

# Early prediction of post-ERCP pancreatitis by post-procedure amylase and lipase levels: A systematic review and meta-analysis



## Authors

Hemant Goyal<sup>\*1,2</sup>, Sonali Sachdeva<sup>\*3</sup>, Syed Ali Amir Sherazi<sup>\*4</sup>, Shweta Gupta<sup>4</sup>, Abhilash Periseti<sup>5</sup>, Aman Ali<sup>6</sup>, Saurabh Chandan<sup>7</sup>, Benjamin Tharian<sup>8</sup>, Neil Sharma<sup>5</sup>, Nirav Thosani<sup>9</sup>

## Institutions

- 1 University of Texas at Houston, McGovern School of Medicine, Texas, United States
- 2 Mercer University School of Medicine, Internal Medicine, Macon, Georgia, United States
- 3 Boston University Medical Center, Medicine, Boston, Massachusetts, United States
- 4 John H. Stroger Hospital of Cook County, Medicine, Chicago, Illinois, United States
- 5 Parkview Health System, Advanced Interventional Oncology and Surgical Endoscopy, Fort Wayne, Indiana, United States
- 6 Wilkes-Barre General Hospital, Endoscopy, Wilkes-Barre, Pennsylvania, United States
- 7 CHI Health Creighton University Medical Center, Gastroenterology & Hepatology, Omaha, Nebraska, United States
- 8 University of Arkansas for Medical Sciences, Department of Medicine, Division of Gastroenterology & Hepatology, Little Rock, Arkansas, United States
- 9 University of Texas McGovern Medical School, Gastroenterology, Hepatology and Nutrition, Houston, Texas, United States

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## Bibliography

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Georg Thieme Verlag KG, Rüdigerstraße 14,  
70469 Stuttgart, Germany

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## Corresponding author

Hemant Goyal, University of Texas at Houston, McGovern School of Medicine, 6431 Fannin, MSB 4.234, Houston, Tx 77030  
Fax: 713.500.6699  
[doc.hemant@yahoo.com](mailto:doc.hemant@yahoo.com)

## ABSTRACT

**Background and study aims** Post-ERCP pancreatitis (PEP) is the most common complication attributed to the procedure, its incidence being approximately 9.7%. Numerous studies have evaluated the predictive efficacy of post-procedure serum amylase and lipase levels but with varied procedure-to-test time intervals and cut-off values. The aim of this meta-analysis was to present pooled data from available studies to compare the predictive accuracies of serum amylase and lipase for PEP.

**Patients and methods** A total of 18 studies were identified after a comprehensive search of various databases until June 2021 that reported the use of pancreatic enzymes for PEP.

**Results** The sample size consisted of 11,790 ERCPs, of which PEP occurred in 764 (6.48%). Subgroups for serum lipase and amylase were created based on the cut-off used for diagnosing PEP, and meta-analysis was done for each subgroup. Results showed that serum lipase more than three to four times the upper limit of normal (ULN) performed within 2 to 4 hours of ERCP had the highest pooled sensitivity (92%) for PEP. Amylase level more than five to six times the ULN was the most specific serum marker with a pooled specificity of 93%.

**Conclusions** Our analysis indicates that a lipase level less than three times the ULN within 2 to 4 hours of ERCP can be used as a good predictor to rule out PEP when used as an adjunct to patient clinical presentation. Multicenter randomized controlled trials using lipase and amylase are warranted to further evaluate their PEP predictive accuracy, especially in high-risk patients.

\* These authors contributed equally.

## Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) use has increased in the United States in recent years, with over 150,000 inpatient ERCP procedures being performed each year [1]. Complications related to the procedure have also increased with time and include post-ERCP pancreatitis (PEP), post-procedural bleeding, infection of the biliary tree (cholangitis, cholecystitis), sepsis, and intestinal perforation [1,2]. PEP is the most common and serious adverse event attributed to this procedure, resulting in an annual estimated cost of over \$200 million in the United States [3]. A meta-analysis of 108 randomized controlled trials (RCTs) comprising 13,296 patients reported a 9.7% overall global incidence of PEP and 13% in North America [1–4]. The same meta-analysis also showed an increased PEP incidence in high-risk patients (14.7%). The majority of PEP cases were mild, with a mortality rate of 0.7% [4]. A minority of patients (0.5%) with PEP develop severe diseases, requiring additional resources and extended hospital stay [4]. Given the burden on patients and clinicians, early recognition and aggressive PEP management are paramount.

Moreover, most ERCP procedures are now being performed in the outpatient setting, a significant change in the last decade [5]. These patients are sometimes kept in the hospital under observation (for less than 24 hours) to monitor for development of ERCP-related complications, especially PEP [5]. As the number of outpatient ERCP procedures continues to grow, the need for guidelines related to safe patient discharge and hospitalization becomes magnified. Early measurements of lipase/amylase have been proposed to be convenient indicators of PEP; they may be of high diagnostic value and can guide management decisions if used timely and appropriately, especially in patients with atypical symptoms. Studies have described use of amylase and lipase levels within 2 to 6 hours of ERCP to predict PEP [6]. However, reliable evidence about the standard time to the test and acceptable elevation levels is lacking [6]. In addition, it is well known that there can be a transient increase in pancreatic enzyme levels in up to 75% of patients after ERCP that may be clinically insignificant, especially in asymptomatic patients [7]. This systematic review and meta-analysis aimed to determine the threshold value of 2 to 4 hours post-procedure serum amylase and lipase levels in predicting PEP. The objective was to analyze the appropriate threshold level of pancreatic enzyme elevation to predict/exclude PEP.

## Methods

### Search strategy and study selection

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2009 guidelines [8]. We searched PUBMED/MEDLINE, EMBASE, and Google Scholar databases (inception to June 4, 2021) using keywords and/or Medical Subject Headings (MeSH) for ERCP, pancreatic enzymes, lipase, and amylase. Duplicate studies identified in all databases were deleted manually. In addition, two authors in-

dependently reviewed the references and selected studies for full-text screening.

### Inclusion and exclusion criteria

Studies were included if they met the following preset inclusion criteria: 1) articles with patients enrolled for diagnostic and/or therapeutic ERCP; 2) pancreatic enzyme measurement within 2 to 6 hours of the procedure; 3) studies with data on the sensitivity and specificity of post-procedure early amylase/lipase in predicting PEP; 4) studies containing enough information required to build a 2×2 contingency table; and 5) published articles in English (abstracts, preprints excluded). Small case series of under 50 patients, review articles, animal models, and any articles where amylase and/or lipase were not studied as the primary objective to diagnose PEP were excluded.

### Data extraction and quality assessment

We extracted data regarding study design, patient characteristics, procedure details, reported outcomes, and limitations (► **Table 1**). Two authors (SG and SAAS) independently screened all records identified through database research. A third author (HG) addressed differences in opinion that arose from the same. Each eligible study was thoroughly reviewed to extract the following information: study author, time period, country/region, sample size, enzymes and hours after the ERCP procedure they were measured, the definition used for diagnosing PEP, preventive measures used before the procedure, if any, and data for the 2×2 contingency table for each studied test (true positives, false positives, false negatives, and true negatives). Six subgroups were made according to the data available for various enzyme thresholds for both lipase (Groups 1 and 2) and amylase (Groups 3 to 6) (► **Table 2**). The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used to assess the quality of diagnostic accuracy of studies included in this meta-analysis [9].

### Data analysis

Review Manager 5.4 software (Cochrane Collaboration, Oxford, England) was used to obtain figures of methodological quality. Meta-Disc 1.4 software was used to construct forest plots for pooled sensitivity, specificity, Positive and Negative Likelihood Ratio, Diagnostic Odds Ratio, and Summary receiver operating characteristics (SROC) curves for each subgroup [10]. Random-effects model was employed for pooled analysis because of the presence of significant heterogeneity among the studies. Heterogeneity was assessed using the Cochran Q test and I<sup>2</sup> statistics. Sources of heterogeneity for each subgroup were detected using meta-regression analysis; sensitivity analysis was also performed by omitting each included study one by one. Deeks' funnel plots were used for the detection of any publication bias.

## Results

### Literature search

An initial electronic search of all databases yielded a total of 2420 studies. After the removal of duplicates, 241 studies were screened. Of these, 179 were excluded, and full texts of

► **Table 1** Population and procedure characteristics of the studies included in the meta-analysis.

