Risk Factors for Post-Endoscopic Retrograde Pancreatography Pancreatitis: A Retrospective Chart Review in a Regional Hospital in Japan

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Keywords

Adverse event · Emergency · Off hours · Cholangiography · Pancreatography

Abstract

Background: Endoscopic retrograde pancreatography (ERCP) is sometimes complicated by post-ERCP pancreatitis (PEP), which is a severe adverse effect. **Objective:** The present study was performed to (i) evaluate the risk factors for PEP and (ii) compare the risk of PEP after ERCP performed in the off hours versus regular hours. **Methods:** This retrospective study included 374 patients who underwent ERCP from January 2013 to December 2017. Among these patients, 38 (10.2%) developed PEP. The potential risk factors for PEP were evaluated by multivariate regression analysis, and the risk of PEP was compared between ERCP performed during regular hours and off hours. **Results:** The independent risk factors for PEP were a relatively younger age (<75 years; $p = 0.024$), female sex ($p = 0.002$), a history of pancreatitis ($p = 0.044$), and performance of pancreatography ($p = 0.010$). Use of a diclofenac suppository and performance of pancreatic stenting were not preventive for PEP after ERCP. The compli-

cation rate of PEP did not differ between ERCP performed during the off hours versus regular hours. **Conclusions:** A relatively younger age (<75 years), female sex, a history of pancreatitis, and performance of pancreatography were potential risk factors for PEP, whereas the risk of PEP was not different between ERCP performed during the off hours versus regular hours.

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Introduction

Endoscopic retrograde pancreatography (ERCP) plays an important role in the diagnosis and treatment of pancreatic and biliary system disorders [1–4]. Post-ERCP pancreatitis (PEP) is one of the most serious complications of ERCP. In recent years, computed tomography and/or magnetic resonance cholangiopancreatography (MRCP) have become more highly applicable diagnostic approaches for pancreatic and biliary system diseases than ERCP [5–9].

The risk factors for PEP are indicated in both international and Japanese medical practice guidelines [10–15]. The patient-related risk factors of PEP include female sex,

a history of pancreatitis, a history of PEP, sphincter of Oddi dysfunction, and intraductal papillary mucinous neoplasm, and the technical-related risk factors for PEP include difficult cannulation, endoscopic sphincterotomy, precut sphincterotomy, and pancreatography [10–15]. Although PEP has a very guarded prognosis and may be fatal in some cases, most previous studies were performed in high-volume centers [16, 17]. Although these risk factors are consistently reported in the medical guidelines and references, complete prevention of PEP has not been achieved because of the possible presence of other underlying risk factors for PEP [18–21].

Several reports have indicated that the risk of adverse events is higher when several endoscopic therapies, including emergency endoscopic hemostasis, are performed in the off hours than during regular hours [22, 23]. Although the risk associated with emergency off-hours ERCP was not clearly evaluated, emergency ERCP appears to be effective for several diseases, including acute cholangitis. The present retrospective chart review was performed to (i) evaluate the risk factors for PEP in a regional hospital in Japan and (ii) determine whether the risk of PEP is higher after ERCP performed during off hours than regular hours.

Materials and Methods

This retrospective single-center study was conducted at the Karatsu Red Cross Hospital (Karatsu, Saga, Japan) and included all patients who underwent ERCP from January 2013 to December 2017. A total of 1,094 patients underwent ERCP, and 717 were excluded from the study because they had a history of previous ERCP treatment. Another 3 patients were excluded due to the lack of a serum amylase concentration in the medical records. Finally, 374 patients who had undergone ERCP were analyzed in the study.

ERCP was conducted after the induction of analgesia and sedation by intravenous diazepam and pentazocine. All ERCP procedures were performed by several expert endoscopists with ≥ 10 years of experience and trainees with < 10 years of experience. All evaluated patients underwent their first ERCP procedure and had no history of endoscopic sphincterotomy, papillary balloon dilatation, or bile or pancreatic duct stenting. PEP was diagnosed based on new-onset abdominal pain lasting > 24 h after ERCP with an increased serum amylase level of > 3 times the upper limit of normal, which was defined by Cotton's criteria [24].

