Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(11) 1–10

DOI: 10.1177/03000605211058381
journals.sagepub.com/home/imr
SAGE

Factors related to the spontaneous passage of common bile duct stones through the papilla: a single-center retrospective cohort study

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Abstract

Objective: Common bile duct (CBD) stones can spontaneously pass through the papilla. This study explored factors associated with stone passage by comparing differences in the clinical features of stones retained in the CBD and excreted stones.

Methods: Data were retrospectively collected for all patients who were hospitalized in our center between March 2016 and May 2021 with clinical, laboratory, or imaging evidence of CBD stones. All patients underwent endoscopic retrograde cholangiopancreatography (ERCP) and were classified into two groups: group A (stones extracted by ERCP, $n = 86$) and group B (stones discharged before ERCP, $n = 15$). Demographic data, biochemical and radiological findings were compared between the groups.

Results: Stone size (0.82 *vs.* 0.33 cm), and levels of total bilirubin (58.2 *vs.* 28.8 μmol/L), gamma-glutamyl transpeptidase (416.7 *vs.* 193.9 U/L), alkaline phosphatase (191.9 *vs.* 123.1 U/L), carbohydrate antigen 19-9 (603.7 *vs.* 37.2 U/mL), and α-L-fucosidase (37.4 *vs.* 22.6 U/L) were significantly higher in group A than in group B. Logistic regression analyses showed that stone size was the only factor significantly associated with spontaneous passage of CBD stones.

Conclusions: CBD stones less than 0.33 cm in size may be self-expelled through the papilla.

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Keywords
Common bile duct stone, endoscopic retrograde cholangiopancreatography, gamma-glutamyl transpeptidase, alkaline phosphatase, carbohydrate antigen 19-9, α-L-fucosidase, retrospective analysis

Date received: 18 July 2021; accepted: 14 October 2021

Introduction

The presence of common bile duct (CBD) stones, the most common cause of biliary obstruction worldwide, is a prevalent digestive disorder that can cause serious complications associated with considerable mortality, such as obstructive suppurative cholangitis, gallstone pancreatitis, and liver parenchyma inflammation.[1–3] Until recently, the advice was to endoscopically or surgically remove CBD stones once a diagnosis was established.[4] Endoscopic retrograde cholangiopancreatography (ERCP) is the most common approach for CBD stones.[5] However, ERCP is an invasive procedure that is associated with several complications, including post-ERCP pancreatitis, retroperitoneal perforation, and post-sphincterotomy bleeding.[6,7] Moreover, some CBD stones can spontaneously pass through the papilla. Previous studies have shown that stones with diameters <5 mm were more likely to spontaneously pass.[8,9] Therefore, it is imperative to confirm whether stones still exist in the CBD before ERCP.

The American Society for Gastrointestinal Endoscopy (ASGE) guidelines suggest performing magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) prior to ERCP.[10] MRCP has 77% to 100% sensitivity and 73% to 99% specificity for detecting CBD stones.[11] EUS has a reported sensitivity of 75% to 100% and a specificity of 85% to 100%.[11] However, EUS and MRCP do not have perfect negative predictive ability. EUS has higher technical requirements, which limits its clinical applicability. Interestingly, it has been reported that computed tomography (CT) scans have a sensitivity of 65% to 88% for detecting CBD stones.[12] Meanwhile, the revised ASGE guidelines in 2019 recommend CT for the risk stratification of patients suspected to have CBD stones.[13] Therefore, in our center, MRCP and CT are combined to confirm that stones still exist in the CBD before ERCP.

This study enrolled 101 cases of suspected choledocholithiasis treated with ERCP, and the patients were divided into two groups: group A (stones extracted by ERCP, $n=86$) and group B (stones discharged before ERCP, $n=15$). Clinical data were compared between groups A and B in detail to further explore the factors related to CBD stones that spontaneously discharged.

