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Risk Models for post-ERCP Pancreatitis (PEP) Smoking and Chronic Liver Disease are Predictors of Protection against PEP

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Abstract

OBJECTIVES—We investigated which variables independently associated with protection against or development of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) and *severity* of PEP. Subsequently we derived predictive risk models for PEP.

METHODS—In a case-control design, 5254 patients had 8264 ERCPs, 211 had PEP and 22 had severe PEP. We randomly selected 348 non-PEP controls. We examined seven established- and nine investigational variables.

RESULTS—In univariate analysis, seven variables predicted PEP: younger age, female gender, suspected sphincter of Oddi dysfunction (SOD), pancreatic sphincterotomy, moderate-difficult cannulation (MDC), pancreatic stent placement, and lower Charlson score. Protective variables were: current smoking, former drinking, diabetes and chronic liver disease (CLD, biliary/transplant complications). Multivariate analysis identified seven independent variables for PEP, three protective (current smoking, CLD-biliary, CLD-transplant/hepatectomy complications) and four predictive (younger age, suspected SOD, pancreatic sphincterotomy, MDC). Pre- and post-ERCP risk models of seven variables have a C-statistic=0.74. Removing age (7th variable) did not significantly affect the predictive value (C-statistic=0.73) and reduced model complexity. *Severity* of PEP did not associate with any variables by multivariate analysis.

CONCLUSIONS—By using the newly identified protective variables with three predictive variables we derived two risk models with a higher predictive value for PEP compared to prior studies.

Keywords

acute pancreatitis; cigarette smoking; chronic liver disease; ERCP

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INTRODUCTION

Pancreatitis is a serious potential complication of endoscopic retrograde cholangiopancreatography (ERCP). Post-ERCP pancreatitis (PEP) occurs in 3.5% of all ERCPs¹ and up to 40–60% of high risk ERCPs.^{2,3} Measures that reduce PEP risk in high risk patients are prophylactic stenting of the pancreatic duct⁴ and possibly rectal indomethacin.^{5–7}

Counseling of patients about ERCP and PEP necessitates stratifying patients into low and high risk categories. Previous studies developed risk stratification schemes with two different combinations of patient and procedural predictors.^{2,3} One scheme included women, normal bilirubin, suspected sphincter of Oddi dysfunction (SOD) and difficult cannulation² and the other included pain during procedure, pancreatic duct cannulation, prior history of PEP and number of cannulation attempts.³ The observations draw attention to patient predictors for PEP, but do not establish which variables are predictive for PEP.

There is some consensus which variables are predictors for PEP based on consistent reporting of specific predictors by at least two of four large multicenter prospective studies.^{2,8–10} Patient predictors include women,^{2,9,10} age > 60 years,^{8–10} prior history of PEP,^{2,8} and suspected SOD.^{2,8} Procedural predictors include pancreatic sphincterotomy,^{2,10} moderate/difficult cannulation (MDC)^{2,10} and ≥ 2 pancreatic duct contrast injections.^{2,8,9} A limitation is that these predictors may be confounded by the effects of unknown predictors or those with a doubtful or unclear association to PEP.

Predictors for *severity* of PEP are not well established, primarily due to limited data. Three of the four large, prospective multicenter studies reported a total of only 18 cases of severe PEP out of 415 cases of PEP.^{2,8,10} Most patients were young women with suspected SOD, MDC and normal bilirubin.

Based on our recent observations¹¹ we hypothesized that cardiovascular disease (CVD) associates with PEP and *severity* of PEP. We previously reported that current alcohol and former cigarette-smoking are potential predictors for PEP and those former smokers were older and had a higher frequency of CVD.¹¹ In support of our hypothesis, CVD is a major risk factor for pancreatic atheroma^{12,13} and pancreatic hypoperfusion with resulting ischemia is an early event in acute pancreatitis.¹⁴

To both test our hypothesis and to develop risk models that predict PEP, we used a retrospective case-control design. In contrast to our prior study,¹¹ we collected all new data, increased the study span by 3.7 years to increase the PEP sample size and statistical power, and included additional variables.

