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ORIGINAL ARTICLE

# Endoscopic retrograde cholangiopancreatography-related complications for bile duct stones in asymptomatic and symptomatic patients

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## Abstract

**Background and Aim:** Current guidelines recommend the removal of common bile duct (CBD) stones by endoscopic retrograde cholangiopancreatography (ERCP) for both asymptomatic and symptomatic patients. We conducted this study because of the limited research comparing the risks of ERCP-related complications between these two groups.

**Methods:** This retrospective study involved 1491 patients with native major duodenal papilla diagnosed with choledocholithiasis at three institutions in Japan. The rates of ERCP-related complications, including post-ERCP pancreatitis (PEP), cholangitis, bleeding, and perforation, were compared using one-to-one propensity score matching between the asymptomatic and symptomatic patients.

**Results:** Complications were observed in 112 (7.5%) of the 1491 patients (asymptomatic group: 31/172 [18.0%] *vs* symptomatic group: 81/1319 [6.1%], $P < 0.001$). The rate of severe complications was higher in the asymptomatic group than that in the symptomatic group (asymptomatic group: 5/31 [16.1%] *vs* symptomatic group: 3/81 [3.7%], $P = 0.036$). In the propensity-matched asymptomatic and symptomatic patients, the incidences of PEP, cholangitis, bleeding, and perforation were 18/143 (12.6%) *vs* 4/143 (2.8%) ($P = 0.003$); 4/107 (3.7%) *vs* 6/107 (5.6%) ($P = 0.75$); 1/140 (0.7%) *vs* 3/140 (2.1%) ($P = 0.62$); and 2/140 (1.4%) *vs* 2/140 (1.4%) ($P = 1.0$).

**Conclusions:** ERCP for asymptomatic patients with CBD stones is associated with a higher risk of overall and severe complications than that for symptomatic patients with CBD stones; the overall rate is influenced by the high incidence of PEP in the asymptomatic group. Endoscopists should explain the risk of ERCP-related complications for asymptomatic patients before performing the procedure.

## Introduction

Common bile duct (CBD) stones can cause acute cholangitis and biliary pancreatitis. Available guidelines generally recommend endoscopic retrograde cholangiopancreatography (ERCP) as the first-line treatment for CBD stones.[1–4]

ERCP procedures have a high risk of complications, including post-ERCP pancreatitis (PEP), cholangitis, bleeding, and perforation, with an overall incidence of 4.0–15.9% of patients.[5,6] If ERCP is used as a prophylactic treatment for asymptomatic patients with benign CBD stones, usually performed to prevent possible CBD stone-related complications, endoscopists are encouraged to advise patients about ERCP-related complications.

Recent studies have shown that ERCP for asymptomatic patients with CBD stones has a higher incidence of PEP than that for symptomatic patients.[7–10] When endoscopists perform ERCP for patients with asymptomatic CBD stones, overall ERCP-related complications, including not only PEP but also cholangitis, bleeding, and perforation, should be considered. Nevertheless, there are limited data about overall ERCP-related complications associated with ERCP for asymptomatic CBD stones. This multicenter retrospective study examines this question in a large cohort.

## Methods

***Study design.*** Our study included 1491 patients with native major duodenal papillae who were treated for CBD stones by ERCP at Kumamoto City Hospital, Kumamoto Chuo Hospital, and Saiseikai Kumamoto Hospital in Japan between April 2012

and February 2020. We used some of this data pool (April 2012 to March 2018) in our previous report comparing the incidence of PEP in asymptomatic and symptomatic patients.[7] The institutional review boards of the participating institutions approved the present study. This study was conducted according to the ethical standards in the Declaration of Helsinki. Consent was obtained based on an opt-out methodology.

***Patient selection.*** The studied patients met the following inclusion criteria: (i) Having CBD stones detected during ERCP, (ii) presence of a native major duodenal papilla, and (iii) having either a normal upper gastrointestinal tract or a history of Billroth I gastrectomy. Exclusion criteria were (i) a history of ERCP, (ii) a history of Billroth II or Roux-en-Y reconstruction, and (iii) lack of CBD stone detection during ERCP.

***ERCP procedures.*** The ERCP procedures were performed by 38 endoscopists using side-viewing duodenoscopes (Olympus JF-260, TJF-260V; Olympus Medical Systems, Tokyo, Japan). This group of clinicians included 18 trainees who had performed fewer than 200 ERCP procedures and who were assisted by experienced endoscopists. The pre-surgery medications including midazolam and pethidine hydrochloride, and scopolamine butylbromide or glucagon were injected intravenously.

After selective biliary cannulation, endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), or endoscopic papillary large balloon dilation (EPLBD) was performed. In our institutions, we use the EST cutting direction toward the 11–12 o'clock position, and the incision range of the EST is limited to the transverse fold by protocol.