Materials and methods

Patients

Shulan (Hangzhou) Hospital, in affiliation with the Shulan International Medical College Review Board, approved this study. All patients signed informed consent before ERCP. We retrospectively reviewed electronic clinical medical records for all patients who underwent ERCP with suspected choledocholithiasis by imaging examinations (MRCP/CT) between

1 March 2016 and 1 May 2021. We excluded patients <18-years-old, those with a history of gastric, liver, or biliary surgery (partial hepatectomy, Roux-en-Y gastric bypass, Billroth I or II, choledocholithotomy, choledochojejunostomy, or hepaticojejunostomy), abdominal organ transplantation such as liver or kidney transplantation, prior ERCP, a history of malignancy including hepatobiliary and pancreatic malignancies, colorectal cancer, gastric cancer, lung cancer, or hematological malignancies, intraductal papillary mucinous tumors of the pancreas, serous or mucinous cystadenoma in the head of the pancreas, or benign diseases of the primary liver or bile duct or pancreas (including liver cirrhosis of various causes, primary sclerosing cholangitis, alcoholic liver disease, viral hepatitis including inactive hepatitis B virus carriers, autoimmune liver disease, autoimmune pancreatitis, chronic pancreatitis, pancreas divisum, and annular pancreas). We reviewed demographic data (age, sex, and body mass index [BMI]), liver function test results (alanine transaminase [ALT], aspartate aminotransferase [AST], total bile acids [TBA], gamma-glutamyl transpeptidase [γ-GGT], alkaline phosphatase [ALP], total bilirubin [TB], direct bilirubin [DB], indirect bilirubin [IB], cholinesterase [CHE], glycine proline dipeptidyl aminopeptidase [GPDA], α-L-fucosidase [AFU], total cholesterol [TC], triglycerides, high-density lipoprotein cholesterol [HDLC], low-density lipoprotein cholesterol [LDLC], and adenosine deaminase [ADA]), imaging findings (CBD diameter and stone diameter), time from admission to ERCP, pre-ERCP temperature, neutrophil ratio, and levels of white blood cells (WBCs), C-reactive protein (CRP), and carbohydrate antigen 19-9 (CA 19-9). Measurements of the CBD diameter and stone size were obtained by imaging examinations (MRCP/CT) before ERCP. A true positive CBD stone was defined as the visualization of a stone or stone fragments that were later removed on ERCP.

ERCP procedure

ERCP was performed with standard side-view duodenoscopes (Olympus TJF 260/JF 240, Olympus Optical Corporation, Tokyo, Japan). After successful intubation of the duodenal papilla, a contrast agent was injected into the CBD. An appropriate contrast medium was selected, i.e., one that clearly showed the filling defect (without splintering or obvious shape change) and the diameter of the CBD (especially the diameter of the CBD at the distal end of a stone). We usually used a spiral net basket (MWB-2X4/3X6, Wilson-Cook Medical Incorporated, Winston-Salem, NC, USA), but we also used a retrieval balloon catheter (FS-QEB-XL-A, Wilson-Cook Medical Incorporated; or M00547110, Boston Scientific Corporation, Marlborough, MA, USA) or both. When the stones were larger than 1.2 cm, we usually used a mechanical lithotripsy basket (FS-LXB-3X6, Wilson-Cook Medical Incorporated). Endoscopic nasobiliary drainage (ENBD) was a routine procedure after stone extraction to prevent cholangitis. In group B patients, an ENBD was also advised to be placed unless they refused. The nasobiliary ducts were usually placed for 3 to 5 days and would be removed when the patients were discharged. All ERCP findings, extraction models, and complications were recorded.

Statistical analysis

Data are presented as mean ± SD or median (interquartile range [IQR]) for normally or nonnormally distributed variables, respectively. Numerical data were compared using the independent Student's t test and Mann–Whitney U test. Categorical variables were compared using

the χ^2 test or Fisher's exact test. A p-value <0.05 was used to indicate statistical significance. Multivariate regression analyses were used to determine significantly associated risk factors. All statistical analyses were performed using IBM SPSS for Windows version 19.0 (IBM Corp., Armonk, NY, USA).

