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Date:
2018-01-01

Citation:
Papachristos, A., Howard, T., Thomson, B. N. & Thomas, P. R. (2018). Predicting post-endoscopic retrograde cholangiopancreatography pancreatitis using the 4-h serum lipase level. ANZ Journal of Surgery, 88 (1-2), pp.82-86. https://doi.org/10.1111/ans.13665.

Persistent Link:
https://hdl.handle.net/11343/291535

Title:

Predicting Post-ERCP Pancreatitis using the 4-hour Serum Lipase Level

Running Title:

Predicting Post-ERCP Pancreatitis

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No financial support has been received for this study.

Tables: 3

Figures: 0

Supplementary information: 2 tables, 2 figures

Abstract Word Count: 203
Total Word Count: 3982

Key Words: ERCP, Pancreatitis, Lipase, Amylase, Rural health

Abstract

Introduction

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a complex therapeutic procedure that is complicated by pancreatitis in 3-5% of cases. The aim of this study is to determine whether a 4-hour post-ERCP serum lipase level is superior to the serum amylase level in predicting the occurrence of Post-ERCP Pancreatitis (PEP).

Methods

We performed a retrospective review of prospectively collected data on 543 consecutive patients undergoing therapeutic ERCP at a single centre. Serum lipase and amylase levels were measured at 4-hours post-procedure and were recorded as a factor of the upper limit of normal: Amylase Factor (AF) and Lipase Factor (LF). Sensitivity and specificity were compared using receiver-operating characteristics and the Youden index (YI).

Results

A total of 506 procedures were considered for analysis. PEP occurred in 19 patients (3.8%). A LF of < 10 was useful for the exclusion of PEP with a sensitivity of 100% and a specificity of 94%, YI = 0.94. In contrast, an AF < 3 yielded a sensitivity of 79% and specificity of 94%, YI = 0.73.

Discussion

Serum lipase measured at 4-hours post-ERCP better excludes PEP than serum amylase measured at the same time-point. Patients with a LF < 10 may be safely considered for same-day discharge.

Abstract Word Count: 203

Total Word Count: 3982

Introduction

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a complex therapeutic procedure, used with increasing frequency in the management of biliary and pancreatic pathology[1]. Historically, ERCP was commonly a diagnostic procedure, however with improved imaging technology and accessibility of Computer-Tomography Intravenous Cholangiopancreatography (CT-IVC) and Magnetic Resonance Cholangiopancreatography (MRCP), ERCP has become primarily a therapeutic procedure. The most common complication of ERCP is pancreatitis, occurring in approximately 3-5% of cases[2-6], which can range from mild to life-threatening. Originally patients were routinely admitted for observation after ERCP to ensure they did not develop Post-ERCP Pancreatitis (PEP), however, in recent years there has been a growing trend to perform the procedure as a day case. In a rural setting, patients are often geographically isolated and it is therefore crucial to be able to predict which patients will go on to develop PEP and which patients can be safely discharged.

The use of clinical assessment in predicting PEP has been shown to be unreliable, as post-procedural pain is common and conversely a large proportion of patients who subsequently develop PEP are asymptomatic for a number of hours[7]. Many studies have examined the risk factors associated with PEP[1-17] and the serum amylase level measured at 4-hours post-ERCP has been shown to be a useful predictor of PEP, with Negative Predictive Values (NPV) of 0.97-0.99[7, 13, 15]. However, in the diagnosis of acute pancreatitis in other settings, the serum lipase level has been shown to be a more sensitive and specific marker than the serum amylase level[18, 19]. In addition, serum lipase rises earlier than amylase[20] and therefore, we hypothesise that a 4-hour post-procedure serum lipase level is a better predictor of PEP.

We aim to determine whether a 4-hour post-ERCP serum lipase level is superior to the serum amylase level in predicting the occurrence of PEP, and based on this data, to develop a practical discharge algorithm for patients undergoing ERCP.

Materials and Methods

We performed a retrospective review of prospectively collected data of patients undergoing therapeutic ERCP at a single regional centre (NHW) over a five-year period. All patients had serum lipase and amylase levels measured four hours after their procedure.

All procedures were performed by a single endoscopist, accredited in ERCP by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy (CCRTGE), and were carried out in the operating theatre with an anaesthetist administering sedation or general anaesthesia. An Olympus side-viewing duodenoscope was used (Olympus Australia, Notting Hill, VIC, AUS) and all patients received prophylactic antibiotics.

