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GNS HEALTHCARE

Accurate Prediction of Clinical Disease Progression in Patients With Advanced Fibrosis Due to NASH Using a Bayesian Machine Learning Approach

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Introduction

- While liver biopsy is currently considered the ‘gold standard’ for the diagnosis of nonalcoholic steatohepatitis (NASH) and advanced fibrosis,[1] it has significant limitations, including sampling error, and potentially serious complications including pain, bleeding, injury to other organs, and, rarely, death[2]
- Due to these risks, noninvasive dynamic markers represent a large, unmet medical need
- To date, biomarkers for NASH have been evaluated primarily by univariate analysis or as composite scores
- GNS Healthcare’s Reverse Engineering and Forward Simulation (REFS™) proprietary machine learning platform allows complete and unbiased integration of all available markers into a single predictive measure, allowing for quantification and evaluation of predictive performance provided by noninvasive markers alone compared with complete measures, including invasive testing[3]

Objectives

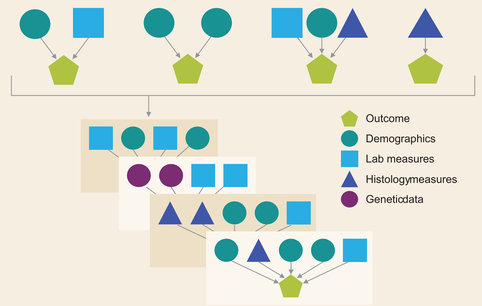
- To identify key noninvasive or invasive factors, combinations of factors, and subpopulations that impact progression to cirrhosis and cirrhosis-related clinical events
- To determine the extent to which only noninvasive measures of fibrosis can be used to predict these outcomes

Methods

- Study population:
  - 219 adults with NASH and bridging fibrosis (modified Ishak Stages 3–4), and 258 adults with NASH and compensated cirrhosis (modified Ishak Stages 5–6) were enrolled in a Phase 2b placebo-controlled trial of simtuzumab (GS-US-321-0105 [ClinicalTrials.gov NCT01672866] and GS-US-321-0106 [NCT01672879] for bridging fibrosis and cirrhosis patients, respectively), a monoclonal antibody directed against lysyl oxidase-like 2
  - Analyses included 475 patients with available data: 381 in the training cohort and 94 in the validation cohort
  - The trials were stopped at Week 96 due to lack of efficacy, so treatment groups were combined for this analysis
- Outcome measures:
  - We performed survival modeling of time to progression to cirrhosis in patients with bridging fibrosis or adjudicated clinical events (eg, ascites, newly diagnosed varices, variceal hemorrhage, hepatic encephalopathy, ≥2-point increase in Child-Pugh-Turcotte score, Model for End-stage Liver Disease score ≥15, liver transplantation, and death) in patients with cirrhosis
- Predictors:
  - 2 sets of models were run for each outcome: 1st, a full model incorporating all available baseline clinical, histologic, and serum fibrosis marker data; and 2nd, a noninvasive model excluding measures obtained from invasive procedures

Modeling Approach and REFS Analytic Platform

Visualization of REFS Enumeration of Model Fragments and Reverse Engineering of Prediction Model Ensemble



- REFS was used to build the survival models using a Weibull distribution
- Selection of a single model underestimates prediction error; thus REFS learns an ensemble of the most probable models (N=256) given the data
  - Ensemble constructed via Monte Carlo sampling of the posterior model landscape
  - Model additions/subtractions scored based on a maximum entropy structural prior, with complexity also penalized by the Bayesian information criterion[3]
  - Linear, additive, and quadratic terms allowed to accommodate nonlinear effects and subpopulations
  - Confidence of the importance of a given predictor towards predicting the outcome determined by selection frequency among ensemble
- Model evaluation
  - The predictive performance of the survival model ensembles was assessed in-sample and by internal 3-fold cross validation (CV) in the training set, and further validated in a test sample (20% of cohort)
  - The performance measure used is the Concordance index (C-index): probability that for a pair of randomly selected patients, the patient with the higher risk prediction will experience an event before the other sample

Results

Baseline Demographics and Characteristics

	Study 105 Bridging Fibrosis n=174	Study 106 Compensated Cirrhosis n=207
Age, y (range)	53 (22–66)	55 (22–66)
Male, n (%)	66 (38)	73 (35)
Diabetes, n (%)	116 (67)	142 (69)
Ishak fibrosis stage (n; % higher score)	3/4 (100/74; 43)	5/6 (66/141; 68)
Mean ELF (SD)	9.78 (1.07)	10.66 (1.06)
Mean HVPG, mm Hg (SD)	NA	12.9 (5.12)
Endpoint	Time to onset of cirrhosis	Time to cirrhosis-related clinical event

ELF, Enhanced Liver Fibrosis test; HVPG, hepatic venous pressure gradient; NA, not available; SD, standard deviation.

