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ORIGINAL ARTICLE

Prospective Study Correlating External Biliary Stenting and Pancreatic Fistula Following Pancreaticoduodenectomy

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Abstract

Background Postoperative pancreatic fistula (POPF) is the most common complication of pancreaticoduodenectomy (PD). Sometimes POPF is associated with biliary fistula (BF) or "mixed" fistula. The purpose of this study is to assess whether the severity of the fistulae, when present, is decreased with an external biliary stent in place.

Methods In this single-center study, we assessed patients who underwent elective PD from January 2014 to December 2017. Patients were divided into two groups: standard PD (ST-PD) vs. PD with external biliary stent (PD-BS). Demographic, preoperative, intraoperative, and postoperative variables were analyzed, including complications according to the Clavien-Dindo classification, and those specific to pancreatic surgeries, and mortality rates within 90 days of operation.

Results A total of 128 patients were included (65 in ST-PD group and 63 in PD-BS group). Postoperative complications occurred in 61.7% of patients (32.8%, Clavien-Dindo ≥ III) and were more common among patients in the PD-BS group (44.4% vs. 23.1%; $p = 0.03$). POPF was also more common among patients in the PD-BS group (39.7% vs. 18.5%; $p = 0.008$). No statistically significant differences were found for any other complications.

Conclusion Based on the results of our study, placement of a transanastomotic external biliary stent does not reduce the rate of pancreatic or biliary fistulae, or their severity; in fact, POPF is more likely when biliary exteriorization is present.

Trial Registration NCT04654299

KEY WORDS Postoperative pancreatic fistula · Pancreaticoduodenectomy · Morbidity · Biliary stent

Introduction

Pancreaticoduodenectomy (PD) is the standard-of-care procedure for multiple conditions occurring in the pancreatic head and the periampullary region. Despite technical advances, this surgery is still associated with significant perioperative morbidity and mortality rates.[1] The most serious complication after PD is postoperative pancreatic fistula (POPF), which can become difficult to manage and even be fatal.[1, 2] Sometimes, POPF is associated with postoperative biliary fistula (POBF), making its management increasingly complex. Efforts to decrease POPF rates have led to the development of several anastomosis techniques, such as pancreaticojejunostomy and pancreaticogastrostomy with or without internal or external pancreatic duct stents, with variable outcomes reported in medical literature.[3–6] Our study's hypothesis was that separating pancreatic and biliary secretions by means of an external biliary stent could potentially reduce the rate of complex POPF as it relieves pressure on the biliopancreatic limb and prevents both secretions from mixing. The purpose of our study was to compare the rate of complications after PD in patients with a biliary stent vs. patients without one (standard PD).

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Materials and Methods

Data Collection

This single-center study looked at patients who consecutively underwent PD between January 2014 and December 2017 and

met the inclusion criteria. All patients were operated by the same surgical team, headed by four surgeons. They were divided into two groups: standard PD (ST-PD) and PD with external biliary stent (PD-BS). Patients were consecutively operated on and patients were assigned alternately to each treatment group after laparotomy, if considered resectable, with no other criteria influencing the assignment to one treatment group or the other.

The inclusion criteria were as follows: provision of informed consent; patient age > 18 years old; elective PD performed for primary pancreatic disease. The exclusion criteria were the following: PD with multivisceral resection (organ other than duodenum, pancreas, gallbladder, and bile duct); patients with peritoneal or liver metastases found during surgery.

Preoperative Assessment

At our center, all patients with periampullary neoplasms complete abdominal imaging testing (CT and/or MRI) to determine diagnosis and/or assess the vascular anatomy and its potential infiltration. Further tests include chest CT and blood tests to include tumor markers and liver function panels. Preoperative biliary drainage is performed in case of cholangitis, total bilirubin > 15 mg/dl, or lower elevated levels if expected time until surgery is greater than 2 weeks.

Surgical Technique

All patients underwent PD per the Whipple procedure.[7] Frozen pathological analysis was performed on the biliary and pancreatic resection margins for all of them. Once the surgical specimen was removed, reconstruction was performed using the method described by Child.[8] Pancreatic anastomosis was done by means of end-to-end or duct-to-mucosa pancreaticojejunostomy. Occasionally, pancreaticogastrostomy was performed. Internal stenting of the major pancreatic duct using a multiperforated, 10-cm-long, 5-Fr stent was standard for all patients. The same bowel loop underwent hepaticojejunostomy with or without external biliary drainage. Anastomosis was performed with a single-layer, interrupted suture with long-lasting, absorbable monofilament.

