

World Journal of *Clinical Cases*

World J Clinical Cases 2019 May 6; 7(9): 1006-1092





REVIEW

- 1006** Evaluation and management of acute pancreatitis
Chatila AT, Bilal M, Guturu P

ORIGINAL ARTICLE

Retrospective Cohort Study

- 1021** Rituximab-induced IgG hypogammaglobulinemia in children with nephrotic syndrome and normal pre-treatment IgG values
Marzuillo P, Guarino S, Esposito T, Di Sessa A, Orsini SI, Capalbo D, Miraglia del Giudice E, La Manna A

Retrospective Study

- 1028** Causes associated with recurrent choledocholithiasis following therapeutic endoscopic retrograde cholangiopancreatography: A large sample sized retrospective study
Deng F, Zhou M, Liu PP, Hong JB, Li GH, Zhou XJ, Chen YX

CASE REPORT

- 1038** Laparoscopic appendectomy for elemental mercury sequestration in the appendix: A case report
Norčič G, Čebren Ž, Sever P, Grosek J, Tomažič A
- 1043** Sofosbuvir/Ribavirin therapy for patients experiencing failure of ombitasvir/paritaprevir/ritonavir + ribavirin therapy: Two cases report and review of literature
Sato K, Yamazaki Y, Kobayashi T, Takakusagi S, Horiguchi N, Kakizaki S, Andou M, Matsuda Y, Uraoka T, Ohnishi H, Okamoto H
- 1053** Management of the late effects of disconnected pancreatic duct syndrome: A case report
Yamada R, Umeda Y, Shiono Y, Okuse H, Kuroda N, Tsuboi J, Inoue H, Hamada Y, Tanaka K, Horiki N, Takei Y
- 1060** Nerve coblation for treatment of trigeminal neuralgia: A case report
Yang XH, Li Y, Yang LQ, Wu BS, Ni JX
- 1066** Adult-onset mitochondrial encephalopathy in association with the MT-ND3 T10158C mutation exhibits unique characteristics: A case report
Fu XL, Zhou XX, Shi Z, Zheng WC
- 1073** Rare variant of pancreaticobiliary maljunction associated with pancreas divisum in a child diagnosed and treated by endoscopic retrograde cholangiopancreatography: A case report
Cui GX, Huang HT, Yang JF, Zhang XF

- 1080** Crizotinib-induced acute fatal liver failure in an Asian *ALK*-positive lung adenocarcinoma patient with liver metastasis: A case report
Zhang Y, Xu YY, Chen Y, Li JN, Wang Y
- 1087** Coexistence of breakpoint cluster region-Abelson1 rearrangement and Janus kinase 2 V617F mutation in chronic myeloid leukemia: A case report
Shi XB, Jiang JF, Jin FX, Cheng W

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Wilbert Aronow, MD, Professor, Statistical Worker, Department of Medicine, Davar, J (reprint author), Royal Free Hosp, Dept Cardiol, Carcinoid Heart Dis Clin, Pond St, London NW3 2QG, England., Valhalla, NY 10595, United States

AIMS AND SCOPE

World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The primary task of *WJCC* is to rapidly publish high-quality Case Report, Clinical Management, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Meta-Analysis, Minireviews, and Review, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, etc.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2018 Edition of Journal Citation Reports cites the 2017 impact factor for *WJCC* as 1.931 (5-year impact factor: N/A), ranking *WJCC* as 60 among 154 journals in Medicine, General and Internal (quartile in category Q2).

**RESPONSIBLE EDITORS
FOR THIS ISSUE**

Responsible Electronic Editor: Yun-Xiaojuan Wu Proofing Editorial Office Director: Jin-Lei Wang

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

May 6, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Retrospective Study

Causes associated with recurrent choledocholithiasis following therapeutic endoscopic retrograde cholangiopancreatography: A large sample sized retrospective study

Feng Deng, Mi Zhou, Ping-Ping Liu, Jun-Bo Hong, Guo-Hua Li, Xiao-Jiang Zhou, You-Xiang Chen

ORCID number: Feng Deng (0000-0001-9463-5661); Mi Zhou (0000-0002-7326-3747); Ping-Ping Liu (0000-0001-6053-9049); Jun-Bo Hong (0000-0002-0123-8868); Guo-Hua Li (0000-0002-8722-8600); Xiao-Jiang Zhou (0000-0003-4622-6040); You-Xiang Chen (0000-0003-4218-6133).

Author contributions: Deng F and Zhou M contributed equally to the study and share the primary authorship of this article; Deng F and Zhou M conceptualized and designed the study and wrote the manuscript; Liu PP collected the data; Hong JB made critical revisions to the manuscript; Li GH helped in interpreting and analyzing the data; Zhou XJ and Chen YX made substantial contributions to the conception, design, and coordination of the study and gave final approval of the version to be published; all authors read and approved the final manuscript.

Institutional review board

statement: This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University.

Informed consent statement: All involved subjects gave their informed consent (written or verbal) prior to study inclusion.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Open-Access: This article is an

Feng Deng, The First Affiliated Hospital of Nanchang University, Nanchang 330000, Jiangxi Province, China

Mi Zhou, Medical College of Nanchang University, Nanchang 330000, Jiangxi Province, China

Ping-Ping Liu, Department of Gastroenterology, The Affiliated Ganzhou Hospital of Nanchang University, Ganzhou 341000, Jiangxi Province, China

Jun-Bo Hong, Guo-Hua Li, Xiao-Jiang Zhou, You-Xiang Chen, Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Nanchang 330000, Jiangxi Province, China

Corresponding author: Xiao-Jiang Zhou, PhD, Associate Professor, Chief Doctor, Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, No. 17, Yongwaizheng Street, Nanchang 330000, Jiangxi Province, China. yfyzxj1970@163.com

Telephone: +86-791-88692540

Fax: +86-791-86292217

Abstract

BACKGROUND

Recurrence of primary choledocholithiasis commonly occurs after complete removal of stones by therapeutic endoscopic retrograde cholangiopancreatography (ERCP). The potential causes of the recurrence of choledocholithiasis after ERCP are unclear.

