Dig Dis Sci (2016) 61:2397–2405
DOI 10.1007/s10620-016-4127-0

ORIGINAL ARTICLE

Insulin Resistance as a Novel Risk Factor for Post-ERCP Pancreatitis: A Pilot Study

Ali Riza Koksal[1] · Salih Boga[1] · Huseyin Alkim[1] · Mehmet Bayram[1] · Meltem Ergun[1] · Canan Alkim[1]

Received: 21 October 2015 / Accepted: 7 March 2016 / Published online: 19 March 2016

Abstract
Background and Aims The relationship between insulin resistance and post-ERCP pancreatitis (PEP) is not known. We aimed to determine the relation between pre-ERCP insulin resistance and risk of PEP, and to evaluate the relationship of insulin resistance with well-established risk factors for PEP.
Methods Consecutive patients who underwent ERCP with the diagnosis of choledocolithiasis between January and December 2013 were enrolled in this prospective study. Pre-procedural insulin resistance state and other risk factors were evaluated according to PEP development.
Results Pancreatitis developed in 16 (11.3 %) of 141 ERCP procedure. Homeostasis model assessment of insulin resistance (HOMA-IR) levels was found statistically significantly higher in patients who developed PEP than the ones who did not (3.37 ± 0.8 vs. 2.38 ± 1.4, $p < 0.001$). Common bile duct (CBD) diameter of the patients developing PEP was found significantly lower than the non-PEP group (10.1 ± 4 vs. 13.4 ± 4.5 mm, $p = 0.01$). Mean procedure time was 33.5 min in PEP group and 27.9 min in non-PEP group ($p = 0.006$). HOMA-IR (OR 2.39), procedure time (OR 1.15), and CBD diameter (OR 0.82) were independent predictors of PEP development.
Conclusions The presence of insulin resistance is an important risk factor for PEP, and these data can be used as a considerable clue to predict the risk of PEP before ERCP and to decrease related morbidity.

Keywords Post-ERCP pancreatitis · Insulin resistance · HOMA-IR

Introduction

Post-ERCP pancreatitis (PEP) is one of the most prevalent complications of the ERCP. The PEP rates reported in different studies were between 1 and 40 % [1–5]. One of the most important reasons for this great difference between the studies is the plenty of potential risk factors that ERCP procedure itself has. The other reason for the wide range of PEP prevalence between different studies is the variable definition of PEP [5–7]. According to the consensus classification made by Cotton et al. [5], PEP was defined as new or worsened abdominal pain with an amylase elevation at least three times of the upper limit of normal for more than 24 h after ERCP, and requiring more than one night of hospitalization. Another definition is the revised Atlanta criteria evolved for acute pancreatitis in 2012 [8]. Furthermore, the European Society of Gastrointestinal Endoscopy (ESGE) guideline recommended that any of two definitions may be used [9].

✉ Ali Riza Koksal
arkoksal@gmail.com

Salih Boga
salihboga@yahoo.com

Huseyin Alkim
alkim65@gmail.com

Mehmet Bayram
drmhbayram@gmail.com

Meltem Ergun
melergun@gmail.com

Canan Alkim
alkimca@hotmail.com

[1] Department of Gastroenterology, Sisli Hamidiye Etfal Education and Research Hospital, Halaskargazi Av. Etfal St. 34371 Sisli, Istanbul, Turkey

PEP risk factors [9–13] are determined by numerous large population-based studies using multivariate analysis. However, there is still a group of patients who do not have any risk factor but develops PEP. Despite focusing on the mechanical, chemical, enzymatic, and microbiologic etiologies, the mechanism of PEP is not fully elucidated [1, 9, 14, 15]. Post-procedural early hyperamylasemia is a common finding after ERCP, but most of these cases do not develop PEP [16]. An exaggerated immune response and an intense proinflammatory cytokine response against oxidative stress are also seen in PEP as seen in other acute pancreatitis cases [9, 17, 18].

