A Clinical Model for the Early Diagnosis of Acute Pancreatitis in the Emergency Department

David X. Jin, MD, Ronilda Lacson, MD, PhD,† Laila R. Cochon, MD, MSc,† Emily C. Alper, BA,† Julia McNabb-Baltar, MD, MPH,* Peter A. Banks, MD,* and Ramin Khorasani, MD, MPH†*

Objective: This study aimed to develop a diagnostic model that predicts acute pancreatitis (AP) risk before imaging.

Methods: Emergency department patients with serum lipase elevated to 3 times the upper limit of normal or greater were identified retrospectively (September 1, 2013–August 31, 2015). An AP diagnosis was established by expert review of full hospitalization records. Candidate predictors included demographic and clinical characteristics at presentation. Using a derivation set, a multivariable logistic regression model and corresponding point-based scoring system was developed to predict AP. Discrimination accuracy and calibration were assessed in a separate validation set.

Results: In 319 eligible patients, 182 (57%) had AP. The final model (area under curve, 0.92) included 8 predictors: number of prior AP episodes; history of cholelithiasis; no abdominal surgery (prior 2 months); time elapsed from symptom onset; pain localized to epigastrium, of progressively worsening severity, and severity level at presentation; and extent of lipase elevation. At a diagnostic risk threshold of 8 points or higher (≥99%), the model identified AP with a sensitivity of 45%, and a specificity and a positive predictive value of 100%.

Conclusions: In emergency department patients with lipase elevated to 3 times the upper limit of normal or greater, this model helps identify AP risk before imaging. Prospective validation studies are needed to confirm diagnostic accuracy.

Key Words: acute pancreatitis, computed tomography, diagnostic model, lipase, magnetic resonance imaging

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The incidence of acute pancreatitis (AP) is increasing in the United States, representing the third leading cause of hospital admissions, the sixth highest cause of total hospital day stays, and the fifth largest contributor to aggregate health care costs for all gastrointestinal (GI) disorders in 2012.[1] Part of the increase in health care expenditures may be attributed to a rise in high-cost imaging examinations such as abdominal computed tomography (CT), particularly during the initial 24 hours of hospitalization.[2,3]

Although early abdominal CT imaging is invaluable when a diagnosis is in doubt and especially when an alternative life-threatening condition needs to be immediately excluded, AP can be diagnosed in most patients based on nonimaging criteria.[4] Moreover, early CT imaging in suspected AP has not been shown to improve clinical outcomes,[3] change management,[5] predict the development of necrosis,[5,6] reveal alternative diagnoses,[5–7] or be superior to clinical scoring systems in predicting disease severity.[8] Despite multiple guidelines recommending against routine usage in the initial management of AP,[9–11] early CT imaging is performed in 40% to 70% of cases.[6,7,12]

The continued reliance on CT for suspected AP may be, in part, attributed to imperfect diagnostic criteria.[4] There is general acceptance that at least 2 of 3 features must be fulfilled for a diagnosis of AP: (1) characteristic abdominal pain, (2) serum lipase and/or amylase elevated to 3 times the upper limit of normal or greater (≥3× ULN), and (3) characteristic findings of AP on contrast-enhanced CT, or less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography. However, each diagnostic criterion is flawed. First, there are no objective data as to what constitutes characteristic abdominal pain. Second, although serum lipase has been shown to be more sensitive and specific than serum amylase for diagnosing AP,[13] the optimal lipase cutoff value is controversial,[14] the positive predictive value (PPV) of lipase values ≥3× ULN is only 38% to 77%,[14–17] and the serum level itself may be affected by time to presentation and underlying comorbidities.[18] Third, CT findings of AP may be absent or equivocal in cases of mild AP, whereas MRI may be more sensitive[19,20] and have greater interobserver agreement.[21] Finally, the 3 diagnostic criteria are each weighted equally. However, their individual predictive values differ[17,20,22] or, in the case of characteristic abdominal pain, are entirely unknown.

Given the shortcomings of the current diagnostic criteria and the continued overutilization of CT imaging at presentation, new clinical tools are needed to accurately differentiate AP from other diagnoses. Based on a priori knowledge, it is conceivable that a number of clinical variables (eg, symptom characteristics such as location, timing, and severity of abdominal pain[4]; medical comorbidities such as gallstones[23]; lifestyle factors such as smoking[24] and alcohol[25]; recent medication changes[26] or endoscopic retrograde cholangio-pancreatography (ERCP)[27]; and laboratory studies such as serum lipase levels[17]) easily ascertainable at time of emergency department (ED) presentation may predict the pre-CT probability of AP. Similar clinical risk prediction models exist for other imaging-intensive diagnoses, such as the Wells criteria for acute pulmonary embolism.[28] However, to date, no such tools for AP exist.

Therefore, the aim of the current study was to derive and validate an AP diagnostic model among ED patients with serum lipase ≥3× ULN. Based on information readily available to clinicians, such a model would accurately identify AP risk before imaging and potentially streamline clinical decision making and management.

