Enhancing ASCVD Risk Prediction in NASH/NAFLD Patients

Jesse Fishman, PharmD, MSc;[2] Ediz Calay, PhD;[1] Pete Vu, PharmD;[2]
Yestle Kim, PharmD, MSc;[2] and Lars Hegstrom, MD, MSHCT[1]

1. Nference, Cambridge MA, USA; 2. Madrigal Pharmaceuticals, West Conshohocken, PA, USA

Background

- Non-alcoholic steatohepatitis (NASH), also known as metabolic dysfunction-associated steatohepatitis (MASH), and non-alcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated steatotic liver disease (MASLD), are burgeoning health concerns in the United States, linked to increased cardiovascular diseases (CVD) risks.[1]
- The leading cause of morbidity and mortality outside of liver disease is CVD among the NASH population.[1]
- The American Heart Association's (AHA) Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator Plus lacks validated efficacy for mortality prediction in NASH/NAFLD patients suggesting that additional variables should be considered to enhance the accuracy.[2,3,4]

Objective

This study aims to augment the predictive accuracy of ASCVD risk and death among NASH patients by proposing alternative logistic regression models.

Methods

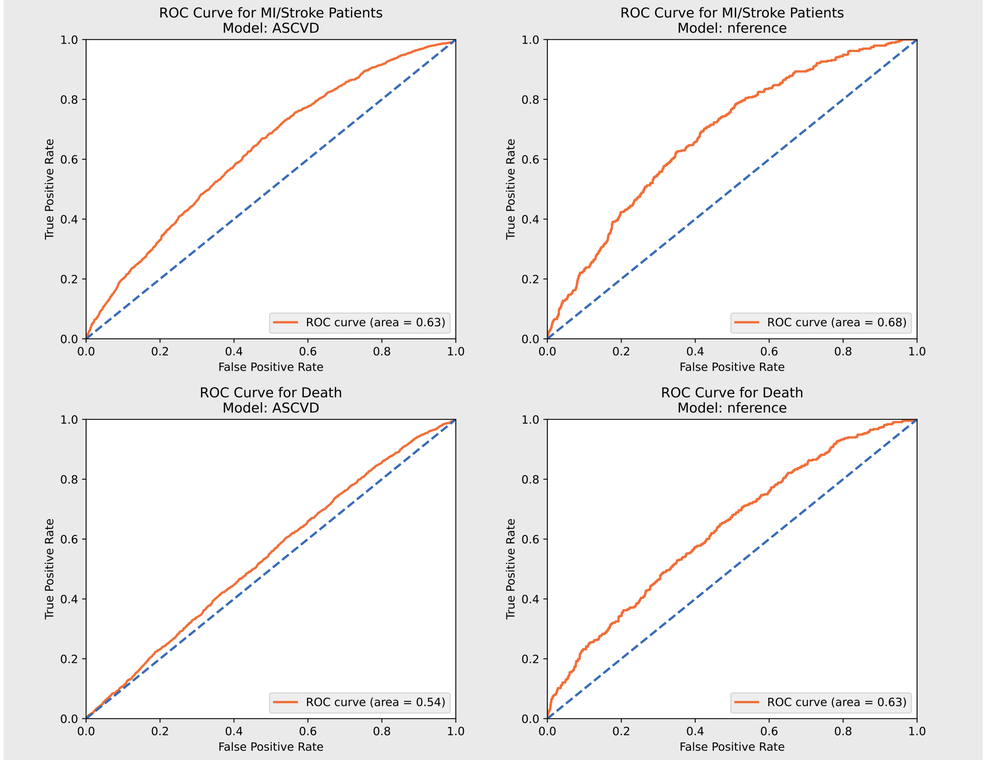
- A retrospective EHR dataset from a large US integrated delivery network health system encompassing multiple sites within the US was curated. A 9,185 patient cohort of biopsy confirmed NASH patients was curated using structured and unstructured data including ICD codes and Clinical Notes. Patients with a history of MI/Stroke before their diagnosis were excluded.
- The variables were constrained to be within 30 days of the NASH diagnosis, and the outcomes were limited to within 10 years and censored by the last available data.
- Demographic, clinical, and laboratory variables underwent a recursive feature elimination process.
- We created two logistic regression models to predict MI/Stroke and Death. An optimal threshold was determined using Youden's J for the output classes of High or Low risk.
- The performance of the AHA's ASCVD Risk Estimator Plus (REP) was compared against our models, which incorporated alternative predictors. A REP score ≥7.5% was considered High Risk. Area Under the Receiver Operating Characteristic curve (AUC) was employed to evaluate and compare both models.
- Survival and time to event curves were generated using the statistical python package lifelines and evaluated for statistical significance at a predetermined alpha of 0.05.

