Clinical Radiology 74 (2019) 735.e15–735.e22

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Peri-ampullary duodenal diverticulum: effect on extrahepatic bile duct dilatation after cholecystectomy

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ARTICLE INFORMATION

Article history:
Received 25 January 2019
Accepted 31 May 2019

AIM: To investigate the effect of peri-ampullary duodenal diverticula (PAD) on extrahepatic bile duct (EHBD) dilatation before and after cholecystectomy.

MATERIALS AND METHODS: During a 5-year period, a total of 860 consecutive patients with prior cholecystectomy were examined using abdominal computed tomography (CT). After exclusion of those with other obstructive EHBD lesions, 61 patients with PAD were recruited for evaluation of EHBD dilatation before and after cholecystectomy and were compared with a randomly sampled control group (n=113) without PAD. EHBD diameter was measured on coronal reconstruction CT using electronic callipers on the picture archiving and communication system monitors by two reviewers in consensus.

RESULTS: There was no significant difference in EHBD diameter between PAD and non-PAD groups (8.2±2.8 versus 7.8±2.3 mm; p=0.276) before cholecystectomy. Compared with preoperative diameter, EHBD was significantly dilated after cholecystectomy (7.9±2.5 versus 9.8±3.4 mm, $p<0.001$), regardless of the presence of PAD; the degree of change was more prominent in the PAD group than in the non-PAD group (3.3±2.4 versus 1.1±1.6 mm; $p<0.001$) after surgery. The size of PAD did not affect the degree of EHBD dilatation after cholecystectomy (p=0.522). In the non-PAD group, the degree of EHBD dilatation was positively correlated with the follow-up interval after cholecystectomy (r=0.298; p=0.002), while the PAD group showed no significant correlation (r=-0.036; p=0.797). In patients with ≥2 mm postoperative EHBD dilatation, PAD incidence was higher than that in other patients (odds ratio, 8.739; $p<0.001$).

CONCLUSION: Regardless of their size or postoperative follow-up duration, PAD induce marked post-cholecystectomy biliary dilatation.

Introduction

Duodenal diverticulum occurs commonly in the general population with an incidence that increases with age; the reported incidence rate was 22% in an autopsy series.[1,2] Peri-ampullary duodenal diverticula (PAD) are the most

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https://doi.org/10.1016/j.crad.2019.05.031
0009-9260/

common type of duodenal diverticula located within a radius of 2–3 cm from the ampulla of Vater.[3] With the increased use of endoscopy or abdominal computed tomography (CT), PAD are frequent incidental findings.[4,5] Although most PAD may not induce a clinical event other than occasional inflammation, rupture, or difficulty in cannulation of the common bile duct (CBD) during endoscopic retrograde cholangiopancreatography (ERCP), a possible association with biliary stone disease or pancreatitis has been suggested.[4–8]

It has been hypothesised that PAD could dilate the bile duct through mechanical compression on the distal CBD or dysfunction of the sphincter of Oddi, depending on their size or exact peri-ampullary location.[9–11] In a recent abdominal CT study, however, patients with PAD did not have a significantly larger CBD diameter compared with a control group without PAD, although there was an increased incidence of cholelithiasis and cholecystectomy in the PAD group[12]; however, functional bile duct dilatation occurs frequently after cholecystectomy due to the absence of the gallbladder, which acts as a reservoir of bile.[13] To the authors' knowledge, no study has compared the presence and degree of biliary dilatation before and after cholecystectomy in patients with and without PAD. The present study sought to investigate the effect of PAD on extrahepatic bile duct (EHBD) dilatation before and after cholecystectomy, and to identify possible clinical factors influencing post-cholecystectomy biliary dilatation in these patients.

Materials and methods

The study protocol was approved by the hospital institutional review board and informed consent was waived because of the retrospective nature of past clinical data analysis.

