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# Predictive biomarkers for acute gallstone pancreatitis in the pediatric population

Maisam Abu-El-Haija [a, 1], Tom K. Lin [a, 1], Soofia Khan [a], Lin Fei [a, b], Tyler Thompson [a], Jaimie D. Nathan [c, *]

[a] Division of Pediatric Gastroenterology Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b] Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center Cincinnati, Ohio, USA
[c] Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

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ABSTRACT

*Background:* Early biomarkers for diagnosis of gallstone pancreatitis (GP) in pediatrics have not been well studied. Reliably differentiating GP from other causes of acute pancreatitis (AP) would allow for early diagnosis and prompt management. We sought to assess biomarkers and clinical variables for early GP diagnosis from a prospectively-enrolled registry of pediatric patients presenting with first AP episode.
*Methods:* Cross-sectional analysis of a prospective acute pancreatitis registry of children enrolled from March 2013 through October 2016 was performed. Fisher's exact test and Wilcoxon rank sum test were used to compare demographic and clinical variables between GP and non-GP groups. A multivariable logistic regression model was derived, and receiver operating characteristic (ROC) curve was built using stepwise selection.
*Results:* 114 subjects were enrolled (21 with GP, 93 as non-GP). Median was statistically higher for GP patients in lipase values X upper limit of normal (ULN) on admission, weight percentile for age, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase. By multivariable analysis, significant predictors were ALT and Lipase xULN. A model built using these two variables for prediction of GP identified an AUROC of 0.85. At a predictive probability of 0.35, the model had an 80% sensitivity, 93% specificity, 76% positive predictive value and 95% negative predictive value.
*Conclusions:* We have developed a model for predicting GP in children that could help guide clinical management of AP patients. Future studies are needed to validate use of laboratory findings and clinical variables in evaluation of gallstone etiology in pediatric AP patients.


## 1. Introduction

Recent reports have shown a rising incidence of pediatric acute pancreatitis (AP), currently estimated to be up to 1:10,000 [1]. One of the most common AP etiologies in adult patients is gallstone pancreatitis (GP), occurring in up to 40% of cases [2]. In children, gallstone disease is a less common etiology for AP, occurring in 10–30% of cases [3,4], but it remains an important pathology for early recognition. According to the International Association of Pancreatology/American Pancreatic Association (IAP/APA) adult-based guidelines, a cholecystectomy performed during the index admission is recommended in GP patients to minimize disease recurrence and complications [5]. The same management guidelines call for urgent endoscopic retrograde cholangiopancreatography (ERCP) in cases of suspected cholangitis [5]. Etiology-guided intervention for GP has been similarly studied in children, with findings of improved patient outcomes including prevention of readmissions due to symptom recurrence when a cholecystectomy is performed during the index admission [6]. These evidence-based best practices highlight the benefit of early GP detection. However, to date there have been limited studies that have attempted to elucidate specific patient characteristics or diagnostic predictors of GP in the pediatric population.

Adult studies have investigated the role of biochemical markers in early diagnosis of GP. The use of amylase and alanine aminotransferase (ALT) to predict GP in patients with high human

* Corresponding author. Cincinnati Children's Hospital Medical Center, Division of Pediatric General and Thoracic Surgery, MLC 2023, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, United States.
*E-mail address:* jaimie.nathan@cchmc.org (J.D. Nathan).
[1] Co-First authors.

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immunodeficiency virus (HIV) prevalence has been previously investigated [7]. Others have reported the use of liver enzyme elevations in the diagnosis or prediction of GP, including a meta-analysis of hepatic profile parameters [8,9]. The use of ultrasonography (US) with or without liver enzyme elevation has shown favorable results in the diagnosis of GP in adults early in the course of the disease [10,11]. Such investigative efforts focused on the pediatric age group have been limited. Retrospective studies have reported on risk factors associated with biliary pancreatitis in children [12,13], as well as a study by Coffey et al. which utilized a triad of gamma-glutamyl transpeptidase (GGT), ALT and lipase within 48 h of presentation as clinical predictors of biliary pancreatitis in children [14]. Prompt differentiation of GP from other causes of AP in children poses significant implications including timely management and intervention in an effort to limit patient morbidity.

Our study aim was to investigate biochemical and clinical variables for early GP diagnosis in a prospectively-enrolled registry of pediatric patients presenting with their first occurrence of AP. A secondary aim was to assess the frequency of radiologic imaging in the accurate diagnosis GP.

## 2. Methods

The study was approved by the Institutional Review Board (2012–4050) at Cincinnati Children's Hospital Medical Center (Cincinnati, Ohio). As per institutional protocol, consent from the parent or legal guardian and assent (for subjects over 11-years-old) was obtained for all enrollees <21-years-old presenting with their first occurrence of AP. The diagnosis of AP was based on achievement of at least 2 of 3 criteria: (1) abdominal pain suggestive of or compatible with pancreatitis, (2) serum amylase or lipase level at or above three times the upper limit of normal, and (3) radiographic findings consistent with acute pancreatitis. Those families and subjects agreeing to inclusion within the registry were prospectively enrolled.