An atherogenic dyslipidemic profile showing prothrombotic and proinflammatory states is known to be developed in patients with insulin resistance. Because patients with insulin resistance have a proinflammatory microenvironment, they are under risk of diseases that have chronic inflammation as the underlying etiology such as cardiovascular diseases, cerebrovascular events, and nonalcoholic steatohepatitis [19–21]. This risk which is caused by maladaptive response to inflammation is thought to be independent from obesity [22–24]. It is shown that individuals with insulin resistance are more vulnerable to acute inflammatory events and insulin resistance has a prognostic value in these situations [25, 26]. According to several studies published in recent years, acute pancreatitis shows a more severe course in individuals who have obesity and insulin resistance [27].

There are two studies in the literature held about obesity and PEP reporting that obesity did not increase the PEP risk [28, 29]. However, there is yet no study found in the literature investigating the relationship between insulin resistance and PEP risk. We suggest that the proinflammatory microenvironment formed by insulin resistance can be a predisposing factor for the development of PEP. So, we aimed to determine whether increased pre-ERCP insulin resistance is associated with an increased risk of PEP, and to evaluate the relationship of insulin resistance with well-established risk factors for PEP.

Methods

Patients' Enrollment

Patients between 18 and 85 years old who underwent ERCP with the pre-diagnosis of choledocolithiasis in endoscopy unit of Gastroenterology Department of Sisli Hamidiye Etfal Education and Research Hospital between January 2013 and December 2013 were enrolled in this study. A detailed physical examination was performed, and each patient was questioned for frequent metabolic disorders such as hyperlipidemia and hypertension. Patients who had malignancy, diabetes, or thyroid disorder and who underwent ERCP previously were excluded. Additionally, patients who had a suspect or strong evidence of malignancy in the pre-procedure assessment and who admitted with acute pancreatitis were also excluded. Choledocholithiasis was diagnosed by two ways: (i) choledocholithiasis demonstrated by magnetic resonance imaging (MRI) and (ii) high suspicion of choledocholithiasis: cholelithiasis together with common bile duct dilatation demonstrated by MRI and sign and symptoms of cholangitis.

All blood samples for pre-procedural analysis were collected after an 8 h overnight fasting, and all of the findings were evaluated at the end of the study to warrant blindness of the investigators. The estimate of insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) index, with the following formula: insulin resistance = fasting plasma insulin (in microunits per milliliter) × fasting plasma glucose (in milligram per deciliter)/405. Patients with HOMA-IR ≥ 2.5 were included in the insulin resistance subgroup. Body mass index (BMI) was computed as body weight (kg)/height (m)^2. Patients with BMI < 25 kg/m^2, BMI: 25–29 kg/m^2, and BMI ≥ 30 kg/m^2 were classified as normal, overweight, and obese, respectively.

Each patient was hospitalized at least for 24 h to secure complete recording of the study data. Fasting blood samples were taken for amylase, lipase, C-reactive protein (CRP), and other biochemical and hemogram tests 24 h after the procedure. Although diagnostic criteria for PEP were accepted as the presence of two of the following three features: (1) A typical pain of acute pancreatitis, (2) serum amylase and/or lipase level elevation more than three times of the upper limit of normal, and (3) characteristic findings of acute pancreatitis at CT scan, all of the patients underwent CT to rule out any possible post-ERCP complication such as duodenal perforation, cholangitic abscess, or contrast cholecystitis even if he/she meets the Atlanta criteria mentioned above. All CT scans were performed 24–36 h after the procedure.

Severity of pancreatitis was determined according to consensus criteria defined by Cotton et al. [5]. Mild pancreatitis was defined as amylase at least three times normal at more than 24 h after the procedure requiring admission or prolongation of planned admission to 2–3 days. Pancreatitis was defined as moderate when hospitalization was needed for 4–10 days and severe when hospitalization needed more than 10 days.