Patients

Patients who underwent cholecystectomy during a 5-year period (from January 2013 to December 2017) and who had pre- and postoperative CT examinations were screened using medical records in the institutional digital archive. Of 860 patients in the baseline population with both pre- and postoperative CT imaging data during the same period, 109 with PAD were initially identified from the imaging interpretation reports. Among the remaining patients without a finding of PAD on CT reports (n=751), 218 were randomly selected according to an earlier hospital registration of a control group (Fig 1). To define the PAD and non-PAD groups, patients with any of the following concomitant conditions were excluded: (1) other causes of obstruction such as biliary stones or tumours, enlarged lymph nodes around the EHBD, or mass lesions in and around the pancreatic head; (2) advanced gallbladder cancers causing undetected recurrences in the EHBD leading to biliary obstruction; (3) previous gastrectomy as another cause of biliary dilatation[14]; and (4) short follow-up interval (≤2 months) between cholecystectomy and postoperative CT examination (Fig 1). Finally, a total of 174 patients (89 men and 85 women aged 18–88 years, mean 63.2±11.8 years) were selected for further analysis.

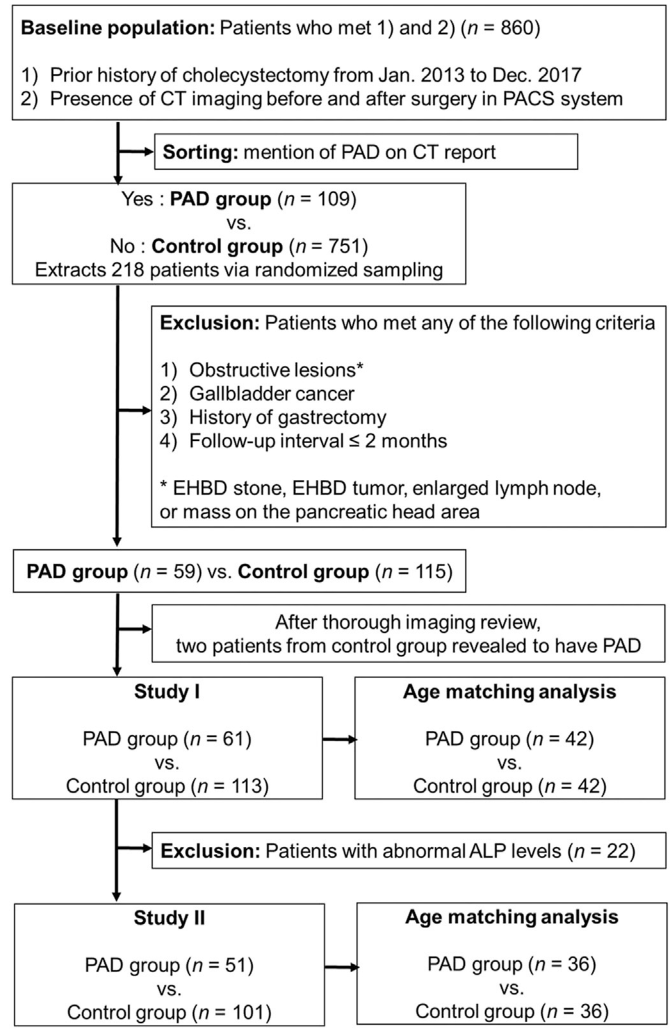

Figure 1 Flow diagram of inclusion in the study.

CT protocol

Pre- and postoperative abdominal CT examinations were performed using either a 16- or 64-section multidetector CT system (Somatom Sensation 16 or Somatom Sensation 64; Siemens Medical Solutions, Erlangen, Germany). The images were acquired in a craniocaudal direction and the imaging parameters were as follows: 0.6 × 64 mm detector configuration, 0.33 seconds gantry rotation time, 5 mm slice thickness, pitch=1, 220–240 mAs effective mAs tube current, and 120–140 kV tube voltage. For contrast enhancement, 120–150 ml of non-ionic iodinated contrast medium (Ultravist 300; Bayer Schering Pharma AG, Berlin, Germany) was administered intravenously using an automatic injector at a rate of 2.5–3 ml/s. Every patient was instructed to fast for at least 6 h before contrast-enhanced CT. Post-contrast imaging was performed approximately 70 seconds after initiation of contrast medium injection. Axial data selection was reconstructed twice for the portal venous phase: first with 5- or 3-mm thick sections at 5- or 3-mm intervals in the axial plane and then with 0.6-mm thick sections at 0.6-mm intervals for reformatting of coronal section images with 2-mm sections at 2-mm intervals. Pre-contrast and/or dynamic imaging studies were also included on a case-by-case basis depending on study indications.

