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ORIGINAL ARTICLE

An Electronic Health Record Model for Predicting Risk of Hepatic Fibrosis in Primary Care Patients

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Abstract

Background One challenge for primary care providers caring for patients with nonalcoholic fatty liver disease is to identify those at the highest risk for clinically significant liver disease.

Aim To derive a risk stratification tool using variables from structured electronic health record (EHR) data for use in populations which are disproportionately affected with obesity and diabetes.

Methods We used data from 344 participants who underwent Fibroscan examination to measure liver fat and liver stiffness measurement [LSM]. Using two approaches, multivariable logistic regression and random forest classification, we assessed risk factors for any hepatic fibrosis (LSM > 7 kPa) and significant hepatic fibrosis (> 8 kPa). Possible predictors included data from the EHR for age, gender, diabetes, hypertension, FIB-4, body mass index (BMI), LDL, HDL, and triglycerides.

Results Of 344 patients (56.4% women), 34 had any hepatic fibrosis, and 15 significant hepatic fibrosis. Three variables (BMI, FIB-4, diabetes) were identified from both approaches. When we used variable cut-offs defined by Youden's index, the final model predicting any hepatic fibrosis had an AUC of 0.75 (95% CI 0.67–0.84), NPV of 91.5% and PPV of 40.0%. The final model with variable categories based on standard clinical thresholds (i.e., BMI ≥ 30 kg/m^2; FIB-4 ≥ 1.45) had lower discriminatory ability (AUC 0.65), but higher PPV (50.0%) and similar NPV (91.3%). We observed similar findings for predicting significant hepatic fibrosis.

Conclusions Our results demonstrate that standard thresholds for clinical risk factors/biomarkers may need to be modified for greater discriminatory ability among populations with high prevalence of obesity and diabetes.

Keywords Fatty liver · Obesity · Veterans · Liver cancer

Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by an accumulation of excess fat in the liver consequent to metabolic syndrome and is the leading driver of increasing chronic liver disease in the world [1–3]. In the United States, NAFLD affects 25–40% of the general adult population [4, 5]. Most NAFLD patients have mild or non-progressive disease. However, in approximately 30% of cases, NAFLD progresses from quiescent liver fat (simple

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steatosis) to more active necroinflammatory disease (nonalcoholic steatohepatitis, NASH) associated with progressive and advanced hepatic fibrosis [6, 7], which may lead to cirrhosis in a substantial proportion of patients [8]. NAFLD is also associated with an increased risk of cardiovascular disease mortality. Patients with advanced hepatic fibrosis are at greatest risk of developing complications of chronic liver disease, cardiovascular disease and overall mortality [9, 10] Thus, NAFLD patients with advanced hepatic fibrosis are the most important subgroup to identify and most urgent to treat.

Clinical information, laboratory tests, and noninvasive liver imaging (Fibroscan) has been shown to both accurately predict and diagnose NAFLD with advanced fibrosis [11, 12]. Clinical information includes age, obesity, and diabetes, while laboratory tests include serum alanine (ALT), aspartate aminotransferase (AST), and platelet count, all of which can be used to calculate the Fibrosis-4 score for liver fibrosis (FIB-4) [13] FIB-4 can predict NAFLD with advanced fibrosis, and is also strongly associated with future risk of severe liver disease outcomes (e.g., cirrhosis) [14, 15]. Given that most patients with NAFLD are initially seen and diagnosed in primary care settings, there has been growing interest in developing clinical care pathways that can be applied in primary care patients to assist in risk stratification, identification, diagnosis, and referral of patients with NAFLD and significant fibrosis. Recently the American Gastroenterology Association (AGA) published a NASH clinical care pathway that entails estimating FIB-4 in high-risk groups with metabolic dysfunction (patients with type 2 diabetes, patients with two or more metabolic risk factors [central obesity, high triglycerides, low HDL (high-density lipoprotein) cholesterol, hypertension, prediabetes, or insulin resistance], and those with incidental findings of hepatic steatosis or elevated aminotransferases) [16]. Those with a FIB-4 score in the intermediate risk category (1.3–2.67) should then receive a Fibroscan for further risk stratification, and those with high FIB-4 (> 2.67) should be referred to specialty care [16]. While this and other pathways build on the findings of different studies showing an association between one or more of the risk factors or tests and advanced fibrosis, the accuracy of an algorithm utilizing an entirety of risk factors and tests in identifying patients with advanced fibrosis is unknown. Furthermore, the performance of these algorithms in relevant populations with high prevalence of metabolic dysfunction is unclear.

