

Prevalence of High Liver Stiffness and a Screening Strategy Using the SODA-2B Score Among US Adults

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Cirrhosis, a rising cause of death in the United States, has an extended preclinical phase characterized by progressive liver fibrosis. Despite the developments in noninvasive fibrosis measurement, there is no recommended screening, in part due to an incomplete understanding of the disease epidemiology on a national scale. Herein, we aim to define the prevalence of liver fibrosis and compare strategies to identify the at-risk population. We analyzed 4,510 US adults with complete liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) in the 2017–2018 National Health and Nutrition Examination Survey to estimate the disease burden of increased liver stiffness. An estimated 11.6 million (95% confidence interval [C.I.], 8.1–15.0 million) US adults had LSM ≥ 9.5 kPa, indicating advanced fibrosis and representing 1 in every 18 adults. Among them, 7.1 million (95% CI, 5.0–9.1 million) had LSM ≥ 12.5 kPa, which is concerning for cirrhosis. LSM ≥ 9.5 kPa is associated with male sex (S), history of other liver diseases (O), diabetes (D), advanced age (A), and an elevated BMI (B). A simple SODA-2B score had a sensitivity of 96.4% in identifying individuals at risk for advanced cirrhosis (LSM ≥ 9.5 kPa) and a negative predictive value of 99.3% in stratifying more than half of the adult population. When the liver function test (LFT) is available, the inclusion of abnormal LFT and elevated fibrosis-4 index can further increase screening efficiency. **Conclusion:** Elevated liver stiffness is prevalent among US adults. A SODA-2B score can risk stratify adults for VCTE-based fibrosis screening. (*Hepatology Communications* 2022;6:898–909).

Chronic liver disease (CLD) is a major threat to our public health. Roughly 60,000 people die from CLD annually in the United States.⁽¹⁾ CLD accounts for >1 million outpatient visits, and CLD-related hospitalizations have risen every year since 2001, overtaking hospitalization rates for heart failure and lung disease.^(2,3) Annual CLD health care costs exceeded US \$29.9 billion in 2015.⁽⁴⁾ As the burden of CLD is driven by cirrhosis complications,

many have argued that early identification by screening for liver fibrosis may improve outcomes and costs.^(5,6)

Several screening programs have been implemented outside the United States, the largest in Spain and England. Caballeria et al.⁽⁷⁾ screened 3,076 randomly selected Spanish adults by using vibration-controlled transient elastography (VCTE), identifying 3.6% of the population with liver stiffness measurements

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operator characteristic; BMI, body mass index; CI, confidence interval; CLD, chronic liver disease; FIB-4, fibrosis-4; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IQR, Interquartile range; LFT, liver function test; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; ROC, receiver operator characteristic; SODA-2B, sex, other liver diseases, diabetes, age, body mass index (2 points); VCTE, vibration-controlled transient elastography.

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(LSMs) more than 9.0 kPa. Abeysekera et al.⁽⁸⁾ used VCTE to screen 3,600 young adults from the United Kingdom and found that 2.4% had LSM ≥ 7.9 kPa and 0.25% had LSM ≥ 11.7 kPa. The prevalence of significant fibrosis in the United States is likely to be higher. In the United States, Long and colleagues⁽⁹⁾ performed VCTE on 3,276 subjects in the Framingham Heart Study and found that 8.8% had LSM ≥ 8.2 kPa. The higher rate of positive findings in the United States may be compounded by additional challenges. First, screening is associated with increased short-term health care costs. It is not clear whether the best strategy is to screen everybody or to screen a selected at-risk population. Second, there could be challenges in linking identified persons to effective care. Third, no effective therapy has been proven to reduce liver fibrosis, while treatment of the underlying CLD remains the primary strategy. If screening for advanced CLD is to be undertaken, data are needed regarding the expected yield and the phenotype of the at-risk population.

Beginning in 2017-2018, the National Health and Nutrition Examination Survey (NHANES) evaluated a nationally representative cross-section of Americans using VCTE.⁽¹⁰⁾ Herein, we evaluated the overall prevalence of advanced fibrosis and cirrhosis using LSMs and characterized the at-risk population to inform the implementation of screening strategies sensitive to the needs of individuals at high risk.

