Original Research


# Do positive bile cultures influence morbidity and mortality after duodenopancreatectomy?

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## Abstract

**Background and aims.** Bacterobilia is associated with postoperative morbidity after pancreatico-duodenectomy (PD), mostly due to infectious complications. Investigating the frequency of bacterial species isolated from intraoperative biliary cultures and associated problems following PD was the goal of this study.

**Methods.** The frequency of isolated bacterial species and surgical complications were evaluated using an ANOVA test. The relationship between biliary cultures and each of the following complications: delayed gastric emptying (DGE), post-operative pancreatic fistula (POPF), biliary fistula and surgical site infectious (SSIs) were evaluated by using the odds ratio.

**Results.** In 340/513 (66%) of the PDs, positive biliary cultures were discovered. In patients with complications following surgery, different polymicrobial biliary cultures were shown to be more prevalent. A noteworthy incidence of biliary cultures confirming the presence of E. Coli, Klebsiella pneumoniae, and Enterococcus fæcalis ($p < 0.001$) was noted in SSIs (surgical site infectious). There was a strong correlation ($p < 0.001$) between the prevalences of polymicrobial biliary cultures containing Escherichia coli, Klebsiella pneumoniæ, Enterococcus fæcalis, and Enterococcus fæcium and POPF. Higher incidence of intra-abdominal collection and DGE was observed in biliary cultures positive for Escherichia coli, Enterococcus fæcalis, and Enterococcus fæcium ($p < 0.001$). Notably, as a distinct complication, Escherichia coli was substantially linked to DGE ($p < 0.01$).

**Conclusion.** While monomicrobial Escherichia coli bacterobilia is linked to DGE as a distinct consequence following PD, specific prevalences of polymicrobial bacterobilia are related with severe complications.

**Keywords:** bactibilia, pancreaticoduodenectomy, pancreatic fistula, delayed gastric empty, biliary fistula

## Introduction

Pancreatic ductal adenocarcinoma (PDAC) represents the most frequently diagnosed malignant tumor of the pancreas, with the worst prognosis [1]. Only 20% of PDAC cases are proposed for duodenopancreatectomy due to their aggressive histopathological type and late diagnosis [2]. Borderline resectability refers to the absence of distant metastases, involvement of superior mesenteric vein (SMV) or portal vein (PV), no encasement of nearby arteries, no extension to the celiac axis, encasement of the superior mesenteric artery (SMA) <180 °, local lymph node metastases [1]. Most patients present in the emergency department with jaundice, which is the most common sign associated with weight loss and fatigue. The differential diagnosis must be made with benign pathology, most commonly choledochal lithiasis [2]. Preoperative biliary drainage (PBD) was developed to improve obstructive jaundice, which affects a number of organs and physiological mechanisms in patients waiting for surgery [3]. However, there are several articles that argue that preoperative biliary drainage should not be done routinely because the rate

DOI: 10.15386/mpr-2812

Manuscript received: 10.09.2024
Received in revised form: 11.01.2025
Accepted: 31.01.2025

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of postoperative complications increases. Preoperative biliary drainage can be performed endoscopically (ERCP-endoscopic retrograde cholangiopancreatography), percutaneous drainage or surgical drainage (biliary bypass or cholecystostomy) [3,4].

However, over the past 20 years, PD has become a common procedure with low mortality and reasonable morbidity because of the multidisciplinary team involved and due to the optimization of the surgical time [5].

While bacterobilia is commonly seen in PD patients, primarily in those who underwent preoperative biliary drainage, there is a paucity of information about the relationship between various biliary bacterial species and postoperative problems following PD [6].

The aim of this study was to evaluate if the patients undergoing duodenopancreatectomy with positive bile cultures will have a poor prognosis than the patients without bactibilia [7].

## Methods

From January 2013 to December 2018, medical data from individuals receiving PD were gathered in hindsight: age, gender, comorbidities, BMI (body mass index), American Society of Anesthesiologists score (ASA Score- derived from the anesthesia record), neoadjuvant treatment use or preoperative biliary decompression (endoscopic, surgical-biliary bypasses, or laparoscopic cholecystostomy), requirements that were among the preoperative medical data. To ascertain the patient's suitability for pancreaticoduodenectomy, routine laboratory testing, chest radiography, contrast-enhanced computer tomography (CT) or MRI (magnetic resonance imaging) were among the preoperative diagnostic procedures. Only those individuals whose computed tomography showed evidence of vascular invasion were subjected to EUS (endoscopic ultrasonography). All patients with a malignant outcome underwent chemotherapy, and some of the patients got neoadjuvant chemotherapy or radiochemotherapy.

