

Influence of periampullary diverticula on endoscopic retrograde cholangiopancreatography

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Abstract. The present study aimed to explore the influence of the presence of periampullary diverticula (PAD) on the implementation of endoscopic retrograde cholangiopancreatography (ERCP). A total of 388 patients with pancreaticobiliary disease who underwent ERCP for the first time between January 2017 and December 2018 were included and they were divided into a PAD group (n=179) and non-PAD (N-PAD) group (n=209) according to the presence or absence of PAD. A logistic regression model was used to analyze the risk factors for PAD. The prevalence of PAD in males was higher than that in females [odds ratio (OR)=2.250, 95% CI: 1.670-3.801]. The prevalence of PAD in patients with bile duct stone was 57.92% and higher than that in patients without stone (OR=4.475, 95% CI: 2.932-7.679). The morbidity of PAD in elderly patients with bile duct stone was higher than in those without stone (OR=6.728, 95% CI: 3.790-11.943). Among the elderly patients, the constituent ratio of males in the PAD group was higher than that in the N-PAD group ($\chi^2=13.543$, $P<0.001$). The constituent ratio of patients who underwent endoscopic sphincterotomy (EST) was lower than that in the N-PAD group ($\chi^2=10.800$, $P<0.001$). In conclusion, the occurrence of PAD was high in elderly males and closely related to the occurrence of bile duct stones.

Introduction

Periampullary diverticula (PAD) or peripapillary diverticula are saccular structures of the duodenal outpouchings, arising within a range of 2-3 cm around the ampulla of Vater (1). Relevant studies have reported that PAD are difficult to identify in patients aged <40 years and the prevalence of PAD increases with advancing age (2-5). Although the presence of PAD is usually asymptomatic, it may increase the occurrence of

diseases such as pancreatitis or choledocholithiasis according to the specific anatomical structure between PAD and the major duodenal papilla and pancreaticobiliary ampulla (3,6). Age is considered to be a confounding factor, since the prevalence of diverticula and bile duct stones both increase along with age (7). Previous studies have demonstrated the association between PAD and the incidence of bile duct stones (8).

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the preferred methods for the diagnosis and treatment of extrahepatic biliary and pancreatic diseases. With the popularity and development of ERCP, the detection rate of PAD has been markedly improved. The estimated occurrence of PAD in patients undergoing ERCP is 10-20% (9), and the prevalence and diameter of PAD increase with age (2-4). However, the influence of PAD on ERCP for the treatment of biliary and pancreatic diseases remains controversial. Certain studies have indicated that the presence of PAD does not increase the risk of failure of selective cannulation (2); however, other studies have demonstrated that the presence of PAD increases the difficulty associated with ERCP and the risk of complications (8,10). Thus, further studies are required in order to fully determine the influence of PAD on ERCP.

In the present retrospective study, clinical and endoscopic data of patients with biliary and pancreatic diseases treated with ERCP over the past 2 years were collected and analyzed. The study was to evaluate the current situation of PAD and to examine the influence of the presence of PAD in elderly patients with bile duct stones who received ERCP treatment.

Materials and methods

Patients. The present single-center retrospective study was performed at the First Affiliated Hospital of Bengbu Medical College (Bengbu, China). The demographic data and details of the ERCP procedure in patients with pancreaticobiliary disease who underwent ERCP between January 2017 and December 2018 were obtained from the electronic ERCP database. Patients undergoing ERCP for the first time with complete information were included in the present study.

Patients who met the following criteria were excluded: i) History of choledochojunostomy; ii) a fistula in the major duodenal papilla; iii) incomplete records of clinical and/or accessory examinations.

A total of 388 included cases were divided into the PAD group (n=179) and the non-PAD (N-PAD) group (n=209).

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Subjects aged ≥ 60 years were defined as elderly (11). All patients with complete information from hospital records on general data, laboratory and imaging examination were used to determine the initial diagnosis and ERCP indications, and contraindications were excluded. This study was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College (Bengbu, China; approval no. 2019KY030).