Participants and Methods

STUDY POPULATION

NHANES is a nationally representative cross-sectional study conducted by the National Center

for Health Statistics at the Centers for Disease Control and Prevention every 2 years since 1999. NHANES enrolls participants using a stratified multistage probability with an oversampling design of certain age and ethnic groups to allow weighted analysis that represents the civilian noninstitutionalized US population.⁽¹¹⁾ All participants are interviewed for demographic, socioeconomic, health, and dietary information. Examinations and laboratory tests are conducted on selected subsets of participants.

MEASUREMENT OF LIVER STIFFNESS

During the 2017-2018 survey, technicians performed VCTE of the liver by FibroScan on all subjects aged 12 years and over. Excluded participants included those who were unable to lie down on the examination table, were pregnant, had an implanted electronic medical device, wore a bandage, or had lesions on the right flank where FibroScan measurements were to be made. VCTE was used to derive an LSM to estimate liver fibrosis and controlled attenuation parameter for hepatic steatosis. NHANES performed LSM on 4,870 subjects aged 20 years and older. Among these, we included 4,510 individuals who had a complete examination in our study. According to NHANES criteria, to be considered as complete, individuals had to comply with a fasting time of at least 3 hours and have 10 or more complete stiffness measurements with liver stiffness interquartile range (IQR)/median $< 30\%$ to ensure low kilopascal variability. Individuals considered to have incomplete elastography were distinctly characterized by a weighted mean body mass index (BMI) of 36.6, representing a total of 6.4 million people (73.6%) with BMI ≥ 30 .

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BACKGROUND INFORMATION ON STUDY SUBJECTS

Self-reported information on age, sex, ethnicity, annual household income, and health insurance was obtained from the questionnaire. We also extracted questionnaire data on the medical history of previously diagnosed conditions, alcohol consumption, and smoking history. Diabetes included participants that were previously diagnosed by a health professional, regardless of the type. Anthropometric measurements of body weight, height, and waist circumference were extracted from the examination data and were used to calculate the BMI. Routine laboratory measurements included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, gamma-glutamyltransferase, ferritin, and creatinine. Abnormal liver function test (LFT) was defined using both a lower cut-off value (ALT, men ≥ 30 U/L and women ≥ 19 U/L; or AST ≥ 33 U/L or ALP ≥ 100 U/L) and a higher cut-off value (ALT, men ≥ 44 U/L and women ≥ 32 U/L; or AST ≥ 40 U/L or ALP ≥ 120 U/L), as recommended.^(12,13) The fibrosis-4 (FIB-4) index was calculated as age (year) \times AST (U/L)/(platelet count [10^9 /L] \times ALT/2 [U/L]).⁽¹⁴⁾ We categorized individuals with FIB-4 index cutoffs at 1, 1.3, 1.45, 2.67, and 3.25. We identified chronic viral hepatitis based on positive hepatitis C virus (HCV) RNA or hepatitis B surface antigen (HBsAg).

ESTIMATING THE PREVALENCE OF ADVANCED FIBROSIS AND CIRRHOSIS

We first examined the national prevalence of elevated LSM across age groups of every 10 years from 20 to 80 years and over 80 years. LSM was categorized into <7 , 7-9.5, 9.5-12.5, and ≥ 12.5 kPa according to the cutoffs for advanced fibrosis and cirrhosis recommended by the latest technical review on the role of elastography in CLDs.⁽¹⁵⁾ We then compared the demographics, annual household income, health insurance, smoking history, alcohol consumption history, anthropometric measurements, and laboratory measurements among individuals with LSM <7 , 7-9.5, or ≥ 9.5 kPa. The *P* values were calculated with chi-squared test and linear regression for binary, categorical, and continuous variables, respectively.

IDENTIFICATION OF RISK FACTORS AND PREDICTORS OF ADVANCED FIBROSIS

We performed univariate logistic regression analysis to determine unadjusted associations between elevated liver stiffness (LSM ≥ 9.5 kPa) and variables that either demonstrated increased prevalence with high LSM or those considered as relevant risk factors based on the following in the literature: age, sex, race, comorbidities (diabetes, hypertension, hyperlipidemia), alcohol consumption, smoking, BMI, and waist circumference. Age, sex, diabetes, hypertension, and hyperlipidemia were used as binary variables. We categorized alcohol consumption into the following four groups: never drinker, moderate drinker (0-7 drinks per week for women and 0-14 drinks per week for men), heavy drinker (>7 drinks per week for women and >14 drinks per week for men), and individuals with a history of daily binge drinking. Smoking history was categorized into never smokers, former smokers, and active smokers. Age, BMI, and waist circumference were used as continuous variables in the model. We then conducted multivariate logistic regression analyses, including these variables, to identify independent risk factors.