International categorization systems were used to assess complications like postoperative pancreatic fistula, delayed gastric emptying (DGE), and upper digestive bleeding, according to Clavien Dindo.

Postoperative hemorrhage was defined as the need for a follow-up visit to the operating room or a postoperative endoscopic intervention due to bleeding, while delayed gastric emptying was defined as the inability to consistently tolerate solid oral intake or the presence of a nasogastric tube on or after postoperative day 10. Any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than three times the serum amylase level was defined as a pancreatic fistula. Biliary leak was defined as the drainage of any volume of fluid clinically consistent with bile from surgically installed drains.

Additionally, data on postoperative complications like POPF, DGE, hemorrhage, biliary fistula, intra-abdominal collections, sepsis, and surgical site infections (SSIs) were analyzed. These data included information on intraoperative management resulting from biliary culture, pancreatic texture, diameter of the Wirsung duct, median blood loss, and operative time.

We punctured the gallbladder and common bile duct to obtain bile samples during surgery in a sterile environment. To identify the bacteria in the samples, routine microbiological assays were performed. After 48 hours, if there was no sign of microbial development, the samples were deemed sterile. Before the skin incision, all patients received intravenous antibiotic prophylaxis for 30 to 60 minutes. Antibiotic therapy was administered to individuals who acquired a clinically significant infection during the postoperative period. Drugs were chosen in these circumstances based on the particular diagnosis and results of the antimicrobial susceptibility test.

Individuals with inadequate information about biliary cultures and/or postoperative history were also eliminated, as were those who underwent palliative biliary and/or gastric bypass for incurable cancers.

The ANOVA test was utilized to examine the variance and heterogeneity of bacterial species obtained from intra-operative biliary cultures, in order to determine any possible associations between the bacteria and each postoperative problem. Every conceivable pair of means is compared in the test. The Tukey test for multiple comparisons was employed in this investigation to assess the statistical significance and any correlation between the prevalence of various bacterial species and each problem. In a regression analysis, the ANOVA test is specifically designed to ascertain the impact that independent variables have on a dependent variable. It is feasible to compare more than two groups simultaneously with the ANOVA test in order to ascertain whether a relationship between them exists.

The impact of identified risk variables (e.g., male sex, BMI $\geq$ 30, Wirsung duct diameter $\leq$ 5 mm, soft pancreatic texture) and polymicrobial bacterobilia on the development of POPF was evaluated using univariate and multivariate logistic regression models. The dependent variable in this study was POPF, while the independent variables were male sex, BMI $\geq$ 30, Wirsung duct diameter $\leq$ 5 mm, soft pancreas texture, and polymicrobial bacterobilia.

## Results

We found 513 patients eligible for this study, patients who underwent pancreaticoduodenectomy. Most of the patients were male – 326 (63.54%), while female patients represents 187 (36.54%). The median BMI was 26.23 kg/m2. Regarding the anesthesia score most of them (84%) had an ASA score I-III (Table I).

Preoperative biliary drainage was performed in 330 patients (64.32%), most of them underwent ERCP with stenting - 295 (89.39%), 17 (5.15%) of them underwent

percutaneous biliary drainage, 10 (3.03%) of them underwent laparoscopic cholecystostomy and 8 (2.42%) were proposed for hepatico-jejunal anastomosis (Table I).

Neoadjuvant treatment was the first intention for 64 (12.47%) patients as described below: chemotherapy alone was proposed for 15 (23.32%) patients, while the other 49 (76.68%) underwent radio-chemotherapy (Table I).

We found in this study that 353 (68.81%) of the patients had a soft gland, while 160 (31.19%) had a firm tissue. Also we found that the diameter of the Wirsung duct was < 5 mm in 144 (28.07%) patients and > 5 mm in 369 (71.93%). The median operative time was 265 min (range 150 min and 520 min) while the median intraoperative blood loss was 350 mL (range 100-750 mL) (Table II).

We found positive bile culture in 340 (66.4%) patients and negative in 173 (33.6%) of the patients. Most of the patients with positive bile culture had a preoperative biliary drainage -289 (85.2%). Moreover, preoperative biliary drainage was found to be strongly associated with positive biliary culture $p < 0.01$) and significantly protective against biliary fistula development $p < 0.05$) (Table II).