MATERIALS AND METHODS

Selection of Case and Control Samples

This study was approved by the University of Michigan Institutional Review Board. We performed an IDX cross-sectional search of our health system's databases and identified 6,505 unique patients who had a total of 8,264 ERCPs performed between 1/1/1997 and 3/31/2009. 1469 patients had an ICD-9 code (577.0) for acute pancreatitis and 211 patients met criteria by Cotton et al¹⁵ for PEP, and had no exclusion criteria (see below). We used a random number generator program to screen the remaining 5036 potential controls for exclusion criteria to select 1.5 control patients for each PEP case for a total of 348 controls. This ratio was selected because initial power calculations of this proportion were similar to higher ratios, assuming a fixed number of PEP cases. To develop a risk model that included

age and gender as variables and controlled for changes in technical/operator and endoscopy-related variables over time, we matched controls to PEP cases by two-year increments of time. Exclusion criteria were identical to a previous study.¹¹

Variable Selection and Definitions

Data was collected for patient variables we hypothesized may influence PEP risk, including alcohol-use, cigarette-smoking, Charlson Comorbidity Score¹⁶ and individual comorbidities, presence/risk of CVD (see review by Anderson et al¹⁷), hypertension, BMI and aspirin. We included NSAID use as a possible patient variable that may influence PEP risk,^{5,6} descriptive data for ERCP indications, and three of the four established *patient variables* consistently reported to influence PEP risk by at least two of the four large, multicenter prospective studies.^{2,8-10} These included age, gender and suspected SOD but not prior history of PEP, the latter because selection bias would have occurred in the process of choosing retrospectively one ERCP among all ERCPs performed for an individual patient. For this reason we extracted data from ERCP reports associated with the first-episode of PEP at the University of Michigan. Finally, we collected data for prophylactic pancreatic stent placement,⁴ and three established *procedural variables* reported to predict PEP by at least two of the four large, multicenter prospective studies,^{2,8-10} including pancreatic sphincterotomy, MDC and 2 pancreatic duct contrast injections.

We defined cigarette-smoking and alcohol-use as current, former or never.¹¹ Quantitative data was frequently absent for cigarette-smoking exposure and alcohol-use and inadequate for analysis. We used previous/common definitions for suspected SOD, pancreatic sphincterotomy, pancreatic injections, MDC and pancreatic stent placement.¹¹

Chronic liver disease (CLD) is one of 19 variables contributing to a Charlson Comorbidity Score¹⁶ (see Table 1) and is defined by having a >6-month elevation in liver transaminases, alkaline phosphatase and/or bilirubin. We defined four categories (and 19 subcategories) of CLD (Table 2) and defined severity (from the Charlson Comorbidity Score¹⁶) as mild (for non-cirrhotic or cirrhotic disease and a Child-Turcotte-Pugh [CTP]¹⁸ score < 7) or moderate-severe (cirrhosis and a CTP score > 7).

Data Collection

We used methods identical to our previous study¹¹ to pool and mask the case and control electronic medical records, to search the entire electronic medical record for data of interest, to reconcile variations in the data recorded in the electronic medical record, and to collect and tabulate data.

Statistical Analyses

The primary outcomes analyzed were PEP and *severity* of PEP, the latter graded as mild, moderate and severe according to the criteria by Cotton et al.¹⁵ Data was analyzed with Stata 12 statistical software (StataCorp, College Station, TX). Descriptive statistics were compiled to evaluate variable distribution prior to modeling. Univariate analyses were performed on all variables. Multivariate logistic regression analysis was also performed to identify independent predictors of PEP, using a stepwise forward technique with inclusion of variables with $P < 0.1$ in the final model. Categorical and dichotomous variables were assessed by χ^2 tests or Fischer's exact test when necessary. Continuous variables were assessed using either two sample t-tests for normally distributed variables or the Wilcoxon rank sum test for non-normal variables.

RESULTS

Clinical characteristics of PEP and control groups

The most common indications for ERCP in the cohort were choledocholithiasis (24.3%), suspected SOD (22.9%), biliary stricture (9.7%), cyst/neoplasm (9.7%), abnormal liver function tests (8.8%), cholangitis (5.9%), bile leak (5.7%) and other categories (all < 5% each). The PEP case sample had a lower median Charlson score (Table 1) compared to the control sample, attributable to lower frequencies of diabetes mellitus and chronic liver disease (CLD). The two most common etiologic/anatomic categories of CLD (Table 2) were liver transplant or hepatectomy complication (CLD-transplant/hepatectomy complications) and extra-hepatic biliary tract disease (CLD-biliary).

