

Validation Hypertriglyceridemic Acute Pancreatitis

External Validation of a Predictive Model for Acute Pancreatitis Risk in Patients With Severe Hypertriglyceridemia

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Abstract:

Objective: We previously developed a predictive model to assess the risk of developing acute pancreatitis (AP) in patients with severe hypertriglyceridemia (HTG). In this study, we aimed to externally validate this model.

Methods: The validation cohort included cross-sectional data between 2013 and 2017. Adult patients (≥ 18 years-old) with triglyceride levels $\geq 1,000$ mg/dL were identified. Based on our previous four factors-predictive model (age, TG, excessive alcohol use, and gallstone disease), we estimated the probability of developing AP. Model performance was assessed using area under receiver operating characteristic curve (AUROC).

Results: In comparison to the original cohort, patients in the validation cohort had more prevalent acute pancreatitis (16.2% vs 9.2%, $p < 0.001$) and gallstone disease (7.5% vs 2.1%, $p < 0.001$). Other characteristics were comparable and not statistically significant. The AUROCs were almost identical: 0.8337 versus 0.8336 in the validation and the original cohorts respectively. In univariable analyses, the highest increase in odds of AP was associated with HTG, followed by gallstones, excessive alcohol use, and younger age.

Conclusion: This study externally validates the four-factor predictive model to estimate the risk of AP in adult patients with severe HTG (TG $\geq 1,000$ mg/dL). Younger age was confirmed to place patients at high risk of AP. The clinical risk categories suggested in this study may be useful to guide treatment options.

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Key words: Predictive model, external validation, acute pancreatitis, hypertriglyceridemia

Abbreviations and Acronyms:

AP (acute pancreatitis), ASCVD (atherosclerotic cardiovascular disease), AUROC (area under receiver operating characteristic curve), FRAX (Fracture Risk Assessment Tool), HTG (hypertriglyceridemia), IQR (interquartile range), OR (odds ratio), TG (Triglyceride level), and AUROC (area under receiver operating characteristic curve).

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INTRODUCTION

Acute pancreatitis (AP) can be associated with severe complications, financial burden, negative impact on quality of life, and occasionally can be potentially life-threatening with significant morbidity (1). Severe hypertriglyceridemia (HTG), defined as TG \geq 1000 mg/dL, is a well-described risk for AP, thought to be an etiological factor in approximately 10% of all AP patients (2). It is the third most common etiology after excessive alcohol intake and gallstone disease and is the most common etiological factor (up to 56%) of AP in pregnant women (3). HTG is a frequently silent disease with several possible etiologies including genetic (like lipoprotein lipase deficiency and apolipoprotein CII deficiency), plurigenetic, and secondary disorders (such as obesity, diabetes, alcohol, pregnancy, and certain medications) (4-6). HTG is usually incidentally noted on screening lipid panel, occasionally by physical exam findings such as eruptive xanthomas, or first identified during hospitalization for AP (7). With adequate control of their triglycerides level (TG), the risk of future AP decreases significantly (4).

The occurrence of AP in patients with HTG can vary based on certain patient characteristics (8). In a previous cross-sectional study, we identified four significant clinical factors associated with the risk of developing AP: younger age, excess alcohol intake, gallstone disease, and severity of HTG (8). Although most of these risk factors are well-recognized, there was no risk calculator to predict the probability of developing AP based on individual patient characteristics. Using these factors, we developed a predictive model to estimate the risk probability of occurrence of AP (9). This predictive model had an area under receiver operating characteristic (AUROC) curve of 0.8336 indicating good predictability. Approaches for validation of predictive model include internal cross-validation or validation in separate external cohort. In this study, we aimed to externally validate this model using a different retrospective cross-sectional cohort matching the retrospective nature of the original study to assess its predictive utility (8). The use of an external cohort is an accepted method for validation and it was used in other predictive models like FRAX score (10).