Image and statistical analysis

All CT images were retrieved from the picture archiving and communication system (PACS) and simultaneously analysed. For comparative analysis, the latest follow-up CT images were compared with those taken just before cholecystectomy. EHBD diameter was evaluated on coronal reconstructed images at the PACS monitor using electronic callipers. Diameter was measured consistently before and after cholecystectomy in each patient at the same level between the hilum and upper border of the pancreatic head by two radiologists (with 23 years and 1 year of experience in abdominal imaging, respectively) in consensus. According to the variable level of cystic duct orifice insertion into the EHBD, measurement level was either at the CBD or common hepatic duct (CHD). To avoid possible overestimation of EHBD diameter at and around the cystic duct orifice, the CHD juxta-proximal or CBD juxta-distal to the cystic duct orifice was excluded from measurement. The longest dimensions of PAD on axial or coronal reconstruction images of initial CT examinations were also measured and recorded for future analysis by the same radiologists.

A paired sample *t*-test was used for comparisons of EHBD diameter before and after cholecystectomy in the same patient. To compare the EHBD diameter between PAD and non-PAD groups, an unpaired *t*-test was performed. Patient age, postoperative follow-up interval, and serum alkaline phosphatase (ALP) levels were compared between the groups with an unpaired *t*-test, while patient sex was compared with the chi-square test. After comparison of age distribution between the groups using a linear-by-linear association test, propensity score matching was performed to control for the possible confounding effects of age before and after exclusion of patients with abnormally high serum ALP levels. Pearson's correlation analysis was performed to evaluate the relationship between the degree of EHBD dilatation and follow-up duration in each group, as well as to determine the relationship between size of PAD and pre- or post-operative EHBD diameter. To identify the factors associated with significant (2 mm or more) biliary dilatation, multivariate logistic regression analysis was performed for the clinical data. All probabilities were two-tailed, and statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS 22.0 software (SPSS, Chicago, IL, USA).

Results

Among 174 patients, 61 were classified in the PAD group including two who were newly determined to have PAD during review of CT images, while the other 113 were classified in the non-PAD group (Fig 1). The EHBD was significantly dilated after cholecystectomy in all 174 patients of both groups (preoperative diameter: 7.9±2.5 mm;

Table 1
Patients characteristics before and after age matching.

Parameter	Before age matching			After age matching		
	PAD group	non-PAD group		PAD group	non-PAD group	
	(*n*=61)	(*n*=113)	*p*-Value	(*n*=42)	(*n*=42)	*p*-Value
Age, mean±SD, years	65.8±11.2	61.82±11.9	0.033[a]	64.6±9.5	64.6±9.5	1.000[a]
Age, group, *n* (%)						
<30	0 (0)	1 (0.9)	0.037[c]	-	-	1.000[c]
31–40	1 (1.6)	5 (4.4)		-	-	
41–50	5 (8.2)	10 (8.8)		3 (7.1)	3 (7.1)	
51–60	14 (23)	35 (31)		12 (28.6)	12 (28.6)	
61–70	17 (27.9)	32 (28.3)		14 (33.3)	14 (33.3)	
71–80	18 (29.5)	26 (23)		11 (26.2)	11 (26.2)	
81–90	6 (9.8)	4 (3.5)		2 (4.8)	2 (4.8)	
Sex, *n* (%)						
Male	36 (59)	53 (46.9)	0.127[b]	24 (57.1)	18 (42.9)	0.190[b]
Female	25 (41)	60 (53.1)		18 (42.9)	24 (57.1)	
EHBD diameter, mean±SD, mm						
Preoperative	8.2±2.8	7.8±2.3	0.276[a]	8.1±2.8	7.8±2.4	0.603[a]
Postoperative	11.5±4	8.9±2.6	<0.001[a]	11.3±3.7	8.8±2.3	<0.001[a]
Difference in diameter (post−pre)	3.3±2.4	1.1±1.6	<0.001[a]	3.2±1.9	1±1	<0.001[a]
Follow-up duration,[d] mean±SD, months	25.7±20.1	26.5±18.4	0.790[a]	26.2±19.3	26.5±16.5	0.942[a]
PAD diameter, mean±SD, mm	19.1±10.5	-		18±9.1	-	
ALP,[e] mean±SD, IU/l	94.5±41.9	85.7±53	0.263[a]	85.5±28.4	84.3±36.9	0.863[a]

