Incidence and risk factors of residual bile duct stones after extraction by endoscopic retrograde cholangiopancreatography

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Abstract
Background: Residual bile duct stones may be found eventually after confirmation of complete stone removal.

Aims: we retrospectively investigated the incidence and risk factors of residual bile duct stones after extraction by endoscopic retrograde cholangiopancreatography (ERCP).

Methods: We conducted a retrospective review of all ERCP sessions that underwent endoscopic bile duct stone extraction between April 2014 and March 2019. A total of 505 patients were enrolled to evaluate the incidence and risk factors of residual bile duct stones after ERCP.

Results: The rate of residual stones was 4.8% (24/505). Residual stones were detected by CT (12/24) or MRCP (12/24). In univariate analyses, a large number of stones (P = 0.01), long procedure time (P = 0.005), and performance of the pancreatic duct guidewire placement method (P-GW) for selective bile duct cannulation (P = 0.01) were the factors involved in residual stones. In multiple logistic regression analysis, performing P-GW was retained as the only independent factor of residual stones (odds ratio [OR], 3.4; 95% CI, 1.1–9.5; P = 0.02).

Conclusions: When removing bile duct stones with a pancreatic guidewire in place, paying attention to residual stones is necessary.

Background
Bile duct stones become life-threatening when acute cholangitis occurs; thus, appropriate diagnosis and treatment are important [1]. Because techniques such as endoscopic sphincterotomy (EST) have been widely used, endoscopic retrograde cholangiopancreatography (ERCP) is the first choice for treating common bile duct (CBD) stones [2]. Recent improvement of stone extraction instruments and tools has made the endoscopic treatment of bile duct stones easier [3–6], and stones can be completely extracted in approximately 85–95% of cases [7, 8]. However, even if the bile duct stones are confirmed to have been completely removed, cases of having residual stones are reported. For preventing the retention of residual bile duct stones, complete bile duct clearance is generally confirmed by balloon-occlusion cholangiography [9]. However, in the previous reports, balloon-occlusion cholangiography can miss residual stones in 11–30% of cases [10–14]. Missed bile duct
stones can result in recurrent biliary symptoms, cholangitis, and pancreatitis, and they can have significant cost implication with the need for repeat imaging and/or procedures [10].

To date, the risk factors of residual bile duct stones after extraction by ERCP have not been thoroughly evaluated. Hence, we retrospectively investigated the incidence and risk factors of residual bile duct stones after extraction by ERCP.

Methods
Patients
We conducted a retrospective review of all ERCP sessions that underwent endoscopic bile duct stone extraction and balloon-occlusion cholangiography at the end of the procedure to confirm complete bile duct clearance between April 2014 and March 2019. This study enrolled 505 patients to evaluate the incidence and risk factors of residual bile duct stones after ERCP.

Study definition and measurements
We checked the electronic medical records of patients and recorded their age, sex, and endoscopic procedure. We also assessed whether residual bile duct stones were discovered after ERCP. Residual stone cases were defined as those cases with bile duct stones that have remained and detected by initial follow-up imaging such as CT or MRCP within 2 months after endoscopic stone extraction. Considering that the possibility of residual stones falling from the gallbladder to the CBD could not be ruled out, we excluded cases of bile duct stone recurrence of more than 2 months after the first ERCP session. We also excluded postgastrectomy cases, except distal gastrectomy with Billroth I reconstruction.

In this study, we primarily aimed to investigate the incidence and risk factors of residual bile duct stones after extraction by ERCP despite performing balloon-occlusion cholangiography at the end of examination to confirm complete bile duct clearance.

This study was approved by the ethics review board at our hospital and complied with the Declaration of Helsinki, as revised in Brazil 2013. All patients also provided written informed consent for ERCP.

Procedures
All ERCPs were performed under the supervision of an expert with experience in over 1000 ERCP procedures. In our institution, biliary cannulation is first attempted using the conventional contrast
cannulation (CC). However, when biliary cannulation is difficult to perform by CC but a guidewire can be placed in the pancreatic duct, pancreatic duct guidewire placement method (P-GW) is employed as the second choice. Then, we typically place a pancreatic stent over the guidewire used in the P-GW at the end of the examination to prevent pancreatitis. Therefore, in such cases, we remove bile duct stone with the pancreatic duct guidewire in place (Fig. 1a, b, c). The high-frequency device used in EST had a 120-watt endocut mode.

