Risk Factors for Post-ERCP Pancreatitis in High- and Low-Volume Centers and Among Expert and Non-Expert Operators: A Prospective Multicenter Study

Pier Alberto Testoni, MD[1], Alberto Mariani, MD[1], Antonella Giussani, MD[1], Cristian Vailati, MD[1], Enzo Masci, MD[1], Giampiero Macarri, MD[2], Luigi Ghezzo, MD[3], Luigi Familiari, MD[4], Nicola Giardullo, MD[5], Massimiliano Mutignani, MD[6], Giovanni Lombardi, MD[7], Giorgio Talamini, MD[8], Antonio Spadaccini, MD[9], Romolo Briglia, MD[10], Lucia Piazzi, MD[11] and the SEIFRED Group[12]

OBJECTIVES: **Prospective studies have identified a number of patient- and procedure-related independent risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis, with different conclusions, so various questions are still open. The endoscopist's expertise, case volume, and case mix can all significantly influence the outcome of ERCP procedures, but have been investigated little to date.**

METHODS: **We identified patient- and procedure-related risk factors for post-ERCP pancreatitis and the impact of the endoscopist's experience and the center's case volume, using univariate and multivariate analysis, in a multicenter, prospective study involving low- and high-volume centers, over a 6-month period.**

RESULTS: **A total of 3,635 ERCP procedures were included; 2,838 (78%) ERCPs were performed in the 11 high-volume centers (median 257 each) and 797 in the 10 low-volume centers (median 45 each). Overall, 3,331 ERCPs were carried out by expert operators and 304 by less-skilled operators. There were significantly more grade 3 difficulty procedures in high-volume centers than in low-volume ones ($P<0.0001$). Post-ERCP pancreatitis occurred in 137 patients (3.8%); the rates did not differ between high- and low-volume centers (3.9% vs. 3.1%) and expert and non-expert operators (3.8% vs. 5.5%). However, in high-volume centers, there were 25% more patients with patient- and procedure-related risk factors, and the pancreatitis rate was one-third higher among non-expert operators. Univariate analysis found a significant association with pancreatitis for history of acute pancreatitis, either non-ERCP- or ERCP-related and recurrent, young age, absence of bile duct stones, and biliary pain among patient-related risk factors, and >10 attempts to cannulate the Vater's papilla, pancreatic duct cannulation, contrast injection of the pancreatic ductal system, pre-cut technique, and pancreatic sphincterotomy, among procedure-related risk factors. Multivariate analysis also showed that a history of post-ERCP pancreatitis, biliary pain, >10 attempts to cannulate the Vater's papilla, main pancreatic duct cannulation, and pre-cut technique were significantly associated with the complication.**

CONCLUSIONS: **A history of pancreatitis among patient-related factors, and multiple attempts at cannulation among procedure-related factors, were associated with the highest rates of post-ERCP pancreatitis. Pre-cut sphincterotomy, although identified as another significant risk factor, appeared safer when done early (fewer than 10 attempts at cannulating), compared with repeated multiple cannulation. The risk of post-ERCP pancreatitis was not associated with the case volume of either the single endoscopist or the center; however, high-volume centers treated a larger proportion of patients at high risk of pancreatitis and did a significantly greater number of difficult procedures.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg.

[1]Division of Gastroenterology and Gastrointestinal Endoscopy, Università Vita-Salute San Raffaele, IRCCS San Raffaele Hospital, Milan, Italy; [2]Digestive Endoscopy Unit, A. Murri Hospital, Fermo, Italy; [3]Digestive Endoscopy Unit, S.Croce e Carle Hospital, Cuneo, Italy; [4]Digestive Endoscopy Unit, Policlinico G. Martini, Messina, Italy; [5]Gastroenterology and Gastrointestinal Endoscopy Unit, S.G. Moscati Hospital, Avellino, Italy; [6]Digestive Endoscopy Unit, Catholic University, Rome, Italy; [7]Digestive Endoscopy Unit, A. Cardarelli Hospital, Napoli, Italy; [8]Pancreatic Endoscopy Unit, Policlinico G. Rossi, Verona, Italy; [9]Gastroenterology Unit, San Pio Hospital, Vasto, Italy; [10]Gastroenterology and Gastrointestinal Endoscopy Unit, S. Andrea Hospital, La Spezia, Italy; [11]Division of Gastroenterology and Gastrointestinal Endoscopy, Ospedale Generale Regionale, Bolzano, Italy; [12]Members of the SEIFRED Group are listed in the Appendix online. **Correspondence:** Pier Alberto Testoni, MD, Division of Gastroenterology and Gastrointestinal Endoscopy, IRCCS San Raffaele Hospital, Via Olgettina 60, Milano 20132, Italy. E-mail: testoni.pieralberto@hsr.it
Received 4 August 2009; accepted 11 February 2010

ENDOSCOPY

INTRODUCTION

Pancreatitis is still one of the most feared and frequent complication associated with endoscopic procedures involving the Vater's papilla (endoscopic retrograde cholangiopancreatography, ERCP), with an incidence ranging from <2% up to 40% (1,2). Differences in the criteria used for defining this complication, data collection methods, case mix, and levels of endoscopic expertise are factors that very likely influence the reported rates.

Although ~80% of episodes of post-ERCP pancreatitis are mild, a number of patients may develop severe pancreatitis requiring prolonged hospitalization, intensive care, and utilization of major hospital resources (3); these patients also risk significant morbidity and mortality. Despite technical improvements in recent years and endoscopists' growing experience with ERCP procedures, the incidence of post-procedure pancreatitis has not yet dropped and efforts are still being made to identify factors potentially associated with the risk and minimize the incidence and severity.

