


Post-ERCP pancreatitis

Frequency and risk stratification from four tertiary care referral hospitals in South East Asia

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Abstract

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is a dreaded complication. But the frequency of this complication varies widely (1%–40%) among the literature and across geographical regions. With uncertainty in the estimation of occurrence and having no accepted, safe, effective method to prevent it, identification of its frequency and predictable risk factors is very crucial in a local or regional setting. The aim of this study was to identify the frequency of PEP and its risk factors from 4 tertiary care referral centers from a country in the South East Asia Region. This cross-sectional study was done on 1042 consecutive ERCP in adult patients (age >18 years) with baseline serum amylase levels less than 3 times the upper level of standard value. On the basis of clinical features and the amylase level at 24 hours (the next morning), the procedure was evaluated to confirm PEP. The frequency of PEP was calculated and procedure, patient, or operator-related independent risk factors for occurring PEP were analyzed using univariate and multivariate analyses. The study found 204 (19.6%) cases of PEP. In multivariate regression analysis, young age, suspected Sphincter of Oddi Dysfunction, recurrent pancreatitis, needle papillotomy, and pancreatic sphincterotomy were significant risk factors. The univariate analysis also found difficult cannulation and pancreatic duct injection with contrast as significant risk factors. Both patient-related and procedure-related risk factors acted independently for the development of PEP, which occurred in 19.6% of cases. This multicenter assessment of the frequency and risk factors for PEP in our patients would be extremely beneficial for future prevention of this complication.

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography, PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis, SOD = sphincter of Oddi dysfunction.

Keywords: frequency, post-ERCP pancreatitis, risk factors

1. Introduction

Despite considerable advances in the endoscopic retrograde cholangiopancreatography (ERCP) technique in recent years, post-ERCP pancreatitis (PEP) continues to be one of the most feared and severe complications, resulting in significant morbidity and occasional mortality.^[1,2] The widely used criterion to define PEP in a consensus paper proposed by Cotton et al. in the year 1991 was 24 hours post procedure amylase level at least 3 times above the upper level of the standard value along with the characteristic of newly developed abdominal pain consistent with pancreatitis and severity of symptoms demanding hospital

admission or extending the hospital stay of already hospitalized.^[3] The reported incidence of this complication varies widely in the literature and across geographical regions. Several studies have shown that PEP ranged from 1% to 31%, whereas in high-risk patients often found to occur between 25% and 40% of cases.^[1,3,4] The vast majority (80%–90%) of PEP episodes are minor, but in 0.3% to 0.6% of instances, serious pancreatitis can develop, necessitating longer hospital stays and the use of major hospital resources.^[5,6]

Mechanisms triggering post-ERCP pancreatitis are incompletely defined, but many possibilities have been suggested. Instrumentation, hydrostatic injury, and an insult from

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chemicals or allergic contrast agents obstructing the papilla or pancreatic sphincter are among the most possible proposed mechanisms.^[7] However, the ultimate mechanism is the activation of inflammatory pathways. At the outset, damage to the pancreatic acinar cell by an intracellular local inflammatory response that releases pro-inflammatory cytokines into the circulation causes further damage.^[5,8] Finally, the extent of the resulting systemic inflammatory response determines the severity of PEP.^[9]

From the aforementioned process, it is obvious that a number of factors, both technical and patient-related, may be involved in the pathogenesis of post-ERCP pancreatitis and that these factors may work alone or in concert.^[2] Patient-related factors include suspected sphincter of Oddi dysfunction (SOD), prior incidents of post-ERCP pancreatitis, female gender, and younger age have been identified previously.^[2,5,10] Among the procedure-related factors, repeated injections of contrast into the pancreatic duct, pancreatic sphincterotomy, difficulties during cannulation, and needle-knife pre-cut have been reported.^[5,10]

Most patient-related factors and operator technical factors for the occurrence of PEP are modifiable if they were recognized in advance. Identification of predictable risk factors is crucial for the detection of high-risk cases, where ERCP is best to avoid or where protective or pharmacological measures can be adopted to enhance its prevention. Furthermore, the rate of occurrence varies widely across geographical regions. The purpose of this study was to estimate the frequency of PEP and to identify patient, procedure, and operator-related independent risk factors for its occurrence from a country in the South East Asia region.

