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Blood Urea Nitrogen Elevation Is a Marker for Pediatric Severe Acute Pancreatitis

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Abstract

Objective: The natural course of patients who develop acute pancreatitis (AP) can range from mild to severe acute pancreatitis (SAP). The aim of this study was to evaluate for early predictors of developing SAP during the first episode of AP in a prospective pediatric cohort.

Methods: Clinical data were prospectively collected and subsequently analyzed for pediatric patients presenting with their first episode of AP between March 2013 and January 2017 to Cincinnati Children's Hospital Medical Center.

Results: A total of 118 patients were included in the analysis, and 22 (18.6%) developed SAP. Patients who developed SAP had significantly higher values of blood urea nitrogen (BUN) ($P = 0.007$), magnesium ($P = 0.04$), glucose ($P = 0.03$), sodium ($P = 0.03$), and C-reactive protein ($P = 0.02$). A logistic regression model with BUN as a predictor of SAP was superior to any other combination of variables (area under the receiver operating characteristic curve, 0.75; 95% confidence interval, 0.61–0.89; sensitivity, 63%; specificity, 81%; positive predictive value, 43%; negative predictive value, 91%).

Conclusions: This study generated a predictive model using elevated BUN as a significant predictor of SAP. The findings are useful for early identification of pediatric patients at higher risk of developing SAP.

Keywords

BUN; pancreas; predictive modeling

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Acute pancreatitis (AP), acute recurrent pancreatitis, and chronic pancreatitis are becoming more frequently recognized in the pediatric population.^{1,2} Acute pancreatitis is reported to be increasing in incidence in pediatrics, up to 1:10,000, approaching the incidence in the adult population.³ The natural course of pediatric AP can range from a mild presentation with spontaneous resolution to severe acute pancreatitis (SAP). Severe acute pancreatitis can occur in up to 15% to 34% of pediatric AP cases.^{4–8} Early identification of patients at risk of developing SAP is crucial, as it is associated with significant health system cost, as well as increased patient morbidity and mortality.^{2,9–11} Identification of these patients early in presentation can guide early interventions, stratify those who may need transfer to specialized centers or require intensive care unit (ICU) level care and could eventually lead to targeted therapies resulting in improved patient outcomes.

Clinical scores for predicting SAP in adults have been developed; however, these often fall short of high predictive accuracy.¹² Moreover, adult scoring systems are not generalizable to pediatric-aged patients, as age is a component of many of the scores and etiologies of AP in the pediatric population differ from those in adult AP.¹ Pediatric prediction of SAP has been studied; however, these efforts have implemented variable classifications for SAP, as there had not been a universally accepted criterion.^{5–8,13} A new pediatric classification of AP, which defines mild AP, moderately severe AP, and SAP, was recently published by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Pancreas Committee.⁴ This new classification calls for the need to establish predictive models using the newly published pediatric criteria.

In the present study, through a prospectively collected pediatric cohort of patients with first AP attack, our aim was to evaluate for early predictors of SAP. We hypothesized early predictors of SAP would be identified using our prospective cohort.

MATERIALS AND METHODS

The study was approved by the institutional review board of the Cincinnati Children's Hospital Medical Center (CCHMC) (IRB #2012-4050). Pediatric patients presenting with their first episode of AP between March 2013 and January 2017 were prospectively identified, and written consent was obtained for inclusion in a local REDCap (Research Electronic Data Capture) database hosted at CCHMC. REDCap is a secure, web-based application designed to support data capture for research studies.¹⁴ Patients seen at CCHMC were initially identified through an alert from the electronic medical record system capturing any patient with a serum amylase and/or lipase ≥ 3 times the upper limit of normal. Inclusion within the database required patients to meet INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) criteria for AP,¹⁵ be presenting with the first episode of AP, and be between ages 0 and 21 years at presentation. Clinical data collected within the database included demographic data, initial laboratory values on presentation to medical care, subsequent laboratory values, initial vital signs and clinical course, resuscitation fluid type and rate (aggressive intravenous [IV] fluid hydration defined by $1.5\times$ maintenance IV fluid within first 24 hours of admission), mode of nutrition intake/administration (oral, enteral, and parenteral) on admission, imaging findings, SAP

manifestations, and other relevant clinical data. These data were collected from the database and analyzed for the study.