Results

This study included 101 patients with clinical, biochemical, or radiological suspicion of CBD stones. Their ages ranged from 19 to 90 years, with a mean age of 58.1 years. Among the 101 patients, 47 (46.5%) were male and 54 (53.5%) were female. The most common presenting complaint was upper abdominal pain. The proportion of patients with upper abdominal pain was 81.4% (70/86) in group A and 80.0% (12/15) in group B. Fifteen patients presented with complaints of nausea and vomiting (all in group A). Fever with or without chills was present in 10 patients (all in group A).

There were significant differences between groups A and group B in stone size (0.82 *vs.* 0.33 cm) and levels of TB (58.2 *vs.* 28.8 μmol/L), ALP (191.9 *vs.* 123.1 U/L), CA 19-9 (603.7 *vs.* 37.2 U/mL), γ-GGT (416.7 *vs.* 193.9 U/L), and AFU (37.4 *vs.* 22.6 U/L) (Figure 1, all $P < 0.05$). However, there were no significant differences between group A and group B in age, BMI, or levels of ALT, AST, DB, WBC, and CRP (Table 1). The proportion of male patients and those with a CBD diameter greater than 1 cm were not significantly higher in group A than in group B (Table 2). Comparing group A with group B by univariate analyses showed that larger stone size, and higher levels of γ-GGT and AFU were not conducive to the spontaneous discharge of stones into the intestinal tract (Table 3, $P < 0.05$). However, multivariate analyses showed that stone size was the only relevant factor (hazard ratio: 0.001, 95% confidence interval: 0.001–0.057, $P = 0.017$).

After ERCP, 44 patients in group A underwent ENBD and 40 underwent ENBD and cholecystectomy. One patient's CBD stone failed to be completely removed by ERCP because the diameter of the stone was nearly 6 cm. This patient underwent ENBD after ERCP and was followed up with choledocholithotomy. In another patient, titanium clips were used to close the perforation because of type II gastrointestinal perforation, and plastic stents were placed in the biliary and pancreatic ducts. In group B, after ERCP, seven patients underwent ENBD, seven received ENBD and cholecystectomy, and one patient underwent small duodenal papillotomy and balloon sweeping, without indwelling nasobiliary duct.

Discussion

As early as 1983, Levine et al. pointed out that 90% of CBD calculi could pass spontaneously.[14] Since then, increasing attention has been paid to the spontaneous discharge

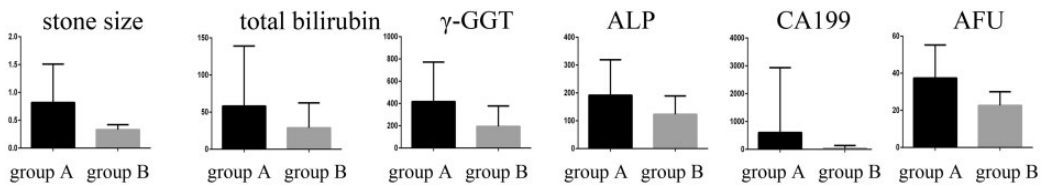

Figure 1. Comparison of numerical data between groups A and B (significant differences, $p < 0.05$; group A, cases of stones extracted by ERCP; group B, cases of stones discharged before ERCP).

Table 1. Comparison of numerical variables in patients with common bile duct stones who underwent endoscopic retrograde cholangiopancreatography.

