Longitudinal ALT Trajectories are Generally Stable Among Patients with Non-Alcoholic Fatty Liver Disease (NAFLD): An Investigation Using Artificial Recurrent Neural Networks

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INTRODUCTION & AIM

- Serum alanine aminotransferase (ALT) is a biomarker used to monitor liver injury.

- Little is known about ALT fluctuations over short intervals or the influence of patient characteristics on ALT trajectory in patients with NAFLD.

- This study modeled longitudinal variability in ALT and estimated the probability of a patient transitioning from their baseline level.

METHODS

- TARGET-NASH is a longitudinal observational cohort of over 7,000 patients with NAFLD receiving usual care at 65 sites across the US and Europe

- Using available data, the transition between ALT categories was modelled using a recurrent neural network.

- 80%-20% data split into training-testing approach was utilized to fit the model and assess accuracy.

- Age, sex, body mass index (BMI), race/ethnicity, ALT date, hypertension, diabetes, cardiovascular disease and statin use were identified a priori.

- A multivariable logistic model was used to calculate odds ratio of ALT increase from ALT at index date

- Exclusions:
  - Patients with cholecystitis, sepsis or liver cancer
  - ALT values recorded during hospitalization
  - Patients without labs within 3 years prior to enrollment OR <3 labs between 3 years prior to enrollment and the data cut

Characteristics of the Adult Cohort at Enrollment

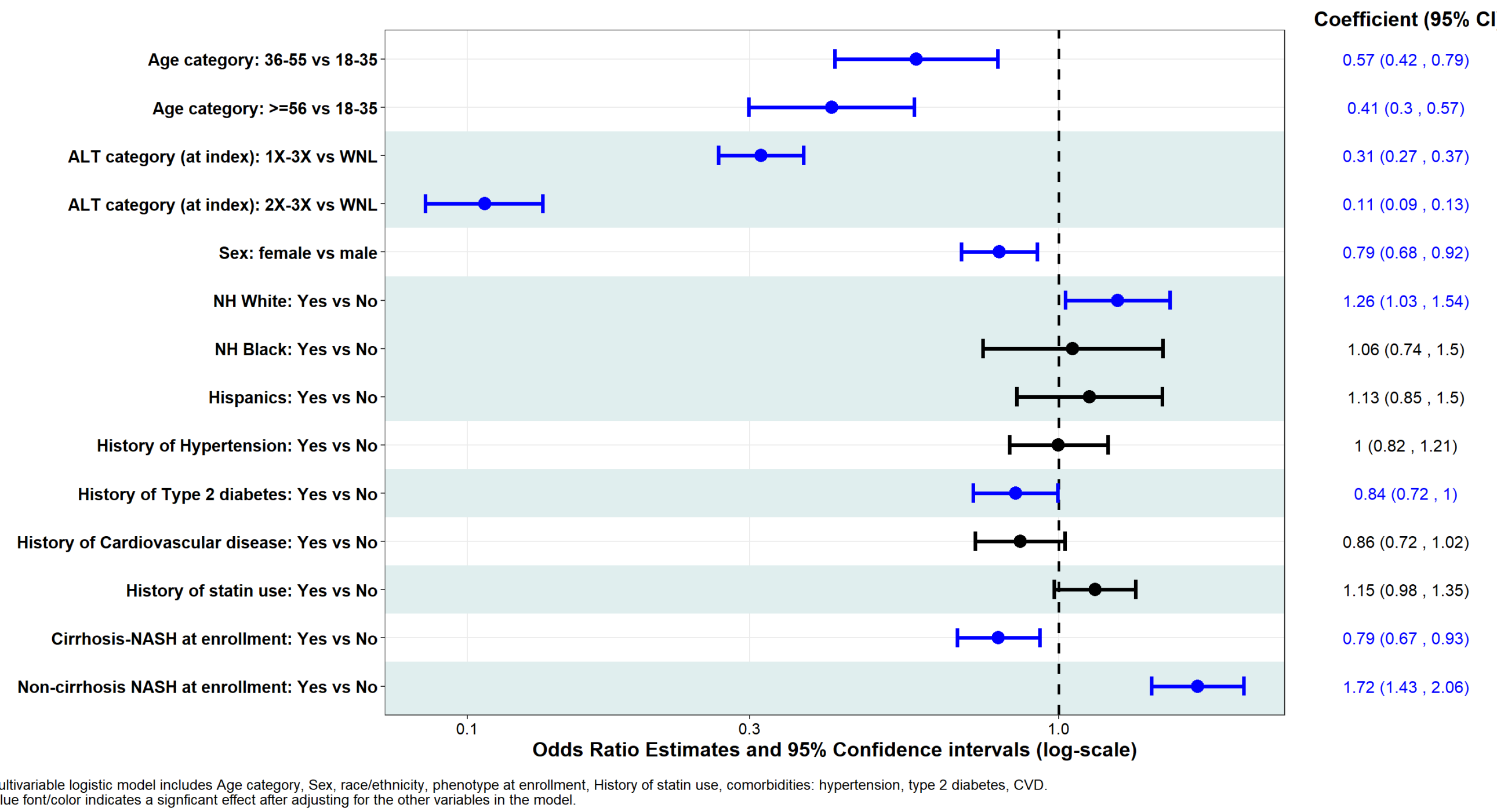|	
Number enrolled = **3,664**	Type 2 diabetes = **54%**
Median age = **59**	CV disease = **22%**
Sex, female = **58%**	Statin use = **46%**
Ethnicity, white = **76%**	NASH = **44.3%**
Median BMI = **32 kg/m2**	Cirrhosis = **40.4%**
Hist. of hypertension = **74%**	NAFLD = **15.3%**