The size of the dilation balloon was based on the diameter of distal CBD. If the balloon measured <12 mm, minor EST was rarely performed before EPBD; if the balloon measured >12 mm in diameter to extract large and multiple stones, minor EST was performed before EPLBD. Stone removal was performed using a basket, a balloon catheter, and/or endoscopic mechanical lithotripsy, if necessary.

If patients required biliary drainage, a plastic drainage stent (straight type) or nasobiliary drainage stent was inserted based on the operator's decision. If patients were undergoing antithrombotic treatment, ERCP procedures were performed using guidelines published by the Japan Gastroenterological Endoscopy Society.[11]

Rectal nonsteroidal anti-inflammatory drugs were administered to and/or prophylactic pancreatic stent placements were performed in patients at high risk for PEP based on the endoscopists' decision.

***Primary and secondary outcomes.*** The primary outcomes of this study were the incidence rates of overall ERCP-related complications and the severity. The secondary outcomes were the incidence rates and severities of each ERCP-related complication, that is, PEP, cholangitis, bleeding, and perforation.

***Study definitions.***

- Asymptomatic patients had CBD stones but no symptoms, such as abdominal pain, and no hematological abnormalities, such as elevated liver enzymes or serum bilirubin at the time of ERCP. Patients with transient cholestasis without acute cholangitis before ERCP and normal blood tests and without symptoms at the time of ERCP were included in the asymptomatic group in this study.
- Symptomatic patients had CBD stones and typical physical symptoms and elevated liver enzymes and serum bilirubin.
- ERCP-related complications and their severity were diagnosed based on consensus criteria.[12]
- Difficult biliary cannulation was one that exceeded 10 min for the procedure.[13]

***Statistical analysis.*** Patient categorical variables were compared using chi-square test, or Fisher's exact test, as appropriate. Continuous variables were compared using Welch's *t*-test.

We conducted one-to-one propensity score matching with a caliper and a standard deviation of 0.2 to adjust patients' baseline characteristics, and the scores were calculated using a logistic regression model. All factors shown in Table 1 were used to calculate propensity scores. A total cohort was used to construct propensity scores to examine the effect of symptoms for bleeding and perforation. Patients with biliary pancreatitis ($n = 94$) and acute cholangitis ($n = 926$) were excluded while calculating propensity scores to examine the effect of symptoms for PEP and post-ERCP cholangitis, respectively.

A $P$ value of <0.05 indicated statistical significance. All statistical analyses were conducted using EZR software version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, this software is a modified version of R commander (version 2.7-1), which was designed to add statistical functions frequently used in biostatistics.[14]

## Results

***Patient characteristics.*** Our study included 1491 patients with choledocholithiasis: 94 patients with biliary pancreatitis, 926 patients with acute cholangitis, 299 patients with obstructive jaundice without cholangitis, and 172 patients with asymptomatic CBD stones. Tables 1 and 2 present the detailed patient characteristics of the asymptomatic and symptomatic groups in the total and matched cohorts. In the matched cohort, patient characteristics were well balanced between the two groups.

***Complications of ERCP in the total cohort.*** Table 3 shows the rates of the complications of ERCP in the total cohort.

The rate of ERCP-related complications was 7.5% (112/1491). The rate of ERCP-related complications was higher in the asymptomatic group than in the symptomatic group (18.0% *vs* 6.1%, respectively; $P < 0.001$). The rate of severe ERCP-related complications was higher in the asymptomatic group than that in the symptomatic group (asymptomatic group: 5/31 [16.1%] *vs* symptomatic group: 3/81 [3.7%], $P = 0.036$).

When comparing the asymptomatic and symptomatic groups, a significant difference was seen in the incidence rates of PEP (12.2% [21/172] *vs* 2.7% [35/1319] ($P < 0.001$). There was no significant difference between the asymptomatic and symptomatic groups in the incidence rates of cholangitis, bleeding, and perforation: 2.3% (4/172) *vs* 1.4% (19/1319) ($P = 0.33$), 1.7% (3/172) *vs* 1.6% (21/1319) ($P = 0.75$), and 1.7% (3/172) and 0.5% (6/1319) ($P = 0.075$), respectively.

