



Outcomes of Pancreatic Fistula After Pancreaticoduodenectomy

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ABSTRACT

Background: The occurrence of postoperative pancreatic fistula (POPF) after pancreaticoduodenectomy (PD) is a major contributor to morbidity and mortality. Hence, it is imperative to decrease the occurrence of clinically significant POPF to enhance the overall morbidity outcomes associated with PD. This study seeks to assess the outcomes of pancreatic fistula following PD.

Methods: This study was a combined prospective and retrospective analysis of patients who underwent PD at Al-Thawra Modern General Hospital between January 2016 and April 2021. A total of 42 patients were included in the analysis.

Results: Among the 42 patients who underwent PD, 40% were male and 60% were female. The age distribution showed that 5% of patients were under 20, 14% were between 20 and 40, and 81% were above 40. The primary indications for PD were malignant periampullary tumors in 83.3% of patients, solid pseudopapillary tumors of the pancreas in 7.1% of patients, chronic pancreatitis in 4.76% of patients, duodenal adenocarcinoma in 2.38% of patients, and trauma in 2.38% of patients. Among the patients, 30 (71.43%) had a successful recovery without evidence of pancreatic fistula (PF), whereas 12 (28.57%) developed POPF. Among the 12 patients with POPF, 3 (7.14%) had a biochemical leak, 5 (11.9%) had a grade B fistula, and 4 (9.53%) had a grade C fistula according to the revised ISGPS definition. Of the patients with POPF, those with a biochemical leak did not experience significant morbidity and were managed conservatively. Patients with grade B fistula (5 patients) had an extended hospital stay of approximately 2-3 weeks and received percutaneous drainage as an intervention. One patient (8.33%) with grade C fistula required reoperation because of bleeding, and 3 patients (25%) developed septic shock and subsequently died, resulting in an overall mortality rate of 25% among patients with POPF.

Conclusion: POPF following PD remains a serious complication of substantial morbidity and mortality. Further improvements in the prevention, early detection, and management of POPF are necessary to reduce postoperative morbidity and mortality. Using the ISGPS definition and grading of PF aids in the clinical assessment and management of PF.

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1. Introduction:

Pancreaticoduodenectomy (PD), which has been called a ‘formidable’ operation ^[1], and known as the Whipple procedure, is a complex and demanding surgical intervention for both patients and healthcare systems ^[1]. It involves resecting the pancreatic head using various techniques such as classic PD, pylorus-preserving PD (PP-PD), and duodenum-preserving pancreatic head resection (DPPHR) ^[2]. PD was initially described in 1935 as a two-stage procedure with high mortality rates, but subsequent modifications, including the adoption of a one-stage procedure with choledochojejunostomy by Whipple in 1945, led to improved surgical outcomes ^[3].

Pancreatic cancer ranks as the fourth leading cause of cancer-related death in the US and Europe, and it is known for its resistance to nonsurgical treatments ^[4-10]. Surgical resection, particularly pancreaticoduodenectomy (PD), provides the only chance for a cure, with curative resection being the key factor for determining outcomes ^[11-13]. PD has gained importance in treating chronic pancreatitis, alleviating intractable pain, and addressing destructive injuries to the duodenal-pancreatic complex ^[14-21]. However, despite improved operative mortality rates (3% to 5%), postoperative morbidity remains high, ranging from 30% to 65% ^[22,23]. Efforts are currently directed toward reducing morbidity rates because complications significantly contribute to overall mortality ^[23]. The progress in perioperative intensive care has had a notable impact on reducing medical complications like myocardial issues, pulmonary complications, and thromboembolic events ^[14,24]. As a result, the focus of efforts to decrease morbidity rates has shifted towards addressing the four most common complications associated with pancreatic resection, specifically pancreatic fistula (10% to 34% incidence), delayed gastric emptying (8% to 45% incidence) ^[14], intra-abdominal abscess (1% to 12% incidence) ^[24], and abdominal hemorrhage (3% to 13% incidence) ^[25-28].