MATERIALS AND METHODS

Study design:

This is a retrospective cross-sectional study spanning from April 2013 to May 2017 in an urban safety-net hospital in Chicago, Illinois. We aimed to externally validate the predictive model from our original study that spanned from January 2003 to March 2013 (8). No patients from the original study were included in this validation cohort.

Variables:

Inclusion criteria were adult patients (aged ≥ 18 years) with TG ≥ 1000 mg/dL at any point of time (i.e. whether as inpatient or outpatient) during the study period. Data were gathered via electronic medical chart review from the same healthcare system as the original cohort. We aimed to gather the significant variables based on our previous study along with the basic demographic data. The important variables collected were age, gender, self-identified race, TG level, cholelithiasis, excessive alcohol intake, and history of AP. We aimed to assess the risk of developing the first episode of acute pancreatitis only. Our results do not apply to the risk of recurrent AP. Diagnosis of HTG-AP was based on the presence of TG ≥ 1000 mg/dL in addition to two out of the following three criteria (11): classical abdominal pain of AP, lipase level more than or equal three times the upper limit of normal, and evidence of AP on imaging studies like CT abdomen. If the patient had multiple TG levels, the TG level at the time of the AP episode was collected. If multiple episodes of AP occurred, only the data at the time of the initial episode were collected. In patients without AP, the highest level of TG was collected with age at time of collection used for analysis. Excessive alcohol intake was based on the documentation of heavy or binge alcohol drinking as defined by CDC as reported in our previous study (8). Cholelithiasis was based on imaging documentation of gallstones or gall bladder sludge. HTG severity was coded as a binary categorical variable: severe from 1,000 to 1999 mg/dL and very severe $\geq 2,000$ mg/dL based on Endocrine Society guidelines (2). Those with very severe HTG ($\geq 2,000$ mg/dL) appear to be at highest risk for developing AP (2, 12). Our lab's triglycerides assay is based on the enzymatic (Glycerol Phosphate Oxidase) method performed on Beckman Coulter Chemistry Analyzer, AU 5800. The instrument is equipped with methodology to ensure that the results are accurate when dealing with very high TG levels up to 20,000 mg/dL). Alcohol, cholelithiasis, alcohol abuse, and AP were expressed as binary variables, coded as 'yes' or 'no'. Age was used a continuous variable, presented in years. Race was coded as: African American, Latino, Caucasian, Asian, and others.

Sample size estimation:

Power analysis was performed to estimate sample size based on our original cohort. We used 2-sided comparison between means (for continuous variables) and proportions (for categorical variables), power of 0.90 and type I error of 5%. Prevalence of AP among HTG in the original cohort was 9.2% which was accounted for in the calculation. We estimated that 436, 398, and 276 patients would be adequate to detect significance for age, alcohol abuse, and severity of HTG respectively. On the other hand, 2,555 patients would be needed to detect significance for cholelithiasis. Based on this power estimate, we aimed for a minimum of 436 patients and we agreed that it would not be feasible to account for cholelithiasis. Database search identified 597 patients who were included in the study.

Statistical Analysis:

Descriptive statistics for categorical variables were reported as percentages and for continuous variables we used either mean \pm standard deviation or median with interquartile range (IQR). To assess significance of association, χ^2 test was used for categorical variables and independent-samples *t*-test was used for continuous variables. Binary multivariable logistic regression was used to estimate odds ratios, confidence intervals, and p-values. We predicted the risk probabilities for developing AP using the formula developed in our original study and mentioned below (8). Age is a continuous variable, presented in years. Presence of alcohol or gallstones was presented as 'one', and the absence was presented as 'zero'. The presented of TG 1,000 to 1,999 was presented as 'zero' while $TG \geq 2,000$ was presented as 'one'. A receiver operating characteristic (ROC) curve was used afterwards to assess performance of the predicted probabilities as compared to the actual occurrence of AP. In addition, the ROC curve output was compared to the one created by the original model. A two-tailed p value < 0.05 is considered significant.

