World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i20.777

World J Gastrointest Endosc 2016 December 16; 8(20): 777-784
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Combination of two-hour post-endoscopic retrograde cholangiopancreatography amylase levels and cannulation times is useful for predicting post-endoscopic retrograde cholangiopancreatography pancreatitis

Shiro Hayashi, Tsutomu Nishida, Hiromi Shimakoshi, Akiyoshi Shimoda, Takahiro Amano, Aya Sugimoto, Kei Takahashi, Kaori Mukai, Tokuhiro Matsubara, Masashi Yamamoto, Sachiko Nakajima, Koji Fukui, Masami Inada

Shiro Hayashi, Tsutomu Nishida, Hiromi Shimakoshi, Akiyoshi Shimoda, Takahiro Amano, Aya Sugimoto, Kei Takahashi, Kaori Mukai, Tokuhiro Matsubara, Masashi Yamamoto, Sachiko Nakajima, Koji Fukui, Masami Inada, Department of Gastroenterology and Hepatology, Toyonaka Municipal Hospital, Osaka 560-8565, Japan

Author contributions: All authors contributed to this manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Toyonaka Municipal Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis retrospectively used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. However, this study was announced on the website at our hospital for a certain period and subjects who did not want to be used their data in this study were guaranteed the right to refuse.

Conflict-of-interest statement: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Data sharing statement: Dataset is available from the corresponding author at hayashishiro1976@yahoo.co.jp, when data sharing was anonymized and the project was approved by the Institutional Review Board of Toyonaka Municipal Hospital.

Manuscript source: Invited manuscript

Correspondence to: Shiro Hayashi, MD, Department of Gastroenterology and Hepatology, Toyonaka Municipal Hospital, 4-14-1 Shibahara, Toyonaka, Osaka 560-8565, Japan. hayashishiro1976@yahoo.co.jp
Telephone: +81-6-68430101
Fax: +81-6-68583531

Received: June 29, 2016
Peer-review started: July 1, 2016
First decision: August 5, 2016
Revised: August 30, 2016
Accepted: September 21, 2016
Article in press: September 22, 2016
Published online: December 16, 2016

Abstract

AIM

To estimate the efficacy of 2 h post-endoscopic retrograde cholangiopancreatography (ERCP) serum amylase levels and other factors for predicting post-ERCP pancreatitis.

METHODS

This was a retrospective, single-center cohort study of consecutive patients who underwent ERCP from January 2010 to December 2013. Serum amylase levels were measured 2 h post-procedure, and patient- and procedure-related pancreatitis (PEP) risk factors were

analyzed using a logistic model.

RESULTS

A total of 1520 cases (average age 72 ± 12 years, 60% male) were initially enrolled in this study, and 1403 cases (725 patients) were ultimately analyzed after the exclusion of 117 cases. Fifty-five of these cases developed PEP. We established a 2 h serum amylase cutoff level of two times the upper limit of normal for predicting PEP. Multivariate analysis revealed that a cannulation time of more than 13 min [odds ratio (OR) 2.28, 95%CI: 1.132-4.651, P = 0.0210] and 2 h amylase levels greater than the cutoff level (OR = 24.1, 95%CI: 11.56-57.13, P < 0.0001) were significant predictive factors for PEP. Forty-seven of the 55 patients who developed PEP exhibited 2 h amylase levels greater than the cutoff level (85%), and six of the remaining eight patients who developed PEP (75%) required longer cannulation times. Only 2 of the 1403 patients (0.14%) who developed PEP did not exhibit concerning 2 h amylase levels or require longer cannulation times.

CONCLUSION

These findings indicate that the combination of 2 h post-ERCP serum amylase levels and cannulation times represents a valuable marker for identifying patients at high risk for PEP.

Key words: Serum amylase levels; Cannulation time; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Predictor

Core tip: Serum amylase levels have a high negative predictive value (NPV; 95%-100%) and have therefore previously been used to predict post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) to facilitate patient discharges. However, the positive predictive value (PPV) of serum amylase is highly variable (4%-62%); therefore, a more useful PEP predictor is needed. In this retrospective study, we identified useful predictive factors *via* multivariate analysis and the combination 2 h amylase levels and cannulation times. The 2 h amylase levels exhibited a good NPV (99%) and a poor PPV (22%) similar to those of previous reports but exhibited a sensitivity of only 86% with respect to PEP detection. However, the combined use of the above two variables increased the sensitivity to 96%; thus, this combination may enable clinicians to detect patients at high risk for PEP during the early phase of treatment.

Hayashi S, Nishida T, Shimakoshi H, Shimoda A, Amano T, Sugimoto A, Takahashi K, Mukai K, Matsubara T, Yamamoto M, Nakajima S, Fukui K, Inada M. Combination of two-hour post-endoscopic retrograde cholangiopancreatography amylase levels and cannulation times is useful for predicting post-endoscopic retrograde cholangiopancreatography pancreatitis. *World J Gastrointest Endosc* 2016; 8(20): 777-784 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i20/777.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i20.777

INTRODUCTION

Acute pancreatitis is a common post-endoscopic retrograde cholangiopancreatography (ERCP) complication and is therefore known as post-ERCP pancreatitis (PEP). PEP may result in procedure-related death and is often unpreventable. Moreover, no medications appear to be effective with respect to acute pancreatitis treatment[1,2]. Andriulli *et al*[3] conducted a systematic review of 21 selected surveys involving 16855 patients exhibiting a 3.5% incidence of PEP and observed that 0.11% of those patients died. Although many PEP prophylactic treatments have been reported[4-6], only prompt aggressive intravenous hydration is reportedly effective at reducing morbidity and mortality[7-10]. Therefore, early PEP identification is important, as it facilitates early intervention and may prevent disease progression and death.