	Age	Alanine aminotransferase	Aspartate aminotransferase	Total bilirubin	Direct bilirubin	Indirect bilirubin
Total patients	58.1 ± 17.5	144.0 [272.8]	83.5 [141.5]	26.5 [48.8]	13.5 [38.5]	10.0 [13.0]
Group A	59.0 ± 17.6	134.0 [277.5]	82.0 [140.0]	29.0 [52.0]	17.0 [41.0]	11.0 [13.0]
Group B	52.6 ± 16.6	151.0 [228.0]	114.0 [210.0]	16.0 [20.0]	7.0 [12.0]	9.0 [9.0]
	γ-glutamyl transpeptidase	Alkaline phosphatase	Cholinesterase	Total bile acids	Glycine proline dipeptidyl aminopeptidase	α-L-fucosidase
Total patients	294.5 [433.8]	147.5 [133.0]	7046.8 ± 1989.5	14.3 [120.8]	136.6 ± 60.0	35.8 ± 17.5
Group A	320.0 [440.5]	156.0 [144.5]	7043.8 ± 2064.9	14.6 [139.9]	138.7 ± 60.6	37.4 ± 17.8
Group B	118.0 [238.0]	98.0 [90.0]	7072.8 ± 1246.1	9.7 [68.9]	119.0 ± 55.8	22.6 ± 7.4
	Total cholesterol	Triglyceride	High density lipoprotein cholesterol	Low density lipoprotein cholesterol	Adenosine deaminase	Temperature
Total patients	4.7 ± 1.2	1.5 ± 0.9	1.2 ± 0.5	2.6 ± 0.9	11.0 [5.0]	36.9 ± 0.5
Group A	4.7 ± 1.2	1.5 ± 0.9	1.2 ± 0.5	2.6 ± 0.9	11.0 [5.0]	36.9 ± 0.5
Group B	4.4 ± 0.9	1.2 ± 0.5	1.3 ± 0.6	2.3 ± 0.5	9.0 [3.3]	36.7 ± 0.2
	White blood cell count	Neutrophil ratio	C-reactive protein	Carbohydrate antigen-199	Time from admission to ERCP	Body mass index
Total patients	6.2 [3.4]	67.5 ± 13.8	5.3 [22.6]	13.0 [56.7]	3.0 [4.0]	23.6 ± 3.3
Group A	6.1 [3.3]	67.5 ± 14.0	6.0 [23.6]	17.6 [64.7]	3.0 [3.0]	23.6 ± 3.2
Group B	6.2 [3.4]	67.3 ± 13.4	5.0 [3.5]	5.4 [14.2]	4.0 [5.0]	23.6 ± 3.8

Data are presented as mean ± SD or median [IQR] for normally or nonnormally distributed parameters, respectively. Group A, cases of stones extracted by ERCP; Group B, cases of stones discharged before ERCP. ERCP, endoscopic retrograde cholangiopancreatography.

of CBD stones. In 2004, Collins et al. found that more than one third of choledocholithiasis could pass spontaneously within 6 weeks of laparoscopic cholecystectomy.[15] In 2011, Lefemine et al. presented data showing that more than half of patients with obstructive jaundice experienced spontaneous passage of gallstones from the CBD.[16] These findings suggested that CBD stones could often spontaneously pass without the need for endoscopic or surgical drainage procedures.[8] Thus, it is imperative to identify specific predictors of CBD stones that will spontaneously pass.

In 1985, a study reported that serum bilirubin >25 μmol/L, serum ALP >250 U/L, and a CBD width >10 mm were associated with an increased probability of CBD stones being present.[17] In 1994, a study by Barkun et al. showed that ALP >300 U/L and AST >120 U/L had sensitivities of 79% and 81%, respectively, for predicting the presence of CBD stones.[18] Later, Pereira-Lima et al. reported that γ-GGT, ALP, and TB were sensitive indicators of CBD stones.[19] Recently, several studies have concluded that γ-GGT is the most sensitive marker for predicting the presence of CBD stones, and it is also associated with the highest predictive value and diagnostic accuracy.[19,20] In this study, we found that levels of TB, ALP, and γ-GGT were significantly higher in group A than in group B ($P < 0.05$). Univariate analyses showed that higher γ-GGT levels were not conducive to the spontaneous discharge of stones into

Table 2. Comparison of categorical variables in patients with common bile duct stones who underwent endoscopic retrograde cholangiopancreatography.