Postoperative pancreatic fistula (POPF) is a common and significant complication following pancreaticoduodenectomy, with an incidence of 10% – 34% in high-volume centers ^[29]. Pancreatic fistula can be categorized as internal or external, involving leakage of pancreatic secretions from the pancreatic duct into the peritoneal or pleural cavity, hollow viscus, or skin ^[30]. The development of pancreatic fistula is influenced by various factors, including surgical technique, gland texture, pancreatic duct size, blood loss, high BMI, stent placement, older age, and high nutritional risk score ^[29]. POPF can range from asymptomatic to causing complications such as abscesses, bleeding, infections, pneumonia, sepsis, and even mortality ^[29].

Efforts have been made to define and standardize pancreatic fistula classification to facilitate outcome comparisons and improve management strategies. The International Study Group of Pancreatic Fistula (ISGPF) initially proposed a widely accepted definition ^[31] for pancreatic fistula, but subsequent studies revealed certain limitations. As a result, they introduced a revised definition in 2016 to address these limitations which aimed to better characterize the severity grades of POPF ^[33-36].

Management of pancreatic fistula involves restricting the patient’s oral intake while using long-acting somatostatin analogs and providing total parenteral nutrition to maintain adequate nutrition. This treatment is continued for 2-3 weeks, with close observation for improvement. If no improvement is observed, surgical intervention may be considered ^[37].

Despite advancements in surgical techniques and perioperative care, pancreatic fistula remains a challenging problem in the postoperative management of patients undergoing pancreaticoduodenectomy. Therefore, this study aimed to determine the incidence of POPF following PD, to classify pancreatic fistula according to the updated grading of the ISGPF, and to determine the morbidity and mortality related to pancreatic fistula. By addressing these objectives, our research enhances the

understanding and management of POPF in the context of PD.

2. Patients and Methods

This is a combined analysis of retrospective and prospective studies that were set up to evaluate the outcome of pancreatic fistula post-PD.

This study was conducted on all patients who underwent pancreaticoduodenectomy at Al-Thawrah Modern General Hospital during the period from January 2016 to March 2021 with a total number of 42 patients.

Data Collection

Using a questionnaire to fill in the variables for each patient who underwent PD.

Data were collected from the inpatient follow-up, operative notes, and the operating surgeon.

Study variables

- Age
- Sex
- Indications for PD
- The type of PD
- Incidence of POPF
- Grade of POPF
- Morbidity associated with POPF.
- Mortality associated with POPF.

Definitions and Grading

A pancreatic fistula is defined as an abnormal connection between the cells lining the pancreatic duct and another surface that contains pancreatic fluid rich in enzymes [31]. Postoperative pancreatic fistula (POPF) was diagnosed when the amylase level was more than three times the upper normal serum value, starting from the third day after surgery, and when it was associated with a deteriorated clinical condition causally linked to the leakage from the pancreas. Pancreatic fistulas were categorized as a "biochemical leak" (BL) if they were asymptomatic. In such cases, it was approved to keep the drain in place for an extended period after discharge. Grade B included patients who received specific treatments to promote fistula healing, such as

percutaneous or endoscopic drainage of abdominal collections, or angiographic procedures. Grade C was reserved for patients of organ failure, who required reoperation, or died because of complications arising from POPF.

Operative Procedures

The operative procedures of classic pancreaticoduodenectomy (PD) and pylorus-preserving pancreaticoduodenectomy (PPPD) were performed according to established surgical protocols.

