

RESEARCH ARTICLE

# Identification of risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis in a high volume center

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## Abstract

### Background/Objectives

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Several patients' or procedure related risk factors for post-ERCP pancreatitis (PEP) have been suggested. The aim of this study was to validate the risk factors for PEP in a high-volume center.

### Methods

All patients undergoing first time ERCP at a tertiary referral center between December 2010 and October 2013 were retrospectively included. PEP was defined according to the Atlanta Classification.

### Results

344 patients were included in the final analysis. The risk to develop PEP was increased in patients with chronic pancreatitis (odds ratio 3.7) and after inadvertent cannulation of the pancreatic duct (odds ratio 2.2), which occurred in 26.5% of the patients. Inadvertent cannulation occurred significantly more frequently in patients with difficult cannulation of the papilla duodeni major (odds ratio 12.7;  $p < 0.001$ ). ERCP on call was associated with an increased risk for difficult cannulation (odds ratio 3.0).

### Conclusion

Inadvertent cannulation of the pancreatic duct is a procedure related risk factor for PEP. Measurements on preventing inadvertent cannulation of the pancreatic duct should be established and studies on prophylactic measurements should focus particularly on patients with inadvertent cannulation of the pancreatic duct.

## OPEN ACCESS

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## Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a well-established therapeutic procedure for benign and malignant diseases of the biliopancreatic system. However, post-ERCP pancreatitis (PEP) is the most frequent complication of this procedure with an incidence of about 3–4% in unselected patients and up to 15% in high-risk patients [1–3]. Although most of the cases take a mild or moderate course, about 10% of all patients with PEP develop severe pancreatitis with an estimated pancreatitis-related mortality rate of 3% [1].

Over the last decades, several risk factors for PEP have been suggested. Female sex, young age, non dilated common bile duct, sphincter oddi dysfunction and previous incidence of pancreatitis are considered to be patient related risk factors [4–8]. Furthermore, difficult cannulation of the papilla and procedures associated with cannulation of the pancreatic duct such as pre-cut papillotomy and injection of contrast agent into the pancreatic duct seem to be procedure related risk factors [5–7, 9, 10].

Generally, mechanical trauma of the papilla during ERCP can lead to an edema or spasm of the sphincter of oddi and subsequently restrain the outlet of pancreatic juice thereby causing an elevation of the intrapancreatic pressure. As a consequence, pancreatic secretion is forced to the surrounding pancreas parenchyma, causing autodigestion, a critical event in the pathophysiology of acute pancreatitis [11, 12]. Moreover, cannulation of the pancreatic duct can lead to a damage of the epithelium [13]. In addition to the mechanical and hydrostatic damage, chemical, enzymatic, microbiological, allergic, and thermal factors can further favor PEP [14, 15].

The aim of this study was to validate the supposed and to possibly identify new risk factors for PEP in a high volume tertiary referral center.

## Patients and methods

All patients undergoing first time ERCP at the department of endoscopy between December 2010 and October 2013 were included in the study. The endoscopic database, medical charts and laboratory data were analyzed retrospectively.

First time ERCP was performed in 403 patients. 37 patients were excluded due to intended cannulation of the pancreatic duct for pancreatolithiasis, stenosis of the pancreatic duct, or suspected IPMN (intraductal papillary mucinous neoplasm). Further, 22 patients who suffered from acute pancreatitis at the time of ERCP were also excluded. This resulted in 344 patients which were included into the final analysis. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Ethikkommission der Medizinischen Fakultät der Technischen Universität München, project number 321/14). The ethics committee waived the need for written informed consent for this retrospective study. The number of ERCPs during the 35-month study period was 1425 in total which were performed by twelve endoscopists. Therefore, the average number of yearly ERCP per endoscopist was about 40.

Statistical analyses were performed using IBM SPSS Statistics 23 (SPSS Inc., Chicago, Illinois, USA). For descriptive data, mean  $\pm$  standard deviation was used for normally distributed data and median (range; interquartile range, IQR) for not normally distributed data. For explorative data analysis, a chi-square test was used to calculate the odds ratio or spearman's correlation to evaluate a statistical relation of suspected risk factors and PEP, inadvertent cannulation of the pancreatic duct, and difficult cannulation of the papilla duodeni major, respectively. P-values  $< 0.05$  were considered to be statistically significant.

Levels of difficulty for cannulation of the papilla duodeni major were categorized as easy (1–5 attempts) and difficult ( $>5$  attempts) cannulation. PEP was defined according to the Atlanta Classification [16].

## Results

In total, 344 patients were included in the final analysis. Patients' characteristics are shown in [Table 1](#).

### Incidence of PEP

PEP occurred in 6.1% (21/344) of all patients. All cases were classified as mild pancreatitis.

