Is ESR Important for Predicting Post-ERCP Pancreatitis?

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ABSTRACT

BACKGROUND: Pancreatitis remains the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), resulting in substantial morbidity and occasional mortality. There are notable controversies and conflicting reports about risk factors of post-ERCP pancreatitis (PEP).

AIM: To evaluate the potential risk factors for PEP at a referral tertiary center, as a sample of the Iranian population.

MATERIALS AND METHODS: Baseline characteristics and clinical as well as paraclinical information of 780 patients undergoing diagnostic and therapeutic ERCP at Taleghani hospital in Tehran between 2008 and 2012 were reviewed. Data were collected prior to the ERCP, at the time of the procedure, and 24–72 hours after discharge. PEP was diagnosed according to consensus criteria.

RESULTS: Of the 780 patients who underwent diagnostic ERCP, pancreatitis developed in 26 patients (3.3%). In the multivariable risk model, significant risk factors with adjusted odds ratios (ORs) were age <65 years (OR = 10.647, $P = 0.023$) and erythrocyte sedimentation rate (ESR) >30 (OR = 6.414, $P < 0.001$). Female gender, history of recurrent pancreatitis, pre-ERCP hyperamylasemia, and difficult or failed cannulation could not predict PEP. There was no significant difference in the rate of PEP in wire-guided cannulation versus biliary cannulation using a sphincterotome and contrast injection as the conventional method.

CONCLUSIONS: Performing ERCP may be safer in the elderly. Patients with high ESR may be at greater risk of PEP, which warrants close observation of these patients for signs of pancreatitis after ERCP.

KEYWORDS: cholangiopancreatography, pancreatitis, complication

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Introduction

Pancreatitis, the commonest adverse event following endoscopic retrograde cholangiopancreatography (ERCP), has been found to occur at widely varying rates, in 1% to 15.1% of pateints.[1–4] Post-ERCP pancreatitis (PEP) has been found at lower rates in recent studies because noninvasive methods, such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS), have superseded diagnostic ERCP.[5] Despite improvement of our knowledge, equipment, and methods for ERCP, complications are still a significant hazard with this procedure.

PEP is the most common severe complication.[1,6,7] Numerous studies have looked at risk factors for PEP,[1–4,6–16] with varied results, possibly because of different study designs, different candidate predictor variables, and differences between settings.

Precise identification of risk factors is of great importance for recognition of high-risk cases in which ERCP should be avoided if possible or protective modalities should be considered to minimize patients' risk of morbidity and mortality. We know that inflammatory biomarkers are useful at 24–48 hours post procedure in predicting PEP, and a few studies have evaluated pre-procedure inflammatory markers, especially C-reactive protein (CRP) elevation, as predictors of PEP.[17–23] None of the previous studies has focused on pre-ERCP erythrocyte sedimentation rate (ESR) as a potential risk factor for PEP.

Despite the importance of identifying risk factors for PEP, no generalized study is available regarding the Iranian population. The present study examined prospectively the potential patient- and procedure-related risk factors, including ESR, for PEP in Iranian population.

Materials and Methods

During a four-year period (2008–2012), 780 patients who underwent ERCP in a tertiary care hospital were analyzed in this prospective study. The patients were referred to this center from different parts of Iran, which enhances the ability to generalize the findings for the Iranian population. All patients gave their written informed consent to participate in this research before the ERCP procedure, and the study protocol was approved by the ethics committee of the Research Center for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All the patients were hospitalized before ERCP. Indications for ERCP were determined by participating endoscopists

before the procedure, on the basis of generally accepted diagnostic indications for ERCP.[5] Laboratory evaluations, including those of alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin, and serum amylase, were performed on the first day of hospitalization, and the results were used as pre-ERCP laboratory parameters. Serum amylase was also measured 30 minutes before and 3 hours after ERCP.

Patients in acceptable condition were discharged one to two days after ERCP; otherwise, they received longer inpatient care based on the severity of their complications and illness. All the patients had a follow-up visit two weeks after discharge from hospital. Patient- and procedure-related data, including demographics, characteristics, clinical information and technical details, and findings from ERCP procedures were recorded prospectively on a detailed data sheet. ESR was measured during the 24 hours before performing ERCP. ESR above 30/hour was considered abnormal.

