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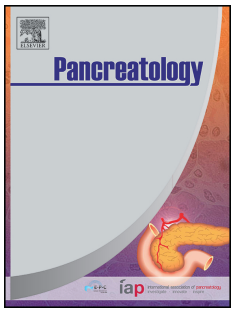

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A Prognostic Tool to Predict Severe Acute Pancreatitis in Pediatrics

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Abbreviations: acute pancreatitis (AP), Area Under the Receiver Operating Characteristic Curve (AUROC), Children's Hospital of Los Angeles (CHLA), Children's Hospital of Pittsburgh of UPMC (CHP), Cincinnati Children's Hospital Medical Center (CCHMC), electronic medical record (EMR), emergency room (ER), receiver operating characteristic (ROC), severe acute pancreatitis (SAP), upper limit of normal (ULN)

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Maisam Abu-El-Haija: principle investigator, responsible for study design, participating in each phase of the study, writing and revising the manuscript and approving the final version for submission.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Background/Objectives: Approximately 15-20% of pediatric patients with acute pancreatitis (AP) develop severe disease. Severity scoring tools were developed for adult patients, but have limitations when applied in children. We aimed to identify early predictors of severe acute pancreatitis (SAP) on hospital admission for early risk stratification of patients.

Methods: Retrospective review of AP admissions was conducted. The **derivation cohort** included cases at Cincinnati Children's Hospital Medical Center (CCHMC) between 2009 and 2013. Clinical data collected during the first 24 hours of admission were analyzed and a predictive model was derived through statistical analysis. The performance of the model was evaluated in a **validation cohort** from 2 more institutions other than CCHMC.

Results: In the **derivation cohort** 19% of the 284 admissions were SAP. A generalized linear mixed effect model analysis revealed that lipase, albumin and white blood count (WBC) play a role in the development of SAP (area under the receiver operating curve (AUROC 0.76)). In the **validation** cohort of 165 AP cases, SAP ranged from 8-20% at the three institutions. Performance of the model in this cohort was comparable to the derivation model (AUROC 0.77). There were 369 encounters in the **combined derivation and validation pool** (AUROC 0.76).

Conclusions: The prognostic severity tool with 3 variables (lipase, albumin, and WBC) obtained within 24 hours of admission can be applied to predict SAP in pediatric patients.

Key words: pediatric pancreatitis; prognostic markers; prognostic model; severe acute pancreatitis

Introduction

The incidence of acute pancreatitis (AP) in children has been increasing over the past decades and is estimated to be 3.6 – 13.2 cases per 100,000/year, an incidence close to that of adult patients.[1-4] Outcomes are generally favorable, although a relatively high percentage (15-20%) of patients develop severe disease, depending on the definition used to define severe acute pancreatitis (SAP).[5-7] Early stratification of patients at higher risk of developing SAP may improve outcomes by alerting the treating physician to provide more aggressive management and vigilance. SAP carries an increased morbidity that leads to longer hospital stays, higher medical costs, and rarely leads to mortality. There are several prognostic tools used in the adult population, such as the Ranson and Glasgow criteria,[8-11] the Balthazar CT severity index,[12] and the APACHE-II score.[9] The sensitivity and specificity of such scoring systems are suboptimal in the pediatric population.[13] The first attempt to develop a prognostic tool for the pediatric population was the pediatric acute pancreatitis score, proposed by the Midwest Multicenter Pancreatic Study Group, and it perfomed favorably compared to Glasgow and Ranson scoring methods in pediatrics.[7] The pediatric acute pancreatitis score was calculated from age and weight specific clinical parameters, and collected at 24 and 48 hours of presentation. A limitation of this pediatric acute pancreatitis score is that it could not be assessed until 48 hours after presentation, and when applied in other studies, had variable sensitivity and specificity for predicting SAP.[5, 14] A study by Coffey et al. was the first to propose an early predictive marker of SAP in children. The study found that a lipase level of ≥7 times the upper limit of normal (ULN) measured within the first 24 hours of admission predicted the development of SAP.[6] Lipase as a single marker in the prediction of SAP has not been validated in larger cohorts.

Previous scoring systems had variable sensitivities and specificities when applied to different patient cohorts. To date, there is no pediatric prognostic severity scoring system that is clinically available to our practice. The aim of our study was to continue to address this knowledge gap by developing and validating a predictive model of severity that can be applied within 24 hours of hospital admission to guide management and improve outcomes of AP in children.

