

Analysis of risk factors and prevention strategies of post-ERCP pancreatitis

Y. LIN¹, X. LIU¹, D.-Q. CAO¹, J.-H. TANG¹, J.-J. WEN¹, T.-F. LI²,
P.-F. LIU², T.-S. XIA²

¹Department of Gastroenterology, The Affiliated Ganzhou Hospital of Nanchang University, Jiangxi, China

²Department of Gastroenterology, Jiangyin Hospital Affiliated to Southeast University Medical College, Jiangsu, China

Ye Lin and Xue Liu contributed equally to this work

Abstract. – OBJECTIVE: To analyze the relevant risk factors and preventive measures for post-endoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis (PEP) so as to improve the diagnosis and treatment levels of ERCP, thus reducing the prevalence rate of PEP.

PATIENTS AND METHODS: The clinical data of 278 patients receiving ERCP from January 2014 to December 2016 were retrospectively analyzed. First, the univariate analysis was conducted for the factors such as gender, age, diameter of common bile duct, whether development occurred in the pancreatic duct and other factors. Then, the multivariate logistic regression analysis was performed for factors showing statistical significance in the univariate analysis so as to analyze the independent risk factors for PEP.

RESULTS: The success rate of ERCP included in the study was 97.12%. The prevalence rate of PEP was 8.27%. Univariate analysis results showed that the prevalence rate of PEP in the group of patients younger than 60 years old was higher than that in the group of patients older than 60 years old (14.14% vs. 5.03%, $p = 0.016$); the prevalence rate of PEP in the group of patients with intubation difficulty was higher than that in the group of patients without intubation difficulty (19.61% vs. 5.73%, $p = 0.004$); the prevalence rate of PEP in the group of patients with operation time more than 60 min was higher than that in the group of patients with operation time less than 60 min (18.60% vs. 6.38%, $p = 0.034$); the prevalence rate of PEP in the group of patients with the pancreatic duct development was higher than that in the group of patients without the pancreatic duct development (50% vs. 6.72%, $p < 0.001$); the prevalence rate of PEP in the group of patients placed with nasobiliary drainage catheters was not higher than that in the group of patients not placed with nasobiliary drainage catheters (18.00% vs. 2.81%, $p < 0.001$). The above five relevant factors were included in

the logistic regression equation for the multivariate analysis, which showed that the age less than 60 years old ($p = 0.002$) and the pancreatic duct development ($p = 0.004$) were independent risk factors for PEP, and nasobiliary drainage ($p = 0.003$) was a protective factor for PEP.

CONCLUSIONS: The occurrence of PEP is associated with the age less than 60 years old, the pancreatic duct development, intubation difficulty and overlong operation time. Among them, the pancreatic duct development and the age less than 60 years old are independent risk factors for PEP. Placing nasobiliary drainage catheters after operation, avoiding the pancreatic duct development, improving the success rate of intubation, reducing ERCP operation time and other methods, can effectively reduce the occurrence of PEP.

Key Words:

ERCP, PEP, Risk factors, Prevention.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a clinically widely used diagnosis and treatment technique for biliary and pancreatic diseases, and it is a relatively more complex operation among endoscopic techniques¹⁻⁴. In the treatment of duodenal and biliary and pancreatic diseases, compared with the traditional operation, ERCP has its advantages over small trauma, easiness to be operated and short recovery time^{1,2}. However, as an invasive operation, both therapeutic ERCP and diagnostic ERCP are complicated, so complications are inevitable, such as pancreatitis, bleeding, perforation and infection, which limit the development of ERCP to a certain

extent. Post-ERCP pancreatitis (PEP) is the most common postoperative complication⁵⁻⁷. Postoperative pancreatitis in patients will not only extend the hospital stay and increase hospital costs, but also seriously threatens the life and health of patients, and severe pancreatitis may lead to death. To broaden the promotion scope of ERCP technique and expand its development space, we explored the risk factors for PEP to reduce its prevalence rate, alleviate its severity and prevent and improve its early prognosis.