**Table 1** Baseline patient characteristics in the total cohort

| | Asymptomatic group ($n = 172$) | Symptomatic group ($n = 1319$) | *P*-value |
|---|---|---|---|
| Age (mean [SD]) | 73.7 (10.2) | 75.3 (14.3) | 0.065 |
| Female (%) | 83 (48.3) | 628 (47.6) | 0.94 |
| Underlying diseases | | | |
| Diabetes mellitus (%) | 14 (8.1) | 90 (6.8) | 0.52 |
| Cardiovascular diseases (%) | 22 (12.8) | 188 (14.3) | 0.73 |
| Cerebrovascular diseases (%) | 5 (2.9) | 122 (9.2) | 0.003 |
| Chronic pancreatitis (%) | 2 (1.2) | 1 (0.1) | 0.037 |
| Dialysis (%) | 6 (3.5) | 41 (3.1) | 0.82 |
| Liver cirrhosis (%) | 2 (1.2) | 11 (0.8) | 0.66 |
| Multiple underlying diseases (%) | 18 (10.5) | 140 (10.6) | 1.0 |
| Antithrombotic treatment | | | |
| Aspirin (%) | 25 (14.5) | 157 (11.9) | 0.32 |
| Thienopyridine (%) | 3 (1.7) | 19 (1.4) | 0.74 |
| Antiplatelet agent other than aspirin and thienopyridine (%) | 3 (1.7) | 21 (1.6) | 0.75 |
| Anticoagulant (%) | 8 (4.7) | 120 (9.1) | 0.059 |
| Dual or triple therapy (%) | 7 (4.1) | 48 (3.6) | 0.83 |
| Billroth-1 reconstruction (%) | 9 (5.2) | 32 (2.4) | 0.045 |
| Presence of gallstones (%) | 116 (67.4) | 819 (62.1) | 0.18 |
| Post-cholecystectomy (%) | 26 (15.1) | 135 (10.2) | 0.066 |
| Performance status3 or 4 (%) | 11 (6.4) | 256 (19.4) | <0.001 |
| Normal serum bilirubin (%) | 172 (100.0) | 496 (37.6) | <0.001 |
| Platelet counts (mean [SD]) ($\times 10^6$/L) | 20.0 (6.6) | 19.1 (7.8) | 0.081 |
| PT-INR | 1.05 (0.19) | 1.2 (0.88) | <0.001 |
| Non-dilated CBD (<10 mm) (%) | 76 (44.2) | 530 (40.2) | 0.32 |
| Periampullary diverticulum (%) | | | 0.86 |
| Extra-diverticular papilla (%) | 45 (26.2) | 331 (25.1) | |
| Intra-diverticular papilla (%) | 8 (4.7) | 55 (4.2) | |
| Antibiotics (%) | 90 (52.3) | 1159 (87.9) | <0.001 |
| Trainees (%) | 35 (20.3) | 202 (15.3) | 0.096 |
| Successful biliary cannulation (%) | 167 (97.1) | 1305 (98.9) | 0.058 |
| Difficult biliary cannulation (%) | 66 (38.4) | 324 (24.6) | <0.001 |
| Contrast-assisted cannulation (%) | 122 (70.9) | 919 (69.7) | 0.79 |
| Wire-guided cannulation (%) | 14 (8.1) | 143 (10.8) | 0.35 |
| PGW-assisted cannulation (%) | 18 (10.5) | 190 (14.4) | 0.20 |
| Precut sphincterotomy (%) | 17 (9.9) | 66 (5.0) | 0.013 |
| Pancreatic injection (%) | 87 (50.6) | 597 (45.3) | 0.19 |
| EST (%) | 130 (75.6) | 970 (73.5) | 0.65 |
| EPBD (%) | 12 (7.0) | 139 (10.5) | 0.18 |
| EPLBD (%) | 25 (14.5) | 196 (14.9) | 1.0 |
| Use of balloon catheter (%) | 136 (79.1) | 1059 (80.3) | 0.69 |
| Use of basket catheter (%) | 79 (45.9) | 591 (44.8) | 0.81 |
| Mechanical lithotripsy (%) | 23 (13.4) | 203 (15.4) | 0.57 |
| Biliary stent placement (%) | 118 (68.6) | 1164 (88.2) | <0.001 |
| Number of CBD stones (mean [SD]) | 2.3 (2.7) | 2.1 (2.5) | 0.41 |
| Size of CBD stones (mean [SD]), mm | 6.2 (4.3) | 6.8 (4.6) | 0.087 |
| Large stones (>10 mm) (%) | 19 (11.0) | 241 (18.3) | 0.018 |
| Absence of prophylactic pancreatic stent (%) | 150 (87.2) | 1103 (83.6) | 0.27 |
| Protease inhibitor (%) | 65 (37.8) | 493 (37.4) | 0.93 |
| Rectal NSAIDs (%) | 18 (10.5) | 109 (8.3) | 0.31 |
| Procedure time (mean [SD]), min | 31.8 (18.2) | 26.4 (15.3) | <0.001 |

CBD, common bile duct; EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy; NSAIDs, nonsteroidal anti-inflammatory drugs; PGW, pancreatic guidewire; PT-INR, prothrombin time-international normalized ratio.

