C0011

Development of a Clinical Screening Tool for Exocrine Pancreatic Insufficiency in Patients With Chronic Pancreatitis

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OBJECTIVE

To develop a clinical screening tool that aids clinicians in the assessment of exocrine pancreatic insufficiency (EPI) in patients with chronic pancreatitis

CONCLUSIONS

- Classification and Regression Tree (CART) provided the best option among 5 evaluated prediction models; the chosen CART includes 10 predictors and 2-5 predictors are needed for a decision call for an individual patient
- CART demonstrated good prediction performance for EPI
- Further exploratory analyses to optimize the EPI screening tool's utility in clinical practice and an external validation is ongoing

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J. Yu, J.J. Kort, and Z. Zhang are full-time salaried employees of AbbVie and may own AbbVie stock or stock options.

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C. Forsmark has received research support from Abbvie, serves as a consultant for Nestle and is a board member of the National Pancreas Foundation.

L.F. Lara serves as a consultant and on a speakers bureau for AbbVie.

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INTRODUCTION

- No specific simple diagnostic tests exist for exocrine pancreatic insufficiency (EPI)[1,2]
- As a result, EPI is often underdiagnosed, including in chronic pancreatitis (CP), and there is an unmet need for clinical tools to help clinicians evaluate patients with CP at risk for EPI[1,3]

METHODS

- We conducted a case-control study in 274 patients with and without EPI and definite CP. Patients were selected by investigators from 6 US pancreatitis centers who have substantial expertise in the diagnosis and treatment of CP and EPI
- Key patient selection: adults with definite CP[4]
- EPI patients were defined as those with Fecal Elastase (FE-1) <200 µg/g stool, or coefficient of fat absorption (CFA) <80% in the absence of concomitant pancreatic enzyme replacement therapy (PERT), or stool fat excretion >10 g/24 h in the absence of concomitant PERT, or secretin-stimulated exocrine pancreas function test <60 mEq/L peak bicarbonate excretion in duodenal fluid and receiving PERT, or a diagnosis of EPI or intestinal or pancreatic malabsorption
- Non-EPI patients were defined as those with FE-1 >200 µg/g stool, or CFA >92% in the absence of concomitant PERT, or stool fat <7 g/day in the absence of concomitant PERT, or secretin-stimulated exocrine pancreas function test >80 mEq/L peak bicarbonate excretion and without a diagnosis of EPI, steatorrhea, or intestinal or pancreatic malabsorption
  - For both EPI and non-EPI patients, CFA and stool fat excretion were in the context of a 72-hour stool collection and a diet that included 100 g of fat daily for 5 days
- Key exclusion criteria included <80% of the 43 designated primary study defined candidate variables available from the medical record, cystic fibrosis, pancreatic cancer, pancreaticoduodenectomy, and extensive small bowel resection
- 64 potential predictor variables were collected from medical records of CP patients with or without EPI, and after pre-processing, 49 variables were entered into predictive modeling
- In a first step, CART was employed to select a parsimonious set of variables (ie, predictors) that could be used to efficiently distinguish CP patients with confirmed EPI from those without EPI; results included the ranking of predictors according to variable importance and a parsimonious set of predictors obtained from the CART model that were trained using the full analysis set (FAS; n = 274)
- The EPI status with metric of EPI misclassification rate (mRate) was used as the endpoint for all prediction models
- 10-fold cross-validation was used to tune the CART model based on the FAS
  - The CART model generated a continuous numeric score to quantify the importance of each variable in distinguishing EPI status
  - The higher the importance score, the more a variable contributed to distinguishing EPI status
  - The decision rule generated by the classification tree predictive model was visualized as a binary tree
  - A subset of the most important predictors was selected in terms of the classification tree; missing data were left as is, and no imputation was performed
- In addition to CART, we trained 4 additional prediction models, including logistic regression with least absolute shrinkage and selection operator regularization (LR with LASSO), support vector machine (SVM), random forest (RF), and gradient boosting machine (GBM) using imputation for missing data and the FAS; training and optimization of each model has been described elsewhere[5,6]
- The 5 prediction models were compared based on training error (mRate), and each model's generalizability was assessed via a 5-fold cross-validation and the generation of average prediction error rates
- Additional performance characteristics of the trained prediction models were generated based on confusion matrices, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)

RESULTS

- Records of 274 patients with CP (160 with EPI and 114 without) were included in this analysis, with demographics of the study population shown in **Table 1**

Table 1. Demographics and Disease Characteristics

	EPI n = 160	Non-EPI n = 114
Age, mean (SD), years	54.8 (14.0)	51.9 (16.8)
Male, n (%)	84 (52.5)	51 (44.7)
White, n (%)	121 (75.6)	79 (69.3)
BMI, mean (SD), kg/m^2	25.3 (5.9)	26.6 (6.2)
Smoker, n (%)		
Current	69 (43.1)	37 (32.5)
Past	44 (27.5)	18 (15.8)
Never	47 (29.4)	59 (51.8)
Alcohol use, n (%)		
Current	27 (16.9)	31 (27.2)
Past	71 (44.4)	23 (20.2)
Never	62 (38.8)	60 (52.6)

BMI, body mass index; EPI, exocrine pancreatic insufficiency.

