

Role of 4-H Serum Lipase Level in Predicting Postendoscopic retrograde Cholangiopancreatography Pancreatitis

Abstract

Introduction: Serum amylase level can rise asymptotically after endoscopic retrograde cholangiopancreatography (ERCP). Thus, its assay can lead to overprediction of post-ERCP pancreatitis (PEP). Lipase assay is used to diagnose other forms of pancreatitis but usually not for PEP. **Objectives:** The aim of this study was to predict whether lipase may be of better use for the early prediction of PEP. **Methods:** One hundred and twenty-five consecutive ERCPs performed over a period of 1 year and 9 months were observed. On admission (baseline) and after ERCP at 4 and 24 h, serum amylase and lipase were measured. Based on sensitivity and specificity from the receiver operator characteristic (ROC) curve, optimal cutoff levels for the enzyme, serum lipase, and amylase levels were employed to predict PEP. **Results:** Out of 125 patients, 26 (20.8%) developed PEP. In multivariate analysis, young age, suspected sphincter of Oddi dysfunction, recurrent pancreatitis, and needle papillotomy were significant risk factors. Considering the optimum cutoff level (single value with the best sensitivity and specificity), both the enzyme amylase and lipase evaluated at 4 h were significant (Chi-square test: $P=0.0001$ for both the enzymes). However, multivariate regression analysis and levels of enzymes at different cutoff values in the ROC found that 4-h lipase levels were more (about 4 times) increased of the upper limit of normal range than amylase levels (1.19 times). **Conclusion:** The enzyme, serum amylase, and lipase evaluated at 4 h after ERCP were satisfactory predictors for PEP. However, when compared, serum lipase was more reliable than amylase.

Keywords: Endoscopic retrograde cholangiopancreatography, lipase, pancreatitis

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has widely been used in treating biliary and pancreatic disorders as a diagnostic and therapeutic procedure since its first introduction in 1968.^[1,2] However, this modality of the procedure is not without complications. After ERCP commonly occurred, adverse events include pancreatitis, hemorrhage, and infection.^[2,3] A careful literature search found that post-ERCP pancreatitis (PEP) is to occur in <1%–40% cases (1%–4% among low-risk cases and 8%–40% in high-risk cases) with a mortality rate ranging between 0.05% and 1%.^[4–6] Among these complications, PEP, although usually mild, is potentially the most severe complication that results in substantial morbidity and occasional mortality.^[7–9] The most commonly encountered risk factors for PEP are previous PEP, needle papillotomy, suspected sphincter of Oddi

dysfunction (SOD), female gender, and young age.^[10–12]

The widely used criteria to define PEP in a consensus paper proposed by Cotton *et al.* in the year 1991 was 24 h post-procedure amylase level at least 3 times above the upper level of the standard value along with the characteristic of newly developed abdominal pain consistent with pancreatitis and severity of symptoms demanding hospital admission or extending the hospital stay of already hospitalized.^[7] In 1996, Freeman *et al.* added serum lipase level instead of serum amylase and a new-onset or worsening of preexisting abdominal pain as the clinical definition of pancreatitis.^[10]

Serum amylase assay at 4 h after ERCP is preferred for the diagnosis of PEP because its level can be compared with 24-h amylase assay. However, PEP can be overpredicted using a 4-h amylase assay because serum amylase value might be increased asymptotically starting from 1½ to 4 h after ERCP. On the other hand,

Sultana Parvin^{1,2},
Md. Samiul Islam³,
Md. Golam Azam¹,
Touhidul Karim
Majumdar²,
Shireen Ahmed¹,
Taslima Zaman⁴,
Rajib Dutta¹

¹Department of Gastrointestinal Hepatobiliary and Pancreatic Disorders, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders, Shahbag, ²Department of Medical Gastroenterology, Sheikh Russel National Gastroenterology Institute and Hospital, Mohakhali, ³Department of Orthopaedics, National Institute of Traumatology and Orthopedic Rehabilitation, Sher-e-Bangla Nagar, ⁴Department of Gastroenterology, Japan East West Medical College and Hospital, Dhaka, Bangladesh

Submitted: 16-Mar-2021

Revised: 28-Jun-2021

Accepted: 27-May-2021

Published: 17-Nov-2021

Address for correspondence:

Dr. Sultana Parvin,
Department of Medical
Gastroenterology, Sheikh Russel
National Gastroenterology
Institute and Hospital, Mohakhali,
Dhaka 1212, Bangladesh.
E-mail: champa.34th@gmail.com

Access this article online

Website:
www.ijabmr.org

DOI:
10.4103/ijabmr.ijabmr_192_21

Quick Response Code:



How to cite this article: Parvin S, Islam MS, Azam MG, Majumdar TK, Ahmed S, Zaman T, *et al.* Role of 4-H serum lipase level in predicting postendoscopic retrograde cholangiopancreatography pancreatitis. *Int J App Basic Med Res* 2021;11:238–42.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

serum lipase level starts to rise between 4 and 8 h after the onset of PEP, reaches to peak at 24 h, and declines within 8–14 days. Considering this, lipase levels measured at 4 h can be a good and valid alternative investigation for the early prediction of PEP. Very few studies have shown the comparison between serum lipase and amylase assay as an early predictor of PEP pancreatitis.^[9,13,14]

The early detection of PEP is very crucial to reduce not only the hazards and expenditure but also allows prompt admission and timely rapid commencement of the necessary supportive care of patients at risk of developing PEP and safe discharge of others. This prospective single-centered study has evaluated both the enzymes serum lipase and amylase at 4 h for the prediction of PEP with special attention to serum lipase if it could be a better than serum amylase for the early prediction.

Methods

Considering expected proportion of event 40% (incidence rates of PEP have been reported to vary from <1% to 40%)^[6] and a margin of error of 10% with 95% confidence interval (CI), we calculated a sample size of at least 92. Using a cross-sectional study design and a nonprobability convenience sampling approach, we investigated on 125 ERCPs conducted during a 1-year and 9-month period. Adult patients (age >18 years) having baseline serum lipase and amylase level <3 times the upper range of standard value were studied, but those having a stent *in situ* or having any contraindication for ERCP were excluded. This research has been approved by the institutional review board of the author’s affiliated institutions.

A predesigned structured questionnaire was filled up containing information regarding clinical history focusing on risk factors for PEP and necessary baseline investigations, including serum lipase and amylase levels. Follow-up data were recorded with serum amylase and lipase level during the procedure and 4 h and 24 h (next morning) after the

procedure. Serum amylase and lipase, were measured according to the laboratory standards [Table 1].^[15,16]

Statistical analyses were carried out using the SPSS (Statistical Package for the Social Sciences) for Windows, Version 23.0 (IBM Corporation, Armonk, New York). “Chi-square” test, binary logistic regression test, and multivariate regression analysis were used for statistical analysis where applicable. Based on sensitivity and specificity from the receiver operator characteristic (ROC) curve, optimal cutoff levels for the enzyme, serum lipase, and amylase levels were employed to predict PEP. $P \leq 0.05$ was considered statistically significant, and the CI was 95%.

Results

Among the patients who underwent ERCP, 125 who satisfied the inclusion criteria were studied. Patients’ ages ranged from 21 to 80 years with a mean of 55.76 ± 13.57 years. Among them, 58.4% were male [Table 2]. In the present study, 26 (20.8%) cases developed PEP [Figure 1]. Multivariate analysis found a significant association between young age, suspected SOD, recurrent pancreatitis, needle papillotomy,

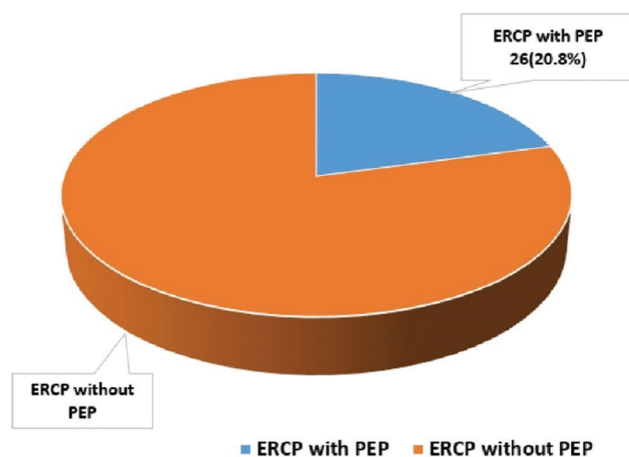


Figure 1: Pie diagram showing the frequency of postendoscopic retrograde cholangiopancreatography pancreatitis

Table 1: Minimum reagent fill volume per kit (Abbott Laboratories)^[15,16]

