Research Article

Risk Factors for Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis after Endoscopic Removal of Common Bile Duct Stones: An Update in Chinese Patients with Choledocholithiasis

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Abstract

Aim: Endoscopic Retrograde Cholangiopancreatography (ERCP) has been widely used in endoscopic surgery for many biliary and pancreatic diseases. Post-ERCP Pancreatitis (PEP) is the most common complication that occurs, even with expert surgeons. However, few reports have addressed the risk of PEP by focusing on the removal of Common Bile Duct Stones (CBDS).

Methods: To detect potential risk factors for PEP after endoscopic removal of CBDS, the medical records of CBDS patients who received ERCP procedures at the First Affiliated Hospital of Nanjing Medical University between January 2021 and December 2023 were retrospectively analyzed. Patient- and procedure-related data were collected, and PEP was reevaluated. Single- and multiple-variable analyses were conducted to identify potential risk factors.

Results: A total of 1,251 procedures were performed in 1,173 patients and PEP occurred in 84 cases (6.71%). Univariate and multivariate logistic regression analyses showed that female sex (P= 0.049, 95% Confidence Interval [CI]: 1.002-2.521), cerebral infarction (P=0.011, 95% CI: 1.197-3.964), acute pancreatitis history (P=0.001, 95% CI: 2.436-7.249), fatty liver disease (P=0.021, 95% CI: 1.140-4.843), common bile duct diameter <10 mm (P=0.005, 95% CI: 1.299-4.313), and Endoscopic Papillary Balloon Dilatation (EBD) (P=0.01, 95% CI: 0.321-0.855) were independent risk factors for PEP in CBDS patients.

Conclusion: Female sex, a history of Fatty Liver Disease (FLD), previous acute pancreatitis, and common bile duct stenosis are risk factors for PEP, whereas EPBD is a protective factor for PEP in patients with CBDS, which should be considered by clinicians.

Introduction

Common Bile Duct Stones (CBDS) are relatively frequent disorders in clinical practice and can cause serious complications, such as obstructive jaundice, acute suppurative cholangitis, and acute pancreatitis, resulting in significant morbidity and mortality if untreated. Endoscopic Retrograde Cholangiopancreatography (ERCP) is a specialized endoscopic procedure for the management of CBDS, and two main methods, Endoscopic Papillary Balloon Dilatation (EPBD) and Endoscopic Sphincterotomy (EST), are generally used for treatment [1]. Compared to transcystic common duct stone removal and laparoscopic choledochotomy, ERCP has become the preferred method for the treatment of CBDS due to the advantages of a simple surgery, reduced trauma, and a high success rate of stone removal [2]. However, ERCP also has procedure-related complications, such as Postoperative Pancreatitis (PEP), cholangitis, bleeding, perforation, and infection. Among these, PEP is the most common and serious complication [3]. PEP is defined as an iatrogenic illness associated with at least a threefold increase in serum amylase (or lipase) at 24 h, with intense pain requiring extended hospitalization [4], which is a crucial factor in morbidity and mortality. At present, there are contrasting reports on the incidence of PEP, ranging from 3% to 15% [5,6]. Although its determinants remain unclear, the development of PEP is thought to be based on a pro-inflammatory cascade caused by pancreatic acinar cell injury during endoscopic surgery, which induces systemic cytokine release. Understanding these mechanisms and the identification of risk factors for PEP will help to adopt prophylactic measures in high-risk patients and reduce morbidity.

The factors related to PEP occurrence identified in different studies vary widely. In pancreaticobiliary diseases, risk factors for developing PEP have been investigated in many studies for years and the relevant factors from the mainstream view include young age, female gender, history of pancreatitis, endoscopic sphincterotomy, papillary balloon dilatation, and pancreatic stent placement [7,8]. There is still controversy regarding some risk factors; however, recent studies have shown that the risk factors for PEP are affected by various factors, such as different regions, races, and surgical purposes (such as the placement of pancreaticobiliary stents, temporary placement of nasobiliary duct drainage, duodenal papilla or pancreaticobiliary duct biopsy, choledochoscopy, CBDS removal, etc.) [9,10]. The majority of the current literature reporting on the risk factors for PEP are based on studies in Western countries, while relatively few reports have been published in Asia, particularly China. Prevention and reduction in the occurrence of PEP has aroused increasing attention from endoscopists. Therefore, this study focused on the risk factors for PEP after successful CBDS removal using ERCP in a Chinese population.