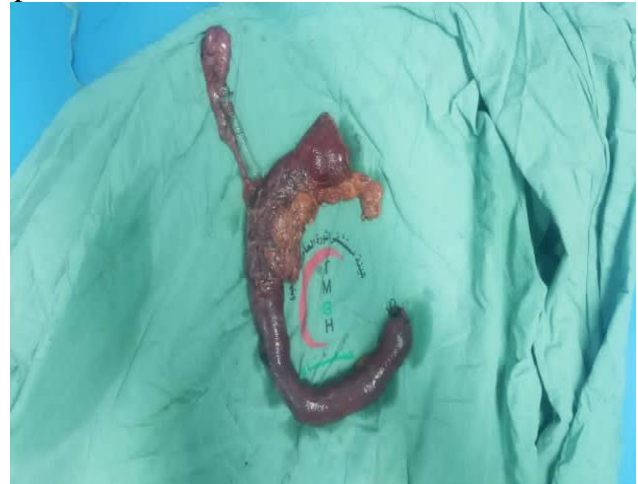


Figure (1): Resected portion in pancreaticoduodenectomy.

For classic PD, the surgical approach involved mobilization of the pancreatic head, duodenum, and surrounding structures to ensure optimal exposure. Subsequently, the stomach and duodenum were transected, and the gallbladder along with the distal bile duct was removed. The pancreas was then carefully transected above the level of the pancreatic duct. Reconstruction was achieved by creating a pancreaticojejunostomy and a hepaticojejunostomy, enabling the reestablishment of gastrointestinal continuity.

In contrast, PPPD aims to preserve the pyloric valve and a larger portion of the stomach. The operative steps for PPPD were similar to those for classic PD, with an additional emphasis on preserving the pylorus. This involved meticulous dissection to spare the pyloric region and a greater portion of the stomach. The subsequent reconstruction phase was adjusted accordingly to accommodate the preserved

stomach, thereby ensuring appropriate anastomosis formation.

These operative procedures adhered to standardized techniques and guidelines. The specific details of each procedure, including surgical incisions, intraoperative considerations, and specific technical variations, were documented for each patient. The choice of PD type (classic PD or PPPD) was determined based on patient characteristics, preoperative evaluations, and surgeon discretion, aiming to optimize patient outcomes.

Overall, the operative procedures of classic PD and PPPD were performed following well-established surgical principles, ensuring meticulous dissection, preservation of critical structures, and appropriate reconstruction techniques to achieve successful surgical outcomes.

Statistical analysis

All variables were initially reviewed and analyzed using the computerized database system SPSS, with descriptive analysis of results and variables predominantly analyzed as frequencies, tables, and percentages.

Ethical aspect

In this study, agreement of the ethical committee at Al-Thawrah Modern General Hospital was performed, and consent from patients was obtained for study publication.

3. Results

A review of the (42) evaluated patients who underwent pancreaticoduodenectomy at Al-Thawra Modern General Hospital in Sana’a from January 2016 to April 2021 showed the following results: Of the 42 patients reviewed for our study, male patients were (22) 52% and female patients were (20) 48% (**Figure 2**). Of these patients, 5% were under the age of 20, 14% were between the ages of 20 and 40, and 81% were above the age of 40 years (**Figure 3**).

