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ORIGINAL RESEARCH—CLINICAL

Identification of Fast Progressors Among Patients With Nonalcoholic Steatohepatitis Using Machine Learning

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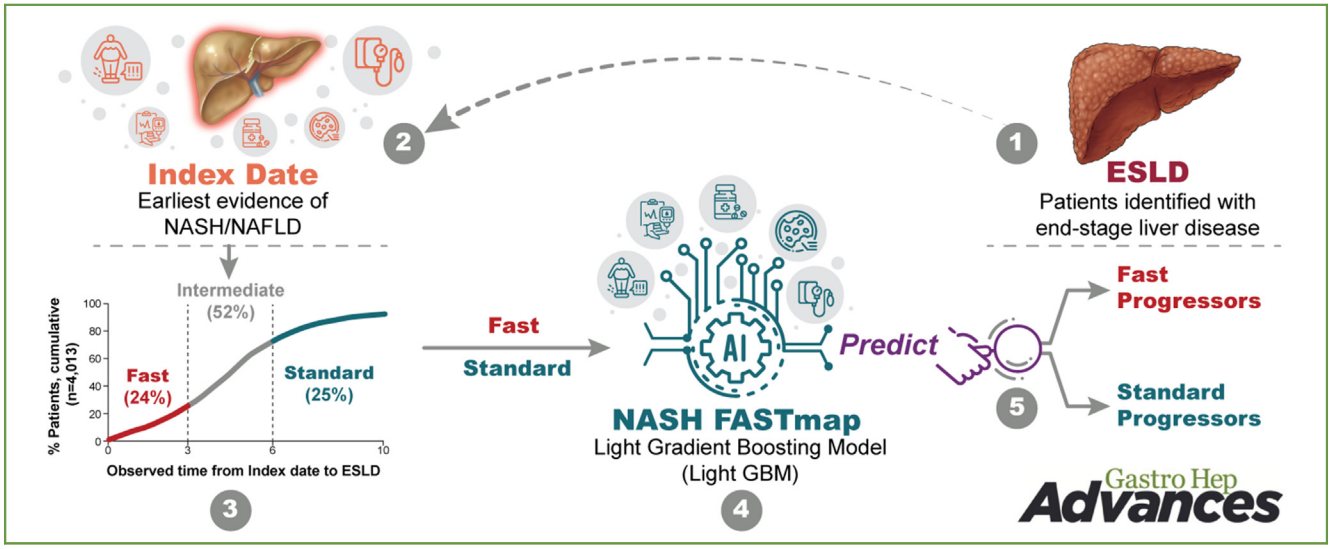

BACKGROUND AND AIMS: There is a high unmet need to develop noninvasive tools to identify nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) patients at risk of fast progression to end-stage liver disease (ESLD). This study describes the development of a machine learning (ML) model using data around the first clinical evidence of NAFLD/NASH to identify patients at risk of future fast progression. **METHODS:** Adult patients with ESLD (cirrhosis or hepatocellular carcinoma) due to NAFLD/NASH were identified in Optum electronic health records (2007–2018 period). Patients were stratified into fast (0.5 and 3 years) and standard progressor (6–10 years) cohorts based on retrospectively established progression time between ESLD and the earliest observable disease, and characteristics were reported using descriptive statistics. Two ML models predicting fast progression were created, performance was compared, and top predictive features from the final model were compared between cohorts. **RESULTS:** Among a total of 4013 NAFLD patients with cirrhosis or hepatocellular carcinoma (mean age 58.6 ± 12.5; 65% female), 24% were fast (n = 951) and 25% standard (n = 992) progressors that were used for modeling. The cohorts were comparable for gender, body mass index, type 2 diabetes, and arterial hypertension, but differed significantly for obesity, hyperlipidemia, and age at index. The final model (NASH FASTmap) is a 44 feature light gradient boosting model which performed better (area under the curve [0.77], F1-score [0.74], accuracy [0.71], and precision [0.71]) than eXtreme gradient boosting model to predict fast progression. **CONCLUSION:** Future fast progression to ESLD in NAFLD/NASH patients can be predicted from clinical data using ML. Electronic health record implementation of NASH FASTmap could support clinical assessment for risk stratification and potentially improve disease management.