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Artifon [11] 2010	Retrospective single institution (USA)	300 PEP 25 (8.3%) (Cotton Criteria)	<b>Age (all)</b> Mean age 53.4 <b>Gender (all)</b> Men 67% Women 33% <b>Criteria used for PEP diagnosis</b> Cotton 199129 Banks 200631	<b>Setting</b> Outpatient 54.5% (278) Inpatient 45.5% (232) <b>Diagnosis</b> Cholelithiasis 58% Malignancy 28% SOD 7% Others 7% <b>Sphincterotomy rate</b> 204 (68%) <b>Biliary stenting</b> Not mentioned <b>PD cannulation</b> 48 (16%) <b>Pre-ERCP preparation</b> Not mentioned <b>Exclusion criteria</b> Recent acute pancreatitis, prior sphincterotomy, prior Billroth II surgery	<b>Amylase</b> At 4 hr after ERCP, serum hyperamylasemia over 1.5-fold had sensitivity, specificity, PPV and NPV of 77%, 63%, 26% and 94%, respectively At 4 hr after ERCP, serum amylase over 300 U/L (3-fold) had sensitivity, specificity, PPV and NPV of 37%, 95%, 55% and 90% respectively <b>Lipase</b> At 4 hr after ERCP, serum lipase over 180 U/L (3-fold) had sensitivity, specificity, PPV and NPV of 39%, 90%, 41% and 90% respectively (with PEP 14.3%) <b>Author conclusion(s)</b> Abdominal pain with 3-fold or higher hyperamylasemia are insufficient to diagnose PEP but 1.5-fold hyperamylasemia at 4 hrs after ERCP had high NPV for PEP	1. Single institution 2. Retrospective design 3. Normal amylase and lipase values not given, we assumed given values were 3-fold elevations.
Gottlieb [12] 1996	Prospective single institution (USA)	231 PEP 23 (10%)	<b>Age (all)</b> Not mentioned <b>Gender (all)</b> Not mentioned <b>Criteria used for PEP diagnosis</b> Cotton 199129	<b>Setting</b> Outpatient 100% <b>Diagnosis</b> Not mentioned <b>Sphincterotomy rate</b> 123 (53%) <b>Biliary stenting</b> Not mentioned <b>Pancreatogram</b> 187 (81%) <b>Pre-ERCP preparation</b> Not mentioned <b>Exclusion criteria</b> Not mentioned	<b>Amylase</b> A 2-hr amylase > 2.5-fold (276 U/L) had sensitivity, specificity, PPV and NPV of 82%, 76%, 28% and 97% respectively <b>Lipase</b> A 2-hr lipase > 4-fold (1000 U/L) had sensitivity, specificity, PPV and NPV of 92%, 55%, 19% and 98% respectively <b>Author conclusion(s)</b> A 2-hr amylase under 2.5-fold and 2-hr lipase under 4-fold have very high NPVs for PEP, such patients can be sent home post procedure	1. Single institution 2. Old criteria used for PEP diagnosis (older study) 3. Patient level details not provided 4. Indications for ERCP not provided 5. All elective outpatient procedures

► Table 1 (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Hayashi [13] 2016	Retrospective single institution trainees or experts performed ERCP (Japan)	1403 PEP 55 (4.5%)	<b>Age (all)</b> Median 73 <b>Gender (all)</b> Men 60% Women 40% <b>Criteria used for PEP Diagnosis</b> Cotton 199/129	<b>Setting</b> Outpatient 100% <b>Diagnosis</b> Choledocholithiasis 55% Malignancy 37% Others 8% <b>Sphincterotomy rate</b> 505 (36%) <b>Biliary Stenting</b> 422 (30%) <b>Pancreatic stent</b> 124 (9%) <b>Pre-ERCP preparation</b> Protease inhibitor used (frequency not defined) Rectal NSAIDs not used <b>Exclusion criteria</b> Gallstone pancreatitis, unreachable papilla, missing procedure time or serum amylase data	<b>Amylase</b> A 2-hr amylase 2 × ULN had sensitivity, PPV and NPV of 84%, 20% and 99% respectively with an OR 36.6 for diagnosis of PEP ( $P < 0.05$ ) Cannulation times 13 minutes or longer associated with higher PEP rates ( $P < 0.05$ ) Procedure times 54 minutes or longer associated with higher PEP rates ( $P < 0.05$ ) Multivariate analysis adjusted for age revealed amylase > 2 × ULN and higher cannulation time were significant predictive factors for PEP ( $P < 0.05$ ) with a combined sensitivity of 96% <b>Lipase</b> Not studied <b>Author conclusion(s)</b> 2-hr post-ERCP amylase levels and cannulation times may be useful markers for predicting development of PEP	1. Single institution 2. Retrospective design 3. All elective outpatient procedures 4. Old criteria used for PEP diagnosis 5. Lipase not studied 6. Routine use of protease inhibitor may have influenced the frequency of PEP
Inatomi [14] 2020	Prospective multicenter observational study (Japan)	1789 PEP 214 (12%)	<b>Age</b> (n = 350) Median 73 <b>Gender</b> (n = 350) Men 48% Women 52% <b>Criteria used for PEP Diagnosis</b> CT scan findings only	<b>Setting</b> All ERCPs Details not provided <b>Diagnosis</b> Choledocholithiasis 42.5% Malignancy 30.5% Others 27% <b>Sphincterotomy rate</b> Not mentioned <b>Biliary stenting</b> Not mentioned <b>PD cannulation</b> Not mentioned <b>Pre-ERCP preparation</b> Not mentioned <b>Exclusion criteria</b> Pancreatitis before ERCP, unreachable papilla, known high amylase, ascites retention or massive tumor invasion, Biliary tract reconstruction	<b>Amylase</b> 2-hr serum amylase 2.75 × ULN had sensitivity, specificity, PLR and NLR of 19%, 91%, 2.11 and 0.89 respectively for diagnosis of CT-defined PEP <b>Lipase</b> Not studied <b>Author conclusion(s)</b> A serum amylase 2.75 × ULN after ERCP highly correlated with development of CT-defined PEP	1. CT findings used for diagnosis of PEP. No consensus criteria used 2. Lipase not studied 3. Procedure details that may affect PEP development not given

▶ Table 1 (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Ito [15] 2007	Prospective single institution experienced operators (> 1000 cases) performed or supervised ERCP (Japan)	1291 PEP 47 (3.6%)	<b>Age</b> Mean age 64 <b>Gender</b> Men 57 % Women 53 % <b>Criteria used for PEP Diagnosis</b> Abdominal pain and abnormal serum amylase level at 24-hour post ERCP Cotton criteria for severity assessment	<b>Setting</b> All ERCPs Details not provided <b>Diagnosis</b> Gallbladder stone 38 % Cholelithiasis 24 % Malignancy 10 % <b>Sphincterotomy rate</b> 270 (20 %) <b>Biliary stenting</b> 60 (4.6 %) <b>PD cannulation</b> Not mentioned <b>Pre-ERCP preparation</b> Protease inhibitor used <b>Exclusion criteria</b> previous sphincterotomy or papillary balloon dilatation, known hyperamylasemia	<b>Amylase</b> 3-hr amylase after ERCP of 2 × ULN, 3 × ULN, 5 × ULN and 10 times ULN had sensitivities of 83 %, 77 %, 55 % and 26 % with corresponding PPV of 21 %, 29 %, 34 %, 39 % A rising trend in amylase 2 × ULN from 3 to 6 hr had 26 % rate of PEP compared to 9 % in declining trend from 3- to 6-hr amylase ( $P < 0.001$ ) <b>Lipase</b> Not studied <b>Author conclusion(s)</b> PEP was associated with increase in amylase > 2 × ULN at 3 hr with elevation at 6 hr. PEP was less likely if the 6-hr amylase fell compared to 3-hr	1. Single institution study 2. The consensus definition of PEP not applied 3. Routine use of protease inhibitor may have influenced the frequency of PEP
Kapetanios [16] 2007	Prospective single institution single operator (Greece)	97 PEP 11 (11 %) 54 octreotide group 43 control group	<b>Age</b> Mean age 64 (octreotide group) Mean age 60 (control group) <b>Gender (all)</b> Men 54 % Women 46 % <b>Criteria used for PEP Diagnosis</b> Abdominal pain and abnormal serum amylase level 3 × ULN at 24-hour post ERCP	<b>Setting</b> All ERCPs Details not provided <b>Diagnosis</b> Cholelithiasis 45 % Jaundice 24 % Cholangitis 11 % Pancreatitis 8 % Malignancy 6 % <b>Sphincterotomy rate</b> 43 (44 %) <b>Biliary stenting</b> Not mentioned <b>PD cannulation</b> Not mentioned <b>Pre-ERCP preparation</b> Octreotide group (n = 54) received octreotide infusion pre-ERCP until 24 hr post procedure <b>Exclusion criteria</b> Not given	<b>Amylase</b> All patients 2-hr amylase after ERCP of 3 × ULN had sensitivity, specificity, PPV and NPV of 72 %, 79 %, 32 % and 95 % respectively 2-hr amylase after ERCP of 5 × ULN had sensitivity, specificity, PPV and NPV of 54 %, 92 %, 46 % and 94 % respectively. Accuracy was 87 % Octreotide group 2-hr amylase after ERCP of 3 × ULN had sensitivity, specificity, PPV and NPV of 78 %, 87 %, 54 % and 95 % respectively 2-hr amylase after ERCP of 5 × ULN had sensitivity, specificity, PPV and NPV of 55 %, 98 %, 83 % and 92 % respectively. Accuracy was 91 % <b>Lipase</b> Not studied <b>Elastase</b> 2-hour elastase > ULN had sensitivity, specificity, PPV and NPV of 72 %, 88 %, 44 % and 96 % respectively <b>Author conclusion(s)</b> A 2-hr amylase after ERCP of 5 × ULN had high NPV for PEP with or without octreotide	1. Single institution 2. Setting details not given 3. Small sample size 4. Use of octreotide infusion is not standard of care 5. Procedure details that may impact development of PEP like PD cannulation not given