MATERIALS AND METHODS

Study Design and Population

This retrospective, observational cohort study was conducted at a large, urban academic medical center and was approved by the

From the *Center for Pancreatic Disease, Division of Gastroenterology, Hepatology and Endoscopy, and †Center for Evidence Based Imaging, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston MA.
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Address correspondence to: David X. Jin, MD, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (e-mail: djin@bwh.harvard.edu).
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institutional review board. The target study population consisted of individuals presenting with suspected AP. All patients receiving medical care in our ED from September 1, 2013, to August 31, 2015, with initial serum lipase ≥3× ULN (≥180 U/L) identified by a daily laboratory query were eligible for inclusion. Patients with any of the following characteristics which impart a lower clinical threshold for immediate imaging at presentation were excluded: (1) transferred from outside hospitals,[29] (2) previously established intra-abdominal metastatic disease,[30] (3) acute traumatic injury,[31] or (4) altered mentation at presentation precluding accurate history taking.

Primary Outcome

The primary outcome was a diagnosis of AP at the time of hospital discharge, after comprehensive review of the admission, hospitalization, and 1-year postdischarge course in each electronic health record (EHR). Given that the entire study population presented with serum lipase levels ≥3× ULN, a diagnosis of AP was established if there was evidence of (1) findings consistent with AP on CT or MRI at any point during the hospitalization or immediate postdischarge period, or (2) abdominal pain considered to be characteristic of AP and not clearly explained by another condition. A review of the EHR was performed, and a final diagnosis of AP was determined by an experienced medical pancreatologist before the selection of candidate predictors. To test inter-rater agreement for the primary outcome, 40 random cases were then independently reviewed by a second pancreatologist blinded to the assessment of the first. All original CT and MRI examinations were evaluated by abdominal radiologists, with radiographic AP defined in accordance to the 2012 revised Atlanta Classification (RAC).[4]

Selecting Model Predictors

A comprehensive list of candidate predictors chosen based on clinical judgment and literature review[14,15,18,23–27,32–44] was compiled by an experienced panel consisting of 3 medical pancreatologists and 1 abdominal radiologist. To develop a clinical tool that would be useful early in the disease course, only variables readily ascertainable from the medical history, physical examination, and initial laboratory studies at presentation were considered. Data for each candidate predictor were extracted from a detailed explicit and implicit review of the EHR by 2 study investigators blinded to the primary outcome. Those predictors with less than 5% prevalence in both AP and non-AP cohorts were excluded from further consideration.

Discrepant Variables and Missing Values

It is conceivable that documentation of certain variables, particularly descriptors of patient-reported symptoms, may differ among medical providers. Such discrepancies were managed a priori by assigning a provider note hierarchy: (1) GI consultant note, (2) hospital admission note, and (3) ED provider/triage note. If a particular note was unavailable, or if a pain descriptor was undocumented, the next note in the hierarchy became the final standard. As an exception, the initial pain severity score (0–10) was extracted primarily from ED provider/triage notes.

Candidate dichotomous variables pertaining to medical comorbidities, lifestyle factors, and symptoms that were undocumented in the entire EHR were treated implicitly as normal (absent). For example, if there was no documentation of left-upper-quadrant pain, it was assumed to be absent. Missing categorical variables pertaining to pain severity levels and laboratory studies (other than serum lipase) were imputed with the statistical mode of individuals with and without AP. Missing continuous variables pertaining to the time elapsed from symptom onset to presentation were imputed with the statistical mean.

Model Derivation

Before model building, the data were divided[45] into a two-thirds derivation set and one-third validation set using a random number generator. These 2 sets were compared to confirm that there were no significant differences in candidate predictors or the primary outcome (Supplementary Table 1, http://links.lww.com/MPA/A657).

Using the derivation set, all candidate predictors associated with $P < 0.20$ in univariable analyses were further assessed by multivariable logistic regression. For predictors pertaining to number of prior AP episodes, pain severity level at presentation, and time elapsed from symptom onset to presentation, model performance using both continuous and categorical representations was assessed. A backward elimination of variables was performed using $P > 0.05$ as an exclusion threshold. As a sensitivity analysis, the model-building process was repeated using a forward-selection and a stepwise approach. Variables independently associated with the primary outcome from all 3 algorithms were incorporated and allowed to stay in the model if they met a significance threshold of $P < 0.05$. Clinically meaningful interactions between pain severity level and time to presentation, and progressively worsening severity and time to presentation, were tested.

Point-based Scoring Model

In an effort to simplify eventual clinical application, a point-based scoring system was constructed using the method described by Sullivan et al.[46] First, the variables and parameters derived from logistic regression modeling were organized into clinically meaningful categories with baseline reference values. Second, integer points were calculated for each category based on their deviation from the reference value, divided by the number of regression units corresponding to one prior episode of AP (1.1595). Finally, the risk of AP associated with each theoretical point total was approximated.