Patients were divided into 2 groups: patients with mild AP and those with SAP that included moderately severe AP (transient organ dysfunction [<48 hours], local pancreatic complications, or exacerbation of previously diagnosed comorbid disease) and SAP (persistent organ dysfunction >48 hours). For the purpose of this study, we grouped together moderately severe AP and SAP, as defined by the published NASPGHAN guideline, in the “SAP” group.⁴ In concordance with these guidelines, organ dysfunction and pediatric systemic inflammatory response syndrome (SIRS) were defined per the International Pediatric Sepsis Consensus.¹⁶ For patients 18 years or older at time of presentation, SIRS was defined by the Society of Critical Care Medicine consensus definition.¹⁷ Local complications were defined as peripancreatic or pancreatic complications including fluid collections, local pancreatic hemorrhage, or necrosis.⁴

To address the study aim, group differences between mild AP and SAP patient characteristics and clinical management were analyzed, along with univariate comparative analyses of various initial laboratory values and presence of SIRS. A predictive model was generated using stepwise selection of statistically significant variables from univariate analysis.

Statistical Analysis

Data were analyzed using SAS, version 9.4 (SAS Institute, Cary, NC). Because of skewed distributions, continuous data were summarized as median (interquartile range [IQR]), whereas categorical data were summarized as frequency counts and percentages. For continuous data, nonparametric Wilcoxon-Mann-Whitney tests were used to compare characteristics and laboratory values between groups; χ^2 and Fisher exact tests were used, as appropriate, for group comparisons of categorical data. To optimize the prediction of SAP, a logistic regression model analysis using stepwise selection was performed to identify variables that predict the development of SAP based on significant P values and the receiver operating characteristic (ROC) curve. $P < 0.05$ was considered statistically significant.

RESULTS

One hundred eighteen patients met criteria for inclusion in the study and were recorded in our database. There were 22 patients (19%) classified within the SAP cohort (moderately severe [$n = 14$] or severe pancreatitis [$n = 8$]) by meeting the criteria for local pancreatic complications or organ dysfunction (Table 1). The patients with SAP or mild AP were similarly distributed among age, sex, weight, height, and body mass index percentile at presentation (Table 2).

Clinical management did not differ between the groups, including IV fluid bolus within 6 hours of admission (46/84 [55%] mild AP, 13/20 [65%] SAP; $P = 0.41$), aggressive IV fluid hydration (42/81 [52%], mild AP, 7/21 [33%] SAP; $P = 0.13$), and initiation of enteral feeds (oral or other) on admission (27/87 [31%] mild AP, 4/21 [19%] SAP; $P = 0.42$) (Table 3). Patients within the SAP category were more likely to be admitted to the ICU during

hospital admission than mild AP patients (47.6% vs 7.4% $P < 0.0001$) (Table 3). There were 2 deaths in the cohort. One was in a patient with previously unrepaired congenital heart disease, admitted for cholecystitis and SAP, and one in a patient with history of cerebral palsy and epilepsy with AP during an acute respiratory failure episode who died after care was withdrawn due to inability to extubate.

For all AP patients with available data, the median length of stay (LOS) was significantly longer in the SAP group ($n = 16$, 15 days) than the mild AP group ($n = 81$, 3.6 days), $P = 0.004$ (Table 3). For patients admitted for AP primarily, LOS was consistently longer in the SAP group ($n = 8$, 9.6 days) than in the mild AP group ($n = 58$, 2.59 days), $P = 0.0002$.

To study predictors of SAP on presentation, univariate analysis of laboratory values at initial presentation showed the SAP group with significantly higher median blood urea nitrogen (BUN) (20.0 vs 10.0 mg/dL, $P = 0.0007$), magnesium (2.1 vs 1.8 mg/dL, $P = 0.04$), glucose (121.5 vs 98.5 mg/dL, $P = 0.03$), sodium (1410.0 vs 1390.0 mmol/L, $P = 0.03$), and C-reactive protein (CRP) (5.5 vs 10.0 mg/dL, $P = 0.02$) (Table 4).