Methods

Data collection for the derivation cohort

We conducted a retrospective chart review of encounters of patients between ages 0-21 years, who presented with AP to Cincinnati Children's Hospital Medical Center (CCHMC) from December 1, 2009 to August 30, 2013. CCHMC is a tertiary medical referral center with 598 pediatric beds. The study was approved by the hospital's institutional review board (IRB) (#2012-4050) and (#2014-4214). Medical documentation of all cases during this time period was captured by query of the Electronic Medical Record (EMR) system, initially identifying 1465 encounters based on International Classification of Diseases, Ninth Revision (ICD-9) codes that started with 577 (acute pancreatitis). The cohort was further narrowed to include only patients with a serum lipase level equal to or greater than three times the ULN within the first 6 days of admission so as to exclude cases in which pancreatitis was not the presenting problem. Our final study cohort included 284 unique encounters.

We collected demographic and clinical variables (age, gender, weight, height, laboratory results, imaging studies) for each encounter. These variables have previously been examined predominantly in adult studies in association with severe pancreatitis. [15-18]

Determination of severity

We defined SAP based on criteria documented in previous pediatric studies by the Midwest Multicenter Pancreatic Study Group [7], Suzuki et al[14], as well as the revised Atlanta criteria[19]. SAP was defined by meeting at least one of the following criteria: 1) admission to the Intensive Care Unit (ICU) due to shock, multi-organ failure, renal failure, or systemic inflammatory response (SIRS); 2) development of local complications such as pancreatic necrosis, abscess, hemorrhage, or a pseudocyst; 3) development of respiratory complications such as pulmonary edema or pleural effusion identified on imaging studies; 4) need for surgical intervention such as pseudocyst drainage or pancreatic necrosectomy; or 5) death secondary to AP.

ICU admissions/transfers: The list of patients admitted to the ICU either directly from the emergency room (ER) or during their hospital stay, was obtained from the EMR. We reviewed the charts of all those patients who were admitted to the ICU and confirmed that they had multi organ failure (MOF) (renal, liver, pulmonary requiring respiratory support) or SIRS (SIRS in children include tachycardia or bradycardia not responsive to fluid resuscitation); tachypnea; elevated or suppressed body core temperatures; and

leukocytosis or leukopenia from the medical documentation. We looked for diagnoses made by the ICU team for MOF, shock, evidence that pressors were used. [20] We relied on medical documentation by the ICU team and involved subspecialists. The other 2 centers involved in the study used the same criteria.

Local Pancreatic Complications: To identify cases with local complications evident on imaging, we identified all encounters from the above described cohort that included Current Procedure Terminology (CPT) codes for abdominal CT (74177, 74178, 74176, 74150, 74160, 74170), abdominal ultrasound (76700, 76770, 76705) and MRI of the abdomen (74181, 74183). We also searched for ICD-9 codes of those admissions that included pancreatic pseudocyst, pancreatic necrosis, peripancreatic necrosis, pancreatic hemorrhage, and pancreatic abscess. Reports for these studies were obtained from the hospital Picture Archiving and Communication System (PACS) and reviewed individually by an experienced pediatric radiologist (D.J.P.) to accurately identify those with local complications, such as necrosis, abscess, hemorrhage and pseudocyst.

Pulmonary complications: were identified by querying the EMR for CPT and ICD-9 codes to identify cases suggestive of pulmonary complications. The queried code names included: pulmonary effusion, pulmonary collapse, pulmonary insufficiency, pulmonary congestion and pulmonary edema. The charts of identified patients were also reviewed and instances in which there was a positive imaging finding were included.

Surgery to the pancreas: Patients who had a surgical procedure due to pancreatitis complication were identified by querying the surgical database, information was confirmed by chart review.

Death: Query of the EMR identified patients who died during admission for AP and was confirmed by chart review.

Statistical analysis

Data were analyzed using SAS®, version 9.3 (SAS Institute, Cary, NC). Categorical data were summarized as frequency counts with percentages, and group comparisons were analyzed using Chi-square tests. When lab values were reported as below the limit of detection (LOD), the values used for analysis purposes were the LOD value divided by the square root of two.[21] If lab values were skewed, log base 10 transformations were applied and presented as geometric means with 95% confidence intervals and normally distributed values were presented as means ± SD. T-tests were used to compare continuous values

and identify variables that may be different in the mild and severe pancreatitis groups. If values were not normally distributed and log transformations were still skewed, then comparisons were analyzed using a Wilcoxon-Mann-Whitney test. Due to the small numbers of some lab values, statistical tests were not run in such cases (lactate dehydrogenase (LDH), CRP and procalcitonin). In order to account for multiple testing, a Bonferroni correction was applied and a p-value of <0.003 was considered statistically significant for the group comparisons. A p-value of < 0.05 was considered statistically significant for all other analyses. To optimize the prediction of SAP, a generalized linear mixed effect model using a binary distribution and logit link function with repeated measures analysis using stepwise selection was performed to identify variables that together predict the development of SAP based on significant p-values and the Receiver Operating Characteristics (ROC) curve. ROC curves were used to develop a prognostic model that we then applied retrospectively in the validation cohort. The final predictive model was developed using the data from combining all cohorts to create a more robust model.