Model Validation and Performance

To estimate the discriminating power of the model between individuals who did and did not have AP, receiver operator characteristic curves were created and the areas under the curves (AUCs) were calculated on both the derivation and validation sets. Optimism was estimated by the difference in AUC between these sets. Calibration was assessed both statistically with the Hosmer-Lemeshow test using deciles and clinically by comparing observed versus expected AP rates in 4 risk groups: low, medium, high, and very high. Diagnostic performance was assessed by calculating the sensitivity, specificity, PPV, and negative predictive value (NPV) at various risk thresholds.

Statistical Analysis

Inter-rater agreement for the primary outcome was assessed via a κ coefficient with confidence interval (CI). Results were expressed as n (%) for categorical variables and medians with interquartile range (IQR) for continuous variables. The Fisher's exact test or χ^2 test was used for comparisons between dichotomous and multicategorical variables, respectively. The Wilcoxon rank sum test was used for comparisons between continuous variables. All analyses were performed using R version 2.8.0 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

Figure 1 presents a flow diagram of study participants. From a total of 509 individuals who fulfilled inclusion criteria, we identified 319 eligible for participation (n = 212 in derivation set, 107 in validation set). Among the final cohort, 182 (57%) patients were determined to have a final discharge diagnosis of AP. In the non-AP cohort, the most common diagnoses were enteritis/colitis (35; 26%), renal failure (14; 10%), previously established pancreatic adenocarcinoma (12; 9%), gastritis/gastroparesis (11; 8%), bowel obstruction/ileus (11; 8%), cirrhosis/acute hepatitis (7; 5%), and hyperglycemia (7; 5%).

Of the 40 randomly selected individuals evaluated by a second reviewer, there was inter-rater agreement on the final diagnosis in all but 2 cases ($\kappa = 0.90$; 95% CI, 0.76–1.00). The first was a 59-year-old diabetic woman who presented with 24 hours of severe epigastric pain, vomiting, and serum lipase of 3500 U/L (58× ULN). Her symptoms rapidly resolved in the ED with intravenous fluids and 2 doses of morphine totaling 6 mg, and she was discharged within 24 hours. Imaging was not performed during the hospitalization; however, MRI approximately 1-month after discharge revealed no pancreatic abnormalities. The reviewers disagreed on whether the rapidity of symptom resolution was characteristic for AP.

The second was a 39-year-old man with chronic pancreatitis due to alcohol use who presented with recurrent severe upper abdominal pain and serum lipase 860 U/L (14× ULN). Neither contrast-enhanced CT on hospital day 3 nor MRI on day 6 revealed findings suggestive of AP. His symptoms gradually improved over a 9-day hospitalization. The reviewers disagreed on whether symptoms were due to AP or chronic pancreatitis.

Model Predictors

The panel identified a total of 54 AP risk factors, encompassing 5 categories: (1) demographic variables, (2) medical comorbidities and history, (3) lifestyle factors, (4) symptoms and signs, and (5) laboratory studies. There were no significant differences in the distribution of nearly all candidate predictors or the cumulative incidence of AP between the derivation and validation sets (Supplementary Table 1, http://links.lww.com/MPA/A657). Nine variables were excluded from analysis because of less than 5% prevalence in both AP and non-AP cohorts (history of autoimmune pancreatitis, hereditary pancreatitis, hypertriglyceridemia, hypercalcemia, cholangitis, biliary colic, an ERCP in prior 7 days, a family history of AP, and surgical or rigid abdomen on physical examination).

Table 1 presents the remaining 45 candidate predictors and their individual effects on AP risk in the derivation set. Among these, 23 had complete data. An additional 14 variables pertaining to presence or location of symptoms were assumed to be absent if undocumented in the EHR. The remaining 8 variables pertaining to pain severity score at presentation, time from symptom onset to presentation, and initial laboratory studies were subjected to imputation when missing. The median number of undocumented variables per patient was 9 (IQR, 7–11). In total, 33 candidate predictors had $P < 0.20$ on univariable analyses.

Multivariable Logistic Regression and Point-Based Models

Table 2 presents the final multivariable logistic regression model; Table 3 presents an analogous point-based scoring model.