Many studies have investigated the factors that increase the risk of PEP[7-10]. Those risk factors can generally be divided into the following two types: Patient-related factors and procedure-related factors. The patient-related risk factors for PEP reportedly include previous PEP, female gender, younger age, normal serum bilirubin levels, and the absence of chronic pancreatitis, whereas the procedure-related risk factors for PEP reportedly include cannulation attempt duration, pancreatic guidewire passage, pancreatic injection, precut sphincterotomy, biliary balloon sphincter dilatation, and failed bile duct stone clearance. No evidence exists indicating that hospital ERCP volume influences PEP occurrence[11,12]. The aforementioned risk factors synergistically increase PEP risk. Serum amylase levels less than 1.5 times the upper limit of normal (ULN) at 2-4 h post-ERCP have a very negative predictive value (NPV) for PEP. The European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend testing serum amylase or lipase levels 2-6 h after ERCP in patients presenting with pain. Patients exhibiting amylase or lipase values less than 1.5 and 4 times the ULN, respectively, may be discharged on the day of ERCP without concern regarding PEP risk[5]. However, very few tests with good positive predictive values (PPVs) for PEP exist. This study aimed to estimate the efficacy of 2 h post-ERCP serum amylase levels and other risk factors for predicting PEP.

MATERIALS AND METHODS

This study was a retrospective single-center cohort study of consecutive hospitalized patients who underwent ERCP or ERCP-related procedures at Toyonaka Municipal Hospital, certified as a teaching hospital by the Japan Gastroenterological Endoscopy Society (JGES)

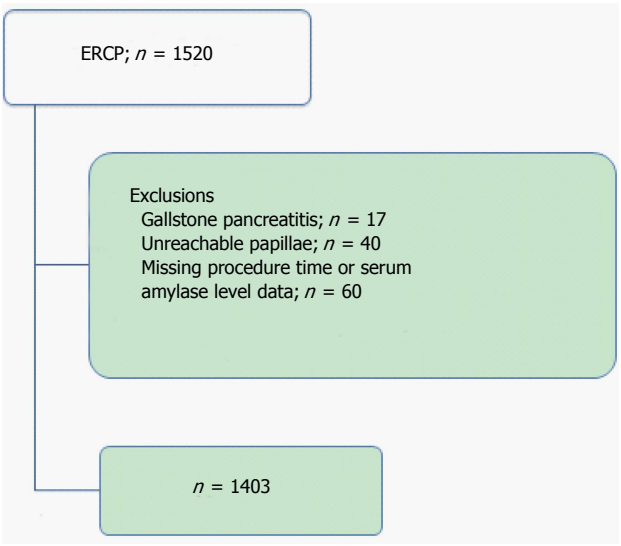

Figure 1 Study flow chart. ERCP: Endoscopic retrograde cholangiopancreatography.

(No. 1239), from January 2010 to December 2013. A total of 1520 procedures were enrolled in this study. Of these cases, 117 procedures with the following conditions were excluded: (1) gallstone pancreatitis, *n* = 17; (2) unreachable papillae, *n* = 40; and (3) missing procedure time or serum amylase level data, *n* = 60 (including cases with pancreatitis before ERCP). A total of 1403 procedures were ultimately analyzed in the present study (Figure 1).

The following demographic and clinical data were collected: Age and sex, ERCP indications, ERCP history, and 2 h post-ERCP serum amylase levels (after scope removal from the patient). The following procedural data were retrospectively collected from patient medical records: Biliary and pancreatic sphincterotomy with and without stent placement, procedure time, cannulation time, and complications. This study was approved by the Institutional Review Board of Toyonaka Municipal Hospital.

ERCP and pharmacological prophylaxis

Trainees or experts performed ERCP because our hospital is a JGES-certified teaching hospital, and trainees were assisted by experts as needed to avoid complications and ensure procedural quality when performing ERPC. We did not use a strict cannulation protocol. Cannulation was attempted *via* the wire-loaded cannulation method, which entails the use of contrast and wire-guided cannulation using a side-viewing duodenoscope (JF260 V: Olympus Optical Co. Tokyo, Japan). Procedure times were measured using a stopwatch, and images were recorded at key points and subsequently reviewed. Patients underwent routine blood tests 2 h after the procedure and the following day and received routine protease inhibitor (200 mg gabexate mesilate × 2/d) treatments until the day after the procedure. No patients received rectal diclofenac or indomethacin for PEP prophylaxis during this period.

Complications

PEP was diagnosed based on consensus criteria[13]. Briefly, PEP was defined as the combination of abdominal pain persisting for at least 24 h after the procedure and a high serum amylase level equivalent to 3 times the ULN at 24 h after the procedure. Bleeding was defined as blood loss requiring emergency endoscopic hemostasis or a transfusion or a hemoglobin level decrease greater than 2 g/dL following ERCP. Perforation was diagnosed endoscopically during ERCP or based on the observation of free air on post-ERCP plain radiography or computed tomography. Procedure-related mortality was defined as any death within 30 d of ERCP.

