

Endoscopic Retrograde Biliary Drainage Causes Intra-Abdominal Abscess in Pancreaticoduodenectomy Patients: An Important But Neglected Risk Factor

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ABSTRACT

Background. Patients with periampullary cancer frequently suffer obstructive jaundice and commonly require preoperative biliary drainage (PBD) for relief and to avoid related complications. Although research has established a correlation between PBD and surgical wound infection, the impact of PBD on major infectious complications (intra-abdominal abscess [IAA]) and overall mortality remains debatable. We hypothesized that PBD could lead to IAA and mortality, and evaluated their correlation in patients undergoing pancreaticoduodenectomy (PD).

Methods. We enrolled patients undergoing PD at an Asian academic medical center between 2007 and 2016. The types of PBD included endoscopic retrograde biliary drainage (ERBD) and percutaneous transhepatic cholangiography and drainage (PTCD). The primary outcome was IAA, defined as the presence of pus or infected fluid inside the abdominal cavity and with documented infectious pathogens.

Results. There was one (0.1%) 30-day mortality and eight (0.9%) 90-day mortalities among 899 consecutive patients examined. More than one-quarter of patients had PBD ($n = 237$, 26.4%; 165 ERBD, 72 PTCD). In the ERBD, PTCD, and non-PBD groups, the IAA rates were 37.0%,

16.7%, and 10.6%, respectively. On multivariate analysis, ERBD (odds ratio 3.67; 95% confidence interval 2.22–6.06; $p < 0.001$) was the only significant factor associated with IAA. No significant factor was found to analyze variables associated with mortality.

Conclusions. ERBD, but not PTCD, is associated with an increased risk of IAA in patients undergoing PD, which suggests that ERBD should be avoided whenever possible to prevent IAA. Further randomized clinical trials should be conducted to validate this relationship.

Periampullary cancers (PACs) are malignant diseases that develop near the ampulla of Vater, including cancer of the second part of the duodenum, head and neck of the pancreas, distal end of the common bile duct (CBD), and the ampulla of Vater.¹ Pancreaticoduodenectomy (PD) is the only potentially curative modality for PACs. Obstructive jaundice, the leading symptom in patients with PAC, impairs liver T lymphocytes and mononuclear cell function in mice models, thereby resulting in susceptibility to infection. In particular, it exacerbates the risk of PD infectious complications and mortality in clinical practice.^{2,3} Consequently, most patients with jaundice undergo preoperative biliary drainage (PBD) to restore biliary flow, including percutaneous transhepatic cholangiography and drainage (PTCD) or endoscopic retrograde biliary drainage (ERBD), to improve immunity and nutrition.⁴

However, recent studies have challenged the routine preoperative placement of biliary stents, which correlated with higher rates of infectious complications and mortality.^{5–9} The rationale for elevated infectious complication rates in patients undergoing PBD could be attributed to the insertion of foreign-body stents, causing dissemination of infectious pathogens from the duodenum due to

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sphincterotomy-related reflux cholangitis with ERBD or from patients' skin by PTCD.¹⁰ The aforementioned risks deteriorate the immune system and increase infectious events, and patients with PD require treatment with intravenous antibiotics to control these secondary and potentially recurrent events. Even worse, patients may have colonization with antimicrobial-resistant microorganisms.

In this study, we assessed the correlation of PBD types with intra-abdominal abscess (IAA; a major infectious complication) and overall mortality in patients with PD.

METHODS

The Ethics Committee of the National Taiwan University Hospital approved this single-center, retrospective study protocol (201803035RIND). Of 910 consecutive patients scheduled to undergo PD between January 2007 and December 2016, we retrieved data from a retrospective review of a prospectively maintained database.¹¹ We excluded 11 cases because the patients underwent ERBD and PTCD concomitantly. We defined PAC according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and pathologic report, as follows: pancreatic ductal adenocarcinoma (PDAC; ICD-9-CM code 157.0), distal CBD cancer (code 156.1), ampulla of Vater cancer (code 156.2), and duodenal cancer (code 152.0). We then used the Charlson Comorbidity Index (CCI) to calculate further scores for each patient.¹² Biliary drainage was achieved via endoscopic placement of a plastic or metal stent. Antibiotic prophylaxis consisted of intravenous cefmetazole 1 g before PD and every 3 h during surgery. In cases of allergy, we used intravenous ciprofloxacin and metronidazole.

Biliary Drainage Procedures

PBD was performed either through ERBD (endoscopic sphincterotomy and placement of an endobiliary stent into the CBD by endoscopic retrograde cholangiopancreatography [ERCP]) or PTCD of the biliary tract under radiologic guidance.^{13,14} A therapeutic duodenoscope (TJF-180 V; Olympus Corporation, Tokyo, Japan) was used to perform ERCP.