Collection of baseline information. Baseline information, including sex, age and diseases, was first retrieved for the patients of the present study. Subsequently, the characteristics including age distribution were analyzed in patients with cholangiolithiasis.

Procedures. All ERCP procedures were performed or supervised by qualified physicians with >10 years of experience in ERCP. The duodenoscope (Olympus JF-260/TJF-260), CleverCut sphincterotome (Olympus Medical Systems Co. Ltd.), guide-wire, dilation balloon, extraction balloon, stone extractor, nasobiliary drainage, various types of biliopancreatic stents and related instruments were applied under X-ray fluoroscopy. The operators and patients received standard radiation protection. Patients received oral dimethicone 30 min prior to surgery and an intramuscular injection of anisodamine, meperidine and/or diazepam (depending on the age and general condition) 15 min prior to surgery for non-anesthetic sedation and analgesia pretreatment.

The position of the papilla was determined after the duodenoscope was moved to the descending part of the duodenum. The shape, opening and the presence of PAD were observed. The type, quantity and long diameter of PAD were recorded in patients with PAD. Conventional selective cannulation was performed using a cutting guide wire. Procedures including pancreatic guide wire-assisted biliary cannulation, pre-cut sphincterotomy, needle-knife fistulosphincterotomy and clip-assisted cannulation were performed when conventional intubation failed. After the guide wire entered the biliary duct, the biliopancreatic duct lesion and its position were confirmed according to the condition of contrast agent under X-ray fluoroscopy. The methods of opening and lithotomy included endoscopic sphincterotomy (EST), endoscopic papillary balloon dilatation (EPBD) and EST+EPBD. One of the three options was performed according to the number and the diameter of stones, and the position and the side bulge length of the papilla. After stone removal, the bile duct was examined by extraction balloon cholangiography to confirm the absence of residual stones. After the stone was removed, the operation of washing by noradrenaline in iced saline solutions, balloon compression and hemostasis using a metal clip was performed according to the papilla bleeding. The biliary stent was simply placed when stones were not able to be removed at one time. The types of PAD and the application of EPBD in PAD patients with bile duct stones are shown in Fig. 1. Of which, Fig. 1A is type I PAD (the duodenal papilla is located inside the diverticulum); Fig. 1B is type II PAD (the duodenal papilla lies at the margin of the diverticulum); Fig. 1C is type III PAD (the duodenal papilla is located near the diverticulum); Fig. 1D shows dilated sphincter using EPBD for type I PAD patients with bile duct stones; Fig. 1E shows the stone removal after EPBD treatment; and Fig. 1F shows that EPBD dilates the sphincter under the X-ray fluoroscopy.

Diagnostic criteria. The diameter of the depressed intestinal wall, which was >5 mm within 2-3 cm of the main nipple on the descending side of the duodenum, was defined as the PAD. The size and quantity of the diverticula were confirmed in relation to the scale of computed tomography and magnetic resonance cholangiopancreatography (MRCP) examination images combined with direct view images acquired with the endoscope with reference to the dilated balloon. A diverticulum with a length ≥ 3 cm was defined as a giant diverticulum, while a quantity ≥ 2 was defined as multiple diverticula (12).

Difficult biliary cannulation refers to the failure of conventional instruments and methods to enter the bile duct (>5 contacts with the papilla whilst attempting to cannulate or >5 min spent attempting to cannulate following visualization of the papilla or >1 unintended pancreatic duct cannulation or opacification) (13).

The criteria for sphincter of Oddi dysfunction (SOD) were as follows (14): i) Typical, episodic biliary or pancreatic pain; ii) >1.5 - to 2.0 -fold elevation in liver-associated enzymes (aminotransferases or alkaline phosphatase levels) or pancreatic enzymes (amylase or lipase) on at least 2 occasions during episodes of pain; iii) MRCP and ERCP revealed dilated common bile duct (bile duct diameter ≥ 10 mm) or main pancreatic ducts (pancreatic duct diameter ≥ 6 mm in the head and ≥ 5 mm in the body), and excluded other biliary and pancreatic diseases; iv) duodenal papillary sclerosis resulted in difficult dilatation and required high-pressure balloon sphincter stretching; v) following EST or sphincter stretching, the clinical symptoms improved significantly.

