

Usefulness of serum amylase and lipase as predictors of the severity of post-endoscopic retrograde cholangiopancreatography pancreatitis

Utilidad de la amilasa y la lipasa séricas como predictores de gravedad en la pancreatitis poscolangiopancreatografía retrógrada endoscópica

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Abstract

Background: Post-ERCP pancreatitis (PEP) is the most common complication of Post-endoscopic retrograde cholangiopancreatography. **Objective:** The objective of the study was to demonstrate whether serum amylase and lipase values correlate with the presence and severity of PEP. **Methods:** We conducted a retrospective, observational, and analytical study of patients who underwent ERCP, those who developed pancreatitis were classified by severity according to the 2012 revised Atlanta criteria and their serum enzyme levels were analyzed. We used ROC (Receiver Operating Characteristics) curves to know the best enzyme cutoff points and analyzed their diagnostic yields. Chi-square, t-distribution, and Mann-Whitney U test were used in the variable analysis and it was considered statistically significant when $p < 0.05$. **Results:** A total 621 patients, 54 presented pancreatitis. For moderately severe and severe forms: lipase level of 1500 U/L had an area under the curve (AUC) = 0.827, 95% CI (0.67-0.98), sensitivity = 72.7%, specificity = 86%, and negative predictive value = 92.5%, $p < 0.05$. Amylase level of 920 U/L presented AUC = 0.65, 95% CI (0.43-0.86), sensitivity = 63%, and specificity = 67%, $p > 0.05$. **Conclusions:** Serum lipase shows correlation with the presence and severity of PEP. Amylase shows no significant correlation with PEP.

Keywords: Amylase. Endoscopic retrograde cholangiopancreatography. ERCP. Lipase. Pancreatitis. PEP.

Resumen

Antecedentes: La pancreatitis poscolangiopancreatografía retrógrada endoscópica (PPCPRE) es la complicación más frecuente de este procedimiento. **Objetivo:** Demostrar si la amilasa y la lipasa séricas se correlacionan con la presencia y la gravedad de la PPCPRE. **Método:** Realizamos un estudio retrospectivo, observacional y analítico de pacientes a quienes se realizó CPRE. Los que desarrollaron pancreatitis se clasificaron por gravedad de acuerdo con la revisión de Atlanta de 2012 y se analizaron sus concentraciones séricas de enzimas. Empleamos curvas ROC (Receiver Operating Characteristics) para conocer los mejores puntos de corte enzimáticos y analizamos sus rendimientos diagnósticos. Usamos las pruebas de ji al cuadrado, t de Student y U de Mann Whitney para el análisis de las variables, y se consideró estadísticamente significativo un valor de $p < 0.05$. **Resultados:** De un total de 621 pacientes, 54 presentaron pancreatitis. Para pancreatitis moderada-

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mente grave y grave, unas cifras de lipasa de 1500 U/l presentaron un área bajo la curva (AUC) = 0.827 (intervalo de confianza del 95% [IC 95%]: 0.67-0.98), con una sensibilidad del 72.7%, una especificidad del 86% y un valor predictivo negativo del 92.5% ($p < 0.05$); y unas cifras de amilasa de 920 U/l presentaron un AUC = 0.65 (IC 95%: 0.43-0.86), con una sensibilidad del 63% y una especificidad del 67% ($p > 0.05$). **Conclusiones:** La lipasa muestra correlación con la presencia y la gravedad de la PPCPRE. La amilasa muestra correlación no significativa con la PPCPRE.

Palabras Clave: Amilasa. Colangiopancreatografía retrógrada endoscópica. CPRE. Lipasa. Pancreatitis. PPCPRE.

Introducción

Acute pancreatitis is the most common complication after endoscopic retrograde cholangiopancreatography (ERCP). Its frequency of presentation is highly variable, but it is usually reported to range between 3% and 10%¹.

The mechanism by means of which post-ERCP pancreatitis (PEP) occurs is not fully understood, but it is suggested that it could be multifactorial^{2,3}. It is thought that it could represent an acute pancreatitis that is different from that caused by other etiologies, based on the pattern of pancreatic enzymes elevation, clinical manifestations, and a poorer prognosis when it occurs in its severe form^{3,4}.

Large studies have identified risk factors that are related to the presence of PEP, which can be classified as factors related to the patient, to the procedure and to the operator¹.