Materials and methods

Study population

The study was a single-center retrospective study performed at First Affiliated Hospital of Nanjing Medical University in China from January 2021 to December 2023. The study enrolled 1251 procedures applied on 1173 patients who had undergone endoscopic CBDS removal successfully by ERCP. The inclusion criteria were as follows: (1) patients who had been diagnosed with CBDS and received ERCP, (2) age over 18 years, (3) physiological papilla. The exclusion criteria were as follows: (1) acute pancreatitis

within 2 weeks prior to ERCP, (2) 18 years of age, (3) undetected CBDS during ERCP, (4) failed stone removal. The patient selection process is shown in Figure 1. As a retrospective study, written informed consent is not required.

Data collection

Information on demographic and clinical variables of included patients was retrospectively extracted from medical records, and the following data were included: sex, age, BMI, history of smoking and drinking, history of hypertension, diabetes, atrial fibrillation, coronary heart disease cerebral infarction, fatty liver disease, history of surgical intervention, including liver transplantation and cholecystectomy, history of ERCP, acute pancreatitis history, blood tests. ERCP method and findings was also collected, including the size and number of stones, common bile duct stenosis, sphincterotomy, papillary balloon dilation and pancreatic duct stent implantation.

Patients who present with two of the following three manifestations are diagnosed of acute pancreatitis [11]: (1) characteristic upper abdominal pain (2) pancreatic enzyme values were greater than three times the upper normal limit, or (3) findings of imaging examination suggesting acute pancreatitis. Pancreatic enzyme tests were performed at 24 hours after the procedure.

Statistical analyses

Statistical analysis was performed using SPSS 26.0. To identify factors independently associated with the occurrence of PEP, multivariate regression analysis was performed using significantly associated factors identified in univariate analyses. A value of p<0.05 was regarded as statistically significant.

Results

From January 2021 to December 2023, a total of 2523 hospitalizations underwent ERCP at First Affiliated Hospital of Nanjing Medical University was identified from discharge diagnosis. Among them, 1,251 procedures were enrolled in our research. The screening processes are shown in Figure 1.

Univariate analysis

Overall, PEP occurred in 84(6.71%) cases in the study population. We evaluated 32 variables, including 15 patient-related factors, four stone-related indexes, three operation-related factors, and 10 blood tests. For patient-related factors, female gender (*P*=0.034, 95% CI: 1.047-3.257), cerebral infarction (*P*=0.005, 95% CI: 1.338-5.171), acute pancreatitis history (*P*=0.001, 95% CI: 2.522-8.507), fatty liver disease (*P*=0.027, 95% CI: 1.119-6.136) were found to be associated with the increased risk of PEP by univariate analysis. Among stone-related indexes, diameter of common bile duct <10 mm (*P*=0.015, 95% CI: 1.175-4.341) was a risk factor significantly associated with PEP. Among operation-related risk factors, only EPBD was found to be a protective factor associated with PEP (*P*=0.003, 95% CI: 0.243-0.740) (Table 1).

Multivariate analysis

Those factors with a *P* value of less than 0.05 were included in the multivariate logistic regression analysis. All factors were determined to be relevant to PEP in multivariate analysis, including female gender (P=0.049, 95% CI: 1.002-2.521), cerebral

infarction (P=0.011, 95% CI: 1.197-3.964), acute pancreatitis history (P=0.001, 95% CI: 2.436-7.249), fatty liver disease (P=0.021, 95% CI: 1.140-4.843), diameter of common bile duct <10 mm (P= 0.005, 95% CI: 1.299-4.313) EPBD (P=0.01, 95% CI: 0.321-0.855) (Table 2).