Noninvasive Models Performed As Well As Full Models Including Liver Histology

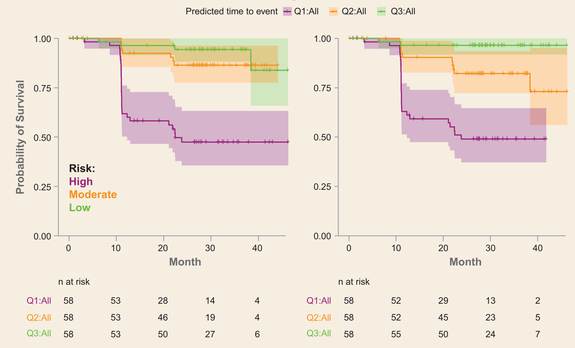
	Predictor Set	C.index (95% CI) In-Sample	3-Fold CV	Test Set
Study 105 Bridging Fibrosis n=174	Full model	0.83 (0.67–0.93)	0.80 (0.63–0.90)	0.73 (0.6–0.87)
	Noninvasive	0.80 (0.63–0.91)	0.79 (0.62–0.90)	0.73 (0.6–0.86)
Study 106 Compensated Cirrhosis n=207	Full model	0.86 (0.71–0.94)	0.69 (0.53–0.82)	0.69 (0.52–0.86)
	Noninvasive	0.87 (0.72–0.94)	0.74 (0.58–0.85)	0.69 (0.52–0.86)

CI, confidence interval.

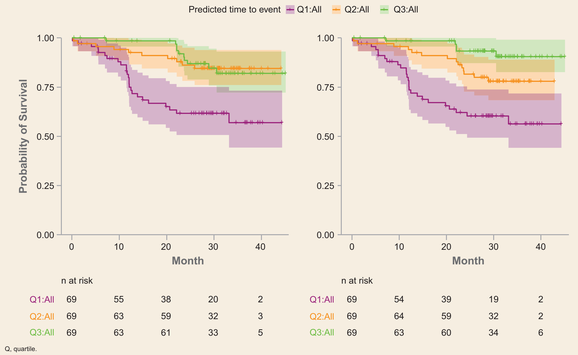
- Models incorporating only noninvasive data performed equally well in predicting progression of disease as models incorporating all available data, including liver histology and morphometry
- Adding genetic information (obtained from Infinium® Omni5 BeadChip [Illumina, Inc., San Diego, California, USA] genotyping on a subset of patients) did not further improve model performance

Disease Progression

Time to Onset of Cirrhosis: Study 105



Time to Onset of Clinical Events: Study 106



Q, quartile.

- Noninvasive models were able to separate patients by risk of disease progression similarly to full models

Study 105: Common Variables

Term	Bridging Fibrosis, n=174 Full Model Ensemble %	Noninvasive Ensemble %
ELF	95.7	93.8
Platelets	95.3	94.1
αSMA (invasive measure)	74.6	NA
ELF test*platelets	15.6	16

αSMA, α-smooth muscle actin.

- ELF test and platelets were the most common variables in the predictive model to identify progression to cirrhosis, and showed an interactive effect
- αSMA was the most commonly observed invasive measure

Study 106: Common Variables

Term	Compensated Cirrhosis, n=207 Full Model Ensemble %	Noninvasive Ensemble %
Hemoglobin	92.6	96.1
Hemoglobin[2]	92.6	95.7
Alkaline phosphatase	49.2	53.1
Lymphocyte/leukocyte ratio	40.2	48.8
NAFLD fibrosis score	30.9	33.2
Total protein	24.6	27.3
Fibrate use	23.4	31.3
Albumin	20.3	17.6
Direct bilirubin	16.4	23

NAFLD, nonalcoholic fatty liver disease.

- A wider variety of noninvasive markers and no invasive markers were commonly observed in models predicting cirrhosis-related clinical events
- Hemoglobin and alkaline phosphatase were most commonly observed

Conclusions

- Models generated using machine learning utilizing only noninvasive data can accurately predict the risk of clinical disease progression in patients with advanced fibrosis due to NASH

References

1. Chalasani N, et al. Hepatology 2017:1-88 [please check this ref citation; missing volume #]; **2.** Tapper EB, Lok AS. N Engl J Med 2017;377:756-68; **3.** Friedman N, Koller D. Mach Learn 2003;50:95-125.

Acknowledgments

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