Development and validation of an algorithm predicting risk of advanced fibrosis that can be adopted in electronic health records (EHR) in a primary care setting is needed for testing and implementing NASH clinical care pathways. We performed a cross-sectional study among randomly selected Veterans in primary care who were tested uniformly with Fibroscan irrespective of their metabolic dysfunction risk factors or FIB-4. We aimed to (1) identify important risk factors for any fibrosis as well as significant hepatic fibrosis; and (2) derive algorithms for risk stratification. Given the Veteran population is disproportionately highly affected with obesity and diabetes, we hypothesized that existing scores and thresholds need to be modified to reliably predict risk of fibrosis and subsequently help to classify patients at high and low risk for having hepatic fibrosis.

Methods

Study Population

We conducted a single center cross-sectional study with prospective recruitment among patients actively registered within primary care at the Michael E. DeBakey Veterans Affairs (VA) Medical Center (MEDVAMC) in Houston, Texas. The study has been described previously [17]. The study was approved by the Institutional Review Boards for MEDVAMC and Baylor College of Medicine. All participants provided written informed consent to take part in the study.

Study Procedures

We identified all Veterans aged 20 to 69 years who were enrolled for primary medical care at MEDVAMC using the VA Corporate Data Warehouse. Within this sampling frame, we excluded patients with alcohol use disorder (defined as AUDIT-C scores ≥ 4 points within 2 years of study-related screening) or active viral hepatitis B (HBV) or C (HCV) based on laboratory values. Among the remaining eligible patients, we employed a random stratified sampling strategy that included: (1) stratifying according to sex and 10-year age-group (male 20–29, male 30–39, female 20–29, etc.); and (2) performing random selection without replacement and with equal allocation from each stratum. Between February 2018 and December 2021, we screened the EHR of 2601 randomly selected patients and identified 1604 patients who fulfilled the study inclusion and exclusion criteria (see Supplementary Materials for exclusion reasons). We sent 1520 of these eligible patients an invitation letter for permission to contact and then contacted by phone those who did not opt-out and invited them to participate in-person. Of the 1179 patients whom we contacted by phone and/or received correspondence back via mail, a total of 731 patients opted-out, 24 did not respond after 3 messages, and 11 scheduled but did not follow up, while the other 413 consented and enrolled although one withdrew later (participation rate, 35.0%). For patients who were eligible and

interested in participating, an in-person appointment was made during which the inclusion and exclusion criteria were verified and consent obtained. Participants completed a survey of lifestyle (including lifetime and current use of alcohol and smoking, physical activity), medication use, and personal and family medical history, and had height and weight measured.

Outcome

The primary outcome for analysis was Fibroscan assessed risk of hepatic fibrosis. Participants underwent Fibroscan (Echosens, Paris, France) examination where vibration-controlled transient elastography (VCTE) was used to obtain measurements of liver fat (controlled attenuation parameter [CAP]) and liver fibrosis (liver stiffness measurement [LSM]). For all examinations, the M probe was applied first; however, the operator switched to the XL probe if needed based on the recommendations of the device and the manufacturer's instructions. The trained operator obtained a minimum of 10 measurements from each participant, and the device calculated the median CAP and LSM values along with the interquartile range. All studies were reviewed by a qualified hepatologist to ensure quality. We excluded unreliable examinations defined as an interquartile range/median ratio > 0.30 when the median LSM was > 7 kPa [18]. A success rate of more than 60% and the ratio of the interquartile range to the median of 10 measurements (IQR/M) being 0.3 or less defined successful readings [19]. We chose the cutoff value of LSM > 7 kPa (vs. ≤7 kPa) for any hepatic fibrosis [20]. In sensitivity analyses, according to recent guidance from EASL [21], we used a higher cut-off for significant hepatic fibrosis (> 8 kPa vs. ≤8 kPa).

EHR Derived Covariates

EHRs of the individuals enrolled in the study were reviewed by a clinical investigator (TNW) to abstract covariate values. We abstracted the most recent values of height and weight from the EHR and calculated body mass index (BMI) as kg/m^2. Hypertension was defined by the presence of diagnosis or treatment in the EHR. We defined type 2 diabetes as evidence of receipt of ≥ 1 prescription for diabetes medications in the EHR or an HbA1c ≥ 6.5%. We defined prediabetes as an HbA1c level of 5.7–6.4%. Other blood biomarkers included alanine transaminase (ALT), aspartate transaminase (AST), platelet count, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. We abstracted values from the EHR within 3 months to an individual's date of Fibroscan (if multiple values were available, we chose the closest to the date of the Fibroscan). FIB-4 was calculated based on ALT, AST, platelet counts, and age (at time of laboratory test completion) using the formula [FIB-4 = age (years)×AST (U/L)/[platelet counts (10^9/L)×sqrt(ALT) (U/L)].