► Table 1 (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Lee [17] 2017	Retrospective single institution cohort experienced operators (> 300 ERCPs) (Korea)	516 PEP 16 (3.1%)	<p><b>Mean age</b> PEP 51.1 No-PEP 63.8</p> <p><b>Gender</b> PEP group Men: 37.5% Women: 62.5% No-PEP group Men 57% Women 43%</p> <p><b>Criteria used for PEP Diagnosis</b> Abdominal pain and serum amylase level &gt; 3 × ULN 24-hour post-ERCP Cotton criteria for severity assessment</p>	<p><b>Setting</b> Not defined</p> <p><b>Diagnosis (overlap)</b> Cholelithiasis 56% Biliary Stricture 28% Other 16%</p> <p><b>Sphincterotomy rate</b> 52 (10%)</p> <p><b>Biliary stenting</b> Not mentioned</p> <p><b>Pancreatogram</b> 68 (13%)</p> <p><b>Pre-ERCP preparation</b> Not defined</p> <p><b>Exclusion criteria</b> History of pancreatitis, surgically altered enteric anatomy</p>	<p><b>Amylase</b> 4-hour amylase &gt; 2 × ULN had sensitivity, specificity, PPV and NPV of 81%, 81%, 12% and 99% respectively for PEP 4-hr amylase &gt; 3 × ULN had sensitivity, specificity, PPV and NPV of 75%, 88%, 17% and 99% respectively for PEP 4-hr amylase &gt; 4 × ULN had sensitivity, specificity, PPV and NPV of 75%, 93%, 26% and 99% respectively for PEP</p> <p><b>Lipase</b> 4-hour lipase &gt; 3 × ULN had sensitivity, specificity, PPV and NPV of 87.5%, 82%, 14% and 99.5% respectively for PEP 4-hr lipase &gt; 4 × ULN had sensitivity, specificity, PPV and NPV of 81%, 86%, 16% and 99% respectively for PEP 4-hr lipase &gt; 5 × ULN had sensitivity, specificity, PPV and NPV of 81%, 89%, 19% and 99% respectively for PEP</p> <p><b>Author conclusion(s)</b> 4-hr post-ERCP amylase and lipase levels are useful in early prediction of PEP</p>	<p>1. Single institution 2. Retrospective design 3. Setting not defined 4. Consensus criteria for PEP not applied 5. Although non-significant, PEP patients were younger and more likely women, no explanation was provided 6. Procedure details like cannulation time, PD cannulations not defined that may affect outcomes</p>
Lv [18] 2020	Single institution retrospective cohort study between January 2011 and November 2016 (China)	206 PEP 21 (10.2%)	<p><b>Age (all)</b> &lt; 50–22% 50–60–23% 61–70–28% 71–80–21% &gt; 80–6%</p> <p><b>Gender(all)</b> Men 45% Women 55%</p> <p><b>Criteria used for PEP Diagnosis</b> Cotton 199/129 Banks 201/230</p>	<p><b>Setting</b> Elective 92% Urgent 8%</p> <p><b>Indication/diagnosis</b> Cholelithiasis 80% Tumor 15% Others 5%</p> <p><b>Sphincterotomy rate</b> 136 (66%)</p> <p>Biliary stenting 28 (14%) PD cannulation 28 (14%)</p> <p><b>Pre-ERCP preparation</b> Not specified</p> <p><b>Exclusion criteria</b> Known pancreatitis, abnormal renal function (serum creatinine &gt; 92 μmol/L), pregnant women</p>	<p><b>Amylase</b> 3-hr post-ERCP serum amylase optimal cutoff was 1834 U/L (normal up to 110) with sensitivity, specificity, PPV and NPV of 60%, 88%, 84% and 69% respectively to diagnose PEP</p> <p><b>Lipase</b> 3-hr post-ERCP serum Lipase optimal cutoff was 380 U/L with sensitivity, specificity, PPV and NPV of 73%, 81%, 79% and 75% respectively to diagnose PEP</p> <p><b>Author conclusion(s)</b> The 3-h post-ERCP serum amylase level is useful for early prediction of PEP. There was no significant difference between 3-h post-ERCP amylase and lipase for predicting PEP</p>	<p>1. Single institution 2. Retrospective design 3. Small sample size 4. Actual lab normal for lipase not defined for calculation of multiplicative value above ULN</p>

▶ Table 1 (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Martin [19] 2016	Retrospective review of clinical trial patient data in single institution (Spain)	510 PEP 36 (7.1%)	<b>Age (all)</b> Mean age 73 <b>Gender (all)</b> Men 47% Women 53% <b>Criteria used for PEP Diagnosis</b> Cotton 199 129	<b>Setting</b> Outpatient 54.5% (278) Inpatient 45.5% (232) <b>Diagnosis</b> Cholelithiasis 62% Malignant stricture 31% Acute pancreatitis 4% SOD* 1% Others 2% <b>Sphincterotomy rate</b> 465 (91.2%) Biliary Stenting 152 (29.8%) <b>PD cannulation</b> not mentioned <b>Pre-ERCP preparation</b> 255 patients had octreotide infusions as part of the original clinical trial, details not given Exclusion criteria previous sphincterotomy, chronic pancreatitis	<b>Amylase</b> 4-hr amylase at a cut-off of 218 U/L (2.2 × ULN) showed a sensitivity, specificity, PPV and NPV 91.7%, 82.5%, 28% and 99% respectively for diagnosis of PEP <b>Lipase</b> 4-hr lipase at a cut-off of 355 U/L (6 × ULN) showed a sensitivity, specificity, PPV and NPV 94.4%, 81.6%, 38% and 99.5% respectively for diagnosis of PEP <b>Author conclusion(s)</b> 4-hr lipase and amylase levels were early markers for PEP and had a good correlation 4 hr after ERCP, but they are not useful to judge severity of PEP	1. Retrospective design, secondary analysis of a randomized trial 2. Effect of octreotide on PEP diagnosis not studied (which is what was studied in the original trial) 3. Single institution
Minakari [20] 2018	Prospective single institution cross-sectional study (Iran)	300 PEP 35 (11.7%)	<b>Mean age</b> All 60.5 with PEP 51.3 Without PEP 61.5 <b>Gender</b> Male 49.7% Female 50.3% <b>Criteria used for PEP Diagnosis</b> Cotton 199 129	<b>Setting</b> Not mentioned <b>Diagnostic and Therapeutic Indication/diagnosis</b> Not specified <b>Sphincterotomy rate</b> Not specified <b>Biliary stenting</b> Not specified <b>PD cannulation</b> Not specified <b>Pre-ERCP preparation</b> Not specified <b>Exclusion criteria</b> History of pancreatitis, surgically altered enteric anatomy or hyperamylasemia	<b>Amylase</b> 2-hr amylase cutoff values for predicting PEP was 241 U/L (2.5 × ULN) had sensitivity, specificity, PPV and NPV of 90%, 87.5%, 49% and 98.7% respectively for PEP 4-hr amylase cutoff of 839.5 IU/L (8 times the ULN) had sensitivity, specificity, PPV and NPV of 97.1%, 95.1%, 72.3% and 99.6% respectively for PEP <b>Lipase</b> 2-hr lipase cutoff values for predicting PEP was 216 IU/L (> 3.5 × ULN), with sensitivity, specificity, PPV and NPV of 97.1%, 87.2%, 50% and 99.6% respectively The 4-hr serum lipase cutoff of 656.5 IU/L (> 10 × ULN) for predicting PEP had sensitivity, specificity, PPV and NPV of 97.1%, 87.2%, 70.8% and 99.6% respectively <b>Author conclusion(s)</b> 2-hr serum lipase levels at cut point of 216 IU/L had the best sensitivity (97.1%) and NPVs (99.6%) for the exclusion of PEP (AUC = 0.954). The 4-hr serum lipase at cutoff levels of 10 times, the ULN demonstrated the same sensitivity (97.1%) but more specificity (94.7%)	1. Single institution 2. ERCP-related confounders associated with PEP – number of cannulation attempts, cannulation time, PD cannulation were not analyzed 3. Severity of PEP not studied 3. PEP patients reportedly younger, no explanation given

