FRI064

Predicting advanced fibrosis using non-invasive clinical tests and modern machine learning methods in TARGET-NASH

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INTRODUCTION

- Liver biopsy is the reference standard for fibrosis staging, but is an invasive procedure with limitations and potential complications.
- There is an unmet need for readily-available non-invasive tests (NITs) to identify patients with non-alcoholic fatty liver disease (NAFLD) with advanced fibrosis for inclusion into clinical trials[1].
- Fibrosis-4 (FIB-4) index uses age, AST, ALT, and platelet count to predict advanced fibrosis. Scores below 1.3 or exceeding 2.67 have been used to identify potential patients without or with advanced fibrosis, respectively.
- Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS) uses age, BMI, impaired fasting glucose or diabetes status, AST, ALT, ALB and platelet count to predict advanced fibrosis. Scores below -1.455 or exceeding 0.676 have been used to identify potential patients without or with advanced fibrosis, respectively.
- The higher thresholds result in higher specificity but lower sensitivity for predicting advanced fibrosis, while the lower thresholds exhibit higher sensitivity but lower specificity[1].

OBJECTIVE

- The aim of this study is to describe the performance characteristics of NITs in predicting advanced fibrosis (stage of 3-4 for Brunt or NAS fibrosis) using modern machine learning methods and real-world data from TARGET-NASH in a population of patients with NAFLD

METHODS

- TARGET-NASH, a longitudinal observational study of participants at 58 sites (46 academic/12 community) in the United States, includes patients with NAFLD defined by biopsy and/or standard phenotypic definitions.
- NITs, including the fibrosis-4 (FIB-4) index and the Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS) that were performed within 6 months of liver biopsies were analyzed. The most recent biopsies with both FIB-4 and NFS for each patient were used in this analysis.
- Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) and accuracy were calculated for several types of predictive models including logistic regression, lasso, boosted trees, and neural networks.
- Models were run two ways:
  - Predicting advanced fibrosis when the probability of advanced fibrosis exceeded 0.5.
  - Predicting advanced fibrosis where a profit matrix gave 50% extra weight to predicting advanced fibrosis when advanced fibrosis was present. Profit matrices assign costs to undesirable outcomes and profits to desirable outcomes with a goal of maximizing the profit. In our case, we are giving greater weight to the correct prediction of patients who have advanced fibrosis.
- Only the individual variable components of FIB-4 and NFS are considered for the models: age, BMI, diabetes status, albumin, platelets, ALT and AST, though models of FIB-4 and NFS were analyzed for comparison.

METHODS

- Models were trained using a random subset of 75% of the available patient cohort. Models were then applied to the remaining 25% of patients (the validation sample).
- Performance characteristics of the various models were generated using the validation sample.

RESULTS

- 859 adult patients with a liver biopsy and both FIB-4 and NFS were included in this analysis.
- Of these patients, 380 biopsies had advanced fibrosis, while 479 biopsies did not have advanced fibrosis.
- Median age was 57 and 60% of the patients were female. 86% of the subjects were Caucasian, 60% had diabetes and median BMI was 33 kg/m^2. Median ALT and AST were 49 IU/L and 41 IU/L, respectively. Median platelet count was 201 x 10^3 and median albumin was 4.2 g/dL. Median FIB-4 score was 1.66 and NFS score -0.29. See Table 1.

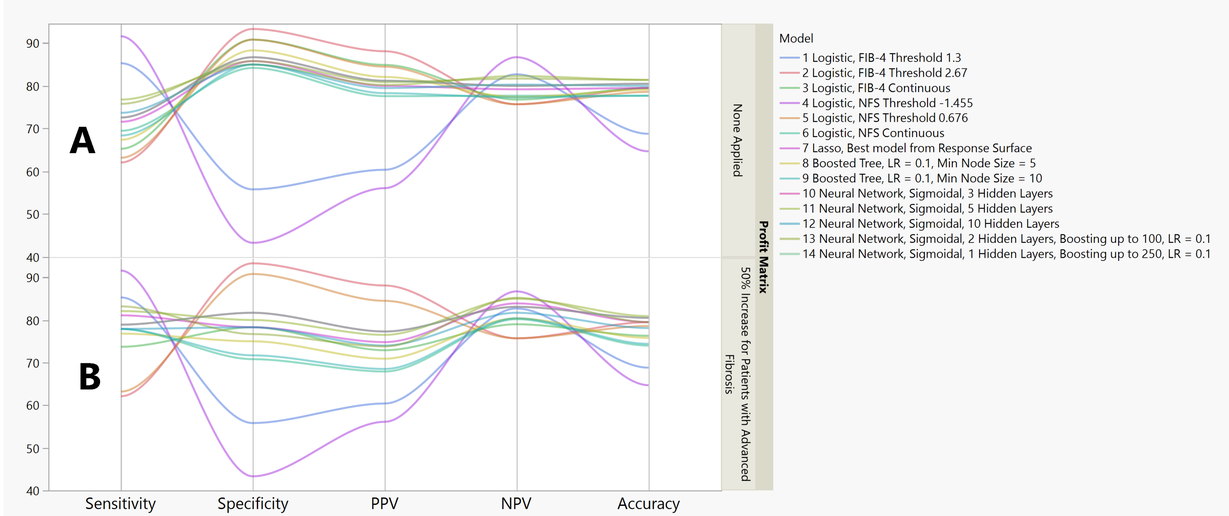
Table 1. Patient and Disease Characteristics