AIM

To analyze the potential causes of the recurrence of choledocholithiasis after ERCP.

METHODS

The ERCP database of our medical center for the period between January 2007 and January 2016 was retrospectively reviewed, and information regarding eligible patients who had choledocholithiasis recurrence was collected. A 1:1 case-control study was performed for this investigation. Data including general characteristics of the patients, past medical history, ERCP-related factors, common bile duct (CBD)-related factors, laboratory indicators, and treatment was analyzed by univariate and multivariate logistic regression analysis and Kaplan-Meier analysis.

open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: February 16, 2019

Peer-review started: February 18, 2019

First decision: March 5, 2019

Revised: March 15, 2019

Accepted: March 26, 2019

Article in press: March 26, 2019

Published online: May 6, 2019

P-Reviewer: Fusaroli P, Gkekas I, Hara K

S-Editor: Ji FF

L-Editor: Wang TQ

E-Editor: Wu YXJ



RESULTS

First recurrence of choledocholithiasis occurred in 477 patients; among these patients, the second and several instance (≥ 3 times) recurrence rates were 19.5% and 44.07%, respectively. The average time to first choledocholithiasis recurrence was 21.65 mo. A total of 477 patients who did not have recurrence were selected as a control group. Multivariate logistic regression analysis showed that age > 65 years (odds ratio [OR] = 1.556; $P = 0.018$), combined history of choledocholithotomy (OR = 2.458; $P < 0.01$), endoscopic papillary balloon dilation (OR = 5.679; $P = 0.000$), endoscopic sphincterotomy (OR = 3.463; $P = 0.000$), CBD stent implantation (OR = 5.780; $P = 0.000$), multiple ERCP procedures (≥ 2 ; OR = 2.75; $P = 0.000$), stones in the intrahepatic bile duct (OR = 2.308; $P = 0.000$), perampullary diverticula (OR = 1.627; $P < 0.01$), choledocholithiasis diameter ≥ 10 mm (OR = 1.599; $P < 0.01$), bile duct-duodenal fistula (OR = 2.69; $P < 0.05$), combined biliary tract infections (OR = 1.057; $P < 0.01$), and no preoperative antibiotic use (OR = 0.528; $P < 0.01$) were independent risk factors for the recurrence of choledocholithiasis after ERCP.

CONCLUSION

Patient age greater than 65 years is an independent risk factor for the development of recurrent choledocholithiasis following ERCP, as is history of biliary surgeries, measures during ERCP, and prevention of postoperative complications.

Key words: Choledocholithiasis; Endoscopic retrograde cholangiopancreatography; Recurrence; Common bile duct

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The potential causes of the recurrence of choledocholithiasis after endoscopic retrograde cholangiopancreatography (ERCP) are unclear. By a large sample sized retrospective study of 954 patients, we concluded that patient age greater than 65 years is an independent risk factor for the development of recurrent choledocholithiasis following ERCP, as is history of biliary surgeries, measures during ERCP, and prevention of postoperative complications.

Citation: Deng F, Zhou M, Liu PP, Hong JB, Li GH, Zhou XJ, Chen YX. Causes associated with recurrent choledocholithiasis following therapeutic endoscopic retrograde cholangiopancreatography: A large sample sized retrospective study. *World J Clin Cases* 2019; 7(9): 1028-1037

URL: <https://www.wjgnet.com/2307-8960/full/v7/i9/1028.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i9.1028>

INTRODUCTION

Due to its minimal trauma and high safety, endoscopic retrograde cholangiopancreatography (ERCP) has become one of the most important methods for the clinical diagnosis and treatment of choledocholithiasis. Currently, ERCP technology is very advanced, but the recurrence of choledocholithiasis after ERCP is still a challenging problem. Follow-up studies have shown that the incidence of choledocholithiasis recurrence after endoscopic treatment is 2%-22%^[1-5]. Many studies have reported that choledocholithiasis is associated with bacterial infection, an abnormal biliary structure, inflammation, endoscopic and surgical treatment, and other factors^[1-3,6-8]. However, risk factors for the recurrence of choledocholithiasis have not been thoroughly defined, and the risk factors identified are different across studies. This study aimed to explore the independent risk factors for stone recurrence by comprehensively analyzing the relevant factors for stone recurrence in a large-sized sample.

MATERIALS AND METHODS

Patients

From January 2007 to January 2016, we retrospectively reviewed cases from a well-designed ERCP database at the First Affiliated Hospital of Nanchang University. The follow-up period was from the date of the initial removal of choledocholithiasis to the date of the visit to the hospital for choledocholithiasis recurrence or more than one year for the control group. The patients with the symptoms of fever, abdominal pain, jaundice, or other typical symptoms who revisited our hospital underwent abdominal computed tomography (CT) and ERCP to confirm choledocholithiasis. The patients who underwent choledocholithiasis removal by ERCP and were confirmed to have had their stones completely removed were enrolled. The exclusion criteria were as follows: (1) History of previous ERCP; (2) Patients with tumors of the liver, gallbladder, common bile duct (CBD), or duodenal papilla; (3) Patients were confirmed not to have had their stones completely removed after first choledocholithiasis removal by ERCP; and (4) Patients with incomplete clinical data. The study was approved by the institutional review board of the First Affiliated Hospital of Nanchang University (No. 2017-040).