Incidence of PEP in patients with intended cannulation of the pancreatic duct was 16.2% (6/37).

### Risk factors for PEP

In univariate analyses, only age was statistically significantly associated with PEP. However, the correlation was weak ( $r = 0.107$ ). All data are presented in [Table 2](#).

Multivariate binary logistic regression analysis including the factors age, chronic pancreatitis in the medical history, normal serum bilirubin, non-dilated extrahepatic bile duct, cannulation of the pancreatic duct, and difficult cannulation of the papilla confirmed only chronic pancreatitis in the patients' medical history ( $p = 0.045$ ) as an independent risk factor for PEP [17, 18]. All 11 patients diagnosed with chronic pancreatitis had an early stage of the disease. The median time period from first diagnosis of chronic pancreatitis to first time ERCP was 5.5 month (IQR, 0–9 month; range 0–72 month). 8 out of 11 patients (73%) had no exocrine or endocrine insufficiency.

### Inadvertent cannulation of the pancreatic duct

Inadvertent cannulation of the pancreatic duct occurred in 91/344 (26.5%) of the patients. The risk to develop PEP was increased after inadvertent cannulation of the pancreatic duct (odds ratio 2.204; 95% CI 0.896 to 5.421), however, this was statistically not significant ( $p = 0.079$ ).

### Risk factors for inadvertent cannulation of the pancreatic duct

Difficult cannulation of the papilla duodeni major, which means more than 5 attempts to intubate the papilla, was statistically significantly associated with inadvertent cannulation of the pancreatic duct in univariate analysis ( $p < 0.001$ ). In contrast, diagnosis of bile duct stones

**Table 1. Patients' characteristics.**

|                                     |                              |
|-------------------------------------|------------------------------|
| Sex, female (n = 344)               | 163/344 (47.2%)              |
| Age (n = 344)                       | 67.0 (17.0–94.0;55.0–75.0)   |
| Body weight, kg (n = 251)           | 73.0 (36.5–185.0; 61.0–83.0) |
| Body height, cm (n = 248)           | 171±10                       |
| BMI, kg/m <sup>2</sup> (n = 245)    | 24.8 (15.6–64.0;21.8–28.1)   |
| <b>Indication for ERC (n = 344)</b> |                              |
| Bile duct stones                    | 142 (41.3%)                  |
| Jaundice of unknown origin          | 100 (29.1%)                  |
| malignant bile duct stricture       | 61 (17.7%)                   |
| unknown bile duct stricture         | 14 (4.1%)                    |
| benign bile duct stricture          | 10 (2.9%)                    |
| others                              | 17 (4.9%)                    |

Data are presented as number (%), mean ± standard deviation, or median (range; IQR) as applicable. ERC, endoscopic retrograde cholangiography.

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**Table 2. Risk factors for post-ERCP pancreatitis.**

| Risk factor                                    | p-value | odds ratio (CI 95%)           |
|--|---------|-------------------------------|
| Female sex                                     | 0.355   | 1.519 (0.623–3.704)           |
| Age  | 0.047*  | Correlation coefficient 0.107 |
| Age < 40                                       | 0.832   | 0.800 (0.102–6.284)           |
| Body weight, Kg                                | 0.630   |                               |
| Body height, cm                                | 0.907   |                               |
| BMI kg/m <sup>2</sup>                          | 0.841   |                               |
| BMI ≥ 25 kg/m <sup>2</sup>                     | 0.601   | 0.753 (0.260–2.184)           |
| Previous pancreatitis                          | 0.602   | 1.744 (0.210–14.459)          |
| Chronic pancreatitis                           | 0.089   | 3.673 (0.741–18.201)          |
| Status post cholecystectomy                    | 0.719   | 0.795 (0.226–2.790)           |
| Juxtapapillary diverticulum                    | 0.730   | 1.250 (0.352–4.443)           |
| Serum bilirubin <1.3 mg/dL                     | 0.370   | 1.561 (0.586–4.161)           |
| Bile duct diameter < 8 mm                      | 0.677   | 0.796 (0.272–2.331)           |
| ERCP on call                                   | 0.868   | 1.192 (0.148–9.578)           |
| Difficult cannulation of papilla               | 0.559   | 1.301 (0.537–3.148)           |
| Inadvertent cannulation of the pancreatic duct | 0.079   | 2.204 (0.896–5.421)           |
| Transpancreatic papillotomy                    | 0.695   | 1.288 (0.362–4.584)           |
| Needle-knife papillotomy                       | 0.743   | 1.418 (0.174–11.540)          |
| Incomplete bile stone removal                  | 0.478   | 0.475 (0.058–3.870)           |
| Diagnosis bile duct stones                     | 0.187   | 1.810 (0.742–4.417)           |
| Diagnosis bile duct stricture                  | 0.181   | 0.502 (0.179–1.403)           |
| Prophylactic use of Diclofenac                 | 0.674   | 1.565 (0.191–12.841)          |
| Pancreatic duct stent                          | 0.229   | 2.174 (0.596–7.927)           |

For dichotomous data, a chi-square test was performed. Pearson and Spearman correlations were used for normally and not-normally distributed intervals, respectively. P-values < 0.05 are considered statistically significant and are indicated by \*. CI, confidence interval; BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography.