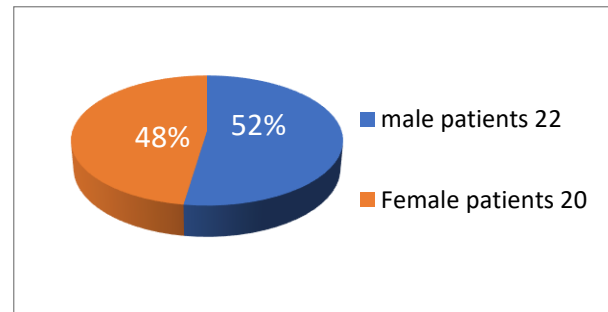


Figure (2): Gender distribution

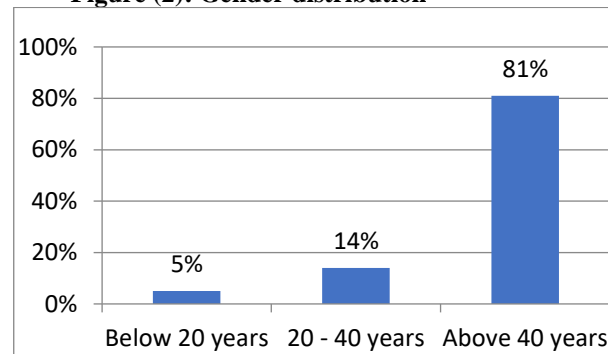


Figure (3): Age distribution

The indications for PD were malignant periampullary tumors in (35) 83.3% of patients, solid pseudopapillary tumors of the pancreas in (3) 7.1% of patients, chronic pancreatitis in (2) 4.76% of patients, first part duodenal adenocarcinoma in (1) 2.38% of patients, and trauma in (1) 2.38% of patients (**Figure 4**).

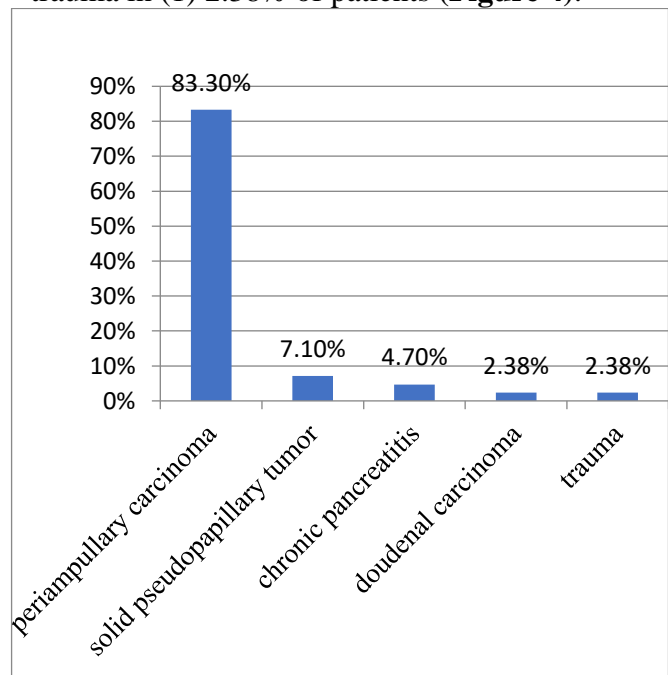


Figure (4): The Indication of PD

The types of pancreaticoduodenectomy performed were classical pancreaticoduodenectomy (PD) in 39 (92.86%) patients and pylorus-preserving pancreaticoduodenectomy (PPPD) in 3 (7.14 %) patients (Figure 5).

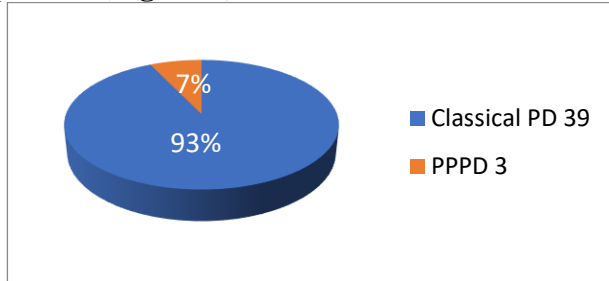


Figure (5): Type of performed surgery.

According to the post-operative course of these patients, 30 (71%) patients recovered well with no evidence of PF and 12(29%) had POPF (Figure 6). Of these, 12 patients 3 (7.14%) had a biochemical leak, (11.9%) grade B fistula, and 4 (9.53%) grade C fistula according to the revised ISGPS definition and grading (Figure 7).