Keywords: Artificial Intelligence; Cirrhosis; Disease Progression; Risk Stratification

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease with up to 30% prevalence worldwide.[1–3] Key risk factors associated with

Abbreviations used in this paper: **ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; ER, emergency room; HbA1C, glycated hemoglobin; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; ICD-9 or ICD-10, International Classification of Diseases 9th or 10th revision; LDL, low-density lipoprotein; LightGBM, light gradient boosting; ML, machine learning; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RFE, recursive feature elimination; SD, standard deviation; SHAP, Shapley Additive exPlanations; T2DM, type 2 diabetes Mellitus; XGBoost, eXtreme Gradient Boosting.**

Most current article

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NAFLD are obesity, type 2 diabetes mellitus (T2DM), hypertension, and metabolic syndrome, all of which are on the rise worldwide.[1,4,5] NAFLD represents a spectrum of pathologies ranging from a benign hepatocellular accumulation of fat to nonalcoholic steatohepatitis (NASH), a progressive form of NAFLD with lobular inflammation, ballooning of hepatocytes, and hepatic injury.[3,6] Up to 44% of patients with NAFLD progress to NASH, which can lead to end-stage liver disease (ESLD) with cirrhosis and/or hepatocellular carcinoma (HCC).[7–10] The majority of the lifetime costs of NASH are associated with ESLD.[11–13]

Published evidence on progression of disease is typically based on descriptions of fibrosis stage progression using paired liver biopsies in small cohorts, and little has been published on predictors of fast progression. A systematic meta-analysis of paired liver biopsies found that the median time of liver fibrosis progression ranges from approximately 14 years/fibrosis stage for patients in early stages of NAFLD to approximately 7 years/stage for patients with NASH. The same review suggests that 20% of patients could progress faster than others, suggesting heterogeneity in NAFLD/NASH progression.[14] Consistent with this heterogeneity in progression, a phase II randomized controlled study of simtuzumab trials reported that 22% of patients starting with F3 fibrosis progressed to cirrhosis within 48 weeks.[15] While genetic and clinical factors have been shown to increase a patient's risk of developing NAFLD and progression to NASH or have changing values over time consistent with observed increases in fibrosis,[15,16] no factors have been clearly shown to predict a future rate of faster progression.

Patients with progressive NAFLD are at higher risk of increased morbidity, mortality, and liver complications.[15,17,18] However, available methods for staging NASH and liver fibrosis focus on the patient's current status rather than the future risk.[6] An early identification of patients at risk of future fast progression would allow optimization of disease management with earlier intervention opportunities to improve care.[19,20]

Machine learning (ML) is increasingly being used in health care to analyze large medical data sets to detect patterns for patient diagnoses and insights on outcomes. Recent studies have demonstrated that ML models perform well to diagnose disease or fibrosis status in NAFLD patients,[21–27] and ML offers an attractive possibility to develop a model predicting fast progression when a patient is first diagnosed with NAFLD. Previously, we used ML to predict patients with NASH,[22] and here we complement and extend our previous work to examine the rate of disease progression. This study describes the development of an ML model to predict the risk of fast progression to ESLD among NAFLD/NASH patients using real-world data from the United States and describes clinical features that potentially differentiate fast progressors.

Methods

Study Design and Data Source

This was a retrospective cohort study based on Optum de-identified electronic health records data set from 2007 to 2018, comprising about 86 million lives with records collected by 150,000 providers, 2000 hospitals, and 7000 clinics in the United States in the course of normal clinical care. Patient records include demographics, diagnoses, procedures, medications, laboratory findings, and physician notes as well as visits to the health-care system including outpatient, inpatient, and emergency room (ER) visits.