ERCP Procedures

All ERCP procedures were performed by one of four expert gastroenterologists in our gastroenterology unit

(HA, CA, ME, ARK). ERCPs were performed with 4.2-mm channel adult type therapeutic Exera CLV-160 model Olympus® duodenoscope (Olympus Medical Systems Corp. Tokyo, Japan). All patients were evaluated by an anesthetist and had appropriate sedation. Cannulation was started with the standard cannulation method, defined as usage of catheter or sphincterotome preloaded with guidewire. The method of biliary cannulation (standard or precut), the presence or absence of pancreatic duct cannulation, extraction of stone or sludge, usage of balloon and/or basket catheter, and pain perceived during the procedure were all recorded. The total time of procedure was defined as the time in minutes calculated by oral to oral insertion to removal of the duodenoscopy probe. Precut sphincterotomy was performed after five or six unsuccessful cannulation attempts. In cases with unsuccessful cannulation, common bile duct diameter (CBD) was obtained from radiological studies. The cases that had papilla precut sphincterotomy with needle knife sphincterotome as the method of common bile duct cannulation were accepted as difficult to cannulate patients. Cases with longer procedure time and cases with usage of both balloon and basket catheters were accepted as difficult ERCP cases. Pancreatic duct cannulation was defined as cannulation of pancreatic duct with the guidewire. Prophylactic pancreatic stent or rectal diclofenac was not applied to any of the patients according to study protocol.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 21 (IBM corp. Chicago IL) program. The variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables. Median and interquartile ranges (Q1–Q3) were given for non-normally distributed variables. Ordinal and continuous variables that do not have normal distribution were compared by Mann–Whitney *U* test. The Student *t* test was used to evaluate differences between the two study groups in normally distributed continuous variables. The proportions of patients with and without PEP were presented by categorical variables using cross-tabulations. The Chi-square test or Fisher's exact test, when appropriate, was used to compare these proportions in different groups. A *p* value less than 0.05 was considered to show a statistically significant result.

The capacity of CBD diameter, procedure time, and HOMA-IR which were found significant on univariate analysis in predicting occurrence of PEP were analyzed using receiver operating characteristics (ROC) curve analysis. When a significant cutoff value was observed, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were presented.

Logistic regression analyses were implemented with SAS 9.4 (Statistical Analysis Software; SAS Institute, Cary, NC). Firth (penalized) logistic regression analysis was used because of the small sample size. The possible factors identified with univariate analysis or in recent studies were further entered into the logistic regression analysis to determine independent predictors of PEP. Different models were formed by including variables as age, gender, cannulation type (precut or standard), bile duct stone identified on ERCP, HOMA-IR, procedure time, pancreatic duct cannulation, CBD diameter, and pre-procedure total bilirubin levels. Variables that were not providing a significant contribution were excluded from the model by backward likelihood ratio stepwise method. Hosmer–Lemeshow goodness-of-fit statistics was used to assess model fit. A 5 % type I error level was used to infer statistical significance.

Ethical Aspect

The study was conducted in accordance with the "Declaration of Helsinki" and was approved by Sisli Etfal Education and Research Hospital Ethics Committee. A verbal and written informed consent was obtained from each patient.

Results

One hundred and forty-one patients were enrolled in the study. The mean age of the patients was 59 ± 15.9 years. Fifty-one (36.2 %) of the patients were male, and 90 (63.8 %) were female. At the initial evaluation done before ERCP, 84 (59.6 %) of the patients were hypertensive, 43 (24.8 %) were hyperlipidemic, 35 (30.5 %) were obese, and 68 (48.2 %) of them had pre-procedure HOMA-IR $\geq$ 2.5 (Table 1).