In the next section, we discuss the construction of a score associated with male sex (S), history of other liver diseases (O), diabetes (D), advanced age (A), and an elevated BMI (B) that is given 2 points. We call this SODA-2B.

DERIVATION AND CALIBRATION OF SODA-2B AND SODA-2B+LF SCORE

To construct a score to predict elevated liver stiffness that is easy to use clinically, we identified independent predictors that demonstrated strong associations with LSM ≥ 9.5 kPa in univariate and/or multivariate analyses that are also easily accessible in an ambulatory setting without additional laboratory tests. We converted age and BMI to binary variables to identify those with age ≥ 50 and obesity (BMI ≥ 30). We also generated a variable for other liver risk factors, including heavy alcohol consumption (>7 drinks per week for women and >14 drinks per week for men), positive HCV RNA, or positive HBsAg. Based on the odds ratio (OR) in predicting

LSM ≥ 9.5 kPa, we constructed a SODA-2B score, which was calculated by granting 1 point for male sex, presence of other liver risk factors, diabetes, age ≥ 50 , and 2 points for BMI ≥ 30 . SODA-2B was designed as an ordinal score to make it easy to calculate. The calibration of point assignment to each variable was based on the respective coefficient in regression models and comparative C-statistics. As a sensitivity test, we also constructed a SODA-2B+LF score that combines SODA-2B and abnormal LFT (1 point) and elevated FIB-4 (2 points), which can be calculated from LFT. Abnormal LFT was defined as ALT men ≥ 44 IU/L, ALT women ≥ 32 IU/L, AST ≥ 40 IU/L, and ALP ≥ 120 IU/L. Elevated FIB-4 was defined as FIB-4 ≥ 2.67 . We used receiver operator characteristic (ROC) analysis to compare and calibrate SODA-2B and SODA-2B+LF in predicting LSM ≥ 9.5 kPa by maximizing the area under the ROC (AUROC) while using FIB-4 as a reference.

ESTIMATION OF THE PERFORMANCE OF SODA-2B IN RISK STRATIFICATION AMONG US ADULTS

To estimate the performance of SODA-2B, we generated 2×2 contingency tables of the population between SODA-2B using cutoffs 1-6 and measured LSM ≥ 9.5 kPa using sampling weights. From the contingency table, we calculated the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios of each SODA-2B cutoff in predicting an elevated liver stiffness ≥ 9.5 kPa. We performed parallel analyses for SODA-2B+LF as sensitivity tests.

All data analyses were conducted with Stata version 16.1 using NHANES-provided sampling weights; graphs were drawn with GraphPad Prism version 9.

Results

PREVALENCE OF ELEVATED LIVER STIFFNESS AMONG US ADULTS

A total of 4,510 persons aged 20 years or older who had a complete liver elastography examination were identified from 9,254 participants in the 2017-2018 cycle of NHANES. These individuals represented

207.8 million adults in the United States. Weighted analysis indicated that 11.6 million (95% confidence interval [CI], 8.1 million-15.0 million), representing 5.6% of US adults, had an LSM higher than 9.5 kPa. This prevalence is similar to that of abnormal fasting blood glucose ≥ 126 mg/dL at 5.5% of the population, corresponding to 11.4 million US adults (95% CI, 9.0 million-13.8 million). Among those with a high LSM, 6.3 million (95% CI, 4.2 million-8.4 million), representing 3.0%, had an LSM above 12.5 kPa (Table 1). Furthermore, an estimated 16.5 million (95% CI, 12.9 million-20.1 million), representing 7.9%, had an LSM between 7 and 9.5 kPa, a value at which early fibrosis cannot be ruled out. The prevalence of LSM ≥ 9.5 increased across age groups until age 50-60 years, at which point it plateaued at 7.8%-8.3% (Table 1; Fig. 1). Prevalence of an LSM ≥ 12.5 kPa was highest among individuals aged 50-60 years, at 5.3%.