**Table 2** Baseline patient characteristics in the propensity-matched cohort

| | Matched asymptomatic group for PEP ($n = 143$) | Matched symptomatic group for PEP ($n = 143$) | *P*-value | Matched asymptomatic group for bleeding and perforation ($n = 140$) | Matched symptomatic group for bleeding and perforation ($n = 140$) | *P*-value | Matched asymptomatic group for cholangitis ($n = 107$) | Matched symptomatic group for cholangitis ($n = 107$) | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| Age (mean [SD]) | 73.3 (10.6) | 72.9 (13.6) | 0.80 | 73.7 (10.4) | 73.8 (13.3) | 0.94 | 72.7 (10.8) | 74.2 (12.5) | 0.35 |
| Female (%) | 72 (50.3) | 79 (55.2) | 0.48 | 71 (50.7) | 67 (47.9) | 0.72 | 57 (53.3) | 53 (49.5) | 0.68 |
| Underlying diseases | | | | | | | | | |
| Diabetes mellitus (%) | 11 (7.7) | 12 (8.4) | 1.0 | 11 (7.9) | 9 (6.4) | 0.82 | 9 (8.4) | 8 (7.5) | 1.0 |
| Cardiovascular diseases (%) | 17 (11.9) | 16 (11.2) | 1.0 | 16 (11.4) | 16 (11.4) | 1.0 | 11 (10.3) | 12 (11.2) | 1.0 |
| Cerebrovascular diseases (%) | 5 (3.5) | 7 (4.9) | 0.77 | 5 (3.6) | 8 (5.7) | 0.57 | 4 (3.7) | 7 (6.5) | 0.54 |
| Chronic pancreatitis (%) | 0 (0) | 0 (0) | 1.0 | 0 (0) | 0 (0) | 1.0 | 0 (0) | 0 (0) | 1.0 |
| Dialysis (%) | 4 (2.8) | 4 (2.8) | 1.0 | 4 (2.9) | 4 (2.9) | 1.0 | 2 (1.9) | 2 (1.9) | 1.0 |
| Liver cirrhosis (%) | 2 (1.4) | 1 (0.7) | 1.0 | 1 (0.7) | 2 (1.4) | 1.0 | 1 (0.9) | 1 (0.9) | 1.0 |
| Multiple underlying diseases (%) | 15 (10.5) | 12 (8.4) | 0.69 | 14 (10.0) | 15 (10.7) | 1.0 | 12 (11.2) | 11 (10.3) | 1.0 |
| Antithrombotic treatment | | | | | | | | | |
| Aspirin (%) | 20 (14.0) | 17 (11.9) | 0.73 | 18 (12.9) | 21 (15.0) | 0.73 | 12 (11.2) | 15 (14.0) | 0.68 |
| Thienopyridine (%) | 3 (2.1) | 3 (2.1) | 1.0 | 3 (2.1) | 1 (0.7) | 0.62 | 1 (0.9) | 1 (0.9) | 1.0 |
| Antiplatelet agent other than aspirin and thienopyridine (%) | 3 (2.1) | 2 (1.4) | 1.0 | 3 (2.1) | 4 (2.9) | 1.0 | 2 (1.9) | 2 (1.9) | 1.0 |
| Anticoagulant (%) | 8 (5.6) | 12 (8.4) | 0.49 | 8 (5.7) | 7 (5.0) | 1.0 | 8 (7.5) | 9 (8.4) | 1.0 |
| Dual or triple therapy (%) | 4 (2.8) | 5 (3.5) | 1.0 | 4 (2.9) | 6 (4.3) | 0.75 | 3 (2.8) | 2 (1.9) | 1.0 |
| Billroth-1 reconstruction (%) | 5 (3.5) | 8 (5.6) | 0.57 | 4 (2.9) | 4 (2.9) | 1.0 | 4 (3.7) | 4 (3.7) | 1.0 |
| Presence of gallstones (%) | 100 (69.9) | 99 (69.2) | 1.0 | 94 (67.1) | 95 (67.9) | 1.0 | 73 (68.2) | 74 (69.2) | 1.0 |
| Post-cholecystectomy (%) | 21 (14.7) | 26 (18.2) | 0.52 | 20 (14.3) | 21 (15.0) | 1.0 | 15 (14.0) | 13 (12.1) | 0.84 |
| Performance status3 or 4 (%) | 11 (7.7) | 16 (11.2) | 0.42 | 11 (7.9) | 15 (10.7) | 0.54 | 10 (9.3) | 9 (8.4) | 1.0 |
| Normal serum bilirubin (%) | 143 (100.0) | 143 (100.0) | 1.0 | 140 (100.0) | 140 (100.0) | 1.0 | 107 (100.0) | 107 (100.0) | 1.0 |
| Platelet counts (mean [SD]) ($\times 10^6$/L) | 20.5 (6.6) | 20.8 (9.3) | 0.77 | 20.4 (6.9) | 20.7 (7.6) | 0.73 | 20.9 (6.8) | 20.3 (5.9) | 0.49 |
| PT-INR | 1.1 (0.20) | 1.2 (0.83) | 0.089 | 1.1 (0.20) | 1.1 (0.16) | 0.93 | 1.1 (0.21) | 1.1 (0.23) | 0.84 |
| Non-dilated CBD (<10 mm) (%) | 64 (44.8) | 65 (45.5) | 1.0 | 60 (42.9) | 61 (43.6) | 1.0 | 46 (43.0) | 42 (39.3) | 0.68 |
| Periampullary diverticulum (%) | | | 0.92 | | | 1.0 | | | 0.77 |

