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## Retrospective Study

# Risk factors for the development of post-endoscopic retrograde cholangiopancreatography pancreatitis in patients with asymptomatic common bile duct stones

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## Abstract

### BACKGROUND

Previous studies have revealed that patients with asymptomatic common bile duct (CBD) stones are at a high risk of developing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). However, no studies to date have addressed the risk factors for PEP in patients with asymptomatic CBD stones.

### AIM

To examine the risk factors for PEP in patients with asymptomatic CBD stones.

### METHODS

Using medical records of three institutions in Japan for 6 years, we identified a total of 1135 patients with choledocholithiasis including 967 symptomatic patients and 168 asymptomatic patients with native papilla who underwent therapeutic ERCP. We performed univariate and multivariate analyses to examine the risk factors for PEP in the 168 patients with asymptomatic CBD stones.

### RESULTS

The overall incidence rate of PEP in all the patients with during study period was 4.7% (53/1135). Of the 168 patients with asymptomatic CBD stones, 24 (14.3%) developed PEP. In univariate analysis, precut sphincterotomy ( $P = 0.009$ ) and biliary balloon sphincter dilation ( $P = 0.043$ ) were significant risk factors for PEP. In multivariate analysis, precut sphincterotomy ( $P = 0.002$ , 95%CI: 2.2-27.8, odds



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ratio = 7.7), biliary balloon sphincter dilation ( $P = 0.015$ , 95%CI: 1.4-17.3, odds ratio = 4.9), and trainee endoscopists ( $P = 0.048$ , 95%CI: 1.01-8.1, odds ratio = 2.9) were significant risk factors for PEP.

## CONCLUSION

ERCP for asymptomatic CBD stones should be performed by experienced endoscopists. When performing precut sphincterotomy or biliary balloon sphincter dilation in patients with asymptomatic CBD stones, the placement of a prophylactic pancreatic stent is strongly recommended to prevent PEP.

**Key words:** Endoscopic retrograde cholangiopancreatography; Post- endoscopic retrograde cholangiopancreatography pancreatitis; Risk factor; Asymptomatic common bile duct stone

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**Core tip:** The objective of this study was to examine the risk factors for the development of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) in patients with asymptomatic common bile duct (CBD) stones. In multivariate analysis, precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were significant risk factors for PEP. ERCP for asymptomatic CBD stones should be performed by experienced endoscopists. When performing precut sphincterotomy or biliary balloon sphincter dilation in patients with asymptomatic CBD stones, prophylactic pancreatic stent placement is strongly recommended to prevent PEP.

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## INTRODUCTION

Endoscopic stone removal through endoscopic retrograde cholangiopancreatography (ERCP) is an effective treatment for common bile duct (CBD) stones. Nevertheless, ERCP is associated with a high risk of treatment-related complications. Post-ERCP pancreatitis (PEP) is the most commonly observed ERCP-related complication, potentially leading to patient mortality<sup>[1,2]</sup>.

The presence of asymptomatic CBD stones is associated with complications, such as obstructive jaundice, acute cholangitis, or biliary pancreatitis. Therefore, available guidelines recommend endoscopic CBD stone removal through ERCP in this setting<sup>[3-6]</sup>.

However, ERCP for asymptomatic CBD stones is associated with a high risk of PEP development<sup>[7-9]</sup>. In our previous study, we performed a propensity-matched analysis including 949 symptomatic CBD patients and 164 asymptomatic CBD patients and revealed that the incidence of PEP was significantly higher in patients with asymptomatic CBD stones than in those with symptomatic CBD stones [24/164 (14.6%) *vs* 28/949 (3.0%),  $P < 0.001$ , odds ratio: 5.6]. In another propensity-matched analysis of 158 matched pairs, a similar result was obtained [24/158 (15.2%) *vs* 5/158 (3.2%), respectively,  $P < 0.001$ , odds ratio: 5.5]<sup>[7]</sup>. These findings were corroborated by those of other retrospective studies<sup>[8,9]</sup>.

Treatment for asymptomatic CBD stones through ERCP aims at the prevention of possible complications associated with the presence of CBD stones. Furthermore, this disease is benign and asymptomatic. Therefore, complete removal of stones through ERCP with a low risk of PEP development is important, particularly in patients with asymptomatic CBD stones.

