

ORIGINAL ARTICLE

Predicting NAFLD prevalence in the United States using National Health and Nutrition Examination Survey 2017–2018 transient elastography data and application of machine learning

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Abstract

This cohort analysis investigated the prevalence of nonalcoholic fatty liver disease (NAFLD) and NAFLD with fibrosis at different stages, associated clinical characteristics, and comorbidities in the general United States population and a subpopulation with type 2 diabetes mellitus (T2DM), using the National Health and Nutrition Examination Survey (NHANES) database (2017–2018). Machine learning was explored to predict NAFLD identified by transient elastography (FibroScan®). Adults ≥ 20 years of age with valid transient elastography measurements were included; those with high alcohol consumption, viral hepatitis, or human immunodeficiency virus were excluded. Controlled attenuation parameter ≥ 302 dB/m using Youden's index defined NAFLD; vibration-controlled transient elastography liver stiffness cutoffs were ≤ 8.2 , ≤ 9.7 , ≤ 13.6 , and > 13.6 kPa for F0–F1, F2, F3, and F4, respectively. Predictive modeling, using six different machine-learning approaches with demographic and clinical data from NHANES, was applied. Age-adjusted prevalence of NAFLD and of NAFLD with F0–F1 and F2–F4 fibrosis was 25.3%, 18.9%, and 4.4%, respectively, in the overall population and 54.6%, 32.6%, and 18.3% in those with T2DM. The highest prevalence was among Mexican American participants. Test performance for all six machine-learning models was similar (area under the receiver operating characteristic curve, 0.79–0.84). Machine learning using logistic regression identified male sex, hemoglobin A1c, age, and body mass index among significant predictors of NAFLD ($P \leq 0.01$). **Conclusion:** Data show a high prevalence of NAFLD with significant fibrosis ($\geq F2$) in the general United States population, with greater prevalence in participants with T2DM. Using readily available, standard demographic and clinical data, machine-learning models could identify subjects with NAFLD across large data sets.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common condition, with global prevalence in adults estimated at 25.2%.^[1] Prevalence in the United States population is estimated at $\geq 34.0\%$,^[2] with the more severe, progressive phenotype, nonalcoholic steatohepatitis (NASH), estimated to affect approximately 3%–5%.^[3,4] An increased prevalence of NAFLD/NASH in recent years is associated with increases in obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome.^[5–7] T2DM is a major risk factor for NAFLD,^[6,8] with global prevalence of NAFLD and NASH estimated at 55.5% and 37.3%, respectively, among patients with T2DM and a reported prevalence of comorbid NAFLD in the United States of 51.8%.^[8] However, there is heterogeneity within the United States, as suggested by a recent prospective study in Texas that reported NAFLD in 37.5% of participants overall and in 69.7% of participants with diabetes.^[9]

Previous studies have investigated the prevalence of NAFLD in the United States population, using the National Health and Nutrition Examination Survey (NHANES),^[1,2] and relied on diagnostic techniques with inherent limitations, such as standard ultrasound and noninvasive biomarkers.^[10] Liver ultrasound transient elastography (FibroScan[®]) is an accurate and noninvasive method to determine the level of steatosis and fibrosis in patients with NAFLD; it is based on controlled attenuation parameter (CAP) and liver stiffness measures, using vibration-controlled transient elastography (VCTE).^[11] Transient elastography data are now available in the NHANES database (2017–2018),^[12] enabling real-world analysis of the prevalence of NAFLD and fibrosis in a representative sample of the United States population. Two recent analyses of these data demonstrated prevalence of fatty liver disease as 35.1%–47.8%^[13] and prevalence of NAFLD in participants with diabetes as 73.2%–84.5%.^[14] These studies were limited by a lack of accurate alcohol consumption data and low cutoffs for CAP^[11] that may have led to misclassification of participants and high prevalence estimates. Therefore, the true prevalence of NAFLD in the general United States population and those with T2DM remains uncertain.

Despite the high prevalence, screening for NAFLD is not currently recommended, even in high-risk groups such as those with T2DM.^[15] Although liver biopsy is the gold standard for NASH diagnosis, because of its invasiveness^[16] it is not without risk; additionally, sampling and interobserver and intraobserver variability^[17,18] make it impractical for use in a broad population. Furthermore, limitations in current noninvasive diagnostic techniques hamper diagnosis,^[10] with a reliance on ultrasound data and epidemiological modeling to project the scale of the problem.^[19] A better understanding of patients with NAFLD who are at risk of progressing will help to identify the population with

the greatest need for intervention and may help reduce disease-related complications and mortality driven by NASH with significant fibrosis.^[20] Noninvasive tools to effectively identify and monitor this population are a major unmet need.^[21] Machine-learning models may be an effective method to identify patients. Although still in its infancy, machine learning is a promising tool in the NASH field, with applications in the assessment of electronic medical records, liver imaging, or histology assessment to improve diagnosis and to identify patients at risk of progression.^[22] In the current cohort analysis, we investigated the prevalence of NAFLD with fibrosis and the associated clinical characteristics and comorbidities in the general United States population and a subpopulation with T2DM assessed by transient elastography (FibroScan[®]) in the NHANES database (2017–2018).^[23] Using demographic and clinical data from NHANES, we explored machine learning as a means to predict NAFLD in participants at high risk, identified by CAP (FibroScan[®]).

MATERIALS AND METHODS

Study design and participants

NHANES is a continuous nationally representative survey of around 5000 United States citizens a year that is conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC).^[24] The survey was approved by the National Center for Health Statistics Research Ethics Review Board at the CDC, and consent was documented from all participants. The current cohort study used anonymized data extracted from the NHANES 2017–2018 database, which included liver ultrasound transient elastography (FibroScan[®]) data.^[12]

We included adult participants ≥ 20 years of age at the date of transient elastography scan, with or without NAFLD, for whom valid reproducible FibroScan[®] measurements (>10 measurements with an interquartile range of $<30\%$ from the median) were available. Participants were excluded if they were pregnant or unsure if they were pregnant at the time of their examination or if they did not have a FibroScan[®] CAP or fibrosis score. Participants were excluded from the NAFLD analysis population if they were considered high alcohol consumers (defined as an average daily consumption of ≥ 20 g/day and ≥ 30 g/day for women and men, respectively,^[25] based on the NHANES alcohol use survey^[26]) or if they had other potential causes of liver disease, including viral hepatitis (defined as positive for serum hepatitis B surface antigen or hepatitis C antibody or if hepatitis B or C was reported) or human immunodeficiency virus (HIV) (reported or serology).