► Table 1 (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Nishino [21] 2008	Retrospective single center cohort (Japan)	1631 PEP 67 (4.2%)	<p><b>Age (all)</b> Median 67 yrs. ≥65 years 814 (50%) &lt;65 years 817 (50%)</p> <p><b>Gender</b> Men 60% Women 40%</p> <p><b>Criteria used for PEP diagnosis</b> Abdominal pain for 24-hour, serum amylase or lipase &gt; 3-fold at 16–18 hr post-ERCP, CT or US evidence of pancreatic swelling</p>	<p><b>Setting</b> Inpatient 100% Indication/diagnosis Diagnostic 56% Therapeutic 44% Further details not given</p> <p><b>Sphincterotomy rate</b> Not mentioned</p> <p><b>Biliary stenting</b> Not mentioned</p> <p><b>PD cannulation</b> Not mentioned</p> <p><b>Pre-ERCP preparation</b> All patients received protease inhibitor solution</p> <p><b>Exclusion criteria</b> All consecutive ERCs included with no exclusion criteria</p>	<p><b>Amylase</b> 4-hr amylase &gt; 3-fold had sensitivity, specificity, PPV and NPV of 90%, 73%, 13% and 99% respectively for PEP 4-hr amylase &gt; 4-fold had sensitivity, specificity, PPV and NPV of 85%, 80%, 16% and 99% respectively for PEP 4-hr amylase &gt; 5-fold had sensitivity, specificity, PPV and NPV of 78%, 86%, 20% and 99% respectively for PEP</p> <p><b>Lipase</b> 4-hr lipase &gt; 6-fold had sensitivity, specificity, PPV and NPV of 97%, 81%, 18% and 99.8% respectively for PEP 4-hr lipase &gt; 8-fold had sensitivity, specificity, PPV and NPV of 97%, 85%, 22% and 99.8% respectively for PEP 4-hr lipase &gt; 9-fold had sensitivity, specificity, PPV and NPV of 97%, 86%, 23% and 99% respectively for PEP 4-hr lipase &gt; 10-fold had sensitivity, specificity, PPV and NPV of 95%, 87%, 24% and 99.7% respectively for PEP</p> <p><b>Author conclusion(s)</b> 4-hr post-ERCP amylase and lipase levels were useful to predict PEP with a near 100% NPVs for both although lipase was a more effective than amylase</p>	<ol style="list-style-type: none"> <li>1. Single institution</li> <li>2. Retrospective design</li> <li>3. Patients with active or old pancreatitis included and significantly higher in PEP group, could have affected the results</li> <li>4. Procedure details not provided that may affect the development of PEP</li> </ol>



▶ Table 1 (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Papachristos [22] 2016	Retrospective single institution analysis (Australia)	506 PEP 19 (3.8%)	<b>Age (all)</b> Median 69 yrs. <b>Gender</b> Men 45% Women 55% <b>Criteria used for PEP Diagnosis</b> Cotton 199 129 Banks 201 230	<b>Setting</b> Not mentioned diagnostic as well therapeutic ERCP <b>Indication/diagnosis</b> Cholelithiasis 56% Stent removal/exchange 12.9% Malignancy 9.6% Bile leak 4.9% Gallstone pancreatitis-4.2% <b>Sphincterotomy rate</b> 451 (83.1%) <b>Biliary stenting</b> 70 (12.9%) <b>Pancreatogram</b> 150 (27.6%) <b>Pre-ERCP preparation</b> Not mentioned <b>Exclusion criteria</b> pre-existing acute gallstone pancreatitis, no post procedure amylase and lipase recorded, inability to reach 2nd part of duodenum	<b>Amylase</b> 4-hr amylase > 1.5-fold had sensitivity, specificity, PPV and NPV of 100%, 87%, 23% and 100% respectively for PEP 4-hr amylase > 3-fold had sensitivity, specificity, PPV and NPV of 79%, 95%, 36% and 99% respectively for PEP 4-hr amylase > 5-fold had sensitivity, specificity, PPV and NPV of 58%, 97%, 42% and 98% respectively for PEP 4-hr amylase > 10-fold had sensitivity, specificity, PPV and NPV of 21%, 99%, 36% and 97% respectively for PEP <b>Lipase</b> 4-hour lipase > 1.5-fold had sensitivity, specificity, PPV and NPV of 100%, 75%, 14% and 100% respectively for PEP 4-hr lipase > 3-fold had sensitivity, specificity, PPV and NPV of 100%, 87%, 23% and 100% respectively for PEP 4-hr lipase > 5-fold had sensitivity, specificity, PPV and NPV of 100%, 90%, 28% and 100% respectively for PEP 4-hr lipase > 10-fold had sensitivity, specificity, PPV and NPV of 100%, 94%, 40% and 100% respectively for PEP 4-hr lipase > 20-fold had sensitivity, specificity, PPV and NPV of 95%, 96%, 36% and 97% respectively for PEP <b>Author conclusion(s)</b> 4-hr lipase post-ERCP better excludes PEP than 4-hr amylase. Patients with 4-hr lipase under 10-fold rise can be safely discharged. It had had 100% sensitivity, 100% NPV with 94% specificity and LR of 17.2	1. Single institution 2. Retrospective design 3. Old known gallstone pancreatitis excluded, but acute gallstone pancreatitis not excluded. No explanation provided.

▶ **Table 1** (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Sutton [23] 2011	Retrospective single institution analysis single operator (Australia)	886 PEP 39 (4.4%)	<p><b>Mean age</b> 65.3 yrs &gt; 75 – 35 %</p> <p><b>Gender</b> Men: 40 % Women: 60 %</p> <p><b>Criteria used for PEP Diagnosis</b> Cotton 199/129</p>	<p><b>Setting</b> Outpatient – most (exact number not provided)</p> <p><b>Indication/diagnosis</b> Gallstones 41 % Malignancy 13 % Biliary sludge 6 % Biliary stent 8 % Biliary stricture 2 % Diverticula 2 % No abnormality 10 % Other 12 %</p> <p><b>Sphincterotomy rate</b> Not mentioned Biliary stenting 76 (7.6 %)</p> <p><b>PD cannulation</b> Not mentioned</p> <p><b>Pre-ERCP preparation</b> No specific preparation</p> <p><b>Exclusion criteria</b> pre-existing pancreatitis, lack of post procedure amylase levels</p>	<p><b>Amylase</b> The mean 4-hr amylase for patients with post-ERCP pancreatitis was 9.0 times the ULN compared with 1.4 times the ULN for those without PEP (<math>P &lt; 0.001</math>). PEP patients were significantly younger, had higher incidence of undergoing pancreatogram Overall usefulness of amylase to recognize PEP with numbers calculated from 2 × 2 contingency table provided are follows 4-hr amylase &gt; 1.5–2.5 times ULN had sensitivity, specificity, PPV and NPV of 17 %, 93 %, 10 % and 96 % respectively for PEP 4-hr amylase &gt; 2.5–5 times ULN had sensitivity, specificity, PPV and NPV of 64 %, 94 %, 32 % and 98 % respectively for PEP 4-hr amylase &gt; 5 times ULN had sensitivity, specificity, PPV and NPV of 83 %, 95 %, 43 % and 99 % respectively for PEP</p> <p><b>Lipase</b> Not studied</p> <p><b>Author conclusion(s)</b> 4-hr serum amylase is a useful indicator to predict PEP. Patients who underwent pancreatogram with 4-hr amylase &gt; 2.5 times and without pancreatogram and 4-hr amylase &gt; 5 × ULN should be admitted</p>	<ol style="list-style-type: none"> <li>1. Single institution</li> <li>2. Retrospective design</li> <li>3. Diagnosis provided were post-ERCP, not indications for ERCP</li> <li>4. Procedure details that could impact rates of PEP like PD cannulation and sphincterotomy rate not given</li> <li>5. PEP patients reportedly younger, no explanation given</li> </ol>