**Table II.** Intraoperative data.

| **Wirsung diameter** | <5mm | >5mm |
|---|---|---|
| | 144 | 369 |
| **Pancreatic texture** | Soft | Firm |
| | 353 | 160 |
| **Blood loss median -mL (range)** | 350 mL (100-750 mL) | |
| **Operative time median (range)** | 266 min (150-520 min) | |
| **Positive biliary cultures** | 340 (66.4%) | |
| **Preoperative biliary drainage** | 289 (85.2%) | |

In the study population, the percentage of positive biliary cultures was statistically significant ($p < 0.01$). The frequency of polymicrobial biliary cultures in postoperative complications was shown by the ANOVA analysis. Additionally, the Tukey test showed that each bacterial species was more common in particular problems and that the null hypothesis was validated ($p < 0.01$). The Tukey test revealed a considerable prevalence of polymicrobial biliary cultures containing Enterococcus fæcalis, Escherichia coli, and Klebsiella pneumoniae in SSIs ($p < 0.01$). We found that the patients who developed postoperative pancreatic fistula were frequently found to have polymicrobial biliary cultures positive for Escherichia coli, Klebsiella pneumoniæ, Enterococcus fæcalis, and Enterococcus fæcium ($p < 0.01$). We also found out that only the soft pancreas and Wirsung duct diameter ≤ 5 mm were significantly correlated with POPF in the univariate analysis ($p < 0.0001$ and p 0.002, respectively) (Table III).

Delayed gastric empty was found in 176 (34.30%) patients, while pancreatic postoperative fistula was found out to be a main factor for patients to develop DGE ($p < 0.01$) (Table III).

Intra-abdominal collection and DGE were more common in patients whose biliary cultures were positive for Escherichia coli, Enterococcus faecalis, and Enterococcus faecium ($p < 0.001$). Interestingly, when DGE was reported as a singular event, the presence of only Escherichia coli in the biliary culture was substantially linked to it, compared to individuals who did not have any complications.

**Table I.** Clinical data and demographic characteristics.

| **Clinical data and demographic characteristics** | | | | |
|---|---|---|---|---|
| **Age (years)** | 64 (34-91) | | | |
| **Gender** | Male | Female | | |
| | 326 (63.54%) | 187 (36.54%) | | |
| **BMI (Kg/m2) Median** | 26.23 | | | |
| **Neoadjuvant treatment** | Chemotherapy alone | Radio-chemotherapy | | |
| | 15 (23.32%) | 49 (76.68%) | | |
| **Preoperative biliary drainage** | ERCP + stenting | Percutaneous biliary drainage | Laparoscopic Cholecystostomy | Surgical Drainage (hepatico-jejunal anastomosis) |
| | 295 (89.39%) | 17 (5.15%) | 10 (3.03%) | 8 (2.42%) |

**Table III.** Correlation between complications and positive bile culture.

| | E.Coli | Klebsiella pneumoniae | Enterococcus faecalis | Enterococcus faecium | p |
|---|---|---|---|---|---|
| **Surgical site infection** | 23 (4.48%) | 28 (5.45%) | 25 (4.87%) | 2 (0.38%) | <0.01 |
| **Postoperative Pancreatic Fistula** | 76 (14.81%) | 64 (12.47%) | 97 (18.90%) | 87 (16.95%) | <0.01 |
| **Delayed gastric empty** | 67 (13.06%) | 3 (0.58%) | 58 (11.30%) | 53 (10.33%) | <0.01 |

## Discussion

It is well known that bacteria play a significant role in predicting infectious problems following pancreatic surgery, and that the primary source of biliary colonization is preoperative biliary drainage [7]. Preoperative biliary drainage has been shown to have possible drawbacks, and its use is only advised for patients who are unable to undergo early surgery. Nevertheless, in routine clinical practice, this indication is frequently disregarded [7].

Before early tumor resection has been completely ruled out, jaundiced individuals with periampullary neoplasms continue to receive biliary drainage in the absence of cholangitis [7]. Furthermore, there is conflicting evidence on the association between bacterobilia and other prevalent post-PD problems like DGE [8], despite reports that it is linked to even noninfectious complications like POPF [9,10].

To the best of our knowledge, however, there is a dearth of information on the prevalence of various biliary bacterial species in postoperative problems following pancreaticoduodenectomy [11]. Our results demonstrated that a sizable percentage of patients undergoing pancreatic surgery had positive intraoperative biliary cultures. The substantial percentage of bacterobilia in our series is justified by the high prevalence of preoperative biliary drainage, which is strongly correlated with the existence of biliary culture [12]. The inclusion of numerous PDAC patients who had already undergone urgent biliary stenting in other hospitals was the primary cause of the non-negligible rate of preoperative biliary drainage we reported [13].

