPS 2007 guidelines were used to classify delayed gastric emptying. (22) (Appendix). Seven patients (35 %) had delayed gastric emptying, and a majority were grade B DGE.

Post operative pancreatic fistula (POPF) was defined and classified according to the ISGPF 2016 guidelines. (21) (Appendix) Though more than half of the patients (11/20, 55 %) had features suggestive of POPF, only 2 had a clinically relevant leak. The rest of the patients had a biochemical leak with no clinical implications on post operative management.

Post pancreatectomy hemorrhage (PPH) was defined and graded as per the 2007 ISGPS guidelines. (23) (Appendix). 2 patients (10 %) had PPH, and while one was managed with angioembolization and percutaneous drainage for infected collection, the other patient required a laparotomy.

Eleven patients (55 %) had surgical site infections (SSIs). These were classified according to the CDC guidelines (71) (Appendix), and most of the patients had either a deep or an organ/ space infection. The other less reported complications seen were a biliary leak, chyle leak, ascites, pneumonia, post operative pancreatitis and central line associated infection seen in 1-2 patients.

Table 15. Postoperative complications

Complications	**N=20 (%)**
Clavien-Dindo	16 (80)
o I	4 (20)
o II	8 (40)
o IIIa	2 (10)
o IIIb	1 (5)
o IVa	1 (5)
o IVb	0 (0)
DGE	7 (35)
o Grade A	2 (10)
o Grade B	3 (15)
o Grade C	2 (10)
POPF	11 (55)
o Biochemical	9 (45)
o Grade B POPF	1 (1)
o Grade C POPF	1 (1)
PPH	2 (10)
o Grade A	0 (0)
o Grade B	1 (5)
o Grade C	1 (5)

SSI	11 (55)
o Superficial incisional	3 (15)
o Deep incisional	4 (20)
o Organ/ space	4 (20)
Others	
o Bile leak	1 (5)
o Chyle leak	1 (5)
o CLABSI	1 (5)
o Pneumonia	2 (10)
o Pancreatitis	1 (5)

DGE: Delayed gastric emptying, *POPF*: Post operative pancreatic fistula, *PPH*: Post pancreatectomy hemorrhage, *SSI*: Surgical site infection, *CLASI*: Central line associated blood stream infection

DISCUSSION

Pancreaticoduodenectomy is a challenging and difficult surgical procedure but it is the surgical treatment of choice for a majority of periampullary and pancreatic malignancies. (18) In the background of advanced medical knowledge and improved surgical techniques the mortality associated with this procedure has decreased in the last two decades to less than 5%.(72) However it still has a high morbidity of 45-60%. (1–3) While most of the literature surrounding post PD outcomes focus on early postoperative complications such as postoperative pancreatic fistula, delayed gastric emptying and surgical site infections (73–75), the literature on long-term morbidity is relatively sparse. One such complication that causes significant morbidity in the long term after a PD is pancreatic insufficiency which encompasses both pancreatic endocrine and exocrine insufficiency.(12,35) The present study is the 1st study that has studied the correlation between pancreatic histopathological findings of both acinar cell density and fibrosis score with post PD endocrine as well as exocrine insufficiency.

Preoperative pancreatic exocrine insufficiency

Ampullary adenocarcinoma was the most common pathology (70%) for which PD was performed. Sixty-five percent of the patients had a preoperative PEI, among which 25% had a moderate and 40 % patients had a severe PEI. The median FE-1 level was 160 µg/g in the present subset of patients. It was similar to the recent bi-center prospective observational study by Kroon et al. where in PD was performed for pancreatic or periampullary malignancies, which showed a 56% PEI with moderate insufficiency in 16% and severe insufficiency in 40% of the patients.(34) Lim et al. demonstrated a similar incidence of preoperative PEI in 65 % of patients with pancreatic cancer before undergoing a PD, with a similar median preoperative FE-1 of 150 µg/g. (33)

This high incidence of an exocrine insufficiency at the time of diagnosis may be explained by confounding factors like pancreatic fibrosis, obstruction of the main pancreatic duct by a

periampullary tumor as well as tumor ingrowth of pancreatic cancer, but the latter two have not been studied in this study. Pancreatic atrophy is also a confounding factor for exocrine insufficiency, but as only two patients had the same further analysis was not done. Hence further studies may be required to study the exact association between these parameters. It has already been proven that pancreatic exocrine insufficiency can cause malabsorption and malnutrition. (12) Based on the findings of this study, it might be prudent to identify severe PEI preoperatively and administer PERT in the preoperative setting to patients undergoing major surgery, such as PD, which may have a beneficial role in peri-operative nutritional parameters. However, further studies are required to analyze the correlation between preoperative exocrine function and patient weight loss and BMI, as well as postoperative outcomes.

Postoperative exocrine insufficiency

There is no gold standard time point for post-pancreatectomy functional assessment. The real incidence of endocrine and exocrine insufficiency was significantly underestimated by 30-day outcome reporting by Lim et al, who reported that up to 78% of postoperative endocrine and exocrine insufficiency are missed by a 30-day reporting and that 48% of subjects may develop exocrine insufficiency even after 90 days. (33) Since a 30-day reporting may underestimate the real prevalence of these insufficiencies, in this study, both exocrine and endocrine pancreatic functions were assessed at 3 as well as 6 months after PD.

At 3 months follow-up, the postoperative incidence of PEI was 70% at 3 months, and 60% of patients had a severe PEI. In a prospective study by Kumar et al., 30 patients who underwent PD for malignancies, a higher PEI of 100 % at 3 months was seen, but 66.7% of patients had a severe pancreatic insufficiency which was similar to the findings of the current study. Their median FE-1 at 3 months was 74 μg/g higher than this study. (55) In the study by Kroon et al., the incidence of PEI (93 %) was higher than the current study at 3 months with 82.7 % patients demonstrating a severe PEI. They also had a lower median FE-1 of 15 μg/g at 3

months. (34)

Further, at 6 months, the current study showed a 90% incidence of PEI at 6 months, with all deficient patients demonstrating a severe decrease in FE-1 and the median FE-1 decreased to 26 μg/g, which showed a significant fall from the preoperative value ($p = 0.001$). Sikkens et al demonstrated a similar incidence (84%) of PEI after PD in patients with pancreatic or periampullary cancer at 6 months following surgery. (76) In a study by Tran et al on 74 patients who underwent PD for either chronic pancreatitis or periampullary malignancies, the incidence of PEI at 6 months was 87.4 % which was similar to the current study. They demonstrated a significant decline in FE-1 values at 6 months. (9) A high incidence (90.3 %) of severe PEI at 6 months similar to the current study was reported by Kroon et al. (34) In a retrospective study of 102 patients with periampullary cancer, Saluja et al noted 97% incidence of PEI at 12 months after PD. (32) Based on these data, it may be prudent to suggest that the testing for pancreatic exocrine insufficiency should be done at least after 6 months from surgery to get a more accurate estimation of the same, and PERT may be initiated as required in deficient patients. If found to be normal, these patients may be reassessed once again at 12 months.; however, the yield may not be different.

New onset exocrine insufficiency

Of 7 patients with normal FE-1 before surgery, 6 of them developed PEI postoperatively. A severe PEI was seen in 57.1 % of patients at 3 months, and this increased to 87.5 % at 6 months. Only 1 patient continued to have a normal FE-1 after surgery. There was a significant decrease in the median FE-1 from 520 μg/g before surgery to 28 μg/g at 3 months and 25 μg/g at 6 months. ($p = 0.028$ and 0.018). In a retrospective study of 28 patients with normal FE-1 before PD, Matsumoto et al demonstrated a significant lowering of FE-1 by 50 % at 3 months and a new onset PEI in 61 % patients at 3 months which increased to 88% at 12 months which was similar to results from this study. (49)

Pre-existing exocrine insufficiency

Of 13 patients who had a deranged exocrine function before surgery, 61.5% had a severe PEI, and the rest, 38.5%, had a moderate PEI. At 3 months, the proportion of severe PEI was the same at 61.5 %. At 6 months, the proportion of patients with severe PEI increased to 92.3%. There was a significant decrease in the median FE-1 from 86 µg/g before surgery to 31 µg/g at 6 months. Matsumoto et al. also demonstrated no difference in the FE-1 at 3 months in patients with preoperatively abnormal FE-1.(49) The significant change in median FEC during follow-up in the present study and the very high incidence of severe PEI at 6 months is an indication that long-term restoration of exocrine function may be improbable. A variety of confounding factors may play a role in the development of postoperative exocrine insufficiency, such as the amount of pancreatic resection, the presence of pancreatic fibrosis, pancreatic atrophy, stenosis of the pancreatoenteric anastomosis and administration of adjuvant therapies. Additionally, accelerated stomach emptying and intestinal transit may result in secondary exocrine insufficiency due to the asynchronous mixing of enzymes with chyme. Pancreatic enzymes are also inactivated due to changes in gastric and duodenal pH, and exocrine pancreatic secretion can be reduced by abnormal postprandial cholecystokinin release. Lastly, tumor recurrence or fibrosis may cause anastomotic obstruction.