The patients' electronic medical records were used to record age, sex, height, weight, indication for ERCP, history of pancreatitis, and a diverticulum near the papilla of Vater. Whether the patient had undergone pancreatography, the administration of a diclofenac suppository, or pancreatic stenting; the ERCP examination period; the ERCP starting time with respect to arrival at the hospital; and whether MRCP was performed before ERCP were also recorded. In terms of the start of ERCP and arrival time of the patient, the regular hours were defined as 08:30–17:00 on week-

days; and off hours were defined as 17:00–8:30 on weekdays or anytime on weekends/holidays.

For the statistical analysis, the chi-square test or *t* test was performed to identify differences in patient characteristics between the 2 groups. A univariate analysis was performed to identify the relevance of several factors analyzed in this study. Two multiple logistic regression models were considered to evaluate the relationships of the evaluated factors with the risk of PEP. The full model was adjusted by all confounding factors (Model 1), and the stepwise model was performed using a stepwise selection method with the same entry and removal significance level of 0.2 (Model 2). Before considering the multivariate analysis, correlation was confirmed between each of the factors that had a reduced correlation rate. The performance of MRCP before ERCP (yes/no) and administration of a diclofenac suppository (yes/no) were considered in the model 2 as necessarily stay variables. The statistical measures used in reporting associations were the OR and 95% CI. All *p* values were two sided; those of < 0.05 indicated statistical significance. All analyses were performed with JMP version 13.2.1 (SAS Institute Inc., Cary, NC, USA).

Results

The potential risk factors for PEP are shown in Table 1. PEP occurred in 38 (10.2%) of the 374 ERCP procedures, which was diagnosed by CT and/or US using the Cotton's criteria [24], which met the guidelines for the management of acute pancreatitis: JPN guidelines 2015 [25]. One patient complicated severe pancreatitis in the Cotton's criteria. The mean age of all the 374 patients was 72.3 ± 13.9 years. PEP more often occurred in younger patients aged < 75 years (65.8%) than in older patients aged > 75 years (34.2%). In terms of sex, women were at higher risk of PEP than men (71.1 vs. 29.0%, respectively). Other patient-related factors including the indication for ERCP, body mass index, history of pancreatitis, a diverticulum near the papilla of Vater, and clinical symptoms were not risk factors for PEP. Among intraoperative ERCP-related factors, only performance of pancreatography was a risk factor for PEP, as it occurred in 81.6% (31/38) of patients; the purpose of ERCP (treatment or observation), administration of a diclofenac suppository, performance of pancreatic stenting, and the procedure period of ERCP were not risk factors for PEP. Neither off-hours ERCP nor regular hours ERCP were a risk factor for PEP.

The results of the univariate analysis are shown in Table 2. These data indicate that female sex and performance of pancreatography were risk factors for PEP. The results of the multivariate analysis are shown in Table 3. All factors evaluated in the present study were evaluated in the multivariate analysis because all were independent of one another with no significant correlation, as shown in Table

4. The multivariate analysis indicated that the risk factors for PEP were an age of <75 years ($p = 0.024$), female sex ($p = 0.002$), a history of pancreatitis ($p = 0.044$), and pancreatography ($p = 0.010$). Neither the start time of ERCP (regular hours or off hours) nor the arrival time of the patient was a risk factor for PEP after ERCP.

Discussion

The present retrospective chart review in a regional single hospital indicated that (i) the risk factors for PEP were a younger age, female sex, performance of pancreatography, and a history of pancreatitis and (ii) the incidence of PEP were not different between regular hours and off hours. The complication rate of PEP in the present study of the patients without the previous ERCP was 10.2%, which is similar to previous reports (3–15% among ERCP procedures) [5, 13, 14, 19]. The present study evaluated 8 factors using a multivariate analysis: 6 factors selected by the stepwise method (age, sex, body mass index, history of pancreatitis, diagnostic or therapeutic ERCP, and pancreatography) and 2 essential factors (administration of diclofenac suppository and performance of MRCP before ERCP). As a result, 4 factors were identified as risk factors for PEP: age, sex, pancreatography, and a history of pancreatitis.