Multi-factor joint diagnosis of ROC curve

Six risk factors were considered to be relevant to PEP: Female gender, cerebral infarction, acute pancreatitis history, fatty liver disease, diameter of common bile duct <10 mm and EPBD. We combined the PEP with 6 risk factors to draw the ROC curve. As show in Figure 2, the AUC was 0.712 with a 95% CI of 0.651-0.773 (P<0.001) for joint factor. The predicting sensitivity, specificity, positive predictive value and negative predictive value were 59.5%, 78.1%, 16.3%, and 96.4% respectively.
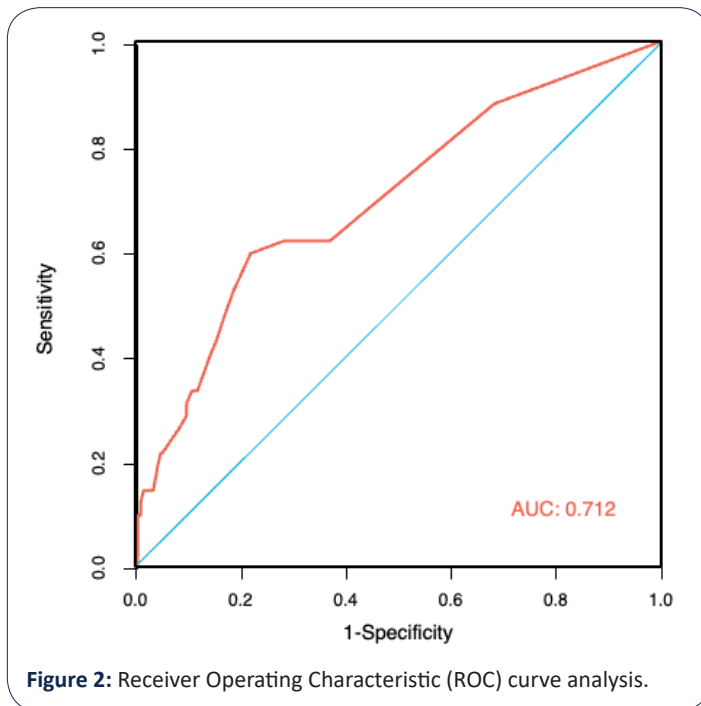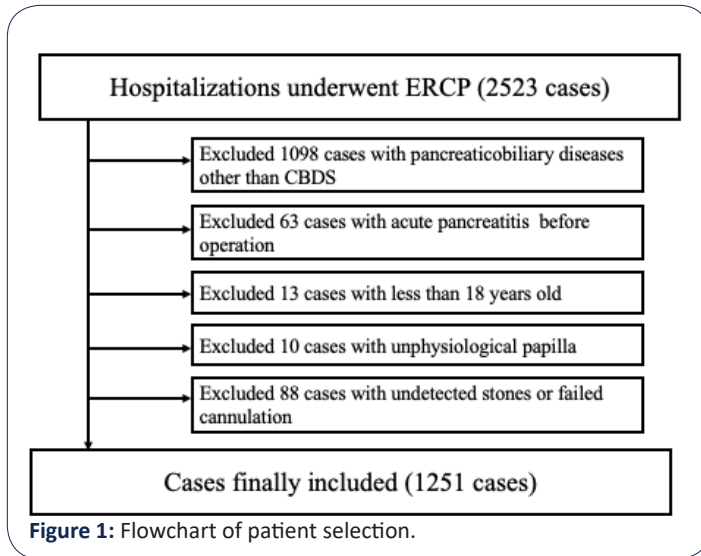

Figure 1: Flowchart of patient selection.

Figure 2: Receiver Operating Characteristic (ROC) curve analysis.

Table 1: Univariate analysis of risk factors for PEP in CBDS patients.