These patients need to be closely monitored for signs and symptoms of malabsorption like steatorrhea, weight loss and fat-soluble vitamin deficiencies. Studies have shown a significant adverse impact of post PD exocrine insufficiency on long-term quality of life, and PERT also has been shown to improve survival in pancreatic cancer equivalent to surgery and chemotherapy. (1,12) Thus, timely identification of pancreatic exocrine insufficiency and case-by-case administration of PERT may be advisable in the preoperative as well as postoperative period.

Endocrine insufficiency

Though the median HbA1c was 5.8% and median FBS was 106 g%, pancreatic endocrine

insufficiency before surgery was seen in 40% of patients. A similarly high prevalence of preoperative DM (43.5 %) was seen by Hartman et in a retrospective study of 37 patients who underwent PD for malignancies or premalignancies. (31) However, in the study by Tran et al which included both benign and malignant etiologies, the incidence of endocrine insufficiency before a PD was much lesser at 13.5 % (9) and a similarly low incidence (11.7 %) of endocrine insufficiency before PD was demonstrated by Saluja et al. (32)

At 3 months follow-up, there was an insignificant decrease in median HbA1c to 5.6 % and a significant decrease in median FBS to 96 g% (p 0.04) at 3 months. The proportion of patients with postoperative endocrine insufficiency decreased to 35%, but this change was not significant. Hartman et al. noted a post PD endocrine insufficiency in 29 % of patients at a median follow-up of 2.7 months, which was similar to this study. (31) Further, at 6 months, the median HbA1c was decreased to 5.7%, the median FBS decreased to 98g %, and a 20 % incidence of endocrine inefficiency was seen at 6 months. Tran et al. demonstrated a similar postoperative incidence of post PD DM of 26 % at 6 months. (9) Saluja et al. demonstrated endocrine insufficiency in 25% of patients after a PD, albeit with a median follow-up of 26 months.(32)

New onset endocrine insufficiency

Of the 12 patients who had normal endocrine functions before surgery, 1 patient (8.3%) developed new-onset endocrine insufficiency at 3 months which reverted at 6 months, and there were 0 patients with endocrine dysfunction at 6 months. This was similar to the prospective study by Lemaire et al in 17 patients who underwent PD, wherein no new-onset DM was seen at 6 months. (77) In a retrospective study by Sakata et al, in 32 patients who underwent PD, new-onset DM was seen only in 2 out of 25 patients (8 %), which was similar to our finding at 3 months, however, their finding was noted at 1 year following surgery. (78) In a prospective study of 50 non-diabetic patients who underwent PD for periampullary cancer, Singh et al. demonstrated new onset endocrine insufficiency in 18 % of patients at a

median follow-up of 7 months, which was much higher than our study. (79) Saluja et al. demonstrated a similar occurrence of new-onset DM in 15 out of 90 patients (17 %), but it was seen to have developed 4 years after surgery. (32)

Though literature reports of incidence of post pancreatectomy diabetes range from 3 to 50 %, this is dependent on many factors like the extent of resection, underlying conditions and duration after surgery. (28,41) The single patient incidence of new-onset DM at 3 months in the current study is not significant as it was a transient finding which was not reflected in the patient's biochemical parameters at 6 months. The zero incidence of new-onset DM at 6 months in this study may be attributed to the short duration of follow-up. Hence a longer a longer duration of follow-up may be required to accurately estimate the effect of PD on pancreatic endocrine functions. This is also supported by the large-scale retrospective studies by Wu et al and Kuskabe et al which showed a high incidence of post PD DM (16-20%) after follow-up of more than 12 months. (40,41)

Pre-existing endocrine insufficiency

In 8 patients with a pre-existing endocrine insufficiency, this study demonstrated a significant decrease in the HbA1c as well as FBS values after surgery which was seen at both the 3rd and 6th months of follow-up. Two patients (25%) at 3 months and 4 patients (50%) at 6 months had normalization of their endocrine functions. Saluja et al. also found an improvement in diabetes after PD in 1 out of 3 patients (33.3 %) who had a recent onset DM. The mean duration of follow-up in their study was 59 months, but the exact duration when reversal of DM was noted was not mentioned. (32) An improvement in DM at a follow-up of 1 year after pancreatic surgery was seen by Sakata et al. in 2 out of 7 (28.5 %) patients. (78) These results were similar to those of the current study but at longer durations of follow-up.

In this study, all 4 patients who had normalization of endocrine parameters at 6 months had obstructive jaundice and highly deranged HbA1c and FBS prior to surgery requiring insulin administration. Three out of 4 had not undergone preoperative biliary drainage. Following

surgery, all 4 patients became insulin-independent, and only one of them required oral hypoglycemic agents transiently for the first month following surgery but not thereafter. Similar normalization of glycemic control after relief of obstructive jaundice has been reported by Kim et al. in 4 patients, 2 of whom had periampullary cancer and 2 patients who had a benign biliary stricture. (80) The presence of hyperbilirubinemia could have been the cause of deranged glycemic control before surgery in the above 4 mentioned patients in this study. This has been shown in a study by Kasahara et al. wherein he demonstrated deranged insulin response at late stages of obstructive jaundice in pancreatic diseases. (81) A loss of effect of incretins on insulin release in biliary obstruction, as demonstrated by Niwa et al. in pancreatic islet cells isolated from bile duct ligated rats, may explain the pathophysiology of glycemic intolerance in obstructive jaundice. (82)

One of the above-mentioned 4 patients had a pancreatic adenocarcinoma with recently diagnosed DM prior to surgery. Pannala et al. demonstrated a causal association between pancreatic cancer and type II diabetes and hypothesized that resection for pancreatic adenocarcinoma may have a beneficial effect on reducing or lowering the risk of diabetes. (83) This may explain the resolution of glycemic intolerance in this patient after curative resection.

Histopathological Analysis of The Pancreatic Parenchyma

The exocrine pancreas, which accounts for 80-85 % of the pancreatic parenchyma, is predominantly composed of acinar cells, which synthesize and secrete the pancreatic enzymes. A reduction in acinar cells can theoretically be associated with pancreatic exocrine insufficiency. The current study included periampullary/ pancreatobiliary malignancies, which often involve the pancreatic duct. This, in turn, can lead to pancreatic parenchymal fibrosis and atrophy. (63) In chronic pancreatitis, pancreatic ductal obstruction, parenchymal fibrosis and acinar cell loss have been shown to have an association with pancreatic exocrine insufficiency. Additionally, acinar damage and fibrosis have been seen to be causative of islet

cell damage causing endocrine insufficiency. (62) However the literature regarding the alterations in these histological parameters and their association with postoperative endocrine and exocrine insufficiency in malignancies is scarce. (9,63,84)

In the current study, acinar cell density and fibrosis score at the pancreatic resection margins of the PD specimen was assessed in all the patients. Most of the patients had acinar cell loss (65 %) in this study. In a retrospective study by Partelli et al. acinar cell content at pancreatic stump was quantitatively measured in patients who had undergone PD and a decreased acinar content <60 % was seen in 42% of patients, however this included all patients that have under gone a PD, irrespective of the primary pathology. (10) Nahm et al. noted a significantly decreased mean acinar score in pancreatic cancer and chronic pancreatitis compared to other patients in a large cohort of patients who underwent any pancreatic resection for any etiology. (11) Korpella et al evaluated acinar density in pancreatic ductal adenocarcinoma patients who underwent any curative intent pancreatic resection. They demonstrated acinar atrophy in 76 % patients. (85) These studies all demonstrate that acinar cell loss may be seen in half or more of patients who suffer from pancreatic and periampullary diseases. However, these studies have all evaluated a significantly heterogenous population of patients, either including both benign and malignant diagnoses or including a multitude of pancreatic surgeries.