(*Continues*)

**Table 2** (Continued)

| | Matched asymptomatic group for PEP ($n = 143$) | Matched symptomatic group for PEP ($n = 143$) | *P*-value | Matched asymptomatic group for bleeding and perforation ($n = 140$) | Matched symptomatic group for bleeding and perforation ($n = 140$) | *P*-value | Matched asymptomatic group for cholangitis ($n = 107$) | Matched symptomatic group for cholangitis ($n = 107$) | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| Extra-diverticular papilla (%) | 35 (24.5) | 31 (21.7) | | 35 (25.0) | 35 (25.0) | | 23 (21.5) | 27 (25.2) | |
| Intra-diverticular papilla (%) | 5 (3.5) | 5 (3.5) | | 5 (3.6) | 4 (2.9) | | 3 (2.8) | 2 (1.9) | |
| Antibiotics (%) | 82 (57.3) | 72 (50.3) | 0.29 | 81 (57.9) | 80 (57.1) | 1.0 | 61 (57.0) | 57 (53.3) | 0.68 |
| Trainees (%) | 22 (15.4) | 25 (17.5) | 0.75 | 22 (15.7) | 22 (15.7) | 1.0 | 15 (14.0) | 16 (15.0) | 1.0 |
| Successful biliary cannulation (%) | 142 (99.3) | 141 (98.6) | 1.0 | 138 (98.6) | 138 (98.6) | 1.0 | 106 (99.1) | 106 (99.1) | 1.0 |
| Difficult biliary cannulation (%) | 45 (31.5) | 47 (32.9) | 0.90 | 46 (32.9) | 44 (31.4) | 0.90 | 31 (29.0) | 30 (28.0) | 1.0 |
| Contrast-assisted cannulation (%) | 104 (72.7) | 100 (69.9) | 0.70 | 103 (73.6) | 101 (72.1) | 0.89 | 78 (72.9) | 79 (73.8) | 1.0 |
| Wire-guided cannulation (%) | 13 (9.1) | 16 (11.2) | 0.70 | 11 (7.9) | 12 (8.6) | 1.0 | 9 (8.4) | 10 (9.3) | 1.0 |
| PGW-assisted cannulation (%) | 16 (11.2) | 16 (11.2) | 1.0 | 16 (11.4) | 15 (10.7) | 1.0 | 11 (10.3) | 10 (9.3) | 1.0 |
| Precut sphincterotomy (%) | 10 (7.0) | 11 (7.7) | 1.0 | 10 (7.1) | 11 (7.9) | 1.0 | 9 (8.4) | 8 (7.5) | 1.0 |
| Pancreatic injection (%) | 71 (49.7) | 63 (44.1) | 0.41 | 68 (48.6) | 74 (52.9) | 0.55 | 51 (47.7) | 48 (44.9) | 0.78 |
| EST (%) | 109 (76.2) | 104 (72.7) | 0.59 | 106 (75.7) | 105 (75.0) | 1.0 | 80 (74.8) | 78 (72.9) | 0.88 |
| EPBD (%) | 10 (7.0) | 13 (9.1) | 0.67 | 9 (6.4) | 7 (5.0) | 0.80 | 7 (6.5) | 8 (7.5) | 1.0 |
| EPLBD (%) | 23 (16.1) | 24 (16.8) | 1.0 | 23 (16.4) | 26 (18.6) | 0.75 | 19 (17.8) | 20 (18.7) | 1.0 |
| Use of balloon catheter (%) | 113 (79.0) | 114 (79.7) | 1.0 | 110 (78.6) | 113 (80.7) | 0.77 | 84 (78.5) | 84 (78.5) | 1.0 |
| Use of basket catheter (%) | 75 (52.4) | 69 (48.3) | 0.55 | 70 (50.0) | 61 (43.6) | 0.34 | 54 (50.5) | 53 (49.5) | 1.0 |
| Mechanical lithotripsy (%) | 17 (11.9) | 24 (16.8) | 0.31 | 17 (12.1) | 13 (9.3) | 0.56 | 15 (14.0) | 19 (17.8) | 0.58 |
| Biliary stent placement (%) | 103 (72.0) | 99 (69.2) | 0.70 | 102 (72.9) | 100 (71.4) | 0.89 | 84 (78.5) | 82 (76.6) | 0.87 |
| Number of CBD stones (mean [SD]) | 2.2 (2.6) | 2.1 (2.6) | 0.60 | 2.2 (2.6) | 2.2 (2.8) | 0.86 | 2.3 (2.8) | 2.0 (2.5) | 0.54 |
| Size of CBD stones (mean [SD]), mm | 6.4 (4.5) | 6.6 (4.1) | 0.69 | 6.2 (4.5) | 5.9 (3.8) | 0.49 | 6.3 (4.9) | 6.8 (4.3) | 0.44 |
| Large stones (>10 mm) (%) | 18 (12.6) | 20 (14.0) | 0.86 | 17 (12.1) | 14 (10.0) | 0.70 | 16 (15.0) | 21 (19.6) | 0.47 |
| Absence of prophylactic pancreatic stent (%) | 126 (88.1) | 122 (85.3) | 0.60 | 121 (86.4) | 124 (88.6) | 0.72 | 93 (86.9) | 94 (87.9) | 1.0 |
| Protease inhibitor (%) | 53 (37.1) | 58 (40.6) | 0.63 | 55 (39.3) | 41 (29.3) | 0.10 | 45 (42.1) | 43 (40.2) | 0.89 |
| Rectal NSAIDs (%) | 13 (9.1) | 18 (12.6) | 0.45 | 12 (8.6) | 13 (9.3) | 1.0 | 9 (8.4) | 11 (10.3) | 0.82 |
| Procedure time (mean [SD]), min | 29.0 (16.7) | 28.9 (18.2) | 0.94 | 29.5 (17.1) | 28.5 (17.0) | 0.62 | 26.9 (14.5) | 28.1 (13.6) | 0.52 |