2. Methods

This prospective multicentre cross-sectional study was conducted over a two-year period in four tertiary care teaching hospitals. On an average 800 to 1000 ERCPs performed per year in each of these four tertiary care centers. Using a convenient sampling technique, the study included 1042 adult patients (age > 18 years) having baseline serum amylase levels less than 3 times of upper level of standard value. Patients having any contraindication for ERCP or a stent in situ by previous ERCPs and cases with trainee involvement were excluded. A diagnosis of post-ERCP pancreatitis was made if the patients had pancreatic-type abdominal pain (epigastric pain radiating to the back), tenderness that required analgesia and lasted for at least 24 hours after the procedure, and a serum amylase level at least 3 times the normal upper limit.^[3,11] According to Vege,^[12] 14 risk factors (patient-related: young age, female gender, suspected SOD, history of recurrent pancreatitis, history of post-ERCP pancreatitis, normal serum bilirubin level; procedure-related: pancreatic duct injection, difficult cannulation, pancreatic sphincterotomy, pre-cut access, balloon dilation; operator or technique-related: trainee participation, nonuse of a guidewire for cannulation, failure to use a pancreatic duct stent in a high-risk procedure) were evaluated in univariate and multivariate analyses. In order to prevent the possible influence of inter-endoscopist related variables a minimum standardization was set as per a recent review article on setting up strict national standard of endoscopist for ERCP published from USA.^[13] The advocated mandatory standards for technical skills of ERCP, including the number (>200 to 250) of performed ERCPs, and ≥85% to 90% successful cannulation rate. Despite the fact that this was our minimum criteria, no less than an associate professor with less than ten years of expertise did not perform ERCP on our study subjects. According to the revised Declaration of Helsinki, appropriate informed written consent was obtained from each patient or legal guardian. The Sheikh Russel National Gastro-liver Institute and Hospital's Ethical and Scientific Committee approved the protocol. A pre-designed structured questionnaire containing clinical history,

information based on the above-mentioned PEP risk factors, baseline serum amylase level was recorded. Follow-up data were recorded with serum amylase level at 24 hours (the next morning) after the procedure to confirm post ERCP pancreatitis. Statistical analyses were done using the SPSS (Statistical Package for the Social Sciences) for Windows, Version 23.0 (IBM Corporation, Armonk, NY). “Chi-square” test, binary logistic regression, and multivariate regression analysis were used for statistical analysis where applicable. A $P \leq .05$ was considered statistically significant, and the confidence interval was 95%.

3. Results

A total of 1042 patients who underwent ERCP and met the inclusion criteria were studied. Among them, 57.2% were male, with a mean age of 54.08 ± 14.00 . Choledocholithiasis was the most common indication found in 50% of cases (Table 1). In the present study, 204 (19.6%) cases developed post ERCP pancreatitis (PEP) (Fig. 1). Among the patient-related risk factors for PEP, young age and suspected SOD were highly significant in univariate analysis (Table 2). Further, analysis of procedure and operator-related risk factors revealed pancreatic duct injection with contrast, difficult cannulation (If >8 attempts

Table 1
Baseline characteristics of subjects and indication of ERCP (n = 1042).

Characteristics	Value
Age	
20–39 yr	181 (18.1)
40–60 yr	478 (45.9)
>60 yr	375 (36.04)
Mean (\pm SD)	54.08 \pm 14.00
Sex	
Male	596 (57.2)
Female	446 (42.8)
Indications of ERCP	
Choledocholithiasis	518 (49.7)
Cholangiocarcinoma	92 (8.8)
Periampullary carcinoma	91 (8.7)
Carcinoma head of the pancreas	85 (8.2)
Papillary stenosis	84 (8.1)
Chronic pancreatitis	74 (7.1)
Carcinoma gallbladder	48 (4.6)
Biliary stricture	35 (3.4)
Others	15 (1.4)

Values are presented as frequency, mean, or percentage (percentage in parenthesis). ERCP = endoscopic retrograde cholangiopancreatography, SD = standard deviation.