NAFLD was defined as CAP ≥ 302 dB/m, which was previously identified as the optimal cutoff for accurate

diagnosis of hepatic steatosis $\geq 5\%$ using Youden's index, with a sensitivity and specificity of 0.80 (95% confidence interval [CI], 0.75–0.84) and 0.83 (95% CI, 0.69–0.92), respectively.^[11] Higher or lower cutoffs, respectively, improved specificity and sensitivity but resulted in underestimation or overestimation of the prevalence of steatosis.^[11] Fibrosis grades were determined by liver stiffness, using VCTE with cutoffs of 8.2 kPa, 9.7 kPa, and 13.6 kPa for fibrosis grades $\geq F2$, $\geq F3$, and F4, respectively, optimized using Youden's index.^[11] Participants without NAFLD were defined as CAP < 302 dB/m and VCTE < 8.2 kPa. Those falling into an intermediary range with marginal steatosis (274–302 dB/m) and fibrosis (VCTE 8.2–13.6 kPa) were defined as borderline steatosis. CAP and VCTE criteria for stratification are shown in Table 1. Patients with T2DM were defined as those with a diagnosis of or receiving treatment for diabetes.

NHANES analyses

Participants were analyzed as the overall population with transient elastography data or categorized based on age, ethnicity, or whether they had previously been diagnosed with T2DM. Participants were stratified based on the presence of steatosis and fibrosis stage, as described above.

After participants with heavy alcohol use, viral hepatitis, or HIV were excluded, the age-adjusted prevalence of NAFLD and its fibrosis stages was expressed as a percentage of the overall population and of the T2DM subpopulation. The prevalence of fibrosis in the subpopulations with NAFLD and NAFLD with T2DM was assessed. The prevalence of NAFLD was also assessed in the following subpopulations: within age groups 20–39, 40–59, 60–74, and 75+ years of age in the overall population and in those with T2DM; within

ethnic groups in the overall population. Demographics, clinical characteristics, and metabolic comorbidities of participants with and without NAFLD and with NAFLD with mild (stage F0–F1) versus significant (stage F2–F3) fibrosis, based on CAP and VCTE cutoffs (Table 1), were compared in the overall population and in those with T2DM to identify any imbalances among the subgroups. Participants with fibrosis stage F4 were excluded from this analysis due to the small sample size.

Age-adjusted measures corresponding to the proportion of adults 20–39, 40–59, and ≥ 60 years of age in the United States 2010 population^[27] were calculated for all analyses except prevalence of NAFLD by age, for which weighted prevalence was calculated. Data are presented descriptively.

NAFLD prediction using machine learning

Predictive modeling using different machine-learning approaches with demographic and clinical data from NHANES was applied to test the ability to predict NAFLD in participants identified by transient elastography. The analysis population included participants ≥ 20 years of age with valid transient elastography measurements with or without NAFLD and excluded those with high alcohol consumption, viral hepatitis, and HIV, as described above. Using a supervised learning approach, data were split randomly between training and validation sets (75% training, 25% validation) to tune and test model parameters. Six different machine-learning models were fit to the training set: two interpretable models (logistic regression and elastic net), two tree-based methods (conditional single-classification tree and random forest [RF]), and two nonlinear, noninterpretable approaches (support vector machine [SVM] and neural network).

Over 100 features were input to the models, including demographic characteristics (e.g., age, race/ethnicity,

TABLE 1 NAFLD populations and definitions

Population	CAP (dB/m)	Fibrosis score, VCTE (kPa)	Overall population, n ^a	T2DM subpopulation, n ^a
Non-NAFLD (simple steatosis)	< 302	< 8.2	2605	353
NAFLD	≥ 302	–	1226	468
NAFLD F0–F1	≥ 302	≤ 8.2	875	310
NAFLD F2	≥ 302	8.2–9.7	78	40
NAFLD F3	≥ 302	9.7–13.6	84	42
NAFLD F4 (cirrhosis)	≥ 302	> 13.6	57	38
Cryptogenic cirrhosis	< 302	> 13.6	33	11
Borderline steatosis ^b	274– < 302	8.2–13.6	33	11
Control	< 274	8.2–13.6	66	16

Abbreviations: CAP, controlled attenuation parameter; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

^aUnweighted.

^bDid not meet criteria for NAFLD using CAP but met criteria for fibrosis using VCTE.

sex, marital status, and education), clinical characteristics (e.g., body mass index [BMI]), clinical characteristics based on laboratory parameters (e.g., glycated hemoglobin [HbA1c], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and bilirubin), and comorbidities (e.g., diabetes and hypertension). Ten-fold cross-validation with five replications was used to tune and select the optimal parameters in each model. Covariates for which less than 10% of data were missing were imputed using an RF approach. The most appropriate models were selected using area under the receiver operating characteristic curve (AUROC), and sensitivity, specificity, and predictive values were used to evaluate model performance using the test data.

RESULTS

Participants

The survey data set included 5494 participants who had a completed transient elastography assessment.^[23] Of these, 4471 participants ≥ 20 years of age with valid reproducible transient elastography measurements were included in the overall population in this cohort study.

After 640 participants with high alcohol consumption, hepatitis, and HIV were excluded, 1226 participants were classified as NAFLD, as determined by CAP and VCTE, while the remaining 2605 were non-NAFLD based on CAP score. In total, 908 of the 4471 participants in the overall population had a diagnosis of T2DM (T2DM subpopulation), of whom 468 had NAFLD (Figure 1).

In participants with NAFLD in the overall population and in the T2DM subpopulation, respectively, the unweighted mean (SD) age was 54.8 (15.8) and 61.0 (12.3) years, and a slight majority (55.6% and 54.1%) were men. A sizable proportion of participants in the overall population and in the T2DM subpopulation was of non-Hispanic White ethnicity (36.2% and 32.7%, respectively), followed by Mexican American (18.2% each) and non-Hispanic Black (18.1% and 19.4%, respectively).

