

## Prospective Study

## Post-endoscopic retrograde cholangiopancreatography pancreatitis: Risk factors and predictors of severity

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### Abstract

#### AIM

To detect risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) and investigate the predictors of its severity.

#### METHODS

This is a prospective cohort study of all patients who underwent ERCP. Pre-ERCP data, intraoperative data, and post-ERCP data were collected.

#### RESULTS

The study population consisted of 996 patients. Their mean age at presentation was 58.42 ( $\pm$  14.72) years, and there were 454 male and 442 female patients. Overall, PEP occurred in 102 (10.2%) patients of the study population; eighty (78.4%) cases were of mild to moderate degree, while severe pancreatitis occurred in 22 (21.6%) patients. No hospital mortality was reported for any of PEP patients during the study duration. Age less than 35 years ( $P$  = 0.001, OR = 0.035), narrower common bile duct (CBD) diameter ( $P$  = 0.0001) and increased number of pancreatic cannulations ( $P$  = 0.0001) were independent risk factors for the occurrence of PEP.

#### CONCLUSION

PEP is the most frequent and devastating complication after ERCP. Age less than 35 years, narrower median CBD diameter and increased number of pancreatic

cannulations are independent risk factors for the occurrence of PEP. Patients with these risk factors are candidates for prophylactic and preventive measures against PEP.

**Key words:** Pancreatitis; Obstructive jaundice; Endoscopic retrograde cholangiopancreatography

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**Core tip:** Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases. However, ERCP is not a procedure without morbidities. Post-ERCP pancreatitis (PEP) remains the most devastating and frequent complication after ERCP. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients. Age less than 35 years, narrower median common bile duct diameter and increased number of pancreatic cannulations were identified to be independent risk factors for the occurrence of PEP.

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## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases<sup>[1]</sup>. However, ERCP is not a procedure without morbidities<sup>[2]</sup>. Post-ERCP pancreatitis (PEP) remains the most common and serious complication after ERCP<sup>[3]</sup>. The reported incidence of PEP is around 5%<sup>[4,5]</sup>. This rate may increase up to 20%-40% in high risk patients. Although the majority of PEP cases are of mild degree, it can be severe and life threatening in a substantial proportion of cases<sup>[6]</sup>.

Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients<sup>[1,7,8]</sup>. Being convinced with a number of patient-related risk factors, some gastroenterologists and surgeons prefer adoption of alternative management strategies for ERCP whenever possible in high risk patients. Similarly, some endoscopists try to avoid procedure-related risk factors to increase the safety of the procedure. All these factors make identification of risk factors for PEP be of paramount importance for the practice of ERCP.

Many patient and procedure related factors have been suggested to be associated with increased likelihood of PEP<sup>[8]</sup>. The trigger mechanism and pathogenesis for PEP

remain unclear<sup>[9]</sup>. The aim of this study was to detect risk factors for PEP and investigate the predictors of its severity in a tertiary high volume referral surgical center in Middle East in Egypt.

## MATERIALS AND METHODS

This is a prospective cohort study of all patients who underwent ERCP between August 2012 and September 2014. Excluded patients were those who presented with obstructed stent, active pancreatitis, previous endoscopic sphincterotomy, biliary complications after liver transplantation, dye allergy, pregnancy, or mental disability.

Patients were admitted 24 h before the procedure. Baseline laboratory assessment of liver functions, blood count and serum amylase level were done prior to ERCP. No pre-ERCP treatment was used to decrease the risk of PEP. In our center, ERCP is performed under general anesthesia with endotracheal intubation in left semi prone position with monitoring of oxygen saturation, heart rate, and blood pressure. The procedure was performed by experienced endoscopists who had performed at least 1500 ERCPs over the last 10 years. Selective bile duct cannulation was carried out in all patients, but pancreatic duct cannulation was performed when necessary. When three or more attempts were needed due to difficulty in cannulation, precut papillotomy was selectively performed. In addition, endoscopic papillotomy for stone extraction using balloon, basket and mechanical lithotripsy, bile duct placement of either plastic or self-expanding metallic stent, as well as brush cytology and dilation, were performed when indicated. Pancreatic duct stenting was not used to minimize PEP in our practice.