Univariate Analysis of PEP

The PEP case sample differed from the control sample (Table 3) by having a lower mean age, more women and a higher frequency of variables known to be associated with PEP – suspected SOD, ≥ 2 pancreatic injections, pancreatic sphincterotomy and MDC. The PEP case sample also had a higher frequency of pancreatic stent placement, a lower median Charlson score and a lower frequency of former drinkers, current smokers, diabetes and CLD. The latter finding was attributable to a lower frequency of CLD-transplant/hepatectomy complications and CLD-biliary groups (Table 3).

Multivariate Analysis of PEP

Multivariate forward stepwise regression analysis identified three independent predictors of protection against PEP (Table 4), including current smoking, CLD-biliary and CLD-transplant/hepatectomy complications, and four independent predictors for PEP, including younger age, suspected SOD, pancreatic sphincterotomy and MDC.

Risk Model Scoring System

We derived two risk models based on six of the seven independent variables for PEP: three protective (current smoking, CLD-biliary, CLD-transplant/hepatectomy complications) and three predictive (suspected SOD, pancreatic sphincterotomy, MDC). The seventh independent variable, younger age, we excluded from the model because it had little impact on predicting PEP (C-statistic increased from 0.73 to 0.74) and added significant complexity to generating a risk score. Six independent predictors were assigned points based on the beta coefficients of the regression analysis³ (Table 5, top panel). Cumulative risk scores (Table 5, bottom panel) were divided into quantiles, three for the pre-ERCP model (<0, 0, 1) and four for the post-ERCP model (<0, 0, 1, ≥ 2). Odds ratios for PEP in the pre-and post-ERCP models ranged from 0.4–2.8 and 0.4–7.3, respectively. Figure 1 shows the probability for PEP for a given patient, assuming a baseline PEP risk of 3.5%.¹

PEP severity

PEP was mild in 22.7% (n=48), moderate in 66.8% (n=141) and severe in 10.4% (n=22), compared to a systematic review reporting respective frequencies of 45%, 44% and 11%.¹ Across PEP *severity* groups there was no significant difference in median Charlson comorbidity scores or individual comorbidities (data not shown). By univariate analysis (Table 6) PEP *severity* associated only with the CVD criteria, previous myocardial infarction (MI) ($P=0.038$) and aspirin use ($P=0.046$). In the forward stepwise regression multivariate analyses, there were no significant predictors for PEP *severity* but aspirin use approached statistical significance ($OR=2.5$, $P=0.069$).

DISCUSSION

By multivariate analysis we identified three independent predictors of protection against PEP and four predictors for PEP but no predictors for PEP severity. The most important new findings are the three predictors of protection, current smoking, CLD-biliary and CLD-transplant/hepatectomy complications. By including these variables with variables independently predictive of PEP (suspected SOD, pancreatic sphincterotomy and MDC) we derived two risk models. The pre-ERCP risk model has four variables (suspected SOD, current smoking, CLD-biliary and CLD-transplant/hepatectomy complications) and the post-ERCP model has all six (pre-ERCP variables plus pancreatic sphincterotomy and MDC). Removing age, a 7th independent variable from the model, did not significantly affect the predictive value (C-statistic=0.73) and significantly reduced the complexity of generating a risk score.

The predictive value for PEP (C-statistic=0.73) of our model is higher compared to the multi-regression logistic model from two (of the four) multicenter studies (C-statistic < 0.70).^{8,9} Two other studies developed predictive risk models for PEP. Escalating risk for PEP correlated with an increasing risk score derived by Friedland et al³ (from four variables) and with incremental inclusion of four variables identified by Freeman et al² (women, normal serum bilirubin, difficult cannulation and suspected SOD). In contrast to our current study, however, the investigators did not report the discrimination value of the models (C-statistic, area under the receiver operating characteristic (ROC) curve, or AUC). In addition, these studies had less statistical power due to fewer PEP cases (n=103–131)^{2,3} and did not include investigational variables examined in the current study.

Similar to Freeman et al,² our post-ERCP risk model includes suspected SOD and MDC. In contrast, our risk model did not include women, which was a significant variable only in the univariate analysis, but includes pancreatic sphincterotomy, CLD-biliary, CLD-transplant/hepatectomy complications and current smoking. We omitted two variables that added little power to the predictive model, including age ($P=0.027$) and multiple pancreatic injections ($P=0.06$). To confirm the generalizability of the risk model to community practice we report that a modified risk model that eliminates liver transplant patients (a tertiary care bias) retains similar predictive power.