NHANES analyses

Prevalence of NAFLD and fibrosis

The age-adjusted prevalence of NAFLD in the overall United States population ≥ 20 years of age was 25.3%

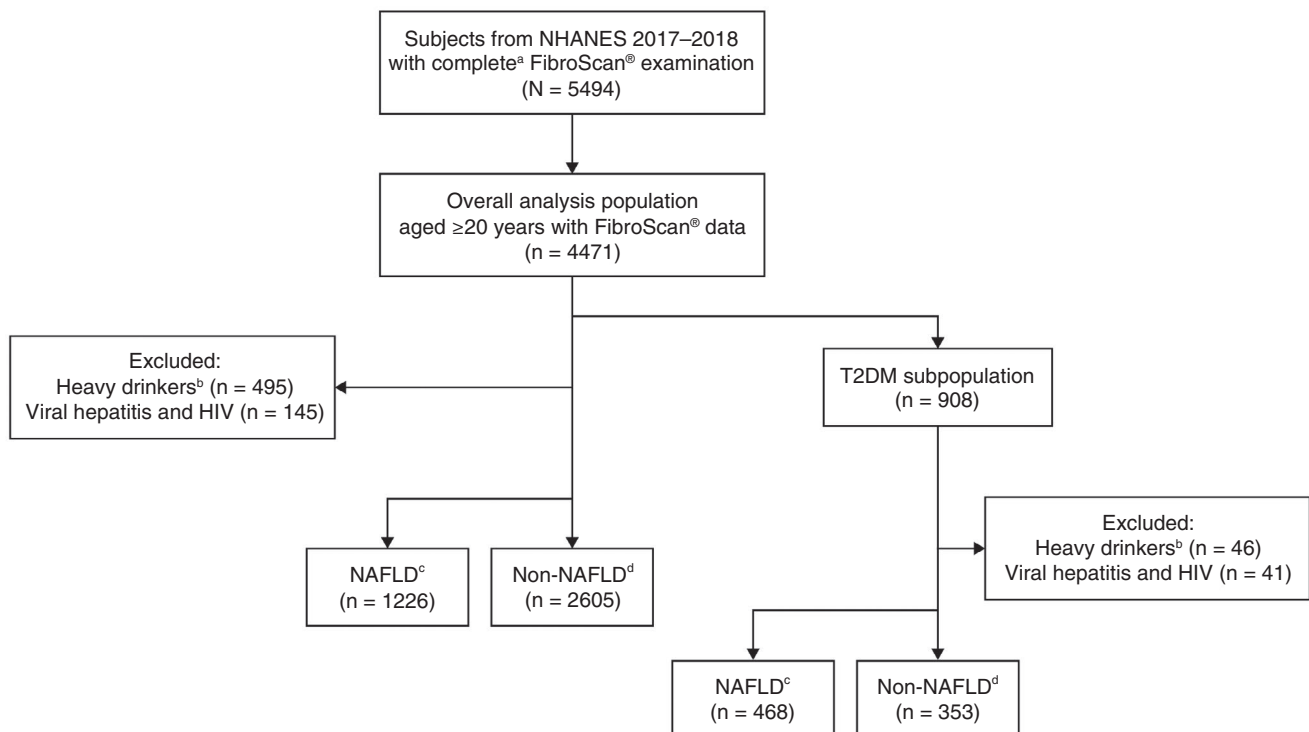


FIGURE 1 Participant disposition. ^aComplete transient elastography (FibroScan[®]) examination was defined as a fasting time of ≥ 3 hours, ≥ 10 complete stiffness (E) measures, and a liver stiffness interquartile range/median E $< 30\%$. ^bHeavy drinker was defined as drinking an average of ≥ 20 g/day and ≥ 30 g/day for women or men, respectively, based on the NHANES alcohol use survey. ^cNAFLD was defined as CAP ≥ 302 and VCTE ≥ 8.2 , including cryptogenic cirrhosis (CAP < 302 , VCTE > 13.6), borderline steatosis (CAP 274–302, VCTE 8.2–13.6), and control (CAP < 274 , VCTE 8.2–13.6). ^dNon-NAFLD was defined as simple steatosis, CAP < 302 , and VCTE < 8.2 . Abbreviations: CAP, controlled attenuation parameter; E, ≥ 10 complete stiffness measures; HIV, human immunodeficiency virus; NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography

(95% CI, 23.2%–27.4%), based on transient elastography data. The age-adjusted prevalence of NAFLD with mild fibrosis F0–F1 and with significant fibrosis F2–F4 was 18.9% (95% CI, 17.0%–20.7%) and 4.4% (F2, 1.5% [95% CI, 0.9%–2.1%]; F3, 1.5% [95% CI, 0.9%–2.2%]; F4, 1.4% [95% CI, 0.8%–1.9%]), respectively

(Figure 2A). In the T2DM subpopulation, the age-adjusted prevalence of NAFLD was considerably higher at 54.6% (95% CI, 47.5%–61.7%), with a higher prevalence of mild F0–F1, 32.6% (95% CI, 27.2%–38.0%), and significant F2–F4, 18.3% (F2, 6.0% [95% CI, 2.2%–9.9%]; F3, 4.5% [95% CI, 1.8%–7.3%]; F4,

