

## Cohort Study

# The influence of stone size on spontaneous passage of common bile duct stones in patients with acute cholangitis: A retrospective cohort study

Sarat Sanguanlosit, Vichit Viriyaroj, Hariruk Yodying, Thammanij Rookkachart, Suun Sathornviriyapong, Thana Boonsinsukh\*

Department of Surgery, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakhon Nayok, 26120 Thailand



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## ABSTRACT

**Background:** The common bile duct (CBD) stones passage in patients with cholangitis was unclear. This study aimed to evaluate the effect on CBD stone sizes and predicting factors on spontaneous passage in patients with cholangitis.

**Method:** The medical records of cholangitis at Her Royal Highness Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University from January 2014 to December 2019 were retrospectively reviewed. Patients with acute cholangitis from CBD stones underwent ERCP in the same admission were enrolled.

**Result:** Of the 96 patients, The rate of spontaneous passage of CBD stones was 19.8%. By univariate analysis, factors significantly associated with a predictor of spontaneous CBD stone passage in patient with cholangitis were single CBD stone ( $p = 0.001$ ), CBD stone diameter  $< 5$  mm ( $p < 0.001$ ), and clinical symptom improved before ERCP procedure ( $p = 0.004$ ). Multivariate logistic regression analyses also revealed that these three factors were significantly associated with spontaneous passage. From ROC curve analysis, stone size of less than 4.85 mm was more likely to pass spontaneously with acceptable sensitivity (81.8%) and specificity (78.9%).

**Conclusions:** CBD stone diameter  $< 5$  mm, single CBD stone and improved clinical symptom before ERCP procedure are key predictors of spontaneous CBD stone passage in cholangitis.

## 1. Introduction

Acute cholangitis is an increase in bile duct pressure and biliary bacterial infection due to an obstructed biliary tree. The most common cause of obstruction is common bile duct stones (CBD stones) [1]. Without treatment, the obstruction can lead to an ascending spread of infection resulting in septicemia and organ failure. The mortality rate is 20–30% [1,2].

Treatment of cholangitis is intravenous fluid resuscitation, antibiotics and biliary drainage. Endoscopic retrograde cholangiopancreatography (ERCP) is the choice of biliary drainage which should be performed early for moderate and severe cases, according to the severity grading of the updated Tokyo Guidelines of 2018 [3]. Moreover, recent studies show early ERCP (within 48 h of admission) in all grading of cholangitis is associated with shorter hospital stays, decrease costs and lower mortality rate [4–8].

Nevertheless, the authors found the spontaneous passage of common bile duct stones in some patients with acute cholangitis. Few previous

studies reported 21–73% of patients with previous or current evidence of ductal stones passed their stones spontaneously [9–14] and the stones have passed naturally when clinical symptoms improved and hematological parameters returned to normal [10]. Other studies found that intrahepatic bile duct dilatation, stone diameter, and distal bile duct stones were radiological predictors of stone passage [11] and stones less than 5 mm in diameter were more likely to spontaneously passed [12]. Unfortunately, there was a lack of data about bile duct stones passage in patients with cholangitis.

This study aimed to evaluate whether stone sizes have an affect on spontaneous passage of CBD stones in patients with cholangitis. The secondary objective was to identify other predictors for spontaneous passage of CBD stones in patients with cholangitis.

## 2. Materials and methods

This research is in line with the STROCCS criteria [15]. The medical records of patients with cholangitis at Her Royal Highness Princess

\* Corresponding author. Department of Surgery, Faculty of Medicine, Srinakharinwirot University, 62 Moo 7, Ongkharak, Nakhon Nayok, 26120, Thailand.  
E-mail address: [thanab@g.swu.ac.th](mailto:thanab@g.swu.ac.th) (T. Boonsinsukh).

Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University from January 2014 to December 2019 were retrospectively reviewed. We enrolled patients with acute cholangitis underwent ERCP in the same admission. The exclusion criteria were patients who did not received ultrasound, CT scan or MRI before ERCP and the cause of cholangitis was not from CBD stones.

All patients with acute cholangitis were admitted in hospital. Ultrasound, CT scan or MRI were performed to confirm diagnosis and revised by radiologists. The patients received immediate intravenous antibiotic and ERCP was done in the same admission. The ERCP procedure was done with standard technique using general anesthesia with endotracheal tube.

### 2.1. Definition

Endoscopic retrograde cholangiopancreatography (ERCP) is endoscopy used for diagnostic and therapeutic pancreaticobiliary disease, such as common bile duct stones, bile duct tumor or pancreatic tumor.

Cholangitis and severity were defined according to Tokyo Guidelines 2018 criteria [3] which diagnostic from systemic inflammation (fever, shaking chills, abnormal white blood cell or C-reactive protein), cholestasis (jaundice or abnormal liver function tests) and imaging (biliary dilation or evidence of etiology such as biliary stones).