Why women did not associate with PEP and younger age added little predictive value to the model is likely because both variables are surrogate markers of suspected SOD. Our data mirrors prior observations of suspected SOD patients,^{19,20} which were 89% women (predicts SOD with $OR=6.8$, $P<0.001$) and significantly younger (43.1 years $\pm$ 12.4 vs 52.5 years $\pm$ 16.5, $P<0.0001$). Hence, these observations would explain why none of the four multicenter prospective studies reported all three variables (women, younger age, suspected SOD) as independent predictors for PEP.^{2,8–10}

In the current, large study (n=211 cases of PEP) we found that current smoking is independently *protective* against PEP. This finding contrasts with a recent report that active smoking is an independent predictor of PEP, but the study is underpowered (n=36 cases of PEP) and investigators omitted established PEP variables from the analysis (≥ 2 pancreatic injections, moderate/difficult cannulation, suspected SOD, prior history of PEP).²¹ The importance of a sufficiently powered study is underscored as we previously reported that current cigarette-smoking is protective against PEP in univariate analysis ($P=0.001$) but not in multivariate analysis ($P=0.055$),¹¹ in an underpowered study of 123 PEP cases.

That current smoking protects against PEP seems to contradict clinical observations that smoking is an independent, dose-dependent risk factor for acute pancreatitis^{22–24} and with experimental data that cigarette smoke increases pancreatic inflammation^{25,26} and reduces

pancreatic blood flow.²⁷ There are at least three hypotheses why current smoking reduces PEP risk. Nicotine (present in cigarettes) may activate the nicotinic anti-inflammatory pathway,²⁸ which reduces pancreatic inflammation and severity of experimental pancreatitis,²⁹ thus mirroring the anti-inflammatory effects of this pathway observed in ulcerative colitis³⁰ and in other conditions.²⁸ Nicotine also relaxes the sphincter of Oddi in experimental models,³¹ which may reduce sphincter spasm and obstruction as a cause of PEP, and may also have direct, protective effects by reducing secretagogue-evoked cell necrosis in dispersed pancreatic acini.³²

The relationship between biliary and/or liver disease and PEP is not clear from previous studies which mostly evaluated the association of bilirubin levels to PEP. Freeman et al² reported that normal serum bilirubin doubled the risk for PEP. Data from three other large multicenter prospective studies conflicts with this observation,^{8–10} but could be attributable to using different surrogate markers for normal serum bilirubin. In the current study, there was a significantly lower frequency of PEP in mild-and moderate/severe CLD (see definitions in Methods). By univariate and multivariate analyses, CLD-biliary and CLD-transplant/hepatectomy complications associated with a lower frequency of PEP. This protective relationship may have occurred because both CLD variables predicted lower odds of MDC: CLD-biliary ($OR=0.4$, 95% CI 0.1–0.9, $P=0.037$) and CLD-transplant/hepatectomy complications ($OR=0.3$, 95% CI 0.1–0.7, $P=0.004$). One possible explanation for easier biliary cannulation is that liver transplantation at the University of Michigan involves dilating the papilla (with a dilating catheter in the operating room) before constructing a biliary duct-to-duct anastomosis over a 5 Fr “stent” crossing the papilla. Why biliary cannulation is easier in CLD-biliary is less clear. Although 52% of this group had primary sclerosing cholangitis (PSC), the frequency of PSC was similar in the control and PEP groups.

The results of our study do not support the hypothesis that CVD associates with PEP or PEP severity. In the univariate analysis of PEP there was a nonsignificant trend towards less frequent CVD in the PEP case sample compared to the control sample (10.4% vs 15.5%; $P=0.099$). The univariate analysis of PEP severity, however, yielded a significant association of PEP severity with previous MI and aspirin use (the latter we interpret as a marker of CVD and/or previous MI), but no significant variable emerged from the multivariate analysis. There is a possibility of a type II error (false negative association) because only 22 patients had severe PEP.

Although an observational retrospective case control study has inherent disadvantages such as confounding by unknown predictors, missing data and incorrect reporting of the predictors, our study has major strengths including the size and statistical power and the *a priori* selection of established variables and numerous hypothesis driven variables related to CVD. With the exception of a high rate of missing data for BMI (22.9% [128/559]) due to missing height data, all other variables had an acceptable rate of missing data < 5%.³³ The completeness of the data collection was due to the quality of the electronic documentation and the use of the EMERSE search engine to systematically identify data within the electronic medical record.¹¹ The collection of the smoking data was interview-based,¹¹ which is more reliable than self-reporting³⁴ and the accuracy of the smoking data is implied by noting that the smoking-linked disease Chronic Obstructive Pulmonary Disease (COPD) was far more frequent in former smokers (10.6–12.3%) and current smokers (4.3–10.0%) compared to never smokers (0.0–1.6%).