$$\text{Calculated probability} = \frac{\text{Exp}(-1.960 - 0.069 * \text{Age} + 1.362 * \text{Alcohol} + 1.373 * \text{Gallstones} + 1.575 * \text{TG dichotomous})}{1 + \text{Exp}(-1.960 - 0.069 * \text{Age} + 1.362 * \text{Alcohol} + 1.373 * \text{Gallstones} + 1.575 * \text{TG dichotomous})}$$

We compared the original and validation cohorts by cohort level confidence intervals following fixed effects meta-analysis concepts. For continuous variables, confidence intervals were calculated based on the sample size, standard deviation, and calculated standard error of the mean. For categorical variables, confidence intervals were calculated based on the proportion, sample size, calculated probability and standard error of the mean. The confidence intervals of different variables were compared for 95.0%, 99.0%, and 99.9% (13).

Statistical analysis was done using SPSS version 24 (IBM) and Microsoft Excel version 2016. There were no missing data and no sub-group analysis. The study was approved by the institutional review board of our institution.

RESULTS

Comparison of the baseline characteristics of the validation and original cohorts is shown in Table 1. In our initial study, 1157 patients met the inclusion criteria of being adult (aged ≥ 18 years) and having TG ≥ 1000 mg/dL between January 2003 and March 2013. In the current validation study, 597 patients were identified using the same criteria between April 2013 and May 2017. We found significant difference in gallstone prevalence between the validation and original cohorts (7.5% versus 2.1%, $P < 0.001$). In comparison of the groups with AP, the prevalence of AP was higher (16.2%) in the validation cohort compared to 9.2% in the original cohort, $p < 0.01$. We did not find any other significant differences between the groups.

Multivariable analysis for the four significant factors for developing AP in both cohorts is shown in Table 2. All the four independent risk factors had comparable odds ratios and confidence intervals. In comparison of patients between severe and very severe HTG, AP was 5.4- and 4.3-fold more prevalent among the latter group in both validation and original cohorts respectively. Patients who developed AP were younger in both cohorts. AP was 1.9- and 2.8-fold more prevalent in patients < 50 years in the validation and original cohorts respectively.

Excessive alcohol use was two folds higher in patients with AP as compared to those without in both cohorts (Table 2). AP was more prevalent in males as compared to females in the validation and original cohorts (37.0% vs 16.0% and 34.7% vs 15.6% respectively). Excess alcohol use among ethnic groups was similar in both cohorts: African Americans (41.0% vs 41.0%), Latino (21.2% vs 24.8%), whites (35.5% vs 35.6%), Asians (18.2% vs 16.7%), and others (15.4% vs 36.4%). Gallstone disease was 3.1- and 4.0-fold higher in patients with AP as compared to those without in the validation and original cohorts respectively. Gallstone disease was more common in females in both cohorts.

The predicted model for developing AP using the formula developed in our original study achieved area under the receiver operating characteristic curve (AUROC) of 0.8337 ($p < 0.001$) in this validation cohort as compared to

0.8336 in the original cohort as shown in Figure 1. To predict the risk of developing AP in the original study, we suggested three cut-off values: low risk $<4.4\%$, intermediate risk $4.4\text{--}12\%$, and high risk $\geq 12\%$. A cut-off of $\geq 4.4\%$ had sensitivity of 94.4% and specificity 52.9% in the original cohort versus 62.9% and 86.4% in the validation cohort respectively. A cut-off of $\geq 12\%$ had sensitivity 71.0% and specificity 81.7% in the original cohort versus 32.0% and 97.4% in the validation cohort respectively. Based on the data from the validation cohort, we propose a new low risk cut-off value of 1.4% with better sensitivity in both cohorts. A cut-off value of $\geq 1.4\%$ has sensitivity 98.1% and specificity of 15.4% in the original study versus 87.6% and 61.2% in the validation study respectively as shown in table 3. Clinical examples of risk categories are shown in table 4.