Patients and Methods

Patients

A total of 278 patients receiving ERCP examination and treatment at the Affiliated Ganzhou Hospital of Nanchang University and Jiangyin Hospital Affiliated to Southeast University Medical College from January 2014 to December 2016 were selected, including 154 males and 124 females, aged 19-88 years old with an average age of (64.05 ± 15.69) years old. Based on ERCP diagnosis, there were 150 patients with bile duct stones, 54 patients with benign stenosis, 30 patients with malignant tumors, 21 patients with simple bile duct dilatation, 6 patients with sclerosing cholangitis, 5 patients with suppurative cholangitis, 4 patients with Oddi sphincter dysfunction, 3 cases with Vater ampulla carcinoma, 2 cases with main pancreatic duct dilatation and 3 normal subjects. Among them, 22 patients received ERCP twice, and 2 patients received it for 3 times (Table I). Signed written informed consent was obtained from all participants before the study. This investigation was approved by the Ethics Committee of the Affiliated Ganzhou Hospital of Nanchang University.

Table I. Classification of ERCP patients.

Diseases	No.	%
Bile duct stones	150	53.40
Benign stenosis	54	19.42
Malignant tumors	30	10.79
Simple bile duct dilatation	21	7.55
Sclerosing cholangitis	6	2.16
Suppurative cholangitis	5	1.80
Oddi sphincter dysfunction	4	1.44
Vater ampulla carcinoma	3	1.08
Main pancreatic duct dilatation	2	0.72
Normal	3	1.08
Total	278	100

Methods

Observation indexes: (1) basic information of patients: age, gender, operation history, history of underlying diseases, etc.; (2) preoperative examination indexes: biochemical indexes, amylase, coagulation function, magnetic resonance cholangiopancreatography (MRCP) or computed tomography (CT) results, etc.; (3) intraoperative operation records: operation time, whether there was the pancreatic duct development, whether a stent was placed, intraoperative operation, intraoperative diagnosis, etc.; (4) postoperative records: postoperative laboratory indexes including blood, electrolytes and blood amylase, and clinical symptoms including abdominal pain, hematemesis and melon.

Statistical Analysis

All statistics were performed using Statistical Product and Service Solutions 20.0 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY, USA). The *t*-test was performed for the comparison of continuous data and χ^2 test for the count data. When the theoretical frequency $T < 1$, the Fisher exact method was used to calculate the *p*-value, for $1 < T < 5$, the continuous correction χ^2 test was used, and for $T > 5$, the Pearson χ^2 -test was used. Univariate analysis was used to evaluate the relationship between PEP and relevant risk factors. The statistically significant factors were screened for the multivariate logistic regression analysis. $p < 0.05$ suggested that the difference was statistically significant.

Results

General Data

In this study, 278 patients receiving ERCP included 12 patients receiving diagnostic ERCP and 266 patients receiving therapeutic ERCP. ERCP was successful in 270 patients and failed in 8 patients, suggesting that the success rate is 97.12%. PEP occurred in 23 out of 278 patients, suggesting that the prevalence rate of PEP is 8.27%.

Univariate Analysis Results

The analysis of factors relevant to patients showed that the prevalence rate of PEP in the group of patients younger than 60 years was significantly higher than that in the group of patients older than 60 years old (14.14% vs. 5.03%, $p = 0.016$) (Table II). Intergroup differences in gender, with or without hypertension, diabetes melli-

Table II. Univariate analysis of PEP and general relevant risk factors.

Influencing factors		n	Pancreatitis (no.)	%	χ^2	p
Gender	Male	154	14	9.09	2.164	0.125
	Female	124	9	7.26		
Age	≥ 60	179	9	5.03	1.356	0.016
	< 60	99	14	14.14		
Hypertension	Yes	104	10	9.62	1.498	0.617
	No	174	13	7.47		
Diabetes mellitus	Yes	48	1	2.08	3.349	0.234
	No	230	22	9.57		
Liver cirrhosis	Yes	11	1	9.09	0.009	0.372
	No	267	22	8.24		
History of pancreatitis	Yes	36	2	5.56	2.138	0.223
	No	242	21	8.68		
History of cholecystectomy	Yes	54	8	14.81	0.915	0.216
	No	224	15	6.70		
Duodenal diverticulum	Yes	71	3	4.23	5.462	0.411
	No	207	20	9.66		
Positive bilirubin	Yes	194	19	9.79	0.984	0.326
	No	84	4	4.76		
Several times of removing stone	Yes	48	4	8.33	0.006	0.863
	No	230	19	8.26		
First time of ERCP	Yes	228	19	8.33	0.047	0.528
	No	50	4	8.00		

tus, cirrhosis, with or without history of pancreatitis and cholecystectomy and other factors were not statistically significant (Table II). The widest common bile duct diameters of patients were quantitative data, which were detected using the independent-samples *t*-test. According to the PET receiving status, the patients were divided into the pancreatitis group and non-pancreatitis group, and there was no difference in the common bile duct diameter between the two groups (1.108 cm vs. 1.244 cm, $p = 0.645$) (Table III).