The current study demonstrated parenchymal fibrosis 85 % of the patients. 45 % patients had a mild fibrosis while 40 % of them showed marked fibrosis. There was no significant difference in the distribution of acinar cell density or extent of fibrosis between the different groups of malignancies. Tran et al reported 100 % fibrosis in patients who underwent PD. However, the study included both chronic pancreatitis and periampullary malignancies. They demonstrated mild fibrosis in 49 % of the patients, similar to the current study; and marked fibrosis in 28 % which was lesser than the current study. Uchida et al. demonstrated pancreatic fibrosis in all 22 patients who underwent a PD for periampullary malignancies. 54.5 % patients had a severe fibrosis and 45.5 % had a mild fibrosis. These results were

similar to the current study. (84) These results indicate that periampullary malignancies are often associated with pancreatic fibrosis.

Correlation between histological findings and postoperative exocrine and endocrine insufficiency

In context to exocrine insufficiency, in the complete cohort of 20 patients, there was no significant correlation between the acinar cell density and exocrine functions, preoperatively as well as post operatively. A higher acinar score has been reported to be significantly associated with postoperative pancreatic fistula in PD as well as other pancreatic resection surgeries. (10,11) A decreased acinar score has also been shown in a single study to be associated with exocrine insufficiency. In this study by Yuasa et al the acinar cell density was measured as a proportion of acinar cell area on histology slides and correlated with ^{13}C-labeled mixed triglyceride breath test. A significant correlation was noted between the acinar cell area of the pancreatic stump and the % dose ^{13}C cumulative at 7 hours in patients undergoing PD ($R = 0.30$, $P = 0.007$). (63) However, this finding was not corroborated in the current study.

A significant inverse correlation between fibrosis score and FE-1 and a significant correlation between pancreatic exocrine insufficiency at 3 months was seen. This was not observed at 6 months. In a subgroup analysis of the separate cohorts with normal preoperative exocrine function or pre-existing exocrine dysfunction, no significant correlation between acinar cell density or fibrosis score and postoperative exocrine function was noted.

Tran et al also noted a similar strong inverse correlation between pancreatic fibrosis and postoperative FE-1, albeit at 6 months, and their study included a heterogenous population including both chronic pancreatitis (25 %) and periampullary malignancies (75 %), while our study used a homogenous population of only malignancies and chronic pancreatitis was excluded. (9) Uchida et al studied exocrine function of the pancreatic remnant by multiplying the volume of the external pancreatic drain with its amylase levels and correlated

it with the grade of fibrosis of pancreatic stump and noted a significant inverse correlation between these. The exocrine assessment was done in the early post operative period between days 7-14. (84)

The data from this study support the hypothesis that while pancreatic fibrosis is associated with exocrine insufficiency and can be used to stratify the risk for the same 3 months. The study also shows that a similar approach for pancreatic acinar score may not be supported. The patients who have significant pancreatic fibrosis may be offered a more vigilant approach to monitoring for exocrine insufficiency so that timely treatment with PERT may be initiated.

Further, for endocrine function, no significant correlation was seen between acinar cell density and preoperative as well as postoperative HbA1c or FBS values or endocrine insufficiency in the whole cohort. Similarly, the fibrosis score showed no correlation with endocrine functions preoperatively and post operatively. In 12 patients who had a normal preoperative endocrine function, acinar cell loss was inversely correlated to HbA1c at 3 months and fibrosis was inversely correlated to HbA1c at 6 months. In the 8 patients with pre-existing endocrine insufficiency, at 3 months follow up, a significant inverse correlation between the acinar cell loss and HbA1c values.

This implies that irrespective of the preoperative endocrine functions, at 3 months, acinar cell loss is associated with lower HbA1c values, signifying improved glycemic control and that if there in normal endocrine function before surgery, then increased fibrosis also is associated with lower HbA1c at 6 months. This is an unexpected finding. There are no studies directly comparing acinar cell density or fibrosis score with endocrine function in patients who have undergone pancreatic resection or in those who have a periampullary or pancreatic disease, benign or malignant. The study by Tran et al studied pancreatic fibrosis but not its direct association with endocrine dysfunction, and though the study showed significant correlation between fibrosis and endocrine tissues loss, no significant correlation was noted between

endocrine loss and post operative endocrine insufficiency. (9)

In the whole cohort of 20 patients where no association was demonstrated between the histological parameters and peri operative endocrine function, 7 patients had loss of acinar cells. In the cohort of 12 patients with normal preoperative endocrine function, where acinar loss has seen to be associated with improved glycemic control after surgery, acinar loss as such was seen only in 3 patients. These numbers are very less to extrapolate the findings of the study to a larger population. In the cohort of patients with pre-existing endocrine dysfunction, the net number of patients was low (8) and there was also an improvement in endocrine functions after surgery which has been hypothesized to be due to relief of jaundice. There may be other confounding factors also which may have influenced the post operative endocrine functions which are beyond the scope of this study. Thus, the association of acinar loss and fibrosis with improvement in post-surgery glycemic control, needs to be corroborated after accounting for possible confounders.

Further studies with a larger sample size may be required to conclusively describe and explain the association between histological parameters and endocrine dysfunction after surgery.

SECONDARY OUTCOME: COMPLICATIONS

All patients were assessed for major and minor complications and graded according to Clavien -Dindo scale. Though 80% of patients had some postoperative complication, most of them (60 %) had minor complications with a Clavien-Dindo score of I-II, and only 20 % had major complications with a score of III-IV. The most common complications were post operative pancreatic fistula and surgical site infections both seen in 55 % of patients.

Post operative pancreatic fistula (POPF): The overall incidence pancreatic fistula formation in the current study was 45 % while literature mentions a varied incidence 4 to 60 % (49,73,86,87) A majority of the patients in this study were males, the median PD diameter was 3.5 mm and the most common pathology was ampullary carcinoma. All these 3 factors

have been shown to be independent risk factors for POPF after PD. (87–91) This could explain the high over all rate of POPF int this study.

However, in current study, of the 11 patients with POPF, only 2 patients had a clinically relevant POPF (CR-POPF) (10 %) and the rest had a biochemical leak managed medically. This incidence is not higher than that reported in literature. (88,92,93). Retrospective study by Liu et demonstrated a similar incidence 7.6 % of CR-POPF(92) and Li et al in a metanalysis of Blumgart anastomosis after PD showed incidence of CR-POPF as 0-38 %, higher than current study. (93) In a meta-analysis of 27 studies pooled incidence of CR-POPF was 17 %, also higher than the current study. (88) A strict adherence to standardized surgical technique by all the surgeons in the department may explain the low incidence of CR-POPF in this study.

Delayed gastric emptying (DGE): The other common complication seen in this study was delayed gastric emptying and it was seen in 45 % patients (Grade A: 10 %, B: 15 %, C: 10 %). A majority had a grade B/C DGE. However, as a feeding tube was routinely placed in all patients, all with DGE could be successfully managed medically. The incidence of DGE in various studies range widely from 17- 45 %. (73,91,92,94,95) . A similarly high incidence of DGE as in the current study was shown in the prospective study by Liu et al (36.2%) wherein most patients had a similar rate of grade A DGE (22.4%). (96) A high incidence of grade B/C DGE was demonstrated in a retrospective study by Robinson et al (24 %). (95) The population in our study was predominantly male and a pylorus resecting PD was the routinely performed surgery in the department. There was also a high rate of intra-abdominal collection and POPF in this study. All these factors which have been shown in studies to be associated with a high risk for DGE (96,97) may explain the high incidence of DGE in the current study.