The case mix is reportedly the factor with most influence. Prospective studies using univariate and multivariate analysis on large series of patients have identified a number of specific risk factors, either patient- or procedure-related, associated with a higher incidence of post-ERCP pancreatitis (4–12). In four prospective studies giving separate figures for standard- and high-risk patients, the incidence of pancreatitis was 1.6% and 7.8% (13), 3.4% and 29.2% (14), 3.6% and 19.1% (4), and 0.4% and 18.8% (6), depending on the presence or absence of known risk conditions. It is essential to identify patients at high risk of this post-procedure complication so as to avoid unnecessary ERCP procedures or adopt protective technical or pharmacological measures.

Independently from the patient- and procedure-related risk factors, the endoscopist's expertise has been considered another factor that can influence the outcome of ERCP procedures and therefore the incidence of procedure-related pancreatitis too. Few studies have specifically addressed the question. One reported a significant difference in the rates of post-ERCP complications between low- and large-volume centers, with fewer cases of pancreatitis in the large-volume ones (5); another study showed significantly lower rates of pancreatitis among endoscopists with current ERCP volumes >40 procedures/year (15). However, besides factors widely recognized as involving a higher risk of pancreatitis, other conditions are still debated and require further investigation.

The aim of this study was to identify patient- and procedure-related risk factors for post-ERCP pancreatitis and the impact of the endoscopist's experience and the center's case volume on the rates, using univariate and multivariate analysis, in a multicenter, prospective study involving low- and high-volume centers in Italy.

METHODS

The study was conducted in 21 centers, 10 (47.6%) in the north, five (23.8%) in the center, and six (28.6%) in the south of Italy, over a 6-month period (February–July 2007); 11 and 10 centers, respectively, had an ERCP volume higher and lower than 200 procedures/year (large- and low-volume centers).

Study protocol

The study was designed and coordinated by the University Vita-Salute San Raffaele Gastroenterology and Gastrointestinal Endoscopy Division, appointed by the Italian Society of Digestive Endoscopy. Approval of the protocol was obtained from the ethics committees in all centers. Informed consent was routinely obtained from all patients undergoing ERCP for every diagnostic and therapeutic procedure and for data management for scientific purposes, in each center.

Each endoscopist in the study entered the data for all consecutive ERCPs attempted during the study and prospectively recorded patient- and procedure-related data on a detailed data collection sheet at the time of the ERCP. The data collection sheet included the patient's main details, indication for the procedure, patient-related risk factors, if present, technical details of the procedures, final diagnoses, procedure-related complications, post-procedure clinical and enzymatic 24-h or 48-h course (if needed on the basis of 24-h enzyme profile), antibiotic and analgesic treatments. More than one indication or procedure could be listed, as applicable. Data were then stored in a data base system for computer analysis. Adherence to the protocol was verified by a monitoring system that included on-site visits planned at intervals throughout the study.

Patients were excluded for any of the following reasons: (i) age <18 years; (ii) pregnancy; (iii) mental disability; (iv) active pancreatitis at the time of the procedure; (v) contrast allergy; and (vi) need for urgent ERCP within 12 h.

Baseline biochemical tests for liver function, amylase, and blood count were done before the procedure; blood count and amylase were repeated 6 h and 24 h after the procedure. In cases with persistently high 24-h amylase, the enzymatic profile was re-assessed at 48 h. All patients were kept in hospital and followed-up for 24 h after the procedure to assess their clinical conditions and check for post-procedure pancreatitis; if complications arose, patients stayed in hospital until they recovered.

Contrast medium was injected in all cases using a standard nonionic, iodinated, low-osmolar radiological contrast agent (Ultravist, Iopromide, Bayer Schering Pharma, Berlin, Germany, 300 mg/ml). Pharmacological prophylaxis of post-ERCP pancreatitis (adopted by routine or in selected cases in 6/11 and 4/10 high- and low-volume centers, respectively) was avoided during the 6-month study period. Post-procedure pancreatic stenting for post-ERCP pancreatitis prevention was adopted in high-risk cases in 3/11 and 1/10 high- and low-volume centers, respectively.

Risk factors for post-ERCP pancreatitis, either patient- or procedure-related, were identified on the basis of earlier multivariate analyses from prospective studies reported in the literature (4–10).

Patient variables

Measurements of the biliary and pancreatic ductal system, when visualized, were reported. The common bile duct diameter was calculated to within 2 cm of the papilla; the main pancreatic duct was measured at the head of the pancreas and adjusted for patient's age. All measures were adjusted for X-ray magnification. If there was a stricture, duct diameter was measured distally.

Chronic pancreatitis was defined as the presence of pancreatic ductal abnormalities according to Cambridge criteria (16). The definition of suspected sphincter of Oddi dysfunction (SOD) referred to a functional or structural abnormality of the sphincter, thought to be the cause of recurrent abdominal pain or pancreatitis, independently of manometric findings. The classification of SOD was based on the revised Milwaukee classification (17); type 3 SOD was suspected in cases with recurrent characteristic pain and a non-dilated pancreatico-biliary ductal system at trans-abdominal ultrasound or magnetic resonance pancreatico-biliary imaging, and normal pancreatico-biliary enzymes.

Eleven patient-related risk factors were included in the data sheet and evaluated for the study: (i) history of acute pancreatitis; (ii) earlier ERCP-related pancreatitis; (iii) acute recurrent pancreatitis; (iv) female sex; (v) young age; (vi) biliary pain; (vii, viii) diameter of common bile duct <10 mm with the gallbladder and <12 mm without; (ix) no bile duct stones; (x) normal serum transaminases and alkaline phosphatase; and (xi) bilirubin <2 mg/dl.