The indication for ERCP was choledocholithiasis in all of the cases. Total cannulation success rate was 88.7 %, and mean procedure time was 28.6 ± 7.6 min. The mean diameter of the CBD was 13.1 ± 4.5 mm. While the standard method was used in 94 (66.7 %) of the patients for cannulation, in 47 (33.3 %) of the patients precut sphincterotomy was tried. Balloon catheter was used in 90 (63.8 %) and basket catheter was used in 18 (12.8 %) of the patients and in 17 (12.1 %) of them both balloon and basket catheters were used. Mechanical lithotripsy was performed in 6 cases. There was no catheter usage in 16 (11.3 %) patients because of the unsuccessful procedure. Cases with

Table 1 Prevalence of PEP for different categorical variables

	Total	PEP	Non-PEP	PEP (%)	*p* value
Gender					
Male	51	4	47	7.8	0.41
Female	90	12	78	13.3	
Hyperlipidemia					
Present	35	7	28	20	0.06
Absent	106	9	97	8.5	
Hypertension					
Present	84	8	76	9.5	0.42
Absent	57	8	49	14	
BMI					
<25 kg/m^2	36	2	34	5.6	
25–29 kg/m^2	62	8	54	12.9	0.44
≥ 30 kg/m^2	43	6	37	14	
HOMA-IR					
<2.5	73	4	69	5.5	0.03
≥2.5	68	12	56	17.6	
Cannulation type					
Standard technique	94	10	84	10.6	0.78
Precut technique	47	6	41	12.8	
Success rate of the ERCP					
Successful	125	14	111	11.2	0.87
Unsuccessful	16	2	14	12.5	
Catheter type					
None	16	2	14	12.5	0.73
Balloon	90	10	80	11.1	
Basket	18	1	17	5.6	
Combined	17	3	14	17.6	
Stone in ERCP					
Present	128	13	115	10.2	0.16
Absent	13	3	10	23.1	
Pancreas cannulation					
Present	28	7	21	25	0.01
Absent	113	9	104	8	
Pain during the procedure					
Present	50	6	44	12	0.85
Absent	91	10	81	11	
Anesthetic drugs					
Propofol + fentanyl	81	6	75	7.4	0.11
Midazolam + pethidine	60	10	50	16.7	

BMI body mass index, *HOMA-IR* homeostasis model assessment of insulin resistance

apparent bile stone or sludge extraction on ERCP ($n = 81$), cases with evident calculi seen in cholangiogram, but could not have stone extraction due to inadequate anesthesia or technical problems ($n = 18$) and cases with evident calculi seen in the initial cholangiogram and had no evidence of bile duct stone in the final cholangiogram although stone extraction from papillary orifice during ERCP was not demonstrated ($n = 15$) were considered as bile duct stone identified on ERCP. Additionally, cases with unsuccessful cannulation in the first procedure but had stone extraction in the latter ERCP ($n = 14$) were also included to "bile duct stone identified on ERCP" group. Eventually, a total of 128 (90.8 %) patients had bile duct stone identified on ERCP, whereas remaining 13 (9.2 %) patients had no evidence of bile duct stone. Cases with bile duct stones in proximal common bile duct or intrahepatic bile ducts and cases with stones larger than the diameter of distal common bile duct could not have their bile stones extracted at the first ERCP session. Also prolongation of sedation time was another reason for the failure of stone extraction in the first ERCP session. Biliary plastic stents were placed in 21 (14.9 %) patients who had incomplete clearance of stones or insufficient emptying of contrast material or bleeding due to sphincterotomy. Unintentional pancreatic duct cannulation by the guidewire was occurred in 28 (19.9 %) of cases. In two of these cases, contrast agent injection to the pancreatic duct without acinarization was done. Propofol + fentanyl combination was used in 81 (57.4 %) of the patients, whereas midazolam + pethidine was used in 60 (42.6 %) of them. Pain perception despite the administration of anesthetic agent was noted in 50 (35.5 %) patients (Table 1).

