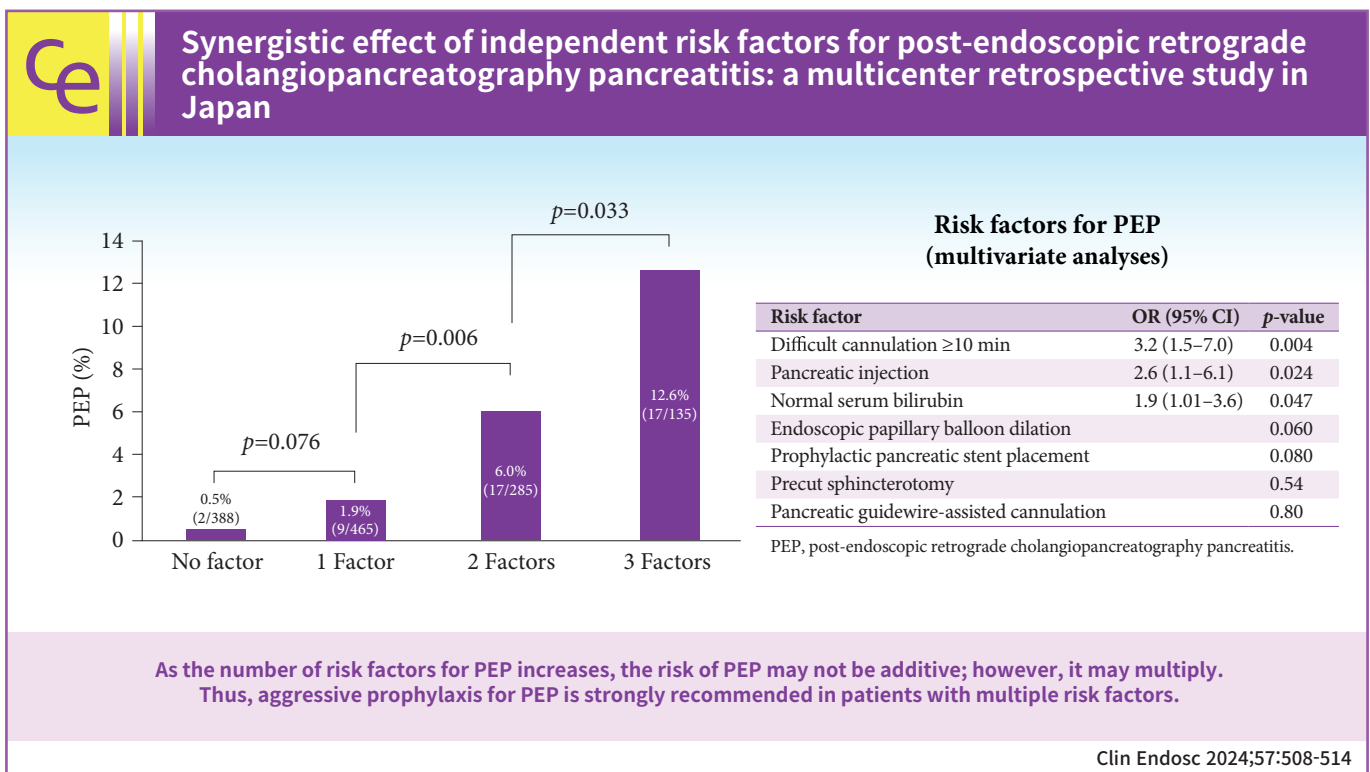


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# Synergistic effect of independent risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis: a multicenter retrospective study in Japan

Hirokazu Saito<sup>1</sup>, Yoshihiro Kadono<sup>2</sup>, Takashi Shono<sup>3</sup>, Kentaro Kamikawa<sup>4</sup>, Atsushi Urata<sup>4</sup>, Jiro Nasu<sup>5</sup>, Masayoshi Uehara<sup>4</sup>, Ikuo Matsushita<sup>3</sup>, Tatsuyuki Kakuma<sup>6</sup>, Shunpei Hashigo<sup>1</sup>, Shuji Tada<sup>1</sup>