Most PEP episodes are described as mild (around 90%) and the rest develop moderate or severe pancreatitis (around 10%)⁵.

There are several methods that attempt to reduce the frequency of PEP, such as employing cannulation techniques that minimize ampullary trauma, using pancreatic duct stents, rectal administration of non-steroidal anti-inflammatory drugs (NSAIDs), or specific intravenous hydration protocols¹. However, even with the use of such measures, it is difficult to completely prevent this particular complication⁶.

There are scales for predicting the development of PEP based on the risk factors related to its occurrence⁷⁻⁹, but they contemplate too many variables and this makes them impractical.

There are only a few studies specifically in patients undergoing ERCP that evaluate the usefulness of determining serum amylase and lipase for predicting pancreatitis severity^{2,6,10-12}, which show that elevations of their values are correlated with the presence of severe forms of pancreatitis and that can be used as predictors; however, cutoff values, severity rating criteria and diagnostic performance differ.

Amylase and lipase quantification can be found to be available in our country's hospitals, and carrying out a study to evaluate the usefulness of these enzymes in PEP could be of great importance, since, if any usefulness is demonstrated, we would have a diagnostic tool that could be applicable to our population and that would give us a guideline for making better clinical decisions.

The purpose of this study is to demonstrate whether amylase and lipase values are correlated with the presence and severity of PEP.

Methods

We carried out a retrospective, observational, analytical study at Hospital Juárez de México, in hospitalized patients who underwent ERCP in the period comprised between March 2016 and February 2019. The inclusion criteria were the following: patients with scheduled or urgent ERCP at the same hospital, indomethacin application, hospital stay after ERCP, and having a complete medical record and amylase or lipase records after the procedure. Non-inclusion criteria were: patients younger 18 years of age, referred from another hospital, previous history of pancreatitis, oncological patients, and those with complications other than pancreatitis or resulting from it.

Indomethacin was rectally administered, at a single 100-mg dose, with the patient already in the room and at the start of the procedure. Taking a blood sample for amylase and lipase to be quantified is systematically carried out, on the day the procedure is performed at 18:00 h; considering the schedule in which the procedures are usually carried out, it implies that between the performance of the ERCP and the take of the blood sample for analysis, a time of 4-8 h elapses.

We use the Atlanta¹³ classification and definitions for pancreatitis diagnosis and severity categorization.

The study population was divided in two groups, according to pancreatitis presentation. We determined the frequency of PEP. Patients were classified according to the type of presentation into mild, moderately severe

and severe pancreatitis, and then in two groups: one with those who had the mild form and the other with those who had severe forms, that is, those with moderately severe or severe pancreatitis. We compared amylase and lipase values between both groups. The data obtained were summarized as percentages, medians, percentiles, means, and standard deviation. For the analysis of qualitative variables, we used the Chi-square test, and for continuous variables, we used Student's t-test and Mann–Whitney's U-test, depending on their normal or free distribution. The statistical tests that were used were two-tailed, and $p < 0.05$ was considered statistically significant.

We used Receiver Operating Characteristics (ROC) curves to find out amylase and lipase values cutoff points as predictors of pancreatitis severe forms. We determined the sensitivity, specificity, positive predictive value, and negative predictive value of the cutoff values found for each enzyme in the prediction of severe forms. For data analysis, we used the SPSS program, version 25, for Windows.

Results

A total of 621 patients met the inclusion criteria of the present study, with women to men ratio of 2.1:1. Out of all patients, 567 did not have pancreatitis and 54 did, and thus the frequency of this complication is 8.7%. PEP diagnosis was established by clinical criterion plus laboratory criteria in 52 patients, and by clinical criterion plus local complication by imaging (tomography) retrospectively in two patients.

Table 1 compares the main characteristics of patients with and without pancreatitis.

When the abdominal pain variable was examined, we found that all patients with pancreatitis developed abdominal pain, defined as epigastric pain radiating to the back, of new onset or exacerbation of previous pain. It should be noted that 21.3% of patients who did not develop pancreatitis also had abdominal pain after the procedure; with the Chi-square test, we confirmed that said observed differences are statistically significant ($p < 0.05$).

Of the blood samples for pancreatic enzymes quantification, 100% were taken between 4 and 8 h after the ERCP procedure. Of the entire patient sample, 92.4% had both amylase and lipase measurements. About 97% of the reports of the results of these enzymes are obtained in a period of <12 h after the ERCP procedure, and 100% before 17:00 h.