▶ Table 1 (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Tadehara [24] 2019	Retrospective single tertiary university (2 hospitals) (Japan)	804 PEP 78 (9.7%)	<b>Mean age (all)</b> 71 yrs <b>Gender</b> Men: 62% Women: 38% <b>Criteria used for PEP diagnosis</b> 2 of 3 of following 1. Acute upper abdominal pain 2. Elevated pancreatic enzymes in blood/urine 3. US, CT, or MRI findings of acute pancreatitis	<b>Setting</b> Not specified, all ERCPs screened for inclusion <b>Indication/diagnosis</b> Diagnostic 37.7% Therapeutic 62.3% No more information given <b>Sphincterotomy rate</b> Not given <b>Biliary stenting</b> Not specified <b>PD cannulation</b> Not specified <b>Pre-ERCP preparation</b> Not specified <b>Exclusion criteria</b> Acute or chronic pancreatitis, kidney dysfunction (eGFR $\leq$ 44 mL/min), history of cholangiojejunostomy	<b>Amylase</b> The 3-hr post-PEP serum amylase optimal cutoff was 171 with sensitivity of 85.9%, specificity of 76.3%, with PPV of 27.7% and NPV of 97.9% <b>Lipase</b> The 3-hr post-PEP serum lipase optimal cutoff was 342 with sensitivity of 85.9%, specificity of 86.7%, with PPV of 40.5% and NPV of 98.1% <b>Author conclusion(s)</b> The AUCs were 0.908 for lipase [95%CI: 0.880–0.940, $P < 0.001$ ] and 0.880 for amylase [95%CI: 0.846–0.915, $P < 0.001$ ], indicating both are useful for early diagnosis. By comparing the AUCs, lipase was found to be significantly more useful for early diagnosis of PEP than amylase ( $P = 0.023$ )	1. Single institution 2. Retrospective design 3. Over 80% of screened patients excluded, may have impacted findings 4. Tertiary center treating complex patients, findings may not be generally applicable 5. Procedure details that could impact rates of PEP like PD cannulation and sphincterotomy rate not given
Testoni [25] 2019	Prospective design single operator (Italy)	409 PEP 19 (4.6%)	<b>Mean age (all)</b> 63.9 yrs <b>Gender</b> Men: 59% Women: 41% <b>Criteria used for PEP diagnosis</b> 1. Epigastric pain persisting for 24 hr 2. Serum amylase $> 5 \times$ ULN 3. With or without leukocytosis	<b>Setting</b> Not specified, consecutive patients recruited <b>Indication/diagnosis</b> No information given <b>Sphincterotomy rate</b> Not given <b>Biliary stenting</b> Not specified <b>PD opacification</b> 198 (48%) <b>Pre-ERCP preparation</b> IV pentazocine chloride or hyoscine-N-butyl bromide <b>Exclusion criteria</b> Preexisting hyperamylasemia, known pancreatic like pain, previous sphincterotomy, choledochoduodenal anastomosis, chronic pancreatitis, pancreatic cancer, renal failure, pregnancy, age $< 18$ years	<b>Amylase</b> 2-hour amylase $> 5$ -fold had sensitivity, specificity, PPV and NPV of 23%, 98%, 46% and 95% respectively for PEP 4-hr amylase $> 5$ -fold had sensitivity, specificity, PPV and NPV of 59%, 95%, 42% and 97% respectively for PEP 8-hr amylase $> 5$ -fold had sensitivity, specificity, PPV and NPV of 77%, 97%, 63% and 98% respectively for PEP <b>Lipase</b> Not studied <b>Author conclusion(s)</b> Although highest prediction of PEP was with amylase levels $5 \times$ ULN 8 hr post procedure, serum amylase at 4 hr post-ERCP is reliable to predict risk of PEP, is cost effective and is recommended particularly in outpatients undergoing ERCP especially when PD opacification has occurred.	1. Small study 2. Excluded pancreatic cancer patients 3. Indications for ERCP not specified 4. Amylase $> 5 \times$ ULN taken as diagnostic criteria for PEP, standard criteria at the time were not applied (Cotton)

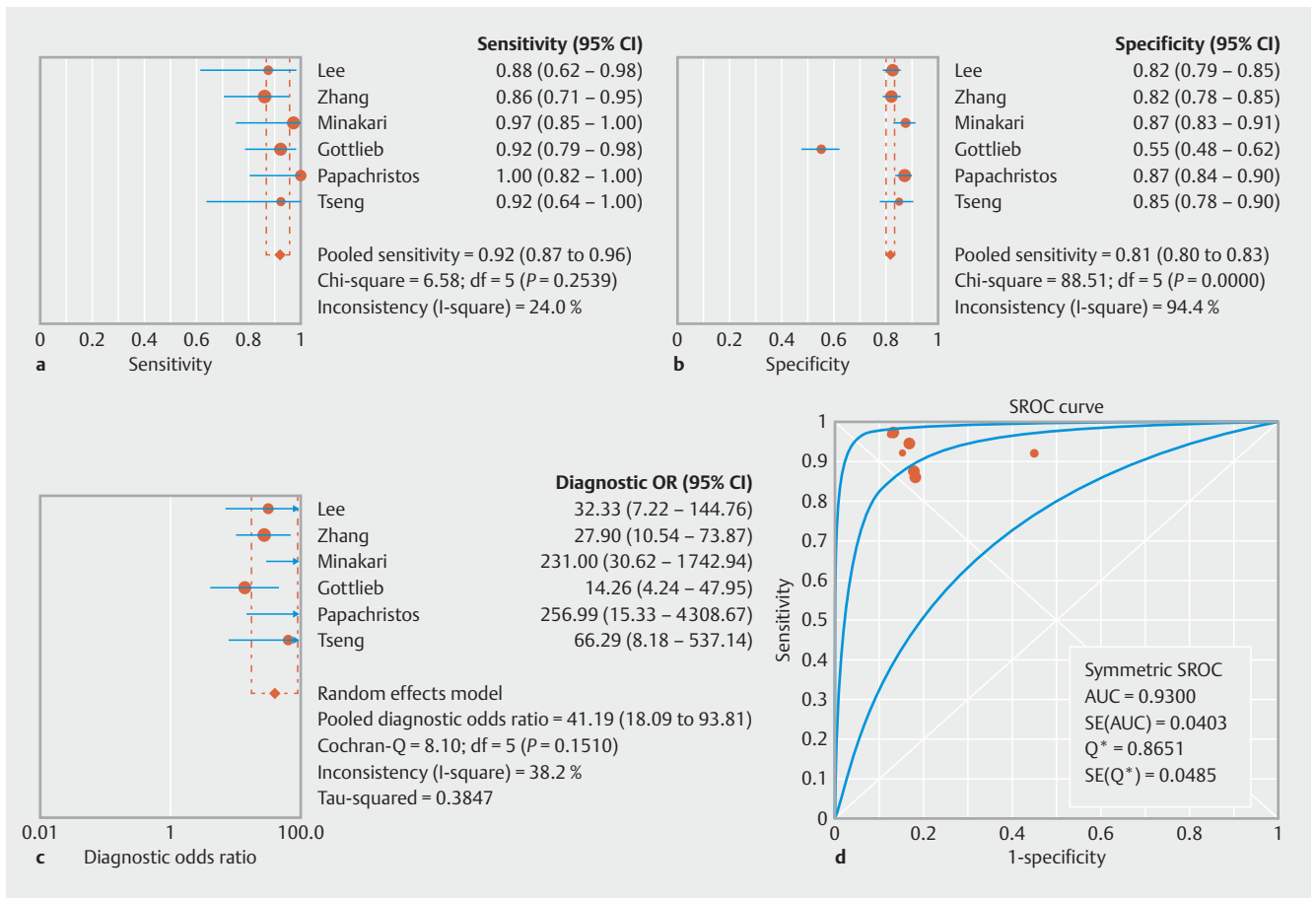
► Table 1 (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Thomas [26] 2001	Prospective design single institution single operator (Australia)	263 PEP 10 (3.8%)	<b>Median age</b> 68 yr > 80 yr 17 % <b>Gender (all)</b> Men 99 (38 %) Women 164 (62 %) <b>Criteria used for PEP diagnosis</b> Cotton 199/129	<b>Setting</b> Outpatient Inpatient <b>Indication/diagnosis</b> Stone:pain/jaundice 47 % Malignancy 17 % Intraop cholangiogram abnormality 12 % Bile leak/other 9 % Cholangitis 7 % Pancreatitis 6 % SOD 5 % <b>Sphincterotomy rate</b> 163 (62 %) <b>Biliary stenting</b> not mentioned <b>PD cannulation</b> 133 (51 %) <b>Pre-ERCP preparation</b> Not specified <b>Exclusion criteria</b> not mentioned	<b>Amylase</b> ROC characteristics of the 4-hr amylase level showed good test performance with the AUC being 0.96 ( $P < 0.001$ ) 4-hr amylase level normal: Sensitivity of 100 %, specificity 82 %, PPV 15.4 % and NPV 100 % 4-hr amylase 1.5 × ULN: Sensitivity of 100 %, specificity 88.5 %, PPV 20 % and NPV 100 % 4-hr amylase 2 × ULN: Sensitivity 90 %, specificity 93 %, PPV of 24 % and NPV 99.6 % 4-hr amylase 3 × ULN: Sensitivity of 70 %, specificity 95 %, PPV 37 % and NPV 99 % <b>Lipase</b> Not done <b>Author conclusion(s)</b> 4-hr serum amylase > 1.5 × ULN post-ERCP was useful to exclude PEP with 100 % NPV while cut-off of 3 × ULN amylase was more specific for PEP.	1. Single institution 2. Small study 3. Inclusion and exclusion criteria not defined 4. Setting of procedure not given
Tseng [27] 2011	Prospective design, single institution (Taiwan)	150 PEP 13 (8.7%)	<b>Age</b> not given <b>Gender (all)</b> not given <b>Criteria used for PEP diagnosis</b> Cotton 199/129	<b>Setting</b> Not specified <b>Indication/diagnosis</b> Cholelithiasis 47 % Malignancy 15 % Dilated biliary tract 7 % SOD 1 % Other 22 % <b>Sphincterotomy rate</b> Not given <b>Biliary stenting</b> not mentioned <b>PD cannulation</b> Not given <b>Pre-ERCP preparation</b> Not specified <b>Exclusion criteria</b> End-stage renal disease, known acute pancreatitis, history of pancreatic or biliary surgery, positive pre-ERCP urine trypsinogen-2 dipstick test	<b>Amylase</b> 3-hour amylase > 3 × ULN had sensitivity, specificity, PPV and NPV of 46 %, 94 %, 43 % and 95 % respectively <b>Lipase</b> 3-hour lipase > 3 × ULN had sensitivity, specificity, PPV and NPV of 92 %, 85 %, 36 % and 99 % respectively 3-hour lipase > 5 × ULN had sensitivity, specificity, PPV and NPV of 85 %, 89 %, 42 % and 98 % respectively Urinary trypsinogen 2 3-hour positive urinary trypsinogen-2 had sensitivity, specificity, PPV and NPV of 85 %, 97 %, 73 % and 98.5 % respectively <b>Author conclusion(s)</b> PPV of rapid urinary trypsinogen-2 strip test if markedly superior to amylase and lipase for diagnosing PCP at 3 hr after ERCP	1. Single institution 2. Very small study 3. Patient details not given 4. Procedure details that could impact rates of PEP like PD cannulation and sphincterotomy rate not given