Forty-four (31.2 %) of the patients developed hyperamylasemia and 16 (11.3 %) of them developed PEP. An oozing hemorrhage was seen in 4 (2.8 %) patients, biliary stent was placed to their CBD in the end of the procedure, and none showed evidence of serious bleeding. Post-ERCP cholangitis was seen in 6 (4.2 %) patients. Perforation, death, and any other procedural complication were not developed. There was no severe pancreatitis case. Only one case was moderate and the rest were mild pancreatitis cases. The length of hospitalization was 60 [48–72] h in PEP group, and 24 [24–36] h in non-PEP group. Clinical and laboratory features of patients who developed PEP are given in Table 2. ALT (73; (50–117) vs. 46; (28–98), $p = 0.03$), HOMA-IR (3.37 ± 0.8 vs. 2.38 ± 1.4, $p < 0.001$), and insulin levels (13.2 ± 3.1 vs. 9.4 ± 5.9, $p < 0.001$) were found statistically significantly higher in patients who developed PEP than the ones who did not. Also platelet count and mean platelet volume (MPV) were found statistically significantly lower in PEP group. Mean procedure time was 33.5 min in PEP group and 27.9 min in non-PEP group ($p = 0.006$). CBD diameter of the patients developing PEP was found significantly lower than the non-PEP group (10.1 ± 4 vs. 13.4 ± 4.5 mm, $p = 0.01$). The PEP rate in females was 13.3 % and it was 7.8 % in males and this difference was not statistically significant ($p = 0.41$). PEP rate was statistically significantly higher in patients who had pancreatic duct cannulation than the ones who did not have (25 vs. 8 %, $p = 0.01$). PEP rate was statistically significantly higher in patients who had a HOMA-IR ≥ 2.5 than the ones who had a HOMA-IR < 2.5 (17.6 vs. 5.5 %, $p = 0.03$). Patients who had pre-procedural hyperlipidemia had a PEP rate of 20 %, whereas the ones who did not have hyperlipidemia had a PEP rate of 8.5 %, and this difference was not statistically significant ($p = 0.06$). There was no statistically significant difference for PEP rates between patients who had a BMI ≥ 25 kg/m^2 and BMI < 25 kg/m^2 (13.3 vs. 5.6 %, $p = 0.20$). There was no statistically significant difference between catheter type groups in terms of PEP rates (Table 1). Six patients underwent mechanical lithotripsy and none developed PEP; however, hyperamylasemia was observed in two of them.

ROC analysis was revealed the area under curve (AUC) for HOMA-IR to predict PEP as 0.77 ($p < 0.001$). The optimal cutoff value was 2.99 with a sensitivity of 75 %, specificity of 73.6 %, PPV of 26.7 %, and NPV of 95.8 %. Both procedure time and CBD diameter before ERCP showed a favorable test performance to predict PEP, with an AUC of 0.69 ($p < 0.01$) and 0.70 ($p < 0.01$), respectively (Fig. 1; Table 3).

Age, gender, cannulation type (precut or standard), bile duct stone identified on ERCP, HOMA-IR, procedure time, pancreatic duct cannulation, common bile duct (CBD) diameter, and pre-procedure total bilirubin levels were included in logistic regression analysis performed by firth method. While there were nine predictors in the first step of backward likelihood ratio logistic regression analysis, cannulation type, including precut or standard cannulation, was excluded in step two. Bile duct stone identified on ERCP was excluded in step 3, bilirubin level was excluded in step 4, and pancreatic duct cannulation and gender were excluded in step 5 by the regression analysis automatically. Lastly age was excluded in step 6 from the analytic model. The remaining variables at the seventh step in logistic regression analysis were HOMA-IR (OR 2.399, p 0.004), procedure time (OR 1.155, p 0.009), and CBD diameter (OR 0.829, p 0.03), and these variables were established as the independent predictors of PEP risk (Table 4).

Discussion

Pancreatitis is the most prevalent one among the complications seen after ERCP. Although it is usually mild and shows regression in a short time with conventional treatment, it is still an important clinical problem because it increases the total time of hospitalization. It also can cause an important morbidity and mortality if pancreatic necrosis, abscess, or pseudocyst develops. Because of these, it is important to know or predict the risk of PEP before ERCP procedures in order to give decision to perform ERCP, to plan the periprocedural management of the patient, and to inform the patient or his/her relatives. The prevalence of PEP is reported between 1 and 7 % in trials in which PEP is evaluated according to the consensus definition [5, 30–32]. Because all of the patients enrolled in our study were inpatients, we could not use consensus definition criteria. Although this may seem as a limitation, it provided us an opportunity for a close follow-up and correct and complete laboratory data collection. The relatively high rate of PEP in the present study may be due to strict follow-up criteria