SD, standard deviation; EHBD, extrahepatic bile duct; PAD, peri-ampullary duodenal diverticulum; ALP, serum alkaline phosphatase.
[a] Unpaired *t*-test.
[b] Chi-square test.
[c] Chi-square test with linear-by-linear association.
[d] Interval between cholecystectomy and last follow-up CT scan.
[e] The highest serum alkaline phosphatase level was obtained for each patient from medical records.

postoperative diameter: 9.8±3.4 mm; $p<0.001$). There was no significant difference in sex, preoperative EHBD diameter, or time interval between surgery and the last follow-up CT examination, but the mean age in the PAD group was greater than in the non-PAD group (Table 1). EHBD dilatation after cholecystectomy was more prominent in the PAD group than in the non-PAD group (3.3±2.4 versus 1.1±1.6 mm; $p<0.001$; Fig 2). In propensity-adjusted comparisons to eliminate the aging factor, the results in matched cohorts again indicated that EHBD diameter in the PAD group increased more prominently after cholecystectomy than in the non-PAD group (3.2±1.9 versus 1.0±1.0 mm; $p<0.001$; Table 1).

After exclusion of patients with abnormal serum ALP levels to rule out the possibility of subclinical obstructive lesions, the PAD group still showed significant EHBD dilatation after cholecystectomy, compared with that in the non-PAD group (3.4±2.1 versus 0.9±1.2 mm; $p<0.001$; Table 2). Age-matched analysis within this population also showed substantial differences in EHBD dilatation between patients with and without PAD (3.4±1.8 versus 1.0±1.1 mm; $p<0.001$; Table 2).

In the non-PAD group, the degree of EHBD dilatation was positively correlated with the follow-up interval after cholecystectomy (r=0.298; p=0.002), while the PAD group showed no significant correlation (r=-0.036; p=0.797; Fig 3). There was a positive correlation between the size of PAD and the preoperative EHBD diameter (r=0257; p=0.046); however, no significant correlation was observed between the size of PAD and the postoperative