▶ Table 1 (Continuation)

Study	Design	Total patients	Patient characteristics	Procedure (ERCP) characteristics	Outcomes/results	Limitations
Zhang [28] 2019	Retrospective single institution (China)	Total 498 PEP 36 (7%)	<b>Mean age</b> PEP 62.4 No PEP 62.5 <b>Women</b> PEP 72% No-PEP 49% ( <i>P</i> =0.008) <b>PEP diagnosis criteria</b> Cotton 199/129 Banks 201/230	<b>Setting</b> Not specified <b>Indication/diagnosis</b> Not specified <b>Sphincterotomy rate</b> All 78% PEP 83% No-PEP 77% ( <i>p</i> NS) <b>Biliary stent placement</b> Not specified <b>PD cannulation</b> All 13% PEP 31% No-PEP 12% ( <i>P</i> =0.003) <b>Pre-ERCP preparation</b> Diclofenac suppositories 50 mg 30 min before ERCP <b>Exclusion criteria</b> History of pancreatic disorders, history of surgical gastrointestinal reconstruction, previous h/o ERCP, ERCP-related perforation found	<b>Amylase</b> 3-hr amylase > 1 × ULN had sensitivity, specificity, PPV and NPV of 92%, 71%, 20% and 99% respectively 3-hr amylase > 1.5 × ULN had sensitivity, specificity, PPV and NPV of 78%, 83%, 26% and 98% respectively 3-hr amylase > 2 × ULN had sensitivity, specificity, PPV and NPV of 67%, 89%, 31% and 97% respectively 3-hr amylase > 2.5 × ULN had sensitivity, specificity, PPV and NPV of 58%, 91%, 34% and 97% respectively <b>Lipase</b> 3-hr Lipase > 1 × ULN had sensitivity, specificity, PPV and NPV of 100%, 59%, 16% and 100% respectively 3-hr Lipase > 2 × ULN had sensitivity, specificity, PPV and NPV of 94%, 75%, 22% and 99.7% respectively 3-hr Lipase > 3 × ULN had sensitivity, specificity, PPV and NPV of 86%, 82%, 27% and 99% respectively 3-hr Lipase > 4 × ULN had sensitivity, specificity, PPV and NPV of 78%, 87%, 32% and 98% respectively 3-hr Lipase > 5 × ULN had sensitivity, specificity, PPV and NPV of 69%, 90%, 35% and 97% respectively <b>Author Conclusion(s)</b> 3-hr lipase is as good as amylase for PEP prediction. Patients receiving diclofenac suppositories before ERCP with amylase activity < 1.0-fold ULN or lipase activity < 2.0-fold ULN at 3 hr post ERCP have very low probability of developing PEP	1. Retrospective design 2. Single institution 3. Preexisting pancreatic disorders excluded but details not provided for specific disease states like cancer 4. Setting and indications not defined

PD, pancreatic duct; ERCP, endoscopy retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; SOD, sphincter of Oddi dysfunction; NPV, negative predictive value; PPV, positive predictive value; ULN, upper limit of normal; CT, computed tomography; PLR, positive likelihood ratio; NLR, negative likelihood ratio.



► **Fig. 1** a Sensitivity, b specificity, c diagnostic odds ratio, and d SROC curve for subgroup 1 (lipase >three to four times the ULN).

62 articles were reviewed that ultimately led to 18 studies that met the inclusion criteria [11–28] (**Supplemental Fig. 1**). Reference screening of the 18 included studies did not generate any additional studies for review.

### Characteristics of included studies

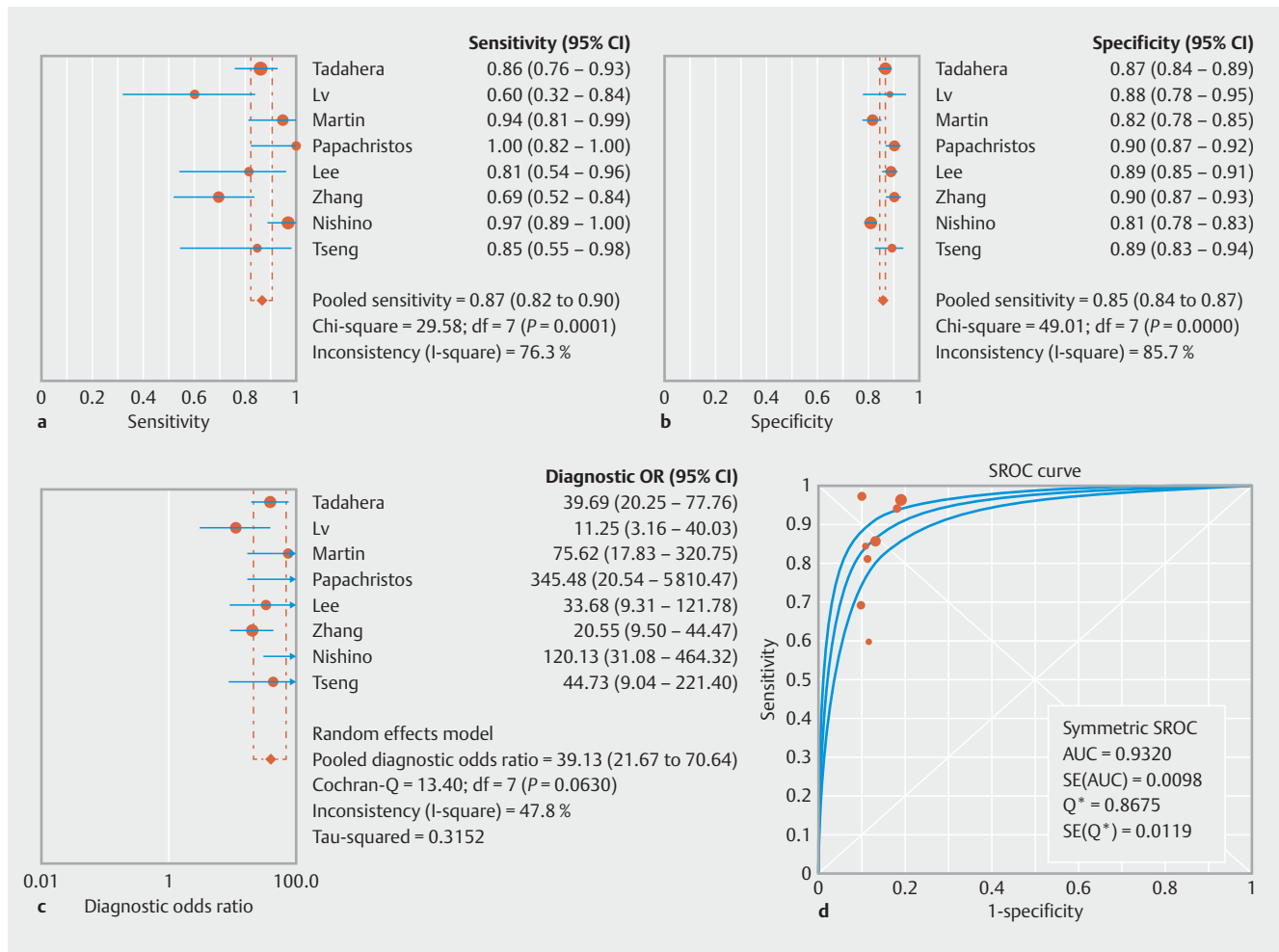
The study characteristics are summarized in ► **Table 1**. The included studies yielded a sample size of 11,790 patients that underwent ERCP, of which 764 (6.5%) developed PEP. All studies except one [14] were performed at a single center. Seven studies were prospective [14–16, 20, 25–27] while 11 were retrospective [11–13, 17–24, 28] in design. Ten studies were from Asia [13–15, 17, 18, 20, 21, 24, 27, 28], three each from Europe [16, 9, 25] and Australia [22, 23, 26] and two from the United States [11, 12]. Six studies reported the setting of ERCPs [11, 13–16, 23, 25, 26] with one being 100% inpatient [21], two being 100% outpatient [12, 13], two being mixed [11, 19] and one mostly outpatient [23] (exact incidence not given). Indications of ERCP were reported by 12 studies [11, 13–19, 22, 23, 26, 27], with choledocholithiasis being the most common indication followed by malignancy.