Distal stones were defined as stones impacted in the distal third of the CBD.

Classification of the macroscopic appearance of the Papilla of Vater [16] was defined as regular papilla (type 1), small papilla (type 2), protruding papilla (type 3) and creased papilla (type 4).

### 2.2. Statistical analysis

Demographic data and outcomes were collected, including age, gender, liver function test, severity of cholangitis, length of hospital stay, clinical symptoms (body temperature and abdominal sign) before ERCP procedure, CBD diameter, CBD stone diameter, number of bile duct stones and site of bile duct stone (proximal and distal), rate of spontaneous passage stone which diagnosis by ERCP, success rate of ERCP, type of the Papilla of Vater, the time from hospital arrival to ERCP, morbidity and mortality. Statistical analysis was performed using the SPSS (version 23) software (Statistical Procedures for Social Sciences; Chicago, Illinois, USA). Demographic data are presented as means or median, SD and percent. The difference of variables between spontaneous CBD stone passage and CBD stone non-passage were tested using independent sample *t*-test or Mann-Whitney *U* test for quantitative variables and Chi-squared test or Fisher's exact test for categorical data. A *p*-value of less than 0.05 was considered statistically significant. The significant variables in univariate analysis were all included in a forward stepwise multiple logistic regression model to identify the independent predictors for spontaneous passage of CBD stones in patients with cholangitis. An odds ratio with a 95% confidence interval that did not include unity was considered significant. Statistically significant variables were tested through ROC curve analysis to determine a threshold above which chance to pass spontaneously is recommended. The cut-off point was identified by the maximum value of the Youden index ( $J = \text{sensitivity} + \text{specificity} - 1$ ).

## 3. Result

A total of 96 patients enrolled into the study. There were 39 men and 57 women with mean age of  $63.5 \pm 18.3$  years. Most severity of cholangitis was mild (47.9%). The mean CBD and CBD stone diameter were  $12.6 \pm 5.0$  and  $7.9 \pm 4.9$  (mm). Most patients had single CBD stone (56.3%), distal CBD stone (90.6%) and clinical symptom improved before ERCP procedure (66.7%). The median time from hospital arrival to ERCP was 28 h (range, 1–250 h). 19.8% of patients with cholangitis passed their stones spontaneously. The median length of hospital stay

was 6 days (range, 2–37 days). The most common type of the Papilla of Vater was type 1 (53.1%). Post-ERCP complication occurred in 12.5%. The most common complication was pancreatitis (9.4%), and the others were recurrent cholangitis (2.1%) and bleeding (1%). Two patients died from hospital-acquired pneumonia and multi-organ failure. Patient characteristics are shown in Table 1.

In the univariate analysis, 3 variables were statistically significantly associated with a predictor of spontaneous CBD stone passage in patient with cholangitis (Table 2). They were single CBD stone ( $r = 0.33$ ,  $p = 0.001$ ), CBD stone diameter  $< 5$  mm ( $r = 0.53$ ,  $p < 0.001$ ), and clinical symptom improved before ERCP procedure ( $r = 0.30$ ,  $p = 0.004$ ).

Three predictors for spontaneous passage of CBD stones in cholangitis were found to be significant in the multivariate logistic regression analysis (Table 3). They were single CBD stone (Odds ratio 18.296; 95% CI 2.578–129.869,  $p = 0.004$ ), CBD stone diameter  $< 5$  mm (Odds ratio 5.902; 95% CI 1.186–29.358,  $p = 0.03$ ), and clinical symptom improved before procedure (Odds ratio 11.091; 95% CI 1.167–105.442,  $p = 0.036$ ).

Receiver Operating Characteristics (ROC) Curve Analysis was used to define a threshold for CBD stone diameter. The threshold was defined for the value with maximal sensitivity and specificity. Regarding CBD stone size, according to our results a stone larger than 4.85 mm has low chance to pass spontaneously (AUC 0.832; 95%CI 0.722–0.942,  $p < 0.001$ ). This cut-off has sensitivity of 81.8%, specificity of 78.9% (Fig. 1).