The biliary stent consisted of a multiperforated, natural rubber tube, measuring 3.5 mm in diameter, that we placed transanastomotically (Fig. 1), with exteriorization sited at 20 cm utilizing the Witzel jejunostomy approach (Fig. 2). Then, either antecolic or retrocolic gastrojejunostomy was performed. Two drains were usually placed at the site, one on the right, with subhepatic placement, and the other one on the left, near the pancreatic anastomosis.

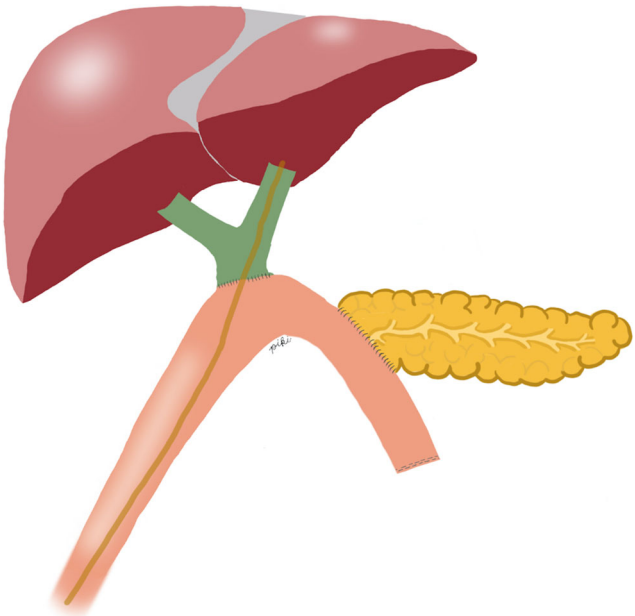

Fig. 1 Biliary stent placed into biliary duct transanastomotically

Variables

The following variables were studied: epidemiological—age, sex, past medical history, medication, American Society of Anesthesiology (ASA) classification; clinical—jaundice; serological tests—leukocytes, amylase, hemoglobin (gr/dl), preoperative bilirubin, creatinine, prothrombin time, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA 19-9); radiological/diagnostic—diagnostic tests performed (CT/MRI/endoscopic ultrasound [EUS]), vascular infiltration (arterial and/or venous), and preoperative biliary drainage (endoscopic retrograde cholangiopancreatography [ERCP] or percutaneous transhepatic cholangiography); surgical—diameter of the bile duct (greater or less than 10 mm), pancreatic consistency (hard vs. soft), diameter of the

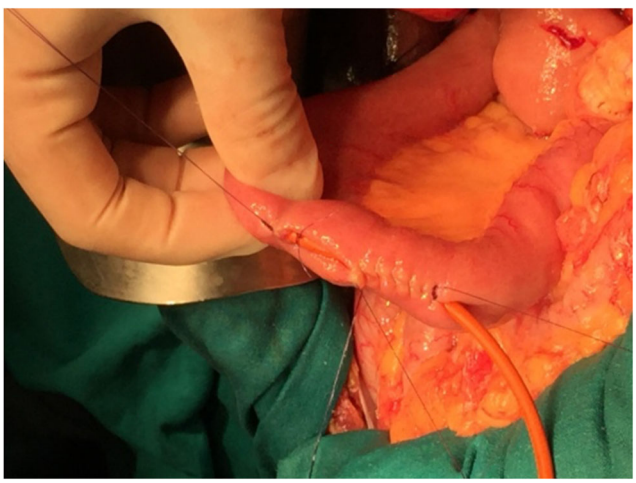

Fig. 2 Biliary stent exteriorization utilizing the Witzel jejunostomy approach

pancreatic duct (greater or less than 3 mm), type of pancreatic anastomosis, antecolic or retrocolic gastrojejunostomy, intraoperative transfusion, vascular resection (venous or arterial); postoperative course—complications were assessed at 90 days using the Clavien-Dindo classification, and those defined as Clavien-Dindo grade IIIa or higher were considered major.[9] The complications were taken from the clinical and nursing notes of the patients' electronic records. For the specific complications of pancreatic surgery, the definitions of the International Study Group on Pancreatic Surgery (ISGPS) of delayed gastric emptying (DGE),[10] postpancreatic hemorrhage,[11] and postoperative pancreatic fistula[12] were used. For bile leakage, we used the definition and severity grade classification by the International Study Group of Liver Surgery.[13] Operative mortality was defined as death within 90 days of the PD or during admission within the same hospital stay.