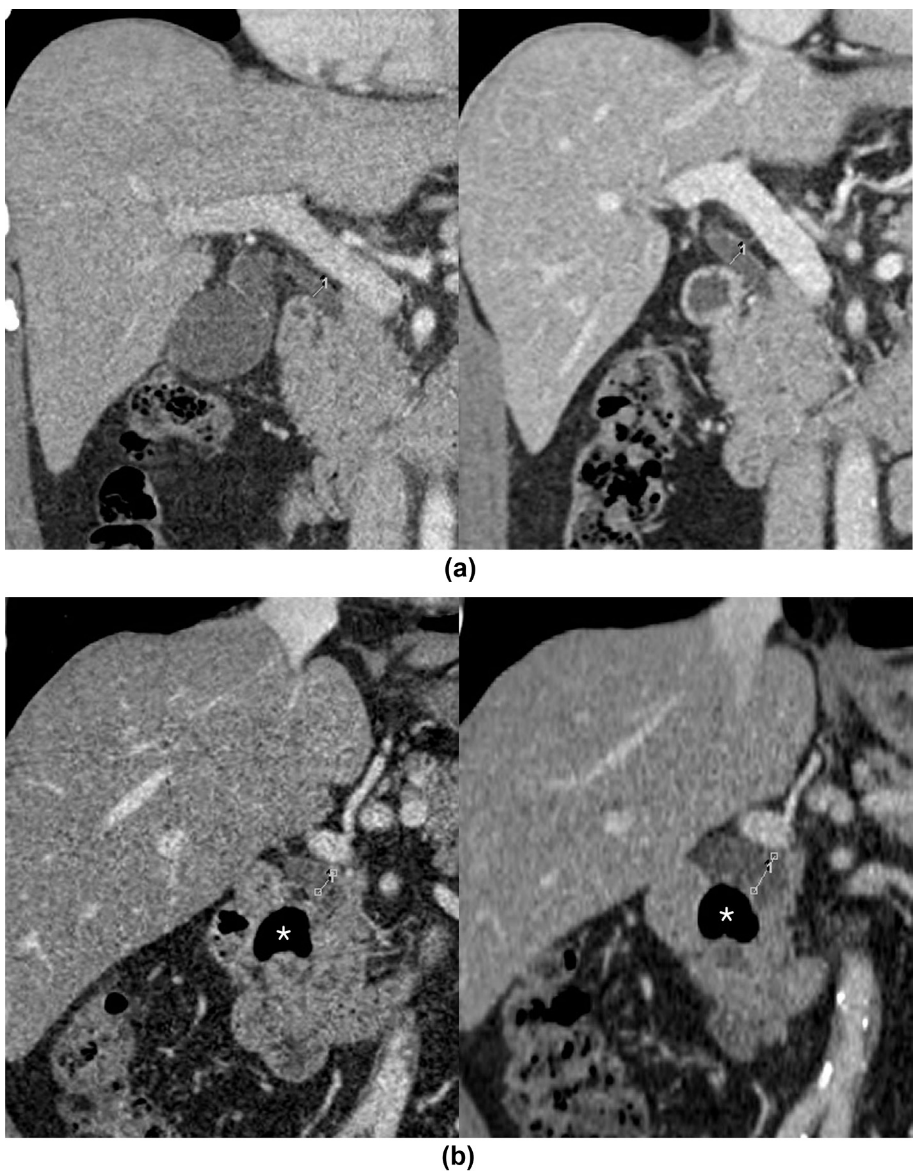

Figure 2 EHBD dilatation after cholecystectomy. In a 56 year-old man without PAD shows mild EHBD dilatation (from 6–8 mm in width) 8 months after the operation (a), while another 67 year-old man with PAD (asterisk) shows remarkable EHBD dilatation (from 10–15 mm in width) after cholecystectomy (b). Left and right images on each figure are coronally reconstructed images before and after cholecystectomy, respectively.

Table 2
Analysis of patients with normal serum alkaline phosphatase (ALP) levels before and after age matching.

Parameter	Before age matching			After age matching		
	PAD group	non-PAD group		PAD group	non-PAD group	
	(*n*=51)	(*n*=101)	*p*-Value	(*n*=36)	(*n*=36)	*p*-Value
Age, mean±SD, years	66.1±11.1	62±11.7	0.042[a]	63.7±9.5	63.7±9.5	1.000[a]
Age, group, *n* (%)						
<30	0 (0)	1 (1)	0.040[c]	-	-	1.000[c]
31–40	0 (0)	5 (5)		-	-	
41–50	4 (7.8)	6 (5.9)		3 (8.3)	3 (8.3)	
51–60	14 (27.5)	33 (32.7)		12 (33.3)	12 (33.3)	
61–70	12 (23.5)	28 (27.7)		10 (27.8)	10 (27.8)	
71–80	15 (29.4)	25 (24.8)		10 (27.8)	10 (27.8)	
81–90	6 (11.8)	3 (3)		1 (2.8)	1 (2.8)	
Sex, *n* (%)						
Male	29 (56.9)	46 (45.5)	0.188[b]	20 (55.6)	18 (50)	0.637[b]
Female	22 (43.1)	55 (54.5)		16 (44.4)	18 (50)	
EHBD diameter, mean±SD, mm						
Preoperative	8.1±2.7	7.9±2.4	0.593[a]	7.9±2.6	7.8±2.4	0.761[a]
Postoperative	11.5±3.9	8.8±2.6	<0.001[a]	11.4±3.7	8.8±2.5	0.001[a]
Difference in diameter (post−pre)	3.4±2.1	0.9±1.2	<0.001[a]	3.4±1.8	1±1.1	<0.001[a]
Follow-up duration,[d] mean±SD, months	27.5±20.1	26.6±18	0.773[a]	27.5±20.1	27.9±16.6	0.934[a]
PAD diameter, mean±SD, mm	19.3±10.4	-	-	17.6±8.5	-	-

SD, standard deviation; EHBD, extrahepatic bile duct; PAD, peri-ampullary duodenal diverticulum.
[a] Unpaired *t*-test.
[b] Chi-square test.
[c] Chi-square test with linear-by-linear association.
[d] Interval between cholecystectomy and last follow-up CT scan.

EHBD diameter (r=0129; p=0.319; Fig 4). Moreover, size of PAD was not substantially correlated with differences in the EHBD diameter before and after cholecystectomy (p=0.523; Fig 4).