DISCUSSION

Predictive models are commonly used in clinical practice like the Fracture Risk Assessment Tool (FRAX) score to estimate the 10-year risk of fractures and the atherosclerotic cardiovascular disease (ASCVD) risk score to estimate the 10-year and lifetime risks for ASCVD (14, 15). The strength of the predictive model is based on the AUROC that reflects the accuracy of the model. AUROC of 0.9 to 1 is considered as 'excellent', 0.8 to 0.9 is 'good', 0.7 to 0.8 is 'fair', 0.6 to 0.7 is 'poor', and 0.5 to 0.6 is 'fail' (16). In a population-based cohort of 141,320 women, the AUROC for FRAX score in estimating major osteoporotic fractures was 0.65 and for estimating hip fractures was 0.82 (10). The ASCVD risk score had AUROC of 0.71 to 0.82 in external validation studies in USA and Europe (17). When the ASCVD score was validated in an Asian population, which was underestimated in the original cohort, it yielded AUC of 0.63 (16). This highlights that caution should be used in applying predictive models in different ethnic groups.

In this study, we externally validated our predictive model to estimate the probability of developing AP based on the four significant factors identified in our earlier study (age, excessive alcohol, gallstone disease, and severe HTG) (8). Both original and validation cohorts were similar in clinical features (age, gender, and ethnicity), and the prevalence of risk factors except for gallstone disease that was more prevalent in the validation cohort. The increased prevalence of acute pancreatitis in the validation cohort was possibly secondary to the increased prevalence of gallstone disease. In both cohorts, the highest odds ratio among the four risk factors was HTG followed by gallstones, excessive alcohol use, and age. Patients who developed AP were significantly younger in

both cohorts. Younger age had a strong impact on the predicted probability and a difference of 40 years in age can change the predicted probability up to 15 folds. It is unclear why younger patients are at increased risk to develop AP. Speculations include differences in protective factors, access to medical care, or lifestyle differences of those who develop AP at different ages.

The predictive model performed strongly in both the original cohort and the current external validation one with AUROC of 0.8336 and 0.8337 respectively. Validated now externally, this is the first predictive model to help clinicians estimate the risk of AP in patients with severe HTG. The cut-off value of 12% for high-risk patients had a good specificity in both cohorts. In this study, we lowered the low risk category to <1.4% based on sensitivity and specificity. The proposed three risk categories may represent the following typical patients. Low risk category will include older patients (≥ 56 years) with TG ≥ 2000 mg/dL without alcohol and gallstones. Intermediate risk categories may include younger patients (≤ 33 years) with TG between 1000 to ≤ 1999 mg/dL and no other risk factors or older patients with TG ≥ 2000 mg/dL and one additional risk factor. High risk category would be younger patients (≤ 42 years) with TG ≥ 2000 mg/dL and one additional risk factor. For the older patients, to be in the high risk category, they need to have TG more than 2000mg/dL and have both gallstones and alcohol excess (see also Table 4).

This study has some limitations, such as the cross-sectional design and the need for longer duration of follow-up. The majority of the patients were Latino and African American in both cohorts. Caucasians and Asians were inadequately represented. As shown with the ASCVD risk calculator, the AUC may not be the same for different ethnicities (15). This suggests that this predictive model may be useful mainly in Latino and African American patients. Further studies are needed in other populations to ensure its validity. The study was underpowered for cholelithiasis for feasibility. However, gallstones were shown to be a statistically significant risk factor. Due to the cross-sectional nature of our studies, we could not assess the time factor in predicting the risk of AP and may need further longitudinal studies to evaluate it. In addition, the predictive model was not tested for any mode of therapy and may need prospective studies to assess its utility regarding treatment and possible prevention of AP.