Outcome measurements

The primary outcomes were risk factors for recurrence of choledocholithiasis. Choledocholithiasis recurrence was defined as recurrence of symptoms of fever, abdominal pain, jaundice, or other typical symptoms, and choledocholithiasis was confirmed by abdominal B-scan ultrasonography, CT, or magnetic resonance cholangiopancreatography 6 mo after the stones were completely removed. The patients were classified into two groups: Recurrence and control groups. The following clinical data were recorded: (1) General characteristics, including sex, age, time from disease onset to stone removal, and history of drinking and smoking; (2) Past medical history, including history of hypertension, diabetes, hepatitis B, fatty liver, cirrhosis, cholecystectomy, biliary-enteric anastomosis, choledocholithotomy, or Billroth II gastrectomy; (3) ERCP-related factors, including endoscopic mechanical lithotripsy (EML), endoscopic papillary balloon dilation (EPBD), endoscopic sphincterotomy (EST), CBD stent implantation, endoscopic nasobiliary drainage, and the number of ERCP procedures; (4) CBD-related factors, including the presence of a combined biliary tract infection, gallstones, stones in the intrahepatic bile duct, a bile duct-duodenal fistula, CBD stenosis, duodenal ulcers, periampullary diverticula (PAD) or ectopic duodenal papilla, duodenal papilla shape, bile duct angle referring to the angle between the horizontal part of the CBD and a horizontal line^[9], common bile diameter, CBD diameter, and the number of stones; and (5) Laboratory indicators and treatment, including total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, gallbladder parameters, triglycerides, and the use of preoperative antibiotics.

Statistical analysis

Continuous variables are reported as the mean and standard deviation (SD), and categorical variables are reported as absolute numbers and percentages. Variables found to be statistically significant in the univariate logistic regression analysis were introduced into a multivariate logistic analytic model (stepwise regression) to identify independent risk factors with odds ratios (ORs) and 95% confidence intervals (CIs). A *P*-value < 0.05 was considered statistically significant. Data were analyzed using SPSS software (v17.0; SPSS Inc., Chicago, IL, United States).

RESULTS

General characteristics

From January 2007 to January 2016, 477 patients revisited the hospital for their choledocholithiasis recurrence. Among these patients, the second and several instance (≥ 3 times) recurrence rates were 19.5% (93/477) and 44.07% (41/477), respectively. The average number of instances of stone recurrence was 1.45, and the average time to first stone recurrence was 21.65 mo. A 1:1 case-control study was used for this investigation, and the controls were 477 patients without choledocholithiasis recurrence after ERCP in more than one year of follow-up. The average age of all patients was 57.43 ± 14.92 years, and the study included 445 males (46.65%) and 509 females (53.35%). There were more patients > 65 years old in the recurrence group than in the control group (OR = 2.437, 95%CI: 1.818-3.266; *P* = 0.000). No statistically significant differences between the two groups were observed in terms of sex, weight, time from the onset of stone removal to recurrence, or history of drinking or smoking (Table 1).

Table 1 General characteristics compared between the recurrence group and control group

Variable	Recurrence group (n = 477)	Control group (n = 477)	OR (95%CI)	P-value
Sex (male/female)	216/261	229/248	1.116 (0.865-1.439)	0.399
Age > 65 yr (Y/N)	181/296	134/343	2.437 (1.818-3.266)	0.000
Weight (kg), mean ± SD	57.94 ± 16.80	58.24 ± 11.31	0.992 (0.980-1.004)	0.196
¹ Recurrence time (d), mean ± SD	17.77 ± 19.30	17.85 ± 17.25	1.000 (0.993-1.007)	0.950
History of drinking (Y/N)	42/423	61/416	0.677 (0.447-1.026)	0.066
History of smoking (Y/N)	69/395	86/391	0.794 (0.562-1.123)	0.192

¹Recurrence time was defined as time from the onset of stone removal to recurrence. OR: Odds ratio; 95%CI: 95% confidence interval; Y: Yes; N: No.

Univariate analysis

On univariate analysis, significant differences were noted between the two groups in terms of medical history: A medical history of cholecystectomy (OR = 1.4, 95%CI: 1.085-1.806; *P* = 0.01) and choledocholithotomy (OR = 3.255, 95%CI: 2.114-5.01; *P* = 0.000) (Table 2). Moreover, significant differences in ERCP-related factors were observed: ERCP with EML (OR = 2.068, 95%CI: 1.375-3.11; *P* = 0.000), EPBD (OR = 5.669, 95%CI: 3.594-8.941; *P* = 0.000), EST (OR = 1.701, 95%CI: 1.197-2.417; *P* = 0.003), CBD stent implantation (OR = 3.737, 95%CI: 2.587-5.398; *P* = 0.000), and multiple ERCP procedures (OR = 3.043, 95%CI: 2.242-4.13; *P* = 0.000) (Table 3). CBD-related factors, such as complications including biliary tract infections (OR = 1.034, 95%CI: 1.007-1.061; *P* = 0.014), stones in the intrahepatic bile duct (OR = 2.687, 95%CI: 1.919-3.762; *P* = 0.000), PAD (OR = 1.607, 95%CI: 1.227-2.105; *P* = 0.001), bile-duct duodenal fistula (OR = 2.324, 95%CI: 1.088-4.964; *P* < 0.05), CBD stenosis (OR = 1.661, 95%CI: 1.051-2.626; *P* < 0.05), CBD diameter (OR = 1.988, 95%CI: 1.589-2.486; *P* = 0.000), and choledocholithiasis diameter ≥ 10 mm (OR = 1.580, 95%CI: 1.202-2.067; *P* = 0.001) also showed significant differences between the two groups (Table 4). Additionally, compared with patients in the control group, patients in the recurrence group used fewer antibiotics before ERCP (OR = 0.523, 95%CI: 0.385-0.711; *P* = 0.000) (Table 5).