In the analysis of factors relevant to operations, common operations were selected in the study, such as the pancreatic duct development, balloon dilatation, endoscopic sphincterotomy (EST), endoscopic nasobiliary drainage (ENBD), intubation difficulty and operation time. The results showed that the prevalence rate of PEP in the group patients with intubation difficulty was higher than that in the group of patients without intubation difficulty (19.61% vs. 5.73%, $p =$

0.004); the prevalence rate of PEP in the group of patients with operation time ≥ 60 min was higher than that in the group of patients with operation time < 60 min (18.60% vs. 6.38%, $p = 0.034$); the prevalence rate of PEP in the group of patients with the pancreatic duct development was higher than that in the group of patients without the pancreatic duct development (50% vs. 6.72%, $p < 0.001$); the prevalence rate of PEP in the group of patients with nasobiliary drainage was higher than that in patients without nasobiliary drainage (18.00% vs. 2.81%, $p < 0.001$) (Table IV). $p < 0.05$ in the above five factors indicated that their differences were statistically significant.

Multivariate Logistic Regression Analysis Results

Factors showing statistical significance in the univariate analysis were included into the multivariate logistic regression analysis with the presence of ERCP as a dependent variable and these

Table III. Analysis of the relationship between the widest diameter of common bile duct and PEP.

Group	No.	Mean	SD	SE	p
Pancreatitis	23	1.108	0.549	0.073	0.645
Non-Pancreatitis	255	1.244	0.627	0.032	

Abbreviation: SD, standard deviation; SE, standard error.

Table IV. Univariate analysis of PEP and intraoperative operation.

Influencing factors		n	Pancreatitis (no.)	%	χ^2	P
Pancreatic duct development	Yes	10	5	50.00	17.208	< 0.001
	No	268	18	6.72		
Balloon dilatation	Yes	113	6	5.31	2.124	0.516
	No	165	17	10.30		
EST	Yes	147	13	8.84	0.465	0.580
	No	131	10	7.63		
Intubation difficulty	Yes	51	10	19.61	7.359	0.004
	No	227	13	5.73		
Pancreatic duct stent	Yes	5	0	0	1.532	0.848
	No	273	23	8.42		
Bile duct stent	Yes	48	3	6.25	0.694	0.261
	No	230	20	8.70		
Operation time	< 60 min	235	15	6.38	9.188	0.034
	≥ 60 min	43	8	18.60		
ENBD	Yes	178	5	2.81	15.017	< 0.001
	No	100	18	18.00		

Abbreviation: EST, endoscopic sphincterotomy; ENBD, endoscopic nasobiliary drainage.

factors as independent variables. The results revealed that an age less than 60 years old ($p = 0.002$) and the pancreatic duct development ($p = 0.004$) were independent risk factors for PEP, and nasobiliary drainage ($p = 0.003$) was a protective factor for PEP (Table V).

Discussion

Compared with the traditional operation, ERCP is characterized by non-invasive operation, a wide range of applications, high success rate, and other advantages^{1,2}. However, as an invasive operation, ERCP is inevitably accompanied with complications such as bleeding, perforation, infection, and pancreatitis¹⁻⁴. PEP is one of the most common complications of ERCP, and in few cases, it can develop into severe pancreatitis⁵⁻⁷. This study explored the risk factors for PEP in various ways and aimed to effectively prevent the occurrence of PEP in combination with relevant clinical practices, so as to further expand the development space of ERCP.

In this work, the prevalence rate of PEP in patients younger than 60 years old was significantly higher than that in patients older than 60 years old. It was included in the multivariate analysis, which showed that it was an independent risk factor for PEP. The reason for the higher prevalence rate in young patients may be that ERCP operation leads to the hyperemia and edema of nipples and blocks pancreatic juice discharge, and the pancreatic secretion function, sensitivity, and activity of the young and middle-aged people are relatively stronger than those in old people. Therefore, the serum amylase value and abdominal signs of young patients after ERCP must be closely monitored, and if necessary, drugs inhibiting trypsin can be used for prevention.

A study⁸ with a large sample size showed that the history of pancreatitis is an independent risk factor for PEP. The reason may be that underlying diseases and susceptible factors of patients with past history of pancreatitis are relatively more, and their sensitivity to the operation is stronger, which is more likely to lead to the occurrence of

Table V. Multivariate logistic regression analysis of PEP and relevant risk factors.