ERCP data were recorded in a standardized manner including all potential risk factors for PEP. Patients were hospitalized for 24 h after the procedure and observed for symptoms and signs of post-ERCP complications. Complete blood picture and serum amylase level were determined routinely after 6 h and 24 h.

PEP was defined and classified according to the consensus definition and grading system<sup>[10]</sup>. PEP was defined as new or worsened abdominal pain together with a serum amylase level at least three times normal at more than 24 h after ERCP and necessitating hospitalization for more than one night. PEP was graded according to the length of hospital stay and the need for intervention. Mild PEP required hospitalization for 2-3 nights, moderate PEP required hospitalization for 4-10 nights, and severe pancreatitis required hospitalization for more than 10 d, or required intervention or was complicated by pseudocyst<sup>[10]</sup>.

Descriptive data are presented as means and standard deviation or medians with range according to the data distribution. Comparison of means was done by  $\chi^2$  test for categorical data or Student's *t* test for continuous data. Difference was considered significant when a *P*-value was less than 0.05. Independent risk factors for PEP were assessed by multiple logistic

**Table 1 Risk factors for pancreatitis after endoscopic retrograde cholangiopancreatography *n* (%)**

	No pancreatitis 894 (89.9)	Pancreatitis 102 (10.2)	<i>P</i> -value
<b>Patient related factors</b>			
Median age (yr)	60	48	0.0001
Age group			
< 35	32 (7.2)	20 (39.2)	0.0001
> 35	415 (92.8)	31 (60.8)	
Sex			
Male	510 (57)	44 (43.1)	0.05
Female	384 (43)	58 (56.9)	
Median serum bilirubin (mg%)	10.6	12.5	0.76
< 2	124 (88.6)	16 (11.4)	
> 2	770 (90)	86 (10)	0.72
Median CBD diameter (mm)	16	10	0.0001
< 10	70 (7.8)	58 (56.9)	
> 10	824 (92.2)	44 (43.1)	0.0001
Indication for ERCP			
Malignant	402 (45)	40 (39.2)	0.43
Benign	492 (55)	62 (60.8)	
Type of papilla			
Normal	540 (60.4)	56 (54.9)	0.01
Atrophic	18 (2)	8 (7.8)	
Pregnant	68 (7.6)	2 (2)	
Tumour	64 (7.2)	4 (3.9)	
Redundant	66 (7.4)	12 (11.8)	
Juxtadiverticular	68 (7.6)	16 (15.7)	
Small	60 (6.6)	2 (2)	
Long	10 (1.1)	2 (2)	
<b>Procedure related factors</b>			
Number of cannulation attempts			
< 5	660 (73.9)	58 (56.9)	0.01
≥ 6	234 (26.1)	44 (43.1)	
Number of pancreatic cannulations	0	2	0.0001
< 3 times	864 (96.6)	60 (58.8)	
> 3 times	28 (3.4)	42 (41.2)	0.0001
Method of cannulation			
Conventional	640 (89.4)	76 (10.6)	0.7
Precut	252 (90.6)	26 (9.4)	
Biliary sphincter balloon dilatation			
No	654 (73.2)	86 (84.3)	0.08
Yes	240 (26.8)	16 (15.7)	

CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography

regression. Statistical analyses of the data in this study were performed using SPSS software, version 17 (Chicago, IL).

## RESULTS

From August 2012 to September 2014, a total of 1296 patients underwent ERCP at Gastrointestinal Surgical Center, Mansoura University, Egypt. The study population consisted of 996 cases after exclusion of those who presented with obstructed stent ( $n = 66$ ), active pancreatitis ( $n = 24$ ), previous endoscopic sphincterotomy ( $n = 110$ ), biliary complications after liver transplantation ( $n = 36$ ), dye allergy ( $n = 10$ ), pregnancy ( $n = 14$ ), or mental disability ( $n = 10$ ).