Multivariate analysis

Multivariate stepwise logistic regression analysis showed that age > 65 years (OR = 1.556, 95%CI: 1.079-2.244; *P* = 0.018), history of choledocholithotomy (OR = 2.474, 95%CI: 1.417-4.320; *P* = 0.001), EPBD (OR = 5.545, 95%CI: 3.026-10.162; *P* = 0.000), EST (OR = 3.378, 95%CI: 1.968-5.797; *P* = 0.000), CBD stent implantation (OR = 5.562, 95%CI: 3.326-9.301; *P* = 0.000), multiple ERCP procedures (OR = 3.601, 95%CI: 1.778-3.805; *P* = 0.000), stones in the intrahepatic bile duct (OR = 2.359, 95%CI: 1.516-3.668; *P* = 0.000), PAD (OR = 1.579, 95%CI: 1.090-2.289; *P* = 0.016), choledocholithiasis diameter ≥ 10 mm (OR = 1.599, 95%CI: 1.117-2.290; *P* = 0.010), biliary-duodenal fistula (OR = 2.720, 95%CI: 1.094-6.765; *P* = 0.031), no use of preoperative antibiotics (OR = 0.527, 95%CI: 0.346-0.801; *P* = 0.003), and biliary tract infections (OR = 1.059, 95%CI: 1.021-1.099; *P* = 0.003) were independent risk factors for the recurrence of choledocholithiasis after ERCP (Table 6). A Kaplan-Meier analysis showed that as age increased, the rate of choledocholithiasis recurrence increased proportionally (Figure 1).

DISCUSSION

The recurrence rate of choledocholithiasis after ERCP is reported to be 2%-22%^[1-5]. In our studies, once choledocholithiasis recurred, the next recurrence rate increased in proportion to the number of instances of recurrence, as reported previously^[1,10]. Several risk factors have been reported in various studies^[1-3,6-8]. This study showed that age > 65 years, history of choledocholithotomy, EPBD, EST, CBD stent implantation, multiple ERCP procedures (≥ 2), stones in the intrahepatic bile duct, PAD, choledocholithiasis diameter ≥ 10 mm, bile duct-duodenal fistula, biliary tract infection, and no preoperative antibiotic use were independent risk factors for the recurrence of choledocholithiasis after ERCP.

It has been reported that the recurrence rate of choledocholithiasis in elderly patients (age > 65 years) can be as high as 30%^[11]. The specific mechanism is unclear, but Keizman *et al*^[4] believe that elderly patients have more risk factors for the recurrence of stones, such as CBD dilatation, CBD angulation, and PAD, which are related to the recurrence of stones. PAD is rare in patients younger than 40 years of

Table 2 Past medical history compared between the recurrence group and control group

Variable	Recurrence group (n = 477)	Control group (n = 477)	OR (95%CI)	P-value
Hypertension (Y/N)	84/393	63/414	1.405 (0.985-2.002)	0.060
Diabetes (Y/N)	34/441	26/452	1.334 (0.788-2.261)	0.284
Hepatitis B (Y/N)	37/440	34/438	1.083 (0.668-1.758)	0.746
Fatty liver (Y/N)	15/462	23/454	0.641 (0.330-1.244)	0.189
Liver cirrhosis (Y/N)	17/460	10/461	1.704 (0.772-3.760)	0.187
Cholecystectomy (Y/N)	252/225	212/265	1.400 (1.085-1.806)	0.010
Biliary-enteric anastomosis (Y/N)	5/471	2/475	2.521 (0.487-13.06)	0.270
Choledocholithotomy (Y/N)	88/389	31/446	3.255 (2.114-5.010)	0.000

Y: Yes; N: No.

age. It is found more often in older patients, and the occurrence of PAD increases with increasing age.

The surgical removal of choledocholithiasis, whether open or laparoscopic, is seldom performed and is usually reserved for patients in whom ERCP has failed^[12]. Laparoscopic CBD exploration is considered in patients with larger stones in whom ERCP has failed. Stone recurrence caused by a history of choledocholithotomy may be due to long-term compression of the biliary tract by the T-tube placed during the choledocholithotomy leading to necrosis and scarring of the epithelial cells of the biliary tract, which easily cause biliary tract stenosis and disorders of biliary excretion^[13].

Under physiological conditions, the sphincter of Oddi functions as a “switch” that controls the excretion of pancreatic juice and bile and prevents the reflux of intestinal fluid. Intraoperative ERCP surgeries, such as EPBD, EST, and multiple ERCP procedures, can cause dysfunction of the sphincter of Oddi, which cannot be restored within a short period of time. Then, the barrier against intestinal fluid reflux weakens or disappears, and intestinal fluid can reflux into the bile duct. Because intestinal fluid contains a large amount of bacteria, digestive juices, and food residues, when it refluxes into the bile duct, it changes the bile duct loop and leads to bile duct infection^[14]; the colonized bacteria produce β -glucuronic acid, which is associated with the formation of bilirubin calcium stones^[5,6,15,16], thus promoting the recurrence of stones. Because bacterial contamination of the bile duct is a common finding in patients with choledocholithiasis, incomplete duct clearance may put patients at risk of cholangitis. Therefore, it is important for endoscopists to ensure that adequate biliary drainage is achieved in patients with choledocholithiasis that cannot be retrieved^[17]. However, stents have been placed for long periods of time, leading to bile salt deposition and adherence to the stents. The stents can be a nidus for CBD stones. Bile duct stent placement affects biliary tract dynamics, predisposing the patient to cholestasis. On the one hand, siltation of bile is conducive to bacterial reproduction. On the other hand, concentration of bile stimulates inflammatory changes in the bile duct mucosa, resulting in the precipitation of bile bacteria, shedding cells, and inflammatory cells, which promote the recurrence of stones^[18].