Analysis of PEP predictive factors

Patient- and procedure-related PEP risk factors were analyzed *via* logistic regression using the following factors: Sex, native papilla, cannulation time, total procedure time, endoscopic nasobiliary drainage, endoscopic biliary stent (EBS) placement, precut sphincterotomy, endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), pancreatic duct brush cytology, and 2 h amylase levels. Cannulation time was defined as the time from papilla identification until successful biliary cannulation, and procedure time was defined as the time from papilla identification until the scope was removed from the patient. PEP development was analyzed in relation to the following factors *via* univariate logistic regression: Patient-related factors (sex, age, and native papilla), procedure-related factors (cannulation time, total procedure time, endoscopic nasal pancreatic drainage, EBS, endoscopic metallic stent, endoscopic pancreatic stent, precut sphincterotomy, EST, EPBD, and pancreatic duct brush cytology), and 2 h post-ERCP amylase levels.

Statistical analysis

All continuous variables are expressed as the mean ± SD, except for the nonparametric variables, which are expressed as the median and range. Categorical variables are expressed as the number in each category or the frequency. Continuous variables were compared using student's *t* test, whereas categorical variables were compared using a χ^2 test or Fisher's exact test when appropriate. Receiver operating characteristic (ROC) curve analysis was used to determine the 2 h amylase level cutoff, the cannulation times, and the procedure times for predicting PEP. Univariate and multivariate logistic regression analyses were performed to identify complication-related factors. A *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using JMP software (ver. 11.1.1, SAS Institute Inc., Cary, NC, United States).

RESULTS

Patients and ERCP procedures

Patient characteristics are summarized in Table 1. A total

Table 1 Patient characteristics

Patients	*n*
Male, %	846, 60%
Age, median (range)	73 (12-99)
Native papilla	668, 47.6%
Indication	
Malignancy	522
Choledocholithiasis	771
Others	110
Cannulation time, median (range)	5 min (1-185)
Procedure time, median	37 min (3-185)
2 h amylase median (range)	97 IU/mL (10-3502)
ERCP and related procedures	
Total ERCP	1403
ENBD	362
EBS	380
EMS	42
EPS	124
Precut	35
EST	505
EPBD	20
EPLBD	38
Pancreatic duct brush	15

ERCP: Endoscopic retrograde cholangiopancreatography; EBS: Endoscopic biliary stent; EMS: Endoscopic metallic stent; EPS: Endoscopic pancreatic stent; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ENBD: Endoscopic nasobiliary drainage.

of 1403 procedures (725 patients) were analyzed in the present study. The median age of the study population was 73 years, and 846 patients were male (60%). A total of 688 patients (59%) exhibited naive papillae. ERCP was performed for choledocholithiasis (n = 771); biliary malignancies from pancreatic cancer (n = 203); biliary malignancies from common bile duct cancer (n = 161); other biliary malignancies, including gallbladder cancer, intrahepatic bile duct cancer and other metastatic cancers (n = 158); and other conditions (n = 110). The median cannulation time was 5 min (range 1-185), and the median procedure time was 37 min (range 3-185 min). Primary cannulation was successful in 97.7% of cases. The median 2 h post-ERCP amylase level was 97 IU/L.

Complications

The overall complication rate was 4.8%. PEP developed in 55 patients (4.5%, 95%CI: 3.02-5.07), and perforation and bleeding occurred in 5 (0.35%, 95%CI: 0.15-0.83) and 8 patients (0.57%, 95%CI: 0.28-1.12), respectively (Table 2). All the patients who developed PEP improved with conservative therapy. The 2 h amylase cutoff value for predicting PEP was 264 IU/L (AUC: 0.93) (Figure 2) and remained 264 IU/L when limited to naïve papilla cases (n = 688). This cutoff level was 2.2 times the ULN at our hospital; thus, we established a serum amylase cutoff level of 2 times the ULN (240 U/L) for predicting PEP. Patients with an amylase level greater than 2 times the ULN (47/238, 19.8%) exhibited a significantly higher PEP rate than patients with a lower amylase level (8/1165, 0.7%) (P < 0.0001). Two-hour post-ERCP amylase levels greater than 2 times the ULN exhibited an NPV and a PPV for PEP of 99.3% and 19.8%, respectively.

Table 2 Complications

Complications	*n*, % (95%CI)
Bleeding	8, 0.57 (0.28-1.12)
Perforation	5, 0.35 (0.15-0.83)
Pancreatitis	55, 3.9 (3.02-5.07)
(severe pancreatitis)	[3, 0.2 (0.073-0.64)]
Procedure-related death	0, 0

The cannulation and procedure time cutoff values for predicting PEP were 13 (AUC: 0.93) and 54 min (AUC: 0.72), respectively (Figure 2), and similar results (13 and 55 min) were observed in naïve cases. Patients with cannulation times ⩾ 13 min exhibited a significantly higher PEP rate (34/327, 10.4%) than patients with shorter cannulation times (21/1075, 2.0%) (P < 0.0001), and patients with procedure times ⩾ 54 min exhibited a significantly higher PEP rate (33/359, 9.2%) than patients with shorter procedure times (22/1044, 2.1%) (P < 0.0001).