Indications for ERCP were malignant obstructive

jaundice due to periampullary tumor ( $n = 460$ , 46.2%) or hilar cholangiocarcinoma ( $n = 2$ , 0.2%), calcular obstructive jaundice ( $n = 512$ , 51.4%), benign biliary stricture ( $n = 10$ , 1.0%), and post-cholecystectomy biliary leakage ( $n = 12$ , 1.2%). The mean age at presentation was  $58.42 (\pm 14.727)$  years. There were 554 male in comparison to 442 female patients, with a male to female ratio of 1.3:1.

Overall, PEP occurred in 102 (10.2%) patients of the study population. Eighty (78.4%) cases were of mild to moderate degree, while severe pancreatitis occurred in 22 (21.6%) patients. The median length of hospital stay in patients with pancreatitis was 3 d (range, 2–15 d). No hospital mortality was reported for any of PEP patients during the study duration. Univariate analysis showed that patient age and narrower CBD diameter are statistically significant patient-related risk factors associated with occurrence and severity of PEP, while increased number of cannulation attempts and pancreatic cannulation more than three times were significant procedure-related risk factors associated with occurrence and severity of PEP. Indication for ERCP was not significantly associated with occurrence of pancreatitis ( $P = 0.4$ ), but it was significantly associated with the severity of PEP ( $P = 0.009$ ) (Tables 1 and 2).

Multivariate analysis after binary logistic regression analysis revealed that patient age less than 35 years ( $P = 0.001$ , OR = 0.035), narrower median CBD diameter ( $P = 0.0001$ ) and increased number of pancreatic cannulations ( $P = 0.0001$ ) were independent risk factors for the occurrence of PEP (Table 3).

## DISCUSSION

PEP is the most common and serious complication after ERCP<sup>[8]</sup>. PEP is associated with higher morbidity and mortality beside its effect in increasing the consumption of hospital resources<sup>[11]</sup>. Identification of clinical and procedural correlates for PEP is of crucial importance in the practice of ERCP. It affects the medical decision regarding patient choice, adoption of pharmacological prophylactic measures, avoidance of procedural risk factors, and determination of the time of discharge after the procedure<sup>[1,7,8]</sup>. Risk factors for PEP have been a matter of controversy and the pathogenesis of PEP is not fully understood yet<sup>[9,11]</sup>. This study reports risk factors for PEP according to the experience of a tertiary high volume surgical center in Egypt.

Despite advanced accessories and novel techniques in ERCP, complication rate after ERCP remained unchanged over the last decade<sup>[7,12]</sup>. According to previous reports, the incidence of PEP ranges from 5% to 40%. This great discrepancy in the reported rates can be attributed to heterogeneity of the definition of PEP and its grading system, variability in data collection, inclusion of diagnostic ERCP in the study, and difference in expertise among endoscopists<sup>[13]</sup>. The incidence of PEP in this cohort was 10.2% with adoption of the consensus definition of PEP<sup>[10]</sup>. Mild to moderate PEP occurred in 80

