

Investigating possible risk factors and prognostic markers for post-endoscopic retrograde cholangiopancreatography pancreatitis

Post-endoskopik retrograd kolanjiyopankreatografi pankreatiti için olası risk faktörlerinin ve prognostik belirteçlerin araştırılması

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Background and Aims: Endoscopic retrograde cholangiopancreatography is a renowned technique used in the diagnosis and treatment of biliary and pancreatic diseases. It is observed that post-endoscopic retrograde cholangiopancreatography pancreatitis is the most common postoperative complication. In this study, we aim to present the endoscopic retrograde cholangiopancreatography results of our hospital and to investigate the possible risk factors and prognostic markers for post-endoscopic retrograde cholangiopancreatography pancreatitis. **Materials and Method:** Patients who underwent endoscopic retrograde cholangiopancreatography for various reasons between 2015 and 2018 were included in the study. Patient data were obtained from hospital records as the study was designed retrospectively. **Results:** Among 829 patients, 740 (89.3%) patients (male: 52.3%; mean age: 60±18 years) did not develop post-endoscopic retrograde cholangiopancreatography pancreatitis and 89 (10.7%) patients (male: 42.7%; mean age: 58±20 years) developed post-endoscopic retrograde cholangiopancreatography pancreatitis. The most common diagnosis in the endoscopic retrograde cholangiopancreatography was choledocholithiasis (49.9% vs 49.4%), and the second most common diagnosis was fibrotic strictures (23.5% vs 25.8%) in both of these groups. These diagnoses were followed by malignancies, sphincter Oddi dysfunction, periampullary diverticulum, bile leak, and other causes. Post-endoscopic retrograde cholangiopancreatography; aspartate aminotransferase, alanine aminotransferase, white blood cell count, neutrophil count, neutrophil percentage, lymphocyte count, lymphocyte percentage, neutrophil-lymphocyte ratio values were found to be significantly higher in the post-endoscopic retrograde cholangiopancreatography pancreatitis group than in the non-post-endoscopic retrograde cholangiopancreatography pancreatitis group ($p < 0.05$). **Conclusion:** Early diagnosis and early treatment of post-endoscopic retrograde cholangiopancreatography pancreatitis are of utmost importance. Risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis differ according to the studies. Further prospective studies are warranted.

Key words: ERCP, PEP, pancreatitis, NLR, neutrophil, lymphocyte

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is used for the imaging of the choledochus and pancreatic canal under X ray by injecting a contrast medium through Papilla Vateri by passing through the duodenum with a side-view endoscope. ERCP is included in advanced endoscopic techniques and used in the diagnosis and treatment of biliary and pancreatic diseases. ERCP is still widely used all over the world because it has lower risk and complication rates than surgery,

Giriş ve Amaç: Endoskopik retrograd kolanjiyopankreatografi, safra ve pankreas hastalıklarının tanı ve tedavisinde yaygın olarak kullanılan bir tekniktir. Endoskopik retrograd kolanjiyopankreatografi sonrası pankreatit en sık görülen postoperatif komplikasyondur. Bu çalışmada, hastanemizde yapılmış endoskopik retrograd kolanjiyopankreatografilerin sonuçlarını sunup, endoskopik retrograd kolanjiyopankreatografi sonrası gelişen pankreatit için olası risk faktörlerini ve prognostik belirteçleri sorgulamayı amaçladık. **Gereç ve Yöntem:** 2015-2018 yılları arasında çeşitli nedenlerle hastanemizde endoskopik retrograd kolanjiyopankreatografi yapılan hastalar çalışmaya dahil edildi. Çalışma retrospektif olarak tasarlandığından hasta verileri hastane kayıtlarından elde edilmiştir. **Bulgular:** Çalışmaya alınan 829 hastanın 740'ında (%89.3) (erkek: %52.3; ortalama yaş: 60±18 yıl) endoskopik retrograd kolanjiyopankreatografi sonrası pankreatit gelişmemiş ve 89'unda (%10.7) (erkek: %42.7; ortalama yaş: 58±20 yıl) post-endoskopik retrograd kolanjiyopankreatografi pankreatiti gelişmiştir. Her iki grupta da, endoskopik retrograd kolanjiyopankreatografide en sık tanı koledokolitiyazis (%49.9'a karşı %49.4) ve ikinci en sık tanı fibrotik darlıklar (%23.5'e karşı %25.8) olarak tespit edildi. Bu tanıları maligniteler, sfinkter Oddi disfonksiyonu, periampuller divertikül, safra kaçağı ve diğer nedenler izledi. Endoskopik retrograd kolanjiyopankreatografi sonrası aspartat aminotransferaz, alanin aminotransferaz, beyaz kan hücresi sayısı, nötrofil sayısı, nötrofil yüzdesi, lenfosit sayısı, lenfosit yüzdesi, nötrofil-lenfosit oranı değerleri post-endoskopik retrograd kolanjiyopankreatografi pankreatiti grubunda diğer gruba göre anlamlı olarak yüksek tespit edildi ($p < 0.05$). **Sonuç:** Post-endoskopik retrograd kolanjiyopankreatografi pankreatiti gelişimi sonrasında erken teşhis ve tedavi hayati önem taşımaktadır. Post-endoskopik retrograd kolanjiyopankreatografi pankreatiti için risk faktörleri ve prognostik belirteçler çalışmalara göre farklılık göstermekle birlikte hala ideal bir belirteç bulunamamıştır. Bu konuda çok merkezli prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: ERCP, PEP, pankreatit, NLO, nötrofil, lenfosit