Table 1. Baseline Demographics and Clinical Characteristics

Cohort Statistics	Count (%)
Sample Size	
Total Number	9185.0 (100.0%)
Past Medical History	
Hypertension	6831.0 (74.4%)
Type 2 DM	206.0 (2.2%)
Smoker	
Smoker	1803.0 (19.6%)
Non-Smoker	7382.0 (80.4%)
Gender	
Female	4589.0 (50.0%)
Male	4596.0 (50.0%)
Race	
*White / Asian / Unknown / Other	9012.0 (98.1%)
*Black or AA	173.0 (1.9%)
Observed Outcomes	
Decompensated Cirrhosis	4383.0 (47.7%)
MI / Stroke	1904.0 (20.7%)
Death Within 10 yrs	2139.0 (23.3%)
Data Coverage	
Mean Years After Diagnosis (Std. Dev.)	8.18 (5.9)

*Race was grouped into categories used in ASCVD REP Equation

Figure 1. Comparison of ROC Curves between ASCVD REP and Our Models



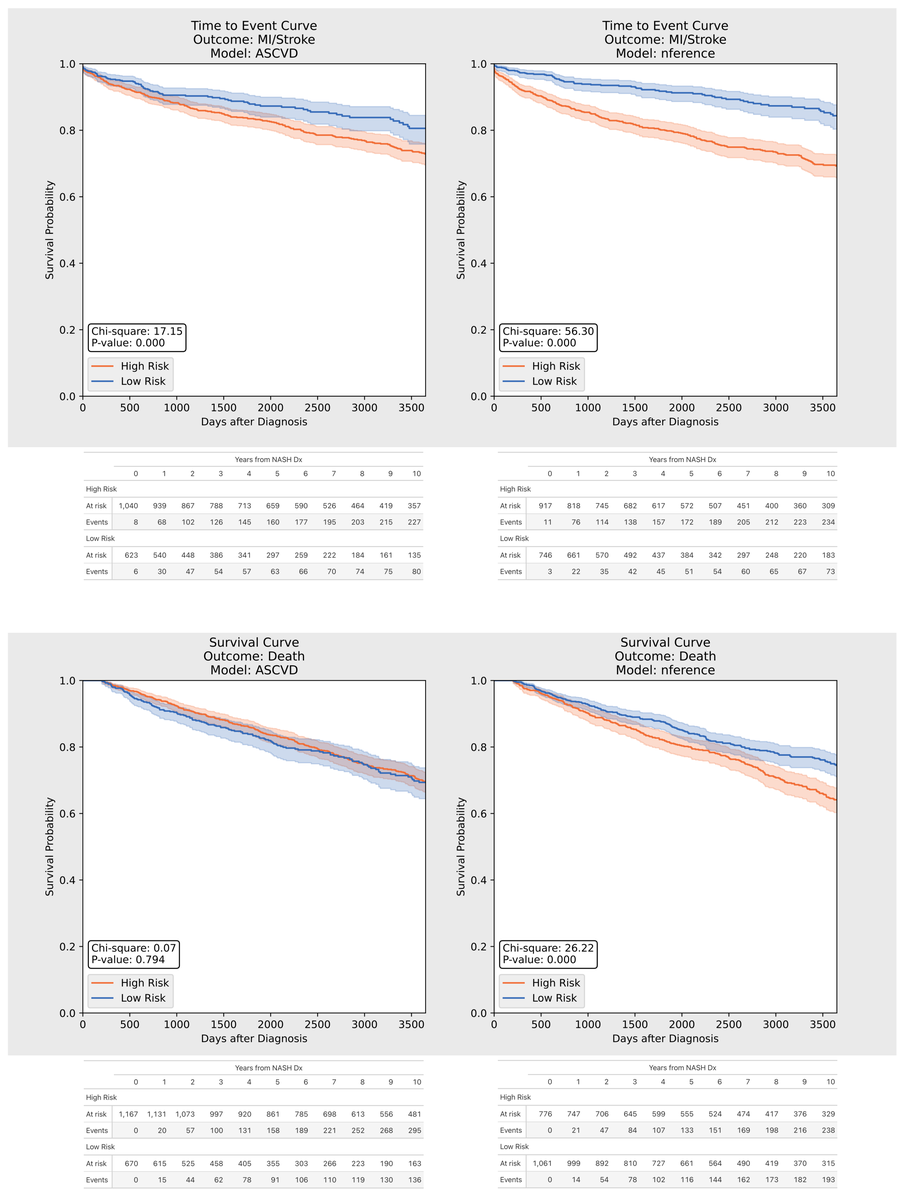
The AUROC curves increased when incorporating additional liver specific variables (0.63 -> 0.68 and 0.54 -> 0.63 for MI/Stroke and Death Outcomes, respectively).