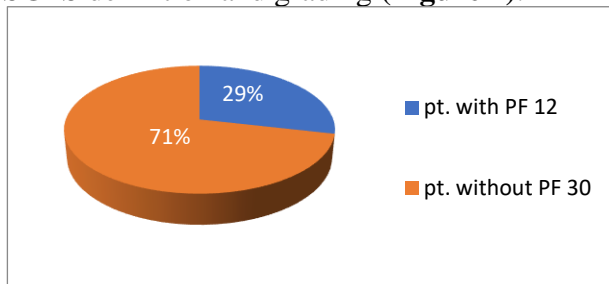


Figure (6): Percentage of pancreatic fistulas

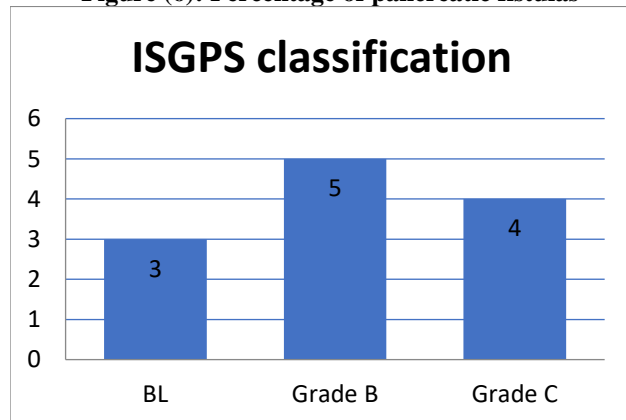


Figure (7): Classification of PF using the updated definition and grading of the ISGPS.

Regarding morbidity of patients with pancreatic fistula, patients with BL classification had no

significant morbidity related to pancreatic fistula. patients with grade B (5 patients) had a prolonged stay at the hospital for about 2-3 weeks and were repositioned off the drain which represents about 41.66% of patients with pancreatic fistula and 11.9% of the total patients. Indeed, the patient classified as Grade C them was re-operated due to bleeding and represented about 8.33 % of patients with pancreatic fistula 2.38% of the total cases, and 3 patients developed septic shock and death representing 25% of patients with PF and 7.14% of the total patient, so the total mortality rate among patients who had a POPF was 25% and 7.14% from total cases (Figure 8).

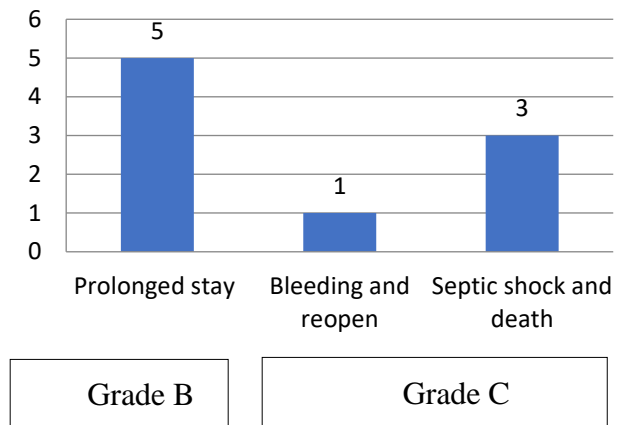


Figure (8): morbidity and mortality of patients with PF

4. Discussion

Pancreaticoduodenectomy (PD) is a challenging and intricate surgical procedure associated with a notable incidence of complications. Despite recent advancements in intensive care management and surgical techniques leading to a significant reduction in postoperative mortality rates, PD continues to exhibit a considerable prevalence of postoperative morbidity.

In the 42 patients reviewed for our study, demographic variables of the patients showed that PD was performed more in the male gender, (22) of the patients were males and (20) were females. Most patients who underwent PD were above the age of forty, 5% of these patients being under the age 20, 14% between the age of 20 and

40, and above the age of 40 years, with the most common indication for the procedure being periampullary tumors in 83.3% of patients, solid pseudopapillary tumors of the pancreas in 7.1% of patients, chronic pancreatitis in 4.76% of patients, duodenal adenocarcinoma in 2.38% of patients, and trauma in 2.38% of patients. The dominating type of PD performed was classical PD in 39 (92.86%) patients and PPPD in 3 (7.14%) patients.

The demographic characteristics and indications for PD demonstrated consistency across multiple studies. Nikhil et al. analyzed 60 patients, reporting a distribution of male (67%) and female (33%) participants with a mean age of 55.26 ± 7.24 years. The primary indications for PD included periampullary carcinoma (51.5%), second-part duodenal adenocarcinoma (10.6%), distal cholangiocarcinoma (13.6%), head of pancreatic carcinoma (16.7%), uncinate process carcinoma (4.5%), and head of pancreatic mass due to chronic pancreatitis (3.1%) [38].