Multicenter validation of the severity predictor tool

Children's Hospital of Pittsburgh of UPMC (CHP), Children's Hospital of Los Angeles (CHLA) and CCHMC participated in the retrospective validation of the predictive model. The validation cohort included admission encounters with AP between September 1, 2013 and June 30, 2014. The case selection was performed as previously described for the derivation cohort. A chart review was conducted at each institution to extract the variables that are part of the severity tool: lipase, WBC and albumin levels at the time of admission. The cases were classified as mild or severe. A case was considered severe if at least one of the above described criteria was met.

Results

1. Demographics

The derivation cohort consisted of 284 cases of AP requiring admission to CCHMC between December 1, 2009 and August 30, 2013. There were 187 unique patients; of which 143 patients (50% of admissions) had a single admission. Forty-four patients (23%) comprised the other 141 admissions as a

result of recurrence of AP. Mean age was 12 years, and 50% were males. Table 1 shows the basic demographic characteristics of the derivation cohort.

2. Severe pancreatitis

Patients were categorized into two groups: mild AP and SAP. SAP was identified in a total of 54 admissions, or 19% of cases of the derivation cohort. Some patients fulfilled more than one criterion. Criteria used to define SAP are shown in Table 2. Most of the severe cases (85%) required admission to the ICU. Of the patients with SAP, 16.7% had developed a local pancreatic complication, and 5 of these cases (9%) met criteria for SAP by having a pseudocyst alone (excluding the 5 patients who were classified as having SAP based on having a pseudocyst only without meeting other criteria did not change our results significantly. Albumin and WBC were still significant and the Area Under the Receiver Operating Characteristic Curve [AUROC] improves only slightly to 0.78 from 0.76.). Forty-three percent of the patients with SAP developed respiratory complications, one case underwent a pancreatic surgery and there was only 1 death. Supplemental Table 1 shows the breakdown of which criteria each patient met to be categorized as SAP.

3. Predictors of severity

Derivation cohort: We examined several parameters collected within the first 24 hours of presentation to our facility (Table 3). Univariate analysis identified lipase (p=0.01) and albumin (p=0.01) to be significantly different between the mild and the severe groups. The sensitivities and specificities for the cutoff values of lipase or albumin as a single predictive marker of SAP changed as the values increased or decreased. The higher the lipase value, the lower the sensitivity, but higher the specificity of predicting SAP. In the case of albumin, the lower the albumin level the lower the sensitivity, but higher the specificity of predicting severe disease. A generalized linear mixed effect model analysis was performed to identify variables that together contribute to the development of SAP. This analysis identified an additional parameter: WBC that appeared to predict the development of SAP. This final cohort included 223 encounters (223 encounters from the 284 encounters had complete data for all three predictor variables); 61 were excluded from the model due to incomplete data for one or more of the three predictor variables.

Albumin (p=0.0003) and WBC (p=0.01) were significantly associated with the development of SAP (Table 4). Although lipase (p=0.09) was not significantly associated with SAP, it was kept in the model due to its clinical association with AP. The AUROC of this predictive model is 0.76 (95% CI: 0.69, 0.84), higher than the AUROC of any individual marker alone (Figure 1).

Validation cohort: There were 165 patient encounters in the validation cohort, which included patients from CHP, CHLA and CCHMC. Demographic patient characteristics were not statistically different between the validation and the derivation cohort (Table 1). The rates of SAP from the total number of AP patients seen at each institution were: 4/50 at CHP (8%), 9/55 at CHLA (16.4%), and 12/60 at CCHMC (20%).

The same generalized linear mixed effect model analysis was performed on this data, (146 of the 165 encounters had complete data for all three predictor variables and were used in the model). Lipase (p=0.57) was not found to be significantly different between the mild and severe groups in the validation cohort but albumin (p=0.002) and WBC (p=0.03) were significantly different (Table 4). The ROC curve that describes the validation cohort using the original model was comparable to the derivation ROC, with an AUROC=0.77 (95% CI: 0.67, 0.88) (Figure 2).