Serum amylase		Serum lipase	
Reactive ingredients	Concentration	Reactive ingredients	Concentration
2-chloro-4-nitrophenyl- α -D-maltotriose (mmol/L)	2.25	Cholic acid (mmol/L)	5.34
Sodium chloride (mmol/L)	350	1,2-diglyceride (mmol/L)	1.1
Calcium acetate (mmol/L)	6	Monoglyceride lipase (U/mL)	≥ 0.86
Potassium thiocyanate (mmol/L)	900	Glycerol kinase (U/mL)	≥ 1.34
Sodium azide (%)	<0.1	Glycerol-3-phosphate oxidase (U/mL)	≥ 40.0
-	-	Peroxidase (U/mL)	≥ 1.34
-	-	Colipase (U/mL)	≥ 40.0
-	-	TOOS (%)	0.068
-	-	ATP (mmol/L)	0.66
-	-	Deoxycholate (mmol/L)	36.0
-	-	4-aminoantipyrine (%)	0.12

TOOS=N-ethyl-N-(2-hydroxy- 3-sulfopropyl)-m-toluidine, ATP=Adenosine triphosphate

and PEP [Table 3]. The enzyme amylase level at 4 h in the ROC curve found a test result of 149 IU/L (area under the curve [AUC] of 0.967) where the optimal cutoff levels were 1.19-fold increase of the highest level of the standard range, showing the highest sensitivity and specificity of 88 and 92, respectively [Figure 2a]. On the other hand, serum lipase level at 4 h also showed good test result (AUC of 0.963) where the optimal cutoff levels were 3.82-fold (298 IU/L) increase of the highest level of standard range, showing the highest sensitivity and specificity of 96 and 89, respectively [Figure 2b]. Again, the enzyme serum amylase level at 24 h in the ROC curve found to have good test performance (AUC of 0.998) where the optimal cutoff levels were 3.10 times (388 IU/L) the highest level of the standard range, showing the highest sensitivity and specificity of 96 and 99, respectively [Figure 2c]. On the other hand, serum lipase level at 24 h also showed good test performance (AUC of 0.991) where the optimal cutoff levels were 3.60 times (281 IU/L) the upper level of the normal range, showing the highest sensitivity and specificity of 96 and 97, respectively [Figure 2d]. When the ROC curve summarized in a tabulated form, 4-h lipase level showed good test performance (AUC of 0.963), where the cutoff value 298 U/L was 3.82 times the highest level of the standard range, showing the highest sensitivity and specificity of 96 and 89, respectively [Table 4]. In multivariate regression analysis, both the amylase and lipase are significantly increasing while ERCP with PEP ($P < 0.001$); but the change in lipase was greater than amylase [Table 5].

Discussion

Pancreatitis after ERCP can be a substantial threat that often results in notable morbidity and occasional mortality.^[8,9] Although its reported incidence has varied among studies, when considering low-risk and high-risk groups together, it occurs after <1%–40% of procedures.^[6] In this study, we diagnosed PEP by measuring the enzyme, lipase, and amylase values following the consensus paper of Cotton *et al.* (1991). To the best of our knowledge, this is the pioneer paper from Bangladesh on the early diagnosis of PEP using serum lipase or amylase.

In the present study, 26 (20.8%) out of 125 patients developed PEP. A study on 238 subjects in Indonesia reported PEP to occur in 63 (26%) cases.^[17] Another study in Ohio, USA, found 23% PEP.^[18] Another recent study on 300 cases reported 11.7% of PEP.^[19] The incidence of PEP varies due to the wide variation of cases, overall follow-up, the definition of the PEP, associated risk factor, comorbid conditions, and expertise of the intervening endoscopist.^[20] Regarding risk factors, young age, suspected SOD, recurrent pancreatitis, and needle papillotomy have been identified as a significant risk factor for PEP in multivariate analysis. Cheng *et al.* similarly found age, suspected SOD, and history of PEP as a significant risk factor.^[8]

Plotted in the ROC curve, both the enzyme assay (lipase or amylase) at 4 h after ERCP showed good test performance

Table 2: Basic characteristics of the subjects (n=125)

Characteristics	Value
Age (years)	
20-39	19 (15)
40-60	53 (42.4)
>60	53 (42.4)
Mean±SD	55.76±13.57
Sex	
Male	74 (55.1)
Female	51 (44.9)

Values are presented as frequency, mean or percentage. Percentage in the parenthesis. SD=Standard deviation

Table 3: Multivariate analysis showing risk factors for postendoscopic retrograde cholangiopancreatography pancreatitis

Risk factors	OR	95% CI
Significant		
Young age	2.853	0.645-12.61
Suspected SOD (yes/no)	2.959	0.351-24.939
Recurrent pancreatitis (yes/no)	1.134	0.086-14.970
Needle papillotomy/precut access	2.840	0.720-11.212

Binary logistic regression test was done to see any significant association. SOD=Sphincter of Oddi dysfunction, OR=Odds ratio, CI=Confidence interval