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Post-ERCP pancreatitis (PEP) is the most common postoperative complication (1.3–15%) (3,4). PEP is often mild, but sometimes may be a life-threatening clinical picture. PEP also increases the length of hospitalization and causes an increase in costs (4,5). In this study, first, we aimed to present the ERCP results of our hospital and second to investigate the possible risk factors and prognostic markers for PEP.

MATERIALS and METHOD

A total of 829 patients who underwent ERCP for various reasons were included in the study between 2015 and 2018. Because the study was designed retrospectively, patient data were obtained from hospital records. The study was done with accordance to the declaration of Helsinki and ethical guidelines (Fortaleza, Brazil, October 2013). Ethics committee approval was obtained from Adana City Training and Research Hospital Clinical Research Ethics Committee (2020-71-1159).

Acute pancreatitis (AP) diagnosis was established in the presence of at least 2 out of the 3 criteria below:

1. Abdominal pain is consistent with AP.
2. Serum amylase elevation ≥ 3 times the upper limit of normal.
3. Contrast-enhanced computed tomography, magnetic resonance imaging, or abdominal ultrasonography findings consistent with AP.

Patients with missing data were not included in the study.

Statistical Analyses

The data are presented as the mean, median, standard deviation (SD) and percentages. All analysis was performed using IBM SPSS Statistics, V.20.0 (Armonk, NY: IBM Corp.). The comparison between two groups of quantitative biochemistry variables was performed with Student's t-test for independent samples. Changes in quantitative biochemistry variables across different pre and post treatment were analyzed by covariance model within and between groups. Pre treatment measures used as covariate in this covariance models. We used Fisher's exact test and the chi-square test to assess the association between two qualitative variables. All tests were two-tailed and $p < 0.05$ was considered as statistically significant.

RESULTS

A total of 829 patients who underwent ERCP for various reasons between 2015 and 2018 were included in the study. 740 (89.3%) patients (male: 52.3%; mean age: 60 ± 18 years) did not develop PEP and 89 (10.7%) patients (male: 42.7%; mean age: 58 ± 20 years) developed PEP. No statistically significant difference was found between the two groups in terms of age and gender.

The demographic and laboratory parameters of the patients before and after ERCP are presented in Tables 1 and 2.

The percentage of patients referred from the emergency department was higher in the PEP developed group than the other group (65.2% vs 50.3%; $p < 0.05$).