Table 2 Comparison of PEP and non-PEP groups

	PEP	Non-PEP	*p* values
Age (years)	60 ± 15	58.8 ± 16.1	0.97
BMI (kg/m^2)	29.8 ± 3	27.9 ± 4.4	0.44
AST (U/L)	54 (39–69)	34 (23–80)	0.16
ALT (U/L)	73 (50–117)	46 (28–98)	0.03
WBC (/mm^3)	6820 (5880–9200)	6085 (5927–7650)	0.20
HCT (%)	36.2 (34–40)	38.7 (34–42)	0.15
MPV (fl)	8.9 ± 0.9	9.7 ± 1.2	0.01
Platelet count (/mm^3)	237,168 ± 68,029	294,259 ± 112,605	0.05
Total bilirubin (mg/dl)	1.5 ± 0.9	1.8 ± 1.8	0.69
HOMA-IR	3.37 ± 0.8	2.38 ± 1.4	<0.001
Insulin (uIU/ml)	13.2 ± 3.1	9.4 ± 5.9	<0.001
Glucose (mg/dl)	96 (84–111)	97 (87–116)	0.75
Total cholesterol (mg/dl)	186 (163–249)	188 (155–236)	0.46
Triglyceride (mg/dl)	113 (94–170)	137 (97–176)	0.70
HDL (mg/dl)	42.1 ± 16	40.6 ± 15.5	0.71
LDL (mg/dl)	131.2 ± 32.4	123 ± 53	0.38
Procedure time (min)	33.5 ± 9	27.9 ± 7.2	0.006
CBD diameter (mm)	10.1 ± 4	13.4 ± 4.5	0.01
Hospitalization length (h)	60 (48–72)	24 (24–48)	<0.001

Mean and ± standard deviations were given for normally distributed variables. Median and interquartile ranges (Q1–Q3) were given for non-normally distributed variables

BMI body mass index, *HOMA-IR* homeostasis model assessment of insulin resistance, *CBD* common bile duct

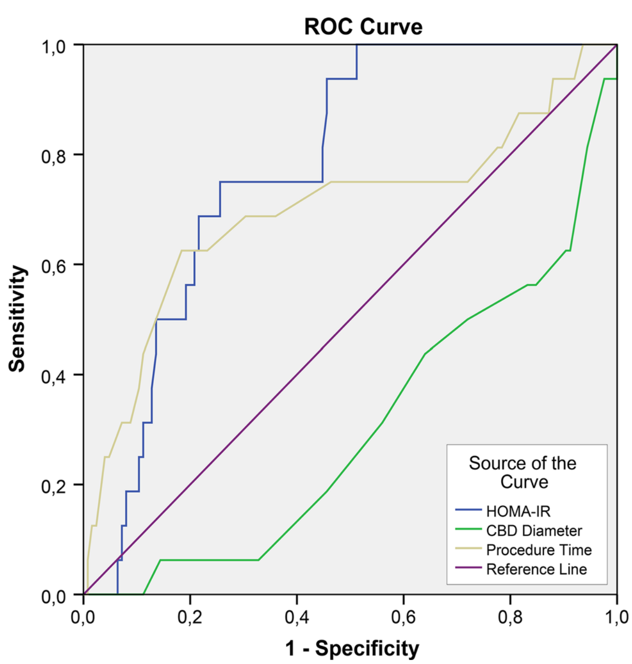

Fig. 1 ROC analysis for HOMA-IR, CBD diameter, and procedure time (AUC: 0.77, 0.70 and 0.69, respectively)

used. If patients without any abdominal pain or discomfort were discharged immediately after ERCP, they should not admit to the hospital if the pain they feel later is mild or relieves spontaneously. Patients might also admit to another hospital in case of emergency. To diminish these possibilities and to secure complete recording of the study data, patients were hospitalized at least for 24 h after ERCP procedure. Therefore, it is not surprising to see lower rates of pancreatitis in studies where post-ERCP amylase and lipase levels were not investigated routinely. Besides, studies using different criteria reported similar rates to the rate (11.3 %) found in our study [33]. The incidence of hyperamylasemia without pancreatitis is reported between 16.5 and 39.4 % [7, 34, 35]. Hyperamylasemia rate was similarly found high in our study (31.2 %).