Logistic regression analysis of PEP predictors

We analyzed the ability of patient- and procedure-related risk factors to predict PEP. Univariate analysis identified 10 significant predictive factors for PEP: Female sex, native papillae, cannulation time, total procedure time, EBSs, precut sphincterotomy, EST, EPBD, pancreatic duct brush cytology, and 2 h amylase levels (Table 3).

Multivariate analysis adjusted for age revealed that cannulation times longer than 13 min (OR = 2.28, 95%CI: 1.132-4.651, P = 0.0210) and 2 h amylase levels 2 times the ULN (OR = 24.1, 95%CI: 11.56-57.13, P < 0.0001) were significant predictive factors for PEP (Table 4).

DISCUSSION

The consensus PEP definition and severity grading system developed by Cotton *et al*[13] has been used for more than 20 years, but PEP remains a primary concern for endoscopists performing ERCP, as it is the most frequent post-ERCP complication, with an incidence of 3.5% in unselected patients[3,5]. Approximately 90% of cases are of mild-to-moderate in severity; however, PEP results procedure-related death in 3% of PEP cases[3]. Many prophylactic treatments have been reported, and the most recent ESGE guidelines recommend rectal NSAID administration for PEP prophylaxis[5]. However, PEP is difficult to prevent, and few medications are effective at treating PEP once it develops. Only prompt aggressive intravenous hydration is reportedly effective with respect to decreasing morbidity and mortality[2,7,8,10]. Appropriate and early fluid therapy can mitigate PEP severity[14]; therefore, PEP must be diagnosed, and

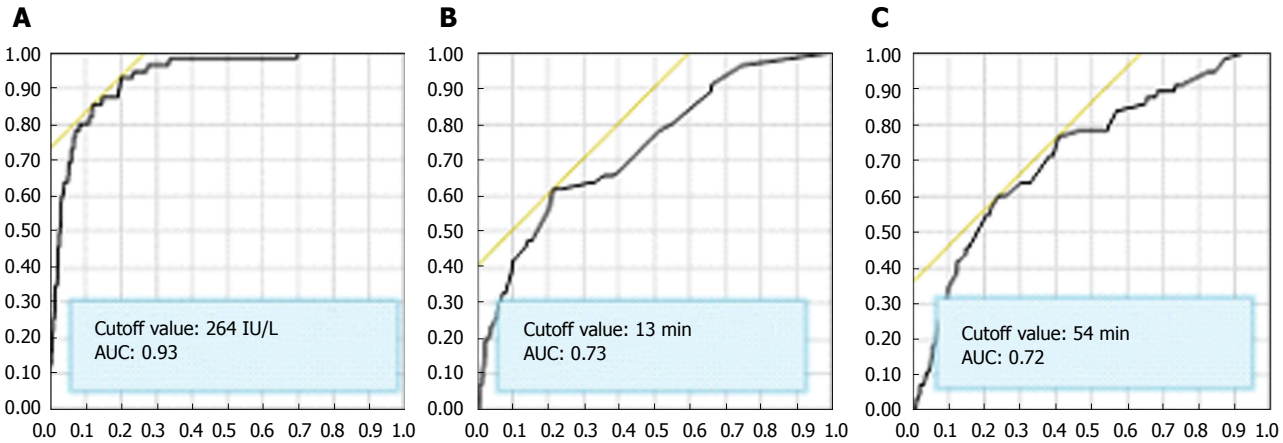

Figure 2 Receiver operating characteristic curve of 2 h amylase levels (A), cannulation times (B), and procedure times (C). AUC: Area under the curve.

Table 3 Univariate analysis of pancreatitis predictors

Predictors	Odds ratio	95%CI	*P* value
Sex (female)	0.53	0.31-0.92	0.0245
Native papilla	5.62	2.73-11.6	< 0.0001
ENBD	0.77	0.43-1.38	0.4313
EBS[1]	2.62	1.18-5.85	0.0129
EMS	0.37	0.13-1.08	0.0784
EPS	0.47	0.22-1.00	0.0528
Precut	0.23	0.08-0.61	0.0102
EST	0.49	0.28-0.84	0.0099
EPBD	0.22	0.06-0.78	0.0405
EPLBD	-	-	0.3983
Pancreatic duct brush	6.42	1.75-23.5	0.0186
2 h amylase ⩾ 2 times ULN	36.6	17.6-76.3	< 0.0001
Cannulation time ⩾ 13 min	5.82	3.33-10.2	< 0.0001
Procedure time ⩾ 54 min	4.70	2.70-8.18	< 0.0001

[1]EBS: Including with and without EST. EBS: Endoscopic biliary stent; EMS: Endoscopic metallic stent; EPS: Endoscopic pancreatic stent; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; ULN: Upper limit of normal; EPLBD: Endoscopic papillary large balloon dilation; ENBD: Endoscopic nasobiliary drainage.