Statistical Analysis

Possible predictors of any hepatic fibrosis included age, gender, diabetes, prediabetes, hypertension, FIB-4, BMI, LDL, HDL, and triglycerides. Age was categorized into > 50 and ≤ 50 years. The cut-off values for FIB-4, BMI, LDL, HDL, and triglycerides were selected based on published values or lab reference values but also empirically identified using Youden's index [22]. There were very few missing values among the studied covariates ranging from 2 values for FIB-4 to 7 for triglycerides. K-nearest neighbors imputation was used based on LSM and all covariates. The final predictor variables were selected using two methods: (1) Forward selection logistic regression to identify variables that are significantly associated with LSM > 7 kPa (any fibrosis) with a statistical significance level of ≤ 0.05; and (2) Random Forest (RF) classification model to identify importance of variables associated with LSM > 7 kPa (any hepatic fibrosis); we split the data into an 80% subset for model training and a 20% subset for testing. Given the class imbalance observed in our data (far fewer cases with fibrosis compared to those without fibrosis), oversampling was conducted before running the RF classification model [23]. We used "GridSearchCV" for RF with a wide range of parameters: 'max_depth': [5 [5]25], 'max_features': ['sqrt'], 'min_samples_leaf': [5 [5]25], 'min_samples_split': [10 [10]50], 'n_estimators':[100[100]500] to get the best parameters [24]. The RF classification model was performed using parameters selected from the "GridSearchCV" [24]. Variables identified in both the logistic regression and RF classification approaches were included in a final multivariate logistic regression model and its area under the receiver operating characteristic curve (AUC) was calculated. We calculated sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of the models. In a sensitivity analysis, we ran the final predictive model using the same predictor variables but with standard clinical cut-off values for BMI (≥ 30 vs. <30), and FIB-4 (≥ 1.45 vs. <1.45 and ≥ 1.3 vs. <1.3) and adding a predictor for significant hepatic steatosis (≥ 290 vs. <290). We also examined the ability of the models for predicting at least significant hepatic fibrosis (i.e., LSM > 8 kPa). All analyses were performed using SAS Enterprise Guide 7.1 and Python 3.11.

Results

We included data from 344 patients in the current analysis (Table 1). The mean age was 51.14 years ± 11.31 years. The racial/ethnic distribution was 34.9% non-Hispanic White, 40.4% non-Hispanic Black, 17.2% Hispanic, 7.5% other, and 56.4% were women. Of the 344 patients, 37.9% had significant hepatic steatosis (defined as CAP ≥ 290). Thirty-four (9.9%) had any hepatic fibrosis (i.e., LSM > 7 kPa) and 15 (4.4%) significant hepatic fibrosis (i.e., LSM > 8 kPa). Compared to patients without any hepatic fibrosis (LSM ≤ 7 kPa), those with hepatic fibrosis were older (> 50 years, 70.6% vs. 53.6%), more likely to be male (61.8% vs. 41.6%), and more likely to have hypertension (52.9% vs. 36.8%). Patients with any fibrosis were also more likely to have elevated BMI, triglycerides, and FIB-4 but lower HDL than patients without fibrosis (Table 2). Patients with significant hepatic fibrosis were more likely to have prediabetes and diabetes.

Table 1 Characteristics of the study population ($N = 344$)

Variable	Category	N (%)
Age		
mean ± sd (yrs)		51.14 (± 11.31)
	≤ 50 years	154 (44.8)
	> 50 years	190 (55.2)
Gender		
	Female	194 (56.4)
	Male	150 (43.6)
Race/Ethnicity		
	Non-Hispanic White	120 (34.9)
	Non-Hispanic Black	139 (40.4)
	Hispanic	59 (17.2)
	Other	26 (7.5)
Smoking status		
	Never	214 (62.2)
	Former	89 (25.9)
	Current	39 (11.3)
	Missing	2 (0.6)
Alcohol drinking status		
	Never/rarely	115 (33.4)
	Former	30 (8.7)
	Current	195 (56.7)
	Missing	4 (1.2)
BMI, mean ± sd (kg/m^2)		31.63 (± 6.33)
Diabetes		63 (18.3)
Hypertension		132 (38.4)
Triglycerides, mean ± sd (mg/dL)		135.46(± 90.12)
LDL, mean ± sd (mg/dL)		114.02(± 36.56)
HDL, mean ± sd (mg/dL)		52.14(± 20.04)
FIB-4, mean ± sd		1.03(± 0.50)
AST, mean ± sd (IU/L)		27.17(± 13.79)
ALT, mean ± sd (IU/L)		25.18(± 11.69)
LSM, mean ± sd		5.13 (± 2.33)
CAP, mean ± sd		267.13 (± 64.71)