Figure 1. Trained CART Decision Tree With Risk Scores at Leaf Nodes

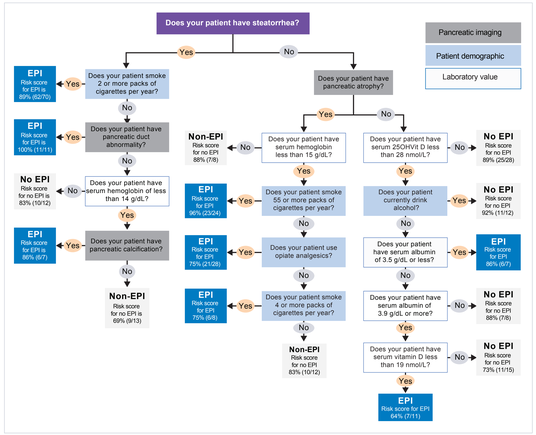

Table 2. Rank List of 49 Predictors Entered into CART and Predictors Selected in Trained CART

Variable	Relative Importance
Smoking, cigarette packs/year	**1**
Pancreatic atrophy	**0.7465**
Steatorrhea	**0.6893**
Alcohol use	**0.6058**
Serum hemoglobin level, g/dL	**0.5858**
Serum 25-OH vitamin D level, nmol/L	**0.5439**
BMI, kg/m^2	> 0
Smoking	> 0
Pancreatic duct contour abnormality	**0.4406**
Weight, lbs	> 0
Serum albumin, g/dL	**0.3928**
Diarrhea	> 0
Number of known acute pancreatitis episodes	> 0
Age, years	> 0
Pancreatic parenchymal calcification	**0.2768**
Use of opiate analgesics	**0.2697**
Pancreatic duct dilatation >7 mm	> 0
Age at diagnosis of chronic pancreatitis	> 0
Pancreatic duct calculus	> 0
History of necrotizing pancreatitis	> 0
History of recurrent acute pancreatitis	> 0
Weight loss, lbs	> 0
Flatulence	> 0
Lack of appetite	> 0
Race	> 0
Feeling of urgency to rush to the toilet (for a bowel movement)	> 0
Use of anti-motility agents	> 0
Alcohol, drinks/day	> 0
Serum hemoglobin A1c, %	> 0
Sex	> 0
Abdominal pain	0
Use of anxiety-relevant medications	0
Use of sleep disturbance-relevant medications	0
Bloating	0
Genetic defect in the cystic fibrosis transmembrane conductance regulator	0
Diabetes	0
Disability	0
Family history in first or second degree relative of (and/or): cystic fibrosis, chronic pancreatitis, pancreatic cancer, acute pancreatitis	0

BMI, body mass index; CART, Classification and Regression Tree.
Predictors shown in bold were selected by the CART model.

Variable	Relative Importance
History of gallstone(s)	0
Serum lipase, U/L	0
Serum magnesium, mg/dL	0
Nausea	0
Pancreas divisum	0
Pancreatic duct structure	0
Serum pre-albumin, mg/dL	0
Serum retinol binding protein	0
Serum vitamin A, µg/dL	0
Serum vitamin E, µg/dL	0
Weight loss ratio, lbs/mo	0

BMI, body mass index; CART, Classification and Regression Tree.
Predictors shown in bold were selected by the CART model.

Table 3. Confusion Matrix for Trained CART

	Actual Condition	
	EPI	Non-EPI
EPI	142	24
Non-EPI	18	90

- Sensitivity: 142 / (142 + 18) = 0.8875
- Specificity: 90 / (24 + 90) = 0.7895
- PPV: 142 / (142 +24) = 0.8554
- NPV: 90 / (18 + 90) = 0.8333

Table 4. Comparison of Training Error and Average Prediction Error Among the 5 Predictive Models

	Full		5-Fold Cross-Validation	
	mRate[a]	AUC	mRate[b]	AUC
CART	0.1533	0.8893	0.3141	0.6823
LR with LASSO	0.2555	0.8427	0.2992	0.7692
SVM	0.0657	0.9834	0.2848	0.7845
RF	0.3066	0.7455	0.3103	0.7682
GBM	0.1569	0.9239	0.3212	0.7410

CART, Classification and Regression Tree; GBM, gradient boosting machine; LR with LASSO, logistic regression with least absolute shrinkage and selection operator regularization; RF, random forest; SVM, support vector machine.
[a]mRate: training error estimated based on the full analysis set.
[b]mRate: average prediction error estimated based on the 5-fold cross-validation.