Combined analysis of derivation and validation cohorts: From the total cohort of 449 patients, there were 369 encounters used in the model that had complete data for the three predictors in the combined pool (derivation cohort at CCHMC and validation cohorts from CCHMC, CHLA and CHP). The model included lipase, albumin, and WBC. Albumin (p<0.0001) and WBC (p=0.0004) were significant predictors of the development of SAP, while lipase was not significant in the combined analysis (p=0.36) [Table 4]. The AUROC for the model was 0.76 (95% CI: 0.70, 0.83) and 0.76 (0.70, 0.82) with or without lipase, respectively, and performed better than any single parameter: lipase 0.61 (0.54, 0.68), albumin 0.71 (0.65, 0.78), and WBC 0.59 (0.51, 0.68) (Figure 3).

The equation used to generate this final model is based on three variables (lipase, albumin, and WBC), and provides a predictive probability for the development of SAP. Based on the ROC curve, the model performs best at a predictive probability value of 18 with a sensitivity of 68% and specificity of 71%.

Discussion

We continue to face challenges in recognizing children at risk for SAP early in the disease course in this heterogeneous patient population. Only a few pediatric studies have been conducted in the quest to develop an early severity prediction tool. The first pediatric scoring system, the PAPS score, was proposed by the Midwest Multicenter Pancreatic Study Group in 2002.[7] This system incorporated eight parameters: age, weight, WBC, LDH, calcium, albumin, fluid sequestration and rise in BUN.[7] Four elements were to be scored upon admission and four at 48 hours. The PAPS score requires waiting 48 hours for completion, and its sensitivity and negative predictive values have varied in different cohorts. [5, 14, 22] From our study, we also found that high admission WBC was associated with the development of SAP. We did not determine a specific cutoff value for WBCs, but rather used WBC as a continuous predictor and found that as it increased, the probability of developing SAP increased.

Coffey et al. proposed lipase as a single early marker of severity to be applied within 24 hours of admission.[6] The study was based on a retrospective analysis. Their derivation cohort included 73 encounters with 34% of the cases categorized as SAP. The study also looked for an association between several laboratory and clinical parameters and the development of SAP from which the best single predictor of SAP was lipase. Lipase is used as one of the 3 criteria for diagnosing AP according to the Atlanta criteria;[19] it is therefore available in almost all encounters. A lipase cutoff value of ≥7 x ULN was determined from the ROC analysis, with an AUROC of 0.8. A lipase value that was ≥7 x ULN predicted SAP with an 85% sensitivity and 56% specificity.[6] In our study, using the combined derivation and validation cohort data, a lipase cutoff value of ≥7 x ULN as a single predictor of SAP gives a sensitivity of 78% and specificity of only 38%. Thus more patients would be falsely predicted to develop SAP if lipase was used alone in this manner. Attempts to validate the results of Coffey's study showed that lipase elevation > 7 x ULN had lower sensitivity and specificity compared to the original study in predicting SAP. [22]

Our derivation cohort included 284 encounters of AP. Although the AUROC for lipase as a single marker in this cohort was only 0.68, our analysis shows that as lipase increases, the probability of SAP increases. A possible explanation of how lipase fared differently in different studies to predict SAP, may be due to patient sample size differences and selection bias represented by the different patient populations

served by each institution. Also, the definitions of severe pancreatitis vary from one study to another, mainly due to the absence of a consistent definition of SAP in pediatrics.[13, 23] The lack of a consistent, universally accepted definition of SAP in pediatrics will continue to be a limitation to prognostic studies until a consensus agreement is reached on the best definition that can be used in practice.

Albumin is part of the Modified Glasgow scoring system for acute pancreatitis and is also known as a negative prognostic factor in numerous processes. Lower albumin levels have been reported to accompany severe inflammatory conditions.[24, 25] Our analysis showed that lower albumin levels are associated with more severe disease course.

We derived a predictive model through generalized linear mixed effect modeling that contained other variables as well, which also appeared to play a significant role in the development of SAP. This model simultaneously takes into account the values for those three predictor variables to compute a predicted probability. This is an advantage over traditional scoring systems that do not account for how these values concurrently relate to each other in predicting an outcome. The AUROC for the derivation model was 0.76, greater than the AUROC of each individual variable (lipase, albumin, and WBC) (Figure 1).

Analysis of the multicenter validation cohort included 146 encounters. In the analysis of this cohort we did not find lipase to be a significant variable, but there was a significant association of WBC and albumin with SAP. Retaining or eliminating lipase as a factor in the model did not significantly affect the performance of the model. The AUROC for the model in the combined derivation and validation cohorts with all 3 variables (lipase, albumin, and WBC) was 0.76, which was comparable to the AUROC for the model without lipase (0.76). Adult studies failed to demonstrate that lipase levels are significantly associated with the development of SAP.[26] However, lipase levels are assessed in most instances when evaluating patients for AP since this is a primary clinical diagnostic parameter. Being a parameter that is assessed in the majority of AP cases and the fact that previous pediatric studies showed a promising effect to using lipase in severity prediction; we opted to leave lipase in our model. Future prospective studies are needed to more definitively determine the role of lipase elevation as a predictor of SAP in the pediatric population.