The definition of large balloon dilation is that the dilation of the columnar balloon in the papillary sphincter is ≥ 12 mm (15). ERCP-related adverse reactions, including pancreatitis, cholangitis, hemorrhage and perforation, were defined according to the American Society for Gastrointestinal Endoscopy guidelines (16).

Statistical analysis. SAS 9.4 software (SAS Institute Inc.) was used for statistical analysis. Count data are expressed as n(%) and the chi-squared test was used to analyze these data. Data with a normal distribution are expressed as the mean \pm standard deviation and the Student's t-test was adopted for the comparison of these data between groups. Univariate and multivariate logistic regression analyses were used to assess the influencing factors of PAD. $P < 0.05$ was considered to indicate a statistically significant difference.

Sample size calculation was performed according to the following formula:

$$N = \frac{2 \left(\frac{Z_{\alpha} + Z_{\beta}}{2} \right)^2 (\overline{pq})}{(P_0 - P_1)^2}$$

where P_0 is the incidence of bile duct stones in the N-PAD group and P_1 is the incidence of bile duct stones in the PAD group. Q is the mean value of $(1-P_0)$ and $(1-P_1)$. The sample proportion of the two groups was 1:1 and the total sample size was $n=2N$. In a previous study (17), $P_1=0.47$ and $P_0=0.16$ had been calculated and the required sample for each group was 70. The sample size in the present study was in accordance with this.

Table I. The characteristics of cases who received endoscopic retrograde cholangiopancreatography treatment between the two groups.

Variables	Total	N-PAD	PAD	Statistics	P-value
Age, mean \pm SD	67.60 \pm 14.71	63.91 \pm 15.58	71.91 \pm 12.34	t=-5.63	<0.001
Sex, n (%)				$\chi^2=19.766$	<0.001
Male	202 (52.06)	87 (41.63)	115 (64.25)		
Female	186 (47.94)	122 (58.37)	64 (35.75)		
Disease, n (%)				$\chi^2=24.002$	0.001
Pancreatic diseases	5 (1.29)	5 (2.39)	0 (0.00)		
SOD	13 (3.35)	8 (3.83)	5 (2.79)		
Ampullary and papillary tumors	15 (3.87)	14 (6.70)	1 (0.56)		
Malignant bile duct stricture	85 (21.91)	65 (31.10)	20 (11.17)		
Bile duct stones combined with cholecystolithiasis	17 (4.38)	7 (3.35)	10 (5.59)		
Bile duct stones combined with acute cholangitis	26 (6.70)	11 (5.26)	15 (8.38)		
Benign bile duct stricture	11 (2.84)	8 (3.83)	3 (1.68)		
Bile duct stones	216 (55.67)	91(43.54)	125 (69.83)		

SOD, sphincter of Oddi dysfunction; PAD, periampullary diverticula.