On multivariate logistic regression analysis, patients with EHBD dilatation ≥2 mm were much older (p=0.014) and the follow-up interval was much longer (p<0.001) than in patients with EHBD dilatation <2 mm. The proportion of patients with PAD was significantly higher in the group with EHBD dilatation ≥2 mm than in others (46 of 81 versus 15 of 93; odds ratio, 8.434; 95% confidence interval, 3.834–18.552; p<0.001), while patient sex or elevated serum ALP level showed no significant difference in ability to induce EHBD dilatation (Table 3).

Discussion

Biliary stone disease and neoplastic conditions are common causes of obstruction and dilatation,[15] but CBD diameter is also increased by various clinical factors including the aging process.[16] Several reports have examined the impact of cholecystectomy or the presence of PAD on CBD dilatation, and have analysed their association with functional biliary dilatation.[7,13,17,18] After cholecystectomy, the absence of a bile reservoir may cause functional dilatation of the bile duct, and especially the extrahepatic portion[13]; moreover, PAD can trigger sphincter dysfunction, depending on proximity to the ampulla of Vater,[17] or can exert a mass effect on the bile duct, depending on size.[18] Prior studies have shown that the presence of PAD increases the incidence of cholelithiasis, resulting in biliary obstruction.[7] In an age-matched control group study, Lee *et al.* recently reported that PAD could induce cholelithiasis, while the presence of PAD itself did not lead to CBD dilatation.[12]

In the present study, EHBD was significantly dilated in patients with PAD compared with that in patients without PAD after cholecystectomy; and the mean age of patients with PAD was significantly greater than that of patients without PAD. This age difference between the groups was consistent with the fact that the incidence of PAD increases with age[8,19]; however, correction for age with propensity score matching was necessary to rule out the aging factor and clarify the relationship between the presence of PAD and EHBD dilatation. The overall trend in EHBD diameter between the groups showed no notable change even after adjustment for age in the present study. Several researchers have focused on the influence of cholecystectomy on bile duct dilatation.[13,20–22] In the present study, patients in the non-PAD group showed that the degree of post-cholecystectomy EHBD dilatation was more prominent with longer follow-up intervals; this supports previous studies in which short-term follow-up did not show any significant dilatation,[20,21] although significant dilatation occurs after long-term follow-up.[13,22] Interestingly, however, there was no significant correlation between the degree of EHBD dilatation and post-operative follow-up duration in the PAD group. The results of this study suggested that the presence of PAD might disrupt time-related factors such as patient age or the follow-up period.

PAD has been thought to induce post-cholecystectomy EHBD dilatation through the synergistic effect of functional dilatation and various PAD-induced effects including possible sphincter dysfunction[23] and/or biochemical