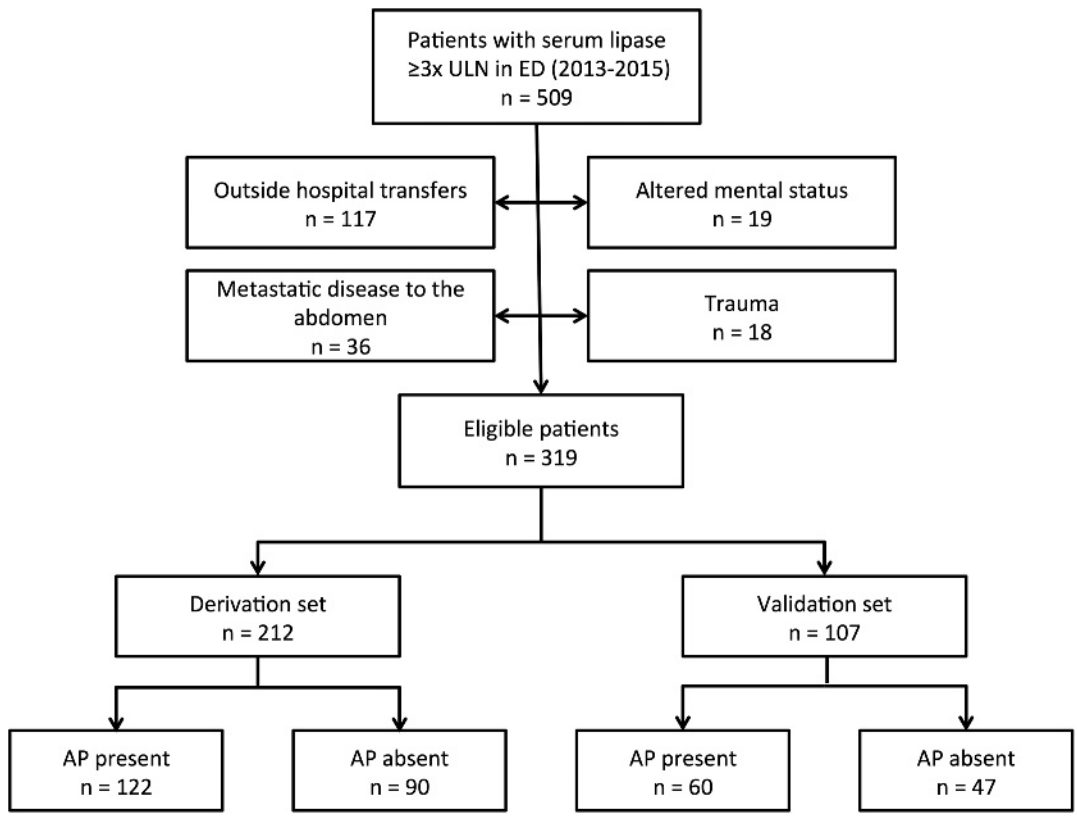

FIGURE 1. Flow diagram of study participants.

TABLE 1. Candidate Predictors and Univariable Analysis in the Derivation Set

Predictor*	Entire Derivation Cohort	Individuals With AP	Individuals Without AP	Missingness†, n (%)	*P*
Overall	212	122	90	—	—
Demographic factors					
Age, y	49.0 (35.3–65.0)	47.5 (33.8–58.3)	55.0 (39.0–72.0)	0	0.009‡
Sex, male	96 (45.3)	53 (43.4)	43 (47.8)	0	0.53
Race				0	0.59
White	121 (57.1)	72 (59.0)	49 (54.4)	—	—
Black	42 (19.8)	22 (18.0)	20 (22.2)	—	—
Hispanic	35 (16.5)	21 (17.2)	14 (15.6)	—	—
Other	14 (6.6)	7 (5.7)	7 (7.8)	—	—
Medical cormobidities and prior history					
Charlson Comorbidity Index	1 (0–3)	1 (0–2)	2 (0–4)	0	0.001‡
Prior AP	59 (27.8)	52 (42.6)	7 (7.8)	0	<0.001‡
No. prior AP episodes	0 (0–1)	0 (0–2)	0 (0–0)	0	<0.001‡
Chronic pancreatitis	18 (8.5)	15 (12.3)	3 (3.3)	0	0.03‡
Pancreatic tumor	8 (3.8)	1 (0.8)	7 (7.8)	0	0.03‡
Cholelithiasis	37 (17.5)	31 (25.4)	6 (6.7)	0	<0.001‡
Cholecystitis	10 (4.7)	9 (7.4)	1 (1.1)	0	0.07‡
Choledocholithiasis	7 (3.3)	7 (5.7)	0	0	0.99
Cholecystectomy	44 (20.8)	30 (24.6)	14 (15.6)	0	0.11‡
Abdominal surgery in prior 2 mo	22 (10.4)	8 (6.6)	14 (15.6)	0	0.04‡
Medication change in prior 2 wk	29 (13.7)	12 (9.8)	17 (18.9)	0	0.06‡
Lifestyle factors					
Smoking (ever)	85 (40.1)	44 (36.1)	41 (45.6)	0	0.16‡
Smoking (current)	47 (22.2)	28 (23.0)	19 (21.1)	0	0.75
Alcohol use (current)	74 (34.9)	47 (38.5)	27 (30.0)	0	0.20‡
Symptoms and signs					
Time from onset to presentation, d	2 (0–4)	1 (0–2.25)	4 (1–7)	17 (8.0)	<0.001‡
Pain severity at presentation, out of 10				23 (10.8)	<0.001‡
Mild (0–3)	56 (26.4)	5 (4.1)	51 (56.7)	—	—
Moderate (4–6)	30 (14.2)	16 (13.1)	14 (15.6)	—	—
Severe (7–10)	126 (59.4)	101 (82.8)	25 (27.8)	—	—
Acute in onset (within prior 7 d)	106 (50.0)	70 (57.4)	36 (40.0)	72 (34.0)	0.04‡
Epigastric	116 (54.7)	92 (75.4)	24 (26.7)	91 (42.9)	<0.001‡
Right upper quadrant	50 (23.6)	35 (28.7)	15 (16.7)	156 (73.6)	0.04‡
Left upper quadrant	24 (11.3)	18 (14.5)	6 (6.7)	181 (85.3)	0.07‡
Upper abdominal	89 (42.0)	60 (49.2)	29 (32.2)	100 (47.2)	0.01‡
Radiating to back	77 (36.3)	53 (43.4)	24 (26.7)	111 (52.4)	0.01‡
Progressively worsening severity	35 (16.5)	25 (20.5)	10 (11.1)	164 (77.3)	0.07‡
Constant in presence	50 (23.6)	35 (28.7)	15 (16.7)	148 (70.0)	0.04‡
Similar previous symptoms	71 (33.5)	52 (42.6)	19 (21.1)	136 (64.2)	0.001‡
Interferes with sleep	26 (12.3)	20 (16.4)	6 (6.7)	180 (84.9)	0.04‡
Interferes with eating	53 (25.0)	32 (26.2)	21 (23.3)	140 (66.0)	0.63
Nausea	136 (64.2)	87 (71.3)	49 (54.4)	44 (20.8)	0.01‡
Vomiting	103 (48.6)	62 (50.8)	41 (45.6)	48 (22.6)	0.45
Diarrhea/loose stools	48 (22.6)	25 (20.5)	23 (25.6)	92 (43.4)	0.38
SIRS at presentation	55 (25.9)	32 (26.2)	23 (25.6)	0	0.91
Laboratory studies§					
Lipase, U/L				0	<0.001‡
≥3 to <10× ULN (180–599)	114 (53.8)	44 (36.1)	70 (77.8)	—	—
≥10 to <20× ULN (600–1199)	39 (18.4)	26 (21.3)	13 (14.4)	—	—
≥20× ULN (≥1200)	59 (27.8)	52 (42.6)	7 (7.8)	—	—
Alanine aminotransferase >50 U/L	62 (29.2)	39 (32.0)	23 (25.6)	9 (4.2)	0.27