Postoperative Management

On days 3 and 5 postsurgery, amylase in drain fluid was tested to find out whether there was a POPF. The biliary stent was checked daily to assess proper bile output. If no complications arose, the biliary stent was closed on day 5 postsurgery and later removed in an outpatient, follow-up visit 3 weeks after the procedure. In case of clinically significant POPF or POBF, the stent was kept until the fistula was resolved. At our institution, biochemical leakage is managed conservatively, and interventional radiology techniques, such as percutaneous drainage, are used whenever possible for higher grades. If the patient's evolution was poor after percutaneous drainage, or if they presented with generalized peritonism or associated hemorrhage, reoperation was performed.

Follow-up

Patients were followed up with an outpatient consultation 3 weeks after their surgery to have their surgical wound assessed and biliary stent removed. Patients with pancreatic malignant neoplasms had these additional follow-up visits: outpatient visits every 3 months during the first 2 years for follow-up testing, including tumor markers and CT or MRI; then every 6 months until the 5-year mark; and then every year indefinitely. Patients with benign pathologies were seen annually for a physical exam, nutritional evaluation, and blood test.

Statistical Analysis

Continuous variables are represented by the means (standard deviation) if the distribution was normal or medians [interquartile range] if it was non-normal. The categorical variables are presented as frequencies. The chi-squared test was used to compare categorical variables and the Student t-test was used for continuous variables. $p < 0.05$ was considered statistically significant. The Statistical Package for the Social Sciences (SPSS, release 22.0 for Mac) was used for all analyses.

The study has been reported in line with the STROCSS criteria[14] and has been registered at ClinicalTrials.gov (NCT04654299). The study was approved by the Ethical and Research Studies Committee of our institution, and informed consent was obtained from all patients.

Results

During the study period, 128 patients underwent PD, 65 of whom were ST-PD and 63 PD-BS. One patient in the PD-BS group ended up being excluded because their biliary stent accidentally came out after laparotomy closure. The mean age of all patients was 63.6 ± 10.67 years (28–83 years), 65.63 ± 10.46 years vs. 61.6 ± 10.58 years ($p = 0.03$) for the ST-PD and PD-BS study groups, respectively. No significant differences were found in the breakdown by sex. Most patients were classified as ASA II (60% ST-PD vs. 61.9% PD-BS; $p = 0.82$) (Table 1).

The predominant preoperative diagnosis was a malignant neoplasm of head of pancreas, with no significant differences between the two study groups. All other diagnoses and their breakdown by study group are shown in Table 1. All patients had a CT scan performed as a diagnostic imaging test. Other diagnostic tests performed included MRIs (8 patients), PET scans (12 patients), and EUS (38 patients). No significant differences were found between the two study groups regarding the patients' diagnoses (Table 1). Out of 46 patients with pancreatic malignant neoplasm, only 4 received neoadjuvant therapy (2 in each study group). We found no significant differences in serum CA 19.9, bilirubin, or albumin levels. Preoperative biliary drainage was performed in 80 patients (63%), with no significant differences between both study groups (Table 1).

As for intraoperative considerations, venous resection was conducted in 22 patients (17.2%), 11 from each study group (17.5% PD-BS vs. 16.9% ST-PD; $p = 0.93$). One (1) patient from each study group underwent arterial resection. A common finding was a dilated bile duct (≥ 10 mm), present in 79.1% of all patients (86% ST-PD vs. 71.4% PD-BS; $p = 0.089$). The pancreatic consistency, major pancreatic duct diameter, the type of pancreatic anastomosis performed, whether the gastrojejunostomy was antecolic or retrocolic, and the intraoperative transfusion rate are recorded in Table 2.