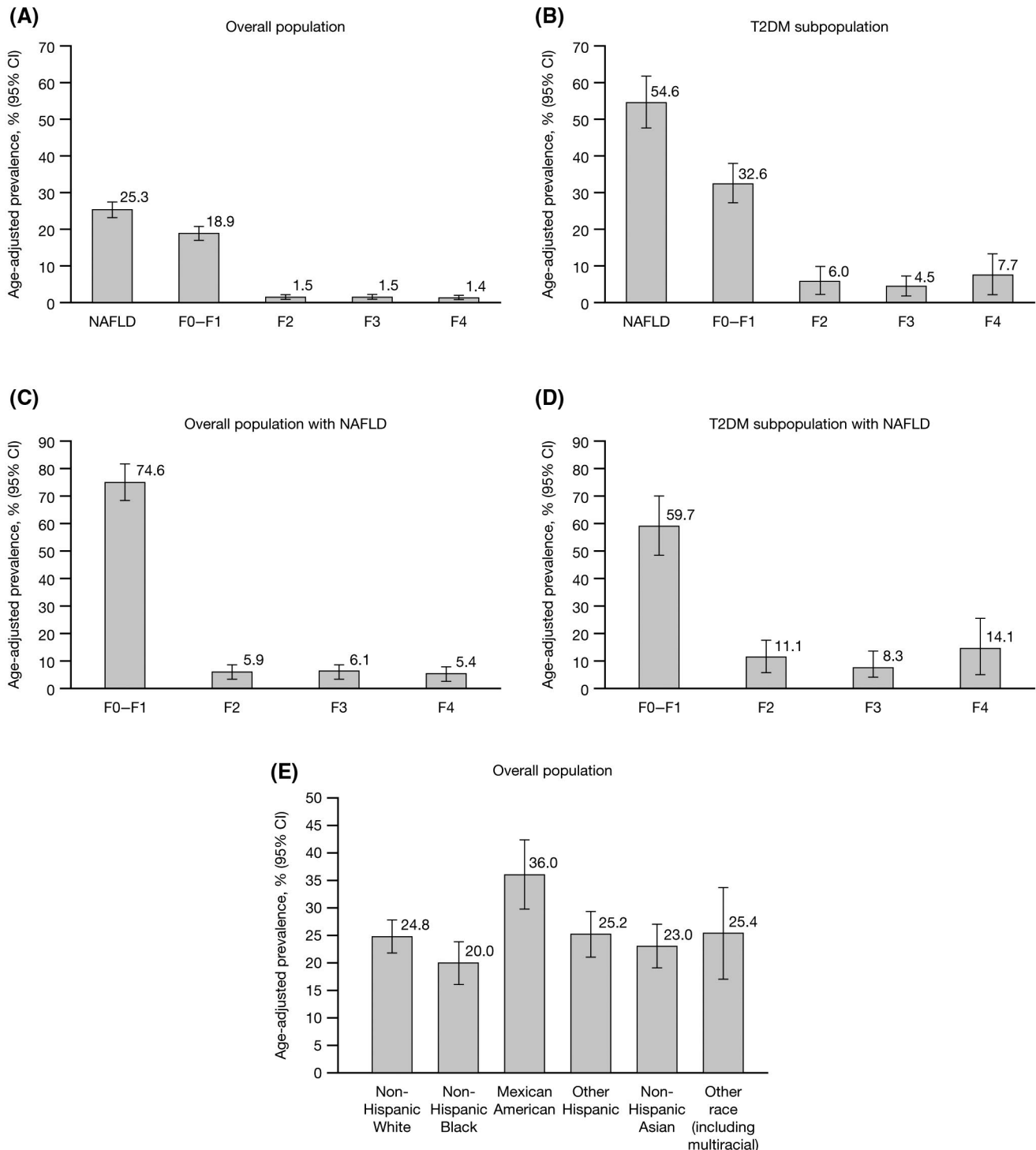


FIGURE 2 Age-adjusted prevalence of NAFLD and fibrosis. (A) NAFLD and fibrosis stages in the overall population and (B) participants with T2DM. (C) Fibrosis among participants with NAFLD in the overall population and (D) participants with T2DM. (E) NAFLD by ethnicity. Abbreviations: CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus

7.7% [95% CI, 2.1%–13.3%]), fibrosis noted in these participants compared with the overall population (Figure 2B). When the age-adjusted prevalence of fibrosis was assessed as a percentage of the NAFLD populations (Figure 2C,D), a higher prevalence of significant fibrosis (33.5%; grade F2–F4) was observed in the T2DM subpopulation with NAFLD (F2, 11.1% [95% CI, 4.8%–17.5%]; F3, 8.3% [95% CI, 3.6%–12.5%]; F4, 14.1% [95% CI, 4.4%–24.4%]; Figure 2D) compared with the overall NAFLD population (17.4%; F2, 5.9% [95% CI, 3.4%–8.3%]; F3, 6.1% [95% CI, 3.5%–8.2%]; F4, 5.4% [95% CI, 3.0%–7.6%]; Figure 2C).

In the overall population, the weighted prevalence of NAFLD was lowest at 21.3% (95% CI, 18.3%–24.2%) in the 20–39-year-old age group compared with a prevalence of approximately 36.0% in the 40–59, 60–74, and ≥ 75 age groups. Conversely, among participants with T2DM, the highest prevalence (70.5%; 95% CI, 56.3%–84.7%) was noted in the 20–39-year-old age group. Prevalence in participants with T2DM who were 40–59, 60–74, and ≥ 75 years of age was 68.0% (95% CI, 59.2%–76.8%), 62.4% (95% CI, 55.6%–69.1%), and 52.4% (95% CI, 40.5%–64.3%), respectively.

The age-adjusted prevalence of NAFLD was also assessed within individual ethnic groups in the overall population. Prevalence ranged from 20.0% to 36.0%, with the highest prevalence among Mexican American participants (Figure 2E).

Demographics, clinical characteristics, and metabolic comorbidities associated with NAFLD with/without fibrosis

Age-adjusted demographics, clinical characteristics, and metabolic comorbidities in participants with and without NAFLD, and with NAFLD with F0–F1 and F2–F3 fibrosis, in the overall population and in those with T2DM are shown in Table 2. Across all groups, the mean age was similar, and the greatest proportion of participants was of non-Hispanic White ethnicity. NAFLD was more prevalent in male individuals in the overall population, and the proportion increased with fibrosis stage. In the T2DM subpopulation, a slight majority of participants with NAFLD and NAFLD with mild fibrosis were female participants; however, significant fibrosis ($\geq F2$) was more prevalent in the male participants.

In the NAFLD group, 73.9% of participants had a BMI ≥ 30 kg/m² and a mean (standard error [SE]) waist circumference of 113.5 (1.05) cm. The mean (SE) CAP measurement was 333.5 (2.3) dB/m, the fibrosis-4 index (Fib-4) was 0.9 (0.02), the NAFLD fibrosis score was -1.3 (0.05), the liver stiffness measurement on FibroScan[®] was 7.9 (0.3) kPa, and the FibroScan[®]-aspartate aminotransferase (FAST) score was 0.21 (0.01). Participants in this group had a history of (or had received treatment for) hypertension (44.6%), diabetes

(29.6%), or hypercholesterolemia (43.1%). Compared with participants without NAFLD, those with NAFLD generally had elevated levels of ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), HbA1c, and triglycerides, and reduced high-density lipoprotein (HDL) cholesterol. Clinical characteristics were generally more pronounced in the subpopulation with F2–F3 fibrosis compared with F0–F1 fibrosis, as expected. Most participants with F2–F3 fibrosis (93.7%) had a BMI ≥ 30 kg/m², and this group also had elevated ALT, AST, GGT, and HbA1c, a greater mean FAST score, and a generally greater prevalence of metabolic comorbidities compared with those with mild fibrosis (Table 2).