(Continued on next page)

TABLE 1. *(Continued)*

Predictor*	Entire Derivation Cohort	Individuals With AP	Individuals Without AP	Missingness†, n (%)	*P*
Aspartate aminotransferase >50 U/L	64 (30.2)	40 (32.8)	24 (26.7)	16 (7.5)	0.21
Alkaline phosphatase >130 U/L	66 (31.1)	35 (28.7)	31 (34.4)	5 (2.4)	0.49
Total bilirubin, mg/dL				3 (1.4)	0.17‡
Normal (0–1)	160 (75.5)	95 (77.9)	65 (72.2)	—	—
Moderately elevated (1.8–4)	38 (17.9)	22 (18.0)	16 (17.8)	—	—
Severely elevated (>4)	14 (6.6)	5 (4.1)	9 (10.0)	—	—
White blood cells <4 or >12 × 10^3 cells/mm^3	64 (30.2)	42 (34.4)	22 (24.4)	0	0.12‡
Hematocrit, %				0	0.04‡
Low (<36)	76 (35.8)	34 (27.9)	42 (46.7)	—	—
Normal (36–48)	132 (62.3)	87 (71.3)	45 (50.0)	—	—
Elevated (>48)	4 (1.9)	1 (0.8)	3 (3.3)	—	—
Blood urea nitrogen >23 mg/dL	45 (21.2)	14 (11.5)	31 (34.4)	0	<0.001‡
Creatinine >1.2 mg/dL	49 (23.1)	15 (12.3)	34 (37.8)	0	<0.001‡
Albumin <3.5 g/dL	38 (17.9)	17 (13.9)	21 (23.3)	3 (1.4)	0.07‡
Lactate >2.2 mmol/L	18 (8.5)	10 (8.2)	8 (8.9)	131 (61.8)	0.91

Values are n (%) for categorical variables and median (IQR) for continuous variables.

*The following variables were excluded because of less than 5% prevalence in both cohorts: autoimmune pancreatitis, hereditary pancreatitis, hypertriglyceridemia, hypercalcemia, cholangitis, biliary colic, ERCP in prior 7 days, family history of AP, and surgical or rigid abdomen.

†Missing dichotomous "symptoms and signs" assumed to be absent. Missing "pain severity at presentation" and laboratory variables imputed with statistical mode of individuals with and without AP. Missing "time from onset to presentation" variables imputed with statistical mean.

‡$P < 0.20$ and included in multivariable analysis.

§Initial laboratory values used. Cutoffs based on institutional standards.

SIRS indicates systemic inflammatory response syndrome.

Derivation of the points system with corresponding AP risk is presented in Supplementary Tables 2 and 3, http://links.lww.com/MPA/A657.