	P value	OR (95% CI)
Basic characteristics		
Age (>65y)	0.102	1.520(0.921-2.510)
Female gender	0.034	1.847(1.047-3.257)
BMI	0.306	0.956(0.876-1.042)
Smoking	0.535	1.263(0.604-2.643)
Drinking	0.991	1.005(0.398-2.541)
Hypertension	0.131	0.637(0.355-1.143)
Coronary heart disease	0.892	0.945(0.418-2.138)
Cerebral infarction	0.005	2.630(1.338-5.171)
Diabetes	0.457	1.325(0.631-2.783)
Acute pancreatitis history	0.001	4.631(2.522-8.507)
Atrial fibrillation	0.172	2.033(0.735-5.625)
Fatty liver disease	0.027	2.620(1.119-6.136)
Operation history		
Liver transplantation	0.886	0.892(0.189-4.222)
Cholecystectomy	0.676	1.115(0.669-1.859)
History of ERCP	0.339	1.362(0.722-2.570)
Disease-related factors		
Number of Stones=1	0.431	0.791(0.442-1.416)
Maximum Stone Diameter ≥10 mm	0.34	1.306(0.755-2.261)
Diameter of Common Bile Duct <10 mm	0.015	2.258(1.175-4.341)
periampullary diverticula	0.087	0.555(0.283-1.090)
Operation-related factors		
EST	0.153	1.526(0.855-2.726)
EPBD	0.003	0.424(0.243-0.740)
pancreatic duct stent	0.252	1.560(0.718-3.547)
Blood examination before ERCP		
Alanine aminotransferase	0.269	1.002(0.999-1.005)
Aspartate aminotransferase	0.365	0.997(0.991-1.003)
Alkaline phosphatase	0.176	0.998(0.995-1.001)
γ-glutamyl transferase	0.325	0.999(0.998-1.001)
Serum total bilirubin	0.561	1.009(0.979-1.039)
Conjugated bilirubin	0.765	0.993(0.950-1.038)
Total cholesterol	0.156	0.820(0.623-1.079)
Triglyceride	0.148	0.729(0.474-1.119)
Fasting plasma glucose	0.512	1.039(0.927-1.164)
Blood urea nitrogen	0.426	0.955(0.852-1.070)
Serum creatinine	0.932	1.000(0.994-1.007)
Serum uric acid	0.726	1.001(0.998-1.003)

Table 2: Multivariate analysis of risk factors for PEP in CBDS patients.

	P value	OR (95% CI)
Basic characteristics		
Female gender	0.049	1.589(1.002-2.521)
Cerebral infarction	0.011	2.178(1.197-3.964)
Acute pancreatitis history	0.001	4.201(2.436-7.249)
Fatty liver disease	0.021	2.349(1.140-4.843)
Disease-related factors		
Diameter of Common Bile Duct <10 mm	0.005	2.367(1.299-4.313)
Operation-related factors		
EPBD	0.01	0.524(0.321-0.855)

Discussion

Although the success rate of endoscopic treatment for CBD stones using ERCP is improving, PEP remains a major concern. In this study, we evaluated the risk factors for PEP in patients with CBDS and found that female sex, history of FLD, cerebral infarction, previous acute pancreatitis, and common bile duct stenosis significantly increased the risk of PEP, whereas EPBD reduced this risk.

Although several studies have not found an association between sex and PEP, most have reported that women are more prone to develop PEP [12], which could be attributed to the higher frequency of biliary stones and Sphincter of Oddi Dysfunction (SOD) [13]. Consistent with the majority of previous studies, our results also confirmed an increased incidence of PEP in female patients compared to males.

The association between younger age and PEP remains controversial. Many reports have suggested that younger patients have an increased risk of PEP [14,15]. The higher incidence of PEP in younger patients has been explained by more active pancreatic exocrine function, smaller common bile duct diameter, and a higher incidence of SOD. Unfortunately, there are no unified standards for the definition of younger age among studies, since cut-off values of 35, 50, and 60 years have all been used. Conversely, a study involving 11,497 ERCP procedures grouped patients as 18-50 years, 50-65 years, 65-80 years, and >80 years and showed that younger age was insignificant in developing PEP [16]. This finding was also confirmed by later studies [17]. Accordingly, age was not an independent predictor of pancreatitis in our study of patients with CBDS.

A large data analysis study by Reddy et al. revealed an association between NAFLD and acute pancreatitis [18]. In line with this, a recent study by Sbeit et al. [19]. Showed that NAFLD is a significant risk factor for PEP. A higher incidence of PEP in obese patients has also been previously reported. Fujisawa et al. found that the rate of PEP was significantly higher in obese patients than in normal weight patients [20]. Kim et al. showed that obesity was an important risk factor for moderately severe and severe PEP [21]. Therefore, obese patients with high NAFLD rates may have more severe PEP due to abnormal lipid metabolism. However, high BMI was not a significant risk factor in our study, likely because we addressed this research among Asian populations who tend to have a relatively low average BMI. Along with obesity,