Table 4 Age-adjusted multivariate analysis of pancreatitis predictors

Predictors	Odds ratio	95%CI	*P* value
Sex (female)	1.46	0.77-2.75	0.2431
Native papilla	1.78	0.75-4.48	0.1908
Endoscopic biliary stent	0.61	0.23-1.45	0.2810
Precut	1.71	0.43-6.00	0.4288
EST	1.18	0.60-2.35	0.6278
EPBD	1.94	0.34-8.91	0.4296
Pancreatic duct brush	3.15	0.54-15.5	0.1870
2 h amylase ⩾ 2 times ULN	25.4	12.2-59.9	< 0.0001
Cannulation time ⩾ 13 min	2.63	1.34-5.23	0.0051
Procedure time ⩾ 54 min	1.23	0.389-3.67	0.7183

EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; ULN: Upper limit of normal.

treatment must be initiated during the early phase of the disease to prevent severe acute pancreatitis development and progression.

Numerous studies have identified factors that increase PEP risk. Among these factors, the measured amylase levels after ERCP have been evaluated for the prediction of PEP[15-17]. Many reports have shown the effectiveness of the 2-8 h amylase measurement. Generally, the NPVs are 95%-100%, the PPVs are 4%-62%, the sensitivity values are 23%-100% and the specificities are 63%-98%, although some differences in the definition of PEP and amylase cutoff levels exist across studies (Table 5).

Consequently, the ESGE guidelines indicate that 2-4 h amylase levels have very high NPVs but do not demonstrate sufficient PPVs (evidence level 2+)[4] and therefore recommend measuring serum amylase or lipase levels 2-6 h after ERCP in patients presenting with pain who are to be discharged on the day of their ERCP procedure (recommendation grade B). In this study, 2 h amylase levels exhibited a good NPV of 99% and a poor PPV of 20%, findings consistent with the above results, as well as a good sensitivity (84%) for the diagnosis of PEP. Previous studies have reported values of 70%-90%, particularly studies using the Consensus Criteria PEP definition. A PPV of 20% is not sufficient to identify PEP but may be suitable for identifying patients at high risk for developing PEP. Moreover, 2 h amylase levels may enable clinicians to identify high-risk patients requiring early acute PEP treatments, such as infusion therapy.

Previous studies have demonstrated that difficult cannulation is a risk factor for PEP[12,18,19]. Tian *et al*[20] reported that cannulation time is a more accurate measure of cannulation difficulty in ERCP than other parameters. Moreover, Halttunen *et al*[21] reported that cannulation attempts lasting > 5 min may increase the incidence of PEP and that procedures lasting less than 5 min had a lower PEP rate (2.6%) than longer procedures (11.8%). The most recent ESGE guidelines state that PEP risk factor analyses have demonstrated that cannulation attempts lasting > 10 min had an odds ratio (OR) of 1.76 (1.13-2.74) with respect to PEP development and that the pooled incidences of PEP in patients with and without this risk factor were

Table 5 Previous reports of hourly variations in post-endoscopic retrograde cholangiopancreatography amylase levels

Ref.	Year	*n*	Time[1] (h)	Amylase cut off	Sensitivity	Specificity	PPV	NPV	Definition of PEP
LaFerla *et al*[23]	1986	20	2	800	n.d.	n.d.	n.d.	Unlikely	Amy > 1200
Gottlieb *et al*[24]	1996	231	2	276	82	76	15	98	Consensus criteria
Testoni *et al*[25]	1999	409	2	5 ×	23.1	98.2	46.2	94.9	Amy > 5 × ULN
			4	5 ×	53.8	95	42.4	96.8	
			8	5 ×	76.9	96.9	62.5	98.4	
Testoni *et al*[26]	2001	1185	6-8	3 ×	n.d.	n.d.	n.d.	100	Pancreatic type pain
Thomas *et al*[27]	2001	263	4	2 ×	90	92.9	24.3	99.6	Consensus criteria
			4	3 ×	70	95.3	36.8	98.8	
Kapetanos *et al*[28]	2007	97	2	3 ×	72	79	32	95	Consensus criteria
			6	3 ×	82	75	30	97	
Ito *et al*[16]	2007	1291	3	3 ×	77	n.d.	29	n.d.	Amy > 1 × ULN,
			6	3 ×	85	n.d.	24	n.d.	with pain at 24 h
Nishino *et al*[29]	2009	1631	4	3 ×	89.8	72.9	12.7	99.4	Consensus criteria
			4	4 ×	84.7	80.4	16	99.2	
Artifon *et al*[30]	2010	300	4	1.5 ×	77	63	26	94	Consensus criteria
Sutton *et al*[15]	2011	959	4	2.5 ×[2]	80	80.4	11.1	99.2	Consensus criteria
			4	2.5 ×[3]	100	91.8	4.3	100	(mod/severe only)
Our study	2015	1403	2	2 ×	85.5	85.8	19.8	99.3	Consensus criteria
			2	2 ×[4]	96.4	68.8	11.2	99.8	

[1]Hourly variations in serum amylase measurements after the procedure; [2]With pancreatogram; [3]Without pancreatogram; [4]Longer cannulation time. Consensus criteria: Amy > 3 × ULN with pain at 24 h. n.d.: Not described; ULN: Upper limit of normal.

10.8% and 3.8%, respectively. ROC curve analysis was performed in the present study and demonstrated that the cannulation and the procedure time cutoff values for predicting PEP were 13 (AUC: 0.93) and 54 min (AUC: 0.72), respectively. The incidences of PEP in patients with and without cannulation attempts lasting > 13 min were 10.4% and 2.0%, respectively, and the incidences of PEP in patients with and without cannulation times lasting > 10 min were 9.6% and 2.1%, respectively (data not shown), findings similar to those reported by Halttunen *et al*[21]. Multivariate analysis indicated that cannulation time is another significant PEP risk factor; therefore, we propose that cannulation time is a reliable marker for predicting PEP, in addition to 2 h post-ERCP amylase levels.