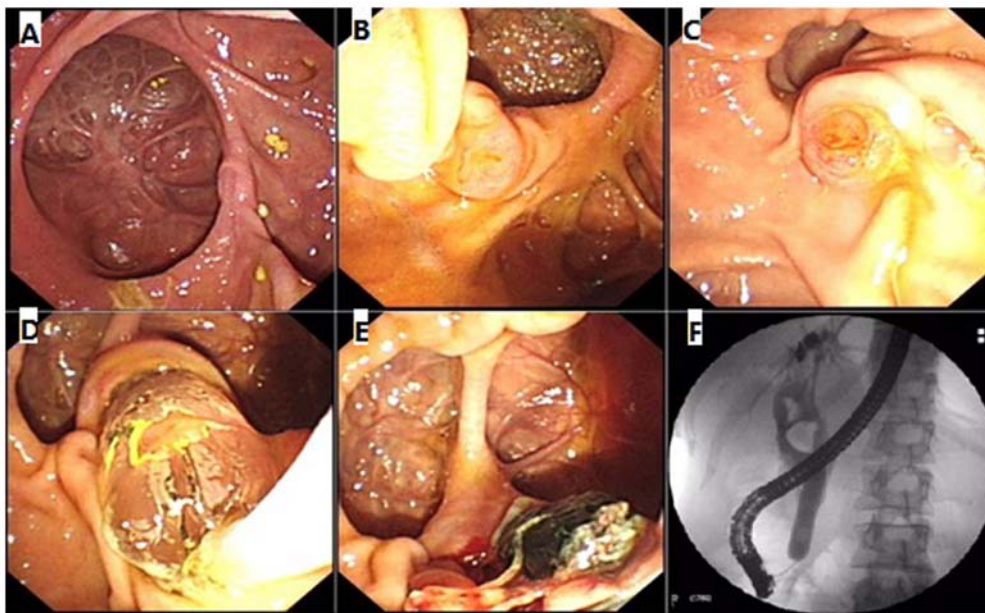


Figure 1. Papilla opening and lithotomy. (A) Type I PAD; (B) type II PAD; (C) type III PAD; (D) dilated sphincter by EPLBD; (E) stone removal; (F) EPLBD dilates the sphincter under the X-ray fluoroscopy. EPLBD, endoscopic papillary large balloon dilation; PAD, periampullary diverticula.

Results

Patients. A total of 388 patients with complete information who underwent ERCP for the first time were included, with a mean age of 67.60 \pm 14.71 years (range, 36-93 years), and the male to female ratio was 1.09. The mean age of the 179 patients in the PAD group was 71.91 \pm 12.34 years and that of the 209 cases in the N-PAD group was 63.91 \pm 15.58 years. There were statistical differences in age and sex between the PAD and N-PAD groups (Table I).

Prevalence of PAD in patients. In the present study, the prevalence of PAD was 56.93% (n=115) in males, 58.08% (n=150) in

subjects with age \geq 60 years and 57.87% (n=125) in cases with bile duct stones, respectively.

Univariate regression analysis for PAD. As shown in Table II, the differences were discovered regarding male (OR=2.250, 95% CI: 1.670-3.801), age \geq 60 years (OR=3.021, 95% CI: 1.855-4.902), ampullary and papillary tumors (OR=0.052, 95% CI: 0.007-0.403) between the PAD and N-PAD groups.

Multivariate binary logistic regression analysis for PAD. The results of the multivariate binary logistic regression indicated that the prevalence of PAD in males was 2.519-fold that in females (OR=2.519, 95% CI: 1.586-3.999). The risk of PAD

Table II. Univariate and multivariate binary logistic regression analysis for PAD.

Variables	OR (95% CI)	OR (95% CI)	P-value
Sex			
Male	2.250 (1.670-3.801)	2.519 (1.586-3.999)	<0.001
Female	Reference	Reference	
Age, years			
<60	Reference	Reference	
≥60	3.021 (1.855-4.902)	3.066 (1.798-5.228)	<0.001
Disease			
Pancreatic diseases	-	-	
SOD	0.455 (0.144-1.436)	0.727 (0.217-2.433)	0.605
Ampullary and papillary tumors	0.052 (0.007-0.403)	0.054 (0.007-0.429)	0.006
Malignant bile duct stricture	0.224 (0.127-0.396)	0.181 (0.099-0.330)	<0.001
Bile duct stones combined with cholecystolithiasis	1.040 (0.381-2.835)	0.841 (0.290-2.442)	0.751
Bile duct stones combined with acute cholangitis	0.993 (0.436-2.262)	1.176 (0.486-2.842)	0.719
Benign bile duct stricture	0.273 (0.070-1.057)	0.380 (0.091-1.591)	0.006
Bile duct stones	Reference	Reference	

SOD, sphincter of Oddi dysfunction; OR, odds ratio.

among the elderly was 3.066-fold that of younger patients (OR=3.066, 95% CI: 1.798-5.228). The occurrence of PAD in patients with malignant bile duct strictures was 0.181-fold that of bile duct stones (OR=0.181, 95% CI: 0.099-0.330; Table II).