Patient Population

The study population was identified based on the presence and absence of disease diagnoses or procedures using the International Classification of Diseases 9th and/or 10th revision (ICD-9 or ICD-10, respectively) and Current Procedural Terminology (see Supplemental Information for a full medical coding list). All adult patients with diagnoses of ESLD (liver cirrhosis and/or HCC) and NAFLD/NASH were included. Patients with any other causes of liver disease were excluded. For all included patients, the index date was identified retrospectively from the ESLD diagnosis date (Figure 1). The index date was the observed start of NAFLD/NASH, which was the earliest diagnosis of either NAFLD/NASH or one of 4 comorbidities commonly associated with NASH (T2DM, obesity, hyperlipidemia, or hypertension) used as proxies for NAFLD/NASH due to underdiagnosis in the population. For patients with index date proxies, all had a subsequent diagnosis code for NAFLD/NASH in their patient record. A 12-month period free of any relevant diagnosis codes prior to the index date was required. Time of disease progression (the dependent variable in our analysis) was established retrospectively as the time between the first date of diagnosis of cirrhosis and/or HCC and the index date. Patients were classified into the following cohorts based on individual time of progression: fast progressors (0.5–3 years), intermediate progressors (>3–6 years), and standard progressors (>6 years–10.5 years [limited by end of data source]). Patients progressing within 0.5 years were not considered part of any cohort.

Statistical Analysis

Descriptive statistics were used to compare the fast and standard progressor cohorts by clinical characteristics at index (data windows by category described below), comorbidity load at index, and interactions with the health-care system in 3 timeframes (the year after the index date, the year before cirrhosis/HCC, and year after cirrhosis/HCC). Charlson comorbidity index[28] was calculated using ICD codes recorded within ±6 months of the patient's index date. Outpatient, inpatient, and ER visits for each patient were identified in the database for each time frame of interest, regardless of the visit reason, and the proportion of patients with one or more interactions was reported. Differences in means between the 2 cohorts were assessed by *t*-tests for continuous variables and differences in distribution by chi-square tests for categorical variables; the significance threshold was set at 0.05.

Development of a ML Model

The fast and standard progressor cohorts were used for model development, and the data set was further split into training (75%) and test (25%) data sets. Independent variables (features for modeling) were identified from data available around the index date and included demographics (at index);

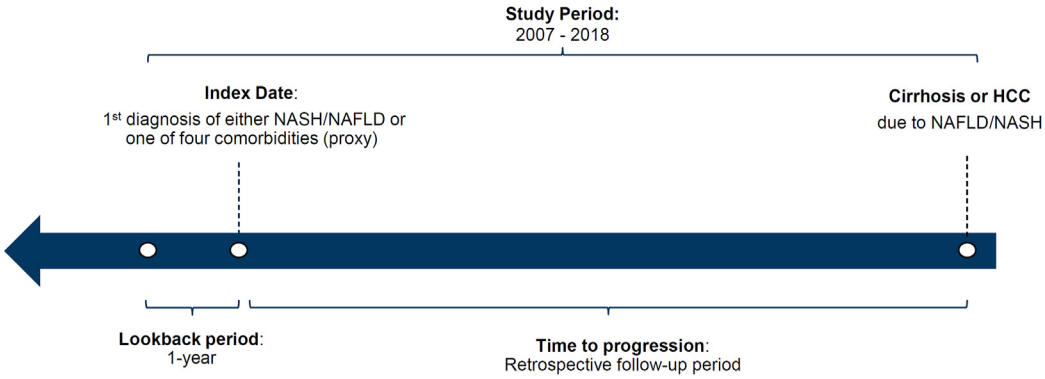

Figure 1. Study period and patient identification. Proxies for index date are 4 comorbidities frequently associated with NASH: type 2 diabetes, obesity, hyperlipidemia, and hypertension.

average laboratory test result values (± 3 months); anthropometric measures values (including height, weight, and body mass index [BMI]; ±3 months); frequency of comorbidities determined by ICD codes (±6 months); treatments for hyperlipidemia, hypertension, and T2D (±6 months); and the rate of change of laboratory values/anthropometric measurements calculated as the slope of the best fit line for all measurements from −2 years to +1 year (see Supplemental Information for medical coding details). Time frames were determined by sensitivity analysis, and any data within 6 months of the earliest date of ESLD were excluded. Individual features used for modeling were chosen based on prevalence in the population (ie, comorbidities occurring in at least 30% of the population) or clinical relevance. Features with no statistical difference between the 2 cohorts were still considered for modeling because such features could have predictive power in a model in combination with another feature.