Other elements that could be early predictors for SAP, are C-reactive protein (CRP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN) and procalcitonin have been reported in the literature as

markers of severity [27-30] and may be early predictors in pediatric SAP. We were unable to investigate the role of these markers because of the infrequent use in our population.

This study has limitations given that it's retrospective in nature, however, to our knowledge, it represents the largest pediatric sample size for prognostic scoring of AP to date. Etiologies of pancreatitis were not collected, and chronic pancreatitis patients were not separated. We were merely interested in identifying markers that would help the clinician stratify the patients on presentation, regardless of etiologies and underlying conditions.

Amylase levels are also used in the diagnosis of acute pancreatitis. However, we chose to get our final cohort based on lipase elevation and not amylase elevation, because lipase is known to be a more specific marker for diagnosing AP and lipase without amylase is sufficient to make the diagnosis.[31] Moreover, physicians at CCHMC are more likely to check lipase levels than amylase or both (only 82% of these patients also had amylase levels drawn), so we had more a comprehensive cohort when lipase was used to select patients for inclusion. As a limitation, we may have missed a small number of patients who had positive imaging findings without elevated lipase. In our practice, clinicians obtain serum labs prior to obtaining imaging in most cases. Studies have reported the negative predictive value of serum lipase in diagnosing AP to be 94-100%. [32]

Our model performs best at a predictive probability of 18 as a cutoff with a sensitivity of 68% and specificity of 71%. At the predictive probability of 18, the positive predictive value (PPV) is 35% while the negative predictive value (NPV) is 91%, an outcome that is desired. In other words, if the equation puts the patient in the mild category by having a predictive probability of less than 18, there is a high degree of confidence that this patient will not develop a severe disease.

In conclusion: we present an early severity prognostic model to be used for AP in pediatric patients within 24 hours of presentation. Our model has applicability as a predictive tool for clinicians to better stratify patients presenting to the hospital or emergency room, allowing the provision of early interventions or closer monitoring of patients who are more likely to progress to severe disease. Future prospective studies are needed to further evaluate the application and utility of this model. The goal is to provide medical teams with a calculation tool through a computer based program, in which they would input the values for each of the three parameters and the tool would output the predictive probability of

developing SAP in individuals who present with AP. Further management can thus be directed with the ultimate goal of improving outcomes of AP in pediatrics.

Figure legends:

Figure 1.

AUROC of the multivariable model in the derivation cohort at CCHMC (n=223) with curves of the univariate markers. AUROC of the predictive model is 0.76, better than the AUROC of each individual parameter alone.

Figure 2.

Comparison of the AUROC between derivation (n =223) and validation cohorts (n=146). AUROC is 0.76 for the derivation cohort and 0.77 for the validation cohort.

Figure 3. AUROC of the multivariable model based on combined data of the derivation and validation cohorts (n=369) with curves of the univariate predictors. AUROC of the predictive model is 0.76, better than the AUROC of each individual parameter alone.

Supplemental table 1: The table shows in detail what criteria the patients met to be classified as having severe acute pancreatitis. By definition, each patient had to meet at least one criterion.

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Table 1. Demographic characteristics for the derivation and validation cohorts

	Derivation	Validation	P-value
Number of admissions with AP	284	165	-
Number of unique patients	187 (65.8%)	137 (83.0%)	-
Patients presented with one episode	143 (76.5%)	115 (83.9%)	
Patients presented with recurrent episodes	44 (23.5%)	22 (16.1%)	
Mean age (years)	12.7 ± 4.9	12.9 ± 5.2	0.68
Male	142 (50.0%)	69 (41.8%)	0.09

Demographic characteristics of the derivation (CCHMC) and validation cohorts (CCHMC, CHLA, CHP). There is no statistical difference of main demographic characteristics between the derivation and validation cohorts.

Table 2. Criteria for severe pancreatitis

	Number of Admissions (% of total)
ICU admission	45 (15.8%)
Local complications	9 (3.2%)
Respiratory complication	23 (8.1%)
Surgery to the pancreas	1 (0.4%)
Death	1 (0.4%)
Total number of SAP	**54 (19.0%)**

Criteria for severe pancreatitis and the frequency of each criterion in the derivation cohort.