Table 1. Demographics and laboratory results of patients before ERCP

Parameters	PEP (n: 89)		Non-PEP (n: 740)		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
Age (Years)	57	19	60	18	$p \geq 0.05$
Gender (Male, %)	42.7		52.3		$p \geq 0.05$
Laboratory Data					
AST (U/L)	221	263	179	189	$p \geq 0.05$
ALT (U/L)	258	204	217	198	$p \geq 0.05$
Albumine (g/dl)	3.9	0.5	3.9	0.6	$p \geq 0.05$
Total bilirubin (mg/dl)	3.6	3.3	4	4.7	$p \geq 0.05$
Direct bilirubin (mg/dl)	2.9	3	3.2	4	$p \geq 0.05$
White blod cell ($10^9/L$)	10.9	4.9	10.3	4.9	$p \geq 0.05$
Neutrophile ($10^9/L$)	8.3	4.9	7.8	4.9	$p \geq 0.05$
Lymphocyte ($10^9/L$)	1.4	0.7	1.6	0.9	$p \geq 0.05$
Neutrophile/Lymphocyte Ratio	8.2	9.1	7.8	10	$p \geq 0.05$
Hemoglobine (g/dl)	12.6	1.4	12.6	1.9	$p \geq 0.05$
Hematocrit (%)	37.9	4	38	5.4	$p \geq 0.05$
Platelets ($10^9/L$)	262	82	259	91	$p \geq 0.05$

ERCP: Endoscopic retrograde cholangiopancreatography, PEP: Post ERCP pancreatitis, Std. :Standard, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

Table 2. Demographics and laboratory results of patients after ERCP

Parameters	PEP (n: 89)		Non-PEP (n: 740)		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
Age (Years)	57	19	60	18	p ≥0.05
Gender (Male, %)	42.7		52.3		p ≥0.05
Laboratory Data					
AST (U/L)	81	64	60	73	p <0.05
ALT (U/L)	156	113	110	120	p <0.05
Total bilirubin (mg/dl)	2.6	3.6	2.7	4.6	p ≥0.05
Direct bilirubin (mg/dl)	2	3	2	3.7	p ≥0.05
White blood cell (10 ⁹ /L)	10.3	3.3	9	3.7	p <0.05
Neutrophil (10 ⁹ /L)	7.9	3.1	6.3	3.6	p <0.05
Lymphocyte (10 ⁹ /L)	1.5	0.7	1.8	0.8	p <0.05
Neutrophil/Lymphocyte Ratio	7.4	7.8	4.9	6.1	p <0.05
Hemoglobin (g/dl)	12.3	1.6	12.3	1.7	p ≥0.05
Hematocrit (%)	37.1	4.7	37.1	4.9	p ≥0.05
Platelets (10 ⁹ /L)	248	77	254	90	p ≥0.05

ERCP: Endoscopic retrograde cholangiopancreatography, PEP: Post ERCP pancreatitis, Std.: Standard, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

Table 3. Corresponding groups according to details of ERCP procedure

		PEP	Non-PEP	
		N (%)	N (%)	
Sphincterotomy Type	Classical	65 (73%)	562 (75.9%)	p >0.05
	Needle-tipped	24 (27%)	178 (24.1%)	
Biliary stent	Placed	35 (39.3%)	260 (25.1%)	p >0.05
	Not placed	54 (60.7%)	480 (64.9%)	
Biliary metallic stent placed		1 (3%)	8 (3%)	p >0.05
Biliary plastic stent placed		34 (97%)	252 (97%)	
Pancreatic stent placed		1 (0.1%)	1 (1%)	p >0.05
Pancreatic stent not placed		88 (98.1%)	739 (99.1%)	

ERCP: Endoscopic retrograde cholangiopancreatography, PEP: Post ERCP pancreatitis.

In both of the groups, the most common diagnosis in the ERCP was choledocholithiasis (49.9% vs 49.4%), and the second most common diagnosis was fibrotic strictures (23.5% vs 25.8%). These diagnoses were followed by malignancies, sphincter Oddi dysfunction (SOD), perampullary diverticulum, bile leak, and other causes.

No statistically significant difference was found between sphincterotomy type (classical, needle-tipped), biliary stent application, biliary stent type (plastic, metallic) or the number of stents applied and PEP development (Table 3).

There was no significant difference between the two groups in terms of albumin, aspartate aminotransferase (AST), alani-

ne aminotransferase (ALT), total bilirubin, direct bilirubin, white blood cell count (Wbc), neutrophil count, neutrophil percentage, lymphocyte count, lymphocyte percentage, neutrophil-lymphocyte ratio (NLR), platelet, hemoglobin, and hematocrit values before ERCP.