Potential independent variables with >70% missing values were removed. For features missing ≤70% values, missing values were not imputed. Variance thresholds were defined as the point where further reduction of the threshold resulted in the loss of key clinical features of interest. Thus, continuous features with variance <0.1 and categorical features with variance <0.05 were removed from the analysis. Multicollinearity was assessed by evaluating the variance inflation factor and recursive removal of features with the highest variance inflation factor value until all values were <5.

Two models, a light gradient boosting model (LightGBM) and eXtreme Gradient Boosting model (XGBoost), were developed. Recursive feature elimination (RFE) was used to rank and select the most important features for a LightGBM[29] model to reduce over-fitting. In RFE, all original features are ranked according to importance to the model, and each iteration results in the (backward) elimination of the weakest feature(s).[30] To determine the best model for each iteration, Bayesian hyperparameter optimization of the receiver operator characteristic-area under the curve (AUC) metric was performed at each step using 5-fold cross-validation. The XGBoost model was also trained using the RFE-selected features.

Model Evaluation and Selection

The performance of both models was determined using the 25% of patients reserved for testing and evaluated with multiple metrics. The LightGBM and XGBoost models were compared based on key performance criteria, including sensitivity, specificity, precision, accuracy, F1 score, and AUC. AUC is independent of the cutoff value and was therefore considered the primary criteria for comparing overall model performance and model selection. Sensitivity-precision thresholds for each model were determined by optimizing the F1 score, which indicates the ability of the model to identify true positives (recall) and the rate of false positives (precision). The performance stability of the model was checked by determining model performance across 50 different train-test splits. The model was retrained in each training data set and then tested in each test data set. In the final model, the relative importance of features was determined by Shapley Additive exPlanations (SHAP).[31] The model interpretation was aided by SHAP and partial dependence plots. Feature relevance was validated with clinical experts on the study team.

Statistics to describe differences in model feature values between the fast and standard progressor cohorts were created as described above. Statistical applications for data analyses and model development included Python 3.7.3, Redshift, and Excel.

Results

Identification of Fast vs Standard Progressors

Data from 4013 NAFLD/NASH patients with ESLD (either cirrhosis or HCC due to NAFLD/NASH; 65% female, mean age 58.6 ± 12.5 at index) were included in the study. Of 4013 patients, 951 (24%) were classified as fast, 2070 (52%) as intermediate, and 992 (25%) as standard progressors (Figure 2).

Demographic and Clinical Characteristics of the Fast vs Standard Progressor Cohorts

Statistically significant differences were observed between cohorts for 76 of the 148 features considered to train the model (Table 1). For example, a higher proportion of patients among the fast progressors had obesity at index (24% vs 18%, $P < .01$) and a lower proportion had hyperlipidemia (49% vs 58%, $P < .01$) than standard progressors. No significant differences between cohorts were

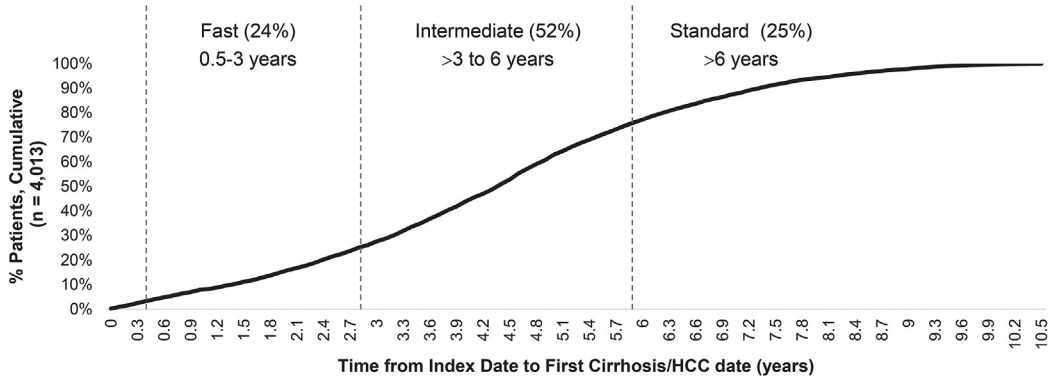

Figure 2. Cohort classification of patients based on time of progression from index date to the date of cirrhosis or hepatocellular carcinoma (HCC).

observed at the index date with respect to the proportion of patients with hypertension (58% vs 56%, $P = .35$) and T2DM (43% vs 44%, $P = .43$). Comorbidity load at the index date tended to be higher in the fast progressor cohort, with 25% of fast progressors having a Charlson comorbidity index score >2 vs 12% of standard progressors (Figure A1). Descriptions of additional comorbidities occurring in at least 20% of the overall study population can be found in Supplemental Information.