Additional evidence that our data is reliable is that we confirmed that suspected SOD,^{2,8} pancreatic sphincterotomy,^{2,10} and MDC^{2,10} were independent predictors for PEP. Also, we showed that prophylactic pancreatic stent placement⁴ occurred significantly more frequently

in the case sample (30.3% vs 14.9%) by univariate but not multivariate analyses, likely because stenting was a surrogate marker of other predictors for PEP. Similar to our previous study,¹¹ and in contrast to three of the prospective multicenter studies,^{2,8,9} 2 pancreatic duct contrast injections was not a significant risk factor for PEP, likely because of non-standardized reporting of injections on procedure reports and flow sheets.

It has become evident that placement of a prophylactic pancreatic duct stent⁴ or administering indomethacin suppositories immediately after ERCP^{5,6} lowers the risk of PEP in “high-risk” groups. Investigators, however, use different variables to define “high-risk”, including “biliary sphincterotomy for SOD, difficult cannulation, precut sphincterotomy, pancreatic sphincterotomy, biliary balloon dilation of intact papilla for stone extraction, endoscopic ampullectomy, pancreatic brush cytology, all ERCPs that were considered to be at high risk,”³⁵ a prior history of PEP, or two or more out of 5 minor criteria.⁶ Hence to determine which patients would benefit from prophylactic measures requires better definitions of high-risk patients.

In summary, we report three new predictors of protection against PEP (current smoking, CLD-biliary and CLD-transplant/hepatectomy complications) and four independent predictors for PEP (younger age, suspected SOD, pancreatic sphincterotomy, MDC). We derive two risk models using six of the seven independent variables (after omitting age) and show an improved predictive value for PEP (C-statistic = 0.73) compared to prior studies. Our findings are potentially important by identifying overlooked patient predictors of protection against PEP and by generating risk models that conceivably would allow risk assessment pre-ERCP. Prospective study is required to both validate the risk models (to address limitations of the retrospective study design) and to determine whether prophylactic measures lower rates of PEP in high-risk groups defined by our risk models.

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Abbreviations

AIDS	acquired immune deficiency syndrome
BMI	body mass index
CI	confidence interval
CLD	chronic liver disease
CVD	cardiovascular disease
ERCP	endoscopic retrograde cholangiopancreatography
IDX	information data exchange
ICD-9	international classification of diseases 9th edition
MDC	moderate/difficult cannulation
NSAIDs	non-steroidal anti-inflammatory drugs
PEP	post-ERCP pancreatitis
OR	odds ratio

SOD

Sphincter of Oddi

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Figure 1. Probability of PEP
for an individual based on cumulative risk score (Table 4), assuming a baseline PEP risk of 3.5%¹.

Table 1

Charlson comorbidity score - PEP

Variable	Cases (%)	Control (%)	P-value
<u>1 Point</u>			
Previous myocardial infarction	16/211 (7.6)	36/348 (10.3)	0.297
Congestive heart failure	6/211 (2.8)	13/348 (3.7)	0.638
Peripheral vascular disease	5/211 (2.4)	5/348 (1.4)	0.514
Cerebrovascular disease	4/211 (1.9)	13/348 (3.7)	0.311
Dementia	1/211 (0.5)	3/348 (0.9)	1.000
COPD	8/211 (3.8)	20/348 (5.7)	0.424
Connective tissue disease	8/211 (3.8)	6/348 (1.7)	0.164
Ulcer disease	20/211 (9.5)	42/348 (12.1)	0.405
Mild liver disease	32/211 (15.1)	131/348 (37.6)	<0.0001
Diabetes mellitus (mild)	17/211 (8.1)	56/348 (16.1)	0.006
<u>2 Points</u>			
Hemiplegia	0/211 (0)	0/348 (0)	N/A
Renal disease	16/211 (7.6)	33/348 (9.5)	0.538
Diabetes mellitus + organ damage	3/211 (1.4)	13/348 (3.7)	0.125
Any tumor	29/211 (13.7)	40/348 (11.5)	0.430
Leukemia	1/211 (0.5)	1/348 (0.3)	1.000
Lymphoma	1/211 (0.5)	5/348 (1.4)	0.417
<u>3 Points</u>			
Moderate/severe liver disease	5/211 (2.4)	14/348 (4.0)	0.345
<u>6 Points</u>			
Metastatic solid tumor	10/211 (4.7)	15/348 (4.3)	0.835
AIDS	0/211 (0)	1/348 (0.3)	N/A
*MEDIAN TOTAL SCORE (IQR)	0 (0–2)	1 (0–3)	<0.0001