In spite of this, preoperative biliary stenting was demonstrated in this trial to be strongly protective against postoperative biliary fistula [12]. It is important to interpret this finding cautiously. We believe that bile duct dilatation, rather than ERCP alone, played a greater role in the lower rate of biliary anastomotic leakage detected in these patients. Andrianello et al. [12] showed in a series of more than 1600 PDs that the diameter of the bile duct is the main independent factor to predict biliary fistula after PD [14].

Our findings support Krüger's et al. [13] discovery that preoperative biliary drainage raises the possibility of bile colonization. Indeed, we also believe, in line with others [15,16], that drainage should only be done when cholangitis is present or when early upfront surgery is not feasible [17].

Additionally, encouraging hospital boards to perform microbiological surveillance of duodenoscopes could be a strategy to lower the rate of positive biliary cultures following endoscopic preoperative biliary drainage, and consequently the postoperative complications associated with positive biliary cultures [17]. After all ERCP instruments are reprocessed, Ciccozzi et al. recommended that duodenoscope surveillance be carried out on a regular basis to prevent bacterial transfer and, as a result, patient colonization [18,19].

The biliary bacterial flora is polymicrobial in most cases. Interestingly, there was a substantial correlation seen between polymicrobial biliary cultures and intra-abdominal collections, POPF and SSIs [20,21].

The present findings are consistent with the findings of previous studies that have examined the predicted relationship between polymicrobial biliary flora and polymicrobial proliferation of bacteria in intra-abdominal collections and wound infections following pancreatic surgery [11,13,18].

In relation to POPF, our data may indicate a connection between this feared consequence and polymicrobial Gram-negative bacterobilia (Escherichia coli, Klebsiella pneumoniae, Enterococcus fæcalis, and Enterococcus fæcium) [15,22]. Ohgi et al. [6] demonstrated in a retrospective analysis of 264 PDs that patients with positive biliary cultures obtained during the procedure had a considerably greater frequency of clinically relevant postoperative pancreatic fistulas (CR-POPF) [23]. Furthermore, the bacteria found in these patients surgical drain fluid matched those recovered from the biliary culture [24]. Since biochemical leaks were not linked to positive biliary cultures, the investigators conjectured that bacteria may have colonized the ascitic fluid and played a part in the formation of CR-POPF [16,25]. Enterococci were shown to be prevalent in POPF, according to our research's study of every bacterial species isolated from patients experiencing post-operative complications [22,26]. This finding is in part at odds with a recent report by Heckler et al. [27], who showed that Enterococci, despite being representative of the most isolated microbes in the bile duct swab, was primarily associated with lymphatic fistula and that Escherichia coli bacterobilia was associated with severe POPF in a retrospective study of 289 PDs performed on malignancies following preoperative biliary drainage [28]. Similar to Belmouhand's et al. study [22], our study has drawbacks as well, namely a retrospective design and no biochemical analyses to support the detrimental impact of bacterial proteases. However, the potential of unintentional contamination was increased because our microbiological study was done on intraoperative bile collection rather than fluid collected over multiple postoperative days in the abdominal drains [29]. Furthermore, for the first three days following surgery, participants in Belmouhand's study also consistently got metronidazole and cefuroxime as part of their antibiotic regimen.

We found a much greater prevalence of polymicrobial Gram-negative bacterobilia (Escherichia coli, Enterococcus faecalis, and Enterococcus fæcium) in relation to DGE, which is typically linked with POPF, according to our experience. These outcomes are consistent with what Chen's meta-analysis revealed [3,30]. We

need to declare that the consistency of the pancreas was appreciated by the main surgeon, without elastography. This can be a limitation of this study because every surgeon can appreciate differently the consistency of the organ.

Notably, when this occurred as a single complication, a noteworthy finding from our study was the noticeably greater frequency of monomicrobial Escherichia coli bacterobilia and DGE. Eisenberg has previously noted a potential link between bacteria and DGE [30]. This author also discovered that abdominal infections significantly impacted the prognosis of primary DGE [30].

## Conclusion

A reliable method for monitoring and predicting surgical problems following pancreaticoduodenectomy (PD) is intraoperative biliary culture. Monomicrobial Escherichia coli bacterobilia is more common when DGE arises as a singular complication, but polymicrobial bacterobilia is more common in circumstances of significant postoperative problems, such as SSI and POPF.

Antibiotics customized to the outcomes of an antimicrobial susceptibility test conducted on intraoperatively collected biliary samples may decrease the rate of complications after pancreaticoduodenectomy in patients with preoperative biliary drainage.

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