Table 1. Characteristics of patients with and without pancreatitis

	PEP		p
	Yes	No	
Number of patients (%)	54 (8.7)	567 (91.3)	
Age	43.5 years* (28 [†] to 59 [‡])	45 years* (31 [†] to 61 [‡])	0.6
Gender (%)	37 females (68.5) 17 males (31.5)	383 females (67.5) 184 males (32.5)	
Body mass index	28 [§] (3.1 [¶])	27.37 [§] (2.94 [¶])	0.2
Main indications for requesting the procedure, number of patients (%)	PB Choledocholithiasis, 35 (64.8) Cholangitis, 11 (20.3) Biliary fistula, 5 (9.3)	PB Choledocholithiasis, 383 (67.5) Cholangitis, 92 (16) Biliary fistula, 31 (5.5)	

* Median.

[†]25th percentile.

[‡]75th percentile.

[§]Mean.

[¶]Standard deviation.

Note: both groups of patients are highly homogeneous in age and gender, as well as in the main reasons for ERCP to be requested. There is a slight tendency towards a higher body mass index in those who had pancreatitis, but with no statistical significance.

PB: Probable choledocholithiasis; PEP: post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

Pancreatic enzymes characteristics in the groups with and without pancreatitis are shown in table 2.

In the group of patients without pancreatitis, enzymatic elevation of at least three times the upper limit of normal occurred in 33.5% and 14.5% for amylase and lipase, respectively.

When patients with pancreatitis were classified according to severity, 43 (79.6%) were found to correspond to mild, 9 (16.7%) to moderately severe, and 2 (3.7%) to severe pancreatitis.

When the patients with pancreatitis are divided in two groups, enzymes show higher elevation in the moderately severe and severe forms than in the mild form (Fig. 1). When these differences were analyzed between both groups, they are observed to have a free distribution and, therefore, when using Mann–Whitney's U-test, the difference observed for amylase is confirmed not to be statistically significant ($p = 0.052$). However, in the case of lipase, a correlation is shown to exist: the higher the enzymatic elevation, the greater the severity of PEP, a result that is statistically significant ($p < 0.05$).

The ROC curves of each enzyme for the prediction of severe and moderately severe pancreatitis are shown in figures 2 and 3.

Table 2. Pancreatic enzymes characteristics in the study population

	Patients with PEP (n = 54)		Patients without PEP (n = 567)	
	Amylase (U/L)	Lipase (U/L)	Amylase (U/L)	Lipase (U/L)
Mean	925	1253	156	96
Median	860	1180	105	58
Standard deviation	519	658	171	129
Minimum	152	199	7	7
Maximum	2997	3190	2050	1270
25 th percentile	593	835	60	35
75 th percentile	1063	1503	188	99

In the group with PEP, 52 patients both enzymes and 2 only lipase; in the group without PEP, 5 only amylase, 40 only lipase and 522 both enzymes. There was a tendency towards higher enzymatic levels in the group with PEP. The differences observed in the measurements of each enzyme between both groups are statistically significant, with $P < 0.05$.

PEP: post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

The area under the curve (AUC) of the ROC curve for amylase is 0.65, while that for lipase is 0.82. The best cutoff points of the curves were 920 U/L for amylase and 1,500 U/L for lipase (laboratory references: lipase 101 U/L and amylase 51 U/L). Only in the case of lipase is the result statistically significant ($p < 0.05$). The diagnostic values of amylase and lipase cutoff points are shown in table 3.

Discussion

At present, pancreatitis remains the most common and feared complication of ERCP¹⁴. The reported frequency widely varies, from 0.5%¹⁵ to up to 40%¹. In most observational and retrospective studies, such as this one, it ranges from 5 to 7%¹⁴. Prospective studies of unselected patients describe 4 to 8%³. Regarding observations published in Mexico, Montaña et al.¹⁶ and Romero et al.¹⁷ report 9.4% and 6%, respectively. In our study, the frequency was 8.7%.