	Male (%)	Abdominal pain (%)	Cholecystolithiasis (%)	CBD diameter >1 cm (%)
Total patients	46.5	81.2	60.4	60.4
Group A	50.0	81.4	61.6	64.0
Group B	26.7	80.0	53.3	40.0
	Stone extraction methods (1/2/3, %)	CBD stone >0.5 cm (%)	Amylase upregulation pre-ERCP (%)	Amylase upregulation post-ERCP (%)
Total patients	57.4 /13.9 /27.7	49.5	9.9	22.0
Group A	60.4/10.5/27.9	57.0	9.3	32.6
Group B	40.0/33.3/26.7	0.0	13.3	53.3
	Total bilirubin upregulation pre-ERCP (%)	Alanine aminotransferase upregulation pre-ERCP (%)	Balloon dilatation (%)	ENBD (%)
Total patients	55.4	75.2	27.7	98.0
Group A	59.3	75.6	32.6	98.9
Group B	33.3	73.3	0.0	93.3

Group A, cases of stones extracted by ERCP; Group B, cases of stones discharged before ERCP. ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; ENBD, endoscopic nasobiliary drainage. Stone extraction method 1, using a spiral net basket; stone extraction method 2, using a retrieval balloon catheter; stone extraction method 3, a combination of 1 and 2.

the intestinal tract ($P < 0.05$). However, multivariate regression analyses showed that γ-GGT was not associated with spontaneous CBD stone passage. In accordance, other previous studies have also concluded that there is no significant correlation between abnormal liver function and spontaneous discharge of stones.[6,21] Perhaps we lacked a dynamic observation process. Khoury et al. showed that improved γ-GGT levels predicted spontaneous CBD stone passage.[8]

Increased CA 19-9 is associated with not only bile duct carcinoma but also acute cholangitis.[22] Mei et al. showed that elevated serum CA 19-9 levels were an important diagnostic indicator of acute cholangitis, secondary to CBD stones.[23] In this study, we found that CA 19-9 levels were significantly higher in group A than in group B ($P < 0.05$). However, CA 19-9 was not associated with stone retention or spontaneous passage. It has been reported that the properties of AFU in primary hepatocarcinoma are different from those in other human organs,[24] and AFU has been shown to be relevant in the diagnosis of hepatocellular carcinoma.[25] However, there are no reports showing a direct relationship between AFU and cholangitis or CBD stones. Patients with previous or current malignancies were excluded from this study. Unexpectedly, we found that AFU was significantly higher in group A than that in group B ($P < 0.05$). However, regression analyses showed that pre-ERCP AFU level was not an independently correlated factor for the spontaneous excretion of CBD stones.

A previous study concluded that CBD stones <3.5 mm in size were associated with a significantly increased likelihood of spontaneous passage, with an acceptable sensitivity of 71% and specificity of 69%.[8] Meanwhile, our study also concluded that a stone diameter of <0.33 cm was conducive

Table 3. Analysis of factors associated with the spontaneous passage of common bile duct stones.