PAD form adjacent to the biliary and pancreatic duct confluence. When a diverticulum is large, it can directly compress the CBD, resulting in poor bile excretion. When a diverticulum is complicated by duodenal dysfunction, the food and refluxed intestinal fluid can remain in the diverticulum, stimulating long-term inflammation of the sphincter of Oddi, leading to dysfunction, duodenal papillary stenosis, and cholestasis^[19]. PAD promotes the multiplication of beta-glucuronidase-producing bacteria, leading to earlier binding of dissociated glucuronide to bilirubin salts and promoting the pigmentation and formation of stones^[20,21]. Larger stones often require lithotripsy, which may increase the risk of postoperative recurrence of stones. Larger stones cause greater forced expansion of the bile ducts and induce impaired function of normal bile ducts, leading to difficulties in bile excretion, which can easily cause cholestasis and bacterial infections^[22,23]. Biliary tract infections mainly result from preoperative infections and retrograde reflux of intestinal fluid caused by reduced biliary pressure after cholecystectomy. Studies have shown that more than 94.6% of patients with pigmentary stones have positive bacterial cultures in their bile samples^[24]. A variety of causes, such as abnormal biliary anatomy, PAD, abnormal biliary secretion, and biochemistry, can contribute to biliary tract infections. Bile duct bacteria is present, and the resulting beta-glucuronidase causes bilirubin hydrolysis to nonconjugated bilirubin, which can easily combine with calcium to form bilirubin

Table 3 Endoscopic retrograde cholangiopancreatography-related factors compared between the recurrence group and control group

Variable	Recurrence group (n = 477)	Control group (n = 477)	OR (95%CI)	P-value
EML (Y/N)	74/391	40/437	2.068 (1.375-3.110)	0.000
EPBD (Y/N)	111/345	25/461	5.669 (3.594-8.941)	0.000
EST (Y/N)	404/60	382/96	1.701 (1.197-2.417)	0.003
CBD stent implantation (Y/N)	130/334	45/432	3.737 (2.587-5.398)	0.000
ENBD (Y/N)	271/192	282/195	0.976 (0.753-1.266)	0.855
ERCP procedures, mean \pm SD	1.38 \pm 0.55	1.14 \pm 0.39	3.043 (2.242-4.130)	0.000

ERCP: Endoscopic retrograde cholangiopancreatography; EML: Endoscopic mechanical lithotripsy; EPBD: Endoscopic papillary balloon dilation; EST: Endoscopic sphincterotomy; CBD: Common bile duct; ENBD: Endoscopic nasobiliary drainage; Y: Yes; N: No.

calcium and promote gallstone formation^[6,25-29]. The lack of preoperative use of antibiotics may increase the risk of biliary tract infections and promote the recurrence of stones. The presence of a biliary-duodenal fistula is a risk factor for the recurrence of choledocholithiasis. No relevant literature has been reported. Bile duct-duodenal fistulas often exist for a long time, and the refluxed intestinal fluid irritates the biliary mucosa, eventually leading to chronic inflammation.

This study was a single-center retrospective study. Although the clinical data of the patients were comprehensively analyzed and the risk factors for recurrence of choledocholithiasis after ERCP were studied in all aspects, there were still limitations to this retrospective study. This study did not further analyze the accuracy of individual risk factors for predicting the recurrence of choledocholithiasis. In conclusion, patient age greater than 65 years is an independent risk factor for the development of recurrent choledocholithiasis following ERCP, as is history of biliary surgeries, measures during ERCP, and prevention of postoperative complications.

Table 4 Common bile duct-related factors compared between the recurrence group and control group

Variable	Recurrence group (n = 477)	Control group (n = 477)	OR (95%CI)	P-value
Gallstones (Y/N)	274/203	272/205	1.017 (0.787-1.315)	0.896
Intrahepatic bile duct stones (Y/N)	133/344	60/417	2.687 (1.919-3.762)	0.000
Ectopic duodenal papilla (Y/N)	3/462	1/476	3.091 (0.32-29.822)	0.329
Duodenal ulcers (Y/N)	21/443	26/451	0.822 (0.456-1.483)	0.516
PAD (Y/N)	188/276	142/335	1.607 (1.227-2.105)	0.001
Bile duct angle (Y/N)	36/429	25/452	1.517 (0.896-2.570)	0.121
CBD diameter (cm), mean ± SD	1.27±0.73	1.01±0.55	1.988 (1.589-2.486)	0.000
Choledocholithiasis diameter ≥ 10 mm (Y/N)	229/134	126/236	1.580 (1.202-2.067)	0.001
Number of stones (n), (mean ± SD)	1.90 ± 1.19	1.82 ± 1.02	1.12 (0.992-1.265)	0.067
Biliary tract infections (Y/N)	46/418	20/457	2.515 (1.463-4.321)	0.001
Bile-duct duodenal fistula (Y/N)	22/442	10/467	2.324 (1.088-4.964)	0.029
CBD stenosis (Y/N)	51/413	33/444	1.661 (1.051-2.626)	0.030

PAD: Periapillary diverticula; CBD: Common bile duct; Y: Yes; N: No.