CBD, common bile duct; EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy; NSAIDs, nonsteroidal anti-inflammatory drugs; PGW, pancreatic guidewire; PT-INR, prothrombin time-international normalized ratio.

**Table 3** The rates of ERCP-related complications and the severity in the total cohort

| | Asymptomatic group ($n = 172$) | Symptomatic group ($n = 1319$) | *P*-value |
|---|---|---|---|
| Overall ERCP-related complications (%) | 31 (18.0) | 81 (6.1) | <0.001 |
| Severity | | | |
| Mild (%) | 14 (45.2) | 57 (70.4) | 0.017 |
| Moderate (%) | 12 (38.7) | 21 (25.9) | 0.25 |
| Severe (%) | 5 (16.1) | 3 (3.7) | 0.036 |
| Post-ERCP pancreatitis (%) | 21 (12.2) | 35 (2.7) | <0.001 |
| Severity | | | |
| Mild (%) | 10 (47.6) | 27 (77.1) | 0.040 |
| Moderate (%) | 8 (38.1) | 7 (20.0) | 0.21 |
| Severe (%) | 3 (14.3) | 1 (2.9) | 0.14 |
| Cholangitis (%) | 4 (2.3) | 19 (1.4) | 0.33 |
| Severity | | | 0.59 |
| Mild (%) | 2 (50.0) | 13 (68.4) | |
| Moderate (%) | 2 (50.0) | 6 (31.6) | |
| Bleeding (%) | 3 (1.7) | 21 (1.6) | 0.75 |
| Severity | | | 0.25 |
| Mild (%) | 1 (33.3) | 15 (71.4) | |
| Moderate (%) | 1 (33.3) | 4 (19.0) | |
| Severe (%) | 1 (33.3) | 2 (9.5) | |
| Perforation (%) | 3 (1.7) | 6 (0.5) | 0.075 |
| Severity | | | 0.64 |
| Mild (%) | 1 (33.3) | 2 (33.3) | |
| Moderate (%) | 1 (33.3) | 4 (66.7) | |
| Severe (%) | 1 (33.3) | 0 (0.0) | |

ERCP, endoscopic retrograde cholangiopancreatography.