Based on variable importance values from the RF procedure, BMI (> 33 vs. ≤ 33 kg/m^2) was the most important predictor of any hepatic fibrosis (absolute importance value: 0.223209), followed by FIB-4 (0.166798), diabetes (strongest when defined as receipt of ≥ 1 prescription for diabetes medications in the EHR; 0.13611), gender (0.08786) and HDL (0.087508) (Supplementary Table S1). Using forward selection logistic regression, only four variables (BMI, FIB-4, diabetes and HDL) were retained in the model. We therefore elected to include the three variables (BMI, FIB-4, and diabetes) identified and ranked highest from both approaches (logistic regression and RF classification) in the final multivariate model predicting any hepatic fibrosis.

When we used variable cut-offs defined by Youden's index, the final multivariate model predicting any hepatic fibrosis had an AUC of 0.75 (95% CI 0.67–0.84) (Table 3). The NPV of this model was 91.5% (95% CI, 88.5–94.5%) and the PPV was 40.0% (95% CI, 15.2–64.8%). The sensitivity was 17.7% and the specificity was 97.1%. In that model, diabetes was associated with approximately 3-fold increased risk of any hepatic fibrosis (vs. no diabetes, OR, 2.81; 95% CI, 1.26–6.26), FIB-4 > 1 was associated with approximately 4-fold increased risk (vs. FIB-4 ≤ 1; OR, 3.61; 95% CI, 1.62–8.01) and BMI > 33 kg/m^2 was associated with approximately 4-fold increased risk (vs. BMI ≤ 33 kg/m^2, OR, 3.61; 95% CI, 1.67–7.79). The final multivariate models with predictor variable categories based on standard clinical thresholds (i.e., BMI ≥ 30 vs. <30; FIB-4 ≥ 1.45 vs. <1.45; BMI ≥ 30 vs. <30; FIB-4 ≥ 1.3 vs. <1.3) had lower discriminatory ability (AUC 0.65 vs. 0.75; AUC 0.67 vs. 0.75). The NPV of this model was 91.3% and the PPV was 50.0%, while the sensitivity was 14.7% and the specificity was 98.4%. Adding steatosis to the model improved discriminatory ability; however, the model with cut-offs defined by Youden's index (AUC 0.80) continued to perform better than the models with predictor variable categories based on standard clinical thresholds (FIB-4 ≥ 1.45, AUC 0.73; FIB-4 ≥ 1.3, AUC 0.74).

We observed similar findings predicting significant fibrosis (LSM > 8 kPa vs. LSM ≤ 8 kPa). The final multivariable model using three variables (BMI, FIB-4, and diabetes) had an AUC of 0.79 (95% CI, 0.68–0.91) using cut-offs defined by Youden's index and AUCs of 0.70 (95% CI, 0.56–0.84) and 0.75 (95% CI, 0.60–0.89) using typical/standard clinical thresholds (Table 3). The NPV and PPV of these two models were 96.1% and 96.7%, and 25% and 40.0%, respectively, while the corresponding sensitivity and specificity were 13.3% and 26.7%, and 98.2% and 98.2%, respectively.

Table 2 Characteristics of participants with and without hepatic fibrosis (LSM > 7 kPa), or with and without significant fibrosis (LSM > 8 kPa)