Of 19 laboratory values, 11 showed statistically significant differences between the 2 cohorts at the index date (Table A2). Four out of 18 laboratory values for which the rate of change could be calculated showed statistically significant differences in the rate of their change between the 2 cohorts in the 2 years before the index date: alkaline phosphatase total (3.5 u/L/y vs −0.6; $P = .01$); cholesterol high-density lipoprotein (−0.5 mg/dL/y vs 0.9; $P = .01$); cholesterol total (−6.5 mg/dL/y vs −2.1; $P = .04$); and hematocrit (−0.3%/y vs 0.1; $P = .04$).

Interaction of Fast vs Standard Progressors With the Health-Care System

We examined the number of patients in each cohort with annual visits to the health-care system in different settings and time frames to investigate if both fast and standard progressors were receiving regular health care. All patients had at least one health care visit or filled prescription in the year prior to the index date, as required by the patient selection criteria. Most of the patients from each cohort had at least one outpatient visit per year in the year after index ([fast vs standard progressors] 95% vs 95%), the year before cirrhosis (97% vs 99%), and the year after cirrhosis (97% vs 98%) (Figure A2). Consistent with their higher comorbidity load, the fast progressor cohort had a higher percentage of patients with emergency (31% vs 18%) and inpatient (19% vs 14%) visits compared to standard progressors in the year after index (Figure A2). In the year before cirrhosis, fast and standard progressors had similar ER (39% vs 39%) and inpatient (26% vs 22%) visits (Figure A2).

Development of a Model to Predict Risk of Fast Progression to ESLD

LightGBM and XGBoost models were developed as described (see Methods), with 44 features selected for the final model (Table 2) from a total of 148 considered (Supplemental Information). The LightGBM model performed better across a range of metrics (Table 3 and Figure A3). The LightGBM model resulted in a slightly higher receiver operator characteristic AUC (LightGBM 0.77 vs XGBoost 0.76) and a higher F1-score (LightGBM 0.74 vs XGBoost 0.73). The XGBoost model had higher recall than LightGBM, indicating fewer false negatives, but it also had more false positives as indicated by the lower precision. Based on the higher AUC and lower number of false-positive predictions, the LightGBM model was chosen for subsequent use and named the NASH FASTmap model. The NASH FASTmap model correctly predicted 77% (138/180) of fast progressor cohort patients as fast progressors and correctly predicted 66% (109/166) of standard progressor cohort patients as standard progressors (Table 4).

Top model predictors of fast progression included albumin values, BMI, platelet values, rate of change of alkaline phosphatase, and rate of change of BMI. Statistical testing indicated that 5 out of the top 10 predictors were also independent predictors of fast progression: albumin values ($P < .01$); platelet values ($P < .01$); rate of change of alkaline phosphatase ($P = .01$); age at index ($P < .01$) (Table 5). Amongst these top 10 predictors, SHAP and partial dependence plots showed that fast progression prediction increases as the value for platelets, rate of change of alkaline phosphatase, and age increase and as the value for albumin value decreases. The other top 10 features had more complex relationships with fast progression prediction and did not display simple associations.