Clinical characteristics were also generally more pronounced in the T2DM subpopulation compared with the overall population. In the T2DM subpopulation with NAFLD, 81.9% of participants had a BMI ≥ 30 kg/m² and a mean (SE) waist circumference of 121.2 (1.67) cm. Among liver disease features, the mean (SE) CAP measurement was 347.8 (2.74) dB/m, the Fib-4 index was 0.97 (0.04), the NAFLD fibrosis score was -0.22 (0.13), the liver stiffness measurement on FibroScan[®] was 10.3 (1.74) kPa, and the FAST score was 0.28 (0.02). In addition to diabetes, a high proportion of participants in this group had a history of (or had received treatment for) hypertension (50.6%) or hypercholesterolemia (52.6%). Similar to the comparison of participants with and without NAFLD in the overall population, those with T2DM and NAFLD generally had elevated levels of ALT, AST, alkaline phosphatase, GGT, HbA1c, and triglycerides, and reduced HDL cholesterol compared with participants with T2DM without NAFLD. These clinical characteristics were generally seen at the highest levels in the subpopulation with T2DM and F2–F3 fibrosis compared with other groups. Most participants with T2DM and F2–F3 fibrosis (91.6%) had a BMI ≥ 30 kg/m², and this group also had the highest levels of liver-related laboratory parameters, with elevated ALT, AST, and GGT compared with those with T2DM and F0–F1 fibrosis, a greater mean FAST score, and a greater prevalence of hypercholesterolemia and ischemic heart disease compared with any other group (Table 2).

Machine learning

Predictive modeling using six different machine-learning approaches was applied to data from 3831 participants with and without NAFLD to test the ability to predict NAFLD using demographic and clinical data from NHANES in participants identified by transient elastography. The training set included data from 2874 participants, and the remaining 957 were included in the test set. The test performance of the six machine-learning models was very similar

TABLE 2 Age-adjusted demographics, clinical characteristics, and metabolic comorbidities in the overall population and T2DM subpopulation

	Overall population				T2DM subpopulation			
	Non-NAFLD CAP <302 and VCTE <8.2	NAFLD CAP ≥302	NAFLD F0–F1 CAP ≥302 and VCTE ≤8.2	NAFLD F2–F3 CAP ≥302 and 8.2 < VCTE ≤13.6	Non-NAFLD CAP <302 and VCTE <8.2	NAFLD CAP ≥302	NAFLD F0–F1 CAP ≥302 and VCTE ≤8.2	NAFLD F2–F3 CAP ≥302 and 8.2 < VCTE ≤13.6
n ^a	2605	1226	875	162	353	468	310	82
Demographics								
Age, years; mean (SE)	47.2 (0.18)	48.0 (0.28)	48.1 (0.25)	47.9 (0.74)	50.1 (0.38)	49.3 (0.46)	49.8 (0.56)	48.2 (1.26)
Sex, male; %	44.1	57.2	57.3	66.5	39.0	44.8	44.9	61.6
Race; %								
White (non-Hispanic)	60.2	61.0	61.8	57.9	40.5	51.3	43.6	48.6
Black (non-Hispanic)	12.8	8.8	7.5	9.1	20.8	11.7	16.4	9.5
Mexican American	8.0	13.1	13.9	17.4	18.1	18.4	21.2	22.1
Other Hispanic	7.3	7.0	6.8	8.2	6.4	6.8	6.5	10.4
Asian (non-Hispanic)	6.9	5.4	5.8	5.2	8.3	5.7	8.1	6.9
Other	4.8	4.7	4.1	2.1	5.9	6.1	4.2	2.5
Clinical characteristic								
BMI ≥30 kg/m ² ; %	29.1	73.9	73.2	93.7	48.4	81.9	76.7	91.6
Waist circumference, cm; mean (SE)	94.6 (0.67)	113.5 (1.05)	112.2 (1.03)	122.0 (1.35)	105.3 (1.85)	121.2 (1.67)	117.1 (1.94)	123.9 (2.84)
ALT, U/L; mean (SE)	19.9 (0.32)	29.1 (0.83)	28.8 (0.94)	37.0 (2.47)	25.3 (1.43)	32.8 (2.26)	29.3 (2.21)	40.0 (3.86)
AST, U/L; mean (SE)	20.4 (0.25)	23.7 (0.51)	22.4 (0.32)	27.4 (1.83)	21.4 (0.98)	25.4 (1.34)	21.7 (1.06)	29.5 (2.85)
Alkaline phosphatase, U/L; mean (SE)	74.4 (0.97)	81.8 (0.96)	79.9 (0.96)	84.3 (3.95)	79.6 (3.10)	85.6 (2.33)	85.4 (2.61)	87.6 (4.56)
GGT, U/L; mean (SE)	23.7 (0.51)	38.3 (1.78)	34.4 (1.78)	49.8 (3.67)	29.1 (1.65)	43.0 (2.03)	33.7 (2.79)	54.8 (5.33)
HbA1c; %, mean (SE)	5.5 (0.02)	6.1 (0.03)	6.0 (0.04)	6.4 (0.14)	7.1 (0.16)	7.5 (0.14)	7.7 (0.20)	7.6 (0.30)
HDL cholesterol, mg/dL; mean (SE)	55.6 (0.39)	45.8 (0.61)	45.8 (0.57)	43.7 (1.60)	49.4 (1.12)	43.4 (0.93)	43.8 (1.15)	42.4 (2.74)
Triglycerides, mg/dL; mean (SE)	122.0 (2.05)	192.4 (6.51)	194.6 (7.37)	223.6 (29.37)	155.0 (10.01)	222.4 (14.53)	225.6 (14.87)	262.7 (53.74)
Fib-4 index; mean (SE)	1.01 (0.02)	0.94 (0.02)	0.87 (0.02)	1.07 (0.09)	0.97 (0.04)	0.97 (0.04)	0.84 (0.04)	1.13 (0.15)
NAFLD fibrosis score; mean (SE)	-1.98 (0.04)	-1.32 (0.05)	-1.54 (0.06)	-0.84 (0.12)	-0.51 (0.09)	-0.22 (0.13)	-0.49 (0.20)	-0.16 (0.18)
FibroScan [®] CAP, dB/m; mean (SE)	232.8 (1.32)	333.5 (2.27)	339.4 (1.71)	351.0 (2.78)	252.8 (4.71)	347.8 (2.74)	351.8 (3.48)	361.4 (4.38)
FibroScan [®] fibrosis, kPa; mean (SE)	4.6 (0.05)	7.9 (0.30)	5.4 (0.07)	10.1 (0.16)	6.6 (1.29)	10.3 (1.74)	5.7 (0.20)	10.2 (0.26)
FAST score; mean (SE)	0.06 (0.00)	0.21 (0.01)	0.17 (0.01)	0.35 (0.03)	0.11 (0.01)	0.28 (0.02)	0.18 (0.02)	0.41 (0.04)
Comorbidities								
Diabetes; %	8.4	29.6	23.5	44.5	100.0	100.0	100.0	100.0
Hypercholesterolemia; %	32.6	43.1	43.0	50.2	44.9	52.6	52.7	61.0
Hypertension; %	24.3	44.6	44.0	43.4	47.4	50.6	45.2	41.9
Ischemic heart disease; %	4.4	7.2	6.0	10.7	8.2	11.4	10.5	17.0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; FAST, FibroScan[®]-aspartate aminotransferase; Fib-4, fibrosis-4 index; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; SE, standard error; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.
^aUnweighted.