Table 2. Comparison of Variables for Models

Variable Selection Top 15 Variables within 30d of NASH diagnosis were selected using recursive feature elimination for MI and Death Models	MI/Stroke	Death	ASCVD REP
Universal			
Age	✅	✅	✅
Hypertension PMH	✅	✅	✅
Smoker	✅	✅	✅
MI/Stroke and Death Models			
International Normalized Ratio (INR)	✅	✅	❌
Prothrombin time	✅	✅	❌
Total Bilirubin	✅	✅	❌
Alanine Aminotransferase	✅	✅	❌
Alkaline Phosphatase, Serum	✅	✅	❌
Aspartate Aminotransferase	✅	✅	❌
Direct Bilirubin	✅	✅	❌
Hemoglobin A1c, Blood	✅	✅	🟡
Exclusive MI/Stroke			
Platelet Count	✅	❌	❌
Sodium [Moles / Volume] in Serum, Plasma or Blood	✅	❌	❌
Gamma globulin [Mass/volume] in Serum or Plasma by Electrophoresis	✅	❌	❌
HDL	✅	❌	✅
Exclusive Death			
LDL Cholesterol [Mass/volume] in Serum or Plasma	❌	✅	❌
Systolic Blood Pressure	❌	✅	✅
Total Iron binding capacity (TIBC) [Moles/volume] in Serum or Plasma	❌	✅	❌
Gender	❌	✅	✅
Exclusive ASCVD			
Race	❌	❌	✅
Total Cholesterol	❌	❌	✅
Diastolic Blood Pressure	❌	❌	✅
History of DM	🟡	🟡	✅
HTN Medication	❌	❌	✅

🟡 The ASCVD model uses a history of DM, whereas our models use HgA1c

Figure 2. Time to Event and Survival Curves for ASCVD and Our Models



The time to event and survival curves should significant differences in outcomes for both nference models. The difference was statistically significant for the ASCVD MI/Stroke outcome, however was not significant for the death outcome.

Results

- The ASCVD Risk Estimator Plus demonstrated suboptimal predictive accuracy for mortality and myocardial infarction (MI) / stroke events in NASH/NAFLD patients, with an AUC of 0.63 for MI/Stroke events and an even lower AUC of 0.54 for mortality (figure 1). In contrast, our logistic regression models exhibited higher AUCs, with 0.68 for MI/Stroke events and 0.63 for mortality, indicating enhanced predictive accuracy for both outcomes (figure 1).
- The inclusion of liver-specific markers, such as alanine aminotransferase, and other novel predictors, such as INR, helped to achieve greater accuracy. A Kaplan-Meier time to event analysis for 10-year MI/Stroke risk was generated to evaluate the prediction over 10 years, and a similar survival analysis was conducted for mortality. Pearson's chi-squared tests yielded significant statistics of 56.30 (p=0.000) for MI/Stroke and 26.22 (p=0.000) for mortality.
- These findings underscore the potential limitations of the ASCVD Risk Estimator Plus in predicting outcomes for NASH/NAFLD patients and highlight the significance of incorporating liver-specific markers such as ALT and INR and other novel predictors for more accurate risk assessment, which could lead to improved clinical decision-making and patient management strategies in this population.

Conclusion

- Our findings underscore the necessity of revisiting the current CV risk models for NASH/NAFLD patients to incorporate more holistic and disease-specific variables.
- The proposed logistic regression model that includes liver-specific biomarkers, such as ALT and INR, improves the prediction of cardiovascular mortality and MI events, thereby facilitating better clinical decision-making and patient-centered care.

References

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