Postoperative complications were reported in 61.7% of patients, with 32.8% of them being Clavien-Dindo > III. Major complications were more frequent in the PD-BS study group (Table 2). In terms of complications specific to pancreatic surgery, we only had 5 patients (3.9%) with DGE, 4 of whom were from the ST-PD study group and 1 other from the PD-BS

Table 1 Preoperative and demographics variables

Variables	Total *n* = 128	ST-PD *n* = 65	PD-BS *n* = 63	*p* value
Age (years)	63.6 ± 10.67	65.63 ± 10.46	61.6 ± 10.58	0.03
Female	57 (44.5%)	26 (40%)	31 (49.2%)	0.29
Male	71 (55.5%)	39 (60%)	32 (50.8%)	
ASA I	7 (5.5%)	6 (9.2%)	1 (1.6%)	0.05
ASA II	78 (60.9%)	39 (60%)	39 (61.9%)	0.82
ASA III	41 (32%)	19 (29.2%)	22 (34.9%)	0.49
ASA IV	2 (1.6%)	1 (1.5%)	1 (1.6%)	0.98
CT scan	128 (100%)	65 (100%)	63 (100%)	
CA 19-9 (U/ml)	691 ± 2958	631.9 ± 20058.9	740.7 ± 3668.2	0.86
Bilirubin (mg/dl)	3.45 ± 4.21	3.62 ± 4.54	3.45 ± 3.97	0.82
Albumin (g/dl)	4.08 ± 3.2	4.23 ± 4.41	3.91 ± 0.65	0.57
Preoperative biliary drainage	80 (62.5%)	42 (64.6%)	38 (60.3%)	0.6
Preoperative diagnostic				
Pancreatic neoplasm (preop)	91 (71.1%)	45 (49.5%)	46 (50.5%)	0.63
Ampulloma (preop)	15 (11.7%)	11 (73.3%)	4 (26.7%)	0.06
Cholangiocarcinoma (preop)	12 (9.4%)	6 (50%)	6 (50%)	0.95
Pancreatitis (preop)	2 (1.6%)	0	2 (100%)	0.14
Others (preop)	8 (6.3%)	3 (37%)	5 (63%)	0.43

study group (6.2% vs. 1.6%, respectively; p = 0.18). Eight (8) patients (6.3%) developed POBF, 2 from the ST-PD study group and 6 from the PD-BS (3.1% vs. 9.5%; p = 0.13). The most common complication was POPF, which was experienced by 37 patients (28.9%), with a greater occurrence in the PD-BS study group than in the ST-PD (39.7% vs. 18.5%; p = 0.008). The type of fistula according to the ISSPS classification as well as other complications is shown in Table 2. As for POBF, we found no statistical connection to the diameter of the bile duct.

When it came to the external biliary stents, 12 patients produced less than 30 cc of bile daily, so their drains were considered non-functioning. The mean volume of bile drained on days 2 and 5 postsurgery was 270 cc (IQR = 50–475) and

Table 2 Intra- and postoperative variables

Variables	Total *n* = 128	ST-PD *n* = 65	PD-BS *n* = 63	*p* value
Venous resection	22 (17.2%)	11 (16.9%)	11 (17.5%)	0.93
Soft pancreas	62 (48.4%)	30 (51.7%)	32 (53.3%)	0.86
Pancreatic duct < 3 mm	72 (56.3%)	31 (55.4%)	41 (69.5%)	0.11
Pancreaticojejunostomy duct-to-mucosa	74 (57.8%)	39 (60%)	35 (55.6%)	0.61
Pancreaticojejunostomy end-to end	33 (25.8%)	16 (24.6%)	17 (27%)	0.75
Pancreaticogastrostomy	21 (16.4%)	10 (15.4%)	11 (17.5%)	0.75
Intraoperative transfusion	6 (4.7%)	3 (4.6%)	3 (4.8%)	0.96
Clavien-Dindo > IIIa	43 (33.6%)	15 (23.1%)	28 (44.4%)	0.03
Mortality	11 (8.5%)	4 (6.1%)	7 (11%)	0.31
Delayed gastric emptying	5 (3.9%)	4 (6.2%)	1 (1.6%)	0.18
Biliary leak	8 (6.2%)	2 (3.1%)	6 (9.5%)	0.13
Postoperative pancreatic fistula	37 (28.9%)	12 (18%)	25 (39.7%)	0.008
Biochemical	15 (11.7%)	4 (6.2%)	11 (17.5%)	
Tipe B	4 (3.1%)	3 (4.6%)	1 (1.6%)	
Tipe C	18 (14.1%)	5 (7.7%)	13 (20.6%)	
PPF B + C	22 (17.2%)	8 (12.3%)	14 (22.2%)	0.02
Postpancreatectomy hemorrhage	20 (15.6%)	8 (12.3%)	12 (19%)	0.29
Reoperation	26 (20.3%)	8 (12.3%)	18 (28.6%)	0.02

150 cc (IQR = 0–325), respectively. No differences were found in the POBF (p = 0.477) or POPF rates (p = 1) of patients with a non-functioning stent vs. a functioning one.