Intra-Abdominal Abscess and Overall Mortality

IAA was defined as a culture-positive fluid collection from percutaneous drainage,⁸ and the postoperative pancreatic fistula was defined according to the 2016 International Study Group of Pancreatic Surgery.¹⁵ The overall 30- or 90-day mortality included all deaths occurring within 30 or 90 days postoperatively, and duration of hospital stay.

Statistical Analysis

In this study, all statistical analyses were performed using SPSS version 23 (IBM Corporation, Armonk, NY, USA). Data are presented as mean (standard deviation [SD]), number (percentage), or odds ratio (OR) and 95% confidence interval (CI). We compared categorical variables using the Chi-square test or Fisher's exact test if the numbers were < 5. Conversely, continuous data were compared using the nonparametric Mann-Whitney *U* test, and some continuous variables were dichotomized according to predetermined thresholds, which were analyzed as categorical variables. In addition, we performed logistic regression analysis to assess the correlation between types of PBD and IAA/overall mortality, adjusting for clinicopathologic, laboratory, and preoperative antibiotic use. All statistics were two-tailed, and differences were considered statistically significant at $p < 0.05$.

RESULTS

Intra-Abdominal Abscess

Of 899 patients with PD, 56% were males. Mean age at surgery was 62 years. In addition, 237 (26.4%) patients underwent PBD before PD, including 165 ERBD (18.4%) and 72 PTCD (8.0%) procedures. PBD-related immediate adverse effects included cholangitis (Tokyo Guidelines 2013¹⁶), pancreatitis (abdominal pain and pancreatic enzyme levels \geq threefold higher than the upper normal limit), bleeding (clinical evidence of bleeding with the need for intervention or blood transfusion), or bowel perforation (free air located in the abdominal cavity revealed by radiography).^{17,18} Of the 165 patients with ERBD, 33 (20.0%) had immediate adverse effects (16 had cholangitis, 8 had pancreatitis, 8 had bleeding, and 1 had bowel perforation). In contrast, of the 72 patients with PTCD, 15 (20.8%) had immediate adverse effects (8 had cholangitis, 1 had pancreatitis, and 6 had bleeding). There were no significant differences between the two groups.

Furthermore, we categorized the study population into two groups (PBD and non-PBD groups) (Table 1). Mean age (65.2 vs. 60.4 years; $p < 0.001$) and maximal preoperative serum bilirubin level (10.5 vs. 2.8 mg/dl; $p < 0.001$) were higher in the PBD group than in the non-PBD group. Furthermore, higher proportions of CCI score > 2 (79.3% vs. 62.4%; $p < 0.001$), PAC (67.5% vs. 48.6%; $p < 0.001$), and antibiotic use within 1 month before PD (81.9% vs. 45.6%; $p < 0.001$) were observed for the PBD group compared with the non-PBD group. The data implied that PBD patients were more ill compared with those in the non-PBD group. Regarding outcomes, the PBD group exhibited higher IAA (30.8% vs. 10.6%;

TABLE 1 Comparison of the study subjects with and without preoperative biliary drainage

	PBD group [<i>n</i> = 237]	Non-PBD group [<i>n</i> = 662]	<i>p</i> value
Age, years [mean (SD)]	65.2 (12.7)	60.4 (13.5)	< 0.001
Sex			
Female	101 (42.6)	316 (47.7)	0.180
Male	136 (57.4)	346 (52.3)	
BMI [mean (SD)]	23.3 (3.5)	23.4 (3.5)	0.580
Pre-PD maximal value of serum total bilirubin, mg/dl [mean (SD)]			
Any time	10.5 (8.3)	2.8 (5.1)	< 0.001
Within 2 days	3.0 (3.1)	2.7 (5.5)	0.420
Pre-PD use of antibiotics			
≥ Third-generation antibiotics [ref: no]	102 (43.0)	189 (28.5)	< 0.001
Within 30 days [ref: no]	194 (81.9)	302 (45.6)	< 0.001
Charlson Comorbidity Index score			< 0.001
≤ 2	49 (20.7)	249 (37.6)	
> 2	188 (79.3)	413 (62.4)	
Periampullary cancer	160 (67.5)	322 (48.6)	< 0.001
Pancreatitis history	31 (13.1)	123 (18.6)	0.054
Length of hospital stay, days [mean (SD)]	32.4 (22.9)	27.3 (19.3)	< 0.001
Operation time, min [mean (SD)]	348.0 (118.8)	359.2 (130.8)	0.250
Blood loss, ml [mean (SD)]	275.5 (443.5)	240.2 (670.0)	0.450
Postoperative pancreatic fistula ^a	29 (12.2)	85 (12.8)	0.560
Intra-abdominal abscess	73 (30.8)	70 (10.6)	< 0.001
30-day overall mortality	1 (0.4)	0 (0.0)	0.094
90-day overall mortality	5 (2.1)	3 (0.5)	0.020