Technical variables

Eight procedure-related risk factors were included in the data sheet and evaluated for the study: (i) number of attempts to cannulate the Vater's papilla (up to, or >10); (ii) cannulation of the main pancreatic duct; (iii) failed cannulation; (iv) contrast injection into the pancreatic ductal system; (v) pancreatic acinarization after contrast injection, defined as any fluoroscopically observed focal or diffuse parenchymal blush of contrast; (vi) needle knife pre-cut technique; (vii) pancreatic sphincterotomy (through major or minor papilla); (viii) pneumatic dilatation of the biliary sphincter. The cutoff number of 10 attempts at cannulation was derived from earlier studies (4,7–9), one of them that proposed a 4-point risk score based on the number of cannulations (<5, 5–10, 11–20, and >20) (9).

Overall ERCP difficulty was graded from 1 (lowest difficulty=standard ERCP) to 3 (highest difficulty=tertiary ERCP), as proposed by Cotton (18).

Operator variables

For each center, with a high or low volume of ERCPs, operators' expertise was defined on the basis of the total number of procedures performed career-long and the number currently done per year. ERCP experience was defined as low grade if the career-long total performance was fewer than 200 procedures and/or the current number <40 per year (15,19).

Definition and grading of post-ERCP pancreatitis

Pancreatitis was defined as post-procedure, new-onset or with increased abdominal pain persisting for at least 24 h, with an increase in serum amylase at least three times the upper normal value (3). Pancreatitis was classified as mild or severe according to the criteria of the Atlanta International Symposium of 1992 (20). Mild attacks were those with no local or systemic complications and an uneventful recovery; attacks were considered severe if they were associated with the development of organ failure or local complications such as necrosis, abscess, or fluid collections. In all cases, the severity of the pancreatic damage was established on the basis of computed tomography scans within 48 h of the onset of pancreatitis, according to Balthazar's criteria (21), and defined in the institutional review board-approved protocol for management of acute pancreatitis; computed tomography scans were repeated in severe cases depending on clinical needs.

Statistical analysis

Data are presented as frequencies. Differences in the incidence of post-ERCP pancreatitis were compared using a χ^2 or Fisher's exact test for categorical variables. All differences were considered significant at a two-sided P value <0.05. Variables with a P value <0.1 in the univariate analysis were all included in a forward stepwise multiple logistic regression model to identify the independent risk factors for post-ERCP pancreatitis. In this analysis were also included operator's expertise and ERCP volume center, as the two variables that represented the primary aim of the study. An odds ratio with a 95% confidence interval that did not include unity was considered significant. Data were analyzed using the SAS system software (SAS Institute, Cary, NC).

RESULTS

Data were obtained from 21 centers, 10 in northern Italy (five with high and five with low volume), five in the center (three high and two low volume), and six in the south (three high and three low volume). A total of 3,635 ERCP procedures were included in the study; 2,838 were performed in the 11 high-volume centers (78%) and 797 in the 10 low-volume centers. One hundred twenty-five ERCPs were diagnostic (3.4%). The number of procedures in each center ranged from 151 to 302 in the high-volume centers (median 257), and from 9 to 75 in the low-volume ones (median 45). Overall, 3,331 ERCPs were carried out by expert operators and 304 by less-experienced operators. Post-procedure pancreatic stenting for post-ERCP pancreatitis prophylaxis was performed in 64/359 (17.8%) and 4/41 (9.8%) high-risk conditions, in high- and low-volume centers, respectively.

Patients were <30 years old in 2.2% of the series (81 cases), 30–49 in 12.3% (448 cases), 50–69 in 37.4% (1,358 cases), and over 70 in 48.1% (1,748 cases). Males accounted for 49.8% and females accounted for 50.2% of cases.

Tables 1 and **2** list the indications for ERCP, either therapeutic or diagnostic, and maneuvers performed in high- and low-volume centers.

There were significantly more difficulty procedures in high-volume centers than in low-volume ones ($P<0.001$) (**Table 3**).

Overall, post-ERCP pancreatitis occurred in 137 patients (3.8%). It was classified as mild in 120 cases (87.4%) and severe in 17 (12.6%). Pancreatitis-related median hospital stay was, respectively, 4.0 and 26.7 days for mild and severe disease. The ERCP-related mortality rate was 0.19% (seven cases); five deaths were due to acute pancreatitis, one to perforation and another to bradyarrhythmia arising during the procedure. No deaths were reported for mild pancreatitis; the mortality rate for severe pancreatitis was 29.4% (5/17 cases).

ENDOSCOPY

Table 1. Indications for ERCP in high- and low-volume centers

Indication for ERCP	Total no. (%)	High-volume center no. (%)	Low-volume center no. (%)
Choledocolithiasis	1,656 (45.5)	1,218 (42.9)	438 (54.9)
Malignant biliary stricture (known or suspected) [a]	715 (19.7)	568 (20.0)	147 (18.4)
Cholangitis	235 (6.5)	197 (6.9)	38 (4.8)
Suspected SOD	158 (4.3)	152 (5.3)	6 (0.7)
Chronic pancreatitis	134 (3.7)	125 (4.4)	9 (1.1)
Acute recurrent pancreatitis	132 (3.6)	112 (3.9)	20 (2.5)
Benign biliary stricture	128 (3.5)	101 (3.6)	27 (3.4)
Main pancreatic duct strictures (benign or malignant)	95 (2.7)	88 (3.1)	7 (0.9)
Previous acute pancreatitis	90 (2.6)	67 (2.4)	23 (2.9)
Post-surgery biliary leakage	79 (2.2)	59 (2.1)	20 (2.5)
Ampullary neoplasia (known or suspected)	72 (2.0)	55 (1.9)	17 (2.1)
Other	574 (15.8)	492 (17.3)	82 (10.3)
Overall ERCPs	3,635	2,838	797

ERCP, endoscopic retrograde cholangiopancreatography; SOD, sphincter of Oddi dysfunction.
[a]Stricture due to pancreatic cancer or cholangio-/hepatocarcinoma.

