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Original Article

Defining the diagnostic value of hyperlipasemia for acute pancreatitis in the critically ill

Jonah Cohen, MD [a, 1], Kristin L. MacArthur, MD [b, 1], Amporn Atsawarungruangkit, MD [a, 1], Michael C. Perillo, BS [a], Camilia R. Martin, MD, MS [c], Tyler M. Berzin, MD, MS [a], Nathan I. Shapiro, MD, MPH [d], Mandeep S. Sawhney, MD, MS [a], Steven D. Freedman, MD, PhD [a], Sunil G. Sheth, MD [a, *]

[a] Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Dana 501, Boston, MA 02215, United States
[b] Division of Gastroenterology, Boston Medical Center, 85E. Concord Street, Suite 7720, Boston, MA 02118, United States
[c] Division of Neonatology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, United States
[d] Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, United States

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ABSTRACT

Background/objectives: Hyperlipasemia is frequently encountered in patients in the intensive care unit (ICU). The degree to which it should be valued in making the diagnosis of acute pancreatitis (AP) in critically ill patients remains uncertain. We sought to determine the diagnostic accuracy of hyperlipasemia and the optimal lipase cutoff for diagnosing AP in critically ill patients.
Methods: Four hundred and seventeen ICU patients with hyperlipasemia, defined as lipase greater than three times the upper limit of normal from 2009 to 2012 were retrospectively identified. A diagnosis of AP was confirmed by the additional presence of either characteristic abdominal pain or cross-sectional imaging.
Results: The overall positive predictive value (PPV) of hyperlipasemia was 38.1%. Median initial lipase levels were 1164 IU/L in patients with AP and 284.5 IU/L in patients without AP ($p < 0.001$). The optimal diagnostic lipase cutoff of 532 IU/L correlated with a sensitivity, specificity, negative predictive value and PPV of 77.4%, 78.0%, 84.9%, and 67.0% respectively. The most common primary diagnoses in non-AP patients with elevated lipase included shock, cardiac arrest and malignancy.
Conclusions: Physicians should maintain caution when interpreting hyperlipasemia in the critically ill due its relatively low PPV. However, a greater lipase cutoff improves its diagnostic value in AP and helps to reduce unnecessary imaging in these patients.

1. Introduction

Acute pancreatitis (AP) is a condition associated with high morbidity and mortality and early and accurate diagnosis is paramount in improving outcomes [1]. The diagnosis of AP requires the presence of two of the three following criteria: 1) acute onset of persistent, severe, epigastric pain which often radiates to the back, 2) characteristic findings of acute pancreatitis on imaging including contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), or transabdominal ultrasonography, and 3) elevation in serum lipase or amylase to three times or greater than the upper limit of normal [2]. Lipase (triacylglycerol acylhydrolase) which is mainly synthesized and stored within granules in the pancreatic acinar cells is the most sensitive and specific marker for acute pancreatitis currently used in clinical practice [3]. While reference values for normal ranges may vary in different laboratories, the overall sensitivity and specificity of lipase ranges from 85% to 100% [4–6]. However, nonspecific elevations of lipase have

* Corresponding author. Division of Gastroenterology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, E/Rabb 423, Boston, MA 02215, United States.
E-mail address: ssheth@bidmc.harvard.edu (S.G. Sheth).
[1] Co-first authors.

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also been reported. This may partially be explained by extra-pancreatic sources of lipase including enzyme produced by the tongue, esophagus, stomach, duodenum, leukocytes, adipose tissue, and lung [7]. Several conditions other than AP have been associated with an elevated serum lipase, including chronic pancreatitis, acute cholecystitis, bowel obstruction or infarction, duodenal ulcers, pancreatic tumors, diabetic ketoacidosis, celiac disease, trauma, and human immunodeficiency virus infection as well as other conditions associated with prolonged pancreatic ischemia [7–10]. Additionally, lipase is excreted via the kidneys and patients with renal injury may have an elevated lipase as a result of impaired glomerular filtration rate rather than due to acute pancreatitis. Notably, previous work has demonstrated that in patients who are critically ill, hyperlipasemia may be encountered in up to 40%, however the true positive predictive value of lipase greater than three times the upper limit of normal remains unclear [11]. Manjuck et al. evaluated 245 adult critically ill patients admitted to an intensive care unit (ICU) without a diagnosis of acute pancreatitis and found that any abnormal lipase (not necessarily greater than three times the upper limit of normal) was found in 99 patients (40%), but only 11 patients met criteria for diagnose of AP [11]. Moreover, the specific diagnoses of patients with lipase greater than three times the upper limit of normal but without a diagnosis of AP has not been well elucidated in a large series of patients in ICU. The objective of this study was to determine the diagnostic yield by evaluating the positive predictive value of an elevated lipase greater than three times the upper limit of normal for the diagnosis of AP in patients admitted to the ICU. We also sought to characterize alternative diagnoses for patients that did not meet criteria for the diagnosis of AP. Finally, we aimed to define the optimal lipase cut-off for diagnosing AP in the ICU which would maximize sensitivity and specificity.