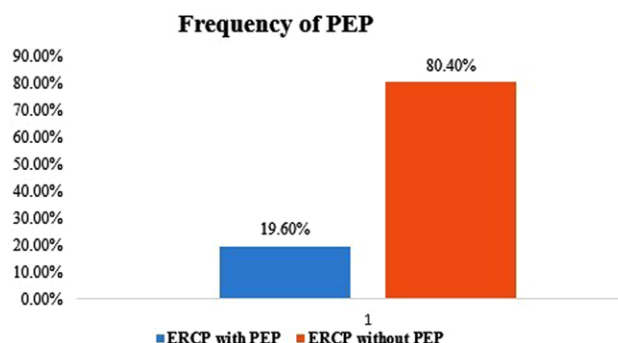


Figure 1. Frequency of PEP. ERCP = endoscopic retrograde cholangiopancreatography, PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis.

Table 2
Univariate analysis of patient-related risk factors for PEP.

Patient-related factors	PEP (n = 204)	Without PEP (n = 838)	P value
Significant			
Age (>50 yr/<50 yr)	30/174	198/640	.006
Suspected SOD (yes/no)	7/197	93/745	.001
Not significant			
Female gender (yes/no)	81/123	359/479	.416
Recurrent pancreatitis (yes/no)	7/197	33/805	.736
History of post ERCP pancreatitis (yes/no)	1/203	06/832	.062
Normal serum bilirubin level (yes/no)	52/152	222/616	.846

Chi-square (χ^2) test was done to measure the level of significance.
ERCP = endoscopic retrograde cholangiopancreatography, PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis, SOD = sphincter of Oddi dysfunction.

Table 3
Univariate analysis of procedure and operator technique-related risk factors for PEP.

	PEP (n = 204)	Without PEP (n = 838)	P value
Procedure-related factors			
Significant			
Pancreatic duct injection with contrast (yes/no)	63/141	63/775	.001
Difficult cannulation (If >8 attempts or prolonged time) (yes/no)	20/184	37/801	.002
Pancreatic sphincterotomy (yes/no)	8/196	6/832	.001
Not significant			
Minor papilla sphincterotomy/cannulation (yes/no)	0/204	0/838	—
Needle papillotomy/Precut access (yes/no)	47/157	188/650	.852
Balloon dilation (yes/no)	0/26	0/99	—
Operator technique-related factors			
Not significant			
Failure to use pancreatic duct stent (yes/no)	19/185	108/730	.162
Trainee (fellow participation) (yes/no)	0/204	0/838	—
None use of a Guidewire for cannulation (yes/no)	0/204	0/838	—

Chi-square (χ^2) test was done to measure the level of significance.
PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis.

or prolonged time), and pancreatic sphincterotomy has a significant association with post ERCP pancreatitis, but no operator-related factor had such association (Table 3). However, in multivariate analysis, young age, suspected SOD, recurrent pancreatitis, needle papillotomy, and pancreatic sphincterotomy were significant risk factors for post ERCP pancreatitis (PEP) (Table 4).

4. Discussion

Endoscopic retrograde cholangiopancreatography (ERCP) is widely recognized as a valuable tool for diagnosing and treating biliary and pancreatic disorders. Post-ERCP pancreatitis

Table 4
Multivariate analysis of risk factors for PEP.

Risk factors	OR	95% CI
Significant		
Young age	2.845	1.739–4.654
Suspected SOD (yes/no)	3.584	1.561–8.232
Recurrent pancreatitis (yes/no)	1.875	0.706–4.980
Needle papillotomy/precut access	1.123	0.723–1.743
Pancreatic sphincterotomy	1.380	0.150–12.675

Binary logistic regression was done to see any significant association.
PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis, SOD = sphincter of Oddi dysfunction.

(PEP) is the most common major complication. The frequency of this problem differs widely from country to country and even center to center, ranging from 1% to 31%.^[1,2] This has led to considerable interest in determining local incidence, risk factors, and potential preventive strategies. To our knowledge, this is the multicenter pioneer research presenting the frequency and risk factors for PEP among the patients of our country.

The mean age of the patients in this research was 54.08 ± 14.00 years, with the majority of the patients falling into the over 40 years age category. Minakari et al,^[14] in a recent study of 300 cases, found that the mean age of the patients was 60.5 ± 16.3 years. El Nakeeb et al,^[15] in their prospective cohort study, also found middle-age predominance. There were 596 (57.2%) males in our study, which states of male predominance. Other studies from the various country also found male predominance.^[15–17] Regarding the indications of ERCP, choledocholithiasis was the most common indication found in nearly half of the study subjects, followed by Cholangiocarcinoma, periampullary carcinoma, and carcinoma head of the pancreas. A prospective study also found the highest cases of choledocholithiasis (32%) as an indication of ERCP, whereas cholangiocarcinoma and carcinoma head of pancreas as the second-highest indications.^[16] Yousuf et al,^[18] in their study, identified biliary ascariasis as the second-highest indication. In our study, there were only 2 cases of ascariasis, which may be due to less ascariasis infestation at the present day (68% in the year 1983 but only 27% in the year 2017) in our country with many antihelminthic programs.^[19,20] However, the rest of the indications in our study were similar to the finding of Yousuf et al.^[18]