Table 2. Maneuvers during ERCP in high- and low-volume centers, by frequency

Maneuver	Total no. (%)	High-volume center no. (%)	Low-volume center no. (%)
Biliary sphincterotomy	1,991 (54.7)	1,474 (51.9)	517 (64.9)
Biliary stone removal	1,524 (41.9)	1,146 (40.4)	378 (47.4)
Biliary stenting	929 (25.5)	691 (24.3)	238 (29.9)
Nasobiliary drainage	635 (17.5)	592 (20.9)	43 (5.4)
Pre-cut technique	308 (8.5)	213 (7.5)	95 (11.9)
Diagnostic ERCP	125 (3.4)	95 (3.3)	30 (3.8)
Failed papillary cannulation	114 (3.1)	90 (3.2)	24 (3.0)
Common bile duct brushing	106 (2.9)	94 (3.3)	12 (1.5)
Biliary stricture dilation	83 (2.3)	72 (2.5)	11 (1.4)
Pancreatic sphincterotomy (major or minor papilla)	155 (4.3)	144 (5.1)	11 (1.4)
Pancreatic endotherapy (major papilla)	158 (4.3)	136 (4.8)	22 (2.8)
Pancreatic endotherapy (minor papilla)	18 (0.49)	17 (0.60)	1 (0.1)
Other	666 (18.3)	524 (18.5)	142 (17.8)
Overall ERCPs	3,635	2,838	797

ERCP, endoscopic retrograde cholangiopancreatography.

Post-ERCP pancreatitis rates progressively decreased with age: 6.2% in patients under 30 years (5/81), 4.7% in those from 30 to 49 years (21/448), 4.4% in those from 50 to 69 years (60/1,358), and 2.9% in those 70 years or over (51/1,748) ($P = 0.03$ comparing patients <30 years and those ≥70 years). Post-ERCP pancreatitis rates were not significantly different with a cutoff of 50 years: 4.9% in the younger (26/529) and 3.6% in the older group (111/3,106).

Post-ERCP pancreatitis rates and distribution by indications and numbers of maneuvers in high- and low-volume centers are reported in **Tables 4** and **5**.

The mean incidence of post-ERCP pancreatitis was 3.9% (112/2,838 cases) in high-volume centers and 3.1% (25/797 cases) in low-volume centers; the difference was not significant ($P = 0.379$). However, compared with low-volume centers, high-volume centers had 25% more patients with clinical conditions placing them at high risk for post-ERCP pancreatitis and significantly more procedures at the highest degree of difficulty.

The mean incidence of post-procedure pancreatitis among expert operators was 3.8% (125/3,331 cases) compared with 5.5% (9/163 cases) among non-experts; although the latter was one-third higher, the difference was, again, not significant ($P = 0.345$).

In high-risk patients, the mean incidence of post-ERCP pancreatitis was 6.2% (4/64 cases) and 8.1% (24/295 cases) among cases undergone or not post-procedure pancreatic stent placement, respectively. The difference was not statistically significant.

Table 3. Grades of difficulty of ERCP in high- and low-volume centers

Degree of difficulty	High-volume centers (2,838)	Low-volume centers (797)
1 (Standard ERCP)	1,284 (45.2%)	326 (40.9%)
2 (Advanced ERCP)	1,268 (44.7%)	437 (54.8%)
3 (Tertiary ERCP)	286 (10.1%)	34 (4.3%)

ERCP, endoscopic retrograde cholangiopancreatography.
Degree of difficulty in high- vs. low-volume centers: $P < 0.001$.

Univariate analysis

Of the 11 patient-related risk factors considered in the study protocol, 6 were significantly associated with post-ERCP pancreatitis: history of acute pancreatitis, either non-ERCP- or ERCP-related and recurrent, young age, absence of bile duct stones, and biliary pain (**Table 6**). Of the eight procedure-related risk factors, five were significantly associated with post-ERCP pancreatitis: >10 attempts to cannulate the Vater's papilla, pancreatic duct cannulation, contrast injection of the pancreatic ductal system, pre-cut technique, and pancreatic sphincterotomy (**Table 7**).

Table 4. Post-ERCP pancreatitis (PEP) rate and distribution by indications to ERCP in high- and low-volume centers

Indication	High-volume centers		Low-volume centers	
	ERCP (no.)	PEP no. (%)	ERCP (no.)	PEP no. (%)
Primary sclerosing cholangitis	14	3 (21.4)	6	0 (0)
Benign biliary stenosis	101	10 (9.9)	27	0 (0)
Acute recurrent pancreatitis	112	11 (9.8)	20	0 (0)
Suspected IPMN	21	2 (9.5)	1	0 (0)
Suspected SOD	152	14 (9.2)	6	0 (0)
Intra-hepatic lithiasis	34	2 (5.9)	7	1 (14.3)
Post-surgery biliary leakage	59	3 (5.1)	20	0 (0)
Previous acute pancreatitis	67	3 (4.5)	23	0 (0)
Choledocolithiasis	1,218	48 (3.9)	438	11 (2.5)
Suspected ampullary neoplasia	55	2 (3.6)	17	2 (11.8)
Chronic pancreatitis	125	4 (3.2)	9	0 (0)
Suspected malignant biliary stenosis	581	9 (1.5)	134	5 (3.7)
Cholangitis	197	6 (3.0)	38	0 (0)
Other	183	1 (0.5)	57	2 (3.5)

ERCP, endoscopic retrograde cholangiopancreatography; IPMN, intraductal papillary mucinous neoplasm; PEP, post-ERCP pancreatitis; SOD, sphincter of Oddi dysfunction.