Table 3. Parameters examined within 24 hours of admission

Parameter	**Mild (n=230)**	**Severe (n=54)**	**P-value**
Age (years)	12.9 ± 4.6	11.6 ± 5.8	0.12
Gender (male)	108 (47.0%)	34 (63.0%)	0.03
BMI percentile	Median 64.3 (IQR: 40.2, 93.4) *n=179*	Median 81.6 (IQR: 36.6, 96.3) *n=50*	0.33
Weight percentile	Median 57.3 (IQR:19.7, 84.5) *n=229*	Median 52.3 (IQR:25.5, 96.0) *n=54*	0.76
Lipase x ULN	10.69 (9.18, 12.44) *n=222*	19.38 (13.99, 26.84) *n=51*	**0.001***
Amylase x ULN	2.37 (2.03, 2.77) *n=186*	3.66 (2.65, 5.04) *n=47*	0.02
Creatinine (mg/dl)	0.57 (0.53, 0.62) *n=206*	0.56 (0.46, 0.70) *n=52*	0.88
Glucose (mg/dl)	107.0 (100.8, 113.7) *n=206*	114.6 (98.5, 133.4) *n=51*	0.40
Sodium (mmol/l)	139.2 ± 3.6 *n=206*	140.8 ± 7.7 *n=52*	0.14
Calcium (mg/dl)	9.2 ± 0.7 *n=206*	9.2 ± 1.0 *n=51*	0.73
Albumin (g/dl)	3.9 ± 0.7 *n=220*	3.5 ± 0.7 *n=54*	**0.0006***
AST (U/l)	47.4 (41.9, 53.7) *n=187*	69.9 (50.8, 96.0) *n=48*	0.03
ALT (U/l)	41.0 (35.4, 47.4) *n=187*	54.4 (36.2, 81.7) *n=48*	0.19
GGT (U/l)	52.4 (40.3, 68.2) *n=89*	118.8 (63.5, 222.4) *n=21*	0.01
Total Bilirubin (mg/dl)	0.60 (0.50, 0.71) *n=98*	0.46 (0.31, 0.70) *n=25*	0.22
Hematocrit (%)	37.4 ± 6.4 *n=183*	37.4 ± 7.0 *n=49*	0.95
WBC (k/µl)	9.6 (8.8, 10.5) *n=183*	11.4 (9.2, 14.3) *n=49*	0.14
Hemoglobin (g/dl)	13.0 ± 2.2 *n=183*	12.8 ± 2.3 *n=49*	0.52
CRP †	Median 1.75 (IQR: 0.35, 4.00) *n=38*	Median 1.60 (IQR: 1.49, 7.90) *n=5*	-
LDH †	Median 661 (IQR: 499, 3215) *n=9*	Median 1349 (IQR: 802, 1896) *n=2*	-
Procalcitonin †	0.1 *n=1*	Median 1.1 (IQR: 0.5, 2.2) *n=6*	-