## 4. Discussion

The overall incidence of spontaneous passage CBD stones in prior studies was between 21 and 73% [9–14]. Tranter et al. [9] found that spontaneous passage of CBD stones occurred more commonly in patients with pancreatitis, biliary colic, and cholecystitis. However, there was no information available about rate of this in cholangitis. Our study found 19.8% of patients with cholangitis passed their stones spontaneously. Murabayashi et al. [17] reported CBD stone in cholangitis spontaneously

**Table 1**  
Demographic data of patients (n = 96).

Characteristics	
Male (%)	39 (40.6)
Age (years; mean $\pm$ SD)	63.5 $\pm$ 18.3
Severity of cholangitis (%)	46 (47.9)
- Mild	35 (36.5)
- Moderate	15 (15.6)
- Severe	
Blood test	
- Total bilirubin (mg/dL; mean $\pm$ SD)	5.86 $\pm$ 5.52
- Direct bilirubin (mg/dL; mean $\pm$ SD)	4.49 $\pm$ 4.48
- Aspartate transaminase (U/L; mean $\pm$ SD)	255.1 $\pm$ 301.5
- Alanine transaminase (U/L; mean $\pm$ SD)	233.9 $\pm$ 243.6
- Alkaline phosphatase (U/L; mean $\pm$ SD)	316.2 $\pm$ 228.4
CBD diameter (mm; mean $\pm$ SD)	12.6 $\pm$ 5.0
CBD stone diameter (mm; mean $\pm$ SD)	7.9 $\pm$ 4.9
Single CBD stone (%)	54 (56.3)
Distal CBD stone (%)	87 (90.6)
Clinical symptoms improved before procedure <sup>a</sup> (%)	64 (66.7)
Time from hospital arrival to ERCP (hours; median, range)	28 (1–250)
Type of Papilla of Vater (%)	51 (53.1)
- 1	3 (3.1)
- 2	35 (36.5)
- 3	7 (7.3)
- 4	
Spontaneous passage of CBD stones (%)	19 (19.8)
Success ERCP (%)	96 (100)
Post-ERCP complications (%)	12 (12.5)
- Pancreatitis	9 (9.4)
- Recurrent cholangitis	2 (2.1)
- Bleeding	1 (1)
Mortality (%)	2 (2.1)
Length of hospital stay (days, median, range)	6 (2–37)

<sup>a</sup> Clinical symptoms improve - no fever and abdominal pain.

**Table 2**

Comparison between patients with spontaneous CBD stone passage and CBD stone non-passage in cholangitis.

Characteristics	Spontaneous CBD stone passage (N = 19)	CBD stone non-passage (N = 77)	P value
Male (%)	5 (26.3)	34 (44.2)	0.156
Age (years; mean ± SD)	56.6 ± 21.5	65.3 ± 17.1	0.085
Blood test	5.10 ± 2.36	6.05 ± 6.05	0.550
- Total bilirubin (mg/dL; mean ± SD)	3.96 ± 1.99	4.63 ± 4.90	0.451
- Direct bilirubin (mg/dL; mean ± SD)	227.6 ± 178.0	261.9 ± 325.4	0.511
- Aspartate transaminase (U/L; mean ± SD)	285.9 ± 353.4	221.1 ± 209.2	0.556
- Alanine transaminase (U/L; mean ± SD)	291.1 ± 202.8	322.4 ± 235.1	0.613
CBD dilate, diameter > 8 mm (%)	13 (68.4)	67 (87)	0.051
CBD stone diameter < 5 mm (%)	15 (78.9)	14 (18.2)	<0.001*
Single CBD stone (%)	17 (89.5)	37 (48.1)	0.001*
Distal CBD stone (%)	19 (100)	68 (88.3)	0.117
Clinical symptoms improved before procedure <sup>a</sup> (%)	18 (94.7)	46 (59.7)	0.004*
Time from hospital arrival to ERCP ≤ 48 h (%)	11 (57.9)	45 (58.4)	0.965
Post-ERCP complication (%)	4 (21.1)	8 (10.4)	0.208
- Pancreatitis	4 (21.1)	5 (6.5)	0.051
Mortality (%)	0 (0)	2 (2.6)	0.478
Length of hospital stay (days; mean ± SD)	6.8 ± 3.7	8.5 ± 5.8	0.311

\*significant at the level of 0.05.

<sup>a</sup> Clinical symptoms improve - no fever and abdominal pain.

**Table 3**

Significant predictors for spontaneous passage of CBD stones in cholangitis by multivariate analysis.

Predictors	Odds ratio	95%CI	P value
CBD stone diameter < 5 mm	15.433	3.805–62.605	<0.001
Clinical symptoms improve before procedure <sup>a</sup>	11.091	1.167–105.442	0.036
Single CBD stone	9.466	1.671–53.636	0.011

<sup>a</sup> Clinical symptoms improve - no fever and abdominal pain.

passed during computed tomography. Moreover, there have on live spontaneous migration of CBD stone during endoscopy [18,19].