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(odds ratio 0.485 (0.291–0.807; p = 0.005) and non-dilated extrahepatic bile duct (odds ratio 0.539 (0.292–0.995); p = 0.046) were associated with lower risk of inadvertent cannulation of the pancreatic duct. All data are shown in [Table 3](#).

### Risk factors for difficult cannulation

The rate of difficult cannulation was 46.2% (159/344). ERCP on call (performed outside the operational hours) was associated with an increased risk of difficult cannulation (>5 attempts) of the papilla duodeni major (odd ratio 3.037 (0.934–9.880), however, this increased risk did not reach statistical significance (p = 0.053). All data are presented in [Table 4](#). Multiple regression analysis including the factors with an odds ratio >1 showed no statistically significant risk factor for difficult intubation of the papilla duodeni major.

### Risk factors for PEP in patients without pancreatic stent and/or diclofenac

9.9% of the patients (34/344) underwent measurements for preventing PEP. In 26 patients, a stent (5 French, various length) was put into the pancreatic duct, 11 patients received diclofenac (100 mg rectally), and 3 of these patients received both. After exclusion of these patients,

**Table 3. Risk factors for inadvertent cannulation of pancreatic duct.**

| Risk factor                   | p-value | Odds ratio (CI 95%)           |
|-------------------------------|---------|-------------------------------|
| Female sex                    | 0.445   | 0.829 (0.512–1.342)           |
| Age                           | 0.585   |                               |
| Age<40                        | 0.879   | 0.922 (0.325–2.614)           |
| Body weight, Kg               | 0.585   |                               |
| Body height, cm               | 0.763   |                               |
| BMI                           | 0.496   |                               |
| BMI $\geq$ 25                 | 0.722   | 1.109 (0.627–1.963)           |
| Previous pancreatitis         | 0.796   | 1.198 (0.303–4.735)           |
| Chronic pancreatitis          | 0.527   | 0.609 (0.129–2.874)           |
| Status post cholecystectomy   | 0.135   | 0.587 (0.290–1.188)           |
| Juxtapapillary diverticulum   | 0.750   | 0.884 (0.415–1.884)           |
| Serum bilirubin               | 0.035*  | Correlation coefficient 0.119 |
| Serum bilirubin <1.3 mg/dL    | 0.180   | 0.676 (0.381–1.200)           |
| Bile duct diameter            | 0.022*  | Correlation coefficient 0.137 |
| Bile duct diameter <8 mm      | 0.046*  | 0.539 (0.292–0.995)           |
| ERCP on call                  | 0.423   | 1.576 (0.514–4.833)           |
| Urgent indication of ERCP     | 0.890   | 0.950 (0.457–1.973)           |
| Difficult cannulation         | <0.001* | 12.741 (6.692–24.255)         |
| Diagnosis bile duct stricture | 0.825   | 1.057 (0.646–1.731)           |
| Diagnosis bile duct stones    | 0.005*  | 0.485 (0.291–0.807)           |

For dichotomous data, a chi-square test was performed. Pearson and Spearman correlations were used for normally and not-normally distributed intervals, respectively. P-values < 0.05 are considered statistically significant and are indicated by \*. CI, confidence interval; BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography.

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subgroup analyses showed an odds ratio close to or greater than 2 regarding PEP for chronic pancreatitis or previous pancreatitis in the medical history, normal serum bilirubin, and inadvertent cannulation of the pancreatic duct (Table 5). However, in multiple regression analysis including these factors, only patients with chronic pancreatitis showed a statistically significant risk to develop PEP (p = 0.045).

## Discussion

This study on risk factors for PEP revealed chronic pancreatitis as an independent risk factor. Furthermore, females as well as patients with normal serum bilirubin and previous pancreatitis seem to define the high-risk patient cohort. These data are mostly in line with current studies and guidelines [17–20]. While a previous study showed a protective effect of chronic pancreatitis, our data showed an increased risk of PEP in patients with chronic pancreatitis [17, 21]. The reason for this effect is not known. It is very likely that the extent of chronic pancreatitis has a significant influence on its relevance as a risk factor for PEP. While a fibrotic gland with the loss of the exocrine compartment is potentially less susceptible to PEP, CP with ongoing inflammation in affected acinar cells is more prone to PEP. And yet, this is speculative, as in none of these studies the incidence of PEP has been evaluated in relation to the stadium (e.g. according to the Cambridge classification) of CP [22]. However, the patients in our cohort had rather early stage of chronic pancreatitis.