Patient-Related Risk Factors

An increased PEP risk in young and female individuals was reported in the study of Freeman et al. [11]. However, different studies with larger scales did not show age and gender as risk factors for PEP [2, 10, 36]. Consistent with these studies, there were no statistically significant differences in terms of age and gender between cases with and without PEP in our study. Although it did not reach a statistical significance, PEP ratio was higher in females compared to males concordantly with most of the studies in this field.

Table 3 Diagnostic accuracy for HOMA-IR, CBD diameter, and procedure time to predict PEP

	AUC	*p* value	Cutoff	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
HOMA-IR	0.77	<0.001	≥2.99	75	73.6	26.7	95.8
CBD diameter	0.70	<0.01	<13.5 mm	81.2	54.4	18.5	95.7
Procedure time	0.69	<0.01	≥29.5 min	75	53.6	17.1	94.3

HOMA-IR homeostasis model assessment of insulin resistance, *CBD* common bile duct, *AUC* area under the curve

Table 4 Firth logistic regression analysis for independent risk factors for PEP

	95 % Confidence interval			
	OR	Lower bound	Upper bound	*p* values
Age	1.04	0.995	1.103	0.07
Gender (female)	1.70	0.294	9.842	0.55
Cannulation type (precut)	1.15	0.265	5.052	0.84
BD stone identified on ERCP (present)	2.69	0.291	24.896	0.38
Procedure time	1.15	1.047	1.275	0.004
Pancreas cannulation (present)	4.53	0.678	30.273	0.11
CBD diameter	0.82	0.687	0.999	0.04
Total bilirubin	0.99	0.542	1.818	0.98
HOMA-IR	2.39	1.320	4.361	0.004

BMI body mass index, *CBD* common bile duct, *HOMA-IR* homeostasis model assessment of insulin resistance, *BD stone identified on ERCP* bile duct stone identified on ERCP

Beyazıt et al. [37] reported significantly lower MPV values than the normal healthy population in cases with acute pancreatitis. Additionally, MPV values were found inversely correlating with the severity of pancreatitis in their study. Compatible with this finding, we found statistically significantly lower pre-ERCP MPV values in PEP group. In a prospective multicenter study, a pre-procedural total bilirubin ≤1 mg/dl was shown as an independent risk factor for PEP [11], whereas Cotton et al. [5] reported that pre-procedure lower total bilirubin levels did not cause any increase in PEP risk. We also did not find any significant relation between bilirubin level and PEP risk.

Small CBD diameter is a known risk factor for PEP. In their study, Nakai et al. [38] found CBD diameter ≤9 mm. as an independent risk factor for PEP development. Similar to these data, mean CBD diameter was significantly lower in PEP group and was found as an independent risk factor for PEP in our study.

Neither PEP risk nor PEP severity showed a relation with BMI in the study of Deenadayalu et al. [28] which was conducted about the PEP risk and obesity. There was also no significant difference between the BMI means of PEP and non-PEP groups in another study searching the relationship between pre-procedural pancreatic steatosis and PEP risk [29]. Concordant with these results, there was no significant relation found between BMI and PEP risk in our study.

The relation between visceral adipose tissue, insulin resistance, and acute pancreatitis development/severity is known [39–43]. In the study of Kumar et al. [44], PEP risk was searched in 25.641 ERCP patients by using a nationwide inpatient data. The presence of diabetes mellitus, obesity, and hyperlipidemia were detected as independent risk factors for PEP in their study. Although we excluded diabetic patients under treatment to evaluate insulin resistance effectively, PEP group showed significantly higher hyperlipidemia and insulin resistance compatible with the results of the study mentioned above. Also an insulin resistance ≥2.5 was found as an independent risk factor.