Why a younger age was a risk factor for PEP in the present study remains unclear. Another study indicated that age was not related to PEP [14]. The exocrine function of the pancreas decreases with aging [26–28], which might help to explain why the incidence of PEP was dependent upon age. The fact that female sex was a risk factor for PEP might be due to the high prevalence of both cholelithiasis and sphincter of Oddi dysfunction [10–14, 29–31]. Several studies have shown that pancreatography directly increases the pressure of the pancreatic duct [32–34], and a history of pancreatitis are risk factors for PEP [10, 11, 14]. These findings are consistent with those of the present study.

Several previous studies have indicated that the use of low-dose rectal diclofenac [19, 35–38] and the performance of pancreatic stenting [39, 40] effectively prevent PEP. The present study did not demonstrate the preventive effect of diclofenac and pancreatic stenting; however, the dose of diclofenac (50 mg, which might not have been enough for the prevention of PEP) and the performance of pancreatic stenting in the present study were limited only to patients who underwent several cannulations during the procedure.

The complication rate of PEP was not different between ERCP performed during regular hours and off

Table 1. Potential risk factors for post-ERCP pancreatitis

Variables	PEP	Non-PEP	<i>p</i> value
<i>Patient-related factors</i>			
Age, years			
≥75	13 (34.2)	171 (50.9)	0.049*
<75	25 (65.8)	165 (49.1)	
Gender			
Female	27 (71.1)	139 (41.4)	0.001*
Male	11 (29.0)	197 (58.6)	
Indications			
No cancer	28 (73.7)	253 (75.3)	0.828
Cancer	10 (26.3)	83 (24.7)	
BMI			
≤19	12 (33.3)	66 (19.9)	0.074
>19	24(66.7)	266(80.1)	
History of pancreatitis			
Yes	3 (7.9)	14 (4.2)	0.336
No	35 (92.1)	322(95.8)	
Diverticulum			
Yes	9 (23.7)	75 (22.3)	0.850
No	29 (76.3)	261 (77.7)	
Symptoms of the arrival time			
Yes	17 (44.7)	188 (56.0)	0.189
No	21 (55.3)	148 (44.1)	
<i>ERCP related factors</i>			
Purpose of ERCP			
Treatment	35 (92.1)	287 (85.4)	0.228
Observation	3 (7.9)	49 (14.6)	
Pancreatography			
Yes	31 (81.6)	199 (59.2)	0.005*
No	7 (18.4)	137 (40.8)	
Diclofenac suppository			
Yes	18 (47.4)	156 (46.4)	0.912
No	20 (52.6)	180 (53.6)	
Pancreatic stenting			
Yes	8 (21.1)	48 (14.3)	0.288
No	30 (79.0)	288 (85.7)	
Time required for ERCP			
≥1 h	7 (18.4)	31 (9.2)	0.102
<1 h	31 (81.6)	305(81.9)	
Start time of ERCP			
Off hours	20 (52.6)	155 (46.1)	0.447
Regular hours	18 (47.4)	181 (53.9)	
Arrival time of the patient			
Off hours	7 (18.4)	61 (18.2)	0.968
Regular hours	31 (81.6)	275 (81.9)	
MRCP before ERCP			
Yes	20 (52.6)	172 (51.2)	0.866
No	18 (47.4)	164 (48.4)	

Data are presented as *n* (%).

* $p < 0.05$.

ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; BMI, body mass index; MRCP, magnetic resonance cholangiopancreatography.