**Table 2 Predictors of severity of pancreatitis after endoscopic retrograde cholangiopancreatography *n* (%)**

	Mild to moderate pancreatitis (80)	Severe pancreatitis (22)	P-value
Patient related factors			
Median age (yr)	52	30	0.0001
Age			
< 35	26 (32.5)	14 (63.6)	0.0001
> 35	54 (67.5)	8 (36.4)	
Sex			
Male	38 (47.5)	6 (27.3)	0.08
Female	42 (52.5)	16 (72.7)	
Median serum bilirubin (mg%)	14.1	9.9	0.3
< 2	8 (50)	8 (50)	
> 2	72 (85.7)	14 (14.3)	0.07
Median CBD diameter (mm)	10	9	0.0001
< 10	42 (52.5)	16 (72.7%)	
> 10	38 (47.5)	6 (27.3%)	0.0001
Indication for ERCP			
Malignant	39 (97.5)	1 (2.5)	0.009
Benign	41 (66.1)	21 (33.9)	
Type of papilla			
Normal	39	17	0.06
Atrophic	6	2	
Pregnant	0	2	
Tumour	4	0	
Redundant	9	3	
Juxtadiverticular	15	1	
Small	2	0	
Long	2	0	
Procedure related factors			
No. of cannulation attempts			
< 5	46 (57.5)	12 (54.5)	0.03
≥ 6	34 (27.5)	10 (45.5)	
Median number of pancreatic cannulations	2	4	0.0001
< 3 times	58 (72.5)	2 (9.1)	0.0001
> 3 times	22 (52.4)	20 (90.9)	
Method of cannulation			
Conventional	58 (72.5)	18 (81.8)	0.07
Precut	22 (52.4)	4 (18.2)	
Biliary sphincter balloon dilatation			
No	70 (87.5)	16 (72.7)	0.1
Yes	10 (12.5)	6 (27.3)	

CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography.

**Table 3 Multivariate logistic regression for analysis of pancreatitis after endoscopic retrograde cholangiopancreatography**

Variable	P-value	Odds ratio	95%CI for EXP(B)	
			Lower	Upper
Age group	0.001	0.035	0.005	0.259
Age	0.519	1.012	0.976	1.050
Sex	0.362	0.143	0.075	0.270
CBD diameter below 10 mm	0.609	0.726	0.212	2.481
CBD diameter	0.000	0.612	0.495	0.757
Difficult cannulation	0.207	0.476	0.150	1.506
No. of pancreatic cannulations below 3	0.117	0.219	0.033	1.460
No. of pancreatic cannulations	0.000	5.258	2.665	10.370
Papilla	0.964			

CBD: Common bile duct.

(8%) patients, while severe PEP occurred in 22 (2.2%) patients. These ratios are concordant with data reported by previous studies<sup>[14-16]</sup>.

Among different patient related risk factors, younger age and non-dilated extrahepatic biliary radicals were independent risk factors for PEP on multivariate analysis

in this study. Also, using a cutoff value of 35 years to divide patients into two groups, the rate of PEP was significantly higher in the younger group by univariate analysis. Younger age has been a subject of controversy regarding its association with PEP<sup>[8]</sup>. Many studies reported an insignificant relation between patient age and likelihood of PEP<sup>[2,17]</sup>. However, Freeman *et al.*<sup>[18]</sup> first reported relatively younger age as a predictor of PEP on multivariate analysis. This finding was confirmed by later studies<sup>[5,16,19]</sup>. Higher incidence of PEP in younger age was explained by the aging effect on pancreatic exocrine function, smaller common bile duct diameter and the higher incidence of sphincter of Oddi dysfunction in younger age<sup>[13,16,18]</sup>.

Management of CBD stones in case of non-dilated extrahepatic biliary system represents a surgical challenge<sup>[20]</sup>. Laparoscopic transcholedochal CBD exploration mandates a CBD diameter of at least 6-8 mm<sup>[21-23]</sup>. According to many studies including this one, normal caliber CBD is associated with increased difficulty of the ERCP procedure<sup>[24-26]</sup>. However, most of recent studies reported absence of association between narrower CBD diameter and PEP<sup>[13]</sup>. Laparoscopic management for surgically fit patients with concomitant gall bladder and CBD stones in case of non-dilated CBD through transcystic CBD exploration or laparoendoscopic Rendezvous is better to avoid or minimize the risk of PEP<sup>[21]</sup>. In case of isolated choledocholithiasis or in patients who are unfit for surgery, prophylactic measures against PEP should be adopted.