Table 5 Laboratory indicators and treatment compared between the recurrence group and control group

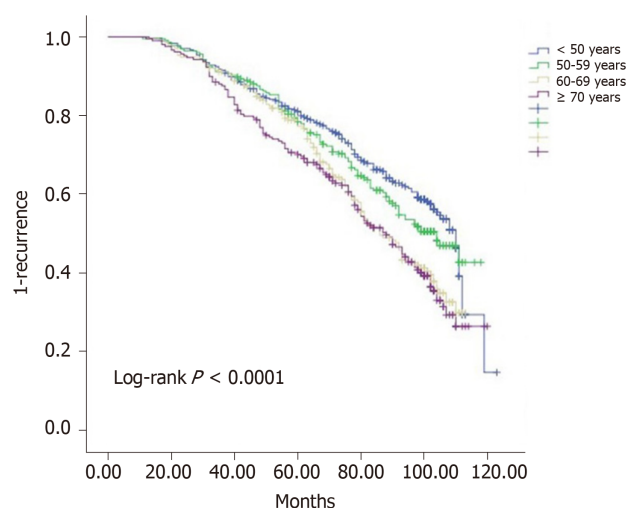
Variable	Recurrence group (n = 477)	Control group (n = 477)	OR (95%CI)	P-value
TBi (umol/L), mean ± SD	53.02 ± 69.91	102.47 ± 126.1	1.000 (0.999-1.001)	0.795
DBi (umol /L), mean ± SD	31.41 ± 44.64	71.21 ± 126.1	1.000 (0.998-1.002)	0.961
ALT (U/L), mean ± SD	129.3 ± 142.91	98.39 ± 127.62	0.999 (0.998-1.000)	0.201
AST (U/L), mean ± SD	96.99 ± 132.68	64.86 ± 103.69	0.999 (0.998-1.000)	0.123
GGT (U/L), mean ± SD	288.3 ± 262.92	306.3 ± 267.96	1.000 (1.000-1.001)	0.441
Cholesterol (mmol /L), mean ± SD	4.77 ± 14.09	4.33 ± 1.53	0.990 (0.886-1.105)	0.852
Triglyceride (mmol /L), mean ± SD	1.30 ± 0.82	1.43 ± 0.85	0.888 (0.742-1.063)	0.197
Used antibiotics before ERCP (Y/N)	336/141	387/85	0.523 (0.385-0.711)	0.000

TBi: Total bilirubin; DBi: Direct bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyltransferase; ERCP: Endoscopic retrograde cholangiopancreatography; Y: Yes; N: No.

Table 6 Multivariate stepwise logistic regression analysis for the recurrence of choledocholithiasis

Variable	OR (95%CI)	P-value
Age > 65 yr	1.556 (1.079-2.244)	0.018
Choledocholithotomy	2.474 (1.417-4.320)	0.001
EPBD	5.545 (3.026-10.162)	0.000
EST	3.378 (1.968-5.797)	0.000
CBD stent implantation	5.562 (3.326-9.301)	0.000
ERCP procedures	2.601 (1.778-3.805)	0.000
Stones in the intrahepatic bile duct	2.359 (1.516-3.668)	0.000
PAD	1.579 (1.090-2.289)	0.016
Choledocholithiasis diameter ≥ 10 mm	1.435 (1.094-1.883)	0.009
Biliary-duodenal fistula	2.720 (1.094-6.765)	0.031
Used antibiotics before ERCP	0.527 (0.346-0.801)	0.003
Biliary tract infections	1.059 (1.021-1.099)	0.003

ERCP: Endoscopic retrograde cholangiopancreatography; EPBD: Endoscopic papillary balloon dilation; EST: Endoscopic sphincterotomy; CBD: Common bile duct; PAD: Periapillary diverticula.



The cumulative rate of choledocholithiasis recurrence (%)

Age (yr)	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr
< 50	0.3	3	8.5	15.2	19	24.4	34.8
50-59	0.4	3.5	8.8	13.3	21.6	39.7	39
60-69	0.5	5.1	9.4	15.6	21.8	35.7	48.6
≥ 70	0.5	4.8	12.4	23.1	29.9	37.2	49

Figure 1 Kaplan–Meier curves showing the recurrence rate of CBD stones according to age (< 50 years, blue line; 50-59 years, green line; 60-69 years, yellow line; ≥ 70 years, red line) (log-rank $P < 0.0001$).

ARTICLE HIGHLIGHTS

Research background

Currently, endoscopic retrograde cholangiopancreatography (ERCP) technology is very advanced, but the recurrence of choledocholithiasis after ERCP is still a challenging problem. The potential causes of the recurrence of choledocholithiasis after ERCP are unclear.

Research motivation

To explore the independent risk factors for stone recurrence by comprehensively analyzing the relevant factors for stone recurrence in a large-sized sample.

Research objectives

The study aimed to analyze the potential causes of the recurrence of choledocholithiasis after ERCP.

Research methods

The ERCP database of our medical center was retrospectively reviewed, and information regarding eligible patients was collected. A 1:1 case-control study was used for this investigation. Data were analyzed by univariate and multivariate logistic regression and Kaplan-Meier analyses.

Research results

Multivariate logistic regression analysis showed that age > 65 years, combined history of choledocholithotomy, endoscopic papillary balloon dilation, endoscopic sphincterotomy, common bile duct stent implantation, multiple ERCP procedures (≥2), stones in the intrahepatic bile duct, perampullary diverticula, choledocholithiasis diameter ≥ 10 mm, bile duct-duodenal fistula, combined biliary tract infections, and no preoperative antibiotic use were independent risk factors for the recurrence of choledocholithiasis after ERCP.