Post pancreatectomy hemorrhage (PPH): The incidence of PPH in literature is 5- 16 %. (73) In the current study a similarly low rate of PPH was seen as only 2 patients (10 %) had PPH and the source of bleed in both these patients were a pseudoaneurysm of the gastroduodenal

artery. Both these patients had a CR-POPF which is a known risk factor for PPH (73,98) and while one patient was managed by angio-embolization and percutaneous drainage, the other required surgical control. The strict adherence to standardized surgical techniques and post operative enhanced recovery strategies may have contributed to our low rates of POPH.

Surgical site infection (SSI): There was a high incidence of SSI in this study (55 %) which was is in the higher range of that reported in the literature (12-50 %). (99) A majority of the patients (55 %) had a history of preoperative biliary drainage, which has been shown to be associated with a high risk of post PD wound infections in the study by Suragul et al. (99) and this may explain the above finding. This study was conducted in a tertiary care referral hospital, and most patients were referred for surgical management after having undergone biliary drainage from another center. Preoperative biliary drainage in the absence of cholangitis is not routinely performed in the department.

The other less commonly seen complications were bile leak, chyle leak, CLABSI, pneumonia and pancreatitis, which were seen only in 1 to 2 patients

LIMITATIONS

1. Short follow-up- A longer follow-up is advisable for an accurate estimation of glycemic tolerance. However, in the current study, follow up was done at 3 and 6 months after surgery owing to the limited study duration and inadequate sample sizes with longer follow up.
2. FE-1 assay is less accurate as it has been shown to be less accurate for estimation of exocrine insufficiency and malabsorption following pancreatic resections. (100) But it is a non-invasive, easy to perform and cost-effective test. Moreover, in a setting as ours with poor postoperative follow-up, a single spot stool sample ensured an acceptable compliance from the patients. Hence this assay was preferred.
3. Small sample size- The sample size in the study was less due to logistical issues causing poor patients' compliance with respect to adequate and timely follow-up after major surgery in a developing country. There are multiple risk factors associated with both endocrine and exocrine insufficiency of pancreas, and these may have the findings of this study but these could not be studied in this study owing to the limited sample size.

STRENGTHS

a) This study is the first in the literature to analyze the correlation between both the histological parameters of acinar cell density and pancreatic fibrosis with preoperative as well as postoperative pancreatic endocrine and exocrine functions.

b) Prospective observational study.

c) A homogenous population of patients undergoing PD for malignant diseases was used.

d) A standardized technique for exocrine as well as endocrine insufficiency assessment

e) Standardized surgical technique throughout the study period.

CONCLUSION

Most of the existing studies on the occurrence of exocrine and endocrine insufficiency following pancreatic cancer resection surgery are retrospective and describe either of the two insufficiencies. The current study offers the benefit of assessing the course of both exocrine and endocrine function prospectively, from the time of pancreatic cancer diagnosis until 6 months following surgery. The high incidence of preoperative (65 %) and postoperative PEI (90 %) in this study indicate that routine perioperative assessment of exocrine function may be beneficial in patients who undergo PD for cancers. This might allow for timely treatment of PEI to ensure good quality of life, and maybe even long-term survival. The 40 % incidence of preoperative endocrine insufficiency indicate that these patients should be routinely evaluated and treated for the same. The low incidence of post PD endocrine insufficiency (20 %), may be attributed to the small period of follow up and further studies with a longer follow up may be required for the same. A transient improvement in endocrine dysfunction despite acinar cell loss/ fibrosis, in short term follow up was noted in this study, but long-term results regarding the same are awaited. Hence, it is important to educate patients regarding post-resection insufficiencies as well as have a protocoled guideline to risk assess patients and identify those at high risk for these insufficiencies to allow for more strict monitoring and early treatment.

This study demonstrated a significant correlation between fibrosis score and PEI and hence it is worthwhile to include reporting of pancreatic fibrosis in routine histopathology of these patients. The association between acinar cell loss and fibrosis with better postoperative glycemic control could be attributed to multiple confounders that were not accounted for in this study. Further studies with larger samples may be required to further study this association.

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IEC CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/ 3473 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3308**

Project title: **"Acinar cell density and fibrosis scoring in pancreaticoduodenectomy specimen for malignancies and its correlation with post-operative pancreatic exocrine and endocrine insufficiency-a prospective study"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.Ch. Dissertation**
Student Name:	**Dr. Shabana**
Guide:	**Dr. Subhash Chandra Soni**
Co-Guide:	**Dr. Vaibhav Kumar Varshney, Dr. Poonam Elhence, Dr. Dharmveer Yadav & Dr. Ashok Kumar Puranik**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

PATIENT INFORMED CONSENT FORM

Participant identification number for this trial: _____

Title of project: Acinar cell density and fibrosis scoring in post pancreaticoduodenectomy specimen for malignancies and its correlation with post operative pancreatic exocrine and endocrine insufficiency

Name of Principal Investigator: Dr Shabana
Tel.No.: 9047532081

The contents of the information sheet dated …….. that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for these individuals to have access to my records.

I agree to take part in the above study.

---------- Date:
(Signatures / Left Thumb Impression) Place:
Name of the Participant: _____
Son / Daughter / Spouse of: _____
Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

Signatures of the Principal Investigator Date:
Place:

1) Witness – 1

Signatures
Name:
Address:

2) Witness – 2

Signatures
Name:
Address:

सहभागी सुचित सहमति प्रपत्र

इस जाचं के लिए सहभागी पहचान नमबर_____

अनुसन्धान शीर्षक : Acinar cell density and fibrosis scoring in post pancreaticoduodenectomy specimen for malignancies and its correlation with post-operative pancreatic exocrine and endocrine insufficiency

मुख्य अन्वेषक का नाम : Dr Shabana फोन नंबर: 9047532081

मैंने दिनांक_____ के सूचना पत्र में दिये गए सभी तथ्यो को पड़ लिया हैं| मुझे समझ आने वालीं भाषा मैं विस्तारपूर्वक बत्ता दिया है और मैनें तथ्यो को भली भांति समझ लिया है| मैं पुष्टि करता हूँ कि मुझे प्रशन पुछने का अवसर दिया गया है|

मुझे अध्ययन की प्रकृति, उद्देश्य और इसके सम्भावित लाभ/जोखिमों और अध्ययन की सम्भावित अवधि अन्य प्रासंगिक जानकारी के बारे में विस्तार पुर्वक समझा दिया गया है | में समझाता हूँ कि इस अध्ययन में मेरी भागिधारी स्वेछिक है और इस अध्ययन से किसी भी समय बिना कोई कारण बताए, बिना मेरी चिकित्सा देखभाल या कानूनी अधिकारों के प्रभावित हुए अपना नाम वापिस ले सकता/सकती हूँ |

मैं समझता हूँ कि इस अनुसन्धान में मेरी सहभागिता से मेरे बारे में एकत्र जानकारी और चिकित्सीय नोटों को एम्स अस्पताल के जिम्मेदार लोगो द्वारा देखा जायेगा| मैं इन व्यक्तियों को अपने रिकोर्ड देखने कि अनुमति प्रदान करता/करती हूँ |

मैं उपयुर्क्त अध्यन में भाग लेने के लिए अपनी सहमति प्रदान करता /करती हूँ |

सहभागी के हस्ताक्षर / बाएं अंगूठे का निशान दिनांक: स्थान:

सहभागी का नाम

पिता/पति का नाम

पूरा पता

यह प्रमाणित किया जाता हे कि उपयुर्क्त सहमति मेरी उपस्थति में ली गईं हैं |

मुख्य अन्वेषक के हस्ताक्षर दिनाक: स्थान:

१) गवाह के हस्ताक्षर

नाम

पता

२) गवाह के हस्ताक्षर

नाम

पता

PATIENT INFORMATION SHEET

Title: Acinar cell density and fibrosis scoring in post pancreaticoduodenectomy specimen for malignancies and its correlation with post-operative pancreatic exocrine and endocrine insufficiency

Name of Participant: .....
You are invited to take part in this research study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.
You are being asked to participate in this study being conducted in AIIMS, Jodhpur because you satisfy our eligibility criteria.