Ten studies evaluated the diagnostic efficacy of both lipase and amylase [12, 17–22, 24, 27, 28], whereas eight reported results for amylase only [11, 13–16, 23, 25, 26]. Lipase and amy-

lase measurements were done within 2 to 4 hours of ERCP in all studies. Eleven studies [11–13, 18–20, 22, 23, 26–28] used established Cotton criteria or Banks (Original or Revised Atlanta) criteria for PEP diagnosis [29–31], while seven studies used other criteria that ranged from abdominal pain with high amylase to CT-scan findings of pancreatic inflammation only without mention of clinical symptoms [14–17, 21, 24, 25] (► **Table 1**). Four studies reported PEP rates of over 10% [14, 16, 18, 20], and two of these did not use established PEP diagnosis criteria [14, 16]. Only experienced operators performed ERCPs in two studies, and these two reported the lowest rates of PEP (3.6% and 3.1%) [15, 17].

### Predictive value of early measurement of serum lipase for detecting PEP (Groups 1, 2)

Six studies reported the diagnostic value of lipase three to four times the ULN [12, 17, 20, 22, 27, 28] and eight studies reported values of five to six times the ULN [17–19, 21, 22, 24, 27, 28] done 2 to 4 hours after ERCP. The pooled sensitivity and specificity of lipase level three to four times the ULN was 92% and 81%, respectively (► **Fig. 1**), with a positive likelihood ratio (PLR) of 4.98 and negative likelihood ratio (NLR) of 0.13 (**Supplemental Fig. 2** and **Supplemental Fig. 3**) with a diagnostic odds ratio (DOR) of 41.19 (► **Fig. 1c**). On the other hand, lipase level five



► **Fig. 2** a Sensitivity, b specificity, c diagnostic odds ratio, and d SROC curve for subgroup 2 (lipase > five to six times the ULN).

to six times the ULN had a lower pooled sensitivity of 87 %, higher pooled specificity of 85 %, higher PLR 6.43, and lower NLR 0.17 with lower DOR of 39.13 (► **Fig. 2** and **Supplemental Fig. 2** and **Supplemental Fig. 3**), compared to the lipase three to four times ULN. Overall, serum lipase three to four times ULN performed 2 to 4 hours after ERCP had the highest pooled sensitivity (92 %) of all six enzyme groups for detecting PEP (► **Table 2**).

### Predictive value of early measurement of serum amylase for detecting PEP (Groups 3 to 6)

All 18 studies reported diagnostic value of amylase for recognizing PEP 2 to 4 hours after the procedure. Nine studies reported amylase one to one and a half times the ULN (Group 3) [11, 15, 17, 18, 22–24, 26, 28], nine reported amylase levels two to two and a half times the ULN (Group 4) [12–14, 17, 19, 20, 23, 26, 28], eight studies reported amylase elevations three to four times the ULN (Group 5) [15–18, 21, 22, 26, 27] and six studies reported amylase five to six times the ULN (Group 6) [15, 16, 21–23, 25]. High amylase levels up to one and a half times ULN had the highest pooled sensitivity for the detection of PEP (► **Fig. 3**). Serum amylase levels five to six times the ULN

had the highest pooled specificity of 93 % (► **Fig. 4**) and highest PLR of 9.97, which was highest in all six groups (including lipase). Groups 4 and 5 (amylase between 2–2.5 and 3–4 times the ULN) (**Supplemental Fig. 4a** and **Supplemental Fig. 5a**) had lower sensitivity and specificity than other groups. Based on this, an elevated amylase level of five to six times the ULN seemed the most reliable test to rule-in a diagnosis of PEP, 2 to 4 hours after ERCP (► **Table 2**).

### Quality of included studies

The methodological qualities of included studies as assessed using QUADAS-2 are shown in **Supplemental Fig. 6**. Most studies, including the retrospective design, attempted to decrease recruitment bias by having consecutive patients and clearly identified index and reference tests. However, no study was randomized or blinded. The overall quality of studies was considered moderate.

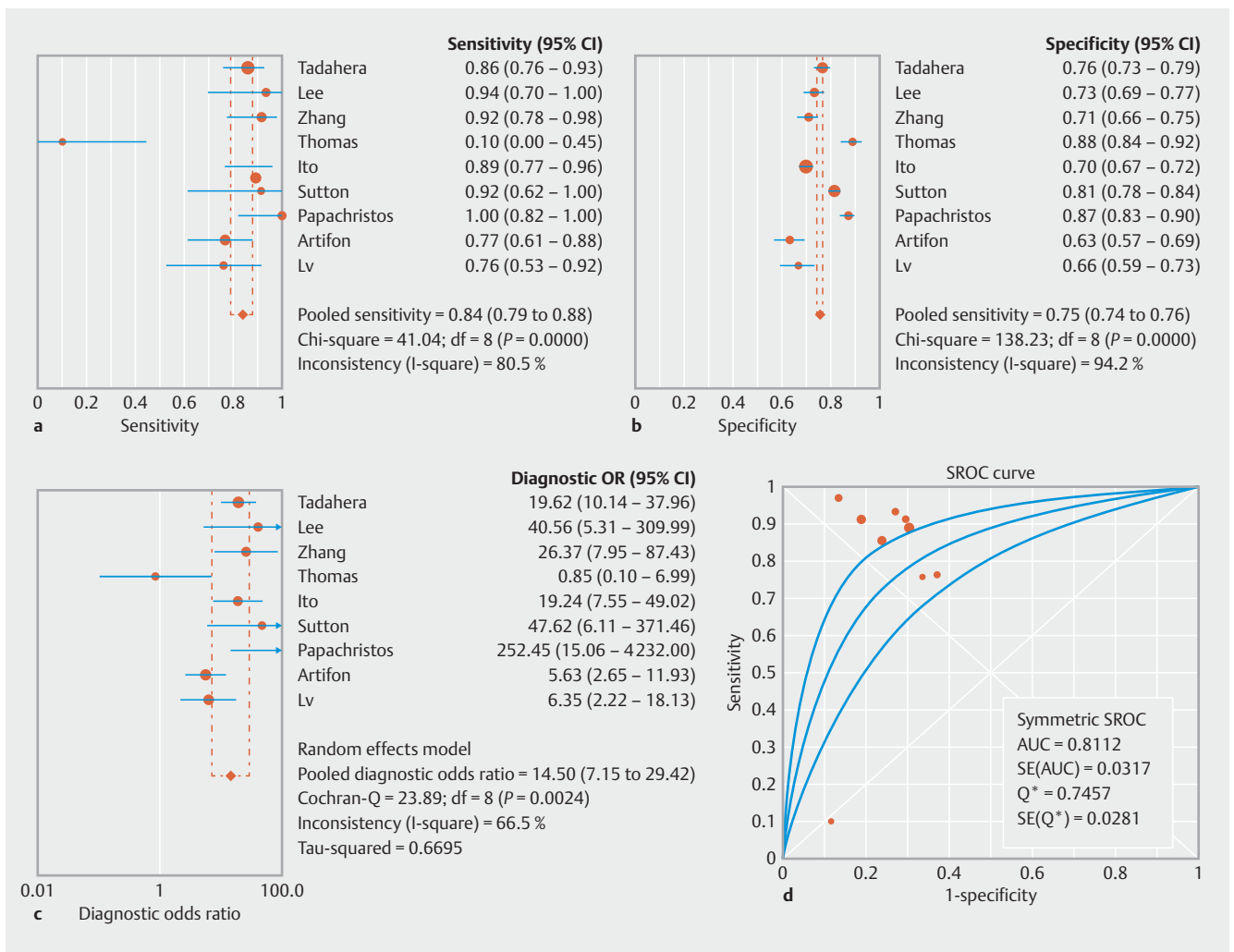
### Sources of heterogeneity

Significant heterogeneity was explored with meta-regression for all the six subgroups; type of study (multicenter vs. single center) and the time of enzyme measurement post-ERCP were

**Table 2** Comparison of diagnostic power of various cut-offs groups of amylase and lipase in predicting early post-ERCP pancreatitis.

Group	Enzyme	Threshold (times ULN)	Pooled Sensitivity	Pooled Specificity	Pooled PLR	Pooled NLR	DOR	Area under the SROC curve
1	Lipase	3–4	92%	81%	4.98	0.13	41.19	0.93
2	Lipase	5–6	87%	85%	6.43	0.17	39.13	0.93
3	Amylase	1–1.5	84%	75%	3.38	0.19	14.50	0.81
4	Amylase	2–2.5	65%	84%	5.47	0.21	25.57	0.91
5	Amylase	3–4	78%	86%	6.91	0.29	26.76	0.90
6	Amylase	5–6	64%	93%	9.97	0.41	25.31	0.88

ERCP, endoscopic retrograde cholangiopancreatography; ULN, upper limit of normal; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; SROC, summary receiver operating characteristic.