with respect to predictive ability. AUROC for test performance ranged between 0.79 and 0.84 (Figure 3; Table 3), with sensitivity and specificity for predictive performance ranging between 0.52 and 0.71 and 0.78 and 0.90, respectively (Table 3). Logistic regression was selected as the model of choice to predict NAFLD in the general population due to its simplicity, ease of interpretation, and similar performance compared with the other models.

Using logistic regression, the risk of having NAFLD was increased by 33% in men versus women (odds ratio [OR], 1.33; 95% CI, 1.07–1.66; $P = 0.010$) and with a 1-point increase in HbA1c (OR, 1.33; 95% CI, 1.21–1.46; $P < 0.001$). Other variables that were statistically significant predictors of NAFLD using logistic regression were a ≥ 1 -point increase in age, BMI, waist circumference, AST, alkaline phosphatase, diastolic blood pressure, HDL, and triglycerides (all $P < 0.05$; Table 4).

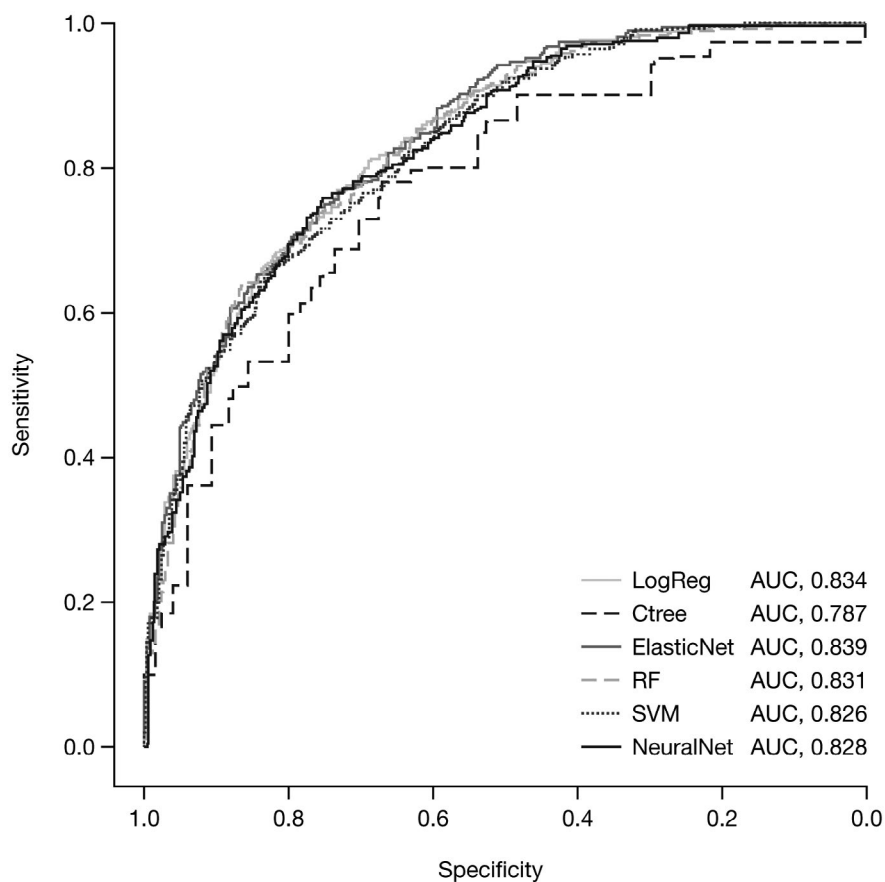


FIGURE 3 Test performance by AUROC for the six machine-learning methods. Abbreviations: AUC, area under the curve; AUROC, area under the receiver operating characteristic curve; Ctree, classification tree; ElasticNet, elastic network; LogReg, logistic regression; NeuralNet, neural network; RF, random forest; SVM, support vector machine

TABLE 3 Predictive performance of the six machine-learning models

Model	AUROC (95% CI)	Accuracy	Sensitivity	Specificity	Predictive value	
					Positive	Negative
LogReg	0.83 (0.81, 0.86)	0.78	0.55	0.89	0.70	0.81
Ctree	0.79 (0.76, 0.82)	0.75	0.53	0.85	0.63	0.80
ElasticNet	0.84 (0.81, 0.86)	0.78	0.56	0.89	0.70	0.81
RF	0.83 (0.80, 0.86)	0.79	0.61	0.88	0.70	0.83
SVM	0.83 (0.80, 0.85)	0.78	0.52	0.90	0.72	0.80
NeuralNet	0.83 (0.80, 0.85)	0.75	0.71	0.78	0.60	0.85

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; Ctree, classification tree; ElasticNet, elastic network; LogReg, logistic regression; NeuralNet, neural network; RF, random forest; SVM, support vector machines.