Variables	LSM ≤ 7	LSM > 7	*P*-value	Variables	LSM ≤ 8	LSM > 8	*P*-value
	n = 310	*n* = 34			*n* = 329	*n* = 15	
	n (%)	n (%)			n (%)	n (%)	
Age, > 50 years	166 (53.55%)	24 (70.59%)	0.058	Age, > 50	180 (54.71%)	10 (66.67%)	0.3625
Gender, male	129 (41.61%)	21 (61.76%)	0.025	Gender, male	140 (42.55%)	10 (66.67%)	0.0655
Diabetes*	50 (16.13%)	13 (38.24%)	0.002	Diabetes*	57 (17.33%)	6 (40%)	0.0382**
Hypertension	114 (36.77%)	18 (52.94%)	0.066	Hypertension	125 (37.99%)	7 (46.67%)	0.4994
FIB-4, > 1.0¶	129 (41.61%)	24 (70.59%)	0.001	FIB4, > 1.1¶	106 (32.22%)	9 (60%)	0.0257
BMI, > 33 kg/m^2¶	102 (32.9%)	22 (64.71%)	< 0.001	BMI, > 33.6 kg/m^2¶	104 (31.61%)	10 (66.67%)	0.009**
HDL, < 42 mg/dL¶	77 (24.84%)	16 (47.06%)	0.006	HDL, < 49 mg/dL ¶	152 (46.2%)	12 (80%)	0.0104
LDL, > 96 mg/dL ¶	218 (70.32%)	19 (55.88%)	0.084	LDL, > 94 mg/dL ¶	238 (72.34%)	8 (53.33%)	0.1418**
Triglycerides, > 176 mg/dL¶	64 (20.65%)	12 (35.29%)	0.051	Triglycerides, > 177 mg/dL ¶	65 (19.76%)	7 (46.67%)	0.0204**

¶ Cut-offs based on Youden's index

* Defined as receipt of ≥ 1 prescription for diabetes medications in the EHR or an HbA1c ≥ 6.5%

** Fisher's exact test

Table 3 The final predictive model for any hepatic fibrosis (LSM > 7 kPa) or significant fibrosis (LSM > 8 kPa)

Any fibrosis (LSM > 7 kPa)			Significant fibrosis (LSM > 8 kPa)	
Variable	OR (95% CI)	AUC (95% CI)	OR (95% CI)	AUC (95% CI)
Cut-offs based on Youden's index				
DM (yes vs. no)	2.811 (1.263–6.256)	0.7544	2.765 (0.905–8.45)	0.7922
FIB-4 (> 1 vs. ≤ 1)	3.606 (1.623–8.011)	(0.6691–0.8396)	4.058 (1.346–12.236)	(0.6767-9077)
BMI (> 33 vs. ≤ 33)	3.609 (1.672–7.79)		4.96 (1.587–15.502)*	
Cut-offs based on clinical thresholds				
DM (yes vs. no)	2.616 (1.198–5.711)	0.6463	2.247 (0.745–6.779)	0.6979
FIB-4 (≥ 1.45 vs. < 1.45)	1.456 (0.584–3.632)	(0.5426-0.7500)	2.065 (0.614–6.942)	(0.5574–0.8384)
BMI (≥ 30 vs. < 30)	2.165 (0.925–5.068)		4.338 (0.935–20.137)	
DM (yes vs. no)	2.635 (1.204–5.769)	0.6674	2.293 (0.751–6.997)	0.7481
FIB-4 (≥ 1.3 vs. < 1.3)	2.102 (0.950–4.652)	(0.5638–0.7709)	3.947 (1.346–11.576)	(0.6021–0.8942)
BMI (≥ 30 vs. < 30)	2.225 (0.947–5.227)		4.615 (0.987–21.579)	

AUC, area under the receiver operating characteristic curve; CI, confidence interval; OR, odds ratio

* BMI (> 33.6 vs. ≤ 33.6 kg/m^2)

Discussion

We used data from a cross-sectional study with prospective enrollment among randomly selected Veterans in primary care who were tested uniformly with Fibroscan irrespective of their metabolic dysfunction risk factors or FIB-4 to identify important risk factors for hepatic fibrosis and derived algorithms for clinical risk stratification. Based on the values of multiple clinical variables attained from structured EHR data, our algorithms can predict with 91.5% NPV (88.5–94.5%) and 40.0% (95% CI, 15.2–64.8%) PPV any hepatic fibrosis risk for the primary care population based on three variables: BMI, diabetes and FIB-4. This algorithm combines the step of risk factor identification (BMI, diabetes) and fibrosis risk stratification (FIB-4). Importantly, our results demonstrate that standard thresholds for clinical risk factors/biomarkers (e.g., BMI ≥ 30 and FIB-4 ≥ 1.45 or FIB-4 ≥ 1.3) need to be modified for greater discriminatory ability among populations with high prevalence of obesity and diabetes. Consequently, modifications may be required for the AGA pathway (or other similar recommended pathways) to be effective in this increasingly common adult population.