Effect 3 (ICC 200; ERBE Corp., Tuebingen, Germany) or ESG-100 in a 50-watt pulse cut slow mode (Olympus Corp., Tokyo, Japan) was also utilized. We discontinued any kind of antithrombotic drugs in principle, and after the appropriate discontinuation period for each drug, EST was performed. For patients who had difficulty in discontinuing antithrombotic drugs, heparin was substituted. Endoscopic papillary large balloon dilatation (EPLBD) was defined as papillary dilatation performed using a ≥ 12-mm diameter balloon, and endoscopic papillary balloon dilatation (EPBD) was defined as papillary dilatation performed using a ≤ 10-mm diameter balloon. EPLBD was performed for the papilla after EST performance or with a history of EST. Complete stone removal was confirmed by balloon-occlusion cholangiography. We injected the contrast at the proximal-side hole of the balloon catheter after stone removal (Fig. 2). We did not perform intraductal ultrasonography (IDUS) or peroral cholangioscopy (POCS) to confirm the presence of residual stones. All patients were given antibiotics, with the type of antibiotic and administration period determined at the discretion of the attending physician. With the aim of preventing post-ERCP pancreatitis, all patients were administered with 600 mg/day of gabexate mesilate on the day of the ERCP procedure. Furthermore, all patients underwent blood tests 3 hours after the procedure and on the following day. Thereafter, we conducted blood and imaging tests as prescribed by the attending physician to ascertain the patient’s condition.

Statistical analysis
Categorical variables are expressed as absolute (n) and relative (%) frequencies and were compared by Fisher’s exact test. For comparisons of continuous data, the two-sample t-test was used if a normal distribution was possible, and the Mann-Whitney test was used if normality could not be
demonstrated. To investigate the risk factors of residual bile duct stones after removal by ERCP, we performed multivariate logistic regression. Furthermore, \( P < 0.05 \) was considered significant.

Statistical calculations were performed using the SAS JMP version 12.2.0 software (SAS Institute, Cary, NC).

Results

Patient characteristics and endoscopic procedures

The median age was 77 years. Numerous cases of native papilla were recorded (68.9%). The mean number of stones, maximum stone diameter, and bile duct diameter were 2.7, 8.6 mm, and 11.3 mm, respectively. The median procedure time was 28 minutes.

Furthermore, the procedures for papilla included EST alone in 66.1%, EST + EPLBD in 23.6%, EPBD alone in 3.6%, and EST + EPBD in 6.7% of recorded cases. Techniques for difficult biliary cannulation included P-GW in 8.5% and precut in 0.6%. The stone extraction devices included mechanical lithotripsy (ML) in 8.3%, balloon in 40.8%, and basket in 50.3%. Patient characteristics are shown in Table 1.

|                      | Value                  |
|----------------------|------------------------|
| Patients, n          | 505                    |
| Age, median (IQR)    | 77 (68-83)             |
| Sex (male/female), n | 279/226                |
| Native papilla, n (%)| 348 (68.9)             |
| Acute cholangitis, n (%) | 112 (22.2)       |
| Postcholecystectomy, n (%) | 87 (17.2)       |
| Stomach (normal/Billroth I), n | 490/15       |
| Presence of diverticulum, n (%) | 237 (46.9)  |
| Number of stones, mean (SD) | 2.7 (3.1)   |
| Maximum stone diameter (mm), mean (SD) | 8.6 (6.1)   |
| Bile duct diameter (mm), mean (SD) | 11.3 (3.6)  |
| Procedure time (min), median (IQR) | 28 (20-40)  |

Endoscopic procedure

|                        | Value                  |
|------------------------|------------------------|
| EST, n (%)             | 334 (66.1)             |
| EST + EPLBD, n (%)     | 119 (23.6)             |
| EPBD, n (%)            | 18 (3.6)               |
| EST + EPBD, n (%)      | 34 (6.7)               |
| P-GW, n (%)            | 43 (8.5)               |
| precut, n (%)          | 3 (0.6)                |
| IDUS to detect bile duct stone, n (%) | 60 (11.9)   |
| Using ML, n (%)        | 42 (8.3)               |
| Balloon extraction, n (%) | 216 (40.8)         |
| Basket extraction, n (%) | 254 (50.3)           |

IQR, interquartile range; SD, standard deviation; EST, endoscopic sphincterotomy; EPLBD, endoscopic papillary large balloon dilatation; EPBD, endoscopic papillary balloon dilatation; IDUS, intraductal ultrasonography; ML, mechanical lithotripsy; P-GW, pancreatic duct guidewire placement method

Incidence and patient characteristics with residual bile duct stones

The rate of residual stones was 4.8% (24/505). Residual stones were detected by CT (12/24) or MRCP
The mean number of residual stones was 2.2, and the mean diameter of residual stones was 5.4 mm. Characteristics of residual stones are shown in Table 2.