Based on this evidence, risk factors for the development of PEP in patients with stones asymptomatic CBD stones must be identified. Currently, however, there are no studies addressing this topic. Therefore, in the present study, we examined the risk factors for PEP development in patients with asymptomatic CBD stones.

## MATERIALS AND METHODS

### **Patients and study design**

We reviewed the medical records of three Japanese hospital from April 2012 to March 2018 and identified 1135 patients with choledocholithiasis—including acute cholangitis, biliary pancreatitis, obstructive jaundice or elevated liver test results without cholangitis, and asymptomatic CBD stones—who were diagnosed with native papilla and gastrointestinal tract without a surgical history or Billroth I reconstruction and who underwent endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), or endoscopic papillary large balloon dilation (EPLBD). Of these, 168 patients with asymptomatic CBD stones were enrolled in this study. Of the 168 enrolled patients, 164 and 4 underwent successful and unsuccessful cannulation, respectively. Those 164 patients in whom successful cannulation was performed were included in our previous study examining the incidence of PEP in patients with asymptomatic CBD stones<sup>[7]</sup>. We performed univariate and multivariate analyses to identify the risk factors for PEP development in patients with asymptomatic CBD stones. This study was approved by the institutional review boards of the participating hospitals.

### **Examination and pretreatment**

Side-viewing duodenoscopes (Olympus JF-260, TJF-260V; Olympus Medical Systems, Tokyo, Japan) were used to examine all patients. Midazolam and/or pethidine hydrochloride and scopolamine butylbromide or glucagon was intravenously injected for sedation and duodenal relaxation, respectively.

### **Endoscopists**

A total of 23 endoscopists participated in this study. Among those, 10 endoscopists were trainees who were supervised by experienced endoscopists.

### **Study definitions**

**Asymptomatic CBD stones:** Asymptomatic CBD stones were defined as CBD stones without symptoms and with normal blood examination results (total bilirubin, direct bilirubin, aspartate aminotransferase/alanine aminotransferase,  $\gamma$ -glutamyltransferase, alkaline phosphatase, white blood count, and C-reactive protein) during ERCP.

**Trainee endoscopists:** Endoscopists were classified as trainees if they had performed < 200 ERCP procedures or were only able to perform Grade 1 biliary procedures (including standard sphincterotomy, removal of stones < 10 mm, and placement of a biliary stent) based on a grading scale for ERCP<sup>[10]</sup>.

**EST, EPBD and EPLBD:** For patients in whom EST, EPBD, or EPLBD was additionally performed at the second session of ERCP after performing any of these procedures at the first session of ERCP, we selected the procedure that was performed at the first session of ERCP. Biliary balloon sphincter dilation included EPBD and EPLBD without EST. A small balloon (diameter, 8 mm) was used to perform EPBD. EPLBD was defined as the procedure for biliary orifice dilation using a large balloon (diameter,  $\geq 12$  mm)<sup>[11]</sup>.

**PEP:** The consensus criteria established by Cotton *et al*<sup>[12]</sup> were used for PEP diagnosis and grading. The diagnostic criteria for PEP were as follows: newly onset or worsened abdominal pain and > 3-fold elevated serum amylase level from normal 24 h after ERCP. Mild PEP cases included those who required new hospitalization or prolongation of hospitalization by 2-3 d. Moderate PEP cases included those who required hospitalization of 4-10 d. Severe PEP cases included those who required prolonged hospitalization (> 10 d), percutaneous drainage, or surgery.

### **Cut-off time for cannulation duration**

In this study, we used 10 min as the cut-off time for a risk factor for PEP development. This value was selected based on a guideline stating that a duration of biliary cannulation > 10 min is a procedure-related risk factor for PEP development<sup>[2]</sup>.

### **Statistical analysis**

Initially, we performed univariate analyses using chi-squared test, Fisher's exact test, or *t*-test to examine differences in clinical risk factors for PEP development between patients with or without PEP. Subsequently, we performed multivariate analysis using a logistic regression model to examine the associations between PEP incidence and risk factors with  $P < 0.10$  in univariate analysis. A  $P < 0.05$  denoted statistical significance. JMP® Pro 13 (SAS Institute, Cary, NC, United States) and R version 3.5.1 (<http://www.R-project.org>) were used for all statistical analyses.