The endoscopist recorded all data prospectively. This included patient demographics, indication for the procedure, procedural details and findings, 4-hour post-procedure serum lipase and amylase levels and the occurrence of PEP or other morbidity and mortality that occurred within 30 days. Specific procedural details included whether cannulation was successful, the need for endoscopic sphincterotomy and whether the pancreatic ducts were opacified (pancreatogram). All pancreatograms were unintentional. A guide-wire was initially passed in all cases to confirm cannulation of the common bile duct prior to contrast injection. All cases were therapeutic and were performed for biliary intervention, with no pancreatic procedures

performed. At our centre we have had CT-IVC facilities available for the last ten years and MRCP on-site for the last three years, negating the need for diagnostic ERCP.

The serum amylase and lipase levels were recorded as a factor of the upper limit of the normal reference range: Amylase Factor (AF) and Lipase Factor (LF). This accounted for any change in the reference range during the study period. Patients were admitted for observation in accordance with a previously described algorithm[15]: if the 4-hour serum amylase level was greater than three times the upper limit of normal (AF ≥ 3) or if there were any clinical concerns.

PEP was defined according the consensus paper published by Cotton et al.[21] and the revised Atlanta classification[22] and required abdominal pain to persist for at least 24 hours associated with an AF ≥ 3 at the same time point. A CT scan may be performed if there is concern regarding perforation or a local complication of pancreatitis such as necrosis or pseudocyst formation, or if there were any clinical uncertainty. Mild pancreatitis resulted in no organ failure or local or systemic complications, moderate pancreatitis resulted in transient organ failure that resolved within 48 hours or local or systemic complications without organ failure, and severe pancreatitis occurred if organ failure persisted for >48 hours[22].

Patients were excluded from the analysis if no post-procedural serum amylase and lipase levels were measured, if the endoscope was not passed to the second part of the duodenum, or if the patient had pre-existing acute gallstone pancreatitis. All patients in whom ERCP was attempted with unsuccessful cannulation of the ampulla were included in the analysis. Ethical approval was obtained from the relevant ethics committee (NHW HREC project 2015-162).

Data were entered into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, Washington, USA) and analysed using Stata 13.0 (StataCorp LP, Texas, USA). Data analysis was performed independently of the endoscopist. All cases of pancreatitis were reviewed to confirm the severity. The endpoints for analysis were to compare the sensitivity and specificity of AF and LF in predicting PEP. Receiver operating characteristics of the AF and LF levels relating to the prediction of PEP were performed by plotting the sensitivity against 1-specificity, and the Youden Index (Sensitivity + Specificity – 1) was used to assess the performance of AF and LF as diagnostic tests. A two-tailed Fisher's exact test was used to compare other procedural variables. P-values below 0.05 were considered statistically significant.

Results:

Demographic details

Between February 2010 and June 2015 a total of 543 procedures were performed. There were 300 females (55%) and the median age of the cohort was 69 years (range 17-98). 38% of patients were aged ≥ 75 years. The indications for ERCP and procedural details are summarised in table 1.

There were three deaths (0.6%) in the series; two occurred during the index admission and were due to the presenting problem of cholangitis and the third occurred four months later as a result of the patient's underlying malignancy. No deaths occurred due to PEP. Complications are summarised in table 1. There was one perforation that occurred during sphincterotomy and one sphincterotomy that resulted in uncontrollable bleeding requiring laparotomy. All cardiorespiratory complications occurred in patients who had emergency ERCP performed for cholangitis.

Data Analysis

Of the 543 procedures, a total of 506 procedures were considered for analysis and 37 patients (6.8%) were excluded; nine patients (1.7%) did not have post-operative serum lipase and amylase levels measured, 24 (4.4%) had pre-existing acute gallstone pancreatitis, two patients (0.4%) had oesophageal strictures, one (0.2%) had a previous Billroth II gastrectomy and another (0.2%) had an obstructing duodenal cancer preventing passage of the scope.

PEP occurred in 19 patients (3.8%): 15 mild (3.0%) and four moderate (0.8%). There were no cases of severe PEP. CT scans were performed in four cases; in one to exclude perforation as a complication of sphincterotomy and in three to exclude pancreatic necrosis. All four CT scans confirmed acute pancreatitis. Patients who had a pancreatogram were significantly more likely to develop PEP ($p<0.0001$). Females had a slightly higher rate of PEP (5% vs 2.2%), however this difference was not statistically significant.