AST, ALT, Wbc, neutrophil, neutrophil percentage, lymphocyte, lymphocyte percentage, and NLR values were significantly higher in the PEP group than in the other group, after ERCP (p < 0.05).

The difference between the differences before and after ERCP was found to be statistically significant for neutrophil, lymphocyte, NLR, and ALT (p < 0.001). A covariance analysis

model was used to take into account the initial values because the difference in the difference for this measurement was affected by the preprocessing value.

DISCUSSION

ERCP is a method of imaging of pancreas, gallbladder, and bile ducts using contrast material with combined use of endoscope and X-rays. Problems in the liver, gallbladder, bile and pancreatic ducts, duodenal diverticula, and fistulas including esophagus, stomach, pancreas, and biliary duct diseases can be diagnosed. During the procedure, some problems can be treated (1,2). In our study, the most common ERCP indications were choledocholithiasis and fibrotic strictures. These diagnoses were followed by malignancies, SOD, peripapillary diverticulum, bile leak, and other causes.

PEP is the most common and serious complication of ERCP. The incidence of PEP was 1.3-15% in various studies (6,7). It was reported that it was more frequent in SOD. Severe PEP is rarely seen (0.3–0.5%) (8-10). In a systematic review involving over 2000 high-risk patients, the incidence of PEP was found to be 14.7%, while mild, moderate, and severe PEP was 8.6, 3.9, and 0.8%, respectively. PEP is affected by many factors, including factors associated with the process and patient. The combination of the experience of the endoscopist, presence of SOD, difficult cannulation, duration of the procedure, type of the procedure, young age, female sex, suspected sphincter of Oddi dysfunction, normal bilirubin and the absence of bile duct stones is associated with a high risk of pancreatitis (11-14). PEP is presented with epigastric pain or abdominal upper quadrant pain, abdominal tenderness with palpation, and elevated amylase and lipase. Early diagnosis and treatment are important (15,16). The diagnosis of PEP is based on the presence of symptoms and signs of AP (abdominal pain, etc.) in addition to increased pancreatic enzyme levels. Patients undergoing severe PEP may need to be followed up and treated in intensive care (13). In a meta-analysis of 15 studies between January 1991 and December 2001; SOD, history of post-ERCP pancreatitis, female sex, pancreatic duct contrast injection, and pre-cut sphincterotomy were determined as independent predictors of PEP. The absence of even common bile duct stones was defined as another risk

factor for PEP, but the diagnosis of SOD was not considered in this study (17). Pancreatic cannulation and contrast injection were reported by PEP (18,19). The experience of the operator is also stated as a risk factor in some studies (19,20). In our study, no statistically significant difference was found between age, gender, type of sphincterotomy (classical, needle-tipped), biliary stent application, type of biliary stent (plastic, metallic), or the number of stents applied and development of PEP. PEP was observed in 89 (10.7%) patients in accordance with the medical literature.

There are many studies in the literature indicating that some whole blood parameters are associated with the development of AP. According to the retrospective study by Zhang et al. which was performed with 974 AP patients; there is a significant association between NLR and the duration of intensive care, the risk of developing persistent organ failure, and mortality (21). Li et al. performed a single-center retrospective study with 359 AP patients and this study revealed NLR to be the most reliable marker of overall survival (22). Jeon et al. performed a retrospective study with 490 AP patients and suggested a relationship between NLR, AP severity, and the development of multi-organ failure (23). In our study, AST, ALT, Wbc, neutrophil, neutrophil percentage, lymphocyte, lymphocyte percentage, and NLR values were significantly higher in PEP group than the other group after ERCP/in period of post-ERCP.

The most important limitation of our study is, that it is single-centered and retrospective. Some patients' datas were not recorded in detail so we could not reach enough data to classify the severity of pancreatitis. Nevertheless, we assume that it will contribute positively to the medical literature because it contains a significant number of patients with PEP.

Today, ERCP has an important role in the diagnosis and treatment of liver, gall bladder, biliary tract, and pancreas. The most important complication is PEP. Early diagnosis and early treatment of PEP are of vital importance. Risk factors for PEP differ according to the studies. A multicenter, large population prospective study is needed.

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