Data are expressed as *n* (%) unless otherwise specified

BMI body mass index, PD pancreaticoduodenectomy, PBD preoperative biliary drainage, SD standard deviation

^aThe 2016 update of the International Study Group definition and grading of postoperative pancreatic fistula

$p < 0.001$) and 90-day mortality (2.1% vs. 0.5%; $p = 0.020$) rates compared with the non-PBD group. We then divided PBD into three categories (non-PBD, ERBD, and PTCD) in the multivariate models (Table 2) because of their distinct procedures. ERBD (OR 3.67, 95% CI 2.22–6.06; $p < 0.001$) was the only significant factor contributing to IAA.

Overall Mortality

In this study, we observed one (0.1%) 30-day and eight (0.9%) 90-day mortalities among 899 consecutive patients with PD. The cause of mortality was IAA-related septic shock in five patients (62.5%), hepatic failure in one patient (12.5%), myocardial infarction in one patient (12.5%), and bowel necrosis in one patient (12.5%). In addition, we selected 90-day mortality as an endpoint for analysis (Table 3). Mean age in the 90-day mortality group was higher than that in the survival group (72.0 vs. 61.5 years, $p = 0.029$). On multivariate analysis, no variable was associated with 90-day mortality (Table 4).

DISCUSSION

Reportedly, IAA is a major surgical complication that warrants prompt antibiotic treatment, prolonged hospital stays, or interventional drainage, otherwise sepsis/septic shock could occur, posing a danger to patient life.¹⁹ This retrospective study assessed whether ERBD or PTCD before PD correlated with a higher rate of IAA or mortality. Although PBD was not associated with mortality, this study illustrated that ERBD, but not PTCD, was the only significant risk factor contributing to IAA development.

To date, several studies have addressed the correlation between PBD and IAA,^{8,20,21} which are consistent with our findings. In addition, recent studies supported the cause-effect correlation between bile contamination and surgical infectious complications^{4,20} because bacterial cultures of infected wounds exhibited a strong correlation with microorganisms found in bile cultures obtained during PD.^{22,23} PD is a complicated procedure involving resection of the distal CBD and pancreatic head followed by

TABLE 2 Adjusted multivariate analysis to predict intra-abdominal abscess

	OR	95% CI	<i>p</i> value
PBD methods (ref: non-PBD)			
ERBD	3.67	2.22–6.06	< 0.001
PTCD	1.17	0.55–2.50	0.676
Age	1.00	0.99–1.02	0.488
Female	1.02	0.69–1.49	0.907
BMI	0.97	0.92–1.03	0.396
CCI score ≥ 2 (ref: CCI < 2)	1.72	1.05–2.82	0.029
Periampullary cancer (ref: no)	1.02	0.66–1.56	0.915
Pancreatitis history (ref: no)	0.73	0.41–1.31	0.302
Pre-PD maximal value of serum total bilirubin			
Any time	1.00	0.96–1.04	0.734
Within 2 days	0.96	0.89–1.03	0.288
Pre-PD use of antibiotics			
\geq Third-generation antibiotics (ref: no)	1.17	0.78–1.76	0.420
Within 30 days (ref: no)	1.56	1.01–2.39	0.060
Postoperative pancreatic fistula ^a (ref: no)	1.06	0.60–1.85	0.837

CI confidence interval, BMI body mass index, PBD preoperative biliary drainage, ERBD endoscopic retrograde biliary drainage, PTCD percutaneous transhepatic cholangiography and drainage, CCI Charlson Comorbidity Index, OR odds ratio, PD pancreaticoduodenectomy

^aThe 2016 update of the International Study Group definition and grading of postoperative pancreatic fistula

construction. Furthermore, at our institute, the proximal CBD is left unclamped before choledochojejunostomy to prevent cholestasis,¹¹ so that bile contamination may spread from the bile duct to the abdominal cavity. In contrast to PTCD, ERBD accounted for more episodes of ascending cholangitis from contamination of enteral pathogens due to sphincter of Oddi dysfunction (sphincterotomy/biliary stenting with ERBD), which may partially explain the correlation between PBD and IAA.