The AF and LF levels are summarised in table 2. A total of 48 patients (9.5%) had a LF ≥ 10, including all 19 patients who developed PEP. In comparison, 84 patients (16.6%) had an AF ≥ 1.5, including the 19 cases of PEP. The performance of AF and LF at various cut-offs in predicting PEP are summarised in table 3. A LF of 10 yielded a sensitivity of 100% and a specificity of 94%, with a NPV of 100%. In contrast, an AF cut-off of 3 gave a sensitivity of 79% and a specificity of 94%, with a NPV of 99%.

Receiver-operating characteristics of AF (Fig. S1) and LF (Fig. S2) demonstrated good test performance. The area under the AF curve was 0.96, p=0.01; 95% confidence interval [0.94, 0.98]

and 0.97 under the LF curve, p=0.007; 95% confidence interval [0.96, 0.99]. The maximum Youden Index for AF was 0.87 at a cut-off of 1.5, compared to 0.94 for LF at a cut-off of 10.

The breakdown of AF and LF levels stratified by the presence or absence of a pancreatogram is displayed in tables S1 and S2. Among patients who did not have a pancreatogram, there was no patient who developed PEP with a LF < 20. Using this cut-off, the specificity increased to 97.5% with a positive likelihood ratio of 40.6. In this group, an AF of 1.5 remained the highest cut-point at which no cases of PEP were missed.

Discussion

Accurately predicting PEP allows both safe same-day discharge of the majority of patients undergoing therapeutic ERCP at our centre, as well as the early instigation of supportive care in the at-risk group. There is no published data on admission practices for ERCP in Australia, however in the majority of metropolitan centres, most patients would be discharged on the day of the procedure in the absence of any clinical concern. In a rural setting, it is particular important to identify patients who will go on to develop PEP, as geographic isolation is common and it is not unusual for patients to travel 200km each way. Freeman et al. reported a readmission rate of 5.7% following same-day therapeutic ERCP[23] – the majority with pancreatitis. There is currently no available data on the readmission rates following ERCP in Australia, however we would expect it to be similar.

The definition of PEP was based on the consensus paper published by Cotton et al.[21] Patients who had signs and symptoms of pancreatitis (upper abdominal pain and tenderness) that persisted for at least 24 hours after the procedure, associated with an amylase level greater than

three times the upper limit of normal at the 24-hour mark, were diagnosed with PEP. We accept that there are limitations to this definition, as the elevation of pancreatic enzymes after ERCP may be non-specific. As seen in our data, it is not uncommon for patients to have raised pancreatic enzymes after ERCP and the majority of these patients do not clinically develop pancreatitis. However, there was no patient who had symptoms and signs consistent with pancreatitis at 24-hours post-procedure with normal pancreatic enzymes. Among patients that developed PEP with an AF < 3 at the 4-hour mark, all had an AF > 3 at 24-hours post-procedure. While the elevation of pancreatic enzymes post-ERCP is not specific for pancreatitis, it is highly sensitive. Therefore, we found the combination of raised enzymes at 24-hours post-procedure > 3 times the upper limit of normal and the clinical symptoms and signs of pancreatitis to be acceptable diagnostic criteria and our rate of PEP was similar to what has previously been reported[2, 4, 6]. In the majority of cases a CT scan was not required. Only four of the nineteen patients with pancreatitis had CT scans, and in three of these cases it was performed 48-72 hours post-ERCP to exclude a local complication of pancreatitis. In one case, a CT was performed on the morning following the procedure as there was a concern regarding perforation.

Previous studies have demonstrated that the AF is a useful test in predicting PEP, however finding an optimal cut-off in sensitivity and specificity was challenging. Sutton *et al.* found that using an AF of 5 in patients who had had a pancreatogram provided a NPV of 98.3%. However, the sensitivity was only 50% as five of the ten patients who went on to develop moderate or severe PEP had an AF of less than 5. Increasing the sensitivity by dropping the AF to 1.5 meant that nine of the 10 patients were identified, however the specificity dropped to 69.7% with a likelihood ratio of 2.97[13]. The goal of creating a practical discharge algorithm is to confidently include all patients who will go on to develop PEP, while maintaining an acceptable specificity so that the number of patients requiring admission is not unnecessarily large.