Data presented as Mean ± SD and Geometric means (95% CI) unless otherwise noted

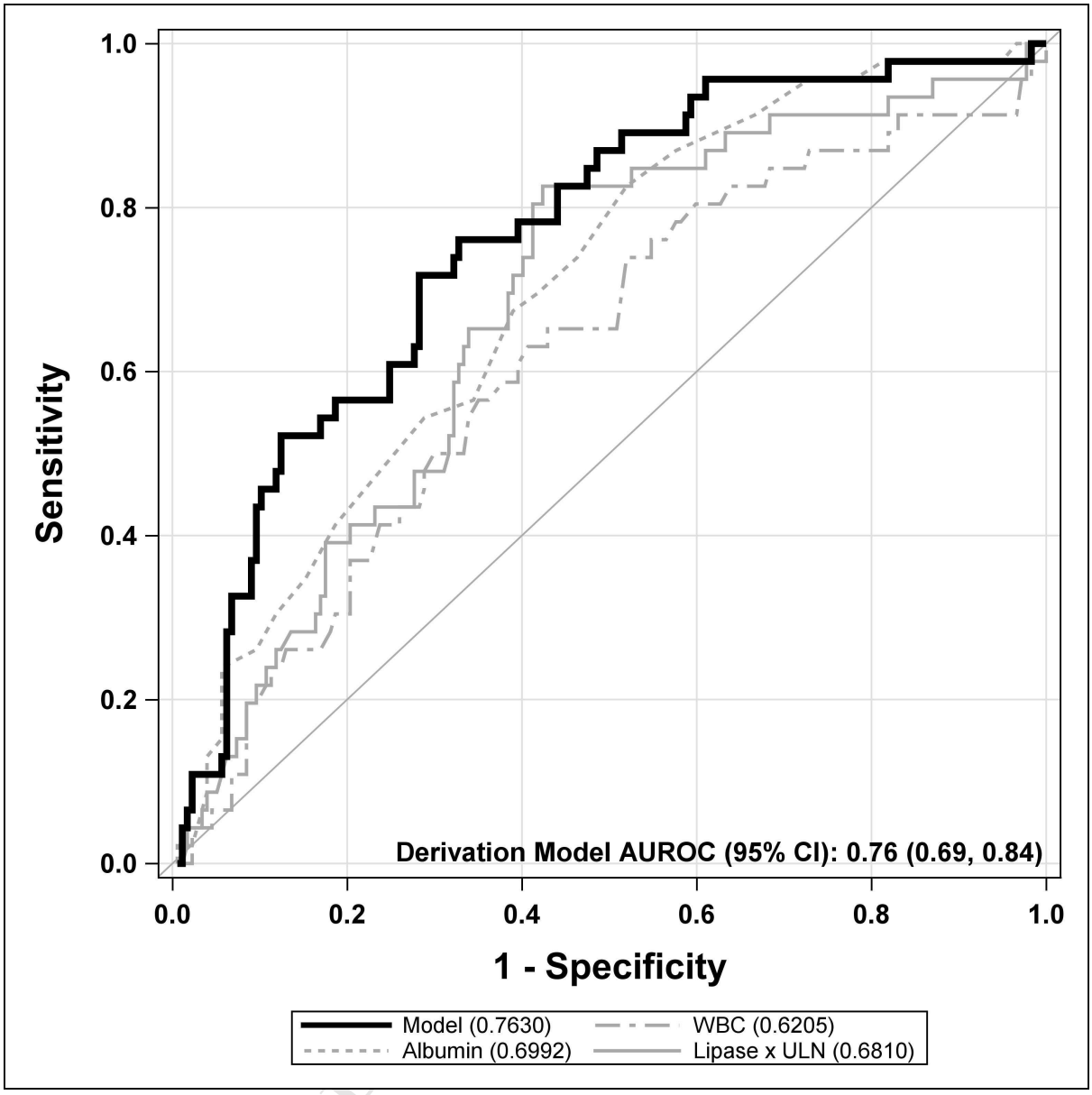
† small numbers - not tested

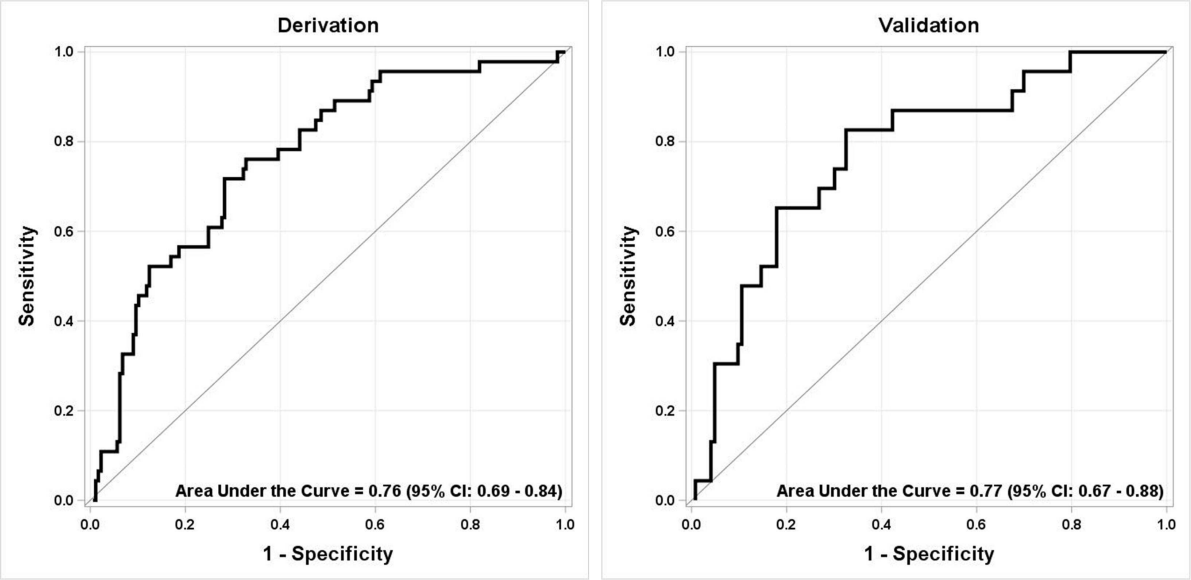
* A p-value < 0.003 was considered statistically significant after a Bonferroni correction to account for multiple testing