Generation of a predictive model using stepwise selection and significant univariate results found BUN alone as the most significant predictor of SAP (Fig. 1) (area under the ROC curve: 0.75; 95% confidence interval [CI], 0.61–0.89; $P = 0.002$; sensitivity, 63%; specificity, 81%; positive predictive value, 42%; negative predictive value, 91%). The generated model had a positive likelihood ratio of 3.36 (95% CI, 1.46–5.25). When a multivariable model was configured, other covariates became nonsignificant when BUN was included in the model, whereas BUN remained significant.

DISCUSSION

This study reports predictors of severity from a prospective pediatric AP cohort using the newly developed NASPGHAN classification. Univariate analysis identified higher BUN, magnesium, glucose, sodium, and CRP values in the SAP group. A predictive model was generated using BUN as the most significant predictor of SAP.

Blood urea nitrogen as a predictor of SAP within the predictive model is comparable to existing pediatric and adult literature. Prior pediatric studies have identified a 48-hour rise in BUN as a potential predictor of SAP.^{5,7} Adult data have shown BUN at admission and BUN rise in 24 hours after admission to be predictive of AP patient mortality.^{18,19} In a more recent study, BUN at admission and at 24 hours after admission were predictive of both SAP and mortality.²⁰ Higher BUN at admission has additionally been identified as a risk factor for longer ICU stay in acute necrotizing pancreatitis.²¹ Our model improves upon this existing literature by utilizing prospectively collected data, the new consensus definition of SAP, and laboratory values early in presentation.

Our predictive model generates an equation on a continuous scale and is not simply a BUN “cutoff.” The higher the BUN value, the more likely the model would be to predict SAP (Fig. 1). Despite our data showing elevated BUN as a significant predictor of severity, glomerular filtration rate and creatinine were similar between the groups, indicating no significant difference in renal function. Although speculative, the physiologic mechanism

for increased BUN in patients with more severe pancreatic disease could be related to intravascular fluid depletion with increased renal reabsorption of urea as a response.^{22,23}

An optimal predictive tool is reliable, applicable early in disease presentation, uses readily available clinical data, and is easy to use.²⁴ Our predictive model achieves many of these characteristics: it is generated from parameters within 24 hours of admission, uses a single laboratory value in a model, is easily clinically available, and is applicable in a user-friendly manner. Importantly, establishment of an AP admission order set provided a framework for standardization of management in the studied cohort.⁹ We built an order set for AP management, which was implemented within the electronic hospital ordering system in early 2014. The order set helped minimize variability in treatment among cohort patients (Table 3).

While our study is novel, it has some limitations. The study was conducted at a single pediatric tertiary care center. Availability of our AP admission order set did allow for a low percentage of missing data in many of our laboratory values, but still not all patients had complete data. The duration of patient symptoms prior to presentation was not quantified or available within the scope of this study; thus, patients may have been at different points in their disease process at initial presentation. Moreover, a validation cohort will be needed in the future.

In conclusion, this is a pediatric prospective cohort study that generated a model predictive of SAP using presenting BUN value as a determinant. The study is a promising initial step in improving ability of early identification of pediatric patients at risk of SAP. The presence of a consensus definition of SAP is a major advancement in the pediatric gastroenterology and pediatric pancreatology fields and calls for the future design of studies that use this standardized classification. Further studies evaluating predictors of SAP in children are needed and will undoubtedly be helpful in moving the field of pediatric AP forward.

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FIGURE 1.

A prognostic model using BUN alone as a significant predictor of SAP (area under the ROC curve, 0.75; 95% CI, 0.61–0.89; $P = 0.002$).

TABLE 1.**Severe Acute Pancreatitis Cases**

	No. Met Criteria (%)
Local complication *	15 (68)
Organ dysfunction—respiratory	5 (23)
Organ dysfunction—renal	5 (23)
Organ dysfunction—cardiovascular	2 (9)
SAP cohort	22/118 (19)
Moderately severe †	14/22 (64)
Severe pancreatitis ‡	8/22 (36)

* Local complications defined as peripancreatic or pancreatic complications including fluid collections or necrosis.

† Transient organ dysfunction (<48 hours), local pancreatic complications, or exacerbation of previously diagnosed comorbid disease.

‡ Persistent organ dysfunction >48 hours.

TABLE 2.