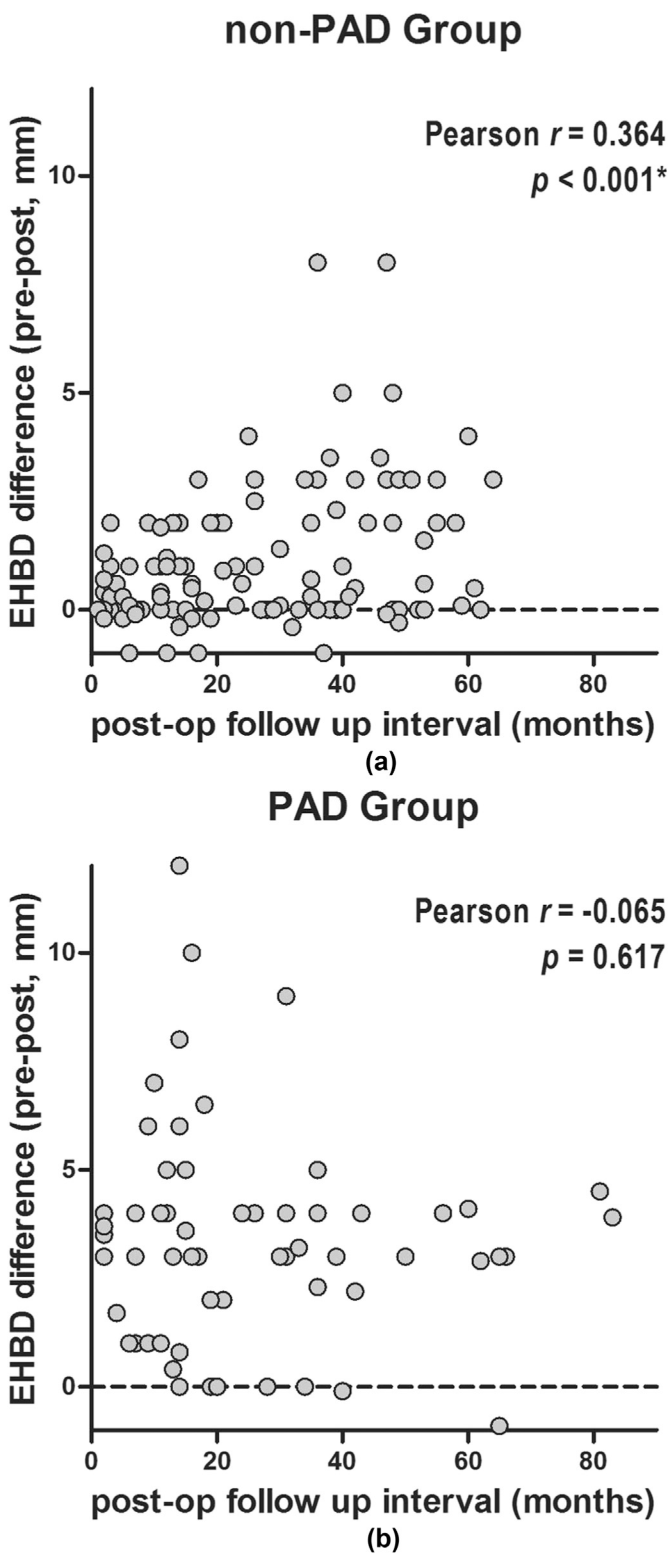

Figure 3 Correlations between post-cholecystectomy follow-up interval (months) and changed EHBD diameter (mm) after cholecystectomy. In the non-PAD group (a), the degree of EHBD dilatation was positively correlated with the follow-up interval after cholecystectomy, while the PAD group (b) showed no significant correlation.

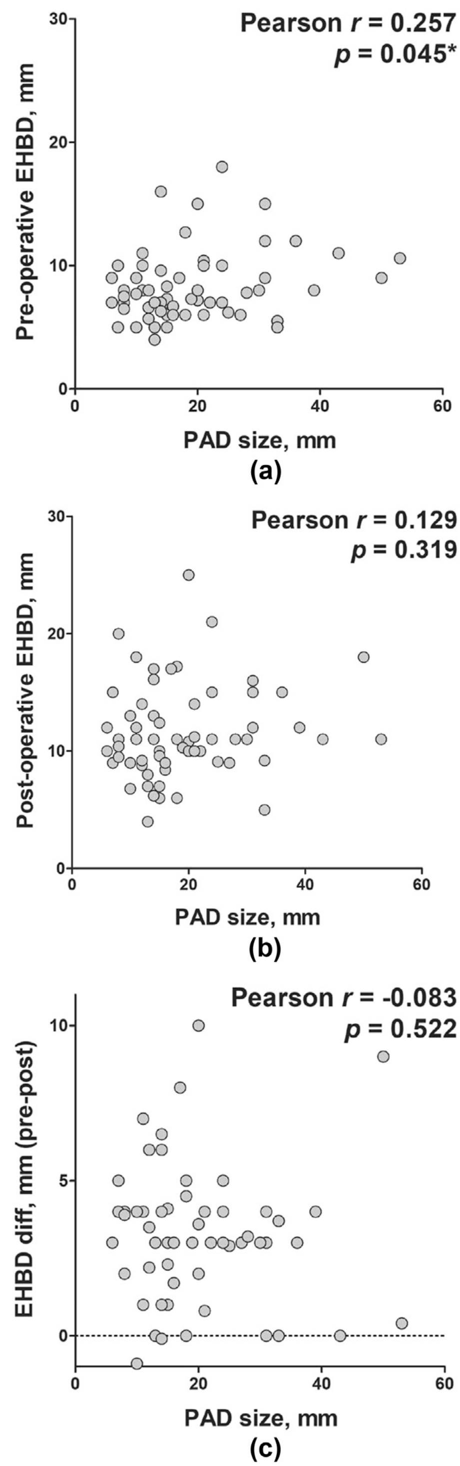

Figure 4 Correlations between size (mm) of PAD and EHBD diameter (mm) in 174 patients undergoing cholecystectomy. There was a positive correlation between PAD size and pre-operative EHBD diameter (a), but there was no significant correlation between PAD size and post-operative EHBD diameter (b) or between PAD size and changed (EHBD) diameter after cholecystectomy (c).