RESULTS

- 3,664 adult patients in the US were followed over a median of 38.2 months (range: 1.7 - 87 months) with 3.9 months (range: 0.5 – 54.2 months) between ALT measure. Median age was 59, white (76%), with a BMI of 32 kg/m^2.

- Patients in higher ALT categories at baseline were younger with a greater percentage of Hispanic or Latino participants vs. lower ALT categories.

- At baseline, 33%, 38%, 15%, 14% of patients had normal ALT, slightly high, high, and very high ALT levels, respectively.

- In the unadjusted model, 39% of patients with normal ALT at baseline remained within that during follow up.

- Among those with slightly high ALT at baseline, 18% remained within that stratum, while those with high (5%) and very high ALT (18%) remained in the same strata throughout as depicted by the darkened colors in Figure 1.

- The probability of transitioning from a normal or a slightly high to a very high ALT level was 2% and 6%, respectively, suggesting that transition from low to high ALT levels is uncommon.

- Risk of transition was higher in Non-Hispanic Whites (24%) and Hispanics (24%), followed by Non-Hispanic Black (21%), and Asians (19%).

- Patients less likely to have changes from their index ALT were older (35-55 and ≥56 vs. 18-35 y/o; 43% and 59% respectively), females vs. males (21%), cirrhotic vs. non-cirrhotic (21%), and those in the ALT 1x-2x and 2x-3x categories compared to those WNL (69% and 89%, respectively) (Figure 2)

- Non-Hispanic (NH) whites and those with non-cirrhotic NASH vs. NAFLD and cirrhosis are 26% and 43% (respectively) more likely to have an increase in their ALT category.