## RESULTS

### *Patient characteristics*

**Table 1** presents patient characteristics. Among the four patients who underwent EPLBD, three underwent EPLBD with EST and one underwent EPLBD without EST.

### *Diagnostic modality for CBD stones*

For the diagnosis of CBD stones, one or more imaging examinations (*i.e.*, ultrasonography, endoscopic ultrasound, computed tomography, and/or magnetic resonance cholangiopancreatography) were performed in all the patients. In patients in whom CBD stones were not detected through the aforementioned examinations, the diagnosis was confirmed based on dilated CBD on imaging examination, elevated serum bilirubin levels, and/or abnormal liver test findings.

### *Rate of successful cannulation*

The rate of successful cannulation in this study was 97.6% (164/168 patients).

### *Incidence rate of PEP in patients with choledocholithiasis*

Among the 1135 patients with choledocholithiasis-including acute cholangitis, biliary pancreatitis, obstructive jaundice or elevated liver test results without cholangitis, and asymptomatic CBD stones-who were diagnosed with native papilla and gastrointestinal tract without a surgical history or Billroth I reconstruction and who underwent EST, EPBD, or EPLBD, the incidence rate of PEP was 4.7% (53/1135 patients).

### *Incidence rates and risk factors for PEP development in patients with asymptomatic CBD stones*

Of the 168 patients with asymptomatic CBD stones, 24 (14.3%) developed PEP. The results of univariate and multivariate analyses are listed in Tables 2 and 3, respectively. In univariate analysis, precut sphincterotomy and biliary balloon sphincter dilation were identified as significant risk factors for PEP development. In multivariate analysis, precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were identified as significant risk factors for PEP development (precut sphincterotomy:  $P = 0.002$ , 95%CI: 2.2-27.8, odds ratio = 7.7; biliary balloon sphincter dilation:  $P = 0.015$ , 95%CI: 1.4-17.3, odds ratio = 4.9; trainee endoscopists;  $P = 0.048$ , 95%CI: 1.01-8.1, odds ratio = 2.9).

### *Severity and mortality rate of PEP in patients with asymptomatic CBD stones*

Among the 24 patients who developed PEP, 10 (41.7%), 10 (41.7%), and 4 (16.7%) showed mild, moderate, and severe PEP, respectively. In this study, one death (0.60% of the total population) was reported among severe PEP cases.

## DISCUSSION

The present study showed that precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were significant risk factors for PEP development in patients with asymptomatic CBD stones.

According to the European Society of Gastrointestinal Endoscopy guidelines, PEP incidence was 3.5% and PEP severity was mild, moderate, and severe (potentially fatal) in 45%, 44, and 11% of the cases, respectively<sup>[2]</sup>. Among 1,135 patients with native papilla who underwent ERCP for choledocholithiasis in our institution during the study period, the overall PEP incidence was 4.7% and PEP severity was mild in 58.5% (31/53), moderate in 30.2% (16/53), and severe in 11.3% (6/53) of the cases. These results are consistent with previously reported results.

For patients with asymptomatic CBD stones, the current guidelines recommend endoscopic stone removal through ERCP<sup>[3-6]</sup>. However, when determining the indication for ERCP in patients with asymptomatic CBD stones, risks associated with ERCP and no treatment for asymptomatic CBD stones should be compared<sup>[13]</sup>.

Although the natural history of asymptomatic CBD stones is unclear because of the lack of data on long-term follow-up outcomes, some studies have investigated the natural history of asymptomatic CBD stones. The rate of spontaneous passage of CBD stones through the major papilla within 4-6 wk after diagnosis is approximately 20%-30%<sup>[14,15]</sup>. A previous study involving 59 patients with asymptomatic CBD stones incidentally diagnosed during cholecystectomy demonstrated that these patients did not develop any complications associated with CBD stones during a follow-up period of > 5 years<sup>[16]</sup>. Conversely, a study involving 3828 patients with CBD stones diagnosed *via* intraoperative cholangiography during cholecystectomy showed that