Research conclusions

In this large sample sized retrospective study, we concluded that patient age greater than 65 years is an independent risk factor for the development of recurrent choledocholithiasis following ERCP, as is history of biliary surgeries, measures during ERCP, and prevention of postoperative complications.

Research perspectives

The pathogenesis of recurrence of choledocholithiasis should be studied in future, as well as the prevention and treatment.

REFERENCES

- 1 Ando T, Tsuyuguchi T, Okugawa T, Saito M, Ishihara T, Yamaguchi T, Saisho H. Risk factors for recurrent bile duct stones after endoscopic papillotomy. *Gut* 2003; **52**: 116-121 [PMID: 12477771 DOI: 10.1136/gut.52.1.116]
- 2 Kim DI, Kim MH, Lee SK, Seo DW, Choi WB, Lee SS, Park HJ, Joo YH, Yoo KS, Kim HJ, Min YI. Risk factors for recurrence of primary bile duct stones after endoscopic biliary sphincterotomy. *Gastrointest Endosc* 2001; **54**: 42-48 [PMID: 11427840 DOI: 10.1067/mge.2001.115335]
- 3 Sugiyama M, Atomi Y. Risk factors predictive of late complications after endoscopic sphincterotomy for bile duct stones: long-term (more than 10 years) follow-up study. *Am J Gastroenterol* 2002; **97**: 2763-2767 [PMID: 12425545 DOI: 10.1111/j.1572-0241.2002.07019.x]
- 4 Keizman D, Ish Shalom M, Konikoff FM. Recurrent symptomatic common bile duct stones after endoscopic stone extraction in elderly patients. *Gastrointest Endosc* 2006; **64**: 60-65 [PMID: 16813804 DOI: 10.1016/j.gie.2006.01.022]
- 5 Kim KY, Han J, Kim HG, Kim BS, Jung JT, Kwon JG, Kim EY, Lee CH. Late Complications and Stone Recurrence Rates after Bile Duct Stone Removal by Endoscopic Sphincterotomy and Large Balloon Dilatation are Similar to Those after Endoscopic Sphincterotomy Alone. *Clin Endosc* 2013; **46**: 637-642 [PMID: 24340257 DOI: 10.5946/ce.2013.46.6.637]
- 6 Kim KH, Rhu JH, Kim TN. Recurrence of bile duct stones after endoscopic papillary large balloon dilation combined with limited sphincterotomy: long-term follow-up study. *Gut Liver* 2012; **6**: 107-112 [PMID: 22375179 DOI: 10.5009/gnl.2012.6.1.107]
- 7 Kim JH, Kim YS, Kim DK, Ha MS, Lee YJ, Lee JJ, Lee SJ, Won IS, Ku YS, Kim YS, Kim JH. Short-term Clinical Outcomes Based on Risk Factors of Recurrence after Removing Common Bile Duct Stones with Endoscopic Papillary Large Balloon Dilatation. *Clin Endosc* 2011; **44**: 123-128 [PMID: 22741123 DOI: 10.5946/ce.2011.44.2.123]
- 8 Song ME, Chung MJ, Lee DJ, Oh TG, Park JY, Bang S, Park SW, Song SY, Chung JB. Cholecystectomy for Prevention of Recurrence after Endoscopic Clearance of Bile Duct Stones in Korea. *Yonsei Med J* 2016; **57**: 132-137 [PMID: 26632393 DOI: 10.3349/ymj.2016.57.1.132]
- 9 Strnad P, von Figura G, Gruss R, Jareis KM, Stiehl A, Kulaksiz H. Oblique bile duct predisposes to the recurrence of bile duct stones. *PLoS One* 2013; **8**: e54601 [PMID: 23365676 DOI: 10.1371/journal.pone.0054601]
- 10 Park BK, Seo JH, Jeon HH, Choi JW, Won SY, Cho YS, Lee CK, Park H, Kim DW. A nationwide population-based study of common bile duct stone recurrence after endoscopic stone removal in Korea. *J Gastroenterol* 2018; **53**: 670-678 [PMID: 29192348 DOI: 10.1007/s00535-017-1419-x]
- 11 Fritz E, Kirchgatterer A, Hubner D, Aschl G, Hinterreiter M, Stadler B, Knoflach P. ERCP is safe and effective in patients 80 years of age and older compared with younger patients. *Gastrointest Endosc* 2006; **64**: 899-905 [PMID: 17140895 DOI: 10.1016/j.gie.2006.05.010]
- 12 Almadi MA, Barkun JS, Barkun AN. Management of suspected stones in the common bile duct. *CMAJ* 2012; **184**: 884-892 [PMID: 22508980 DOI: 10.1503/cmaj.110896]
- 13 Yin Z, Xu K, Sun J, Zhang J, Xiao Z, Wang J, Niu H, Zhao Q, Lin S, Li Y. Is the end of the T-tube drainage era in laparoscopic choledochotomy for common bile duct stones coming? A systematic review and meta-analysis. *Ann Surg* 2013; **257**: 54-66 [PMID: 23059495 DOI: 10.1097/SLA.0b013e318268314b]
- 14 Lu Y, Wu JC, Liu L, Bie LK, Gong B. Short-term and long-term outcomes after endoscopic sphincterotomy versus endoscopic papillary balloon dilation for bile duct stones. *Eur J Gastroenterol Hepatol* 2014; **26**: 1367-1373 [PMID: 25264985 DOI: 10.1097/MEG.0000000000000218]
- 15 Yasuda I, Fujita N, Maguchi H, Hasebe O, Igarashi Y, Murakami A, Mukai H, Fujii T, Yamao K, Maeshiro K, Tada T, Tsujino T, Komatsu Y. Long-term outcomes after endoscopic sphincterotomy versus endoscopic papillary balloon dilation for bile duct stones. *Gastrointest Endosc* 2010; **72**: 1185-1191 [PMID: 20869711 DOI: 10.1016/j.gie.2010.07.006]
- 16 Baek YH, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, Jeon WK, Kim BI. [Risk factors for recurrent bile duct stones after endoscopic clearance of common bile duct stones]. *Korean J Gastroenterol* 2009; **54**: 36-41 [PMID: 19696548 DOI: 10.4166/kjg.2009.54.1.36]
- 17 Bergman JJ, Rauws EA, Tijssen JG, Tytgat GN, Huibregtse K. Biliary endoprotheses in elderly patients with endoscopically irretrievable common bile duct stones: report on 117 patients. *Gastrointest Endosc* 1995; **42**: 195-201 [PMID: 7498682 DOI: 10.1016/S0016-5107(95)70091-9]
- 18 Chopra KB, Peters RA, O'Toole PA, Williams SG, Gimson AE, Lombard MG, Westaby D. Randomised study of endoscopic biliary endoprosthesis versus duct clearance for bile duct stones in high-risk patients. *Lancet* 1996; **348**: 791-793 [PMID: 8813987 DOI: 10.1016/S0140-6736(96)06316-7]
- 19 Lee KM, Paik CN, Chung WC, Kim JD, Lee CR, Yang JM. Risk factors for cholecystectomy in patients with gallbladder stones after endoscopic clearance of common bile duct stones. *Surg Endosc* 2009; **23**: 1713-1719 [PMID: 19118432 DOI: 10.1007/s00464-008-0269-2]
- 20 Zoepf T, Zoepf DS, Arnold JC, Benz C, Riemann JF. The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients. *Gastrointest Endosc* 2001; **54**: 56-61 [PMID: 11427842 DOI: 10.1067/mge.2001.115334]
- 21 Tzeng JJ, Lai KH, Peng NJ, Lo GH, Lin CK, Chan HH, Hsu PI, Cheng JS, Wang EM. Influence of juxtapapillary diverticulum on hepatic clearance in patients after endoscopic sphincterotomy. *J Gastroenterol Hepatol* 2005; **20**: 772-776 [PMID: 15853993 DOI: 10.1111/j.1440-1746.2005.03782.x]
- 22 Tsai TJ, Lai KH, Lin CK, Chan HH, Wang EM, Tsai WL, Cheng JS, Yu HC, Chen WC, Hsu PI. Role of endoscopic papillary balloon dilation in patients with recurrent bile duct stones after endoscopic sphincterotomy. *J Chin Med Assoc* 2015; **78**: 56-61 [PMID: 25241239 DOI: 10.1016/j.jcma.2014.08.004]
- 23 Mu H, Gao J, Kong Q, Jiang K, Wang C, Wang A, Zeng X, Li Y. Prognostic Factors and Postoperative Recurrence of Calculus Following Small-Incision Sphincterotomy with Papillary Balloon Dilatation for the Treatment of Intractable Choledocholithiasis: A 72-Month Follow-Up Study. *Dig Dis Sci* 2015; **60**: 2144-2149 [PMID: 25875753 DOI: 10.1007/s10620-015-3559-2]
- 24 Li X, Zhu K, Zhang L, Meng W, Zhou W, Zhu X, Li B. Periapillary diverticulum may be an important factor for the occurrence and recurrence of bile duct stones. *World J Surg* 2012; **36**: 2666-2669 [PMID: 22911215 DOI: 10.1007/s00268-012-1716-8]
- 25 Cetta F. The role of bacteria in pigment gallstone disease. *Ann Surg* 1991; **213**: 315-326 [PMID: 2009013 DOI: 10.1097/0000658-199104000-00006]
- 26 Seo DB, Bang BW, Jeong S, Lee DH, Park SG, Jeon YS, Lee JI, Lee JW. Does the bile duct angulation affect recurrence of choledocholithiasis? *World J Gastroenterol* 2011; **17**: 4118-4123 [PMID: 22039327]