<sup>1</sup>Department of Gastroenterology, Kumamoto City Hospital, Kumamoto City; <sup>2</sup>Department of Gastroenterology, Tsuruta Hospital, Kumamoto City; <sup>3</sup>Department of Gastroenterology, Kumamoto Chuo Hospital, Kumamoto City; <sup>4</sup>Department of Gastroenterology, Saiseikai Kumamoto Hospital, Kumamoto City; <sup>5</sup>Department of Gastroenterological Surgery, Kumamoto Chuo Hospital, Kumamoto City; <sup>6</sup>Department of Biostatistics Center, Medical School, Kurume University, Kurume City, Japan



**Received:** August 14, 2023    **Revised:** October 2, 2023  
**Accepted:** October 10, 2023  
**Correspondence:** Hirokazu Saito  
 Department of Gastroenterology, Kumamoto City Hospital, 4-1-60,  
 Higashimachi, Higashi-ku, Kumamoto City, Kumamoto 862-8505, Japan  
**E-mail:** arnestwest@yahoo.co.jp

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**Background/Aims:** This study aimed to examine the synergistic effect of independent risk factors on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP).

**Methods:** This multicenter retrospective study included 1,273 patients with native papillae who underwent ERCP for bile duct stones in Japan. Independent PEP risk factors were identified using univariate and multivariate analyses. Significant risk factors for PEP in the multivariate analysis were included in the final analysis to examine the synergistic effect of independent risk factors for PEP.

**Results:** PEP occurred in 45 of 1,273 patients (3.5%). Three factors including difficult cannulation  $\geq 10$  minutes, pancreatic injection, and normal serum bilirubin level were included in the final analysis. The incidences of PEP in patients with zero, one, two, and three factors were 0.5% (2/388), 1.9% (9/465), 6.0% (17/285), and 12.6% (17/135), respectively. With increasing risk factors for PEP, the incidence of PEP significantly increased (1 factor vs. 2 factors,  $p=0.006$ ; 2 factors vs. 3 factors,  $p=0.033$ ).

**Conclusions:** As the number of risk factors for PEP increases, the risk of PEP may not be additive; however, it may multiply. Thus, aggressive prophylaxis for PEP is strongly recommended in patients with multiple risk factors.

**Keywords:** Endoscopic retrograde cholangiopancreatography; Pancreatitis; Risk factors

## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a standard treatment for biliary and pancreatic diseases. However, post-ERCP pancreatitis (PEP) is the most common adverse event of ERCP, and guidelines document the independent risk factors for PEP.<sup>1-3</sup>

However, patients often present with a combination of risk factors for PEP in clinical practice. A prospective study revealed that the odds ratios in female sex alone, and the combination of a normal serum bilirubin level plus female sex, and normal serum bilirubin plus female sex plus difficult cannulation were 2.5, 4.8, and 16.2, respectively.<sup>4</sup> Another randomized controlled study reported the PEP incidence in patients with  $\geq 3$  risk factors to be 32 of 183 (17.5%).<sup>5</sup>

Although endoscopists should consider the interactions between independent PEP risk factors, there is little evidence on this topic. Therefore, this study aimed to investigate the synergistic effect of independent PEP risk factors in patients with common bile duct (CBD) stones, the most common indication for ERCP.

## METHODS

### Patients

This multicenter retrospective study included 1,273 patients with native papillae who underwent ERCP for CBD stones at three institutions in Japan (Saiseikai Kumamoto Hospital, Kumamoto Chuo Hospital, and Kumamoto City Hospital) between April 2012 and March 2020. The exclusion criteria were as follows: (1) individuals with prior ERCP, (2) patients with

a Billroth II or Roux-en-Y reconstruction, (3) patients with biliary pancreatitis, (4) patients who underwent unsuccessful cannulation, and (5) patients with no stones found on ERCP.