However, several other series reported that PBD did not elevate the IAA rate.^{4,24} The disparity in results could be explained by two reasons. First, a diverse definition of the diagnostic criteria was used in clinical research. Some studies defined IAA based on a radiologically proven collection with clinical febrile episodes. In this study, we used a stricter definition with documented microorganism cultures rather than solely fluid accumulation, which was a common presentation in PD patients because of the occurrence of a pancreatic fistula. Second, the strategy of using antibiotics during PD could affect the surgical infectious outcomes. A study investigating the ascites cultures at the end of a large volume of normal saline irrigation (7000 mL) in patients with PD reported that 21.1% of the patients exhibited positive colonization of ascites, which correlated with the risk of surgical infectious complication.²⁵ This aforementioned report implied that occult microorganisms still existed inside the abdominal

cavity so the appropriate use of perioperative antibiotics might attenuate the abdominal cavity contamination and affect IAA occurrence.

Regarding the effect of PBD on mortality, some series reported higher mortality rates in patients undergoing PBD,^{6,26} whereas some review articles revealed that PBD did not exert a substantial impact on overall mortality.^{1,24,27} Notably, the mortality rate in the reports mentioned above could be as high as 12%,²⁶ which was almost sixfold that at high-volume centers (approximately 2%). Owing to complex PD, the quality of surgical skills also interfered with clinical outcomes. In addition, other considerable variations, such as the PBD method, time from drainage to PD, or etiology for PD, existed in published studies, which interfered with these conflicting results. Although PBD did not correlate with mortality, restriction of biliary stenting is extensively advocated with strong clinical evidence.⁵ The current indication for using PBD to relieve jaundice is neoadjuvant therapy, extended waiting periods for PD, or frequent cholangitis.^{25,28}

Traditionally, both ERBD and PTCD were considered as PBD in clinical studies, although the two procedures might have contrary outcomes owing to the drainage mechanisms. For example, pancreatitis mainly occurs after ERBD because of difficult cannulation, sphincterotomy, and unintentional main pancreatic duct injection.²⁹ Notably, during the study period, three planned Whipple operations were converted to biliary bypass because of severe tissue adhesion and friability associated with ERBD-related

TABLE 3 Both potential clinical demographics and postoperative complications associated with 90-day overall mortality

	90-day mortality		<i>p</i> value
	No [<i>n</i> = 891]	Yes [<i>n</i> = 8]	
Age, years [mean (SD)]	61.5 (13.5)	72.0 (9.6)	0.029
Sex			0.840
Female	413 (46.4)	4 (50.0)	
Male	478 (53.6)	4 (50.0)	
BMI [mean (SD)]	23.4 (3.5)	23.5 (4.5)	0.920
Pre-PD maximal value of serum total bilirubin, mg/dl [mean (SD)]			
Any time	4.8 (7.0)	8.1 (6.8)	0.190
Within 2 days	2.8 (5.0)	3.5 (2.7)	0.700
Pre-PD use of antibiotics			
≥ Third-generation antibiotics (ref: no)	285 (32.0)	6 (75.0)	0.010
Within 30 days (ref: no)	491 (55.1)	5 (62.5)	0.680
Charlson Comorbidity Index score			0.210
≤ 2	297 (33.3)	1 (12.5)	
> 2	594 (66.7)	7 (87.5)	
Periampullary cancer	477 (53.5)	5 (62.5)	0.610
Pancreatitis history	153 (17.2)	1 (12.5)	0.730
PBD method			0.051
Non-PBD	659 (74.0)	3 (37.5)	
ERBD	162 (18.2)	3 (37.5)	
PTCD	70 (7.9)	2 (25.0)	
Length of hospital stay, days [mean (SD)]	28.5 (20.2)	53.3 (27.7)	< 0.001
Operation time, min [mean (SD)]	356.4 (128.1)	341.5 (97.2)	0.740
Blood loss, ml [mean (SD)]	251.2 (620.8)	62.5 (35.4)	0.390
Postoperative pancreatic fistula ^a	112 (12.6)	2 (25.0)	0.051
Intra-abdominal abscess	141 (15.8)	2 (25.0)	0.480

Data are expressed as *n* (%) unless otherwise specified

BMI body mass index, *PD* pancreaticoduodenectomy, *PBD* preoperative biliary drainage, *ERBD* endoscopic retrograde biliary drainage, *PTCD* percutaneous transhepatic cholangiography and drainage, *SD* standard deviation