Based on above findings, we used the following markers to predict PEP development: 2 h post-ERCP amylase levels greater than 2 times the ULN and cannulation times greater than 13 min. Figure 3 includes a flowchart depicting these markers. A total of 238 patients (17%) in the present study exhibited 2 h post-ERCP amylase levels greater than 2 times the ULN, 47 of whom (20%) developed PEP, whereas a total of 1165 patients (83%) exhibited 2 h post-ERCP amylase levels less than 2 times the ULN. Eight patients (0.7%) in the latter group developed PEP; however, six of these patients required more than 13 min for cannulation. Thus, only 2 of the 1403 patients (0.14%) who developed PEP did not exhibit concerning 2 h post-ERCP amylase levels or require longer cannulation times. This study demonstrated that cannulation time inclusion may rescue 75% (6/8) of patients with non-concerning 2 h amylase levels and that the combination of 2 h post-ERCP levels and cannulation times exhibited a 96% sensitivity and an 11.2% PPV for the identification of PEP. The latter percentage is not sufficient to identify PEP but may be useful for identifying high-risk patients in whom early treatments, such as aggressive infusions, are necessary.

The present study had several limitations because of its retrospective design. Routine protease inhibitor administration without rectal diclofenac or indomethacin administration may have influenced the frequency of PEP. However, nonsteroidal anti-inflammatory drugs (NSAIDs) were reportedly used infrequently for PEP prevention in clinical practice in Japan until the publication of the 2015 Japanese Guideline[22], which recommends prophylactic NSAID administration to prevent PEP. In addition, we did not strictly evaluate certain PEP risk factors, such as the number of cannulation attempts, pancreatic guidewire, and pancreatic injection, because of the retrospective design of this study. The number of cannulation attempts represents the degree of cannulation difficulty; the most recent ESGE guidelines recommend keeping this number as low as possible[21]. The degree of cannulation difficulty during ERCP is positively correlated with PEP[18]. The degree of cannulation difficulty during ERCP procedures may differ when different methods are used (total cannulation time *vs* number of attempts); thus, grading scales used to evaluate the difficulty of performing ERCP *via* different methods should not be used interchangeably. Tian *et al*[20] reported that cannulation time is a more objective and accurate means of grading cannulation difficulty than the number of papilla cannulation attempts. The ESGE guidelines categorize pancreatic guidewire use and pancreatic injection as definite PEP risk factors. However, it is sometimes difficult to establish if either

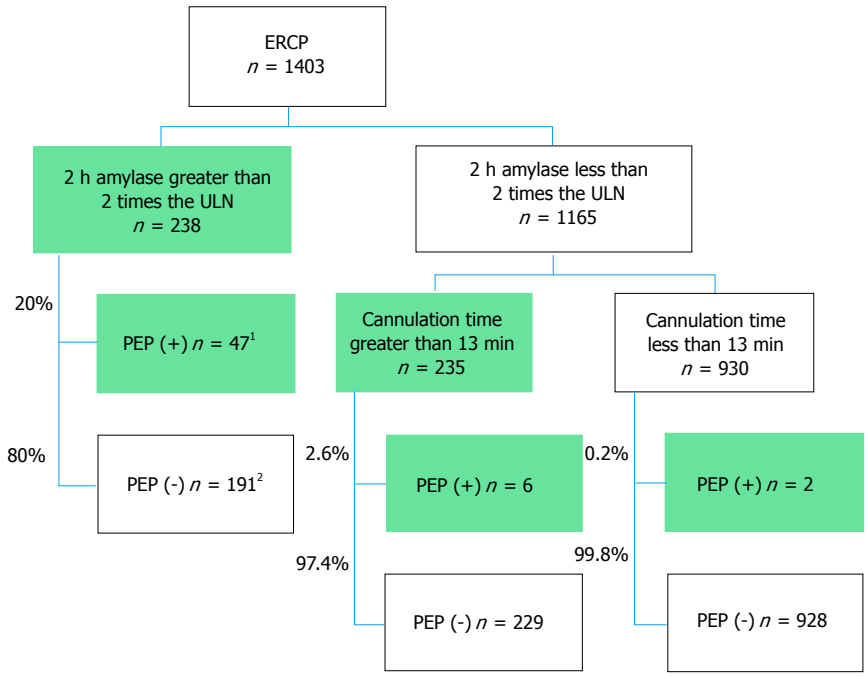

Figure 3 Flow chart using two-hour amylase levels and cannulation times for predicting pancreatitis. [1]Includes cannulation times greater than 13 min, *n* = 28; [2]Includes cannulation times greater than 13 min, *n* = 64. ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post ERCP Pancreatitis; ULN: Upper limit of normal.

procedure has been performed, particularly cannulation, which is performed *via* contrast and wire-guided methods at our institution. In addition, the ESGE guidelines recommend that prophylactic pancreatic stent placement should be strongly considered in patients at high risk for PEP. Prophylactic pancreatic stents were placed in 124 patients in the present study, 9 of whom (7.3%) developed PEP. However, multivariate analysis demonstrated that stent placement did not significantly prevent PEP, perhaps because pancreatic stents tend to be used in patients at high risk for PEP, in accordance with the above guidelines. Therefore, we must target patients at high risk for PEP to evaluate the efficacy of prophylactic pancreatic stent placement. Because of the above limitations, in the present study, we evaluated cannulation time and procedure time as surrogate markers of procedure-related risk factors in the present study. Despite these limitations, we believe that this study has effectively demonstrated that Two-hour post-ERCP amylase levels and cannulation times are useful PEP predictors.