Table 5. Post-ERCP pancreatitis rates and distribution for maneuvers during ERCP in high- and low-volume centers

Maneuver	High-volume centers		Low-volume centers	
	ERCP (no.)	PEP no. (%)	ERCP (no.)	PEP no. (%)
Endotherapy for pancreas divisum	17	3 (17.6)	1	0 (0)
Pre-cut technique	213	20 (9.4)	95	10 (10.5)
Endotherapy for chronic pancreatitis	71	6 (8.4)	11	0 (0)
Failed papillary cannulation	90	7 (7.8)	24	3 (12.5)
Endotherapy for acute recurrent pancreatitis	53	3 (5.7)	3	0 (0)
Diagnostic ERCP	95	4 (4.2)	30	2 (6.7)
Endotherapy for biliary strictures	857	35 (4.1)	261	6 (2.3)
Endotherapy for bile stone disease	3,212	129 (4.0)	938	29 (3.1)
Other	576	12 (2.1)	134	2 (1.5)

ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis.

Endoscopists experience and center ERCP volume were not significantly associated with post-ERCP pancreatitis.

Multivariate analysis

The results of forward stepwise binary logistic regression from the pool of the 21 potential risk factors for post-ERCP pancreatitis identified five risk factors by multivariate analysis, two patient related and three procedure related; these were all independently associated with post-ERCP pancreatitis: history of post-ERCP pancreatitis, biliary pain, >10 attempts to cannulate Vater's papilla, main pancreatic duct cannulation, and pre-cut technique (**Table 8**).

Other patient- and procedure-related risk factors, as well as ERCP low volume (for both operator and center), reported in earlier studies were not associated with any significant risk of post-procedure pancreatitis in this study.

Earlier pancreatitis was the most important patient-related risk factor. Patients with earlier episodes of post-ERCP have an up to eightfold risk of developing the complication again if undergoing either diagnostic or therapeutic ERCP.

Increasing number of attempts at cannulating Vater's papilla was the most risky factor for post-ERCP pancreatitis. More than 10 attempts raised the risk 15-fold, independently of the success rate and other patient- and procedure-related risk factors. The

ENDOSCOPY

Table 6. Univariate analysis of patient-related risk factors

Variable	Incidence of post-ERCP pancreatitis (%)		
	With variable	Without variable	P
Significant			
History of previous post-ERCP pancreatitis	12/60 (20%)	122/3,455 (3.5%)	<0.0001
History of previous pancreatitis	30/440 (6.8%)	105/3,078 (3.4%)	<0.0005
Recurrent idiopathic pancreatitis	12/132 (9.1%)	122/3,354 (3.6%)	<0.005
Absence of common bile duct stones	74/1,614 (4.6%)	60/1,936 (3.1%)	0.03
Biliary pain	63/1,355 (4.6%)	68/2,060 (3.3%)	0.05
Young age			0.0005
Not significant			
Female sex	71/1,755 (4%)	66/1,791 (3.7%)	0.57
CBD <10 mm (gallbladder +)	44/1,013 (4.3%)	86/2,303 (3.7%)	0.40
CBD <12 mm (gallbladder −)	25/608 (4.1%)	99/2,538 (3.9%)	0.81
High ALP and/or transaminase	90/2,237 (4%)	44/1,236 (3.6%)	0.78
Bilirubin <2 mg/dl	59/1,531 (3.8%)	73/1,938 (3.7%)	0.89

ALP, alkaline phosphatase; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography.

Table 7. Univariate analysis of procedure-, operator experience–, and ERCP volume/center–related risk factors

Variable	Post-ERCP pancreatitis incidence (%)		
	With variable	Without variable	P
Significant			
More than 10 attempts to cannulate Vater's papilla	18/120 (15%)	119/3,515 (3.4%)	<0.0001
MPD cannulation	72/784 (9.2%)	64/2,708 (2.4%)	<0.0001
Contrast injection of pancreatic ductal system	59/660 (8.9%)	76/2,706 (2.8%)	<0.0001
Pre-cut technique	30/308 (9.7%)	106/3,155 (3.4%)	<0.0001
Pancreatic sphincterotomy	1/155 (0.6%)	135/3,299 (3.9%)	0.03
Not significant			
Pancreatic acinarization	3/22 (13.6%)	132/3,432 (3.8%)	0.06
Pneumatic dilatation of the biliary sphincter	0	136/3,447 (3.9%)	0.29
Failed papillary cannulation	7/114 (6.1%)	130/3,521 (3.7%)	0.27
Low-ERCP experience (endoscopist)	9/163 (5.5%)	125/3,331 (3.8%)	0.34
Low-ERCP volume (center)	25/797 (3.1%)	112/2,838 (3.9%)	0.38

ERCP, endoscopic retrograde cholangiopancreatography; MPD, main pancreatic duct.

risk significantly increased with between <3 and 4–10 attempts (P<0.0001), and between 4–10 and >10 attempts (P<0.005); between <3 and >10 attempts, the risk of pancreatitis was highly significant (P<0.0001) (**Table 9**).