Risk factors of PAD in elderly patients with bile duct stones.

Among elderly patients, the constituent ratio of males in the PAD group was significantly higher than that in the N-PAD group ($\chi^2=13.543$, $P<0.001$) and the constituent ratio of patients undergoing EST in the PAD group was lower than that in the N-PAD group ($\chi^2=10.800$, $P<0.001$). No statistically significant differences in papilla cannulation, maximum diameter of stone, multiplicity/property of stones, lithotomy status, mechanical lithotripsy, complications, common bile duct diameter and repeated intervention were observed between the two groups ($P>0.05$; Table III).

Discussion

PAD have gradually received increasing attention due to their specific location. With the in-depth development of ERCP, the detection rate of PAD has been greatly increased (9). The present study was performed to explore the current situation of PAD and to analyze the influence of the presence of PAD on the implementation of ERCP. The results confirmed that the prevalence of PAD in elderly patients (age, ≥60 years) was higher, indicating that the presence of PAD is significantly associated with age. The age-prone prevalence of PAD may be related to the deterioration of the muscular wall and the intestinal wall, the weakening of intestinal tone contraction, the slowing of peristalsis and the abnormal retention of intestinal contents in the elderly (5). To date, PAD has been insufficiently studied in elderly populations treated with ERCP. Regarding PAD in elderly patients with bile duct stones, univariate analysis and multifactorial analysis were performed in the present study in

order to further clarify the prevalence of PAD and the impact of PAD on ERCP.

The present study also indicated an association between the occurrence of PAD and sex, as the prevalence of PAD in males was higher than that in females, irrespective of the age of the patients. To the best of our knowledge, the present study was the first to determine that female sex may be a protective factor against PAD. Compared with that in patients with bile duct stones, the occurrence of PAD in patients with ampullary and papillary tumors and malignant bile duct stricture was lower. The prevalence of PAD in patients with bile duct stones was 57.92% and higher than in those without stone. The present results suggested that PAD are closely associated with the occurrence of bile duct stones and Sun *et al* (18) and Hall *et al* (19) also confirmed the relationship between PAD and bile duct stones. In the current study, analysis of patients with or without bile duct stones indicated that the difference in age between the PAD and the N-PAD group was mainly reflected in the population of bile duct stones and patients with bile duct stones exhibited a higher occurrence of PAD than other pancreatic biliary diseases.

The high prevalence of bile duct stones in patients with PAD may be due to the following: PAD causes SOD, resulting in inadequate drainage or regurgitation of bile and pancreatic juice; food deposition in the diverticulum easily occurs secondary to diverticulitis, causing constrictive papillitis, affecting the discharge of biliary sludge and increasing the incidence of retrograde biliary infection; exogenous glucuronidase increases the formation of free bilirubin, which combines with calcium salts to form the core of the stone and the pH value of the bile duct decreases when the bile duct is infected, which may promote the formation of pigment gallstones (20). Therefore, patients with bile duct stones aged ≥60 years were selected as the key research subjects in the present study in order to explore the effects of the presence of PAD on ERCP.

Table III. Effects of PAD in elderly patients with bile duct stones who received ERCP.