What is the purpose of research?
This study will look into the pre-operative pancreatic fibrosis score and acinar cell density, in the post- pancreaticoduodenectomy specimen, and correlate these with post-operative pancreatic exocrine and endocrine insufficiency. If you enroll in it you will be benefitted by early diagnosis of pancreatic insufficiencies which will allow for early management of the same and by way of which you may have a better quality of life. We have obtained permission from the Institutional Ethics Committee for conducting this study.

The study design
The study will be a single center prospective observational study and patients will be recruited from Department of Surgical gastroenterology.

Study Procedures
The study will involve histopathological evaluation of the pancreatic fibrosis score and acinar cell density, in the post- pancreaticoduodenectomy specimen. The study will also involve pre-operative and post-operative analysis of pancreatic exocrine and endocrine functions, by clinical history of steatorrhea; post-operative new onset diabetes mellitus requiring treatment in the form of dietary modifications, oral hypoglycemic agents and/ or insulin; as well as biochemical assay- fecal elastase 1 test, fasting plasma glucose and serum HbA1c levels. You will be informed about each of these tests in detail.

Possible risks to you.
There is added risk of additional blood tests in addition to the risks attributed to the disease and the surgery.

Possible benefits to you
You will have the added benefit of early diagnosis of post-operative pancreatic endocrine and exocrine insufficiency, which will allow for early treatment and possible improvement in quality of life.

Compensation
Nil

Possible benefits to other people
The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

The alternatives you have

If you do not wish to participate, you still will get the histopathology report of your histopathology specimen.

Reimbursement
You will not be paid to participate in this research study.

What should you do in case of injury or a medical problem during this research study?
Your safety is the prime concern of the research. If you are injured or have a medical problem as a result of being in this study, you should contact one of the people listed at the end of the consent form. You will be provided the required care/treatment.

Confidentiality of the information obtained from you
You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, institutional ethics committee and any person or agency required by law like the Drug Controller General of India to view your data, if required. The results of clinical tests and therapy performed as part of this research may be included in your medical record. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?
Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?
The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons.

Can the investigator take you off the study?
You may be taken off the study without your consent.

Right to new information
If the research team gets any new information during this research study that may affect your decision to continue participating in the study, or may raise some doubts, you will be told about that information.

Contact persons
For further information / questions, you can contact us at the following address:

Principal Investigator:
Dr. Shabana
Senior resident Phone: 9047532081
Dept. of Surgical Gastroenterology Email:
drshabanajabbar@gmail.com

Principal guide and Co-Investigator
Dr Subhash Chandra Soni Phone: 8447440689
Assistant professor Email: drscssoni@hotmail.com
Dept. of Surgical Gastroenterology

भागीदारोंकेलिएसूचना

शीर्षक: **Acinar cell density and fibrosis scoring in post pancreaticoduodenectomy specimen for malignancies and its correlation with post-operative pancreatic exocrine and endocrine insufficiency**

प्रतिभागी का नाम:

……

आपको इस शोध अध्ययन में भाग लेने के लिए आमंत्रित किया गया है। इस दस्तावेज़ की जानकारी यह तय करने में आपकी मदद करने के लिए है कि भाग लेना है या नहीं। कृपया बेझिझक पूछें कि क्या आपके पास कोई प्रश्न या चिंता है। आपको एम्स, जोधपुर में आयोजित किए जा रहे इस अध्ययन में भाग लेने के लिए कहा जा रहा है क्योंकि आप हमारी पात्रता मानदंड को पूरा करते हैं।

शोध का उद्देश्य क्या है?

यह अध्ययन प्री-ऑपरेटिव अग्नाशयी फाइब्रोसिस स्कोर और एसाइनर सेल घनत्व में, पोस्ट-पैनक्रियाटिकोडोडेनेक्टॉमी नमूने में दिखेगा, और इनको पोस्ट-ऑपरेटिव अग्नाशय एक्सोक्राइन और एंडोक्राइन अपर्याप्तता के साथ सहसंबंधित करेगा। यदि आप इसमें नामांकन करते हैं तो आपको अग्नाशयी अपर्याप्तता के शीघ्र निदान से लाभ होगा जो उसी के प्रारंभिक प्रबंधन के लिए अनुमति देगा और जिस तरीके से आपके पास जीवन की बेहतर गुणवत्ता हो सकती है। हमने इस अध्ययन के संचालन के लिए संस्थागत आचार समिति से अनुमति प्राप्त की है ।

अध्ययन डिजाइन

अध्ययन एक एकल केंद्र संभावित अवलोकन अध्ययन होगा और रोगियों को सर्जिकल गैस्ट्रोएंटेरोलॉजी विभाग से भर्ती कराया जाएगा।

अध्ययन प्रक्रियाएं

अध्ययन में अग्नाशयी फाइब्रोसिस स्कोर और एसिनार सेल घनत्व का हिस्टोपैथोलॉजिकल मूल्यांकन शामिल होगा, जो पोस्ट-पैनक्रियाटिकोडोडेनेक्टॉमी नमूना में है। अध्ययन में अग्नाशयी एक्सोक्राइन और अंतःस्रावी कार्यों के पूर्व-ऑपरेटिव और पोस्ट-ऑपरेटिव विश्लेषण भी शामिल होंगे, जो कि स्टीयरोरिया के नैदानिक इतिहास द्वारा किया जाएगा; आहार के संशोधनों, मौखिक हाइपोग्लाइसेमिक एजेंटों और / या इंसुलिन के रूप में उपचार की आवश्यकता वाले पोस्ट-ऑपरेटिव नए शुरुआत मधुमेह मेलेटस; साथ ही जैव रासायनिक परख- f ecal el ast ase 1 परीक्षण, उपवास प्लाज्मा ग्लूकोज और सीरम HbA1c का स्तर। साथ ही जैव रासायनिक परख- f ecal el ast ase 1 परीक्षण, उपवास प्लाज्मा ग्लूकोज और सीरम HbA1c का स्तर। आपको इनमें से प्रत्येक परीक्षण के बारे में विस्तार से बताया जाएगा।

आपके लिए संभावित जोखिम

बीमारी और सर्जरी के लिए जिम्मेदार जोखिमों के अलावा अतिरिक्त रक्त परीक्षण का जोखिम भी है।

आपके लिए संभावित लाभ

आपको पोस्ट-ऑपरेटिव अग्नाशयी अंतःस्रावी और एक्सोक्राइन की अपर्याप्तता के शुरुआती निदान का अतिरिक्त लाभ होगा, जो प्रारंभिक उपचार और जीवन की गुणवत्ता में संभावित सुधार की अनुमति देगा।

नुकसान भरपाई

शून्य

अन्य लोगों के लिए संभावित लाभ

शोध के नतीजे भविष्य के मरीजों को चिकित्सा ज्ञान और / या चिकित्सकीय लाभ के उन्नयन के मामले में समाज को लाभ प्रदान कर सकते हैं।

आपके पास विकल्प हैं

यदि आप भाग लेना नहीं चाहते हैं, तो भी आपको अपनी हालत के लिए मानक उपचार मिलेगा।

अदायगी

इस शोध अध्ययन में भाग लेने के लिए आपको भुगतान नहीं किया जाएगा।

इस शोध अध्ययन के दौरान चोट या चिकित्सा समस्या के मामले में आपको क्या करना चाहिए?

आपकी सुरक्षा अनुसंधान की प्रमुख चिंता है। यदि आप इस अध्ययन में होने के परिणामस्वरूप घायल हो गए हैं या चिकित्सा समस्या है, तो आपको सहमति फॉर्म के अंत में सूचीबद्ध लोगों में से एक से संपर्क करना चाहिए। आपको आवश्यक देखभाल / उपचार प्रदान किया जाएगा।

आप से प्राप्त जानकारी की गोपनीयता

आपको अपनी चिकित्सा जानकारी (व्यक्तिगत विवरण, शारीरिक परीक्षाओं के परिणाम, जांच, और आपके चिकित्सा इतिहास) की गोपनीयता के संबंध में गोपनीयता का अधिकार है। इस दस्तावेज़ पर हस्ताक्षर करके, आप अनुसंधान टीम जांचकर्ताओं, अन्य अध्ययन कर्मियों, प्रायोजकों, संस्थागत नैतिकता समिति और कानून के अनुसार आवश्यक किसी भी व्यक्ति या एजेंसी को भारत के ड्रग कंट्रोलर जनरल की आवश्यकता होगी, यदि आवश्यक हो तो आपका डेटा देखने के लिए। इस शोध के हिस्से के रूप में किए गए नैदानिक परीक्षण और चिकित्सा के परिणाम आपके मेडिकल रिकॉर्ड में शामिल किए जा सकते हैं। इस अध्ययन की जानकारी, यदि वैज्ञानिक पत्रिकाओं में प्रकाशित या वैज्ञानिक बैठकों में प्रस्तुत की गई है, तो आपकी पहचान प्रकट नहीं होगी।

अध्ययन में भाग लेने का आपका निर्णय आपको कैसे प्रभावित करेगा?