### Table 2

**Characteristics of residual stones**

| Characteristics                              | Residual cases of bile duct stones, n (%) | Complete extraction group (n = 481) |
|----------------------------------------------|------------------------------------------|-----------------------------------|
| Number of stones, mean (SD)                  | 2.2 (2.3)                                |                                   |
| Maximum stone diameter (mm), mean (SD)       | 5.4 (3.7)                                |                                   |
| Diagnostic image, n (%)                      |                                         |                                   |
| MRCP, n (%)                                  | 12 (50)                                  |                                   |
| CT, n (%)                                    | 12 (50)                                  |                                   |

### Risk factor of residual bile duct stones

In univariate analyses, a large number of stones (P = 0.01), long procedure time (P = 0.005), and P-GW performance (P = 0.01) were the factors involved in residual stones (Table 3). No difference was found in the maximum stone diameter, bile duct diameter, presence of diverticulum, procedures for papilla (EST, EST + EPLBD, EPBD, and EST + EPBD) and lithotripsy frequency between the residual group and complete extraction group.

### Table 3

**Risk factors of residual bile duct stones in univariate analyses**

| Characteristics                              | Residual group (n = 24) | Complete extraction group (n = 481) | P   |
|----------------------------------------------|-------------------------|-----------------------------------|-----|
| Age, median (IQR)                            | 75.5 (67.5–82.25)       | 77.0 (68.0–83.00)                 | 0.81|
| Sex (male/female), n                         | 14/10                   | 265/216                           | 0.84|
| Native papilla, n (%)                        | 15/24 (62.5)            | 333/481 (69.2)                    | 0.5 |
| Cholangitis, n (%)                           | 5/24 (20.8)             | 107/481 (22.2)                    | > 0.99|
| Presence of Gallbladder, n (%)               | 20/24 (83.3)            | 393/481 (81.7)                    | > 0.99|
| Billroth I reconstruction, n (%)            | 1/24 (4.2)              | 14/481 (2.9)                      | 0.52|
| Presence of diverticulum, n (%)             | 11/24 (45.8)            | 226/481 (46.9)                    | >0.99|
| Number of stones, mean (SD)                 | 3.8 (2.9)               | 2.7 (3.1)                         | 0.01|
| Maximum stone diameter (mm), mean (SD)      | 8.5 (4.4)               | 8.6 (6.2)                         | 0.84|
| Bile duct diameter (mm), mean (SD)          | 11.8 (3.6)              | 11.3 (3.6)                        | 0.61|
| Procedure time (min), median (IQR)          | 36 (27–45.5)            | 28 (20–39.0)                      | 0.005|
| EST, n (%)                                  | 16/24 (66.7)            | 318/481 (66.1)                    | > 0.99|
| EST + EPLBD, n (%)                          | 6/24 (25)               | 113/481 (23.5)                    | 0.83|
| EPBD, n (%)                                  | 1/24 (4.2)              | 17/481 (3.5)                      | 0.55|
| EST + EPBD, n (%)                           | 1/24 (4.2)              | 33/481 (6.9)                      | > 0.99|
| Lithotripsy, n (%)                           | 3/24 (12.5)             | 37/481 (7.7)                      | 0.43|
| PGW, n (%)                                   | 6/24 (25)               | 37/481 (7.7)                      | 0.01|

In multiple logistic regression analysis, performing P-GW was retained as the independent factor of residual stones (odds ratio [OR], 3.4; 95% CI, 1.1–9.5; P = 0.02) (Table 4).
### Table 4
Risk factors of residual bile duct stones in multiple logistic regression analysis

|                      | OR  | 95% CI     | P    |
|----------------------|-----|------------|------|
| P-GW                 | 3.4 | 1.1–9.5    | 0.02 |
| Number of stones     | 1.1 | 0.96–1.2   | 0.18 |
| Procedure time       | 1   | 0.99–1.0   | 0.16 |

OR, odds ratio; CI, confidence interval

### Discussion

In this study, the balloon-occlusion cholangiography failed to detect residual bile duct stones in 4.8%. This tool cannot accurately confirm complete bile duct clearance after EST/EPBD for stone extraction.

According to a previous report, residual stones significantly correlate with the presence of diverticulum, stone size, and using of ML and electrohydraulic lithotripsy (EHL). When the lower bile duct is compressed or bent by parapapillary diverticulum, residual stones are generally less likely to pass spontaneously. When the biliary stone is large, that is, when the stones are extracted using ML or EHL, the frequency of residual stones is significantly higher. Therefore, the frequency of fragmented residual stones is high when ML is used [12]. However, in this study, the presence of diverticulum, maximum stone diameter, and frequency of lithotripsy between sessions with or without residual stones have no marked difference.