Discussion

PD is a surgical technique with a high morbidity rate (approximately 20–50%) and a mortality rate of up to 20%; however, in recent years, the outcome of this procedure is improving as it becomes more specialized [14]. POPF remains the most common complication with high associated morbidity and mortality rates, thus being a frequently discussed topic in medical literature. The incidence rate of POPF varies depending on the series studied (with ranges 2–51%).[15] The main purpose of our study has been to assess the postoperative complications and their severity after placing a transanastomotic biliary stent, with the initial hypothesis that the physical separation of biliary and pancreatic secretions would preclude the development of complex fistulae. POPF was seen in 37 of the 128 operated patients (28.9%). This number is consistent with other studies.[16, 17] Out of the 37 patients with POPF, 15 (11.7%) had a biochemical leak, whereas 22 (17.2%) experienced grade B and C PFs. The rate of grade A fistulae/biochemical leak according to McMillan et al. is around 42%.[17] In high-volume pancreatic surgery centers, the rate of grade B–C POPFs is 2–20%.[18] Results in our study for the POPF grade (biochemical leak vs. clinical fistula) showed that 11 patients (17.5%) in the PD-BS study group had a biochemical leak, whereas 14 patients (22.2%) had a clinical (grade B–C) fistula. These rates are in the upper end of the ranges typically found in literature, although it is hard to compare different studies since not all of them look at the amylase levels in drain fluid or follow the same definition of POPF. In our series, we used the definition by the International Study Group on Pancreatic Surgery (ISGPS) because we believed it best to help homogenize results. In the ST-PD group, a biochemical leak was found in 4 patients (6.2%), whereas a clinical fistula was seen in 8 patients (12.3%), which is a statistically significant difference (p = 0.02). These findings oppose our initial hypothesis given we assumed that mixed biliary and pancreatic secretions could contribute to more severe fistulae, should they occur, but it was not the case. In fact, results are statistically significant and point to the opposite: placement of a transanastomotic biliary stent seemingly has more adverse effects when considering the severity of potential fistulae. We have yet to find a clear explanation for this outcome but it paves the way for future research looking into whether the impact of an intraluminal foreign body or the surgical manipulation involved in the procedure could be contributors behind such a significant increase in the morbidity rate. It is possible that the intraluminal foreign body could alter the motility and cause distension and impaired function, increasing the risk of fistula. However, our study data are not sufficient to conclude that this is what happened.

Of the anastomoses performed in PDs, pancreatic anastomosis is the one with the highest rate of complications and associated mortality.[1] A randomized, prospective study by Berger et al. on 197 patients concluded that duct-to-mucosa pancreaticojejunostomy had a higher fistula rate than an invaginated pancreaticojejunal anastomosis (24% vs. 12%; p = 0.04).[19] An alternative reconstruction technique for the pancreatic-digestive tract is the pancreaticogastrostomy. Menahem et al.'s meta-analysis concluded that this technique had a lower POPF and POBF incidence rate, as well as a shorter average length of stay with no statistically significant differences in rates of DGE, or overall morbidity and mortality.[20] A different randomized, prospective study by Figueras-Sabater corroborated that pancreaticogastrostomy resulted in lower POPF rates (p = 0.014) and less severe than pancreaticojejunostomy (p = 0.006).[21] In our series, the most common technique employed was duct-to-mucosa pancreaticojejunostomy; however, this was not the only type of anastomosis performed, which can be a limiting factor in our study. According to our findings, 21 patients (56.8%) developed a POPF after duct-to-mucosa anastomosis, while the same was true for 9 patients (24.3%) after an invaginated pancreaticojejunostomy. These results are consistent with Berger's study.[19] In Berger's study, 7 patients (18.9%) developed a POPF after a pancreaticogastrostomy, all of which were grade A. However, this is inconsistent with the findings by other authors, such as Keck et al., who in their RECOPANC study report that the grade B/C PF rates are similar between both pancreaticogastrostomy and pancreaticojejunostomy groups.[16] As mentioned above, another potential complication is a bilioenteric fistula or biliary fistula (BF). Its incidence rate ranges between 3 and 6% of complications after a PD and there are multiple factors that may contribute to the development of this type of fistula, albeit not being clearly defined.[22] For Antolovich et al., this finding may be associated with the previous use of neoadjuvant therapy,[23] whereas other authors point to a single contributing factor: the diameter of the bile duct being less than 5 mm.[22] In our series, POBF was seen in 8 patients (6.3%, 6 of whom were in the PD-BS study group and the other 2 in the ST-PD group (9.5% vs 3.1%; p = ns). In light of these numbers and contrary to our initial assumption, we can conclude that systematic placement of a biliary stent does not prevent the development of a POBF. We found no statistical connection between the bile duct diameter and the incidence rate of POBF, although we only considered a diameter ≥ 10 mm, which is larger than that used by other authors.[22]