In conclusion, this study validates our previous predictive model in adult patients with severe hypertriglyceridemia (TG $\geq 1,000$ mg/dL). The four independent risk factors (age, excessive alcohol, gallstone disease, and severity of

hypertriglyceridemia) were validated. The age was shown to be a strong driver of the risk with being younger predicts much higher risk. Longitudinal studies utilizing this model and assessing impact of therapies may further enhance its clinical validity

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External Validation – Hypertriglyceridemic Acute Pancreatitis

Table 1 Baseline characteristics for all patients with severe HTG and in patients with and without pancreatitis in the original and validation studies

Variable	Validation Study			Original Study			P Value (B vs. E)*
	Total study population with TG ≥ 1000 mg/dl (A)	Patients who developed acute pancreatitis (B)	Patients who did not develop acute pancreatitis (C)	Total study population with TG ≥ 1000 mg/dl (D)	Patients who developed acute pancreatitis (E)	Patients who did not develop acute pancreatitis (F)	
Patients (No. [%])	597 (100.0)	97 (16.2)	500 (83.8)	1157 (100.0)	107 (9.2)	1050 (90.8)	<0.01
Age (y), mean ± SD	46.5 (11.3)	41.8 (10.7)	47.4 (11.2)	49.2 (11.5)	41.3 (9.9)	50.0 (11.3)	NS
Male sex (No. [%])	435 (72.9)	71 (73.2)	364 (72.8)	875 (75.6)	79 (73.8)	796 (75.8)	NS
Race (No. [%])							
African American	195 (32.7)	27 (27.8)	168 (33.6)	366 (31.6)	30 (28.0)	336 (32.0)	NS
Latino	294 (49.2)	52 (53.6)	242 (48.4)	444 (38.3)	47 (43.9)	397 (37.8)	NS
Caucasian	73 (12.2)	14 (14.4)	59 (11.8)	242 (20.9)	19 (17.8)	223 (21.2)	NS
Asian	24 (4.0)	2 (2.1)	22 (4.4)	66 (5.7)	7 (6.5)	59 (5.6)	NS
Others	11 (1.8)	2 (2.1)	9 (1.8)	39 (3.4)	4 (3.7)	35 (3.3)	NS
Alcohol use	187 (31.3)	54 (55.7)	133 (26.6)	348 (30.1)	62 (57.9)	286 (27.2)	NS
Gallstone disease	45 (7.5)***	17 (17.5)	28 (5.6)	24 (2.1)***	7 (6.5)	17 (1.6)	NS
TG**, median (IQR)	1501.0 (1186.5-2174.0)	3170.0 (1759.0-4885.0)	1401.0 (1153.0-1896.5)	1444 (1196.5-1991.5)	2394 (1552-4339)	1406 (1180.7-1876.5)	NS
1,000-1,999	1287.0 (1115.0-1560.5)	1437.0 (1175.0-1748.0)	1282.0 (1108.8-1549.3)	1301.0 (1150.0-1538.0)	1457.0 (1187.0-1646.5)	1297.0 (1150.0-1525.0)	NS
≥2,000	3203.5 (2376.3-4567.5)	3990.0 (3030.8-5745.0)	2720.0 (2221.3-3581.5)	2739.5 (2273.8-3950.8)	3807.0 (2638.0-6054.0)	2637.0 (2231.0-3358.0)	NS

*P value between patients with acute pancreatitis in the original versus validation cohorts (shaded in gray)

**Reference value for triglycerides is 30 to 150 mg/dL

*** P value <0.001 between the prevalence of gallstones in the total original versus validation cohorts. Of notice.

The confidence intervals of different variables for patients who developed acute pancreatitis in the original and validation studies were calculated for confidence intervals of 95.0%, 99.0%, and 99.9%. The statistical significance was calculated based on the means or proportions.