A forty-two month (March 2013 thru October 2016) cross-sectional analysis of the registry was performed. AP cases with an etiology determined to be unrelated to gallstone pathology were classified as *non-GP*. These secondary causes of AP included viral, systemic illness, drug-induced, metabolic, congenital anomalies, trauma or idiopathic. A GP diagnosis was based on documentation of gallstone(s) or sludge within the gallbladder and/or common bile duct (CBD), or CBD dilation in the presence of elevated liver enzymes, by radiographic imaging (transabdominal US, computed tomography, magnetic resonance imaging, fluoroscopy during ERCP) performed during the AP presentation in the absence of identification of an alternative cause for AP.

### 2.1. Statistical analysis

Fisher's exact test and Wilcoxon rank sum test were used to compare demographic and clinical variables between GP and non-GP groups. In order to optimize prediction of GP, a multivariable logistic regression model was derived based on variables from the univariate analysis with a $p$ value up to 0.2 and others known from the medical literature to be predictive, including exclusion based on potential collinearity, and the Area Under Receiver Operating Characteristic Curve (AUROC) was built using stepwise selection. A $p$-value was considered significant when <0.05. Statistical analyses were conducted using SAS® 9.3 software.

## 3. Results

Within the forty-two month study period, 114 patients were enrolled into the AP registry. Twenty-one (18%) subjects were categorized as having a GP etiology, with the remaining 93 subjects grouped into non-GP etiology. All GP subjects underwent at least one form of radiographic imaging with an etiology of GP being confirmed by ultrasound 21/21 (100%), CT 3/3 (100%), and MRCP 5/7 (71%). Abnormal biliary imaging findings included stone/sludge within the gallbladder and/or CBD, and intrahepatic and/or extrahepatic biliary dilation. In 9 patients, initial evaluation by laboratories and imaging was followed by ERCP due to concern for ongoing CBD obstruction. In 4/9 ERCP procedures, CBD stone/sludge was identified, prompting endoscopic therapeutic intervention of a biliary sphincterotomy with stone/sludge extraction. In the remaining 5 patients in which stone/sludge was not found within the biliary tree, it was presumed the obstructing material had spontaneously passed prior to performance of the ERCP. Endoscopic ultrasound (EUS) was not performed on any of the enrolled subjects.

### 3.1. GP versus non-GP cases

Univariate comparison of GP to non-GP subjects found no significant differences in gender, age distribution, initial amylase elevation X upper limit of normal (ULN), creatinine or total bilirubin (Table 1). Univariate analysis of median values between GP and non-GP subjects were found to be statistically higher for GP patients in: lipase x ULN ($p < 0.004$), weight percentile for age ($p < 0.038$), ALT ($p < 0.001$), aspartate aminotransferase (AST) ($p < 0.001$), gamma-glutamyl transferase (GGT) ($p < 0.001$) (Table 1).

From the multivariable analysis, ALT was significant when comparing GP to non-GP subjects ($p < 0.001$), while lipase x ULN nearly reached statistical significance ($p = 0.059$) (Table 2).

### 3.2. GP prediction model for pediatric AP

As represented in Fig. 1, using ALT and lipase for prediction of GP identified an AUROC of 0.8545 (0.7468, 0.9623). An ALT only model produced an AUROC of 0.8679 (0.7691, 0.9666), and a lipase only model produced an AUROC of 0.6877 (0.5457, 0.8297). There were 97 patients with complete data used to build the model for GP prediction on admission.

At a predictive probability of 0.35, the statistical model was associated with sensitivity of 80%, specificity of 93%, positive predictive value (PPV) of 76%, and negative predictive value (NPV) of 95%.

## 4. Discussion

In this study, we report GP to encompass approximately 18% of all first AP attacks in children, which represents the first study to highlight the role of GP in pancreatitis from a prospective dataset in children. Reliable diagnostic testing for GP can be invaluable given the identified benefits from early therapies that may limit patient morbidity related to delayed recognition. Moreover, the avoidance of invasive interventions (e.g., ERCP, cholecystectomy) is an equally desirable outcome in those patients without a biliary etiology where such therapies would provide no such utility. Limited adult studies have primarily shown that an elevated ALT is predictive of biliary origin in AP with a PPV of 81–95% [9,11,15,16]. Radiologic imaging alone, specifically ultrasound, has its own limitations in the diagnosis of GP with a sensitivity of 67–87% for cholecystolithiasis and a lower sensitivity of 20–50% for choledocholithiasis [17]. Similar studies focused on pediatric GP have been limited. Retrospective studies in children have reported on liver profile abnormalities as risk factors for biliary pancreatitis in

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