इस शोध अध्ययन में भाग लेने के आपके निर्णय से आपकी चिकित्सा देखभाल या जांचकर्ता या संस्थान के साथ आपके संबंध प्रभावित नहीं होंगे। आपका डॉक्टर अभी भी आपकी देखभाल करेगा और आप किसी भी लाभ को खो देंगे नहीं जिसके लिए आप हकदार हैं।

क्या आप शुरू करने के बाद अध्ययन में भाग लेने से रोकने का फैसला कर सकते हैं?

इस शोध में भागीदारी पूरी तरह से स्वैच्छिक है और आपको बिना किसी कारण बताए अध्ययन के दौरान किसी भी समय इस अध्ययन से वापस लेने का अधिकार है।

क्या जांचकर्ता आपको अध्ययन से बाहर ले जा सकता है?

आपको अपनी सहमति के बिना अध्ययन से बाहर ले जाया जा सकता है

नई जानकारी का अधिकार

यदि इस शोध अध्ययन के दौरान शोध दल को कोई नई जानकारी मिलती है जो अध्ययन में भाग लेने के आपके फैसले को प्रभावित कर सकती है, या कुछ संदेह उठा सकती है, तो आपको उस जानकारी के बारे में बताया जाएगा।

संपर्क करें

अधिक जानकारी / प्रश्नों के लिए, आप निम्नलिखित पते पर हमसे संपर्क कर सकते हैं:

मुख्य जाँचकर्ता:

Dr. Shabana
Senior resident
Dept. of Surgical Gastroenterology

Phone: 9047532081
Email:drshabanajabbar@gmail.com

प्रिंसिपल गाइड और सह-जांचकर्ता

Dr Subhash Chandra Soni
Assistant professor
Dept. of Surgical Gastroenterology

Phone: 8447440689
Email: drscssoni@hotmail.com

DATA COLLECTION SHEET

BASIC INFORMATION OF PATIENT

Name	
Age (in years)	
Sex	
Hospital No.	
Address	
Phone number	
Index Diagnosis	

CHIEF COMPLAINTS

RISK FACTORS

NATURE	YES	NO	DURATION	ABSTINENCE

PRE-OPERATIVE WORK-UP

CBC	
LFT	
KFT	
Coagulation parameters	
CEA	
CA 19-9	
CECT/ CE-MRI	

PRE-OPERATIVE PANCREATIC FUNCTIONS:

Fecal elastase 1	
Fasting plasma glucose	
HbA1c	

SURGERY

Procedure:
Date of Surgery:
Intra operative Findings:

HISTOPATHOLOGICAL ANALYSIS:

Acinar cell density	
Fibrosis score	

POST-OPERATIVE FOLLOW UP:

PARAMETERS	TIME
Fecal elastase 1	
Fasting plasma glucose	
HbA1c	
New onset diabetes mellitus	
Other complications	

PLAGIARISM

Thesis

ORIGINALITY REPORT

15%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.karger.com Internet	145 words — 1%
2	Pei-Wen Lim, Kate H. Dinh, Mary Sullivan, Wahid Y. Wassef, Jaroslav Zivny, Giles F. Whalen, Jennifer LaFemina. "Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection", HPB, 2016 Crossref	123 words — 1%
3	link.springer.com Internet	121 words — 1%
4	Alessandro Paniccia, Richard D. Schulick. "Pancreatic Physiology and Functional Assessment", Elsevier BV, 2017 Crossref	115 words — 1%
5	www.pubfacts.com Internet	83 words — < 1%
6	Michael J. Ferrara, Christine Lohse, Yogish C. Kudva, Michael B. Farnell et al. "Immediate post - resection diabetes mellitus after pancreaticoduodenectomy: incidence and risk factors", HPB, 2013 Crossref	78 words — < 1%

APPENDIX

WHO classification of BMI for the Asian population

Body mass index (BMI) was calculated based on the standard formula. The WHO guidelines for the Asian population were used to classify the BMI.

- Normal: 18.5 - 22.9 kg/m^2
- Overweight: 23 - 24.9 kg/m^2
- Obesity: ≥ 25 kg/m^2 (64)

ECOG (Eastern Cooperative Oncology Group) classification of performance status

- 0: fully active and no restriction in pre-disease performance of any activity
- 1: Restriction in strenuous physical activity but is fully ambulatory and able to carry out light or sedentary type of work
- 2: Restriction in carrying out all work activities, but able to do complete self-care; not fully ambulatory but is out of bed or chair for >50% of waking hours.
- 3: Able to do only limited self-care and is confined to bed or chair for >50% of waking hours.
- 4: Completely disabled, unable to perform any self-care and completely bed or chair ridden
- 5: Dead (66)

AJCC 8 STAGING

Pancreatic cancer

T1	Maximum tumor diameter ≤2 cm
T2	Maximum tumor diameter >2 cm, but ≤4 cm
T3	Maximum tumor diameter >4 cm
T4	Tumor involves the CA or the SMA (unresectable primary tumor)
N0	No regional LN metastasis
N1	Metastasis in 1–3 regional LNs
N2	Metastasis in ≥4 regional LNs
M0	No distant metastasis
M1	Distant metastasis

Ampullary and duodenal cancer

T1a	Limited to sphincter of Oddi
T1b	Invasion into duodenal submucosa
T2	Invasion into duodenal muscularis propria
T3a	Invasion into pancreas ≤ 0.5 cm
T3b	Invasion into pancreas > 0.5 cm or duodenal subserosa
T4	Involvement of celiac or superior mesenteric artery
N0	No lymph node involvement
M0	No distant metastasis
M1	Distant metastasis

Distal cholangiocarcinoma

T1	Depth of invasion < 5 mm
T2	Depth of invasion 5-12 mm
T3	Depth of invasion > 12 mm
T4	Tumor involves the celiac axis or the superior mesenteric artery
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N2	Metastasis in ≥ 4 regional lymph nodes
M0	No distant metastasis
M1	Distant metastasis

Clavien-Dindo Classification of surgical complications

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management

IVa	Single organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. *CNS*, central nervous system; *IC*, intermediate care; *ICU*, intensive care unit

2007 ISGPS definitions and grades of delayed gastric emptying

DGE grade	NGT required	Unable to tolerate solid oral intake by POD	Vomiting/gastric distension	Use of prokinetics
A	4–7 days or reinsertion > POD 3	7	+/-	+/-
B	8–14 days or reinsertion > POD 7	14	+	+
C	14 days or reinsertion > POD 14	21	+	+

ISGPS: International study group for pancreatic surgery, *DGE*: Delayed gastric emptying, *NGT*: Nasogastric tube, *POD*: Post operative day

2016 ISGPS definitions and grades of postoperative pancreatic fistula

Event	Biochemical leak	Grade B POPF	Grade C POPF
Drain amylase concentration >3× upper limit of normal serum value	Yes	Yes	Yes
Persisting peripancreatic drainage >3 weeks	No	No	Yes
Clinically relevant change in the management of POPF	No	No	Yes
Percutaneous or endoscopic drainage of POPF-associated collections	No	No	Yes
Angiographic procedures for POPF-associated bleeding	No	No	Yes
Reoperation for POPF	No	No	Yes
Signs of infection related to POPF	No	Yes (without organ failure)	Yes (with organ failure
POPF-related organ failure	No	No	Yes
POPF-related death	No	No	Yes

ISGPF: International Study Group on Pancreatic Fistula; *POPF:* postoperative pancreatic fistula