	Univariate			Multivariate		
Variables	*P* value	HR	95% CI	*P* value	HR	95% CI
Age	>0.05	/	/	>0.05	/	/
Sex	>0.05	/	/	>0.05	/	/
Cholecystolithiasis	>0.05	/	/	>0.05	/	/
Alanine aminotransferase pre-ERCP	>0.05	/	/	>0.05	/	/
Aspartate aminotransferase pre-ERCP	>0.05	/	/	>0.05	/	/
Total bilirubin pre-ERCP	>0.05	/	/	>0.05	/	/
Direct bilirubin pre-ERCP	>0.05	/	/	>0.05	/	/
Indirect bilirubin pre-ERCP	>0.05	/	/	>0.05	/	/
γ-glutamyl transpeptidase pre-ERCP	0.018	0.996	0.994-0.999	>0.05	/	/
Alkaline phosphatase pre-ERCP	>0.05	/	/	>0.05	/	/
Cholinesterase pre-ERCP	>0.05	/	/	>0.05	/	/
Total bile acids pre-ERCP	>0.05	/	/	>0.05	/	/
Glycine proline dipeptidyl aminopeptidase pre-ERCP	>0.05	/	/	>0.05	/	/
α-L-fucosidase pre-ERCP	0.023	0.885	0.796-0.983	>0.05	/	/
Total cholesterol pre-ERCP	>0.05	/	/	>0.05	/	/
Triglyceride pre-ERCP	>0.05	/	/	>0.05	/	/
High density lipoprotein cholesterol pre-ERCP	>0.05	/	/	>0.05	/	/
Low density lipoprotein cholesterol pre-ERCP	>0.05	/	/	>0.05	/	/
Adenosine deaminase pre-ERCP	>0.05	/	/	>0.05	/	/
Temperature pre-ERCP	>0.05	/	/	>0.05	/	/
White blood cells pre-ERCP	>0.05	/	/	>0.05	/	/
Percentage of neutrophils pre-ERCP	>0.05	/	/	>0.05	/	/
C-reactive protein pre-ERCP	>0.05	/	/	>0.05	/	/
Common bile duct diameter >1 cm	>0.05	/	/	>0.05	/	/
Carbohydrate antigen 19-9 pre-ERCP	>0.05	/	/	>0.05	/	/
Time from admission to ERCP	>0.05	/	/	>0.05	/	/
Stone size	0.001	0.001	0.001–0.008	0.017	0.001	0.001–0.057

ERCP, endoscopic retrograde cholangiopancreatography; HR, hazard ratio; CI, confidence interval.

to spontaneous discharge into the intestinal tract (hazard ratio: 0.001, 95% confidence interval: 0.001–0.057, P = 0.017).

A delay in the time between a patient's admission and them undergoing ERCP could theoretically increase the possibility of CBD stones being spontaneously passed.[26] The mean time from admission to ERCP was relatively longer in group B than in group A (5.3 *vs.* 3.2 days), but the difference was not significant. Logistic regression analysis showed that time was not an independent factor for stone passage. Additionally, a previous study showed that advanced age and male sex were associated with the failure of spontaneously passing CBD stones.[8] The revised ASGE guidelines (2019) also deem age >55-years-old to be a moderate risk factor for CBD stones.[13] However, in this study, logistic regression analysis did not show that advanced age or male sex were risk factors for failing to spontaneously pass CBD stones.

The role of imaging in examining for CBD stones was also a focus of this study. Transabdominal US is not a sensitive enough tool for detecting CBD stones, with its sensitivity reported to range from 20% to 80%.[1] Both MRCP and EUS have high diagnostic accuracy for detecting CBD stones.[11] Intraoperative cholangiography is also a common method of evaluating for the presence of CBD stones, with a reported sensitivity of 59% to 100% and specificity of 93% to 100%.[10] It was reported that at least 3% to 10% of patients who underwent cholecystectomy might be complicated with CBD stones.[27] In this condition, there were two main approaches: the single-stage "laparoscopy-first" approach, which relied on intraoperative cholangiography for diagnosis and laparoscopic common bile duct exploration for treatment, and the two-stage "endoscopy-first" approach, which relied on MRCP or EUS for diagnosis and pre- or post-cholecystectomy ERCP for management.[28] There were no significant differences in the mortality, morbidity, or failure rates between laparoscopic CBD clearance and endoscopic bile duct management.[29]

Our study had several limitations. First, it was a retrospective study that was performed in a single medical center. Second, the sample size was not large enough, and the study groups were not similar in the number of patients included.

In conclusion, the spontaneous passage of CBD stones is a common phenomenon. Stone size <0.33 cm is conducive to the spontaneous discharge of CBD stones into the intestinal tract. The observation of dynamic changes in liver function may be a better method for tracking spontaneous stone discharge. The relationship between AFU and choledocholithiasis deserves further study. Finally, we suggest performing EUS prior to ERCP during the two-stage "endoscopy-first" procedure.

Acknowledgement

We thank Ms. Biyao for assisting with the statistical analysis.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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