In conclusion, 2 h post-ERCP serum amylase levels and cannulation times may be useful markers for predicting PEP development. We plan to conduct prophylactic interventions to reduce the incidence of PEP in high-risk patients exhibiting 2 h post-ERCP amylase levels greater than 2 times the ULN or requiring cannulation times greater than 13 min.

COMMENTS

Background

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) may result in procedure-related death and is often unpreventable. So it is important to predict and treat in early phase.

Research frontiers

Post-ERCP serum amylase levels are known as a predictor of PEP, which have good negative predictive value (NPV) and poor positive predictive value (PPV). The aim of this study was to estimate the efficacy of post-ERCP 2 h serum amylase levels and other factors for predicting PEP.

Innovations and breakthroughs

The 2-h amylase levels exhibited a good NPV (99%) and a poor PPV (22%) similar to previous reports but exhibited a sensitivity of 86%, and the combined use with cannulation time increased the sensitivity to 96%.

Applications

Combination of Two-hour post-ERCP amylase levels and cannulation times may be simple useful markers for predicting PEP development in early phase.

Terminology

PEP is one of the major adverse events of ERCP. It is most frequent and sometimes results in death, so that it has been the most concern still now.

Peer-review

This retrospective study was performed to identify the risk factors for PEP, and the authors revealed that two factors of serum amylase levels 2 h after ERCP and cannulation time were significant independent factor. This is well designed study which revealed interesting results.

REFERENCES

1 **Steinberg W**, Tenner S. Acute pancreatitis. *N Engl J Med* 1994; **330**: 1198-1210 [PMID: 7811319 DOI: 10.1056/NEJM199404283301706]
2 **Banks PA**, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006; **101**: 2379-2400 [PMID: 17032204 DOI: 10.1111/j.1572-0241.2006.00856.x]
3 **Andriulli A**, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788 [PMID: 17509029 DOI: 10.1111/