Both models contained 8 predictors, including 3 pertaining to medical comorbidities/history (the number of prior AP episodes, a history of cholelithiasis, and the absence of abdominal surgery in

TABLE 2. Multivariable Logistic Regression Model for Predicting AP Risk

Predictor	β Coefficient	OR (95% CI)	*P*
Medical comorbidities and history			
No. prior AP episodes*	1.1595	3.19 (1.69–7.53)	0.002
History of cholelithiasis	1.9207	6.83 (1.34–45.31)	0.031
Abdominal surgery in prior 2 mo	−1.8196	0.16 (0.027–0.87)	0.039
Symptoms and signs			
Epigastric pain	2.6323	13.91 (4.91–46.14)	<0.001
Progressively worsening severity	1.5368	4.65 (1.30–19.18)	0.024
Time to presentation, d*†	−0.1217	0.89 (0.78–0.97)	0.028
Pain severity at presentation (vs mild)‡			
Moderate	2.3082	10.06 (1.82–68.90)	0.011
Severe	3.5863	36.10 (9.16–196.96)	<0.001
Laboratory studies			
Serum lipase (vs ≥3× to <10× ULN)			
≥10× to <20× ULN	0.6615	1.94 (0.56–7.04)	0.302
≥20× ULN	1.8191	6.17 (1.62–28.31)	0.011
Intercept	−4.4775		<0.001

*Continuous variable.

†Presenting within 1 day, 0; presenting ≥1 to <2 days, 1; and so on.

‡Rated from 0 to 10, where 0 to 3 indicates mild; 4 to 6, moderate; and 7 to 10, severe.

OR indicates odds ratio.

TABLE 3. Point-based Scoring Model for Predicting AP Risk

Predictor	Categories	Points
Medical comorbidities and history		
No. prior AP episodes	0	0
	1	1
	2	2
	3	3
	≥4	4
History of cholelithiasis	No	0
	Yes	2
Abdominal surgery in prior 2 mo	No	0
	Yes	−2
Symptoms and signs		
Epigastric pain	No	0
	Yes	2
Progressively worsening severity	No	0
	Yes	1
Time to presentation, d	<5	0
	≥5	−1
Pain severity at presentation, out of 10	Mild (0–3)	0
	Moderate (4–6)	2
	Severe (7–10)	3
Laboratory studies		
Serum lipase	≥3× to <10× ULN	0
	≥10× to <20× ULN	1
	≥20× ULN	2

prior 2 months), 4 pertaining to presenting symptoms and signs (pain localized to the epigastrium, pain of progressively worsening severity by presentation, the time elapsed from pain onset to presentation, and the pain severity level at presentation), and 1 pertaining to laboratory studies (the extent of serum lipase elevation).

Figure 2 presents receiver operator characteristic curves in the validation set. Both the logistic regression and point-based models achieved excellent discriminatory accuracy (AUC, 0.91 and 0.92, respectively) with minimal optimism (0.05 and 0.03, respectively).

Table 4 compares observed versus expected number of AP events in the validation set across 4 risk groups. Both the logistic regression and point-based models showed excellent calibration in the very high-risk group (≥99% or ≥8 points). The Hosmer-Lemeshow test across deciles showed adequate goodness of fit for the point-based model ($P = 0.07$), but not the logistic regression model ($P = 0.005$).

Diagnostic Performance

Table 5 presents the diagnostic performance of both models at various AP risk thresholds in the validation set with a cumulative AP incidence of 56%. In total, 40% and 45% patients with AP had an estimated risk of at least 99% and at least 8 points, respectively. At these diagnostic risk thresholds, the specificity and PPV were both 100%.

Particular attention was placed on potentially life-threatening conditions that may be misclassified as AP. Six individuals presented with small bowel obstruction, with predicted AP risk ranging from 0.8% to 38%. One individual presented with bowel ischemia, with a predicted AP risk of 24%. Another presented with a spontaneous duodenal wall hematoma in the setting of large-vessel vasculitis, with a predicted AP risk of 82%. There were no cases of bowel perforation in this cohort. The mortality rate among the aforementioned cases was 0%.

Imaging

Among the total study cohort, 185 (58%) individuals underwent at least one CT or MRI examination during their hospitalization. Early CT imaging (<24 hours) was performed in 129 (40%) of 319 cases, with utilization higher among those predicted to have low or medium AP risk (<6 points) compared with those with high or very high AP risk (≥6 points; 46% vs 34%, $P = 0.04$). Of the 129 early CT examinations, 48 (37%) and 21 (16%) were performed in patients who met a diagnostic threshold of at least 6 points (approximately ≥90%) and at least 8 points (approximately ≥99%), respectively.

Case Example

A 50-year-old man without history of AP, cholelithiasis, or abdominal surgery presents with 1-day onset of epigastric pain of worsening severity. His pain severity at ED presentation is rated 7 of 10, and his initial serum lipase is 800 U/L (ULN, 60 U/L). According to the logistic regression model (Table 2), his predicted AP risk would be 98.1%. Using the point-based scoring model (Table 3), his 7 total points would estimate an AP risk of 97.4%.

DISCUSSION

We have derived and validated a diagnostic model and corresponding point-based scoring system for estimating the risk of AP before imaging among patients with serum lipase ≥3× ULN in the ED. The model was developed among a cohort of patients presenting to a tertiary care center over 2 consecutive years. Using predictors readily available at presentation, we were able to estimate AP risk with excellent discriminatory accuracy (AUC, 0.92) and adequate goodness of fit ($P = 0.07$).