Exclusion criteria were a history of biliary sphincterotomy or pre-cut sphincterotomy, pre-procedure active pancreatitis, pregnancy, mental disability, and refusal to participate. ERCP procedures were performed by a total of eight expert endoscopists, almost always with a trainee performing at least part of the procedure. During the procedures, patients were under conscious sedation using a combination of intravenous lidocaine, midazolam, and propofol.

Cannulation was attempted using a sphincterotome. Successful cannulation was defined as free and deep instrumentation of the biliary tree, and a cannulation attempt was defined as sustained contact with the cannulating device and the papilla for at least five seconds.[17] Difficult biliary cannulation was defined as the failure of biliary access despite 10 minutes of attempted biliary cannulation or more than five attempted unintentional pancreatic cannulations.[18] Any complications taking place during or following the procedure were also entered into the records. These included PEP, gastrointestinal perforation, and bleeding. PEP was diagnosed according to the generally accepted criteria defined by Cotton et al,[6] ie, presence of upper abdominal pain 24 hours after an ERCP procedure and a serum amylase level more than three times the upper limit of normal.

Results were expressed as the mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. Multiple linear regression analysis was used to develop an optimal model for predicting PEP with the presence of confounders. The performance of the model was assessed with the Hosmer–Lemeshow goodness-of-fit test. *P* values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 16.0 (SPSS Inc.) for Windows.

Results

Between 2008 and 2012, 780 patients (male:female ratio 393:387, mean age 57.5 years) underwent diagnostic and therapeutic ERCP with the primary diagnosis of hepatobiliary disorders. Of these 780 ERCPs, 105 procedures (13.5%) were carried out in patients with invasive cancers (pancreatic ductal adenocarcinoma, biliary carcinoma, metastatic tumor with biliary obstruction, hepatocellular carcinoma, ampullary carcinoma) because of obstruction and 675 (86.5%) were performed in patients with benign diseases, which included 313 procedures (40.1%) to remove bile duct stones and 362 (46.4%) for benign biliary stricture.

The patients included 393 men (50.4%), and 448 (57.5%) were more than 65 years old. Previous cholecystectomy had been performed in 36.3% of patients and 9.0% had undergone previous ERCP. A total of 80 patients had history of biliary stone diagnosed by a similar procedure. Also, history of confirmed pancreatitis and hepatitis was observed in 27 (3.5%) and 10 (1.3%) patients, respectively (Table 1). Regarding laboratory parameters (Table 2), serum amylase was found to be elevated to more than 200 units/L in 102 patients (13.7%) three hours after ERCP and more than 800 units/L in 60 patients (7.7%).

In all, 446 (70%) participants underwent wire-guided cannulation and others (30%) underwent sphincterotome biliary cannulation using contrast injection as the conventional method.

Successful biliary cannulation was technically achieved in 82.5% of all patients at ERCP, although in 13.0% of them, cannulation failed. Regarding pathologic changes in papilla, tumoral features and ulcerative changes were found in 3.3% and 0.6% of patients. However, papilla was reported as normal in 82.6% of cases.

There were 4.1% major events related to the procedure. Of the 780 patients who underwent diagnostic or therapeutic ERCP, pancreatitis developed in 26 patients (3.3%). Significant bleeding occurred in two patients; the only predictor in multivariable analysis was biliary sphincterotomy. Five patients had duodenal or jejuna perforation. We diagnosed cholangitis (using the criteria of transient worsening of clinical states and liver function tests consistent with cholangitis) in four subjects, all of whom had common bile duct (CBD) stones with biliary stent placement. Table 3 shows the frequency of PEP and raised ESR according to indication for ERCP.

In the multivariable risk model for predicting PEP (Table 4), significant risk factors with adjusted odds ratios (ORs) were age <65 years (OR = 10.647, $P = 0.023$) and ESR >30 (OR = 6.414, $P < 0.001$). Female gender, history of recurrent pancreatitis, pre-ERCP hyperamylasemia, and difficult or failed cannulation could not predict PEP. Regarding the cannulation techniques, there was no difference in the incidence of PEP between guide wire-assisted ERCP or conventional contrast-assisted cannulation.