### Endoscopic treatment

We performed ERCP using a side-view duodenoscope. Pethidine hydrochloride and midazolam were administered intravenously. After selective biliary cannulation, endoscopic papillary balloon dilation using a small balloon of  $<12$ -mm diameter, endoscopic sphincterotomy, or endoscopic papillary large balloon dilation using a large balloon of diameter  $\geq 12$ -mm diameter was conducted for stone extraction or biliary drainage. The decision of whether to use of preventive methods for PEP, such as rectal nonsteroidal anti-inflammatory drugs (NSAIDs) or prophylactic pancreatic stent placement, was based on the operator's decision.

### Study definitions

#### 1) Post-ERCP pancreatitis

The consensus criterion for endoscopic adverse events by Cotton et al.<sup>6</sup> was used for the diagnosis and grading of PEP. To elaborate, PEP was defined as the occurrence of typical abdominal pain accompanied by amylase levels exceeding three times the normal range. We classified PEP into three grades: mild, moderate, and severe PEP based on the need for unplanned hospital admission or the length of hospital stay, which were  $\leq 3$ , 4 to 10, and  $>10$  nights, respectively.

#### 2) Precut sphincterotomy

Although various pre-cutting techniques have been reported

based on the current guidelines,<sup>7</sup> transpancreatic sphincterotomy using a short-tipped sphincterotome over the guidewire was selected as the pre-cutting method in patients with guidewire insertion into the main pancreatic duct. In patients without guidewire insertion into the main pancreatic duct, we selected a pre-cutting method that used a needle knife from the papillary orifice toward the oral side of the papillary bulge.

### Statistical analysis

The chi-square test or Fisher's exact test for categorical variables and Welch's t-test for continuous variables were used in univariate analyses. A multivariate logistics regression model was used to identify the independent risk factors for PEP. The factors that met both a *p*-value of <0.05, as determined by univariate analyses, and the definitive or likely risk factors in the European Society of Gastrointestinal Endoscopy guidelines,<sup>2</sup> were included in the logistic regression multivariate analysis. We used factors that were significant in multivariate analyses to examine the synergistic effect of independent PEP risk factors. The synergistic effects of independent risk factors for PEP were examined based on the number of risk factors. A two-sided *p*-value of <0.05 was denoted as the threshold for statistical significance. The EZR statistical software ver. 1.61 (Saitama Medical Center, Jichi Medical University) was used for all statistical analyses.<sup>8</sup>

### Ethical statement

The present study was approved by the institutional review boards of each participating institution (approval number: 601) and opt-out consent was obtained.

## RESULTS

### ERCP indications

Indications for ERCP in this study were acute cholangitis in 840 patients (66.0%), mild cholangitis in 442 patients (34.7%), moderate cholangitis in 295 patients (23.2%), and severe cholangitis in 103 patients (8.1%); cholestasis without cholangitis in 268 patients (21.1%); and silent CBD stones in 165 patients (13.0%).

### Incidence rates and severity of PEP

PEP occurred in 45 of 1,273 patients (3.5%). PEP was classified as mild in 28 patients (62.2%), moderate in 13 patients (28.9%), and severe in four patients (8.9%).

### Risk factors for PEP

The results of the univariate and multivariate analyses of PEP risk factors are shown in Tables 1 and 2, respectively. In the univariate analysis, there were eight significant risk factors for PEP, including difficult cannulation  $\geq 10$  minutes, pancreatic injection, prolonged procedure time, prophylactic pancreatic stent placement, contrast-assisted cannulation, precut sphincterotomy, pancreatic guidewire-assisted cannulation, and normal serum bilirubin level. Of the 166 patients who underwent pancreatic guide wire-assisted cannulation, 159 patients underwent pancreatic injection. Of the 65 patients who underwent pre-cutting, transpancreatic sphincterotomy using a short-tipped sphincterotome was performed in 63 patients. In two patients without insertion of a guidewire into the pancreatic duct, we selected a pre-cutting method that used a needle knife from the papillary orifice toward the oral side of the papillary bulge. None of the patients underwent needle-knife fistulotomy.