We found that LF was superior to AF in fulfilling these requirements. As seen in table 2, patients who went on to develop PEP had LF levels that were concentrated to the higher end of the spectrum, with only one patient recording a LF of < 20. The fact that corresponding AF levels in these patients had a greater spread – down to as low as 1.5 in a patient who went on to develop moderately severe pancreatitis – is most likely because the lipase level rises earlier than amylase, and hence is better suited to predicting PEP at the 4-hour post-procedure time-point.

Using a LF of 10, no cases of PEP were missed and a specificity of 94% was achieved with a positive likelihood ratio of 17.2. An AF of 3, previously used in the discharge algorithm[15], provided a similar specificity to a LF of 10. However, with a sensitivity of 75%, four out of the 19 cases of pancreatitis were missed. When assessing the value of AF and LF as predictive tests, false negatives are more undesirable than false positives and therefore the discharge algorithm should use the first cut-point at which 100% sensitivity is reached. An AF of 1.5 is the only cut-off at which no cases of PEP were missed, consistent with previous research[13, 15], and at this level our calculated specificity was 86.7% with a positive likelihood ratio of 7.5.

By incorporating the risk factor of a pancreatogram, a higher degree of specificity can be achieved. Based on these results, we propose an algorithm to assess the suitability for discharge following therapeutic ERCP in our regional setting. Patients with a LF of <10 can be safely considered for discharge on the day of the procedure. Patients with a LF of ≥20 should be admitted for observation. If a patient has a LF between 10 and 20, they should be admitted for observation if they have had a pancreatogram, otherwise they may be considered for discharge. Following this algorithm, 8% of our cohort would have been admitted overnight for observation

and 45% of these patients would go on to develop PEP. All cases of PEP would have been admitted.

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Tables and Figures

Table 1: Indication, procedural details and complications

Indication	Patients (%)
Stone: pain / jaundice	305 (56.2)
Removal of stent / blocked stent change	70 (12.9)
Cholangitis	60 (11.0)
Malignancy	52 (9.6)
Bile leak	27 (4.9)
Gallstone Pancreatitis	23 (4.2)
Other	6 (1.1)
Procedural Details	
Sphincterotomy	451 (83.1)
Pancreatogram	150 (27.6)
Failed Cannulation	27 (5.0)
Complication	
Pancreatitis	19 (3.8)
Cardiac (CCF / RAF)	4 (0.8)
Sepsis	3 (0.6)
Respiratory (Pneumonia)	2 (0.4)
Perforation	1 (0.2)
Bleeding	1 (0.2)

Table 2: Amylase Factor and Lipase Factor levels in all patients and the number (%) of patients in that group who went on to develop Post-ERCP Pancreatitis

Lipase Factor	Total	Pancreatitis (%)	Amylase Factor	Total	Pancreatitis (%)
< 1.5	366	0 (0)	< 1.5	422	0 (0)
≥ 1.5 - 3	57	0 (0)	≥ 1.5 - 3	42	4 (9.5)
≥ 3 – 5	15	0 (0)	≥ 3 – 5	16	4 (25)
≥ 5 – 10	20	0 (0)	≥ 5 – 10	15	7 (47)
≥10 - 20	10	1 (10)	≥ 10 – 20	9	3 (33)
≥ 20	38	18 (47)	≥ 20	2	1 (50)

Table 3: Amylase Factor and Lipase Factor utility in predicting Post-ERCP Pancreatitis

Amylase Factor	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Positive Likelihood Ratio
AF ≥ 10	21.1%	98.6%	36.4%	97.0%	14.6
AF ≥ 5	57.9%	96.9%	42.3%	98.3%	18.8
AF ≥ 3	78.9%	94.5%	35.7%	99.1%	14.2
AF ≥ 1.5	100%	86.7%	22.6%	100%	7.5
Lipase Factor	**Sensitivity (%)**	**Specificity (%)**	**Positive Predictive Value (%)**	**Negative Predictive Value (%)**	**Positive Likelihood Ratio**
LF ≥ 20	94.7%	95.9%	47.4%	99.8%	23.1
LF ≥ 10	100%	94.0%	39.6%	100%	16.8
LF ≥ 5	100%	89.9%	27.9%	100%	9.9
LF ≥ 3	100%	86.9%	22.9%	100%	7.6
LF ≥ 1.5	100%	75.2%	13.6%	100%	4.0