TABLE 4 Machine-learning predictors of NAFLD using logistic regression

Clinical characteristic	OR ^b	95% CI	P value
Sex; male versus female	1.33	1.07–1.66	0.010
HbA1c	1.33	1.21–1.46	<0.001
BMI	1.06	1.03–1.09	<0.001
Waist circumference	1.05	1.03–1.06	<0.001
AST	1.03	1.02–1.04	<0.001
Age	1.01	1.01–1.02	<0.001
Diastolic blood pressure	1.01	1.00–1.02	0.010
Alkaline phosphatase	1.00	1.00–1.01	0.018
Triglycerides	1.00	1.00–1.00	<0.001
HDL	0.99	0.98–1.00	0.008

Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

^aBased on a 1-point increase for all numeric covariates.

DISCUSSION

In this real-world cohort study of the NHANES 2017–2018 data set, we found that NAFLD is highly prevalent in the United States adult population, excluding high alcohol consumers. The prevalence of NAFLD by transient elastography was estimated at 25.3%, with a greater prevalence of 54.6% among participants with T2DM. The NAFLD group at risk of progression with significant fibrosis (\geq F2) that may require pharmacologic treatment^[15,28] was estimated to be 17.4% in the entire NAFLD population and 33.5% among those with NAFLD and T2DM. Of note, although non-White Hispanics formed the largest ethnic group among participants with NAFLD, the greatest prevalence of NAFLD (35.5%) was observed among Mexican Americans in our analysis, with the lowest prevalence among non-Hispanic Black participants, as reported.^[29–31] Analyses also highlighted clinical characteristics associated with NAFLD with fibrosis, which were generally more pronounced in the T2DM subpopulation and included higher FAST score, increased BMI, and elevated ALT, AST, GGT, and HbA1c. Using a logistic regression machine-learning model, several clinical characteristics were identified as significant predictors of NAFLD. These results may inform screening strategies, health regulators, and access to treatment as they provide real-world size estimates of the NAFLD population and a potential means of identifying this population using noninvasive methods and readily available, standard demographic and clinical data.

The results presented are consistent with documented estimates for global prevalence of NAFLD in the general population^[1] and in those with T2DM^[8] but are slightly lower than previously documented estimates for the United States population,^[2,13,14] which may be due to methodologic differences in diagnostic

modalities,^[2] participant stratification, and CAP cutoffs.^[13,14] One study using transient elastography data from the NHANES 2017–2018 data set did not take alcohol consumption data into account^[13] as it was not published by NHANES at the time of this publication. In a second study, alcohol use was determined using 24-hour dietary recall with cutoffs of >28 g/day for women and >42 g/day for men; this may have led to inaccuracies and misclassification of participants with NAFLD.^[14] In the current study, alcohol consumption was determined from the recently published NHANES alcohol use questionnaire,^[26] which provides more complete information than dietary recall, enabling exclusion of participants with high alcohol consumption as a potential cause of liver disease based on cutoffs of ≥ 20 g/day and ≥ 30 g/day for women and men, respectively, defined from epidemiologic studies.^[25,32] In addition, both previous analyses of NHANES 2017–2018 data used CAP cutoffs of ≥ 263 and ≥ 285 dB/m to define NAFLD in order to optimize for sensitivity and specificity, respectively.^[13,14] This may have led to estimations of NAFLD prevalence being disproportionately higher than any previous reports and indicates the potential pitfalls of considering CAP cutoffs based on published data in the absence of defined limits. In contrast, in the current study we used a CAP cutoff of ≥ 302 dB/m, which was previously identified as the optimal cutoff for accurate diagnosis of hepatic steatosis $\geq 5\%$ using Youden's index, with a sensitivity and specificity of 0.80 (95% CI, 0.75–0.84) and 0.83 (95% CI, 0.69–0.92), respectively.^[11] Compared with other studies,^[13,14] our study also provided further data on clinical characteristics, including FAST score, in addition to age-related distribution differences in NAFLD prevalence in this most recent NHANES cycle. Of note, in contrast to the overall population where the lowest prevalence was among the younger age group, the highest prevalence (70.5%) in participants with T2DM was in the 20–39-year-old age group. Further studies are needed to investigate this observation; however, this trend confirms the seriousness of this coexisting condition at an early age and supports the evidence for early screening for NAFLD in patients with T2DM.^[33]

The stage of liver fibrosis is an important predictor of outcome in patients with NAFLD, and the risk of liver-related mortality has been shown to increase with increasing fibrosis stage.^[20] Our age-adjusted analysis highlighted a prevalence of significant fibrosis (\geq F2) of 17.4% among participants with NAFLD, which is higher than previous estimates based on the NAFLD fibrosis score (3.2%)^[2] or transient elastography value ≥ 8 kPa (13.8%).^[13] Prior epidemiological modeling suggested that the NASH subgroup within the NAFLD cohort had mostly early stages of fibrosis.^[19] However, the cutoffs used in the current study suggest a relatively consistent distribution of fibrosis severity among prevalent cases, which implies that

many more patients could be at short-term risk of progression to cirrhosis than previously thought. The reasons for this difference are unknown but may reflect the difficulties of modeling the epidemiology of a disease with limited available information. Among participants with NAFLD and T2DM in our analysis, the prevalence of significant fibrosis was higher at 33.5% compared with 15.7%–24.6% in another study using the same data set.^[14] The high prevalence of significant fibrosis in the general United States population and in patients with T2DM highlights the need for efficient noninvasive tools to improve diagnosis rates and for earlier detection of patients that would benefit from further assessment.^[34]