Statistics:

* Wilcoxon rank sum test, otherwise Fisher's exact test.

IQR, interquartile range.

Table 2

Categories of chronic liver disease - PEP

Variable	Cases (%)	Control (%)	Total
Liver transplant/hepatectomy complications	14/211 (6.6)	71/348 (20.4)	85/559 (15.2)
Biliary stricture	9/211 (4.3)	33/348 (9.5)	42/559 (7.5)
Bile leak	3/211 (1.4)	18/348 (5.2)	21/559 (3.8)
Cholangitis	1/211 (0.5)	6/348 (1.7)	7/559 (1.3)
Abnormal liver tests	1/211 (0.5)	14/348 (4.0)	15/559 (2.7)
Biliary disease/cancer (extra-hepatic)	11/211 (5.2)	45/348 (12.9)	56/559 (10.0)
Primary sclerosing cholangitis	7/211 (3.3)	22/348 (6.3)	29/559 (5.2)
Ampullary stenosis	2/211 (0.9)	7/348 (2.0)	9/559 (1.6)
Biliary stricture	1/211 (0.5)	7/348 (2.0)	8/559 (1.4)
Choledocholithiasis	1/211 (0.5)	4/348 (1.1)	5/559 (0.9)
Cholangiocarcinoma	0/211 (0)	3/348 (0.9)	3/559 (0.5)
Biliary metastases	0/211 (0)	2/348 (0.6)	2/559 (0.4)
Non-biliary cancer	3/211 (1.4)	7/348 (2.0)	10/559 (1.8)
Metastases	2/211 (0.9)	7/348 (2.0)	9/559 (1.6)
Hematologic malignancy	1/211 (0.5)	0/348 (0)	1/559 (0.2)
Other	9/211 (4.3)	22/348 (6.3)	31/559 (5.5)
Non-alcoholic fatty liver disease	2/211 (0.9)	3/348 (0.9)	5/559 (0.9)
Viral hepatitis	4/211 (1.9)	3/348 (0.9)	7/559 (1.3)
Drug induced hepatitis	0/211 (0)	2/348 (0.6)	2/559 (0.4)
Idiopathic	2/211 (0.9)	9/348 (2.6)	11/559 (2.0)
Primary biliary cirrhosis	0/211 (0)	4/348 (1.1)	4/559 (0.7)
Hepatic cysts/PCKD *	0/211 (0)	1/348 (0.3)	1/559 (0.2)
Autoimmune hepatitis	1/211 (0.5)	0/348 (0)	1/559 (0.2)