Endpoint	No Advanced Fibrosis (N=479)	Advanced Fibrosis (N=380)	All Patients (N=859)
Demographics			
Age, *years*	55 (42 - 62)	60 (53 - 60)	57 (47 - 64)
Male Sex	43%	37%	40%
White Race	81%	91%	86%
BMI, *kg/m^2*	33 (29 - 38)	34 (29 - 39)	33 (29 - 38)
Diabetes	49%	74%	60%
Laboratory Measurements			
ALT, *IU/L*	52 (33 - 87)	45 (28 - 73)	49 (31 - 80)
AST, *IU/L*	35 (25 - 56)	48 (32 - 73)	41 (28 - 64)
Platelets, *10^3/μL*	237 (191 - 283)	152 (107 - 205)	201 (145 - 263)
Albumin, *g/dL*	4.3 (4.1 - 4.5)	4.0 (3.5 - 4.3)	4.2 (3.9 - 4.5)
Markers of Fibrosis			
FIB-4	1.12 (0.74 - 1.73)	2.85 (1.84 - 4.55)	1.66 (0.98 - 2.93)
NFS	-1.12 (-2.24 - -0.12)	1.06 (-0.15 - 2.29)	-0.29 (-1.58 - 1.21)

Footnote: Continuous variables report median (first quartile, third quartile).

RESULTS

Table 1. Performance Characteristics for Models Predicting Advanced Fibrosis



- Figure 1 summarizes the results of 14 models when no profit matrix is applied (Figure 1A) or a profit matrix is applied (Figure 1B) giving 50% extra weight to correctly predict patients with advanced fibrosis.
- The 4 logistic regression models based on straightforward binary thresholds (Models 1, 2, 4, 5) trade sensitivity for specificity, or vice versa.
- Other models in Figure 1A show less extreme trade-offs between sensitivity and specificity, though specificity is always higher.
- Figure 1B illustrates how the profit matrix can increase model sensitivity making it generally comparable to specificity (evident from the near horizontal lines of non-threshold models).
- Most neural network models provide a good balance between sensitivity and specificity for predicting advanced fibrosis, with 3 of these models (Models 10, 11, 14) providing sensitivity and specificity ≥ 78%. Model 12 had sensitivity and specificity of 77.9 and 78.3, respectively, while Model 13 had sensitivity and specificity of 83.2 and 76.7, respectively. The lasso model has similar performance with greater interpretability for the impact of individual covariates.
- Threshold models are straightforward to apply in practice. Utilizing one of the more complex models above would require the availability of straightforward applications to calculate the outcome from the available data.

CONCLUSIONS

- **Analyzing the individual variables for commonly-used NITs provides a good balance between several performance characteristics for predicting advanced fibrosis using modern modeling techniques.**
- **This improved performance may come at the expense of less easily-interpretable models, or may require applications to classify patients using available data.**
- **It is important to develop and apply prediction models using the same population. Our study uses 859 patients with NAFLD.**
- **Not all outcomes are equal. It is important to consider the costs of correct and incorrect misclassification in order to develop the most useful model.**
- **Future research will expand the above models using other NITs and a wider pool of variables available from TARGET-NASH to improve model performance.**

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References: 1. AS Barritt IV, AS Lok, KR Reddy et al. Routinely Available Noninvasive Tests Perform Well in Identifying Patients with Advanced Fibrosis Due to NASH: Data from the TARGET-NASH Observational Cohort. AASLD. Boston, Massachusetts. Presented Nov 2019.