Hemorrhage is a very dreaded complication. Its incidence according to the different series ranges somewhere between 5

and 12%.[24] Advanced age, elevated bilirubin levels, and the development of a PF are risk factors for postoperative intra-abdominal hemorrhage.[25] This complication was seen in 20 of our patients (15.6%), 12 of whom were in group PD-BS and the remaining 8 in group ST-PD (19% vs. 12.3%; [p = 0.29]). Therefore, we cannot conclude that the use of a transanastomotic biliary stent has any impact on the occurrence of postoperative bleeding.

We observed intra-abdominal abscesses in 29 patients (22.7%), 17 of whom were in group PD-BS and the other 12 in group ST-PD (27% vs. 18.5%; p = NS), which seemingly reflects a greater tendency to abscess development with the use of a stent, likely justified by the greater PF rate seen in this group. This number is higher than the one reported by other studies.[26] Reoperation during the postoperative period after PD may be required, with hemorrhage being the most frequent reason, followed by POPF.[27] Reoperation is associated with an increased average length of stay, an increase in the mortality rate, and other complications such as DGE, POPF, and postoperative hemorrhage.[28] In our series, 18 patients (28.6%) had to undergo reoperation, with POPF as the most common cause. These numbers are higher than those reported in literature[27, 28] and give us an opportunity to reflect on the management of complications and prioritize the use of interventional radiology techniques, reserving surgical approaches for when these fail.

A consequence of all the complications described above is the potential of death, which has typically been high with PDs despite its decline in recent years in highly specialized, high-volume pancreatic surgery centers.[29, 30] In our series, postoperative mortality was 8.6%, which may seem high when compared to controlled and randomized studies with reported rates of 4.9–7.8%.[16, 21, 31] Nevertheless, these numbers are not reproducible in recorded case studies. For example, Nimptsch et al.'s study looks at over 58,000 patients who underwent pancreatic surgery in Germany 2009–2013, with a hospital overall mortality rate of 10.1%. In this study, major pancreatic resection was associated with a higher mortality rate, ranging from 7.3% (distal pancreatectomy) to 22.9% (total pancreatectomy). In addition, Whipple PDs were performed in 10,341 patients with a mortality rate of 10.2%.[32] These numbers suggest that the actual mortality rate of this procedure is likely underestimated.

Our study has several limitations: first, the sample size is limited; thus, interpretation of some of the results may be biased. Second, four surgeons were part of the study. Although every surgeon in our team is experienced, we believe that all surgical techniques may have technical execution differences that may contribute to a certain degree of heterogenicity. Similarly, the surgical team had a free choice to select the type of anastomosis to be performed, which is likely the largest limiting factor in our study, since having a specific type of anastomosis would have made both study groups more homogeneous. Nevertheless, this study paves the way for future research that aims to continue to reduce PF and other complication rates, as well as analyze the specific impact of placing an intraluminal foreign body and of surgical manipulation itself on postoperative complications.

Conclusions

Despite the limitations, according to our results, we can conclude that systematic placement of an external, transanastomotic, biliary stent does not reduce the rate of POPF or POBF, or their severity; in fact, the likelihood of these types of fistula, particularly POPF, increases with this procedure.

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Author Contribution GBF: design of the work, data collection and analysis, drafting the work and revising it critically for important intellectual content, final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

IJT: data collection and analysis, drafting the work and revising it critically for important intellectual content, final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DLG: design of the work, data collection and analysis, drafting the work and revising it critically for important intellectual content, and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability All data generated or analyzed during this study are included in this published article. I confirmed that the data are real and you can get them by consulting the corresponding author.

Declarations

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethical Committee of our institution.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication All authors of the study have consented for the publication of this work.

Conflict of Interest The authors declare no competing interests.

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