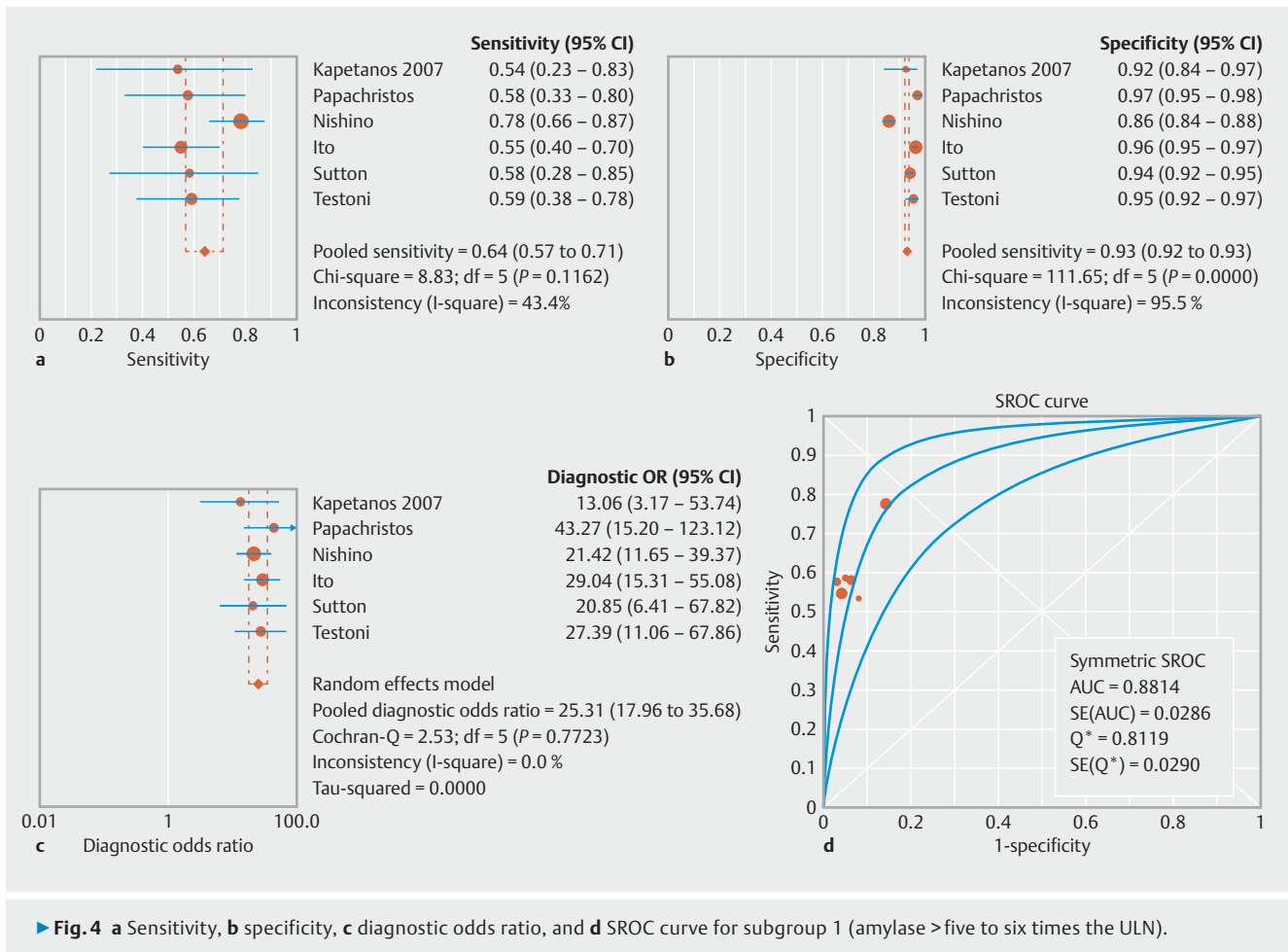


**Fig. 3** a Sensitivity, b specificity, c diagnostic odds ratio, and d SROC curve for subgroup 3 (amylase > 1.5 times ULN).

found to be the sources in the amylase two to two and a half (Group 4) and lipase five to six subgroup (Group 2), respectively (**Supplemental Fig. 7**). The use of prophylactic measures before the ERCP procedure was not a significant contributor to

heterogeneity, nor was the use of different criteria for the diagnosis of PEP. Sensitivity analysis was also attempted for individual groups, and four studies were found to be contributing to high  $I^2$  statistics [12, 14, 21, 26].





## Publications bias

The Deeks' funnel plots were applied in order to evaluate the existence of publication bias. Significant asymmetry ( $P < 0.1$ ) was noted in the funnel plot of only one of the six subgroups (Group 2, Lipase five to six times the ULN), indicating no significant publication bias in the studies we included in the meta-analysis (**Supplemental Fig. 8**).

## Discussion

PEP remains the most common complication of ERCP. Several mechanisms for PEP have been proposed, including thermal injury due to electrosurgical current during biliary or pancreatic sphincterotomy, mechanical injury from instrumentation of papilla and pancreatic duct, enzymatic injury subsequent to intraluminal activation of proteolytic enzymes, hydrostatic injury following injection of contrast medium into the pancreatic duct during sphincter manometry, chemical/allergic injury after injection of contrast medium into the pancreatic duct and infection from the contaminated endoscope and/or accessories [32]. The frequency of PEP depends on patient factors, endoscopist experience, and procedure-related factors. History of previous PEP, female gender, younger age, recurrent pancreatitis, sphincter of Oddi dysfunction are some of the factors

used to stratify the patients at high risk of PEP clinically. Procedure-related factors include difficult and/or repeated cannulation, endoscopic sphincterotomy, precut sphincterotomy, and pancreatic duct injection/instrumentation [33]. Rectal administration of indomethacin has proven beneficial in preventing PEP [34], and Protease inhibitors have shown promising results in some clinical trials as well [35]. However, PEP can still occur despite careful patient selection and the use of prevention strategies.

The originally proposed criteria of PEP have been used since 1991, which includes new-onset upper abdominal pain, serum amylase/lipase levels more than three times the ULN, and requirement of 2 to 3 days of inpatient hospitalization [29]. The severity of PEP has been more recently classified with the use of revised Atlanta criteria for the severity of acute pancreatitis [30]. Despite availability, the adoption of these criteria is variable, as evidenced by varied use in the studies included in our review (► **Table 1**). In addition, there is no consensus on the levels of serum amylase or lipase levels to rule out PEP.

To the best of our knowledge, this is the first meta-analysis to pool the results of all available individual studies with diverse cut-offs for both serum amylase and lipase levels performed 2 to 4 hours post-ERCP to arrive at a reasonable cut-off value to guide clinicians in early recognition of PEP. Measurement of li-

pase and amylase levels is an easy, quick, and useful tool to stratify patients who may be at a high risk of developing this complication. Early identification of low-risk patients based on enzyme levels would guide safe discharge of patients undergoing ERCP in the outpatient setting and aid in detecting PEP early in all settings to plan timely management. Both would ultimately help decrease healthcare utilization and costs.

Our study shows serum lipase with a cut-off more than five to six times ULN is the most accurate enzyme to establish a diagnosis of PEP, considering the sensitivity is closest to the specificity with an area under SROC being close to one. However, lipase levels above three to four times ULN had the highest sensitivity, indicating the best diagnostic power to select patients for same-day discharge, while amylase level five to six times the ULN had the highest specificity indicating the most accurate level to select patients needing monitoring and continued hospitalization. Lipase levels more than three to four times the ULN also had the lowest NLR (0.13). Hence, patients with a lipase level less than three times the ULN measured 2 to 4 hours post-procedure may be safely discharged after an outpatient ERCP.

Our study has some limitations. First, the included studies differed in terms of sample size, study design (prospective vs. retrospective), inclusion and exclusion criteria. Secondly, the included studies are far apart in their year of inception, ranging from 1996 [12] to 2020 [18, 28]. Third, the standard definition used for diagnosing PEP was not uniform across studies, nor was the time of measurement of lipase and amylase (ranged between 2 to 6 hours post-ERCP). Finally, some studies used pre-ERCP prophylaxis measures. In contrast, others did not specify its usage that may have impacted results. However, the heterogeneity analysis did not find this bias. Despite these shortcomings, the results of our study provide data to formulate a simple algorithm that could guide management decisions and predict PEP in a timely fashion to minimize morbidity and mortality and save costs associated with unnecessary routine hospitalization for post-ERCP observation. However, future multicenter studies are warranted in this direction as the number of ERCP continues to rise, especially in the outpatient setting. Thus, our study may also provide strong evidence to design such a multicenter randomized trial.

## Conclusions

Serum lipase more than three times ULN measured within 2 to 4 hours of the ERCP provides a reliable estimate of prediction of PEP in symptomatic patients. These results may be used in routine clinical practice to stratify high-risk patients for prompt decisions of either discharge or close observation in the outpatient/inpatient settings, especially in the context of proper clinical presentation.

## Competing interests

Hemant Goyal: Aimloxy LLC. Sonali Sachdeva, Syed Ali Amir Sherazi, Shweta Gupta, Abhilash Perisetto, Aman Ali, Saurabh Chandan declare that they have no conflict of interest.

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