In this study, out of 1042 patients, 204 (19.6%) developed post ERCP pancreatitis (PEP). Published papers from the USA and India showed that PEP occurred up to 39.5% and 40% cases, respectively.^[7,21] According to a recent review research from Western Asia, PEP can occur in up to 15% of cases in normal circumstances, but up to 25% of cases in high-risk cases.^[22] Nishino and Toki^[23] reported that the incidence of PEP varies with patient susceptibility, associated illness, the concept of defining PEP, the meticulousness of aftercare, case variability, maneuvers performed at the table, and the expertise of endoscopist. The present study evaluated 14 risk factors in three subheadings (patient-related, procedure-related, and operator technique-related factors) according to a worldwide accepted consensus.^[12] The study could detect a total of 5 out of 11 procedure and patient-related risk factors in univariate analysis. Among the procedure-related risk factors, a significant association among pancreatic duct injection with contrast, difficult cannulation (If >8 attempts or prolonged time), pancreatic sphincterotomy, and post ERCP pancreatitis (PEP) was found to be significant. On the other hand, young age and suspected SOD were found to be significant among patient-related factors. A recent study case series of 344 patients at a high-volume center in Germany found age as a significant risk factor.^[23] Another study from Lahore, Pakistan found that pancreatic duct contrast injection was

a major risk factor, which is consistent with our findings.^[1] Nishino et al,^[24] in their series, found injection pressure of contrast medium into the pancreatic duct was not a significant risk factor while doing therapeutic ERCP but was significant in the case of diagnostic cases. However, the role and scope of diagnostic ERCP are very narrow nowadays, and in our study, all the cases were therapeutic. Cheng et al^[4] found minor papilla sphincterotomy/cannulation as a significant risk factor in univariate analysis, but they described biliary orifice balloon dilatation as not a risk factor. In our study, there was no case of minor papilla sphincterotomy/cannulation or balloon dilation, so we could not evaluate these risk factors. About the rest of the 3 operator techniques-related factors, the guidewire was used in all the cases, and there was no involvement of trainees. Still, failure to use the pancreatic duct stent was found in 19 cases of PEP but was not a significant risk factor in both multi and univariate analyses. Two prospective studies from China and Germany are unanimous with our finding.^[10,25]

While considering multivariate analysis, the present study found young age, suspected SOD, recurrent pancreatitis, needle papillotomy, and pancreatic sphincterotomy as significant risk factors for PEP. A recent study in multivariate analysis on 344 patients found age and chronic pancreatitis as a risk factor.^[25] Nishino et al^[24] found age as a significant risk factor for pancreatitis in overall multivariate analysis. Cheng et al^[4] similarly found age, suspected sphincter of Oddi dysfunction, and history of post-ERCP pancreatitis as a significant risk factors. A review article from Scientific Institute San Raffaele, Milan, Italy had stated that post ERCP pancreatitis is the most common complication after needle knife pre-cut papillotomy, with the rate varying from 2% to 34%.^[26]

There were some limitations to the current study. First, the study was conducted at four large tertiary care referral facilities, where the majority of difficult cases are often referred. Thus, the analysis may have overestimated the occurrence of PEP in comparison to the actual scenario. Furthermore, there was a lack of scope in evaluating some known risk factors for PEP, such as the minor papilla sphincterotomy/cannulation or balloon dilation and influence of involvement of trainees.

5. Conclusion

The frequency of PEP was 19.6% in this multicenter study. Both patient-related and procedure-related risk factors were acting independently for the development of PEP. The factors include young age, suspected SOD, pancreatic duct injection with contrast, difficult cannulation, needle papillotomy, pancreatic sphincterotomy, and recurrent pancreatitis. This risk factor stratification would add to the present knowledge of endoscopists for better identification of the high-risk groups and to take appropriate measures for the prevention of post ERCP pancreatitis.

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