Pre-cut technique *per se* was associated with a threefold increase in the risk of post-procedure pancreatitis. Among patients in whom the pre-cut was done before 10 attempts at cannulating the papilla, the pancreatitis rate was significantly higher (P<0.001) than in those without pre-cut or with fewer than 10 attempts (7.6% vs. 3.3%). Comparing cases in whom the pre-cut was associated with fewer than 10 attempts at cannulation and those without pre-cut who needed >10 attempts, the pancreatitis rate did not significantly differ (7.6% vs. 15.4%; P=0.3), even though it was half in the first group.

DISCUSSION

Identifying patients and maneuvers that are at higher-than-normal risk of post-ERCP pancreatitis has practical importance in selecting candidates for the procedure, providing adequate information about their own specific risks, and adopting either pharmacological or technical measures to reduce the likelihood of this complication in those with a high level of risk. The operator's experience must also be taken into account as a potential risk factor, even among patients with a standard risk for post-ERCP pancreatitis.

Table 8. Risk factors for post-ERCP pancreatitis evaluated by multivariate analysis

Risk factor	Odds ratio	95% confidence interval	P value
More than 10 attempts to cannulate Vater's papilla	14.9	10.50–21.26	<0.001
Previous post-ERCP pancreatitis	8.7	3.220–23.857	<0.0001
Pre-cut technique	3.1	2.06–4.76	<0.001
Main pancreatic duct cannulation	2.1	1.226–3.505	0.006
Biliary/pancreatic pain	1.9	1.113–3.438	0.01
Low-ERCP volume (center)	1.3	0.81–1.95	0.30
Low-ERCP experience (endoscopist)	0.7	0.32–1.25	0.19

ERCP, endoscopic retrograde cholangiopancreatography.

Prospective multicenter studies have helped us understand patient- and procedure-related risk factors for post-ERCP pancreatitis though the results are sometimes conflicting. A review that selectively included studies with multivariate analysis of the relationship between patient, procedure, and operator factors and

Table 9. Number of attempts at cannulating Vater's papilla and incidence of post-ERCP pancreatitis

Number of attempts	Total ERCP	No pancreatitis	Pancreatitis	P		
≤3	2,585	2,514	71 (3.0%)	} <0.0001		} <0.0001
4–10	553	517	36 (6.5%)		} <0.005	
>10	120	102	18 (15.0%)			

ERCP, endoscopic retrograde cholangiopancreatography.

post-ERCP pancreatitis found significant risk factors were younger age and SOD dysfunction among patient-related risk factors, and difficulty in cannulation, multiple pancreatic duct contrast injection, and pre-cut sphincterotomy among procedure-related factors (22). In this evidence-based assessment, other frequently reported patient-related risk factors such as female sex and previous pancreatitis, and procedure-related risk factors such as balloon papillary dilatation and pancreatic sphincterotomy were not associated with any increase in the risk of pancreatitis.

These discrepancies led our group to do a meta-analysis of all prospective studies carried out between January 1990 and December 2001, totaling 15 prospective studies each enrolling >100 patients, to identify the risk factors that were recognized in them all (23). This meta-analysis indicated that suspected SOD dysfunction, history of post-ERCP pancreatitis, female sex, pancreatic duct contrast injection, and pre-cut sphincterotomy were independent predictors of post-ERCP pancreatitis. Again, some of the risk factors found in the earlier large review (22) did not coincide with those brought to light by this meta-analysis; however, not all the risk conditions recognized in the meta-analysis were confirmed in subsequent large prospective studies (10–12).

This study confirmed only a history of pancreatitis and biliary pain as a patient-related independent risk condition for post-procedure pancreatitis (multivariate analysis). Previous pancreatitis, either non-ERCP- or ERCP-related or recurrent, was associated with post-procedure pancreatitis in most large prospective studies (4–7,10), though not in two more recent ones (11,12). In this study, the risk of post-procedure pancreatitis was about nine times higher in subjects with a history of acute pancreatitis.

Biliary pain was the other patient-related condition recognized as an independent risk; this is frequently associated with some SOD dysfunction, a condition universally considered at very high risk of pancreatitis.

Younger age and absence of bile duct stones were associated with a high risk of pancreatitis only in the univariate analysis. Younger age was first identified as an independent risk factor for post-ERCP pancreatitis in a multicenter study in 1996 (4) and subsequently confirmed in five other multivariate analyses (10,12,24–26), but not in others (7,11), including our own group's earlier meta-analysis (23). The higher risk might depend on both the lack of age-related atrophy of the gland (27) and the higher prevalence of SOD dysfunction in young people.

Absence of bile duct stones was also associated with an increase in the risk of post-procedure pancreatitis. No stone in a patient suspected of common bile duct lithiasis was already reported as the most potent single risk factor for post-ERCP pancreatitis in a study that did not take into consideration the diagnosis of SOD dysfunction (26).

Female sex, non-dilated bile ducts, isolated increases of serum transaminases, and normal bilirubin were not associated with any clinically significant risk of post-ERCP pancreatitis in this study. The lack of recognition of female sex as a risk factor is in contrast with a number of earlier reports (7,12) and with our earlier meta-analysis (23).

Although small bile duct diameter was reported as a risk factor mainly by centers treating a large number of patients with SOD dysfunction, most multivariate analyses did not consider this finding per se as a risk factor for pancreatitis (4,10–12,24,26,28).

Normal serum bilirubin at the time of ERCP independently doubled the risk of pancreatitis only in an earlier meta-analysis (7), and not in other studies. This variable might, however, have been included together with other features such as small bile duct diameter (5,13,25).