This tool was predicated on the need for a simple and accurate means to rapidly diagnose AP without resorting to imaging confirmation. It confers several clinical advantages over the RAC criteria,[4] which are fulfilled when at least 2 of the following are present: (1) characteristic abdominal pain, (2) serum lipase and/or amylase ≥3× ULN, and (3) typical findings of AP on radiographic imaging.

First, it helps objectively define what constitutes characteristic AP pain. Although frequently described as persistent, radiating

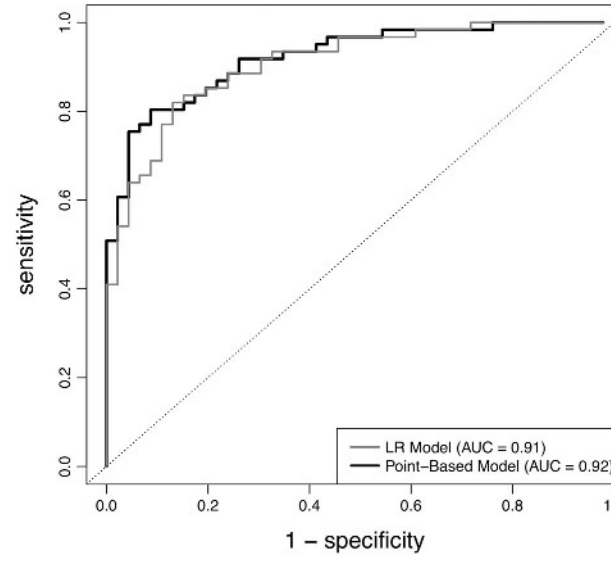

FIGURE 2. Receiver operator characteristic curves of the logistic regression (LR) and point-based models in the validation set with corresponding AUC.

TABLE 4. Observed and Expected AP Across Different Risk Groups in the Validation Set*

	Logistic Regression Model				Point-based Model			
Risk Group	**Threshold, %**	**n**	**Observed AP, n (%)**	**Expected AP, n (%)**	**Threshold**	**n**	**Observed AP, n (%)**	**Expected AP, n (%)**
Low	<5	19	1 (5.3)	0.3 (1.5)	≤2	27	2 (7.4)	1.4 (5.0)
Medium	5 to <90	39	16 (41.0)	19.5 (50.0)	3–5	30	12 (40.0)	16.5 (54.9)
High	90 to <99	25	19 (76.0)	23.8 (95.1)	6–7	23	19 (82.6)	21.8 (95.0)
Very high	≥99	24	24 (100)	23.9 (99.5)	≥8	27	27 (100)	26.9 (99.5)

*Cumulative incidence of AP in validation set: 60 (56%) of 107.

to the back, and associated with nausea and vomiting,[4] we found these descriptors to be nonsignificant on multivariable analysis. Instead, the most predictive symptoms and signs were related to pain severity (≥7 of 10, progressively worsening by presentation), timing (shorter duration from onset to ED presentation), and location (epigastrium).

Second, it delineates the predictive value of serum lipase elevations above 3× ULN. A recent Cochran review determined the diagnostic sensitivity and specificity of serum lipase ≥3× ULN to be 0.79 and 0.89, respectively.[17] However, a wide variety of nonpancreatic pathologies lead to hyperlipasemia,[13–15,18] and studies have reported the PPV of serum lipase ≥3× ULN ranging from 42% to 77% in the ED[15,16] to only 38% in the intensive care unit.[14] We found that incorporating serum lipase elevations beyond 3× ULN into our model helped distinguish AP from non-AP. For example, moderate (≥10× to <20× ULN) and severe (≥20× ULN) elevations of serum lipase increase the odds of AP 2- and 6-fold, respectively, compared with mild elevations (≥3× to <10× ULN). This finding is concordant with prior reports showing greater serum lipase cutoffs to be more specific for AP.[14,15,44] Third, the inclusion of prior AP episodes and a history of cholelithiasis, 2 well-described AP risk factors, provide additional clinical insight. Approximately 16% to 20% of individuals will develop recurrent AP after an initial episode,[32–34] with rates up to 46% in cases of alcoholic pancreatitis.[47] Cholelithiasis is the most common etiology of AP,[23] increasing the risk up to 35-fold in men and 25-fold in women compared with the general population.[36] In addition, we found a recent abdominal surgery to be a negative predictor of AP, decreasing the odds by 6-fold. Although the origins of nonpancreatic hyperlipasemia in postoperative patients have not been specifically described, it is conceivable that many of the surgical procedures in our population (Supplementary Table 4, http://links.lww.com/MPA/A657) and their potential postoperative complications may lead to transient gut inflammation and lipase release.[18]