- DOI: [10.3748/wjg.v17.i36.4118](https://doi.org/10.3748/wjg.v17.i36.4118)]
- 27 **Stewart L**, Ponce R, Oesterle AL, Griffiss JM, Way LW. Pigment gallstone pathogenesis: slime production by biliary bacteria is more important than beta-glucuronidase production. *J Gastrointest Surg* 2000; **4**: 547-553 [PMID: [11077333](https://pubmed.ncbi.nlm.nih.gov/11077333/) DOI: [10.1016/S1091-255X\(00\)80100-6](https://doi.org/10.1016/S1091-255X(00)80100-6)]
 - 28 **Leung JW**, Liu YL, Leung PS, Chan RC, Inciardi JF, Cheng AF. Expression of bacterial beta-glucuronidase in human bile: an in vitro study. *Gastrointest Endosc* 2001; **54**: 346-350 [PMID: [11522976](https://pubmed.ncbi.nlm.nih.gov/11522976/) DOI: [10.1067/mge.2001.117546](https://doi.org/10.1067/mge.2001.117546)]
 - 29 **Begley M**, Sleator RD, Gahan CG, Hill C. Contribution of three bile-associated loci, bsh, pva, and btlB, to gastrointestinal persistence and bile tolerance of *Listeria monocytogenes*. *Infect Immun* 2005; **73**: 894-904 [PMID: [15664931](https://pubmed.ncbi.nlm.nih.gov/15664931/) DOI: [10.1128/IAI.73.2.894-904.2005](https://doi.org/10.1128/IAI.73.2.894-904.2005)]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