2. Materials and methods

Four hundred and seventeen adult patients with elevated serum lipase during admission to an ICU at Beth Israel Deaconess Medical Center, Boston, Massachusetts, between January 2009 and July 2012 were retrospectively identified. We defined an elevated lipase as a value in our clinical assay greater than 180 IU/L which represents three times the upper limit of normal range, which is 0–60 IU/L. Our cohort included any patient that had greater than 180 IU/L at any point while in the ICU to determine primary alternative diagnoses, but we focused on initial lipase readings when determining cut-off points and predictive values to assess the diagnostic yield of elevated lipase in this population. The study protocol was approved by the institutional review board. There were no exclusion criteria.

The diagnosis of AP was confirmed by data extraction from the electronic medical record of patients meeting diagnostic criteria. The diagnosis of AP was ascertained if there was documented evidence of either characteristic abdominal pain or cross sectional imaging including abdominal ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) diagnostic of pancreatitis as per final online record interpretation by attending abdominal imaging radiologists. Characteristic abdominal pain for AP was determined as per 2012 Atlanta Criteria: acute onset of persistent, severe, epigastric pain often radiating to the back with tenderness on palpation on physical examination. If neither characteristic abdominal pain nor diagnostic imaging was present, the alternative primary diagnosis was determined by the principal diagnosis entered in the discharge summary. Alcoholic pancreatitis was defined by a past history of alcoholism (chronic and moderate to heavy use) with report of alcohol consumption within one week prior to presentation and no evidence of biliary pancreatitis. Biliary pancreatitis was defined in the presence of elevated liver function tests and imaging showing cholelithiasis, choledocholithiasis or gallbladder sludge. When imaging was not present, biliary pancreatitis was defined by elevated liver function tests greater than three times the upper limit of normal without additional explanation for these abnormal labs or other etiology for acute pancreatitis. Descriptive statistics were used to analyze patient data and clinical parameters. Categorical data were presented in the form of count and percentage while continuous data were presented in the form of median and quartiles. Depending on the data type, Chi-square test, Fisher's exact, and Mann–Whitney *U* test were used for comparisons between pancreatitis and non-pancreatitis groups using the significant level (alpha) of 0.05. Moreover, we calculated specificity, sensitivity, positive predictive value, and negative predictive value for each cut-off point (e.g. three times the normal upper limit of lipase cut-off point and optimal lipase cut-off point). The optimal cut-off points of lipase level were calculated by maximizing Youden's index. Statistical analyses in this study were performed by using STATA version 14.0 (Stata Corp., College Station, TX) and MATLAB R2016a (MathWorks, Natick, MA).

3. Results

Baseline demographics are presented in Table 1. One hundred and fifty-nine of 417 patients with an elevated lipase during their ICU admission had sufficient evidence to be diagnosed with acute pancreatitis using the aforementioned criteria [2]. Using initial lipase readings, the positive predictive value of hyperlipasemia in the diagnosis of AP was 38.1% (95% CI, 33.4–42.8%) in 159 out of 417 subjects. There were no statistical differences distinguishing AP from non-AP when considering race, social history of alcohol usage and/or smoking, age, in-hospital mortality, and time spent in the ICU (Table 1). The total number of patients who underwent cross sectional imaging in this study was 303 out of 417 patients (72.7%). Moreover, we found that patients ultimately diagnosed with AP ($N = 122$, 76.7%) were equally as likely to have abdominal cross sectional imaging during their stay as those without AP ($N = 181$, 70.2%) ($p = 0.175$). The median initial lipase in patients with AP was 1164 IU/L (584, 2808 interquartile range [IQR]) compared to 284.5 IU/L (213, 523) in non-AP patients, $p < 0.001$ (Fig. 1). When subdividing patients diagnosed with AP, we found that the median first lipase of 1716 (662, 4050) observed in patients with biliary pancreatitis was significantly higher than the median lipase of 840 (409, 1974) observed in patients with alcoholic pancreatitis and ($p = 0.008$) (Fig. 2).

Sensitivity and specificity curve optimization analysis revealed that the optimum cut-off for the initial lipase for the diagnosis of AP in the overall cohort of 417 ICU patients is 532 IU/L (Fig. 3). This correlated with a sensitivity of 77.4% and specificity of 78.0% respectively as well as a negative predictive value (NPV) of 84.9% and elevated the positive predictive value (PPV) from 38.4% to 67.0% (Table 3). Validation cohort analysis of only those patients who underwent cross sectional imaging (303 of 417, 72.7%) confirmed an optimal lipase cutoff also of 532 IU/L (Fig. 4) with a sensitivity of 75.4%, specificity of 74.0%, NPV of 81.7% and PPV of 66.2% (Table 2).

The most common alternative primary diagnoses in patients with hyperlipasemia but who did not meet criteria for diagnosis of acute pancreatitis (258 of 417, 61.9%) included shock or cardiac arrest, malignancy, bowel or biliary obstruction, perforation, ischemia or infection as well as trauma and alcohol intoxication or hepatitis Interestingly, diabetic ketoacidosis (3.9%), acute renal failure (3.1%) as well as intracranial hemorrhage (2.3%) were relatively uncommon alternative primary diagnoses (Table 3).

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