External Validation – Hypertriglyceridemic Acute Pancreatitis

Table 2 Multivariable models for factors associated with acute pancreatitis in patients with severe hypertriglyceridemia

Variable	Validation Study				Original Study				P Value (C vs. F)***
	Acute Pancreatitis (A)	No Acute Pancreatitis (B)	Final Model Adjusted OR (95% CI) ** (C)	Adjusted P Value*	Acute Pancreatitis (D)	No Acute Pancreatitis (E)	Final Model Adjusted OR (95% CI) ** (F)	Adjusted P Value*	
Triglycerides ≥2000 mg/dL (%)	68.0%	20.4%	8.97 (5.30-15.19)	<0.001	58.9%	21.2%	4.8 (3.1-7.4)	<0.001	NS
Gallstone disease (%)	17.5%	5.6%	5.27 (2.36-11.77)	<0.001	6.5%	1.6%	3.9 (1.4-10.8)	0.008	NS
Excessive alcohol use (%)	55.7%	26.6%	4.13 (2.45-6.97)	<0.001	57.9%	27.2%	3.9 (2.5-6.0)	<0.001	NS
Age in years [mean (SD)]	41.8 (10.7)	47.4 (11.2)	0.95 (.93-.97)	<0.001	41.3 (9.9)	50.0 (11.3)	0.93 (0.91-0.95)	<0.001	NS

Abbreviations: OR= Odds Ratio, CI= Confidence Interval, NS=Not significant (P>.05)

Only variables with P-Value <0.1 in the univariable analysis were considered in the multivariable model

* The model was adjusted for age (years), triglycerides (dichotomous: 1000-1999 and ≥2000 mg/dL), excessive alcohol use, and gallstone disease.

***The confidence intervals overlap suggesting no significant difference in a conservative approach.

Table 3 Suggested Cut-offs for risk stratification based on the proposed model

	Validation Study				Original Study			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
≥1.4%	87.6%	61.2%	30.5%	96.2%	98.1%	15.4%	10.6%	98.8%
4.4%	62.9%	86.4%	47.3%	92.3%	94.4%	52.9%	17.0%	98.9%
≥12.0%	32.0%	97.4%	70.5%	88.1%	71.0%	81.7%	28.3%	96.5%

Abbreviations: PPV=positive predictive value; NPV: negative predictive value

Based on this validation study, we propose a low risk cut-off <1.4%, intermediate risk 1.4%–12.0%, and high risk cut-off >12.0% for the development of acute pancreatitis based on the predictive risk model. The previous low risk cut-off in the original study (4.4%) did not perform well in the validation study.

Table 4 Clinical examples for the suggested three risk categories

	Typical Patients	Predicted risk
Low Risk (<1.4%)	- 60 years-old patient with TG≥2000 mg/dL with no excess alcohol use or gallstone disease	1.1%
Intermediate Risk (1.4% to <12%)	- 30 years-old patient with TG=1500 mg/dL with no excess alcohol use or gallstone disease	1.7%
	- 60 years-old patient with TG=3000 mg/dL, history of excess alcohol use and no gallstone disease	4.0%
High Risk (≥12.0%)	- 30 years-old patient with TG=2500 mg/dL, history of excess alcohol use and no gallstone disease	25.0%
	- 60 years-old patient with TG=3000 mg/dL, history of excess alcohol use and presence of gallstone disease	14.2%

Abbreviations: TG=triglycerides.

Predicted risk was calculated using our predictive model based on the risk factors mentioned in the corresponding row.