In a study by Daniel J. Moskovic et al., 121 patients underwent PD, with 43.0% males and 57% females and a median age of 64 years. The leading indications for PD were pancreatic adenocarcinoma (46.3%), ampullary lesions (17.4%), chronic pancreatitis (15.7%), and cystic lesions (14%) [39].

Similarly, Andreas Minh Luu et al. analyzed 722 PD patients, with 50.8% males and 49.2% females, and a mean age of 61 ± 13 years. Malignant lesions (62.9%) were the primary indications for surgery, followed by chronic pancreatitis (29.9%) and benign tumors (12.6%). Pylorus-preserving PD was the predominant procedure (89.3%) [40].

Although these demographic variables and the type of PD performed may contribute to postoperative complications, such as postoperative pancreatic fistula (POPF), the present study lacked sufficient patient numbers to establish correlations between these variables and POPF occurrence.

POPF remains a significant challenge in pancreatic resection, with varying incidence rates reported across studies despite improvements in surgical safety and efficacy [41]. Our study reported pancreatic leakage rates of 28.57%, encompassing biochemical leaks and grade B or C fistulas. Comparable studies have reported rates ranging from 15.6% to 43.0% [38][39][40].

POPF is associated with substantial morbidity and mortality, leading to septic and hemorrhagic complications, organ failure, and death if left uncontrolled.

For example, Joseph J. Cullen et al. reported that out of 375 PD patients, 18% experienced a postoperative pancreatic leak, with 73% of these leaks being clinically significant [42].

In Daniel J. Moskovic et al.'s study, 43.0% of the 121 PD patients developed POPF (Grade A-C), with 28.9% being Grade A, 12.4% Grade B, and 1.7% Grade C [39].

Reviewing Nikhil et al., among the 60 PD patients, 16.66% had Grade A POPF, and 18.18% experienced significant postoperative pancreatic fistula. Among them, 9.09% had Grade B POPF, and 9.09% had Grade C POPF [38].

In a larger volume study conducted by Andreas Minh Luu et al, 17.3% of the 722 patients experienced POPF, with 2.8% having biochemical leaks, 11.4% having grade B leaks, and 3.2% having grade C leaks [40].

Another low-volume study by Amr Mostafa Aziz et al. evaluated 32 patients who underwent PD, with pancreatic leaks occurring in 15.6% of cases [43].

In our study, patients with POPF experienced varying morbidity outcomes. Patients with biochemical leaks had no significant complications. Grade B fistula patients had an extended hospital stay of approximately 2-3 weeks, and percutaneous drainage was employed as an intervention. Among Grade C patients, one underwent re-operation for bleeding and survived, whereas three developed septic shock

and died, resulting in an overall mortality rate of 25% among patients with POPF. Our study's outcomes align with those reported by other low-volume centers.

Comparisons between our study and tertiary centers within Yemen or larger volume centers in Western countries are challenging because of the lack of data on PD outcomes in Yemen. Therefore, our study serves as an initial assessment of outcomes, providing insights into the incidence of POPF, associated morbidity, and mortality. Further analysis is needed to identify potential improvement areas and investigate factors influencing postoperative complications and outcomes after PD.

5. Conclusions

- Pancreatic fistula is a common and serious complication after pancreaticoduodenectomy.
- A pancreatic fistula has significant morbidity and mortality after pancreaticoduodenectomy.
- The ISGPS definition and grading of PF help in the clinical assessment and management of PF.

Recommendation

- Early detection and management of pancreatic fistula help decrease mortality and morbidity.
- Further study to evaluate the risk factors and causes of pancreatic fistula among Yemeni patients.

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Conflicts of Interest and Competing Interests

The authors declare no conflict of interest.

Financial Disclosure

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