j.1572-0241.2007.01279.x]
4 **Dumonceau JM**, Andriulli A, Deviere J, Mariani A, Rigaux J, Baron TH, Testoni PA. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. *Endoscopy* 2010; **42**: 503-515 [PMID: 20506068 DOI: 10.1055/s-0029-1244208]
5 **Dumonceau JM**, Andriulli A, Elmunzer BJ, Mariani A, Meister T, Deviere J, Marek T, Baron TH, Hassan C, Testoni PA, Kapral C. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. *Endoscopy* 2014; **46**: 799-815 [PMID: 25148137 DOI: 10.1055/s-0034-1377875]
6 **Wong LL**, Tsai HH. Prevention of post-ERCP pancreatitis. *World J Gastrointest Pathophysiol* 2014; **5**: 1-10 [PMID: 24891970 DOI: 10.4291/wjgp.v5.i1.1]
7 **Sagi SV**, Schmidt S, Fogel E, Lehman GA, McHenry L, Sherman S, Watkins J, Coté GA. Association of greater intravenous volume infusion with shorter hospitalization for patients with post-ERCP pancreatitis. *J Gastroenterol Hepatol* 2014; **29**: 1316-1320 [PMID: 24372871 DOI: 10.1111/jgh.12511]
8 **Gardner TB**, Vege SS, Chari ST, Petersen BT, Topazian MD, Clain JE, Pearson RK, Levy MJ, Sarr MG. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. *Pancreatology* 2009; **9**: 770-776 [PMID: 20110744 DOI: 10.1159/000210022]
9 **Tenner S**, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; **108**: 1400-1415; 1416 [PMID: 23896955 DOI: 10.1038/ajg.2013.218]
10 **Warndorf MG**, Kurtzman JT, Bartel MJ, Cox M, Mackenzie T, Robinson S, Burchard PR, Gordon SR, Gardner TB. Early fluid resuscitation reduces morbidity among patients with acute pancreatitis. *Clin Gastroenterol Hepatol* 2011; **9**: 705-709 [PMID: 21554987 DOI: 10.1016/j.cgh.2011.03.032]
11 **Loperfido S**, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, De Bernardin M, Ederle A, Fina P, Fratton A. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest Endosc* 1998; **48**: 1-10 [PMID: 9684657 DOI: 10.1016/S0016-5107(98)70121-X]
12 **Williams EJ**, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson ML, Williamson PR, Lombard M. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. *Endoscopy* 2007; **39**: 793-801 [PMID: 17703388 DOI: 10.1055/s-2007-966723]
13 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]
14 **DiMagno MJ**, Wamsteker EJ, Maratt J, Rivera MA, Spaete JP, Ballard DD, Elmunzer J, Saini SD. Do larger periprocedural fluid volumes reduce the severity of post-endoscopic retrograde cholangiopancreatography pancreatitis? *Pancreas* 2014; **43**: 642-647 [PMID: 24713841 DOI: 10.1097/MPA.0000000000000101]
15 **Sutton VR**, Hong MK, Thomas PR. Using the 4-hour Post-ERCP amylase level to predict post-ERCP pancreatitis. *JOP* 2011; **12**: 372-376 [PMID: 21737899 DOI: 10.6092/1590-8577/3223]
16 **Ito K**, Fujita N, Noda Y, Kobayashi G, Horaguchi J, Takasawa O, Obana T. Relationship between post-ERCP pancreatitis and the change of serum amylase level after the procedure. *World J Gastroenterol* 2007; **13**: 3855-3860 [PMID: 17657841 DOI: 10.3748/wjg.v13.i28.3855]
17 **Sultan S**, Baillie J. What are the predictors of post-ERCP pancreatitis, and how useful are they? *JOP* 2002; **3**: 188-194 [PMID: 12432185]
18 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434 [PMID: 11577302 DOI: 10.1067/mge.2001.117550]
19 **Wang P**, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, Huang Q, Zhang X, He LP, Sun WS, Zhao Q, Shi RH, Tian ZB, Li YQ, Li W, Zhi FC. Risk factors for ERCP-related complications: a prospective multicenter study. *Am J Gastroenterol* 2009; **104**: 31-40 [PMID: 19098846 DOI: 10.1038/ajg.2008.5]
20 **Tian C**, Gamboa A, Chaudhury B, Willingham FF, Keilin S, Cai Q. Cannulation time is a more accurate measure of cannulation difficulty in endoscopic retrograde cholangiopancreatography than the number of attempts. *Gastroenterol Rep* (Oxf) 2013; **1**: 193-197 [PMID: 24759965 DOI: 10.1093/gastro/got024]
21 **Halttunen J**, Meisner S, Aabakken L, Arnelo U, Grönroos J, Hauge T, Kleveland PM, Nordblad Schmidt P, Saarela A, Swahn F, Toth E, Mustonen H, Löhr JM. Difficult cannulation as defined by a prospective study of the Scandinavian Association for Digestive Endoscopy (SADE) in 907 ERCPs. *Scand J Gastroenterol* 2014; **49**: 752-758 [PMID: 24628493 DOI: 10.3109/00365521.2014.894120]
22 **Yokoe M**, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, Itoi T, Sata N, Gabata T, Igarashi H, Kataoka K, Hirota M, Kadoya M, Kitamura N, Kimura Y, Kiriyama S, Shirai K, Hattori T, Takeda K, Takeyama Y, Hirota M, Sekimoto M, Shikata S, Arata S, Hirata K. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. *J Hepatobiliary Pancreat Sci* 2015; **22**: 405-432 [PMID: 25973947 DOI: 10.1002/jhbp.259]
23 **LaFerla G**, Gordon S, Archibald M, Murray WR. Hyperamylasaemia and acute pancreatitis following endoscopic retrograde cholangiopancreatography. *Pancreas* 1986; **1**: 160-163 [PMID: 2437564]
24 **Gottlieb K**, Sherman S, Pezzi J, Esber E, Lehman GA. Early recognition of post-ERCP pancreatitis by clinical assessment and serum pancreatic enzymes. *Am J Gastroenterol* 1996; **91**: 1553-1557 [PMID: 8759660]
25 **Testoni PA**, Caporuscio S, Bagnolo F, Lella F. Twenty-four-hour serum amylase predicting pancreatic reaction after endoscopic sphincterotomy. *Endoscopy* 1999; **31**: 131-136 [PMID: 10223361 DOI: 10.1055/s-1999-13660]
26 **Testoni PA**, Bagnolo F. Pain at 24 hours associated with amylase levels greater than 5 times the upper normal limit as the most reliable indicator of post-ERCP pancreatitis. *Gastrointest Endosc* 2001; **53**: 33-39 [PMID: 11154486 DOI: 10.1067/mge.2001.111390]
27 **Thomas PR**, Sengupta S. Prediction of pancreatitis following endoscopic retrograde cholangiopancreatography by the 4-h post procedure amylase level. *J Gastroenterol Hepatol* 2001; **16**: 923-926 [PMID: 11555108 DOI: 10.1046/j.1440-1746.2001.02547.x]
28 **Kapetanos D**, Kokozidis G, Kinigopoulou P, Xiarchos P, Antonopoulos Z, Progia E, Kitis G. The value of serum amylase and elastase measurements in the prediction of post-ERCP acute pancreatitis. *Hepatogastroenterology* 2007; **54**: 556-560 [PMID: 17523321]
29 **Nishino T**, Toki F, Oyama H, Shiratori K. More accurate prediction of post-ERCP pancreatitis by 4-h serum lipase levels than amylase levels. *Digest Endosc* 2008; **20**: 169-177 [DOI: 10.1111/j.1443-1661.2008.00802.x]
30 **Artifon EL**, Chu A, Freeman M, Sakai P, Usmani A, Kumar A. A comparison of the consensus and clinical definitions of pancreatitis with a proposal to redefine post-endoscopic retrograde cholangiopancreatography pancreatitis. *Pancreas* 2010; **39**: 530-535 [PMID: 20093992 DOI: 10.1097/MPA.0b013e3181c306c0]

P- Reviewer: Altonbary AY, Ikeuchi N, Isaji S, Kitamura K, Kikuyama M, Paduani GF **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com