Discussion

This retrospective study used a real-world electronic health record US database to develop and validate the NASH

Table 1. Demographic and Baseline Characteristics of the Study Cohort

Characteristics	Total (n = 4013)	Fast progressors (n = 951) [A]	Standard progressors (n = 992) [B]	*P* value [A vs B]
Age, mean (SD)				
At index date	58.6 (12.5)	59.5 (13.6)	57.2 (11.6)	<.01
At cirrhosis/HCC date	63.1 (12.5)	61.4 (13.6)	64.5 (11.6)	<.01
Gender				
Female	65%	67%	64%	.22
Male	35%	33%	36%	
Race				
African American	4%	3%	4%	.01
Asian	1%	1%	1%	
Caucasian	90%	89%	92%	
Other/Unknown	5%	7%	4%	
Ethnicity				.41
Not Hispanic	91%	90%	92%	
Hispanic	6%	7%	6%	
Unknown	3%	3%	2%	
Measurements, mean (SD)				
BMI, kg/m^2	35.0 (7.3)	34.6 (7.3)	35.0 (7.3)	.29
Height, cm	167.6 (9.4)	167.5 (9.1)	168.3 (9.8)	.15
Weight, kg	98.3 (22.3)	96.5 (21.8)	99.1 (22.1)	.02
Comorbidities				
Hyperlipidemia	55%	49%	58%	<.01
Hypertension	59%	58%	56%	.35
Obesity	22%	24%	18%	<.01
Type 2 diabetes	43%	43%	44%	.43

Data are presented as mean (SD) or n/N (%).
SD, standard deviation.

FASTmap ML model, which can predict the risk of fast progression in NAFLD/NASH patients. NASH FASTmap comprises 44 features (demographics, laboratory, and clinical characteristics commonly captured in clinical practice) at the time of the earliest evidence of NAFLD to predict the future course of the disease. A gene-based ML model to predict the risk of fast fibrosis progression in liver disease has been previously reported,[25] but to our

Table 2. Summary of Features in the Final Model

Category[a]	Number of features in final model	Features in top 10 of predictive importance
Demographics	1	Age at index date
Results of laboratory tests at index date[a]	15	Albumin at index date Platelet count at index date HDL cholesterol at index date
Body size measurements at index date	3	BMI at index date Height at index date Weight at index date
Frequency of comorbid diagnoses[a]	6	Frequency of anxiety diagnoses
Treatment at index date	1	NA
Frequency of health care	1	NA
Rate of change of laboratory test results before the index date[a] (magnitude of change in a year)	14	Rate of change of alkaline phosphatase total (−2 to +1 y relative to index)
Rate of change in body size before the index date (magnitude of change in a year)	2	Rate of change of BMI (−2 to +1 y relative to index)
Index date diagnosis	1	NA

HDL, high-density lipoprotein; NA, not applicable.
[a]Only the main features having high predictive importance are listed in the table.

Table 3. Comparison of Performance Metrics for LightGBM and XGBoost Models

Variable	LightGBM	XGBoost
AUC	0.77	0.76
F1-score	0.74	0.73
Accuracy	0.71	0.67
Precision	0.71	0.63
Recall	0.77	0.88

Thresholds for each model were chosen to maximize F1-score.

Table 4. Confusion Matrix for Modeling Cohort Test Data With LightGBM Model

Progression class by clinical data	Progression class by model prediction		
	Fast	Standard	*Total*
Fast	138 (77)	42 (23)	180 (100)
Standard	57 (34)	109 (66)	166 (100)
Total	195	151	346

Data presented as n (%).

knowledge, NASH FASTmap is the first ML model developed to predict the risk of fast progression in NAFLD patients using variables collected in standard clinical care. Potential use cases for NASH FASTmap include support for clinical decision-making by providers and patients as well as intensified monitoring for those at highest risk.

The effectiveness of ML-based prediction is always impacted by the quality of data used for training and testing. NAFLD and NASH are underdiagnosed, and some patients in our fast progressor cohort may have been diagnosed late in the course of the disease rather than progressing rapidly. To minimize this possibility, proxy comorbid conditions were used to help identify the earliest evidence of disease. All patients had regular health-care interactions in the year prior to the index date, and the only clear difference in health-care system interactions between the fast and standard progressor cohorts was a higher percentage of fast progressor patients with ER and inpatient visits. This suggests that patients in both cohorts had similar access to the health-care system and that the fast progressor cohort was not simply patients failing to receive adequate health care. The NASH FASTmap model was trained and tested using patient health records from the same data set. Future validation on other data sets is needed to support the use of the model, including data on patients in a range of geographic regions and different ethnicities, since this study used a single US patient health record database to both train and test the NASH FASTmap model.