ISGPS definition of postpancreatectomy hemorrhage (PPH)

Time of onset
Early hemorrhage: </= 24 h after the end of the index operation) Late hemorrhage: >24 h after the end of the index operation)

Location
Intraluminal (intraenteric, eg, anastomotidc suture line at stomach or duodenum, or pancreatic surface at anastomosis, stress ulcer, pseudoaneurysm)
Extraluminal (extraenteric, bleeding into the abdominal cavity, eg, from arterial or venous vessels, diffuse bleeding from resection area, anastomosis suture lines, pseudoaneurysm)
Severity of Hemorrhage
Mild- • Small or medium volume blood loss (from drains, nasogastric tube, or on ultrasonography, decrease in hemoglobin concentration <3 g/dl) • Mild clinical impairment of the patient, no therapeutic consequence, or at most the need for noninvasive treatment with volume resuscitation or blood transfusions (2-3 units packed cells within 24 h of end of operation or 1-3 units if later than 24 h after operation) • No need for reoperation or interventional angiographic embolization; endoscopic treatment of anastomotic bleeding may occur provided the other conditions apply

Severe • Large volume blood loss (drop of hemoglobin level by > 3 g/dl) • Clinically significant impairment (eg, tachycardia, hypotension, oliguria, hypovolemic shock), need for blood transfusion (>3 units packed cells) • Need for invasive treatment (interventional angiographic embolization, or relaparotomy)

ISGPS classification of PPH: clinical condition, diagnostic and therapeutic consequences

Grade	Time of onset, location, severity and clinical impact of bleeding		Clinical condition	Diagnostic consequence	Therapeutic consequence
A	Early, Intra/ extraluminal, mild		Well	Observation, blood count, USG and, if necessary, CT	No
B	Early, Intra/ extraluminal, severe	Late, Intra/ extraluminal, Mild*	Often well/ intermediate, very rarely life-threatening	Observation, blood count, USG and CT	Transfusion of fluid/ blood, intermediate care unit (or ICU), therapeutic endoscopy,† embolization, relaparotomy for early PPH
C		Late,	Severely	Angiography,	Localization

		Intra/ extraluminal, severe	impaired, life-threatening	CT Endoscopy**	of bleeding, angiography and embolization, (endoscopy†) or relaparotomy, ICU

ISGPS: International study group for pancreatic surgery, ICU: Intensive care unit, *PPH*: postpancreatectomy hemorrhage. *CT*: Computed tomography, *USG*: Ultrasonography

*Late, intra- or extraluminal, mild bleeding may not be immediately life threatening to patient but may be a warning sign for later severe hemorrage

**Endoscopy should be performed when signs of intraluminal bleeding are present (melena, hematemesis, or blood loss via nasogastric tube).

CDC definition and classification of surgical site infection

Superficial incisional SSI:

- Date of event occurs within 30 days following the NHSN operative procedure (where day 1 = the procedure date) AND
- involves only skin and subcutaneous tissue of the incision AND
- patient has at least one of the following:

  a. purulent drainage from the superficial incision.

  b. organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue

  c. a superficial incision that is deliberately opened AND patient has at least one of the

following signs or symptoms: localized pain or tenderness; localized swelling; erythema; or heat.

d. diagnosis of a superficial incisional SSI by a physician

Deep incisional SSI

- Date of event occurs within 30 or 90 days AND
- involves deep soft tissues of the incision (for example, fascial and muscle layers) AND
- patient has at least one of the following:

a. purulent drainage from the deep incision.

b. deep incision that is deliberately opened or aspirated AND organism(s) identified from the deep soft tissues of the incision AND patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness.

Organ/Space SSI

- Date of event occurs within 30 or 90 days AND
- involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure AND
- patient has at least one of the following:

a. purulent drainage from a drain placed into the organ/space

b. organism(s) identified from fluid or tissue in the organ/space

c. an abscess or other evidence of infection involving the organ/space detected on gross anatomical exam or histopathologic exam, or imaging test evidence definitive or equivocal for infection AND meets at least one criterion for a specific organ/space infection site

MASTERCHART

S.No	Name	UHID	Phone number	DOS	Pathology	Acinar density decrease(nol=0, mild=1)	Fibrosis score (0=none, 1= mild, 2=moderate)	Block no	Biopsy	T stage (AJCC 8)	N stage (AJCC 8)
1	Punma Ram	2021/04/013781	8955119918	4/6/2021	Pancreatic MiNEN	1	2	H/2973/21	pT3N1	3a	1
2	Javari Lal	2021/06/004441	9530051852	21/06/2021	Periampullary adenocarcinoma	1	2	H/3286/21	pT3aN0	3a	0
3	Premlatha	2021/07/004803	9414193674	26/07/2021	Periampullary adenocarcinoma	0	1	H/4128/21	pT2 N1	2	1
4	Chaganlal	2021/08/010931	9928537836	6/9/2021	Periampullary adenocarcinoma	0	1	H/5245/21	pT2N2Mx	2	2
5	Neemba ram	2021/09/005852	9587336562	15/09/2021	Pancreatic ductal adenocarcinoma	1	2	H/5612 /21	pT2N1	2	1
6	Tan sukh	2021/09/010099	9413148085	22/09/2021	Distal Cholangiocarcinoma	0	0	H/5817/2021	pT1cpN0	1	0
7	Gawri devi	2021/09/019660	9680600263	18/10/2021	Periampullary adenocarcinoma	0	1	H/6693 /21	pT3bN1	3b	1
8	Narayan ram	2021/11/011614	9929624408	3011/2021	Periampullary adenocarcinoma	0	0	H/7951 /21	pT3aN2	3a	2
9	Kana ram	2021/10/010261	8107950042	27/12/2021	Periampullary adenocarcinoma	0	1	H/8923 /21	pT1aN0	1	0
10	Raghuveer singh	2021/12/010069	7726911922	28/12/2021	Periampullary adenocarcinoma	1	2	H/8936/21	pT3bN2Mx	3b	2
11	Purkha ram	2022/02/000839	9982539857	07/02/2022	Periampullary Adenocarcinoma	1	1	H/1087/22	pT3bN1	3b	1
12	Padam kanwar	2022/02/012543	9950626459	02/03/22	Duodenal adenocarcinoma	0	1	H/1869 /22	pT4 N0	4	0
13	Ramu ram	2022/02/011041	8432833459	25/02/2022	Distal cholangiocarcinoma	0	1	H/1802 /22	pT2N1	2	1
14	Ram kishor	2022/03/006628	9783835025	23/03/2022	Periampullary Adenocarcinoma	1	2	H/2727/22	pT3bN1Mx	3b	1
15	Mohan ram	2021/11/007778	8529531171	24/03/2022	Pancreatic NET	0	1	H/2778 /22	pT1N1	1	1
16	Padama	2022/02/015478	9950094737	05/04/2022	Periampullary adenocarcinoma	0	1	H/3119/22	pT3aN1	3a	1
17	Goma ram	2022/04/006224	6354092394	18/04/2022	Periampullary adenocarcinoma	1	2	H/3571/22	pT2N2Mx	2	2
18	Sayana Begum	2022/05/000110	9024351462	05/12/2022	Periampullary adenocarcinoma	0	2	H/4478/22	pT3aN1	3a	1
19	Khiya Ram	2022/05/019373	9414134432	06/06/2022	Periampullary adenocarcinoma	0	1	H/5432/22	pT2N0	2	0
20	Rajendra Kumar	2022/06/000695	7733945640	08/06/2022	Periampullary adenocarcinoma	0	0	H/5540/22	pT1bN0	1	0