Table 3
Clinical factors associated with the degree of extrahepatic bile duct dilatation after cholecystectomy in 174 patients.

Factors	Dilatation <2 mm (n=93)	Dilatation ≥2 mm (n=81)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p-Value	OR (95% CI)	p-Value
Sex, n (%)						
Male	49 (52.7)	40 (49.4)	1.141 (0.629, 2.072)	0.664	-	-
Female	44 (47.3)	41 (50.6)				
ALP, IU/l	82 (32.5)	96.6 (62.9)	1.008 (0.999, 1.016)	0.069	-	-
PAD, n (%)						
None	78 (83.9)	35 (43.2)	6.834 (3.373, 13.847)	<0.001	8.739 (3.918, 19.489)	<0.001
Present	15 (16.1)	46 (56.8)				
Follow-up interval, mean±SD, months	21.3±17.1	31.8±19.5	1.031 (1.014, 1.049)	<0.001	1.046 (1.023, 1.069)	<0.001
Age, mean±SD, years	60.7±12.2	66±10.6	1.042 (1.014, 1.072)	0.003	1.043 (1.009, 1.079)	0.014

ALP, serum alkaline phosphatase; PAD, peri-ampullary duodenal diverticulum.

change, leading to cholelithiasis.[7] In subgroup analysis in the present study, despite exclusion of patients with abnormally high ALP levels who may have had undetected cholelithiasis as a cause, significant EHBD dilatation was consistently noted in the PAD group. Cholestasis was not a leading cause of post-cholecystectomy EHBD dilatation in the present cohort. Meanwhile, Kim *et al.* demonstrated that CBD diameter was correlated positively with the size of PAD, consistent with the results in the present study showing a positive correlation between preoperative EHBD diameters and size of PAD.[18] After cholecystectomy, however, EHBD diameter was markedly increased regardless of the size of PAD, suggesting that the combined effect of cholecystectomy and the presence of PAD had a greater role than the size of PAD alone in inducing EHBD dilatation.

The present study had several limitations. First, the retrospective design did not permit evaluation of the type and location of PAD based on ERCP. In a prior endoscopy study on the location of PAD, type I PAD (major papilla present inside the diverticulum) tended to be associated with more frequent CBD stones as well as larger CBD diameters.[18] Future studies using endoscopic evaluation would be helpful to identify the degree of bile duct dilatation according to the type of PAD. Second, the enrolled patients including the non-PAD control group were not disease-free populations; all underwent cholecystectomy for various pathologic conditions. Although an attempt was made to minimise potentially undiscovered causes of benign obstructive lesions, such as partial strictures or small stones by excluding patients with high ALP levels during follow-up after cholecystectomy, the effect of PAD on EHBD diameter could not be determined in the general population with subclinical symptoms in the present study. Lastly, to avoid possible errors regarding the location of cystic duct orifice, the measurement point was determined for each patient in consensus; however, due to the large difference in experience between two observers, there might be a bias that would follow the intentions of more experienced observer during the positioning of electronic callipers.

In conclusion, this study clearly demonstrated that EHBD dilatation becomes more prominent in PAD patients than in the patients without PAD undergoing cholecystectomy, suggesting a provoking effect of PAD to induce marked post-cholecystectomy biliary dilatation regardless of the size of PAD. The presence of PAD could interrupt the relationship between follow-up duration and EHBD dilatation after cholecystectomy. In daily practice, awareness of the effect of PAD would be helpful in assessment of cholecystectomy patients with marked EHBD dilatation to rule out other pathologies such as cholelithiasis or peri-ampullary neoplastic conditions, especially in the clinically silent patients as well as in the occasion of biliary stasis or relevant symptoms.

Conflict of interest

The authors declare no conflict of interest.

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