There are contradicting data on a non-dilated common bile duct as a risk factor for PEP [17, 20]. Our data are conclusive with a metaanalysis by Freeman et al. which did not show an

**Table 4. Risk factors for difficult intubation of the papilla duodeni major.**

| Risk factor                   | p-value | Odds ratio (CI 95%) |
|-------------------------------|---------|---------------------|
| Female sex                    | 0.941   | 0.984 (0.644–1.505) |
| Age                           | 0.982   |                     |
| Age<40                        | 0.134   | 0.479 (0.180–1.277) |
| Body weight, Kg               | 0.778   |                     |
| Body height, cm               | 0.351   |                     |
| BMI                           | 0.247   |                     |
| BMI ≥ 25                      | 0.255   | 0.746 (0.451–1.236) |
| Previous pancreatitis         | 0.808   | 1.169 (0.332–4.113) |
| Chronic pancreatitis          | 0.505   | 0.656 (0.189–2.284) |
| Status post cholecystectomy   | 0.348   | 0.762 (0.431–1.346) |
| Juxtapapillary diverticulum   | 0.726   | 1.124 (0.585–2.158) |
| Serum bilirubin               | 0.148   |                     |
| Serum bilirubin <1.3 mg/dL    | 0.533   | 0.856 (0.526–1.395) |
| Bile duct diameter            | 0.069   |                     |
| Bile duct diameter <8 mm      | 0.283   | 0.760 (0.460–1.255) |
| ERCP on call                  | 0.053   | 3.037 (0.934–9.880) |
| Urgent indication for ERCP    | 0.487   | 1.254 (0.662–2.377) |
| Diagnosis bile duct stricture | 0.759   | 1.071 (0.691–1.659) |

For dichotomous data, a chi-square test was performed. Pearson and Spearman correlations were used for normally and not-normally distributed intervals, respectively. P-values < 0.05 are considered statistically significant and are indicated by \*. CI, confidence interval; BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography.

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increased risk by multivariate analysis. Sphincter oddi dysfunction, another previously described risk factor, was not examined in our patients [4].

Because most of the risk factors such as sex, age, bilirubin level, or bile duct diameter are not influenceable, efforts must be undertaken to minimize the procedure related risk factors and to optimize prophylactic measurements.

Inadvertent cannulation of the pancreatic duct was associated with an increased risk of PEP (odds ration 2.2) in our study and others [17]. Procedures associated with cannulation of the pancreatic duct such as pre-cut papillotomy and injection of contrast agent into the pancreatic duct have also been confirmed as risk factors in other studies [5–7, 9, 10]. However, the reasons for inadvertent cannulation of the pancreatic duct are unclear. Our data show that difficult intubation of the papilla, which means more than 5 attempts, is a statistically significant risk factor for inadvertent cannulation. This seems to happen more frequently during ERCPs

**Table 5. Risk factors for PEP in patients who did not receive PEP prophylaxis.**

| Risk factor                                | p-value | Odds ratio (CI 95%)  |
|--|---------|----------------------|
| Chronic pancreatitis                       | 0.060   | 4.207 (0.834–21.213) |
| Previous pancreatitis                      | 0.524   | 1.972 (0.235–16.539) |
| Serum bilirubin <1.3 mg/dL                 | 0.303   | 1.763 (0.592–5.244)  |
| Inadvertent cannulation of pancreatic duct | 0.280   | 1.803 (0.610–5.329)  |

For dichotomous data, a chi-square test was performed. P-values < 0.05 are considered statistically significant and are indicated by \*. CI, confidence interval.

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on call. Although the reasons for that can be manifold, it is conceivable that ERCPs on call are likely more challenging or performed under difficult conditions.

## Conclusion

Inadvertent cannulation of the pancreatic duct is a procedure related risk factor for PEP. Measurements on preventing inadvertent cannulation of the pancreatic duct should be established and studies on prophylactic measurements should focus particularly on patients with inadvertent cannulation of the pancreatic duct.

## Supporting information

**S1 File. PEP-Risk\_Data.xlsx.**  
(XLSX)

## Author Contributions

**Conceptualization:** VP MS DH HA.

**Data curation:** MS DH.

**Formal analysis:** VP.

**Funding acquisition:** VP MS DH HA.

**Investigation:** VP MS DH HA.

**Methodology:** VP HA.

**Project administration:** VP HA.

**Resources:** MS DH.

**Supervision:** HA.

**Validation:** VP HA.

**Visualization:** VP MS DH HA.

**Writing – original draft:** VP.

**Writing – review & editing:** VP MS DH HA.

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