^aThe 2016 update of the International Study Group definition and grading of postoperative pancreatic fistula

pancreatitis (not included in this study). Furthermore, cholangitis was more common after ERBD, which caused a retrograde influx of duodenal content into the biliary tree and malfunction of biliary stents. Recently, some studies showed that the outcomes after ERBD differed from those after PTCD in patients with hilar cholangiocarcinoma undergoing PBD.^{30,31} Our findings provide an indication of whether outcomes might differ between these two procedures in PAC patients. A randomized controlled trial (RCT) comparing ERBD and PTCD may be required to reach a definitive conclusion. Owing to the diverse presentation of PAC, PDAC patients should be considered as the main study population. The primary outcome parameter was the rate of occurrence of preoperative PBD-related complications during the interval period up to surgery (cholangitis, pancreatitis, bleeding, bowel perforation, or

stent-related occlusion), while the secondary endpoints were postoperative surgical complications, such as wound infection, pancreatic fistula, IAA, or mortality. However, several factors associated with the aforementioned outcomes should be adjusted, including the serum bilirubin level, waiting time for surgery, biliary stent type (plastic vs. metal), stent size, and prophylactic antibiotic regimen before PBD.

This study has the following strengths and limitations. The study design was retrospective and was conducted at a single institute, therefore the findings may not be generalizable. Large, prospective, randomized clinical trials are warranted to validate the correlation between PBD and IAA; however, this is challenging to execute because most patients receive PBD before presenting to surgeons. Furthermore, studies should enroll large case numbers because

TABLE 4 Adjusted multivariate analysis to predict 90-day overall mortality

	OR	95% CI	<i>p</i> value
PBD methods (ref: non-PBD)			
ERBD	3.12	0.45–21.58	0.248
PTCD	5.41	0.59–49.30	0.134
Age	1.06	0.98–1.15	0.102
Female	0.85	0.20–3.63	0.835
BMI	1.00	0.81–1.24	0.956
CCI score ≥ 2 (ref: CCI < 2)	2.72	0.29–24.95	0.374
Periampullary cancer (ref: no)	0.77	0.16–3.73	0.754
Pancreatitis history (ref: no)	1.62	0.17–15.20	0.669
Pre-PD maximal value of serum total bilirubin			
Any time	0.98	0.88–1.10	0.799
Within 2 days	1.02	0.87–1.19	0.768
Pre-PD use of antibiotics			
\geq Third generation antibiotics (ref: no)	4.32	0.82–22.64	0.083
Within 30 days (ref: no)	0.58	0.11–3.07	0.527
Intra-abdominal abscess	1.27	0.23–6.91	0.775
Postoperative pancreatic fistula ^a (ref: no)	0.78	0.08–7.27	0.832

CI confidence interval, PBD preoperative biliary drainage, ERBD endoscopic retrograde biliary drainage, PTCD percutaneous transhepatic cholangiography and drainage, BMI body mass index, CCI Charlson Comorbidity Index, OR odds ratio, PD pancreaticoduodenectomy

^aThe 2016 update of the International Study Group definition and grading of postoperative pancreatic fistula

of the stratification of key factors. Consequently, the data from a consecutive collection of PD provided complementary information to address this issue. Moreover, the overall surgical quality (90-day mortality rate of 0.9%) in this study was comparable with that of other large series,^{22, 24} and this is one of the largest series analyzing PBD (ERBD vs. PTCD) with IAA and overall mortality with the adjustment of potential confounders (e.g. pathologic factor, serum bilirubin levels, or antibiotic use). Next, the choice of biliary stent (plastic vs. metal stents) during ERBD may interfere with the surgical outcomes because metal stents are associated with a higher rate of stent patency.¹⁸ Of the 165 patients with preoperative ERBD, only 10 received a metal stent. We could not perform a subgroup analysis between plastic and metal stents because of the extremely different sample size. Currently, we prefer metal stents for patients in whom neoadjuvant therapy is planned. Further works should be conducted to validate this relationship. Finally, the selection of the PBD method might have been biased by the nature of PACs. ERBD commonly fails because of severe biliary stenosis due to external compression of the cancer or duodenal stenosis, and PTCD becomes a rescue procedure to relieve cholestasis. Although our results favored PTCD, ERBD would be more comfortable and physiologically appropriate for patients in whom neoadjuvant therapy is planned. In this study, only four patients underwent the Whipple operation after

neoadjuvant therapy, all of whom had undergone ERBD (three plastic stents and one metal stent) to prevent hepatotoxicity from chemotherapeutic agents.

CONCLUSIONS

Our study provided further evidence that patients undergoing ERBD before PD are more likely to suffer IAA. This suggested that ERBD should be avoided whenever possible to prevent IAA. Further randomized clinical trials should be conducted to validate this relationship.

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