External Validation – Hypertriglyceridemic Acute Pancreatitis

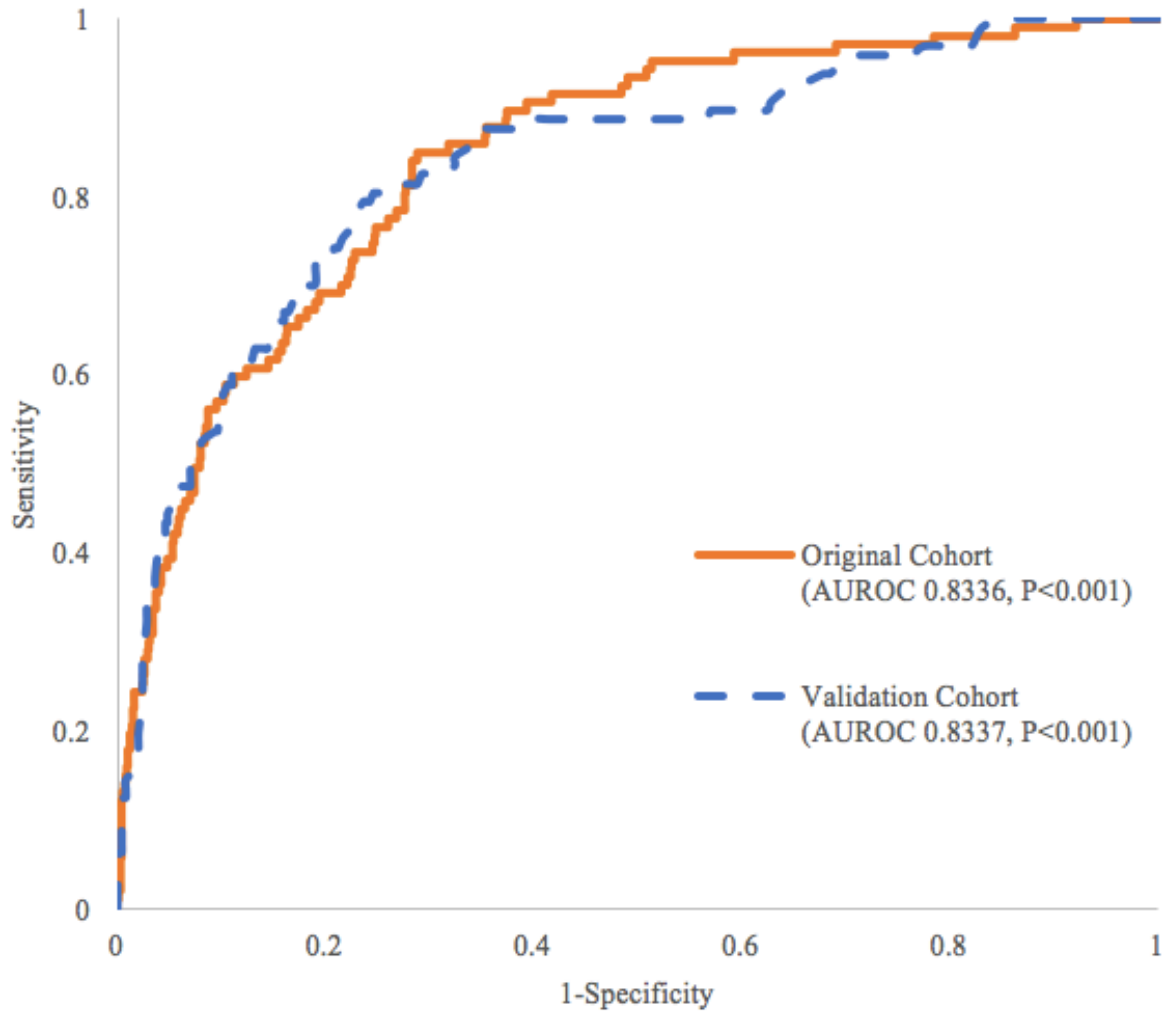


Figure 1 AUROC curve for our predictive model in the original and validation cohorts

Legend Figure 1: The orange solid line represents the area under receiver operating characteristic curve (AUROC) for the predictive model in the original cohort while the blue broken line represents the validation cohort. The strength of the predictive model is based on the AUROC that reflects the accuracy of the model. AUROC of 0.9 to 1 is considered as 'excellent', 0.8 to 0.9 is 'good', 0.7 to 0.8 is 'fair', 0.6 to 0.7 is 'poor', and 0.5 to 0.6 is 'fail' (16).