Importantly, this diagnostic model may help streamline clinical management by obviating the usage of CT in many individuals. Despite multiple guidelines recommending against routine CT imaging in the initial management of AP,[9–11] ED-based abdominal CT is used in 40% to 70% of cases.[6,7,12] Because the diagnostic performance characteristics of the RAC criteria[4] are unknown, and what constitutes characteristic pain is subjective, it is possible that clinicians continue to rely on CT imaging for diagnostic confirmation or to exclude other potentially life-threatening conditions. Once prospectively validated, our model may afford a simple solution to this problem by identifying high-risk individuals with high specificity. In clinical application, the optimal diagnostic risk threshold for AP could be adjusted according to individual patient characteristics. For instance, if symptoms are mild and there is no evidence of the systemic inflammatory response syndrome (SIRS)[43] or organ dysfunction,[4] an estimated AP risk of at least 6 points (approximately ≥90%) may be sufficient to establish

TABLE 5. Diagnostic Performance at Various Predicted AP Risk Thresholds in the Validation Set*

Logistic Regression Model		Point-based Model	
Risk Threshold	**Diagnostic Performance, %**	**Risk Threshold**	**Diagnostic Performance, %**
≥90%		≥6 points	
Sensitivity	71.7	Sensitivity	76.7
Specificity	87.2	Specificity	91.5
PPV	87.8	PPV	92.0
NPV	70.7	NPV	75.4
≥95%		≥7 points	
Sensitivity	60.0	Sensitivity	61.4
Specificity	93.6	Specificity	95.7
PPV	92.3	PPV	94.9
NPV	64.7	NPV	66.2
≥99%		≥8 points	
Sensitivity	40.0	Sensitivity	45.0
Specificity	100	Specificity	100
PPV	100	PPV	100
NPV	56.6	NPV	58.8

*Cumulative incidence of AP in validation set: 60 (56%) of 107.

a diagnosis. Conceptually, this diagnostic threshold could reduce early CT by 37% in our cohort, with imaging eventually used in a minority of patients who fail to clinically improve. However, if pain is severe or markers of severity are present, a higher diagnostic threshold of at least 8 points (approximately ≥99%) may be warranted. In our validation cohort with a 2-year cumulative incidence of 56%, these 2 thresholds captured 77% and 45% of all AP patients, respectively, with specificity of 92% and 100%. In cases when there is legitimate concern for an alternative, life-threatening, diagnosis (eg, hemodynamic instability, abdominal rigidity, lactic acidosis), immediate CT imaging would continue to be appropriate.

Our study has several strengths. First, data from each admission, hospitalization, and postdischarge course were reviewed in great detail, allowing for extraction of medical comorbidity and symptom parameters not available in most large population data sets, yet critical to the diagnosis of AP. Second, patients meeting inclusion criteria were captured through a daily laboratory query of all serum lipase evaluations, allowing for complete identification of the targeted study population. Third, results were internally validated using a separate cohort of patients, minimizing the risk of overfitting the model on the derivation set. Fourth, the diagnostic model lends itself to future research applications, as the implementation of similar risk prediction models into ED clinical decision support tools has been associated with decreased imaging utilization for a variety of disorders.[48]

This study also has potential limitations. First, the retrospective design allowed only for the analysis of candidate predictors documented in the EHR. Despite a thorough review of ED triage/provider, hospital admission, and GI consultant notes from each hospitalization, there still existed missing data among many of the symptom-based variables. In these instances, the absence of documentation was treated implicitly as the absence of the symptom. Although only one predictor in the final model had greater than 50% missingness (pain of progressively worsening severity), prospective studies are needed to validate all 8 parameters before they can be put into clinical use. Second, the final diagnosis of AP remains challenging because of the lack of a clinical or radiographic gold standard. Nonetheless, using all available data, there was excellent inter-rater agreement for the final outcome ($\kappa = 0.90$) between 2 blinded medical pancreatologists. Third, calibration analysis revealed significant deviations between observed and expected AP events among medium-risk individuals, likely secondary to small validation sample deciles causing test instability. Importantly, calibration and discriminatory accuracy were both excellent in the very-high-risk group (≥99% predicted risk), a threshold most relevant to clinicians who may use it as justification to forgo immediate diagnostic imaging. Fourth, this diagnostic model was derived only in patients presenting with serum lipase ≥3× ULN. This prevented direct comparisons between the RAC criteria and our model because up to 20% of AP patients will not meet this lipase threshold and therefore require imaging for diagnostic confirmation.[17] Fifth, the study was conducted among patients presenting to a single tertiary care center over a 2-year period. The cumulative incidence of nonpancreatic hyperlipasemia in our cohort (43%) is somewhat higher than that reported in one regional ED-based study (23%)[15] but lower than in another (52%).[16] This variability likely reflects differences in underlying patient populations, further emphasizing the need for prospective, multicenter validation of our diagnostic model.

In summary, we have derived and validated a simple and accurate clinical tool for diagnosing AP in individuals presenting to the ED with serum lipase levels ≥3× ULN. This model comprises 8 nonimaging parameters easily ascertained from the initial history taking process. Before clinical implementation, prospective multicenter validation studies are needed to confirm its diagnostic accuracy and assess whether use of this tool will substantially reduce unnecessary early CT imaging and streamline care.

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