**Table 1** The characteristics of 168 asymptomatic patients

Characteristics	n (%)
Age [mean (SD)], yr	72.6 (11.2)
Sex, female	77 (45.8)
Billroth I reconstruction	9 (5.4)
Non-dilated CBD (< 10 mm)	99 (58.9)
Pharmacological prevention	82 (48.8)
Protease inhibitor	67 (39.9)
Rectal NSAIDs	15 (8.9)
Trainee endoscopist	39 (23.2)
Pancreatic injections	88 (52.4)
PGW-assisted cannulation	33 (19.6)
Precut sphincterotomy	15 (8.9)
Cannulation time > 10 min	64 (38.1)
Unsuccessful cannulation	4 (2.4)
EST	146 (86.9)
EPBD	14 (8.3)
EPLBD	4 (2.4)
Prophylactic pancreatic stent	27 (16.1)
Procedure time [mean (SD)], min	31.1 (16.4)

CBD: Common bile duct; NSAIDs: Nonsteroidal anti-inflammatory drugs; PGW: Pancreatic guide wire; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation.

approximately a quarter of the patients who did not undergo intraoperative treatment for CBD stones showed unfavorable outcomes<sup>[17]</sup>.

Meanwhile, the risk of procedure-related complications, particularly PEP, should be considered when performing ERCP in patients with asymptomatic CBD stones. The overall incidence rate of ERCP for asymptomatic CBD stone was approximately 20% and the incidence rate of PEP was reportedly between 12.5% and 14.6%<sup>[7,8]</sup>. This high incidence rate of PEP in patients with asymptomatic CBD stones may be attributed to the presence of multiple patient- and procedure-related risk factors, such as normal serum bilirubin levels, non-dilated CBD, and difficult biliary cannulation. In our previous study, we concluded that endoscopists should explain in detail the risk of PEP to patients with asymptomatic CBD stones prior to ERCP<sup>[7]</sup>.

In this study, we showed that precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were significant risk factors for PEP development in patients with asymptomatic CBD stones. In the present study, precut sphincterotomy was performed by expert endoscopists in cases with difficult cannulation.

The current guidelines recommend the placement of a prophylactic pancreatic stent, specifically in patients at a high risk of PEP development<sup>[1,2]</sup>. Therefore, endoscopists should strongly consider this option when performing precut sphincterotomy or biliary balloon sphincter dilation in this population. Several studies have examined the safety of ERCP when performed by trainee endoscopists. Some prospective studies have demonstrated that involvement of trainee endoscopists was not a significant risk factor for PEP development<sup>[18,19]</sup>. However, a multicenter prospective study has reported contrasting results<sup>[20]</sup>. There may be a notion that trainees must gain experience of ERCP. However, ERCP in patients with asymptomatic CBD stones is associated a high risk of PEP development, and ERCP performed by trainee endoscopists is a risk factor for PEP regardless of supervision by an experienced endoscopist. Therefore, ERCP for asymptomatic CBD stones should be performed by experienced endoscopists.

There were several limitations in this study. First, this study was a retrospective study with small cohort. Second, a participating institution in this study suffered tremendous damage due to the Kumamoto earthquake that occurred in April 2016. Thus, ERCP could not be performed after the earthquake, and data obtained from this institution covered only 4 years (April 2012 to April 2016).

In conclusion, precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were identified as significant risk factors for PEP development in patients with asymptomatic CBD stones. Placement of a prophylactic pancreatic stent



**Table 2** Univariate analyses of risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis development in patients with asymptomatic common bile duct stones, *n* (%)