SAP Versus Mild AP: First AP Attack Characteristics

	SAP (n = 22)	Mild AP (n = 96)	P
Age, y	13.8 (7.9–15.9), n = 22	13.5 (10.2–15.9), n = 96	0.96
Sex, male	14 (64)	48 (50)	0.25
Weight percentile	59.1 (9.1–88.9), n = 22	48.3 (23.1–86.9), n = 92	0.45
Height percentile	56.5 (3.1–83.3), n = 22	49.3 (21.9–76.2), n = 90	0.83
Body mass index percentile	63.1 (20.1–89.2), n = 22	58.4 (23.6–92.6), n = 87	0.96

Data presented as median (IQR) or frequency (%).

TABLE 3.**Hospital Course and Management**

	SAP (Total n = 22)	Mild AP (Total n = 96)	P
IV bolus within 6 h of admission, yes	13/20 (65)	46/84 (55)	0.41
IV fluid rate			0.13
Aggressive hydration *	7/21 (33)	42/81 (52)	
Less aggressive hydration †	14/21 (67)	39/81 (48)	
Enteral nutrition on admission, yes	4/21 (19)	27/87 (31)	0.42
ICU admission, yes	10/21 (48)	7/95 (7)	<0.0001
LOS, d	15.1 (7.0–47.4), n = 16	3.6 (1.8–8.2), n = 81	0.0004
SIRS, yes	9/19 (47)	25/83 (30)	0.15

Data presented as median (IQR) or frequency (%).

* Aggressive fluid hydration: received 1.5× maintenance IV fluid within first 24 hours of admission.

† Less aggressive fluid hydration: received <1.5 maintenance IV fluid within first 24 hours of admission.

TABLE 4.

Laboratory Values and Clinical Parameters on Initial Presentation in AP Cohort

	SAP (n = 22)	Mild AP (n = 96)	P
Lipase × ULN	8.6 (4.8–17.8), n = 21	8.4 (3.8–25.3), n = 90	0.90
Amylase, U/L	386.0 (131.5–521.0), n = 12	194.0 (104.0–507.0), n = 75	0.35
Albumin, g/dL	3.3 (2.5–3.8), n = 19	3.7 (3.1–4.1), n = 86	0.08
WBC count, × 1000/μL	13.2 (8.9–17.9), n = 18	9.9 (7.3–14.8), n = 75	0.18
Creatinine, mg/dL	0.6 (0.5–0.7), n = 20	0.6 (0.4–0.6), n = 85	0.43
GFR, mL/min per 1.73 m ²	114.6 (93.1–129.7), n = 19	111.6 (98.7–138.0), n = 73	0.77
Calcium, mg/dL	8.6 (8.2–9.2), n = 20	9.0 (8.5–9.4), n = 83	0.10
AST, U/L	35.0 (24.0–130.0), n = 15	40.5 (21.0–114.5), n = 80	0.54
ALT, U/L	37.0 (13.0–266.0), n = 15	29.0 (21.0–177.0), n = 79	0.85
Hematocrit, %	38.8 (31.8–46.2), n = 14	38.1 (33.3–41.6), n = 67	0.64
Hemoglobin, g/dL	13.8 (10.8–15.9), n = 16	12.8 (11.5–14.0), n = 66	0.44
BUN, mg/dL	20.0 (10.0–23.0), n = 19	10.0 (8.0–13.0), n = 85	0.0007
Magnesium, mg/dL	2.1 (1.8–2.1), n = 12	1.8 (1.7–2.0), n = 31	0.04
Phosphorus, mg/dL	3.4 (2.6–4.0), n = 18	3.8 (3.2–4.4), n = 62	0.21
Glucose, mg/dL	121.5 (95.5–148.5), n = 20	98.5 (88.0–117.0), n = 86	0.03
Sodium, mmol/L	141.0 (138.0–143.0), n = 20	139.0 (137.0–141.0), n = 84	0.03
Total bilirubin, mg/dL	0.6 (0.3–1.6), n = 15	0.5 (0.3–1.2), n = 75	0.98
CRP, mg/dL	5.5 (1.8–18.1), n = 5	1.0 (0.4–2.6), n = 28	0.02
Procalcitonin, ng/mL	0.1, n = 1	0.1 (0.1–0.1), n = 2	—

Data are presented as median (IQR).

Bold *P* value indicates statistical significance, <0.05.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; ULN, upper limit of normal; WBC, white blood cell.