Variates	Total	Group, n (%)		χ^2	P-value
		PAD	N-PAD		
Sex				13.543	<0.001
Male	115	89 (68.99)	26 (41.27)		
Female	77	40 (31.01)	37 (58.73)		
Papilla cannulation				2.694	0.101
Difficult cannulation	30	16 (12.90)	14 (22.22)		
Routine cannulation	157	108 (87.10)	49 (77.78)		
Papilla cutting				10.800	0.001
Simple sphincter stretching	49	42 (33.33)	7 (11.11)		
EST	140	84 (66.67)	56 (88.89)		
Maximum diameter of stone, cm				4.240	0.120
1.0-1.9	112	79 (65.83)	33 (60.00)		
<1.0	42	24 (20.00)	18 (32.73)		
≥ 2	21	17 (14.17)	4 (7.27)		
Multiplicity/property of stones				1.359	0.507
Single	68	43 (34.13)	25 (39.68)		
Multiple	101	71 (56.35)	30 (47.62)		
Mud-like and not formed	20	12 (9.52)	8 (12.70)		
Lithotomy status				-	0.648
Partial stone extraction + biliary stent	10	8 (6.40)	2 (3.17)		
Complete stone extraction	168	111 (88.80)	57 (90.48)		
Biliary stent inserted without stone extraction	10	6 (4.80)	4 (6.35)		
Mechanical lithotripsy				0.619	0.432
Unsuccessful	166	109 (86.51)	57 (90.48)		
Successful	23	17 (13.49)	6 (9.52)		
Complications				-	0.162
Hemorrhage	1	0 (0.00)	1 (1.59)		
Cholangitis	153	106 (82.81)	47 (74.60)		
Pancreatitis	37	22 (17.19)	15 (23.81)		
Common bile duct diameter, cm				0.653	0.419
<1.50	63	40 (31.75)	23 (37.70)		
≥ 1.5	124	86 (68.25)	38 (62.30)		
Repeated intervention				-	0.150
No	177	116 (89.92)	61 (96.83)		
Yes	15	13 (10.08)	2 (3.17)		

PAD, periampullary duodenal diverticula; N-PAD group, patients without PAD; EST, endoscopic sphincterotomy

Selective cannulation of the bile duct through the main papilla is the primary method for ERCP lithotomy and the time and the route of cannulation influence the risk of post-ERCP pancreatitis (21). PAD has been reported to increase the difficulty and operating time of deep cannulation (19). However, the presence of PAD has also been determined to improve the success rate of intubation and to be an independent factor for easier cannulation (22). There was no significant effect on selective bile duct cannulation, even with stricter requirements and time limits for ERCP in elderly patients, and these results are supported by previous studies (22,23). In the present study, multivariate binary logistic regression analysis revealed that the risk of PAD in males was 2.519 times that of females

among the elderly. The means of papilla cutting were different in elderly patients with bile duct stones. The prevalence of elderly patients aged ≥ 60 years who were subjected to simple sphincter stretching was 4.593 times that of those who underwent EST. This result suggested that the presence of PAD may be associated with a decreased usage rate of EST.

Considering the difficulty associated with ERCP, the present study provided suggestions which may be used to circumvent the difficulties associated with ERCP and the following steps may be suggested: i) Careful and complete examination prior to ERCP; ii) risk assessment and implementation of preventive measures for complications prior to ERCP; iii) comprehensive evaluation of indications for ERCP with a strict control of

indications; iv) standardization of ERCP surgery; v) adequate preparation of ERCP operating consumables and instruments.

There are certain limitations to the present study that require to be mentioned: i) this was a retrospective single center study; ii) the conservative attitude of the physicians regarding subjective sphincter incision in patients with PAD. A larger sample size and a well-designed prospective randomized controlled trial are required to further confirm the results of the present study.

In conclusion, the present study indicated that the prevalence of patients with PAD was high among the elderly who received ERCP treatment, males exhibited a higher prevalence of PAD than females.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HZ and XD designed the study. HZ wrote the manuscript. SY and YX contributed to data collection. HZ and DL analyzed and interpreted the data. YX contributed to the literature search. XD critically reviewed the manuscript for important intellectual content. HZ, SY, YX and DL confirmed the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The research protocol was examined and approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College (approval no. 2019KY030).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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