In an ML model such as NASH FASTmap, the combination of a large number of features as well as potential interactions among features are considered by the model, giving it an advantage over simple clinical comparisons. Clinical characteristics including BMI, comorbid conditions commonly linked to the pathophysiology of NAFLD/NASH, and laboratory test values for liver function have previously been demonstrated to be individually associated with progression to later stages of NAFLD/NASH although not the rate of progression.[18,32,33] All were among the features with the highest predictive importance for the risk of fast progression in the NASH FASTmap model. Consistent with the ability of ML models to consider features in combination, not all NASH FASTmap features with predictive importance displayed statistically significant differences in individual comparisons between the fast and standard progression cohorts. Lower platelet counts, lower serum albumin, and higher aspartate aminotransferase levels had high predictive power in NASH FASTmap and statistically significant differences for the fast and standard progressor cohorts (Table 5). In contrast, BMI and glycated hemoglobin lacked a significant difference between the fast and standard progressor cohorts at the time of risk prediction despite their high predictive value (Table 5). Fast progressors also did not have higher rates of T2D or common comorbid conditions such as hypertension and hyperlipidemia (Table 1).

NAFLD/NASH is among the leading indications for liver transplantation[34] and currently accounts for about USD 15.4 billion in health care spending annually in the United States.[35] As the prevalence of NASH is rising,[36] predicting the subset of patients at high risk of fast progression to cirrhosis/HCC can have important economic and clinical implications. NASH FASTmap has the potential to support clinicians and health-care organizations to identify at-risk patients using commonly available clinical data without costly advanced diagnostics tools, particularly in the setting of remote geographic locations or resource-poor economies. Health-care providers would be able to refer their at-risk patients for early clinical decisions and optimization of treatment, enrollment in clinical trials, and determination of an appropriate follow-up schedule to mitigate disease progression.[37]

Conclusion

This study reported the development of an ML model that can identify NAFLD/NASH patients at risk of future fast progression to cirrhosis/HCC based on commonly available medical records. Early identification of fast progressors can support clinicians and health-care systems for optimal disease management in this patient population. Future research to support the use of the model should include validation in other data sets, including patients in a range of geographic regions and different ethnicities.

Table 5. Differences Between Fast and Standard Progressors Based on Top Model Features

Predictive importance	Feature (at index date)	Fast progressor, mean (SD) n = 951	Standard progressor, mean (SD) n = 992	*P* value
1	Albumin (g/dL)	3.9 (0.5)	4.1 (0.4)	<.01
2	BMI	34.6 (7.3)	35.0 (7.3)	.29
3	Platelets ($\times 10^3/\mu$L)	198.5 (78.3)	222.2 (68)	<.01
4	Rate of change[a] of alkaline phosphatase total	3.5 (31.7)	−0.644 (19.5)	.01
5	Rate of change[a] of BMI	−0.018 (2.6)	0.103 (0.16)	.39
6	HDL (mg/dL)	44.4 (14.3)	43 (12.2)	.15
7	Height (cm)	167.5 (9.1)	168.3 (9.8)	.15
8	No. of anxiety diagnoses	0.8 (3.3)	0.2 (0.8)	<.01
9	Weight (kg)	96.5 (21.8)	99.1 (22.1)	.02
10	Age	59.5 (13.6)	57.2 (11.6)	<.01
11	Triglycerides (mg/dL)	161.4 (91.0)	179.1 (91.5)	.01
15	AST (U/L)	46.5 (29.8)	39.9 (23.5)	<.01
16	AST/ALT	1.1 (0.4)	1 (0.4)	<.01
20	HbA1C (%)	7.0 (1.5)	7.0 (1.3)	.96
23	ALP (U/L)	100.4 (45.8)	87.6 (36.7)	<.01
24	LDL (mg/dL)	96.3 (33.8)	102.1 (33.8)	.02
38	Rate of change of AST	0.999 (23.1)	−0.022 (20.6)	.46
42	Rate of change of ALT	−0.207 (23.8)	−1.808 (24.1)	.28

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Rate of change measurements collected between −2 and +1 y relative to the index date.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2023.09.004.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

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