Discussion

We have identified two risk factors for the development of PEP: age <65 years and ESR >30. Several studies have

Table 1. Characteristics and medical history among patients undergoing diagnostic ERCP, with or without PEP.

	WITH PEP (n = 26)	WITHOUT PEP (n = 754)	TOTAL (n = 780)	*P*-VALUE
Male gender	14 (53.8)	379 (50.3)	393 (50.4)	0.4
Age (Years)	59.6 ± 14.9	56.3 ± 18.1	57.5 ± 17.2	0.2
Medical history				
Diabetes mellitus	4 (15.4)	85 (11.3)	89 (11.4)	0.1
Hypertension	5 (19.2)	138 (18.3)	141 (18.1)	0.2
Coronary artery disease	2 (7.7)	61 (8.1)	63 (8.1)	0.4
Cholecystectomy	10 (38.5)	273 (36.2)	283 (36.3)	0.3
Previous ERCP	3 (11.5)	67 (8.9)	70 (9.0)	0.08
Biliary stone	3 (11.5)	77 (10.2)	80 (10.3)	0.2
Cirrhosis	1 (3.8)	10 (1.3)	11 (1.3)	0.06
Pancreatitis	1 (3.8)	26 (3.4)	27 (3.5)	0.2
Hepatitis	1 (3.8)	9 (1.2)	10 (1.3)	0.08
Cholangiocarcinoma	0	6 (0.8)	6 (0.8)	0.07
Pancreatic cancer	0	5 (0.6)	5 (0.6)	0.07
Cigarette smoking	3 (11.5)	94 (12.5)	97 (12.4)	0.3
Alcohol use	1 (3.8)	21 (2.8)	22 (2.8)	0.09
Opium addiction	4 (15.4)	38 (5)	42 (5.4)	0.02

Notes: Data are presented as mean ± SD or *n* (%).
Abbreviation: PEP, post-ERCP pancreatitis.

focused on younger age as an independent predictor of PEP.[1–4,6–17] So in younger individuals, it is important to perform ERCP only when the indication is very strong and there is no other noninvasive substitute for ERCP. Another risk factor for the development of PEP in our study was increased ESR level before ERCP (ESR >30). We found that raised ESR >30 mm/hour is a significant factor that independently predicts increased risk of PEP. Although some studies have evaluated the level of post-ERCP inflammatory markers, especially post-procedure CRP elevation, as predictors of development of PEP,[19–23] it seems that none of the previous studies have focused on pre-ERCP ESR level as a potential risk factor for PEP. However, the findings of previous studies suggest that inflammatory biomarkers are helpful at 24–48 hours post-procedure, so they are not early predictors.

Although it seems that our study is the first study to evaluate pre-ERCP ESR level as a risk factor for developing PEP, many other studies have evaluated the role of pharmacologic agents in reducing the incidence or severity of PEP.[2,10,22–27] Several agents, most of which have an anti-inflammatory

Table 2. Pre-ERCP laboratory parameters among patients undergoing diagnostic ERCP, with or without PEP.

	WITH PEP (n = 26)	WITHOUT PEP (n = 754)	TOTAL (n = 780)	*P*-VALUE
AST	80.7 ± 4.4	88.6 ± 11.3	85.70 ± 3.32	0.3
ALT	126.2 ± 4.3	106.4 ± 11.4	109.83 ± 7.35	0.2
ALP	901.2 ± 36.6	808.3 ± 22.8	822.39 ± 29.40	0.2
Lactate dehydrogenase	460.8 ± 11.6	469.8 ± 21.4	463.66 ± 16.64	0.2
Total bilirubin	7.1 ± 0.1	6.3 ± 0.4	6.41 ± 0.33	0.07
Direct bilirubin	3.5 ± 0.03	3.6 ± 0.5	3.51 ± 0.19	0.3
Pre-ERCP serum amylase	169.3 ± 18.1	168.4 ± 14.3	168.58 ± 15.73	0.1
Post-ERCP serum amylase	596.2 ± 88.8	570.3 ± 44.7	579.32 ± 56.52	0.08
Changes of serum amylase	416.9 ± 21.4	406.4 ± 26.5	384.68 ± 57.49	0.08
Pre-ERCP ESR	48.8 ± 12.4	32.2 ± 18.6	28.6 ± 11.9	0.03

Notes: Data are presented as mean ± SD.
Abbreviation: PEP, post-ERCP pancreatitis.