As in most European countries, including Italy, SOD manometry is generally not routinely done, to avoid confounding definitions regarding the suspicion of SOD dysfunction, we identified as single risk factors a series of conditions such as biliary pain, non-dilated ducts, absence of bile duct stones, bilirubin below 2 mg/dl, and increases in transaminases, which may be associated with abnormalities of the sphincter function. On this basis, SOD dysfunction was suspected only in 4.3% of cases in this series. This low rate might explain why female sex and other conditions did not surface as significant risk factors.

Technical variables found at multivariate analysis independently associated with a risk of pancreatitis were more numerous than patient-related variables and were: multiple attempts at cannulating the Vater's papilla, pancreatic duct cannulation (independently of the number of cannulations and contrast injection), and pre-cut sphincterotomy. More than 10 attempts at cannulating the Vater's papilla raised the risk of pancreatitis about 15-fold; interestingly, the risk rate showed a linear progression between either less than three attempts and four to nine attempts, or between four to nine and >10 attempts. Together with a non-specified "difficult" cannulation and prolonged cannulation time, this was also reported in most earlier analyses (7,10,12,22), using a wide range of cutoffs, with six attempts in two studies (4,7), and 20 in one (8). The high incidence of pancreatitis after repeated attempts at cannulating, independently of pancreatic duct contrast injection, confirms that papillary edema- and sphincter hypertension-related impairment of pancreatic drainage, rather than hydrostatic ductal and contrast agent injury, is a major factor. The fact that difficult cannulation did not reach significance as a risk factor in a study where prophylactic

ENDOSCOPY

pancreatic stents were frequently used (10) further confirms this. These data also suggest that alternative techniques, such as pre-cut sphincterotomy, should be adopted in cases with difficult cannulation, rather than insisting with multiple attempts, and confirm the preventive role of early pre-cut in reducing the risk of pancreatitis, as in another study (29).

Pre-cut sphincterotomy, however, raised the risk of post-procedure pancreatitis threefold. Although pre-cutting was associated with a higher risk of pancreatitis in some studies (4,6,12) and in our earlier meta-analysis (23), increasing the number of reports from tertiary referral centers have since confirmed that complication rates, including pancreatitis, do not differ from standard sphincterotomy (29,30). These observations suggest that the risk of pre-cut is very likely operator dependent. Moreover, this study found that early pre-cut was safer than either delayed pre-cut or multiple attempts at cannulating the papilla, supporting the concept that in expert hands pre-cut might be preferable to repeated cannulation attempts, especially in patients at high risk for post-procedure pancreatitis (7,28).

The fact that pancreatic cannulation and contrast injection were independent risk factors for post-ERCP pancreatitis is in line with most earlier reports (4,5,7,10–12,22,26). Current evidence does not support the notion that the risk of pancreatitis is lower with non-ionic contrast agents than with conventional ionic agents (1). Hydrostatic injury from pancreatic duct overfilling is very likely the main trigger of the pancreatic reaction. Pancreatic sphincterotomy was associated with a high risk of pancreatitis only in the univariate analysis, in agreement with some earlier reports (7,10).

Few reports have looked at the operator's experience as a risk factor for post-ERCP pancreatitis, defining it on the basis of the number of procedures either performed over the whole career or per year or week. Here again, however, results are conflicting. Besides studies that found the endoscopist's expertise was a significant risk factor (4,5,10,15), there were others that were unable to confirm it (7,8,12,31,32). Unexpectedly, one study showed a higher rate, rather than a similar or lower rate, of pancreatitis among endoscopists with higher case volumes (7). Williams *et al.* (31) classified the case volume as <50, 50–100, 100–150, 150–200, and >200 per year, but found no association between the different volumes and post-procedure pancreatitis. Trainee participation was evaluated in three studies (7–10): two found no difference in the incidence of pancreatitis (7,8) between attending physicians and trainees.

In this study, the incidence of post-ERCP pancreatitis was one-third higher among non-expert operators than experts (defined on the basis of both the above parameters); however, the difference was not significant. One possible explanation is that none of the endoscopists in multicenter studies reached the threshold of 300–500 ERCPs/year, above which the pancreatitis rate should diminish, as suggested by Freeman *et al.* (7). Expertise very likely affects successful cannulation and overall performance of the ERCP procedure, including the risk of bleeding and perforation, but appears unable to prevent pancreatitis, which seems to depend more on patient-related risk conditions than technical skill. These findings agree with this study as regards the case volume per center. The mean pancreatitis rate did not significantly differ between high- and low-volume centers. This might reflect the fact that although the pancreatitis rate was one-third higher among low-volume operators, in high-volume centers there were 25% more patients with clinical conditions placing them at high risk for post-ERCP pancreatitis and a significantly larger number of procedures at the highest degree of difficulty.

The present prospective multicenter study, using multivariate analysis, indicates that technique-related risk factors are probably more important and numerous than patient-related ones in the risk of post-ERCP pancreatitis in a large series with not >10% of patients with some SOD dysfunction. More than 10 attempts at cannulating the Vater's papilla, regardless of the success of the procedure, were associated with the highest risk of post-procedure pancreatitis, with a significant, linear rise in risk depending on the number of attempts; pre-cut sphincterotomy, although identified as another significant risk factor, appeared safer when performed early (<10 attempts at cannulating), compared with repeated multiple cannulation. A history of acute pancreatitis, whatever the etiology, was the second most important risk factor and should be taken into consideration before planning an ERCP.

Study Highlights

WHAT IS CURRENT KNOWLEDGE
✓ Identification of patient- and procedure-related risk factors is important in the evaluation of post-endoscopic retrograde cholangiopancreatography pancreatitis, and the impact of the endoscopist's experience and the center's case volume is still debated.