Most studies that investigate PEP use Cotton's 1991 consensus severity definition and classification¹; however, as it has been pointed out, its use has limitations, among others because the degree of severity is subjective, given that this classification uses the definition of prolonged hospitalization, which is decided by the treating clinician¹⁸. In our study, we used the Atlanta review pancreatitis classification¹³, which although not specific to PEP¹, classifies pancreatitis severity according to the presence and duration of

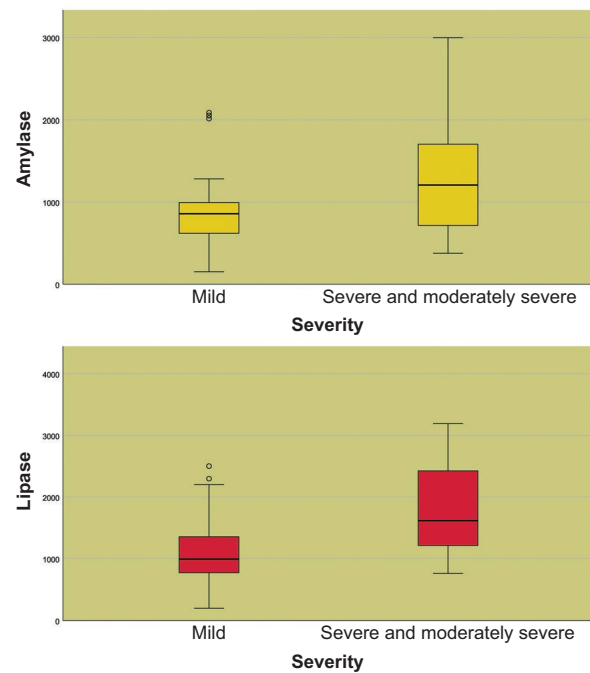


Figure 1. Graphs showing the relationship between enzymatic values and the severity of post-endoscopic retrograde cholangiopancreatography pancreatitis. The higher the amylase and lipase levels, the greater the severity of pancreatitis.

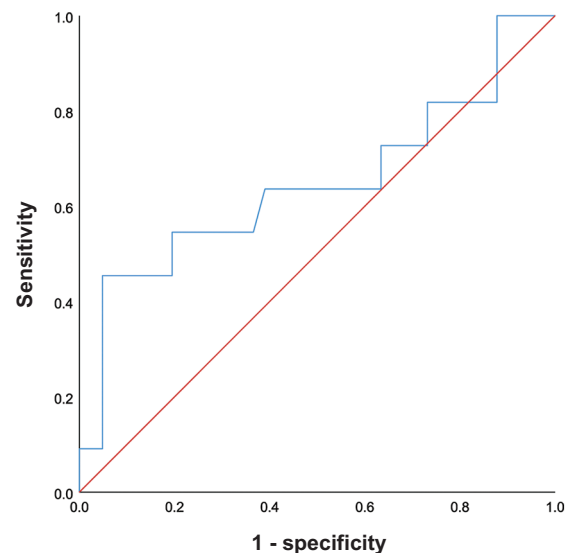


Figure 2. Amylase ROC curve for the prediction of severe and moderately severe pancreatitis in patients with post-endoscopic retrograde cholangiopancreatography pancreatitis. Area under the curve of 0.65 (95% confidence interval: 0.43 - 0.86). Best cutoff value with a sensitivity of 63% and specificity of 67% ($p = 0.13$).

organ failure and local and systemic complications, rather than to hospitalization duration¹⁹. Recent studies on acute pancreatitis use the Atlanta review to

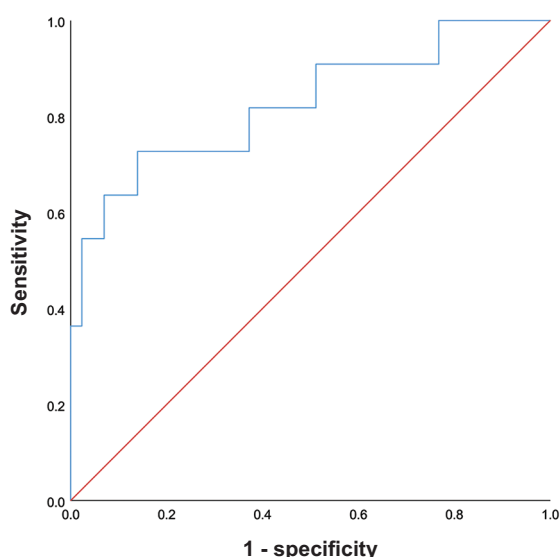


Figure 3. Lipase ROC curve for the prediction of severe and moderately severe pancreatitis in patients with post-endoscopic retrograde cholangiopancreatography pancreatitis. Area under the curve of 0.827 (95% confidence interval: 0.67-0.98. Best cutoff value with a sensitivity of 72.7%, specificity of 86% and negative predictive value of 92.5% ($p < 0.05$).

