Pancreatology xxx (2016) 1–6

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Predicting severe acute pancreatitis in children based on serum lipase and calcium: A multicentre retrospective cohort study

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Calcium
Children
Gastroenterology
Lipase
Pancreatitis
Severity

ABSTRACT

Objective: This study aims to identify predictors of severe paediatric AP based on laboratory trends and peak/trough values on day 2 (D2) after presentation. The performance of identified predictors was first assessed and then combined with the previously validated sensitive predictor serum lipase ≥7 times the upper limit of normal (× ULN) on day 1 (D1).

Methods: A retrospective review of children with AP (January 2000–July 2011) was performed at three tertiary referral hospitals (two in Australia, one in the Netherlands). Trends of candidate predictors were analysed using the percentage change from D1 to D2 or peak/trough values within 48 h after presentation.

Results: 175 AP episodes (including 50 severe episodes [29%]) were identified. Serum lipase ≥50% decrease on D2 (sensitivity 73%, specificity 54%) and calcium trough ≤2.15 mmol/L within 48 h (sensitivity 59%, specificity 81%) were identified as statistically significant predictors for severe AP. By combining the newly identified predictors with the previously validated predictor serum lipase ≥7× ULN on D1 (sensitivity 82%, specificity 53%), specificity improved to predict severe AP on D2 with the addition of: (i) serum lipase ≥50% decrease (sensitivity 67%, specificity 79%), or (ii) trough calcium ≤2.15 mmol/L (sensitivity 46%, specificity 89%).

Conclusions: Serum lipase and calcium, may be helpful in predicting severity of paediatric AP. There may be a clinical role on D1 for using serum lipase ≥7× ULN (high sensitivity), and on D2 for combining D1 serum lipase ≥7× ULN with calcium trough ≤2.15 mmol/L within 48 h (high specificity) to help predict severe paediatric AP.

Introduction

Acute pancreatitis (AP) is a serious condition with significant morbidity and mortality, and an increasing incidence has been reported in recent decades in children [1–3]. In adult AP, early in-hospital demise is mainly caused by multi-organ failure associated with a systemic inflammatory response [4]. The availability of clinical predictors can help identify patients at high risk of such complications, and who are in need of intensive monitoring and intervention [1]. Effective intervention during the "interventional window" period (in the first few days of disease onset) has been reported to reduce morbidity and mortality of adult AP [5]. Early fluid resuscitation has been associated with reduction of the frequency of systemic inflammatory response and multi-organ failure [6,7]. Specific therapies for severe AP, with promising outcomes, may also be available in the future [8].

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http://dx.doi.org/10.1016/j.pan.2016.04.005
1424-3903/

There are a limited number of studies evaluating paediatric AP, including those that identify predictors for a severe course of disease. The application of prognostic scoring systems available for adult AP, including the Ranson criteria [9], the Modified Glasgow score [10], the Acute Physiology and Chronic Health Evaluation (APACHE) II score [11], Bedside Index for Severity in Acute Pancreatitis [12], and Harmless Acute Pancreatitis Score [13], may not be appropriate in paediatric AP because of differences in age, clinical presentation, co-morbidities, aetiologies and laboratory test reference ranges. Furthermore, the Ranson criteria and APACHE II score predict mortality rather than severity.

The first predictive tool for paediatric AP was the Paediatric Acute Pancreatitis Severity (PAPS) score. However this was not found to be superior to the Ranson criteria and Modified Glasgow score in subsequent paediatric studies [14–17]. Its application at 48 h after presentation, results in high specificity (ranging from 81%–88%) but low sensitivity (ranging from 48%–52%) for all three scores [15]. In addition, the PAPS score uses both age and weight, which are highly correlated in children. Coffey et al. developed and validated serum lipase ≥7 times the upper limit of the normal reference range (× ULN) within 24 h of presentation as an early predictor of severe AP in children [18]. This study was further validated in a separate cohort by Fabre et al. [19] Serum lipase ≥7× ULN was associated with relatively high sensitivity (86%) and negative predictive value (89%) but had low specificity (56%) [18]. To date, there is no predictive tool in children with both high sensitivity and specificity.

We aimed to identify predictive laboratory trends and peak/trough values over the first 48 h after presentation in order to develop predictors of severe AP in children to complement and/or improve on the previously validated predictor of lipase ≥7× ULN at 24 h. We analysed the performance of these newly identified predictors alone and then in combination with the previously validated predictor of lipase ≥7× ULN at 24 h.