Figure 1. ALT Transitions Over Time in Adults with NAFLD
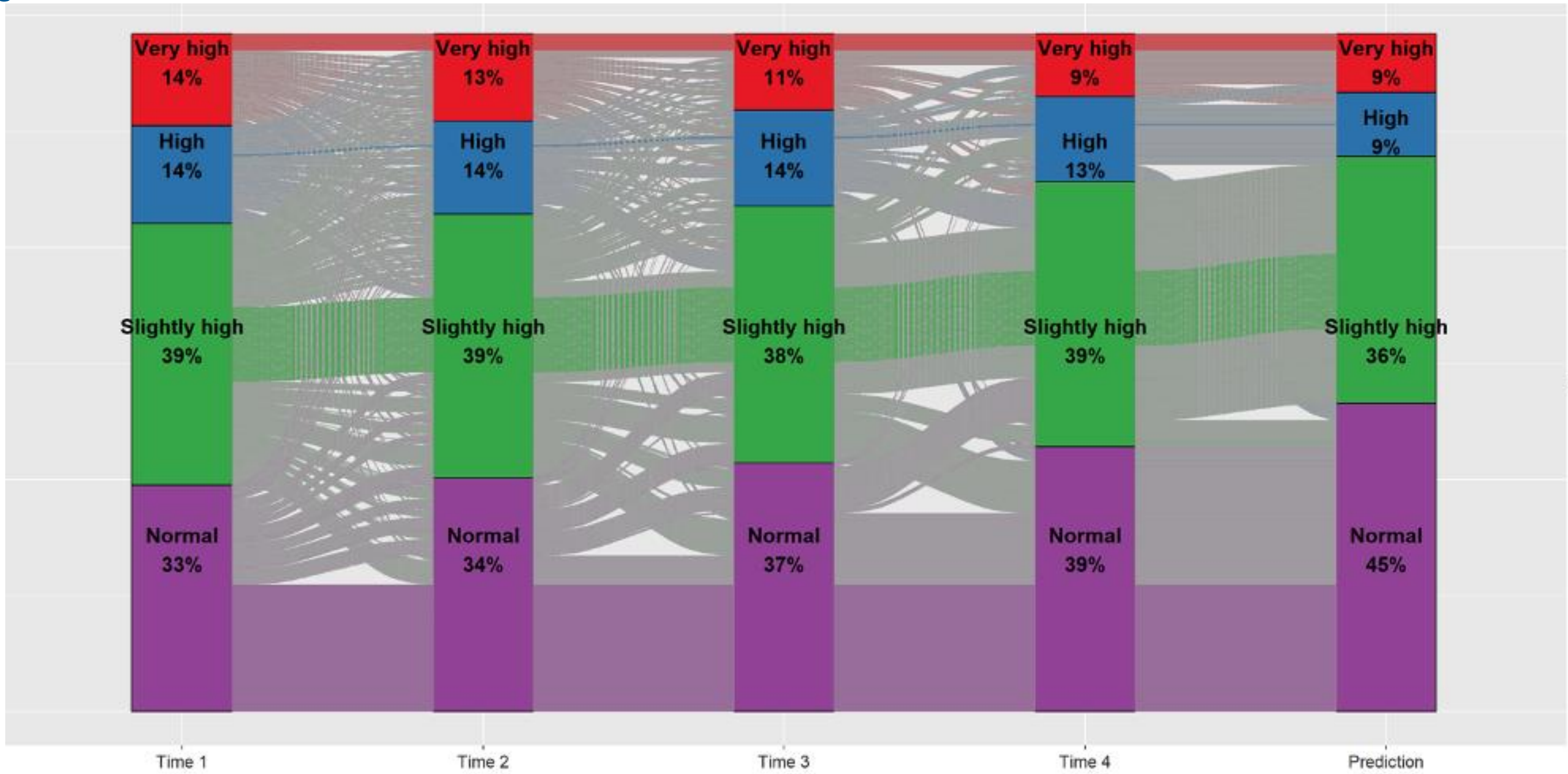
*Time 1, 2 and 3 refer to the dates when a patients has the first, second, and third ALT measures

Figure 2. Risk factors associated with increasing ALT among adult patients enrolled in TARGET-NASH

	Coefficient (95% CI)
Age category: 36-55 vs 18-35	0.57 (0.42 , 0.79)
Age category: >=56 vs 18-35	0.41 (0.3 , 0.57)
ALT category (at index): 1X-3X vs WNL	0.31 (0.27 , 0.37)
ALT category (at index): 2X-3X vs WNL	0.11 (0.09 , 0.13)
Sex: female vs male	0.79 (0.68 , 0.92)
NH White: Yes vs No	1.26 (1.03 , 1.54)
NH Black: Yes vs No	1.06 (0.74 , 1.5)
Hispanics: Yes vs No	1.13 (0.85 , 1.5)
History of Hypertension: Yes vs No	1 (0.82 , 1.21)
History of Type 2 diabetes: Yes vs No	0.84 (0.72 , 1)
History of Cardiovascular disease: Yes vs No	0.86 (0.72 , 1.02)
History of statin use: Yes vs No	1.15 (0.98 , 1.35)
Cirrhosis-NASH at enrollment: Yes vs No	0.79 (0.67 , 0.93)
Non-cirrhosis NASH at enrollment: Yes vs No	1.72 (1.43 , 2.06)

Odds Ratio Estimates and 95% Confidence intervals (log-scale)

Multivariable logistic model includes Age category, Sex, race/ethnicity, phenotype at enrollment, History of statin use, comorbidities: hypertension, type 2 diabetes, CVD.
Blue font/color indicates a significant effect after adjusting for the other variables in the model.

CONCLUSIONS

- Longitudinal ALT trajectories remained relatively stable among patients with NAFLD.

- Understanding the course of ALT fluctuations is important for helping to differentiate natural variation from potential hepatotoxic or beneficial effects of therapeutics.

- Age, ALT at index, sex, NH white, type 2 diabetes, cirrhosis and non-cirrhotic NASH at enrollment are factors associated with ALT change over time

- Next steps include exploration of ALT trends associated with probability of clinical outcomes.

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