NAFLD is the most common chronic liver disease worldwide [25]. NAFLD is projected to become the leading global cause of cirrhosis and hepatocellular carcinoma (HCC) [26]. NAFLD patients with advanced hepatic fibrosis are also at high risk of developing and dying from cardiovascular disease [9, 10]. Mortality from extrahepatic cancers far exceeds that due to HCC-related causes in NAFLD [27], but unlike HCC, the increased risk is not dependent on liver fibrosis stage. Only 30% of NAFLD patients progress to NASH within 5 years and develop any hepatic fibrosis within 10 years [28]. Given that most NAFLD patients will not be seen in hepatology specialty clinics, thus there is a high need for clinical care pathways for use in the primary care setting to assist in risk reduction (e.g., dietary interventions

and pharmacotherapy) as well as for identification of those that have progressed to more clinically significant disease necessitating subspecialty referral [16].

We found that, in examining many risk factors and using multiple model building approaches, the best performing model included terms for BMI, FIB-4, and diabetes. Using RF classification, BMI was the most important predictor of any hepatic fibrosis when the cut-off (> 33 vs. ≤33) was defined by Youden's index. The discriminatory ability of the three most important predictors (BMI, FIB-4, and diabetes) were each diminished when using standard clinical cut-off values compared to when cut-off values were optimized for our study population (AUROC 0.65 and 0.67 vs. 0.75). BMI was not ranked as highly when the standard clinical cut-off (≥ 30 vs. <30) was applied. Thus, in a population of patients with high prevalence of obesity and diabetes, a risk tool using standard clinical cut-off values is unlikely to provide useful discriminatory ability.

This study is unique in that we used structured data elements from the EHR to define the predictor variables of the algorithm for predicting risk of any hepatic fibrosis. Our algorithm can be easily adopted as an electronic trigger tool for automatic identification of patients at risk for hepatic fibrosis because the predictor variables do not require chart reviews or machine learning of unstructured data. The strength of our work is assessing the practical application of the AGA care pathway in the United States population, which provides insights on the implications of incorporating this algorithm into clinical practice. Limitations of our study include the use of Fibroscan examination to define the study outcome rather than a liver biopsy (the gold standard), as well as the single-center design with relatively low participation rate which may lead to possible selection bias. However, our outcome and exposure assessments for the primary analysis are unlikely to be differentially impacted. Our study population has lower prevalence of some risk factors (e.g., diabetes and smoking) that the VA population overall. As a result, we may underestimate the prevalence of significant fibrosis and our findings may not be generalizable. Nonetheless, the increasingly high prevalence of the at-risk population for NAFLD in the United States highlights the need to shift cut-offs to reflect the skewed distribution of these factors in the population. However, due to small sample size and low prevalence of fibrosis, the cut-off value based on Youden's index may need further validation with larger sample size. Although oversampling (i.e., replicating cases to be equal to non-cases; in our study, we replicated 34 cases into 310 cases) is one of the approaches recommended to adjust for imbalanced data, it may cause overfitting. If this is true, our results from the RF classification should be interpreted with caution. Because we derived and tested the model in the same study population, we likely overestimated its discriminatory ability. Therefore, further testing of external validation and effectiveness is required prior to any clinical application and implementation.

In summary, recent practice guidelines, including the AGA's published NAFLD Care Pathway [16], provided a stepwise algorithm to identify adults at risk for clinically significant liver disease. Our study in randomly selected patients in primary care compressed and validated the first step (targeting high risk groups), but reduced the risk factors to obesity and diabetes, and the second step (using FIB-4) using uniformly applied Fibroscan as a gold standard. The intended implementation would be identify patients at high risk of fibrosis who would then be offered further diagnostic tests of fibrosis (e.g., Fibroscan). All the variables used in study were obtained and therefore be used in EMR structured data. However, in our study among a population of Veterans with high prevalence of obesity, a lower level of FIB-4 (FIB-4 < 1) was more strongly associated with risk of fibrosis (vs. 1.45 or 1.3). Additionally, a higher cut-off for BMI was required to better discriminate patients with and without any hepatic fibrosis. When combined into a single model, appropriately characterized terms for BMI, FIB-4 and diabetes have modest discriminatory ability for hepatic fibrosis with high negative but intermediate positive predictive value. Further studies should focus on externally validating this model with modified risk factor cut-offs as well as on the development and implementation of an electronic trigger tool that contains this EHR-adaptable risk model.

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Declarations

Conflict of interest RL serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics. In addition his institutions received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals. Co-founder of LipoNexus Inc. All other authors disclose no conflicts of interest.

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