Table 2. Unadjusted ORs for PEP by univariate analysis

Factors	Unadjusted OR	95% CI	<i>p</i> value
Age, years (<75/≥75)	1.99	0.99–4.03	0.055
Gender, female/male	3.48	1.67–7.25	0.001*
Indications (no cancer/cancer)	0.92	0.43–1.97	0.827
BMI (≤19/>19)	2.02	0.96–4.24	0.065
History of pancreatitis (yes/no)	1.97	0.54–7.20	0.304
Diverticulum (yes/no)	1.08	0.49–2.38	0.849
Symptoms at the arriving time (yes/no)	0.64	0.32–1.25	0.191
Purpose for ERCP (treatment/observation)	1.99	0.59–6.73	0.267
Pancreatography (yes/no)	3.05	1.30–7.12	0.010*
Diclofenac suppository (yes/no)	1.04	0.53–2.03	0.912
Pancreatic stenting (yes/no)	1.60	0.69–3.70	0.271
Time required for ERCP (≥1 h/<1 h)	2.22	0.90–5.46	0.082
Start time of ERCP (off hours/regular hours)	1.30	0.66–2.54	0.448
Arrival time of the patient (off hours/regular hours)	1.02	0.43–2.42	0.968
MRCP before ERCP (yes/no)	1.06	0.54–2.07	0.866

* $p < 0.05$.

PEP, post-ERCP pancreatitis; BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

Table 3. Adjusted ORs for PEP by multivariate analysis

Factors	Model 1 (full) [†]		Model 2 (stepwise) [‡]		
	adjusted OR	<i>p</i> value	adjusted OR	95% CI	<i>p</i> value
Age, years	2.40	0.034*	2.47	1.12–5.42	0.024*
Gender	5.15	0.0002*	4.89	2.13–11.20	0.0002*
Indications	1.03	0.949	–	–	–
BMI	2.18	0.070	2.18	0.96–4.94	0.062
History of pancreatitis	4.30	0.070	4.63	1.04–20.55	0.044*
Diverticulum	0.97	0.954	–	–	–
Symptoms at the arriving time	0.55	0.188	–	–	–
Purpose for ERCP	3.30	0.101	2.76	0.74–10.32	0.131
Pancreatography	2.74	0.035*	3.21	1.32–7.80	0.010*
Diclofenac suppository	0.93	0.854	0.90	0.43–1.90	0.790
Pancreatic stenting	1.18	0.755	–	–	–
Time required for ERCP	1.64	0.407	–	–	–
Beginning time of ERCP	1.38	0.429	–	–	–
Arriving time	1.49	0.447	–	–	–
MRCP before ERCP	1.14	0.750	1.14	0.52–2.51	0.738

* $p < 0.05$.

[†] Considering all potential risk factors.

[‡] Considering age, sex, BMI, history of pancreatitis, purpose of ERCP, pancreatography, diclofenac suppository, and MRCP before ERCP.

PEP, post-ERCP pancreatitis; BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

Table 4. Correlations of pairs of potential risk factors with post-ERCP pancreatitis

Pairs of potential risk factors		Correlation
Positive correlation		
Symptoms of arrival time	Arrival time of the patient	0.34
Pancreatic stent	Pancreatography	0.30
Symptoms of arriving time	Purpose of ERCP	0.26
Time required for ERCP	Pancreatic stent	0.26
Symptoms of arrival time	Beginning time of ERCP	0.22
Negative correlation		
MRCP before ERCP	Purpose of ERCP	-0.21
MRCP before ERCP	Symptoms of arrival time	-0.25

Only correlation coefficients $|r|$ of >0.20 are shown.

ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

hours. The endoscopic therapeutic approach during off hours might have several risk factors, including lack of enough medical staff members and the arising of emergency situations [22, 23, 41, 42]. The present study indicated that off-hours ERCP was not a risk factor for PEP, indicating no reluctance to perform constructive ERCP for emergency cases.

The present single-center retrospective chart review had several limitations: (i) several previous risk factors were not evaluated, including sphincter of Oddi dysfunction, pancreatic sphincterotomy, endoscopic papillary balloon dilatation, and precutting [10, 18], (ii) the difficulty for cannulation was evaluated by the time required for ERCP, and (iii) the endoscopists and operative devices varied during the 5-year observation period.

The present study indicated that several risk factors for PEP after ERCP and the performance of ERCP during off hours were not risk factors for PEP. These findings might facilitate active ERCP during emergency situations even in off hours.

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Statement of Ethics

All patients gave their informed consent, and the research protocol was approved by the institutional review board of Karatsu Red Cross Hospital.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

T.S.: designed the study, and wrote the initial draft of the manuscript. K.M., T.N., A.T., and K.F.: contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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