Methods

Study population

A retrospective cohort review was performed in children with AP derived from three tertiary referral hospitals, two in Australia (Sydney Children's Hospital (SCH), Randwick and John Hunter Children's Hospital (JHCH), Newcastle) and one in the Netherlands (Beatrix Children's Hospital (BCH), Groningen), over the period January 2000–July 2011.

Patients were eligible for inclusion if they were younger than 18 years at the time of hospitalization, and met at least two of the following criteria for paediatric AP: (1) abdominal pain not due to other causes; (2) serum amylase and/or lipase ≥3× ULN; and (3) imaging findings characteristic for pancreatitis [20]. Patients with acute recurrent pancreatitis (ARP) were eligible for inclusion if they had experienced ≥2 distinct episodes of AP along with complete resolution of pain (≥1 month pain-free interval) before diagnosis of the subsequent episode of AP [20]. Every ARP episode satisfying the criteria was considered as a separate episode of AP.

Patients with abdominal pain and/or elevation of pancreatic enzyme levels due to pseudocyst(s) and patients with chronic pancreatitis were excluded [20].

Identification of eligible patients occurred using the hospital diagnostic coding system and by searching laboratory databases for serum lipase and/or amylase ≥3× ULN. Relevant clinical data was collected from the medical records. Collected data included demographics, clinical presentation and course of pancreatitis, laboratory data and radiographic data. Laboratory parameters to test as candidate predictors were selected based on biological plausibility and previously reported prognostic parameters [9–11,14,18,21,22]. The following candidate predictors were analysed: lipase, amylase, C-reactive protein (CRP), lactate dehydrogenase (LDH), creatinine, urea, calcium, sodium, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total protein, white cell count (WCC) and haematocrit. If presentation of the episode of AP occurred in a referring hospital, data from the referral hospital was collected. Unavailable data was recorded as a missing value.

Subjects derived from two of the three institutions (SCH and JHCH) have been previously reported in separate studies [18,23,24]. One of those included the aforementioned study by Coffey et al., which analysed laboratory parameters on day 1 of presentation and identified serum lipase elevation ≥7× ULN within 24 h of presentation as a predictor of severe paediatric AP [18].

Determination of severity

Severity of each AP episode was classified as mild or severe. Severe AP was defined by mortality due to complications of pancreatitis, local complications, need for pancreatic surgery, admission to an intensive care unit (ICU) and development of organ dysfunction. Local complications included necrosis, infected necrosis, and haemorrhage. Organ dysfunction was defined by a systolic blood pressure <90 mmHg or evidence of pulmonary insufficiency (which was PaO_2 <60 mmHg or oxygen requirement along with chest radiographic abnormalities, such as pleural effusion and/or atelectasis) [25]. An episode was considered severe only if the ICU admission and organ dysfunction primarily resulted from AP rather than from a comorbid condition.

Statistical analysis

For each variable selected for trends analysis, the time frames of 0–24 h (D1) and 24–48 h (D2) were collected. To evaluate trends over time, the percentage change from D1 to D2 was calculated using the following formula: (D1 value − D2 value)/D1 value × 100%. For other parameters, a peak or trough value within 48 h was evaluated. Comparisons of demographic data and laboratory parameters between mild and severe AP were performed. Nominal data was evaluated using Chi-square or Fisher's exact test. Continuous data was analysed by the unpaired Student t-test or the Mann–Whitney U test, depending on the normality of distribution. A P-value <0.05 was considered as statistically significant.

Receiver operating characteristic (ROC) curves were then performed for variables significantly associated with the severity of AP to determine optimal and clinically relevant cut-off values for every parameter based on the area under the curve (AUC). Subsequently univariate binary logistic regression analysis was performed on selected cut-offs to determine significance and calculate odds ratios (OR) with 95% confidence intervals (CI). Prior to inclusion in a final multivariate model, parameters were tested for collinearity with a variance inflation factor ≥2 considered problematic. Multivariate binary logistic regression was used to select final predictors for severe AP. The predictive values (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR)) of the individual and combined final predictors were then calculated. Data were analysed using SPSS Statistics for Windows, version 22.0 (IBM Corp., 2013, Armonk, New York, USA).

Ethical approval

The human research ethics boards of the three participating hospitals (South Eastern Sydney Human Research Ethics Committee [10/188] for SCH, Hunter New England Human Research Ethics

Please cite this article in press as: Bierma MJ, et al., Predicting severe acute pancreatitis in children based on serum lipase and calcium: A multicentre retrospective cohort study, Pancreatology (2016), http://dx.doi.org/10.1016/j.pan.2016.04.005