Variable	r	SD	p	OR	95% CI
Age < 60 y	0.211	0.324	0.002	1.234	0.247-1.623
Operation time	0.396	0.515	0.434	1.489	0.679-3.403
Intubation difficulty	0.785	0.667	0.385	2.278	0.454-9.752
Pancreatic duct development	2.618	0.926	0.004	15.347	2.146-76.045
ENBD	-1.699	0.743	0.003	0.156	0.048-0.519

Abbreviation: ENBD, endoscopic nasobiliary drainage.

pancreatitis. The history of pancreatitis in this work is not a risk factor for PEP, which may be related to the small sample size and the lack of statistical data. It is necessary to further expand the sample size and conduct research to a deeper degree after inquiring the disease history of patients. This study also reported three underlying diseases including hypertension, cirrhosis and diabetes mellitus. The results showed that diabetes mellitus, hypertension, and cirrhosis were not related to PEP, which further suggested that the effect of underlying diseases on the occurrence of PEP may not be significant.

The results of this study revealed that there is a significant difference in the prevalence rate of PEP between patients with the pancreatic duct development and those without the pancreatic duct development ($\chi^2 = 17.208, p < 0.001$). It was then included in the multivariate analysis, which showed that it was an independent risk factor for PEP, so it was one of the important risk factors for PEP. In clinical practice, the catheter can be guided by a guide wire to avoid the development of the pancreas. For patients with obstruction, the degree and nature of obstruction of patients need to be assessed in detail before operation. During the operation, the residue of contrast agents can be reduced by the corresponding treatment methods. The speed of these contrast agents needs to be controlled during radiography, and these agents need to be slowly pushed in at the lowest dose leading to the development in the bile duct as far as possible. For high-risk patients, vital signs of them need to be closely monitored after operation, and the preventive use of related drugs such as octreotide can prevent the occurrence of PEP^{2,3}.

Our investigation showed that with the increase the operation time (≥ 60 min), the prevalence rate of PEP was increased significantly. The univariate analysis showed that the operation time was a risk factor for PEP, and the prolonged operation time was mostly caused by intubation difficulty. Currently, the intubation guided by guide wires is a more commonly used clinical technique, which can not only improve the nipple injury caused by repeated intubation, but also avoid excessive injection of contrast agents into the pancreatic duct, thus reducing the occurrence of PEP.

The results of this study showed that the prevalence rate of PEP in patients receiving EST was higher than that in patients not receiving EST, but the difference was not statistically significant. Some scholars argued that EST relieves

the pressures of bile duct and pancreatic duct in septo-optic dysplasia (SOD) patients, and SOD is an independent risk factor for PEP, so EST can enable pancreatic juice to outflow smoothly while reducing the possibility of biliary tract infection, suggesting that EST can reduce the prevalence rate of PEP. If it is operated by experienced endoscopic physicians, the cutting direction is strictly controlled, and the incision is away from the pancreatic duct opening so as to avoid damage to the pancreatic duct^{8,9}.

Some reports suggested that pancreatic duct stent in some high-risk patients can reduce the risk of PEP¹⁰. The placement of pancreatic duct stent can mitigate the biliary sphincter injury and edema of the pancreatic duct and blocked pancreatic effusion in patients caused by intubation difficulty or repeated intubation to a certain degree. However, some people believed that the placement of pancreatic duct stent cannot reduce the risk of PEP. There is no definite conclusion about the timing of placement of pancreatic duct stent before or after sphincterotomy, removal of bile duct stones, and duodenoscopic treatment. In this research, relatively fewer patients were placed with pancreatic duct stent, so it will be studied in depth after the sample size is expanded.

A correct understanding of PEP and relevant risk factors and the intervention in the relevant risk factors are very important measures to prevent postoperative pancreatitis. In combination with the independent risk factors and relevant factors of PEP, it can be concluded that avoiding the development of the pancreatic duct, improving the success rate of intubation and reducing the operation time of ERCP, can effectively reduce the occurrence of PEP¹¹.