The previous studies reported that CBD stone of less than 5 mm in diameter was more likely to spontaneously pass without the need for further intervention and there were an increased rate of stone retention in bile duct with a larger stone size [9,12]. In cholangitis, our study was similar to results that CBD stone size of less than 5 mm tended to pass their stones spontaneously. Additionally, we generated ROC curve analysis for size of stone and found that stone size of less than 4.85 mm was more likely to pass spontaneously with acceptable sensitivity (81.8%) and specificity (78.9%). However, Khoury et al. [11] found a stone larger than 3.5 mm had low chance to pass spontaneously with acceptable sensitivity (71%) and specificity (69%).

Sakai et al. [10] found the CBD stones passed naturally if clinical symptoms improvement and blood biochemical parameters were normalized. Our study showed patients with no fever and abdominal pain before ERCP procedure had spontaneously passage of CBD stone. Unfortunately, there were only blood biochemical parameters at the arrival. we did not repeat blood test before procedure. Some studies suggested that performing MRCP first in patients have improved clinical

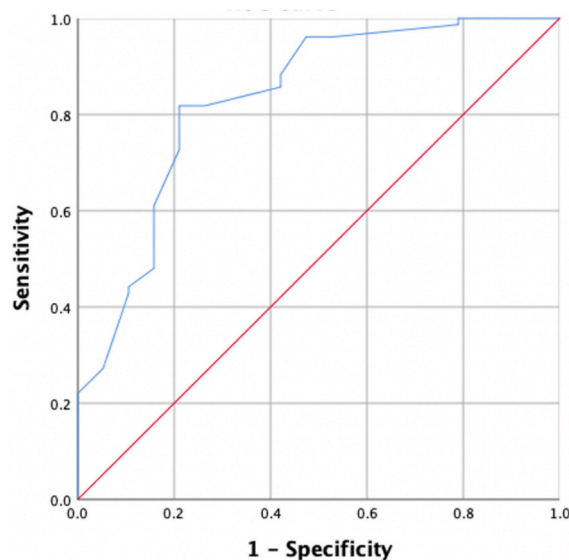


Fig. 1. ROC curve for CBD stones diameter.

and hematological parameters. If the stone has spontaneously passed, it would reduce the exposure of ERCP and complication due to ERCP [10, 20]. Our study found that post-ERCP pancreatitis was 21.1% in spontaneous CBD stone passage.

To the best of our knowledge, there are no previous studies reported that single CBD stone is a predictive factor for spontaneous stone passage as we showed in our study. There were only case reports showed that single CBD stone in cholangitis spontaneously migrated. Murabayashi et al. reported an 85-year-old man with cholangitis from one large CBD stone (15 mm) that had spontaneously passed during computed tomography [17]. Itoi et al. [18] and Cerezo-Ruiz et al. [19] showed single CBD stone can spontaneously passed during endoscopy in patient with cholangitis.

Most studies advised performing early ERCP in patient with cholangitis, especially within 24 h [6]. Delayed ERCP is associated with mobility and mortality [4]. Results from this study could benefit most hospitals that lack of ERCP facilities or when an endoscopist was not always available. We suggested that in the patients with cholangitis from CBD stone, CT scan or MRCP (especially when having a single CBD stone with diameter < 5 mm) and clinical symptoms should be monitored. If CBD stone passed spontaneously, it could reduce the rate of transferring to ERCP center, cost and post-ERCP complications.

The study has several limitations. It was a retrospective study which increases the potential for bias of data collection. In addition, the patients came from a single center, resulting in less diversity of the data and conditions. Future studies with larger samples drawn from diverse communities are needed for generalization of the results to the global population.

## 5. Conclusions

CBD stone diameter <5 mm, single CBD stone and improved clinical symptom before ERCP procedure are key predictors of spontaneous CBD stone passage in patient with cholangitis.

## Data availability

The data used to support the finding of this study are available from the corresponding author upon request.

## Disclosure

The authors have no financial support.

## Declaration of competing interest

The authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2020.10.040>.

## Ethics approval

Approval was granted by Srinakharinwirot University Ethics Committee of Human Research: SWUEC-393/2562E.

## Research registration number

1. Name of the registry: Thai clinical trial registry. 2. Unique Identifying number or registration ID: TCTR20200901007.3. Hyperlink to your specific registration (must be publicly accessible and will be checked): <http://www.clinicaltrials.in.th/index.php?tp=regtrials&menu=trialssearch&smenu=fulltext&task=search&task2=view1&id=6735>.

## Provenance and peer review

Not commissioned, externally peer reviewed.

## Author contribution

**Thana Boonsinsukh:** Data collection, data analysis, literature review, manuscript writing, patient care. **Sarat Sanguanosit:** Data collection, literature review, patient care. **Vichit Viriyaraj:** Data collection, patient care. **Hariruk Yodying:** Data collection, patient care. **Thammanij Rookkachar:** Data collection, patient care. **Suun Sathornviriyapong:** Data collection, patient care.

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