In this cohort, difficult cannulation, denoted by frequent cannulation attempts and pancreatic cannulation more than three times, was associated with a higher risk of PEP. The effect of pancreatic duct injection with contrast dye on PEP could not be evaluated because we did not use the conventional contrast cannulation method. The effect of precut sphincterotomy on PEP is controversial<sup>[11]</sup>. Some authors advocate that precut sphincterotomy causes papillary oedema which retains pancreatic secretion resulting in PEP<sup>[8,24]</sup>. On the other hand, some authors indicate that precut sphincterotomy is usually preceded by difficult cannulation through the conventional approach and that the later, not the precut sphincterotomy itself, is responsible for the development of PEP<sup>[26]</sup>. This is supported by the finding that precut sphincterotomy was not reported as a risk factor for PEP from endoscopists who adopted precut sphincterotomy as a preferred technique from the start not just a salvage procedure after difficult cannulation through conventional cannulation methods<sup>[27]</sup>. Early precut leads to more successful cannulation rate without more hazard of morbidity after ERCP<sup>[28-33]</sup>.

Risk factors for PEP have a synergetic effect<sup>[8]</sup>. Jeurnink *et al.*<sup>[1]</sup> suggested that development of prognostic models and scoring systems based on various patient and procedure related risk factors will help in defining patients at the highest risk for PEP. According to this cohort, young patients (< 35 years) with narrow CBD (< 10 mm) who had shown evidence of difficult

cannulation (high number of cannulation attempts or pancreatic cannulation more than three times) are candidates for prophylactic and preventive measures against PEP<sup>[28]</sup>.

Despite the improvement of techniques of ERCP in recent years and increased experiences, the incidence of PEP has not decreased. Therefore, studies to determine risky patients and predict severity of PEP are very important to give the risk factors prophylactic agents for prevention of PEP<sup>[34-37]</sup>. Pre-ERCP administration of rectal indometacin reduced the overall occurrence of PEP without increasing risk of bleeding<sup>[34]</sup>. Some studies reported that the combination of a temporary prophylactic pancreatic plastic stent placement and rectal non-steroidal anti-inflammatory drugs is recommended for preventing PEP in high-risk cases<sup>[34-36]</sup>. Somatostatin can reduce the incidence of PEP but has not been routinely administered in most of centers nor recommended by guidelines as a prophylactic measure for PEP<sup>[36,37]</sup>. Patients at high risk of PEP should be also monitored for at least 24 h to avoid occurrence of PEP after early discharge<sup>[1,7]</sup>.

In conclusion, PEP is the most frequent and devastating complication after ERCP. PEP is associated with higher morbidity and mortality beside its effect in increasing the consumption of hospital resources. Age less than 35 years, narrower median CBD diameter and increased number of pancreatic cannulations are independent risk factors for the occurrence of PEP. Patients with these risk factors are candidates for prophylactic and preventive measures against PEP.

## COMMENTS

### Background

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases. However, ERCP is not a procedure without morbidities. Post-ERCP pancreatitis (PEP) remains the most common and serious complication after ERCP. The reported incidence of PEP is around 5%. This rate may increase up to 20%-40% in high risk patients. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients.

### Research frontiers

Many studies have tried to identify the risk factors for pancreatitis after ERCP. Many patient and procedure related factors are suggested to be associated with increased likelihood of PEP. The trigger mechanism and pathogenesis for PEP remain unclear.

### Innovations and breakthroughs

ERCP is not a procedure without morbidities. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients.

### Applications

The data in this study suggested risk factors for PEP and investigated the predictors of its severity in a tertiary high volume. Furthermore, this study also provided readers with important information regarding the risk factors for PEP.

### Terminology

PEP remains the most devastating and frequent complication after ERCP. The reported incidence of PEP is around 5%. This rate may increase up to



20%-40% in high risk patients.

## Peer-review

This is an interesting manuscript with a significant number of patients treating an important topic, and the aim of this study was to detect risk factors for PEP and investigate the predictors of its severity in a tertiary high volume referral surgical center in Egypt.

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