Studies^{12,13} have shown that after bile duct stones are removed, ENBD can not only alleviate nipple edema caused by pancreatic duct obstruction, but also reduce the pressure within the pancreatic duct, making the pancreatic juice discharge pathway smooth so as to play an important role in controlling the prevalence rate of pancreatitis. In addition, ENBD can prevent the incarceration of residual small stones, ensure adequate bile duct drainage and alleviate duodenal papilla edema. The study revealed that ENBD was a protective factor for PEP, and postoperative placement of nasobiliary drainage catheter could effectively prevent the occurrence of PEP. During the application of the above measures, drug prevention is also essential. Clinically, intra-

venous rehydration and the use of drugs inhibiting pancreatic enzyme activity and secretion, anti-inflammatory drugs and drugs reducing Oddi sphincter pressure, can reduce the prevalence rate of PEP and improve clinical prognosis.

Conclusions

The occurrence of PEP is related to the age less than 60 years old, pancreatic duct development, intubation difficulty and overlong operation time, in which the pancreatic duct development and the age less than 60 years old are independent risk factors for PEP. Placing the nasobiliary drainage catheter after operation, avoiding pancreatic duct development, improving the success rate of intubation, reducing ERCP operation time and other methods, can effectively reduce the occurrence of PEP.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) MATSUSHITA M, KOYABU M, NISHIO A, SEKI T, OKAZAKI K. Techniques of ERCP with a conventional endoscope in pancreatoduodenectomy anatomy. *Gastrointest Endosc* 2017; 86: 747-748.
- 2) LI DP, ZHANG QY, CHENG J, LI JZ, WANG L. The effect of somatostatin retained enema in the treatment of pancreatic ileus. *Eur Rev Med Pharmacol Sci* 2017; 21: 3476-3481.
- 3) TIERNEY J, BHUTIANI N, STAMP B, RICHEY JS, BAHR MH, VITALE GC. Predictive risk factors associated with cholangitis following ERCP. *Surg Endosc* 2017 Jul 21. doi: 10.1007/s00464-017-5746-z. [Epub ahead of print].
- 4) RODRIGUES-PINTO E, MACEDO G, BARON TH. ERCP competence assessment: miles to go before standardization. *Endosc Int Open* 2017; 5: E718-E721.
- 5) MIINE T, MORIZANE T, KAWAGUCHI Y, AKASHI R, HANADA K, ITO T, KANNO A, KIDA M, MIYAGAWA H, YAMAGUCHI T, MAYUMI T, TAKEYAMA Y, SHIMOSEGAWA T. Clinical practice guideline for post-ERCP pancreatitis. *J Gastroenterol* 2017 Jun 26. doi: 10.1007/s00535-017-1359-5. [Epub ahead of print].
- 6) WANG AY. Medications and methods for the prevention of Post-ERCP pancreatitis. *Gastroenterol Hepatol (N Y)* 2017; 13: 188-191.
- 7) WILCOX CM. Prevention of post-ERCP pancreatitis is more than just suppositories and stents. *Dig Endosc* 2017; 29: 758-760.
- 8) MIYATANI H, MATSUMOTO S, MASHIMA H. Risk factors of post-ERCP pancreatitis in biliary type Sphincter of Oddi dysfunction in Japanese patients. *J Dig Dis* 2017 Sep 12. doi: 10.1111/1751-2980.12541. [Epub ahead of print].
- 9) NAVANEETHAN U, LOURDUSAMY D, GUTIERREZ NG, ZHU X, VARGO JJ, PARS MA. New approach to decrease post-ERCP adverse events in patients with primary sclerosing cholangitis. *Endosc Int Open* 2017; 5: E710-E717.
- 10) OLSSON G, LUBBE J, ARNELO U, JONAS E, TORNQVIST B, LUNDELL L, ENOCHSSON L. The impact of prophylactic pancreatic stenting on post-ERCP pancreatitis: a nationwide, register-based study. *United European Gastroenterol J* 2017; 5: 111-118.
- 11) THOMSON A. Pre-Study ERCP practice as a confounder with respect to ERCP results. *Am J Gastroenterol* 2017; 112: 1477.
- 12) MORI A, ASANO T, MARUYAMA T, OHASHI N, INOUE H, TAKEKOSHI S, OKUNO M. Transnasal ERCP/ENBD using an ultrathin esophagogastroduodenoscope. *J Gastroenterol* 2006; 41: 1237-1238.
- 13) NOJI T, NAKAMURA F, NAKAMURA T, KATO K, SUZUKI O, AMBO Y, KISHIDA A, MAGUCHI H, KONDO S, KASHIMURA N. ENBD tube placement prior to laparoscopic cholecystectomy may reduce the rate of complications in cases with predictably complicating biliary anomalies. *J Gastroenterol* 2011; 46: 73-77.