In the multivariate analysis, difficult cannulation  $\geq 10$  minutes, pancreatic injection, and normal serum bilirubin level were significant PEP risk factors.

### Synergistic effect of the independent risk factors for PEP

Figure 1 shows the incidence rates of PEP according to the number of risk factors. The PEP rates in patients with zero, one, two, and three factors were 0.5% (2/388), 1.9% (9/465), 6.0% (17/285), and 12.6% (17/135), respectively. As the risk factors for PEP increased, the incidence of PEP significantly increased (1 factor vs. 2 factors, *p*=0.006; 2 factors vs. 3 factors, *p*=0.033).

Each PEP risk in patients with two risk factors for PEP were as follows; difficult cannulation for  $\geq 10$  minutes and normal serum bilirubin: 3/36 (8.3%), difficult cannulation for  $\geq 10$  minutes and pancreatic injection: 8/109 (7.3%), and pancreatic injection and normal serum bilirubin: 6/140 (4.3%).

## DISCUSSION

This study aimed to examine the synergistic effects of the independent risk factors for PEP. Our findings suggest that the risk of PEP occurrence multiplied, rather than increased by addition, as the number of risk factors increased.

PEP is the most common and severe adverse event associated with ERCP. Numerous studies have investigated its incidence,<sup>9</sup> and the current guidelines have clearly presented the independent risk factors for PEP.<sup>1-3</sup> According to a large-scale meta-analysis,<sup>9</sup> the incidence of PEP is 9.7%. The incidence of

**Table 1.** Risk factors for PEP (univariate analyses)

Risk factor	Without PEP (n=1,228)	With PEP (n=45)	p-value
Significant factors			
Difficult cannulation $\geq 10$ min	285 (23.2)	29 (64.4)	<0.001
Pancreatic injection	520 (42.3)	36 (80.0)	<0.001
Procedure time (min)	26.4 $\pm$ 15.2	38.8 $\pm$ 16.2	<0.001
Prophylactic pancreatic stent placement	151 (12.3)	17 (37.8)	<0.001
Contrast-assisted cannulation	898 (73.1)	19 (42.2)	<0.001
Precut sphincterotomy	57 (4.6)	8 (17.8)	0.001
Pancreatic guidewire -assisted cannulation	153 (12.5)	13 (28.9)	0.005
Normal serum bilirubin	541 (44.1)	29 (64.4)	0.009
Not significant factors			
Endoscopic papillary balloon dilation	143 (11.6)	10 (22.2)	0.056
Periampullary diverticulum			0.066
No periampullary diverticulum	846 (68.9)	38 (84.4)	
Intradiverticular papilla	54 (4.4)	0 (0)	
Extradiverticular papilla	328 (26.7)	7 (15.6)	
Protease inhibitor	412 (33.6)	21 (46.7)	0.078
Age (yr)	75.1 $\pm$ 14.0	72.5 $\pm$ 15.3	0.28
Female gender	566 (46.1)	24 (53.3)	0.36
End-stage renal failure	16 (1.3)	0 (0)	1.0
Billroth-1 reconstruction	37 (3.0)	1 (2.2)	1.0
Nondilated common bile duct (<10 mm)	488 (39.7)	17 (37.8)	0.88
Cholecystectomy history	136 (11.1)	4 (8.9)	0.81
Common bile duct stones with gallstones	783 (63.8)	26 (57.8)	0.43
Trainee involvement	186 (15.1)	8 (17.8)	0.67
Wire-guided cannulation	120 (9.8)	5 (11.1)	0.80
Endoscopic sphincterotomy	897 (73.0)	30 (66.7)	0.39
Endoscopic papillary large balloon dilation	206 (16.8)	5 (11.1)	0.42
Balloon	984 (80.1)	35 (77.8)	0.70
Basket	593 (48.3)	20 (44.4)	0.65
Mechanical lithotripsy	212 (17.3)	10 (22.2)	0.42
Biliary stent placement	1,059 (86.2)	35 (77.8)	0.12
Stone number $\geq 2$ stones	548 (44.6)	22 (48.9)	0.65
Stone size >10 mm	246 (20.0)	6 (13.3)	0.34
Rectal NSAIDs	118 (9.6)	1 (2.2)	0.12
Performance status 3 or 4	223 (18.2)	5 (11.1)	0.32

Values are presented as number (%) or mean $\pm$ standard deviation.

PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; NSAID, nonsteroidal anti-inflammatory drug.

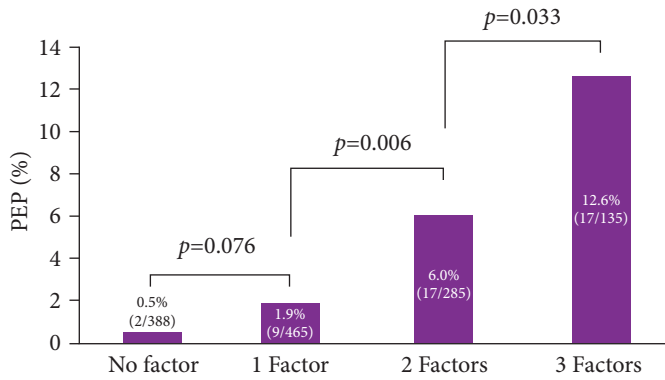
**Table 2.** Risk factors for PEP (multivariate analyses)

Risk factor	OR (95% CI)	p-value
Difficult cannulation $\geq 10$ min	3.2 (1.5–7.0)	0.004
Pancreatic injection	2.6 (1.1–6.1)	0.024
Normal serum bilirubin	1.9 (1.01–3.6)	0.047
Endoscopic papillary balloon dilation		0.060
Prophylactic pancreatic stent placement		0.080
Precut sphincterotomy		0.54
Pancreatic guidewire-assisted cannulation		0.80

PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; OR, odds ratio; CI, confidence interval.

PEP in high-risk patients, defined as those with one or more risk factors, was 14.7%. The study also revealed that PEP was classified as mild in approximately 60% of patients, while it was observed to be moderate to severe in the remaining 40%.<sup>9</sup> Another randomized controlled study found that the incidence of PEP was notably higher in patients with more than three risk factors, with an incidence of 17.5% (32 out of 183 patients).<sup>5</sup> Our findings are in line with these results.

Based on the findings of this study, aggressive prophylaxis of PEP is particularly important in patients with several risk



**Fig. 1.** The incidence rates of post-endoscopic retrograde cholangiopancreatography pancreatitis based on the number of independent risk factors. PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis.

factors. The current guidelines provide recommendations for PEP prophylaxis.<sup>1-3</sup> Prophylaxis by pancreatic stent is an effective strategy for the occurrence of PEP and some meta-analyses have reported a significant reduction in the overall occurrence of PEP (odds ratio, 0.22–0.39) and a reduced occurrence of severe PEP.<sup>10-15</sup>

Rectal NSAIDs are a well-known pharmacological preventive measure for PEP.<sup>1-3</sup> Rectal NSAIDs are reported to reduce the occurrence of PEP with an odds ratio between 0.24 and 0.63.<sup>2</sup> Aggressive hydration is also an effective approach for PEP prevention.<sup>2,3</sup> Recent meta-analyses have demonstrated that the administration of 35 to 45 mL/kg of Ringer’s lactate solution over 8 to 10 hours as part of aggressive hydration contributed to a reduction in PEP incidence, with odds ratios ranging from 0.29 to 0.47.<sup>16-18</sup> Additionally, aggressive hydration decreased the occurrence of moderate-severe PEP, with an odds ratio of 0.16.<sup>16</sup> According to a network meta-analysis, the combination of aggressive hydration and rectal indomethacin is the most effective PEP prevention strategy. Its preventive efficacy was observed to be 70% to 99% higher than that of single prophylactic measures.<sup>19</sup> Therefore, aggressive prophylaxis for PEP with these strategies should be considered in patients with several risk factors for PEP.