Table 3. Frequency of PEP and raised ESR according to indication of ERCP.

INDICATION	ESR	PEP (NO)
Cancer (n: 105)	Raised ESR (n: 67)	6
	Normal ESR (n: 38)	2
Stone (n: 313)	Raised ESR (n: 112)	9
	Normal ESR (n: 201)	1
Benign stricture (n: 362)	Raised ESR (n: 58)	5
	Normal ESR (n: 304)	3

effect, have been tested in clinical trials. In terms of attenuating the inflammatory response, the most promising results have been with non-steroidal anti-inflammatory drugs (NSAIDs), and some standard guidelines recommend the routine use of NSAIDs to prevent PEP.[28] Most of these studies are experimental clinical trials, but it is possible that the main beneficial effect of these drugs is limiting systemic inflammatory response and lowering the level of ESR as a potential risk factor for PEP.

This study could be a guide for future clinical trials on rectal NSAIDs for the prevention of PEP; the effect of these drugs in prevention of pancreatitis, with attention to the level of ESR before ERCP, should be evaluated.

Other risk factors such as female gender, younger age, sphincter of Oddi dysfunction, cannulation difficulty, prolonged procedure time, and repeated injection to the pancreatic duct were not assessed because ERCP procedures were done by an expert and because of the absence of manometry.

Also, other factors such as pre-ERCP bacterial infections might increase ESR level. Some studies on both human and animal models, performed to evaluate the potential role of antibiotics in preventing PEP, found reduced rates of PEP in patients receiving antibiotic prophylaxis prior to ERCP when compared to placebo.[26] However, most studies did not find any role for infections in PEP, except in cases of severe pancreatitis with necrosis. Further studies are required to confirm these findings.

The main limitation of this study was the absence of combined evaluation of CRP and ESR before ERCP. ESR will be raised in almost all patients with any systemic inflammation, so our study is also limited because patients with systemic inflammation were not excluded.

To date, many risk factors for PEP have been reported from high-volume centers. These have included female gender, younger age, sphincter of Oddi dysfunction, cannulation difficulty, prolonged procedure time, and repeated injection to the pancreatic duct. Not all of these factors were analyzed in our study, and our results were not fully consistent with the previous results. Further studies are needed to confirm the current postulations.

Our study evaluated the risk factors of PEP in an Iranian population. It is not clear whether there is any tendency for PEP in different populations. Future investigations may resolve this question.

Conclusion

Performing ERCP may be safer in the elderly and in patients with low levels of serum ESR because they may be less at risk of PEP. Using pre-ERCP anti-inflammatory pharmacologic agents like NSAIDs might be beneficial, by lowering ESR level and reducing related risk of PEP.

Author Contributions

Conceived and designed the experiments: AHMA, MRZ. Analyzed the data: ESA, CB. Wrote the first draft of the manuscript: AHMA. Contributed to the writing of the manuscript: DM. Agree with manuscript results and conclusions: AHMA, MRZ. Jointly developed the structure and arguments for the paper: MM, SZD. Made critical revisions and approved final version: AHMA, MRZ. All authors reviewed and approved of the final manuscript.

Table 4. Multivariable regression analysis of the predictors of PEP with the presence of confounders.

ITEM	MULTIVARIATE *P*-VALUE	ODDS RATIO	95% CONFIDENCE INTERVALS	
			LOWER LIMIT	UPPER LIMIT
Female gender	0.153	2.196	0.746	6.468
Age <65 years	**0.023**	10.647	1.385	81.839
ESR >30	<**0.001**	6.414	2.276	18.073
Pre-ERCP serum amylase	0.876	1.000	0.998	1.001
Sphincterotomy	0.704	1.217	0.442	3.347
Guide wire cannulation	0.832	1.191	0.237	5.988

Notes: Hosmer–Lemeshow goodness of fit: $\chi^2 = 4.689$ and $P = 0.790$.

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