* PCKD, poly cystic kidney disease

Table 3

Univariate Analysis - PEP

Variables	Cases (%)	Control (%)	P-value
* Mean age, y (SD)	47.5 (15.4)	52.1 (16.1)	0.0008
Female	158/211 (74.9)	200/348 (57.5)	<0.0001
Suspected SOD	77/211 (36.5)	51/348 (14.7)	<0.0001
2 Pancreatic injections	10/211 (4.7)	3/348 (0.01)	0.006
Pancreatic sphincterotomy	41/211 (19.4)	19/348 (5.5)	<0.0001
Mod./diff. cannulation	65/211 (30.8)	36/348 (10.3)	<0.0001
Pancreatic stent placement	64/211 (30.3)	52/348 (14.9)	<0.0001
Alcohol-use status			
Never drinker	82/211 (38.9)	125/348 (35.9)	Reference
Current drinker	81/211 (38.4)	106/348 (30.5)	0.456
Former drinker	48/211 (22.7)	117/348 (33.6)	0.035
Cigarette-smoking status			
Never smoking	131/211 (62.1)	184/348 (52.9)	Reference
Current smoking	23/211 (10.9)	60/348 (17.2)	0.022
Former smoking	57/211 (27.0)	104/348 (29.9)	0.192
** Median Charlson Score (IQR)	0 (0–2)	1 (0–3)	<0.0001
Cardiovascular disease (Any below)	22/211 (10.4)	54/348 (15.5)	0.099
Cerebral vascular accident	4/211 (3.3)	13/348 (3.7)	0.311
Transient ischemic attack	3/211 (1.4)	7/348 (2.0)	0.750
Previous myocardial infarction	16/211 (7.6)	36/348 (10.3)	0.297
Angina	2/211 (0.9)	1/348 (0.3)	0.560
Congestive heart failure	6/211 (2.8)	13/348 (3.7)	0.638
Claudication	3/211 (1.4)	5/348 (1.4)	1.000
Coronary stent/angioplasty	4/211 (1.9)	10/348 (2.9)	0.584
Coronary bypass surgery	6/211 (2.8)	10/348 (2.9)	1.000
Hypertension	47/211 (22.3)	92/346 (26.6)	0.268
Diabetes mellitus	20/211 (9.5)	69/348 (19.8)	0.001
* Mean BMI (SD)	28.2 (6.8)	27.7 (6.6)	0.411
Aspirin use	22/211 (10.4)	51/348 (14.7)	0.157
NSAIDS	10/211 (4.7)	14/348 (4.0)	0.673
Chronic liver disease (CLD)	37/211 (17.5)	145/348 (41.7)	<0.0001
Etiology of CLD			<0.0001
No CLD	174/211 (82.5)	203/348 (58.3)	Reference
Transplant/hepatectomy complications	14/211 (6.6)	71/348 (20.4)	<0.001
Biliary (extra-hepatic)	11/211 (5.2)	45/348 (12.9)	<0.001
Non-biliary cancer	3/211 (1.4)	7/348 (2.0)	0.162
Other	9/211 (4.3)	22/348 (6.3)	0.070

Statistics:

* one way ANOVA,

** Wilcoxon rank sum test, otherwise Fisher's exact test.

IQR, interquartile range.

Table 4

Multivariate Analysis – PEP (C-statistic = 0.73)

Variable	OR	95% CI	P-value
<i>Pre-Endoscopic Predictors[‡]</i>			
Suspected SOD	2.1	1.3–3.3	0.001
Current smoking	0.4	0.2–0.8	0.004
CLD-Transplant/hepatectomy complication	0.4	0.2–0.7	0.004
CLD-Biliary	0.4	0.2–0.9	0.024
<i>Endoscopic Predictors</i>			
Pancreatic sphincterotomy	2.8	1.5–5.3	0.001
Moderate/difficult cannulation (MDC)	3.7	2.3–5.9	<0.001

[‡]Removing a 7th variable from the model, younger age (OR=0.986, 95% CI 0.974–0.998, P=0.027), did not significantly affect the predictive value (C-statistic decreased from 0.74 to 0.73) and reduced the complexity of generating the risk score (Table 5).

CLD, chronic liver disease

C-statistic, discrimination value of the model (area under the receiver operating characteristic (ROC) curve, or AUC)

Table 5

Risk Model Variables and Risk Stratification by Risk Score Quantiles – PEP

Risk Model Variables	Points* (Assigned by Beta Coefficient)				
Pre-Endoscopic Variables‡					
Suspected SOD				1	
Current smoking				-1	
CLD-transplant/hepatectomy complications				-1	
CLD-biliary				-1	
Endoscopic Variables					
Pancreatic sphincterotomy				1	
Moderate/difficult cannulation (MDC)				1	
Risk Score Quantiles	Case (%)	Control (%)	Odds of PEP	95% CI	P-value
Pre-ERCP (-2 to 1)*					
< 0	40/211 (19.0)	150/348 (43.1)	0.4	0.27-0.64	<0.001
0**	102/211 (48.3)	159/348 (45.7)	**1.0 (ref)		
1	69/211 (32.7)	39/348 (11.2)	2.8	1.73-4.39	<0.001
Post-ERCP (-2 to 3)*					
< 0	27/211 (12.8)	134/348 (38.1)	0.4	0.25-0.69	0.001
0**	71/211 (33.6)	148/348 (42.5)	**1.0 (ref)		
1	71/211 (33.6)	54/348 (15.5)	2.7	1.74-4.31	<0.001
2	42/211 (19.9)	12/348 (3.4)	7.3	3.62-14.71	<0.001

*Removing a 7th variable from the model, younger age (OR=0.986, 95% CI 0.974-0.998, P=0.027), did not significantly affect the predictive value (C-statistic decreased from 0.74 to 0.73) and reduced the complexity of generating the risk score.