Recent research has suggested that silent CBD stones and choledocholithiasis without acute cholangitis are significant risk factors for PEP.<sup>20-24</sup> Such patients, including those with silent CBD stones, tend to have lower levels of cholestasis than in patients with cholangitis. Therefore, these patients often present multiple risk factors, including normal serum bilirubin levels

and difficulty with selective cannulation. In addition, pancreatic injections are frequently administered to patients who experience challenging cannulation. Therefore, our study findings align with those of previous studies that found a higher risk of PEP in patients without acute cholangitis, including those with asymptomatic CBD stones.

A scoring system would be useful; however, because of the limited number of studies on this topic, no established system is available for the estimation of the synergistic effects of PEP risk factors.<sup>25-29</sup>

This study had several limitations. First, the major limitation of the present study is its retrospective design, which may lead to potential selection bias. Furthermore, although we identified the risk factors for PEP via a multivariate analysis, unmeasured confounding factors associated with PEP incidence may be residual. Second, the sample size of the patients with PEP was small. Further prospective studies are warranted to verify the synergistic effects of the independent risk factors for PEP.

In conclusion, the risk of PEP incidence may not be additive; rather, the risk multiplies as the risk factors for PEP increase. Aggressive prophylaxis is strongly recommended, particularly in patients with several risk factors for PEP.

### Conflicts of Interest

The authors have no potential conflicts of interest.

### Funding

None.

### Acknowledgments

We would like to thank the staff involved in endoscopic retrograde cholangiopancreatography at the participating institutions.

### Author Contributions

Conceptualization: HS; Data curation: HS, YK, TK; Formal analysis: HS, TK; Investigation: HS, YK, TS, KK, AU, JN, MU, IM, SH, ST; Methodology: all authors; Project administration: HS, SH, ST; Resources: HS, YK, TS, KK, AU, JN, MU, IM, SH, ST; Software: HS, TK; Supervision: SH, ST; Validation: HS, TK, SH, ST; Visualization: HS, ST; Writing—original draft: HS; Writing—review & editing: YK, TS, KK, AU, JN, MU, IM, TK, SH, ST.

## ORCID

Hirokazu Saito	<a href="https://orcid.org/0000-0001-8729-9604">https://orcid.org/0000-0001-8729-9604</a>
Yoshihiro Kadono	<a href="https://orcid.org/0000-0003-2358-120X">https://orcid.org/0000-0003-2358-120X</a>
Takashi Shono	<a href="https://orcid.org/0000-0002-7577-2991">https://orcid.org/0000-0002-7577-2991</a>
Kentaro Kamikawa	<a href="https://orcid.org/0000-0002-7783-7584">https://orcid.org/0000-0002-7783-7584</a>
Atsushi Urata	<a href="https://orcid.org/0000-0001-8232-0988">https://orcid.org/0000-0001-8232-0988</a>
Jiro Nasu	<a href="https://orcid.org/0000-0001-8555-7454">https://orcid.org/0000-0001-8555-7454</a>
Masayoshi Uehara	<a href="https://orcid.org/0000-0003-4368-2892">https://orcid.org/0000-0003-4368-2892</a>
Ikuo Matsushita	<a href="https://orcid.org/0000-0001-5160-8823">https://orcid.org/0000-0001-5160-8823</a>
Tatsuyuki Kakuma	<a href="https://orcid.org/0000-0002-3713-3099">https://orcid.org/0000-0002-3713-3099</a>
Shunpei Hashigo	<a href="https://orcid.org/0000-0003-0857-6779">https://orcid.org/0000-0003-0857-6779</a>
Shuji Tada	<a href="https://orcid.org/0000-0001-9087-5457">https://orcid.org/0000-0001-9087-5457</a>

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