To confirm complete bile duct clearance, some endoscopists perform IDUS [15]. Tsuchiya et al. performed IDUS after stone extraction and reported that balloon-occlusion cholangiography did not detect any residual CBD stones in 23.7% (14/59) of the patients [16]. However, accurate evaluation by IDUS to confirm the presence residual stones may be difficult because the procedures for papilla, such as EST, caused pneumobilia, which makes obtaining echo imaging in the bile duct challenging. Therefore, we rarely perform IDUS to confirm the presence of residual stones.

POCS has been described in the evaluation of residual stones that are not detected by cholangiography. POCS is particularly appropriate when pneumobilia exists. Itoi et al. performed POCS and reported that 24% of the patients still had residual stones after stone extraction by ERCP [12]. In a multicenter study evaluating POCS, 11% of patients (7/66) had bile duct stones identified only by POCS [11]. However, considering the cost and complexity, POCS is difficult to perform when confirming complete extraction of bile duct stones in all cases.
In this study, using P-GW was retained as the independent factor of residual stones on multiple logistic regression analysis (odds ratio [OR], 3.4; 95% CI, 1.1–9.5; P = 0.02). Previous studies of P-GW efficacy have reported varied results, with the success rate of biliary cannulation ranging from 43.8–92.6%; furthermore, P-GW techniques are useful for patients with difficult biliary cannulation [17–21]. Another advantage of P-GW, if the procedure can be completed with the guidewire placed in the pancreatic duct, is the ease of placing a pancreatic stent at the end of the procedure. Difficult biliary cannulation is considered as a procedure-related risk factor for post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) [22]. In patients with difficult biliary cannulation who underwent successful biliary cannulation performing P-GW, a pancreatic duct stent should be placed to prevent PEP even if EST is performed [23]. Therefore, we generally place a pancreatic duct stent over the guidewire used in the P-GW at the end of the examination. Therefore, we removed bile duct stone with the pancreatic duct guidewire in place. However, the complexity of this procedure may contribute to the incomplete removal of stones. When we perform P-GW for bile duct stone extraction, we should pay attention to the values of hepatobiliary enzymes in blood tests after the procedure because residual stones may exist. If the increase in hepatobiliary enzymes persists after the procedure, early image evaluations, such as CT and MRCP, should be performed. As mentioned above, IDUS is not useful when pneumobilia exists, and POCS is not available in every institution. To the best of our knowledge, this study is the largest to investigate the risk factors of residual bile duct stones after extraction by ERCP. Some limitations must be considered when interpreting the results. The possibility of a stone falling from the gallbladder to the CBD could not be ruled out; therefore, we excluded cases of bile duct stone recurrence of more than 2 months after the first ERCP session for analysis. However, even for residual stone cases in this study, completely ruling out of falling stones from the gallbladder to the CBD is impossible. In addition, all data were retrospectively collected from a single center. A prospective study with a larger number of cases is necessary. Conclusions We conclude that performing P-GW was a risk factor of residual stones, although it is useful for difficult biliary cannulation and PEP prevention.
Abbreviations
EST, endoscopic sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; CC, the conventional contrast cannulation; P-GW, pancreatic duct guidewire placement method; EPLBD, endoscopic papillary large balloon dilatation; EPBD, endoscopic papillary balloon dilatation; IDUS, intraductal ultrasonography; POCS, peroral cholangioscopy; ML, mechanical lithotripsy; EHL, electrohydraulic lithotripsy; OR, odds ratio; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis

Declaration
☐ Ethics approval and consent to participate
This study was approved by the ethics review board at our hospital. Approval number is 4563.

☐ Consent for publication
Not applicable.

☐ Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

☐ Competing interests
The authors declare that they have no competing interests.

☐ Funding
None.

☐ Authors’ contributions
FA and NK designed the report; FA, NK, MR, MY, SK, SJ, and IY were attending doctors for the patients; IH, MK, and WT contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. FA, NK, and IF organized the report; and FA wrote paper.

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Figures
Figure 1

Fig. 1a: Pancreatic duct guidewire placement method (P-GW) for difficult biliary cannulation

Fig. 1b: Stone extraction with the pancreatic duct guidewire in place Fig. 1c: Placing a pancreatic stent over the guidewire used in the P-GW at the end of the examination for pancreatitis prevention
Figure 2

Balloon-occlusion cholangiography for confirming complete stone removal