Leveraging the wealth of standard demographic and clinical data available in the NHANES data set, we applied machine learning to predict NAFLD in participants at high risk as identified by transient elastography CAP (FibroScan[®]). The test and predictive performance of six different models were noticeably similar in terms of their ability to identify NAFLD. Using logistic regression as the most simple and appropriate model, several clinical characteristics were identified as significant predictors of NAFLD, including male sex, as noted previously,^[9,13,15] and increases in age, diastolic blood pressure, BMI, waist circumference, HbA1c, and liver-related metabolic parameters, including AST, alkaline phosphatase, HDL, and triglycerides, consistent with the associated increased prevalence of obesity, T2DM, and metabolic syndrome.^[5–7] Although an increase in HDL in relation to the presence of NAFLD may appear counterintuitive, it is possible to see such an outcome with machine-learning models in the presence of multiple covariates with potential collinearity. We used elastic net with cross-validation as an approach to incorporate variables with possible colinear variables, with the aim of increasing predictive power and performance, and HDL was still retained by the model. These results add to the growing body of evidence supporting the use of machine learning for diagnosis, staging, and risk stratification of patients with NAFLD,^[22] with potential to replace more costly, invasive, or less accurate diagnostic tools to identify patients requiring further assessment and treatment. Further studies are required to investigate the use of machine-learning models for screening and staging of subjects with NASH to identify the best models for future use and to integrate these into standard patient care.

This study had several limitations. Due to the nature of NHANES and limitations in the data, no patient had biopsy confirmation of NAFLD/NASH, and other potential causes of liver disease, including less common causes of metabolic and genetic liver disease, such as autoimmune hepatitis, primary biliary cholangitis, and hemochromatosis, could not be ruled out. Furthermore, serial measurements over

time were not possible. Sample sizes for some groups were small; because of this, machine-learning predictive models were not investigated for NASH and fibrosis stages. In relation to machine learning, the predictive accuracy of all six models tested was in the range of 0.75 to 0.79, which may be considered low. However, using AUROC as a more precise predictive measure,^[35] the test performance of all six models was similarly accurate (range, 0.79–0.84). Self-reported alcohol consumption, as documented in the NHANES alcohol use survey,^[26] may have underestimated true alcohol consumption. However, these data are more comprehensive than those considered in an earlier study.^[14] Further limitations include representation of the United States population over a short time frame between 2017 and 2018, which is now several years out of date and has an overrepresentation of participants ≥ 60 years of age and of African American and Hispanic participants,^[24] the latter being a population with a high prevalence of NAFLD.^[9,13,31] To account for this, we analyzed the prevalence of NAFLD within individual ethnic groups, showing the highest prevalence in Mexican Americans. A lack of defined guidelines on cutoffs for CAP and VCTE may also be a limitation of this analysis; however, we used cutoffs defined using Youden's index as optimal for detection of hepatic steatosis and fibrosis.^[11] These cutoffs are considered one of the most accurate in the literature, with transient elastography and liver biopsies performed in a prospective approach within 2 weeks of each other, demonstrating consistency in testing diagnostic precision.^[11] We also investigated data in the cutoff range of 274 to 302 dB/m, which we termed borderline steatosis, representing the lowest cutoff and the optimal cutoff determined by Youden's index, respectively.^[11] This group was very small (0.6% of the age-adjusted population with NAFLD) and would not have impacted the overall prevalence of NAFLD with or without fibrosis. It should also be noted that individual fibrosis scores were interpreted based on differences in subpopulations defined by these cutoffs. The large real-world cohort is a strength of this study, with the recent FibroScan[®] data enabling a true determination of the prevalence of NAFLD in the United States. A further strength is the analysis of clinical characteristics, including FAST score in participants with and without T2DM and with NAFLD with mild and significant fibrosis.

In conclusion, data show a high prevalence of NAFLD with significant fibrosis ($\geq F2$) in the general United States population, with a greater prevalence in participants with T2DM. In addition to an increased risk of all-cause and liver-related mortality,^[20] patients with significant fibrosis are at high risk of progressing to end-stage liver disease, with NASH noted as one of the leading causes of liver transplant in the United States.^[36] Despite the prevalence, screening

for NAFLD with or without fibrosis is not currently recommended in clinical practice. Transient elastography (FibroScan®) is a noninvasive tool used to identify subjects at risk of NASH with fibrosis. Using readily available, standard demographic and clinical data, machine-learning models may be used to identify subjects with NAFLD across large data sets in computerized health care systems, with the potential to replace more costly, less accurate, or invasive diagnostic tools. Accurate identification of subjects at high risk of developing NASH may help to mitigate the growing epidemic, reducing the burden on public health, health care systems, and payers.

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CONFLICT OF INTEREST

Dr. Nouredin has advised 89BIO, Abbott, Allergan, Blade, EchoSens, Fractyl, Gilead, Intercept, Novartis, Novo Nordisk, OWL, Roche Diagnostics, Siemens, and Terns; he received research support from Allergan, Bristol-Myers Squibb, Conatus, Enanta, Galectin, Galmed, Genfit, Gilead, Madrigal, Novartis, Shire, Viking, and Zydus; he is a shareholder of or has stock in Anaetos and Viking. Dr. Ntanios, Ms. Malhotra, Dr. Hoover, Dr. Emir, and Mr. McLeod are stockholders and employees of Pfizer Inc. Dr. Alkhouri participated in a speakers' bureau for and received grants/research funding from Gilead and Intercept; he received grants/research funding from Akero, Allergan, Bristol-Myers Squibb, Corcept, Galectin, Genfit, Madrigal, NGM, Pfizer Inc, Poxel, and Zydus.

AUTHOR CONTRIBUTIONS

Mazen Nouredin, Fady Ntanios, Katherine Hoover, Birol Emir, Euan McLeod, and Naim Alkhouri conceived the study design; Mazen Nouredin, Fady Ntanios, Katherine Hoover, Birol Emir, Euan McLeod, and Naim Alkhouri were responsible for the methodology; Mazen Nouredin, Deepa Malhotra, and Birol Emir analyzed the data; Mazen Nouredin and Birol Emir visualized the data; Mazen Nouredin, Fady Ntanios, Deepa Malhotra, Birol Emir, and Euan McLeod validated results; Mazen Nouredin and Fady Ntanios were responsible for investigation, resources, project administration, and funding acquisition; Deepa Malhotra and Birol Emir curated the data; Mazen Nouredin, Fady Ntanios, and Naim Alkhouri supervised; Fady Ntanios, Katherine Hoover, Birol Emir, and Euan McLeod wrote the original draft manuscript. All authors critically

reviewed and edited the manuscript and approved the final version.

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