the effects of atherosclerosis on the rate and severity of pancreatitis have shown contradictory results. Atherosclerosis is a risk factor for high-risk diseases, such as coronary heart disease and cerebral infarction [22]. To the best of our knowledge, this is the first study to define a history of cerebral infarction as a risk factor for PEP in patients with CBDS. The exact mechanism by which a history of cerebral infarction is a risk factor for PEP is unknown. We believe that this may be associated with atherosclerosis, as hyperlipidemia has been described as a significant contributor to atherosclerosis and pancreatitis risk [23]. However, a retrospective study by Harsh et al. seems to disprove our conjecture; they found a lower incidence of PEP in patients with a history of previous myocardial infarction [24]. However, in their analysis, patients with acute coronary syndrome were advised to take antiplatelet agents, such as aspirin, irrespective of the insertion of coronary stents and history of PCI. In our study, the history of drug use was not taken into account as we incorporated lacunar cerebral infarction indicated by radiological imaging, and some patients did not take medication due to mild symptoms. This may partially explain these differences. More research is required regarding cerebral infarction to determine whether a history of drug use could affect the outcome and prognosis of PEP.

A prior history of acute pancreatitis has been considered a risk factor for PEP in many studies [25,26]. A higher risk of PEP with previous acute pancreatitis was found to be associated with a longer procedure time, which is associated with previous parenchymal pancreatic injury [25]. Similar to previous findings, a history of acute pancreatitis was found to be a risk factor for PEP after endoscopic removal of CBDS in our study. Therefore, it is our recommendation that CBDS patients planning to undergo ERCP must be informed about the high-risk of PEP as well as the additional methods to prevent PEP prior to surgery. Moreover, patients should be monitored for a longer duration before discharge to minimize the risk of PEP.

It is not certain whether the common bile duct diameter affects PEP. Some studies have shown a higher PEP incidence in patients with narrow bile ducts [14], whereas others have shown no difference in PEP in patients with different common bile duct diameters [13,27]. Köseoğlu H et al. reported that common bile duct stenosis is a risk factor for PEP only in patients with CBDS [9]. Our data support the hypothesis that a smaller common bile duct diameter is a risk factors for PEP after endoscopic removal of CBDS.

EPBD is widely used because of its ease of operation and the advantage of preserving the function of the Oddi sphincter compared to EST. In our study, contradictory to previous studies, EPBD was found to be a protective factor against PEP. Makoto et al. showed that EPBD for biliary stone removal is associated with a greater risk of PEP, and suggested that EPBD should be avoided, particularly in patients with CBDS [28]. They suggested that the possible mechanism for this is papillary edema or spasm after dilatation and damage to the pancreatic duct during papillary dilatation. If so, placement of a prophylactic pancreatic duct stent could prevent EPBD-related PEP. However, another study by Liao indicated that insufficient dilatation of the papilla appears to be one reason for the increased PEP rate in conventional EPBD [29]. Sufficient papillary dilation may be a protective factor against PEP. Endoscopists in our hospital are experienced and have a longer

duration of EPBD with large papillary dilation (diameter ≥1 cm), which can partly explain the lower incidence of PEP in our study. Moreover, a meta-analysis reported that the EPBD procedure increased the PEP rate only in Western patients, not in Asian patients, which could be due to the different sensitivities of EPBD-related PEP in different ethnic groups [30].

We established a practical nomogram for predicting PEP. According to the ROC curve of the multivariate model, the AUC was 0.712 (95% CI: 0.651-0.773) and it could identify PEP occurrence with an overall sensitivity of 59.5%, specificity of 78.1%, positive predictive value of 16.3%, and negative predictive value of 96.4%. The data revealed high sensitivity and negative predictive value for PEP, which can be used to screen high-risk patients with PEP.

This study had several limitations. First, it was a single-center retrospective study with a limited sample size, and further prospective studies are required to validate the results. Second, several other factors could also affect the risk of PEP, such as the frequency of intraoperative intubation, the amount and frequency of contrast agent injection, the number of times the guidewire enters the pancreatic duct, and the total operation time of ERCP. In future, the impact of new lithotripsy techniques, such as choledochoscopy, on PEP should also be considered. However, to the best of our knowledge, this is the first study to report the risk factors of PEP in Chinese patients with CBDS and demonstrated that female sex, a history of FLD, cerebral infarction, previous pancreatitis, and common bile duct stenosis are statistically significant risk factors, while EPBD is a protective factor associated with PEP after endoscopic removal of CBDS. These findings provide evidence for future clinical decision-making.

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