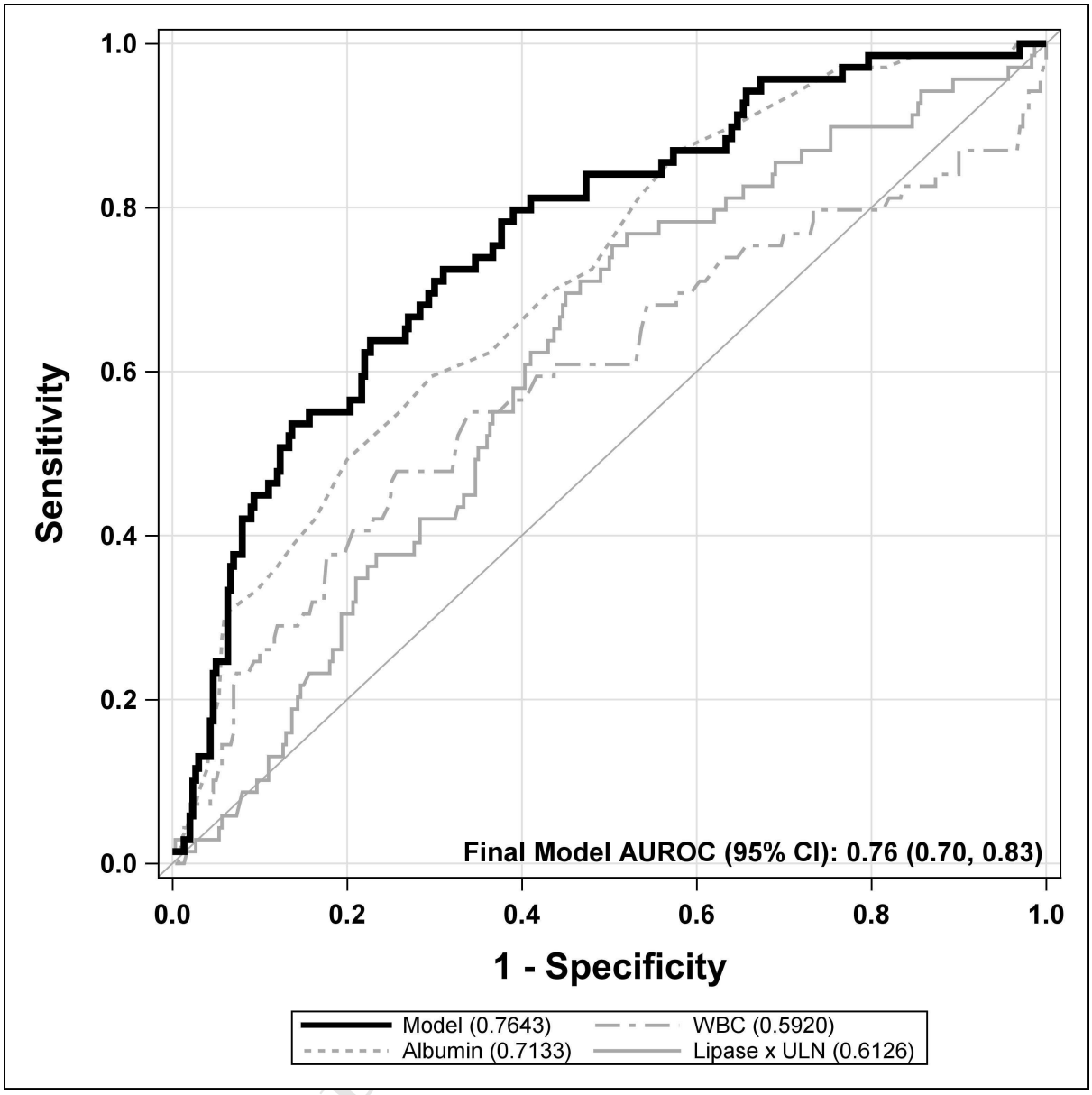
BMI-Body mass Index percentile for age, AST-Aspartate Amino Transferase, ALT Alanine Amino Transferase, GGT-Gammaglutamyl Transferase, WBC-White Blood Cells, CRP-C-Reactive Protein, LDH-Lactate Dehydrogenase

Table 4. P-values for the variables listed from the generalized linear mixed models run on each of the cohorts.

Cohort	Lipase x ULN	Albumin	WBC
Derivation (n=223)	p=0.09	p=0.0003	p=0.01
Validation (n=146)	p=0.57	p=0.002	p=0.03
Combined (n=369)	p=0.36	p<0.0001	p=0.0004


Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
Derivation Model AUROC (95% CI): 0.76 (0.69, 0.84)
Model (0.7630)
WBC (0.6205)
Albumin (0.6992)
Lipase x ULN (0.6810)




Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
Final Model AUROC (95% CI): 0.76 (0.70, 0.83)
Model (0.7643)
Albumin (0.7133)
WBC (0.5920)
Lipase x ULN (0.6126)