**Table 4** The rates of ERCP-related complications and the severity in the propensity-matched cohort

| | Matched asymptomatic group for PEP ($n = 143$) | Matched symptomatic group for PEP ($n = 143$) | *P*-value |
|---|---|---|---|
| Post-ERCP pancreatitis (%) | 18 (12.6) | 4 (2.8) | 0.003 |
| Severity | | | |
| Mild (%) | 8 (44.4) | 3 (75.0) | 0.59 |
| Moderate (%) | 7 (38.9) | 1 (25.0) | 1.0 |
| Severe (%) | 3 (16.7) | 0 (0.0) | 1.0 |
| | Matched asymptomatic group for cholangitis ($n = 107$) | Matched symptomatic group for cholangitis ($n = 107$) | *P*-value |
| Cholangitis (%) | 4 (3.7) | 6 (5.6) | 0.75 |
| Severity | | | 1.0 |
| Mild (%) | 2 (50.0) | 4 (66.7) | |
| Moderate (%) | 2 (50.0) | 2 (33.3) | |
| | Matched asymptomatic group for bleeding and perforation ($n = 140$) | Matched symptomatic group for bleeding and perforation ($n = 140$) | *P*-value |
| Bleeding (%) | 1 (0.7) | 3 (2.1) | 0.62 |
| Severity | | | 1.0 |
| Mild (%) | 1 (100.0) | 1 (33.3) | |
| Moderate (%) | 0 (0.0) | 1 (33.3) | |
| Severe (%) | 0 (0.0) | 1 (33.3) | |
| Perforation (%) | 2 (1.4) | 2 (1.4) | 1.0 |
| Severity | | | 0.33 |
| Mild (%) | 0 (0.0) | 1 (50.0) | |
| Moderate (%) | 2 (100.0) | 0 (0.0) | |
| Severe (%) | 0 (0.0) | 1 (50.0) | |

ERCP, endoscopic retrograde cholangiopancreatography.

**Table 5** Summary of studies comparing the risks of ERCP-related complications for CBD stones between asymptomatic and symptomatic patients

| References | Study design | [asymptomatic group, n] (symptomatic group, n) | Overall complications [asymptomatic group (%)] (symptomatic group (%)) | PEP [asymptomatic group (%)] (symptomatic group (%)) | Cholangitis [asymptomatic group (%)] (symptomatic group (%)) | Bleeding [asymptomatic group (%)] (symptomatic group (%)) | Perforation [asymptomatic group (%)] (symptomatic group (%)) |
|---|---|---|---|---|---|---|---|
| Kim *et al.*[8] | Retrospective | [32] (536) | [15.6%] (10.4%) | [12.5%]* (3.9%) | [3.1%] (0.7%) | [3.1%] (6.0%) | [0%] (0.4%) |
| Saito *et al.*[16] | Retrospective | [67] (358) | [26.9%]* (3.9%) | [16.4%]* (2.2%) | [4.5%]* (0.6%) | [3.0%] (1.1%) | [3.0%]* (0%) |
| Xu *et al.*[9] | Prospective | [53] (274) | [26.4%]* (11.7%) | [20.8%]* (6.9%) | [3.8%] (3.6%) | [3.8%] (1.1%) | [1.9%] (0.4%) |
| Xiao *et al.*[15] | Retrospective | [79] (795) | [12.7%] (9.7%) | [7.6%] (6.9%) | [1.3%] (0.9%) | [3.8%] (1.6%) | [0%] (0.3%) |

CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; PEP, postendoscopic retrograde cholangiopancreatography pancreatitis.
*Statistically significant difference.

***Complications of ERCP in the matched cohort.*** Table 4 shows the rates of complications and the severity of ERCP in the matched cohort. The incidence of PEP in the asymptomatic and symptomatic groups was significantly different, 12.6% (18/143) *vs* 2.8% (4/143), respectively ($P = 0.003$). The incidence rates of cholangitis, bleeding, and perforation were not significantly different when comparing the asymptomatic and symptomatic groups: 3.7% (4/107) *vs* 5.6% (6/107) ($P = 0.75$), 0.7% (1/140) *vs* 2.1% (3/140) ($P = 0.62$), and 1.4% (2/140) *vs* 1.4% (2/140) ($P = 1.0$), respectively. There were no significant differences in the severity of each complication of ERCP in the matched cohort.

## Discussion

This study compared the complications between asymptomatic and symptomatic patients who underwent ERCP for treatment of CBD stones. In the total cohort, the rate of overall complications was higher in the asymptomatic group than that in the symptomatic group. Furthermore, the rate of severe complications was higher in the asymptomatic group than that in the symptomatic group. In the propensity-matched patients, the risk of PEP in asymptomatic patients was higher than that in symptomatic patients; the risks of other ERCP-related complications, including cholangitis, bleeding, and perforations, were similar in both groups.

The result of the high incidence of PEP in the present study was not surprising as we have previously reported that ERCP was associated with a high risk of PEP in asymptomatic patients.[7] In summary, our previous report found the risk of PEP to be higher in the asymptomatic group than in the symptomatic group: 14.6% (28/164) *vs* 3.0% (28/949) ($P < 0.001$).[7] The rates of PEP in asymptomatic patients in the present study were similar to those in other recent studies (7.6–21%).[8–10,15]

When performing ERCP in asymptomatic patients, endoscopists should consider the risk of PEP and other ERCP-related complications, including cholangitis, bleeding, and perforation. Table 5 summarizes the results of previous studies that compare asymptomatic and symptomatic patients and the risk of overall ERCP-related complications.[8,9,15,16] Our previous report found significantly higher incidence rates of ERCP-related cholangitis and perforation in the asymptomatic group than those in the symptomatic group,[16] but three other reports found no differences in the incidence rates of ERCP-related cholangitis and perforation.[8,9,15] However, the results of previous studies are questionable because of their small sample sizes. Furthermore, in the previous studies, some patient characteristics were inconsistent between the two groups.