Table 4: The specific cutoff levels of enzymes regarding the prediction of postendoscopic retrograde cholangiopancreatography pancreatitis

	4 h serum amylase	4 h serum lipase	24 h serum amylase	24 h serum lipase
Cutoff value	149	298	388	281
Amylase level	1.19 times		3.10 times	
Lipase level		3.82 times		3.60 times
Sensitivity (%)	88	96	96	96
Specificity (%)	92	89	99	97
AUC	0.967	0.963	0.998	0.991
PPV	65	71	96	89
NPV	98	99	99	99

Normal serum amylase level in adult: 25-125 IU/L (Abbott Laboratories),^[15] Normal serum lipase level in adult: 8-78 IU/L (Abbott Laboratories).^[16] AUC=Area under the curve, PPV=Positive predictive value, NPV=Negative predictive value

with AUC of 0.967 and 0.963, respectively. Again, levels at 24 h were also able to demonstrate good test performance, with AUC of 0.998 and 0.991 found, respectively. Enzyme level increment at 24 h has confirmed the diagnosis of PEP and has also justified the acceptability of lipase values measured at 4 h for the early diagnosis of PEP.^[7,10] Nishino *et al.*, in their study, reported that lipase assay after ERCP at 4 h was useful for predicting pancreatitis.^[9]

Considering optimum cutoff levels, the performance test of both 4-h serum amylase and lipase in this study found to be significant ($P < 0.0001$ for both enzymes). However,

Table 5: Association of 4-h amylase and lipase in endoscopic retrograde cholangiopancreatography with postendoscopic retrograde cholangiopancreatography pancreatitis group compared to endoscopic retrograde cholangiopancreatography without postendoscopic retrograde cholangiopancreatography pancreatitis group

	Unadjusted		Adjusted	
	β -coefficient (95% CI)	P	β -coefficient (95% CI)	P
4-h amylase				
ERCP with PEP group	547.90 (397.1-698.7)	<0.001	497.7 (342.5-652.8)	<0.001
4-h lipase				
ERCP with PEP group	1442 (1021-1862)	<0.001	1268 (844-1693)	<0.001

Level of significance found by multivariate regression analysis. ERCP=Endoscopic retrograde cholangiopancreatography, PEP=Postendoscopic retrograde cholangiopancreatography pancreatitis, CI=Confidence interval

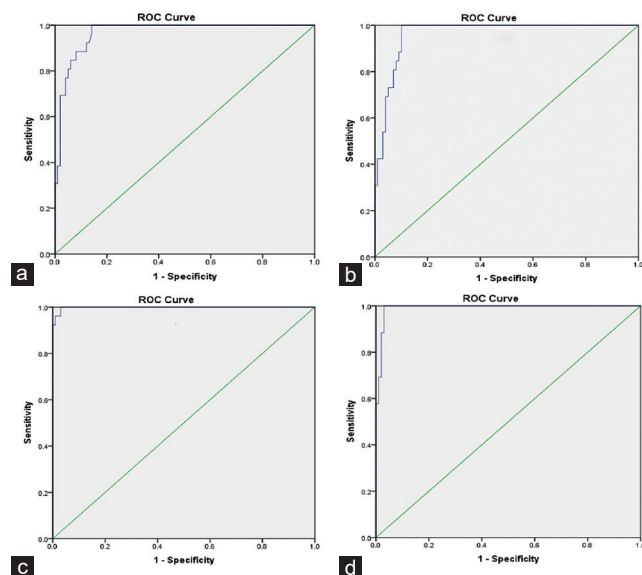


Figure 2: Receiver operator characteristic curve showing test accuracy of (a) 4-h serum amylase (AUC = 0.967), (b) 4-h serum lipase (AUC = 0.963), (c) 24 h serum amylase (AUC = 0.998), and (d) 24 h serum lipase (AUC = 0.991). AUC=Area under the curve

a careful observation of the cutoff levels showed that the level at 4-h lipase was on an average nearly 4 times the upper level of the standard range, which might be very useful for early detection of pancreatitis compared to 4-h amylase (nearly 4-times versus only slightly more than 1-time increase), the same observation explained by Cotton *et al.* (1991) in his consensus paper previously.

Unadjusted and adjusted multivariate regression analysis found that both 4-h serum amylase and lipase level were significantly increasing ($P < 0.001$) while ERCP with PEP. But, if we look at the estimate of change where lipase level had a greater change than amylase, which is the same reflection of more increase of 4 h lipase cutoff value found in ROC. When taking all these issues into account, 4-h serum lipase level is a more reliable indicator in predicting PEP than amylase and for same-day discharge.