** Risk score was calculated from cumulative points (Top Panel). Note: the lowest cumulative score is -2 (and not -3) because no patients have both CLD-biliary and CLD-transplant/hepatectomy complications.

** Baseline category

CLD, chronic liver disease

Table 6

Univariate Analysis – PEP Severity

Variable	Mild-PEP (%)	Moderate-PEP (%)	Severe PEP (%)	P-value
* Mean age, y (SD)	46.7 (14.4)	47.6 (15.9)	49.0 (14.9)	0.835
Female	34/48 (70.8)	108/141 (76.6)	16/22 (72.7)	0.645
Suspected SOD	17/48 (35.4)	51/141 (36.2)	9/22 (40.9)	0.927
2 Pancreatic injections	0/48 (0)	9/141 (6.4)	1/22 (4.5)	0.202
Pancreatic sphincterotomy	12/48 (25.0)	25/141 (17.7)	4/22 (18.2)	0.547
Mod./diff. cannulation	12/48 (25.0)	46/141 (32.6)	7/22 (31.8)	0.623
Pancreatic stent placement	17/48 (35.4)	40/141 (28.4)	7/22 (31.8)	0.639
Alcohol-use status				0.213
Never drinker	22/48 (45.8)	51/141 (36.2)	9/22 (40.9)	
Current drinker	13/48 (27.0)	57/141 (40.4)	11/22 (50.0)	
Former drinker	13/48 (27.0)	33/141 (22.4)	2/22 (9.1)	
Cigarette-smoking status				0.377
Never smoking	32/48 (66.7)	84/141 (59.6)	15/22 (68.2)	
Current smoking	6/48 (12.5)	17/141 (12.1)	0/22 (0)	
Former smoking	10/48 (20.8)	40/141 (28.4)	7/22 (31.8)	
** Median Charlson Score (IQR)	1.0 (0–2.5)	0 (0–2)	0 (0–1)	0.660
Cardiovascular disease (Any below)	3/48 (6.2)	14/141 (9.9)	5/22 (22.7)	0.115
Cerebral vascular accident	0/48 (0)	4/141 (2.8)	0/22 (0)	0.727
Transient ischemic attack	0/48 (0)	3/141 (2.1)	0/22 (0)	0.693
Previous myocardial infarction	3/48 (6.2)	8/141 (5.7)	5/22 (22.7)	0.038
Angina	1/48 (2.1)	1/141 (0.7)	0/22 (0)	0.555
Congestive heart failure	0/48 (0)	6/141 (4.3)	0/22 (0)	0.417
Claudication	1/48 (2.1)	1/141 (0.7)	1/22 (4.5)	0.153
Cardiovascular stent/angioplasty	2/48 (4.2)	2/141 (1.4)	0/22 (0)	0.530
Coronary bypass surgery	0/48 (0)	5/141 (3.5)	1/22 (4.5)	0.331
Hypertension	11/48 (22.9)	32/141 (22.7)	4/22 (18.2)	0.934
Diabetes	6/48 (12.5)	10/141 (7.1)	1/22 (4.5)	0.454
* Mean BMI (SD)	29.8 (7.6)	27.5 (6.4)	29.4 (7.3)	0.325
Aspirin use	1/48 (2.1)	17/141 (12.1)	4/22 (18.2)	0.046
NSAIDS	3/48 (6.2)	5/141 (3.5)	2/22 (9.1)	0.246
Chronic liver disease (CLD)	11/48 (22.9)	24/141 (17.0)	2/22 (9.1)	0.387
Etiology of CLD				0.900
No CLD	37/48 (77.1)	117/141 (83.0)	20/22 (90.9)	Reference
Transplant/hepatectomy complications	5/48 (10.4)	8/141 (5.7)	1/22 (4.5)	
Biliary (extra-hepatic)	3/48 (6.3)	8/141 (5.7)	0/22 (0)	
Non-biliary cancer	1/48 (2.1)	2/141 (1.4)	0/22 (0)	
Other	2/48 (4.2)	6/141 (4.3)	1/22 (4.5)	

Statistics:

*
one way ANOVA,

**
Wilcoxon rank sum test, otherwise Fisher's exact test.

IQR, interquartile range.