Procedure-Related Risk Factors

Pancreatic duct cannulation and contrast injection were reported as factors increasing the PEP risk in most of the studies [1, 5, 10, 35, 45]. Similarly to our results, the PEP ratios in these studies were significantly higher in patients with pancreatic duct cannulation compared to non-cannulated cases.

In our study, difficult cannulation and difficult ERCP were evaluated indirectly by three different parameters: procedure time, cannulation type, and catheter type used. Some authors recommend precut sphincterotomy unless cannulation is not achieved in 10 min and/or ≥10 attempts. Actually, timing of precut sphincterotomy depends on the experience and practice of the endoscopist. Although precut sphincterotomy rate presented in this study may seem relatively high, early precut sphincterotomy is shown to decrease post-ERCP pancreatitis risk [46]. Because pancreatic stent and/or rectal diclofenac were not used according to study protocol, precut sphincterotomy was performed after five or six unsuccessful cannulation attempts as the part of the study protocol not to increase procedure time and associated PEP risk. Because there was no statistically significant difference between groups of anesthesia used in terms of PEP rates, this variable was not considered as a confounding factor. Moreover, there was no statistically significant difference between two groups in terms of mean procedure time and successful cannulation rate.

Mehta et al. [47] investigated the relation between procedure length and ERCP events and reported a similar PEP ratio between the cases with procedure time more or less than 45 min (6.8 vs. 4.5 %, $p = 0.40$). But results of our study revealed prolonged procedure time as an independent risk factor for PEP. Anyway there are multiple studies in the literature reporting that overall ERCP complications including PEP were increasing with the increasing procedure time and/or cannulation attempts, similar to our findings [6, 9, 11, 35].

In the technology status evaluation report about the biliary and pancreatic stone devices published by ASGE in 2009 [48], basket catheter was found to be more risky than the balloon catheter in terms of complication. PEP rates did not show any significant difference in our study when evaluated according to the catheter type used. Although cases in which balloon catheter was used had higher PEP rates than the cases with application of basket catheter (12.1 vs. 5.6 %), this difference did not reach a statistical significance. It is noteworthy that the highest PEP rate in our study was found in cases with combined usage of balloon and basket catheters (17.6 %). This result gives rise to thought that it is mostly the difficulty of the procedure than the type of the catheter used that causes the risk of PEP.

Our study has several potential limitations. Sphincter of Oddi dysfunction, which is an important risk factor for PEP, was not evaluated. Solely naïve choledocholithiasis cases were enrolled in our study to reduce potential confounding effects of other ERCP indications. Moreover, patients with malignancy, prior diagnosis of diabetes mellitus, or any other comorbidities were also excluded. These strict criteria regarding inclusion and exclusion to/from our study population may have caused a selection bias in terms of extrapolating our study results to the general population. Additionally, because the study was designed as a pilot study, we were not able to perform power analysis and sample size justification.

Despite extreme caution and application of every preventive measure, the development of pancreatitis after ERCP is not completely preventable. That is why effective, simple, and accessible methods are needed to predict and prevent PEP. The results of this study yielded a possible association between insulin resistance and PEP development and stated insulin resistance as an independent risk factor. Certainly, these primary results cannot yet establish insulin resistance assessment as a single marker; however, they indicate that insulin resistance may be one of the key components of PEP. Further longitudinal studies investigating the significance of pre-ERCP HOMA-IR levels are warranted to clarify the ability of insulin resistance to predict the risk of PEP, to plan the periprocedural management of the patients, and eventually to aim to decrease the ERCP-related morbidity.

Acknowledgments Special thanks to biostatistician Sinan IYIGUN for advising and performing advanced statistical analyses.

Compliance with ethical standards

Conflict of interest We confirm that there are no financial or other relations that could lead to a conflict to interest.

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