Conclusion

Both the enzyme lipase and amylase assay at 4 h after ERCP were satisfactory predictors for PEP. However, the

change in the upper level of the normal range of serum lipase was greater than that of amylase. Thus, serum lipase assay at 4 h would allow the early prediction of PEP with less possibility of overprediction than amylase. Thereby, it would allow prompt admission of those at risk and early safe discharge of others.

Acknowledgment

The authors express their gratitude to the institute and hospital where the research took place and all the participants and colleagues who made it successful.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Adler DG, Baron TH, Davila RE, Egan J, Hirota WK, Leighton JA, *et al.* ASGE guideline: The role of ERCP in diseases of the biliary tract and the pancreas. *Gastrointest Endosc* 2005;62:1-8.
- Coelho-Prabhu N, Shah ND, Van Houten H, Kamath PS, Baron TH. Endoscopic retrograde cholangiopancreatography: Utilisation and outcomes in a 10-year population-based cohort. *BMJ Open* 2013;3:e002689.
- Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: A multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009;70:80-8.
- Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: A comprehensive review. *Gastrointest Endosc* 2004;59:845-64.
- ASGE Standards of Practice Committee, Anderson MA, Fisher L, Jain R, Evans JA, Appalaneni V, *et al.* Complications of ERCP. *Gastrointest Endosc* 2012;75:467-73.
- Pekgöz M. Post-endoscopic retrograde cholangiopancreatography pancreatitis: A systematic review for prevention and treatment. *World J Gastroenterol* 2019;25:4019-42.
- Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, *et al.* Endoscopic sphincterotomy complications and their management: An attempt at consensus. *Gastrointest Endosc* 1991;37:383-93.
- Cheng CL, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, *et al.* Risk factors for post-ERCP pancreatitis: A prospective multicenter study. *Am J Gastroenterol* 2006;101:139-47.
- Nishino T, Toki F, Oyama H, Shiratori K. More accurate

- prediction of post-ERCP pancreatitis by 4-hr serum lipase levels than amylase levels. *Dig Endosc* 2008;20:169-77.
10. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, *et al.* Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996;335:909-18.
 11. Christoforidis E, Goulimaris I, Kanellos I, Tsalis K, Demetriades C, Betsis D. Post-ERCP pancreatitis and hyperamylasemia: Patient-related and operative risk factors. *Endoscopy* 2002;34:286-92.
 12. Wang P, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, *et al.* Risk factors for ERCP-related complications: A prospective multicenter study. *Am J Gastroenterol* 2009;104:31-40.
 13. Papachristos A, Howard T, Thomson BN, Thomas PR. Predicting post-endoscopic retrograde cholangiopancreatography pancreatitis using the 4-h serum lipase level. *ANZ J Surg* 2018;88:82-6.
 14. Sutton VR, Hong MK, Thomas PR. Using the 4-hour Post-ERCP Amylase Level to Predict Post-ERCP Pancreatitis. *J Pancreas* 2011;12:372-76.
 15. Abbott Laboratories Clinical Chemistry. Amylase Assay on the ARCHITECT cSystems, Abbott Park, IL 60064, USA: Abbott diagnostics; February 2007. Available from: https://www.ilexmedical.com/files/PDF/Amylase_ARC_CHEM.pdf. [Last accessed on 2021 Jun 28].
 16. Abbott Laboratories Clinical Chemistry. Lipase assay on the ARCHITECT cSystems, Abbott Park, IL 60064, USA: Abbott diagnostics; March 2009. Available from: https://www.ilexmedical.com/files/PDF/Lipase_ARC_CHEM.pdf. [Last accessed on 2021 Jun 28].
 17. Makmun D, Abdullah M, Syam AF, Fauzi A. Post-ERCP pancreatitis and its related factors: A prospective study in Cipto Mangunkusumo National General Hospital. *J Dig Endosc* 2019;6:163-8.
 18. Kaw M, Singh S. Serum lipase, C-reactive protein, and interleukin-6 levels in ERCP-induced pancreatitis. *Gastrointest Endosc* 2001;54:435-40.
 19. Minakari M, Sebghatollahi V, Sattari M, Fahami E. Serum amylase and lipase levels for prediction of postendoscopic retrograde cholangiopancreatography pancreatitis. *J Res Med Sci* 2018;23:54.
 20. Nishino T TFe. Prediction of Post-ERCP Pancreatitis. In: Rodrigo L, editor. *Pancreatitis Treatment and Complications*. 1st ed. London, UK: Intech Open Limited; 2012. p. 131-44.