	Without post-ERCP pancreatitis ( <i>n</i> = 144)	With post-ERCP pancreatitis ( <i>n</i> = 24)	<i>P</i> value
<b>Significant risk factors</b>			
Precut sphincterotomy	9 (6.3)	6 (25.0)	0.009
Biliary balloon sphincter dilation	10 (6.9)	5 (20.8)	0.043
<b>Not significant risk factors</b>			
Procedure time $\geq$ 30 min	66 (45.8)	16 (66.7)	0.059
Trainee endoscopist	30 (20.8)	9 (37.5)	0.073
Cannulation time > 10 min	51 (35.4)	13 (54.2)	0.080
Administration of a protease inhibitor	54 (37.5)	13 (54.2)	0.12
Rectal NSAIDs	15 (10.4)	0 (0)	0.13
Female sex	63 (43.8)	14 (58.3)	0.18
PGW-assist cannulation	26 (18.1)	7 (29.2)	0.26
Pancreatic injections	73 (50.7)	15 (62.5)	0.28
Endoscopic sphincterotomy	127 (88.2)	19 (79.2)	0.32
Age [mean (SD)], yr	72.3 (10.8)	74.7 (13.0)	0.33
Absence of pancreatic stent	122 (84.7)	19 (79.2)	0.55
Non-dilated CBD (<10 mm)	86 (59.7)	13 (54.2)	0.61
Unsuccessful cannulation	4 (2.8)	0 (0)	1.0

ERCP: Endoscopic retrograde cholangiopancreatography; NSAIDs: Nonsteroidal anti-inflammatory drugs; PGW: Pancreatic guide wire; CBD: Common bile duct.

should be strongly considered in patients with asymptomatic CBD stones undergoing precut sphincterotomy or biliary balloon sphincter dilation. ERCP for asymptomatic CBD stones should be performed by experienced endoscopists.

**Table 3** Multivariate analysis of risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis development in patients with asymptomatic common bile duct stones

	<i>P</i> value	95%CI	Odds ratio
Precut sphincterotomy	0.002	2.2-27.8	7.7
Biliary balloon sphincter dilation	0.015	1.4-17.3	4.9
Trainee endoscopist	0.048	1.01-8.1	2.9
Procedure time $\geq$ 30 min	0.55	0.45-4.5	
Cannulation time > 10 min	0.57	0.46-4.1	

## ARTICLE HIGHLIGHTS

### Research background

Previous studies have revealed that patients with asymptomatic common bile duct (CBD) stones are at a high risk of developing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). However, no studies to date have addressed the risk factors for PEP in patients with asymptomatic CBD stones.

### Research motivation

Treatment for asymptomatic CBD stones through ERCP aims at the prevention of possible complications associated with the presence of CBD stones. Furthermore, this disease is benign and asymptomatic. Therefore, complete removal of stones through ERCP with a low risk of PEP development is important, particularly in patients with asymptomatic CBD stones. We identified the risk factors for PEP in this population to reduce the incidence of PEP.

### Research objectives

The objective of this study was to examine the risk factors for the development of PEP in patients with asymptomatic CBD stones.

### Research methods

We reviewed the medical records of three Japanese hospital from April 2012 to March 2018 and identified 1135 patients with choledocholithiasis—including acute cholangitis, biliary pancreatitis, obstructive jaundice or elevated liver test results without cholangitis, and asymptomatic CBD stones—who were diagnosed with native papilla and gastrointestinal tract without a surgical history or Billroth I reconstruction and who underwent endoscopic sphincterotomy, endoscopic papillary balloon dilation, or endoscopic papillary large balloon dilation. Of these, 168 patients with asymptomatic CBD stones were enrolled in this study. We performed univariate and multivariate analyses to identify the risk factors for PEP development in patients with asymptomatic CBD stones.

### Research results

Among all the 1135 patients with choledocholithiasis including 967 symptomatic patients and 168 asymptomatic patients, the incidence rate of PEP was 4.7% (53/1135). Of the 168 patients with asymptomatic CBD stones, 24 (14.3%) developed PEP. In univariate analysis, precut sphincterotomy and biliary balloon sphincter dilation were identified as significant risk factors for PEP development in patients with asymptomatic CBD stones. In multivariate analysis, precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were identified as significant risk factors for PEP development in this population.

### Research conclusions

ERCP for asymptomatic CBD stones should be performed by experienced endoscopists. When performing precut sphincterotomy or biliary balloon sphincter dilation in patients with asymptomatic CBD stones, prophylactic pancreatic stent placement is strongly recommended to prevent PEP.

### Research perspectives

An important limitation of this study was that this was a retrospective study with small cohort. Prospective studies with a large number of patients are warranted to further identify the risk factors associated with the development of PEP in patients with asymptomatic CBD stones.

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