WHAT IS NEW HERE
✓ A history of pancreatitis and multiple attempts at cannulation are associated with the highest rates of pancreatitis.
✓ Pre-cut sphincterotomy appears safer when done early.
✓ The risk of pancreatitis is not associated with the case volume of either the single endoscopist or the center, even if high-volume centers perform a larger number of difficult procedures in patients at high risk of pancreatitis.

ENDOSCOPY

REFERENCES

1. Gottlieb K, Sherman S. ERCP and endoscopic biliary sphincterotomy-induced pancreatitis. Gastrointest Endosc Clin N Am 1998;8:87–114.

2. Freeman ML. Adverse outcomes of ERCP. Gastrointest Endosc 2002;56 (Suppl): S273–82.

3. Cotton PB, Lehman G, Vennes J et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991;37:383–93.

4. Freeman ML, Nelson DB, Sherman S et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909–18.

5. Loperfido S, Angelini G, Benedetti G et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc 1998;48:1–10.

6. Masci E, Toti G, Mariani A et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. Am J Gastroenterol 2001;96:417–23.

7. Freeman ML, DiSario JA, Nelson DB et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc 2001;54:425–34.

8. Vandervoort J, Soetikno RM, Tham TCK et al. Risk factors for complications after performance of ERCP. Gastrointest Endosc 2002;56:652–6.

9. Friedland S, Soetikno RM, Vandervoort J et al. Bedside scoring system to predict the risk of developing pancreatitis following ERCP. Endoscopy 2002;34:483–8.

10. Cheng CL, Sherman S, Watkins JL et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. Am J Gastroenterol 2006;101:139–47.

11. Cotton PB, Garrow DA, Gallagher J et al. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc 2009;70:80–8.

12. Wang P, Li ZS, Liu F et al. Risk factors for ERCP-related complications: a prospective multicenter study. Am J Gastroenterol 2009;104:31–40.

13. Sherman S, Ruffolo TA, Hawes RH et al. Complications of endoscopic sphincterotomy: a prospective study with emphasis on the increased risk associated with sphincter of Oddi dysfunction and non-dilated bile ducts. Gastroenterology 1991;101:1068–75.

14. Sherman S, Hawes RH, Rathgaber SW et al. Post-ERCP pancreatitis: randomized, prospective study comparing a low- and high-osmolality contrast agent. Gastrointest Endosc 1994;40:422–7.

15. Rabenstein T, Schneider HT, Nicklas M et al. The impact of skill and experience of the endoscopist on the outcome of endoscopic sphincterotomy. Gastrointest Endosc 1999;50:628–36.

16. Axon ATR, Classen M, Cotton PB et al. Pancreatography in chronic pancreatitis: international definitions. Gut 1984;25:1107–12.

17. Geenen JE, Hogan WJ, Dodds WJ et al. The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter of Oddi dysfunction. N Engl J Med 1989;320:82–7.

18. Cotton PB. Income and outcome metrics for the objective evaluation of ERCP and alternative methods. Gastrointest Endosc 2002;56 (6 Suppl): S283–90.

19. Principles of training in gastrointestinal endoscopy. From the ASGE. American Society for Gastrointestinal Endoscopy. [No authors listed] Gastrointest Endosc 1999;49:845–53.

20. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11–13, 1992. Arch Surg 1993;128:586–90.

21. Balthazar EJ, Ranson JH, Naidich DP et al. Acute pancreatitis: prognostic value of CT. Radiology 1985;156:767–72.

22. Aronson N, Flamm CR, Bohn RL et al. Evidence-based assessment: patient, procedure, or operator factors associated with ERCP complications. Gastrointest Endosc 2002;56 (Suppl): S294–302.

23. Masci E, Mariani A, Curioni S et al. Risk factors for pancreatitis following endoscopic retrograde cholangio-pancreatography: a meta-analysis. Endoscopy 2003;35:830–4.

24. Sherman S, Lehman GA, Freeman ML et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study [Abstract]. Am J Gastroenterol 1997;92:1639.

25. Dickinson RJ, Davies S. Post-ERCP pancreatitis and hyperamy-lasemia: the role of operative and patient. Eur J Gastroenterol Hepatol 1998;10:423–8.

26. Mehta SN, Pavone E, Barkun JS et al. Predictors of post-ERCP complications in patients with choledocholithiasis. Endoscopy 1998;30:457–63.

27. Laugier R, Bernard JP, Berthezene P et al. Changes in pancreatic exocrine secretion with age: pancreatic exocrine secretion does decrease in the elderly. Digestion 1991;50:202–11.

28. Rabenstein T, Schneider HT, Bulling D et al. Analysis of risk factors associated with endoscopic sphincterotomy techniques: preliminary results of a prospective study, with emphasis on the reduced risk of acute pancreatitis with low-dose anticoagulation treatment. Endoscopy 2000;32:10–9.

29. Cennamo V, Fuccio L, Repici A et al. Timing of precut procedure does not influence success rate and complications of ERCP procedure: a prospective randomized comparative study. Gastrointest Endosc 2009;69:473–9.

30. Slot WB, Schoeman MN, DiSario JA et al. Needle-knife sphincterotomy as a precut procedure: a retrospective evaluation of efficacy and complications. Endoscopy 1996;28:334–9.

31. Williams EJ, Taylor S, Fairclough P et al. Risk factors for complication following ERCP: results of a large scale, prospective multicenter study. Endoscopy 2007;39:793–801.

32. Colton JB, Curran CC. Quality indicators, including complications, of ERCP in a community setting: a prospective study. Gastrointest Endosc 2009;70:457–67.