S.No	fe preop	fe 3m	fe-6m	hba1 preop	hba1c-3m	hba1c-6m	fbs preop	fbs-3m	fbs-6m	Age	Age category (1=31-40, 2= 41-50, 3=51-60, 4= 61-70, 5=71-80)	Sex	Clavien dindo	dge (0=none, A/B/C ISGPS grades)	popf (0=none, A/B/C ISGPS grades)	pph (0=none, A/B/C ISGPS grades)	ssi (0=nones, rest- CDC grading)	pneumonia (0=none, 1= present)	acites (0=none, 1= present)	others (0=none, 1= present)
1	110	23	6	6	4.8	5.2	99	79	86	48	2	M	2	0	0	0	0	0	0	chyle leak
2	40	47	47	8	6.5	6.6	210	90	93	80	5	M	2	B	A	0	deep	1	0	aspiration pneumonia
3	260	262	258	7	6.7	6.9	145	96	98	64	4	F	2	C	A	0	organ space	0	0	pneumonia
4	100	47	53	11.1	7.1	6.4	285	198	82	41	2	M	1	0	A	0	0	0	0	0
5	376	22.5	6	11.4	5.7	5.6	245	106	110	65	4	M	1	0	0	0	superficial	0	0	CLABSI
6	41	520	23	11.2	6.9	6.9	267	93	135	53	3	M	0	0	0	0	0	0	0	0
7	160	210	240	5.2	5	5.1	115	96	104	55	3	F	3a	C	B	0	deep	0	0	0
8	27	220	39	6.1	5.9	5.8	98	102	96	48	2	M	2	0	A	0	0	1	0	pancreatitis
9	86	333	44	5.6	6.2	5.8	103	93	105	33	1	M	3a	A	0	B	organ space	0	0	0
10	58	34	42	9.5	5.4	6.9	240	199	185	45	2	M	1	0	0	0	superficial	0	0	0
11	140	313	24	7.7	6.2	5.9	188	101	99	54	3	M	2	B	0	0	deep	0	1	0
12	520	28	28	5.7	6.6	4.8	96	83	94	62	4	F	2	0	A	0	0	0	0	CLASI
13	520	19	25	6.5	7.5	6.2	145	158	101	59	3	M	0	0	0	0	0	0	0	0
14	536	25	24	5.1	5	5.2	88	89	98	63	4	M	4a	A	0	0	superficial	0	0	bile leak
15	86	26	24	5.1	5.6	5.6	92	93	101	32	1	M	0	0	0	0	0	0	0	0
16	1011	101	26	4.4	5	5.6	92	96	101	65	4	F	2	0	A	0	deep	0	0	0
17	907	145	24	4.2	4.5	4.9	88	98	87	60	3	M	1	0	A	0	0	0	0	0
18	37	25	26	5.1	5.2	4.8	101	95	98	52	3	F	2	B	A	0	organ space	0	0	0
19	34	24	24	5.6	5.5	5.1	110	104	93	62	4	M	3b	0	C	C	organ space	0	0	0
20	179	26	31	5.1	5.5	5.9	92	94	88	41	2	M	0	0	A	0	0	0	0	0

S.No	Preop PEI	Postop 3m PEI	Postop 6m PEI	Preop endocrine insufficiency	Postop 3m endocrine insufficiency	Post 6m endocrine insufficiency	pain (0=none, 1= present)	vomiting (0=none, 1= present)	fever (0=none, 1= present)	jaundice (0=none, 1= present)	GI bleed (0=none, 1= present)	Anorexia (0=none, 1= present)	weight loss (0=none, 1= present)	preoperative biliary drainage (0=none, 1= CBD stent)	DM (0=none, 1= present)	HTN (0=none, 1= present)	CAD (0=none, 1= present)	Other comorbidities (0=none, 1= present)	Addictions (0=none, 1= present)	Tobacco (0=none, 1= present)	Alcohol (0=none, 1= present)	Opium (0=none, 1= present)
1	1	2	2	0	0	0	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0
2	2	2	2	1	1	1	0	0	1	1	0	1	1	1	1	1	0	0	0	0	0	0
3	0	0	0	1	1	1	0	0	1	1	0	1	1	1	1	0	0	0	0	0	0	0
4	1	2	2	1	1	0	1	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0
5	0	2	2	1	0	0	1	0	0	0	0	1	1	0	1	0	0	HBV	0	0	0	0
6	2	0	2	1	1	1	1	0	0	1	0	1	1	0	1	0	0	0	0	0	0	0
7	1	0	0	0	0	0	0	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0
8	2	0	2	0	0	0	1	0	0	1	0	0	0	0	0	0	0	HBV	0	0	0	0
9	2	0	2	0	0	0	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0
10	2	2	2	1	1	1	1	0	1	1	0	1	1	1	1	0	0	0	0	0	0	0
11	1	0	2	1	0	0	1	0	0	1	0	1	1	0	1	0	0	0	0	0	0	0
12	0	2	2	0	1	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0
13	0	2	2	1	1	0	1	0	0	1	0	1	1	1	0	0	0	0	1	1	1	0
14	0	2	2	0	0	0	1	0	0	1	0	1	1	1	0	0	0	0	1	1	0	0
15	2	2	2	0	0	0	1	1	0	0	0	0	0	0	0	0	0	MEN-1	1	0	1	0
16	0	1	2	0	0	0	1	0	0	1	0	1	1	1	0	0	0	0	0	0	0	0
17	0	1	2	0	0	0	1	0	0	1	0	1	1	1	0	0	0	0	0	0	0	0
18	2	2	2	0	0	0	1	0	0	1	0	1	1	1	1	0	0	0	0	0	0	0
19	2	2	2	0	0	0	1	0	0	1	0	1	1	1	0	0	0	0	0	0	0	0
20	1	2	2	0	0	0	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0

S.No	BMI (kg/sq.m)	BMI category(1=underweight, 2=normal,3=overweight, 4=obese)	ECOG	Hb (g %)	TLC (x 1000 cells/ mm3)	Platelet counts (x 1000 cells/ mm3)	Total bilirubin (mg %)	Direct bilirubin (mg %)	ALP (IU/L)	Albumin (g %)	CEA (IU/ml)	CA 199 (ng/ ml)	CBD (mm)	PD (mm)	Pancreatic atrophy (0= none, 1= present)	Max tumor diameter (cm)	
1	16	1	1	12.3	6.1	2.2	1.3	0.2	52	3.4	1.3	2300	6	6	1	2	
2	26	4	1	11.9	9.2	2.5	1.6	0.8	163	3.3	1.75	18.8	16	8	1	3	
3	22.6	2	1	8.4	15.6	3.6	0.4	0.2	167	2.5	2.2	29	10	1	0	2	
4	18.6	2	0	13	6.8	0.97	5.5	3.3	440	4.2	1.09	70	18.5	6	0	1.8	
5	21.2	2	1	12.7	5.1	3	5.5	3.3	180	3.9	5.8	543	16	11	0	3.5	
6	20.7	2	1	12.9	8.5	3.2	7.9	4.9	546	3.4	1.8	75	17	3	0	3	
7	25.6	4	0	11	7.3	3.4	7.9	3.7	104	3.1	1.9	156	20	2	0	2	
8	24.5	3	0	11	12	2.4	3.8	2.08	659	3.5	2.15	45	10	2	0	1	
9	18.2	1	0	12.5	10.8	4.3	0.8	-0.3	154	4	0.8	6.08	8	2	0	1.4	
10	25	4	0	13.2	6.2	3.6	3.5	1.8	238	3.9	7.4	530	14	9	0	2.5	
11	19	2	1	10.3	6.08	2.3	18	9	706	3	2.6	699	19	4	0	2.7	
12	19	2	1	11.6	5	2.5	0.7	0.1	56	3.5	0.5	23	6	2	0	1.3	
13	22.4	2	1	14	12	5.5	1.8	0.6	244	3.4	2.7	152	16	2	0	1.5	
14	24	3	1	11.6	12	1.7	11.5	6.4	389	3.3	1.6	142	14.8	4	0	2.5	
15	23.7	3	0	14.5	9.7	3.1	0.3	0.08	109	4.3	1.8	9	6	3	0	2	
16	16.2	1	1	11.3	10.8	2.9	1.6	0.6	48	3.2	0.2	13.5	25	6	0	2.6	
17	18.4	1	0	11.6	10	2.9	19	9	609	2.8	3	48	28	10	0	1	
18	15	1	1	10.3	3.1	1.3	2.7	1.2	725	3.4	3.03	234	20	3	0	2	
19	18	1	1	9.8	8.3	6.1	12	7	326	2.7	2.7	641	13	5	0	2	
20	23.5	3	1	12.7	8.8	3.8	0.5	0.1	89	4.2	5.2	23	5	1	0	6	