The present large-cohort study using propensity score matching analysis demonstrated that there were no differences between the asymptomatic and symptomatic groups when comparing the incidence rates of ERCP-related cholangitis, bleeding, and perforation. Asymptomatic patients in our study had a higher incidence of PEP, which leads to a higher overall complication rate in the asymptomatic group.

Previous reports hypothesized that the high risk of PEP in asymptomatic patients who did not have cholestasis could be due to multiple patient- and procedure-related PEP risk factors such as normal serum bilirubin, non-dilated CBD, and difficult cannulation.[7,9,10,16] It is speculated that biliary cannulation is difficult in asymptomatic patients because the sphincter of Oddi is tightened because of the lower intraductal pressure due to the absence of cholestasis.[7,16] Prospective studies showed that increased risk factors for PEP are known to increase the incidence of PEP additively,[17,18] which supports our hypothesis for the high incidence of PEP in asymptomatic patients. Furthermore, an asymptomatic CBD stone itself may be an important risk factor for PEP because the incidence of PEP was significantly higher in the asymptomatic group than that in the symptomatic group after adjusting for confounding factors. However, its pathogenesis remains unclear.

Although the rates of each of the severe complications were not significantly different in the total and matched cohorts, the overall rate of severe complications was higher in the asymptomatic group in the total cohort. Endoscopists should be aware of this fact and should explain to the patients that severe complications may be more common in asymptomatic patients.

A recent study suggested that ERCP performed for asymptomatic CBD stones by experienced endoscopists was as safe as ERCP performed for symptomatic CBD stones.[15] In another

**Table 6** Summary of studies reporting the natural history of asymptomatic CBD stones

| References | Study design | Patients, *n* | Median follow-up period | Cumulative incidence of biliary complications, *n* (%) |
|---|---|---|---|---|
| Ammori *et al.*[20] | Prospective | 14 | 1.4 years | 4 (29%) |
| Collins *et al.*[21] | Prospective | 46 | 6 weeks | 0% |
| Caddy *et al.*[22] | Retrospective | 59 | 4.8 years | 0% |
| Moller *et al.*[23] | Retrospective | 594 | 30 days | 150 (25%) |
| Hakuta *et al.*[10] | Retrospective | 114 | 3.2 years | 20 (18%) |

CBD, common bile duct.

study, trainee involvement was a risk factor for PEP in patients with asymptomatic CBD stones.[19] Therefore, ERCP performed by experienced endoscopists may improve the safety of ERCP in patients with asymptomatic CBD stones.

When ERCP is indicated for a patient with asymptomatic CBD stones, their natural history should be considered. Reports on this question show a range of findings (Table 6).[10,20–23] A retrospective longitudinal cohort study of 114 wait-and-see patients who did not have an initial ERCP showed an 18% overall biliary complication rate during a median follow-up period of 3.2 years: cholangitis, 14%; cholecystitis, 0.9%; cholestasis, 3.5%; and biliary pancreatitis, 0%.[10]

Based on the results of the present study and previous reports on the natural history of asymptomatic CBD stones, the risk of cholangitis appears to be greater in the wait-and-see group than that in the endoscopic treatment group. However, the risk of pancreatitis appears to be greater in the endoscopic treatment group than that in the wait-and-see group. Although available guidelines recommend endoscopic treatment for asymptomatic CBD stones, endoscopists may need to carefully consider the risk–benefit ratio for ERCP in asymptomatic patients.

There were some limitations to this study. First, this was a retrospective study. Second, although we conducted a one-to-one propensity score matching analysis to balance the baseline patient characteristics, there may be some unmeasured confounding factors. Third, this study evaluated the average risks of ERCP-related complications in the wide range of ERCP procedures performed for CBD stones. Therefore, the specific risks of ERCP-related complications in each ERCP procedure performed for CBD stones were not examined.

In conclusion, ERCP for asymptomatic patients with CBD stones had a higher risk of overall complications than that for symptomatic patients with CBD stones; however, the two groups have equal risks of post-ERCP cholangitis, bleeding, and perforation. The overall rate is influenced by the high incidence of PEP in the asymptomatic group. Furthermore, the overall risk of severe complications may be higher in the asymptomatic group. Asymptomatic CBD stones can be a benign disease with no symptoms, and ERCP in these cases is a prophylactic treatment. Endoscopists should explain the risk of ERCP-related complications in detail before performing the procedure on asymptomatic patients with CBD stones.

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