Table 3. Amylase 920 U/L and lipase 1500 U/L diagnostic values for the prediction of post-endoscopic retrograde cholangiopancreatography pancreatitis severe forms

	Amylase		Lipase	
	%	95% CI	%	95% CI
Sensitivity	63.6	35.4-84.8	72.7	43.4-90.3
Specificity	67.4	52.5-79.5	86	72.7-93.4
Positive predictive value	33.4	17.2-54.6	57.1	32.6-78.6
Negative predictive value	87.9	72.7-95.2	92.5	80.1-97.4
Accuracy	66.7	53.4-77.8	83.3	71.3-91
Odds ratio	3.6	0.9-14	16.4	3.4-80

CI: confidence interval.

classify severity, given that its criteria are easily identifiable²⁰; it has also started being used in PEP¹⁸ and is the one that best reflects its severity²¹.

The percentage of patients with pancreatitis without abdominal pain is low: 2.3%¹¹. We found that the presence of abdominal pain is highly suggestive of a PEP diagnosis, but we observed that it occurs in at least one out of every five patients undergoing ERCP who do not develop pancreatitis.

Hyperamylasemia, defined as an amylase elevation of at least 3 times the normal upper limit without

symptoms of pancreatitis¹¹, occurred in our study in 33.5%; in the literature, it is reported to range from 25 to 75%^{1,11}. The greatest usefulness of imaging tests is for detection of complications, and most patients do not require them for the diagnosis of acute pancreatitis²²; in our study, only in 0.3% were used for diagnosis.

When patients were classified by severity, we found similar percentages to those of the study by Kim et al.¹⁸ on risk factors for PEP using the Atlanta classification, where 83, 12.8%, and 3.5% are reported for mild, moderately severe and severe pancreatitis, respectively.

Most patients with pancreatitis have mild episodes that are self-limiting^{1,14}. Those with moderately severe and severe episodes might eventually experience considerable morbidity and increased mortality^{4,14}. It is quite similar to what is reported for acute pancreatitis from other causes²³. However, the study by Ignatavicius et al.²⁴ suggests that patients with the moderately severe form could be considered within the group of mild PEP due to a similar course of disease; however, in said study, up to 26% of patients with moderately severe disease behaved as those with severe pancreatitis.

The use of pancreatic enzymes to predict PEP severity is supported by several studies. However, the criteria for classifying severity are different, as well as the cutoff values and, evidently, the age groups^{2,6,10-12}.

Our results confirm that there is correlation between enzyme elevation and the presence and PEP severity in the case of serum lipase, as reported in other publications^{2,11,25} whose cutoff value has a negative predictive value of 92.5%; consequently, the lower figures of this cutoff value could be used to rule out moderately severe or severe PEP. In the case of amylase, there is also a less important correlation and with no statistical significance. Our results contrast with reports by several authors who have published higher values, both for sensitivity and specificity, for the same cutoff value and in both enzymes^{6,12,26}.

It is important having carried out the present study because it offers us information that in our hospital environment could be used for clinical decision-making in patients undergoing ERCP, based on an available test. However, the study has some limitations, such as its retrospective nature, which prevents having more accurate information; furthermore, the sample is not that large, which might explain the wide confidence intervals that were obtained, although this could also less possibly be caused by the low

homogeneity of the included population despite the inclusion criteria. External validation is required in other hospitals of our country, or the performance of prospective studies.

This study is the first in Latin America to evaluate the usefulness of pancreatic enzymes as predictors of PEP severity.

Conclusions

A serum lipase value > 1500 U/L is correlated with the occurrence of moderately severe and severe PEP and could be used as a predictive tool.

Serum lipase quantification only in patients with abdominal pain after ERCP appears to be more useful for predicting PEP severe forms than systematic amylase and lipase quantification in all patients undergoing ERCP. Serum amylase shows a non-statistically significant correlation with PEP severe forms.

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Conflict of interests

The authors declare that they have no conflicts of interests.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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