CHARACTERISTICS OF INDIVIDUALS WITH INCREASED LIVER STIFFNESS

To identify population characteristics associated with an increased liver stiffness, we compared demographics, anthropometric measurements, alcohol consumption, smoking history, and laboratory findings across three LSM categories (< 7 , 7-9.5, and ≥ 9.5 kPa) (Table 2). Individuals with a high LSM (≥ 9.5 kPa) were more likely to be older, men, heavy drinkers, and had a higher prevalence of hepatitis C, obesity, diabetes, hypertension, and coronary artery disease. No significant difference in alcohol drinking pattern was noted across the three groups of liver stiffness, although a trend toward a higher prevalence of heavy drinking was noted among those with an LSM ≥ 9.5 kPa. Notably, individuals with a high LSM had rather unremarkable mean liver biomarkers despite trending higher compared to their counterparts, highlighting the challenge to identify these individuals by laboratory tests alone. We observed no significant differences in ethnicity, socioeconomic status, smoking history, or hepatitis B status across LSM groups.

FACTORS ASSOCIATED WITH ELEVATED LIVER STIFFNESS

Unadjusted logistic regression analyses demonstrated that an LSM ≥ 9.5 kPa was positively associated

TABLE 1. POPULATION SIZE WITH INCREASED LIVER STIFFNESS BY AGE

Age Groups (Years)	Observation Number	Total Population*	LSM							
			<7 kPa	7-9.5 kPa	9.5-12.5 kPa	≥12.5 kPa				
			Population Estimate	95% CI	Population Estimate	95% CI	Population Estimate	95% CI	Population Estimate	95% CI
20-30	669	38.7	35.0	28.9-41.2	2.8	1.6-3.9	0.5	0.03-1.0	0.37	0.02-0.7
30-40	708	37.6	33.2	29.4-36.9	2.8	1.6-3.9	0.3	0.09-0.6	1.3	0.7-1.9
40-50	665	32.8	28.6	25.2-32.1	2.5	1.1-3.7	1.1	0.3-2.0	0.5	0.05-1.1
50-60	778	39.8	33.3	28.4-38.1	3.6	2.1-5.1	0.8	0.3-1.2	2.1	1.0-3.3
60-70	947	33.5	27.8	22.3-33.2	3.3	2.3-4.2	0.8	0.3-1.3	1.7	0.9-2.4
70-80	479	18.1	14.3	12.5-16.2	2.3	0.9-3.6	0.7	0.3-1.0	0.8	0.4-1.1
80+	264	7.4	6.3	4.9-7.5	0.50	0.2-0.9	0.3	0.05-0.6	0.3	0.02-0.6
Total	4,510	207.8	178.4	168-189	17.7	13.7-21.7	4.5	3.1-5.9	7.1	5.0-9.1

*All population estimates are listed in millions of individuals.

with age, metabolic comorbidities (diabetes, hypertension, hyperlipidemia), BMI, waist circumference, and chronic viral hepatitis (Table 3). Female sex was associated with a lower risk compared to male counterparts. Notably, race was not associated with elevated liver stiffness in univariate analysis despite the presence of ethnicity-specific genetic predispositions of CLD.

To identify independent factors associated with increased liver stiffness, we examined these variables in a multivariate logistic regression model. Diabetes, BMI, waist circumference, and presence of HCV RNA demonstrated significant association in the multivariate model (Table 3). Heavy alcohol consumption (>7 drinks per week for women/>14 drinks per week for men) showed a positive association. The lack of association with former binge drinking in both analyses was limited by the small available observations in this group and a large CI.

STRATEGIES TO IDENTIFY INDIVIDUALS WITH ADVANCED LIVER FIBROSIS

VCTE is a noninvasive potentially point-of-care test that can be deployed in an ambulatory setting. But its access remains limited across the country, especially in a primary care setting. We sought to evaluate whether factors associated with increased LSM could be used for risk stratification and to identify at-risk individuals. We identified the following five factors that do not need laboratory tests: age, sex, history of diabetes, other liver risk factors (heavy alcohol consumption, history of hepatitis B or C), and obesity (BMI ≥30). These factors in binary form were associated with LSM ≥9.5 kPa in either univariate or multivariate models (Supporting Table S1). Based on this finding, we devised a laboratory-free SODA-2B score, where sex (male), other liver risk factors, diabetes, and age (≥50 years) each has a score of 1, while BMI ≥30 has a score of 2 (Table 4). When laboratory tests, including a liver function panel, are available, abnormal LFT (score of 1) and FIB-4 ≥2.67 (score of 2) can be used to assist the risk stratification, which gives rise to SODA-2B+LF (Table 4; Supporting Table S1). The SODA-2B and SODA-2B+LF scores had an AUROC of 0.76 (95% CI, 0.73-0.79) and 0.79 (95% CI, 0.76-0.82), respectively, in predicting LSM ≥9.5 kPa, both of which significantly outperformed FIB-4 (Fig. 2).

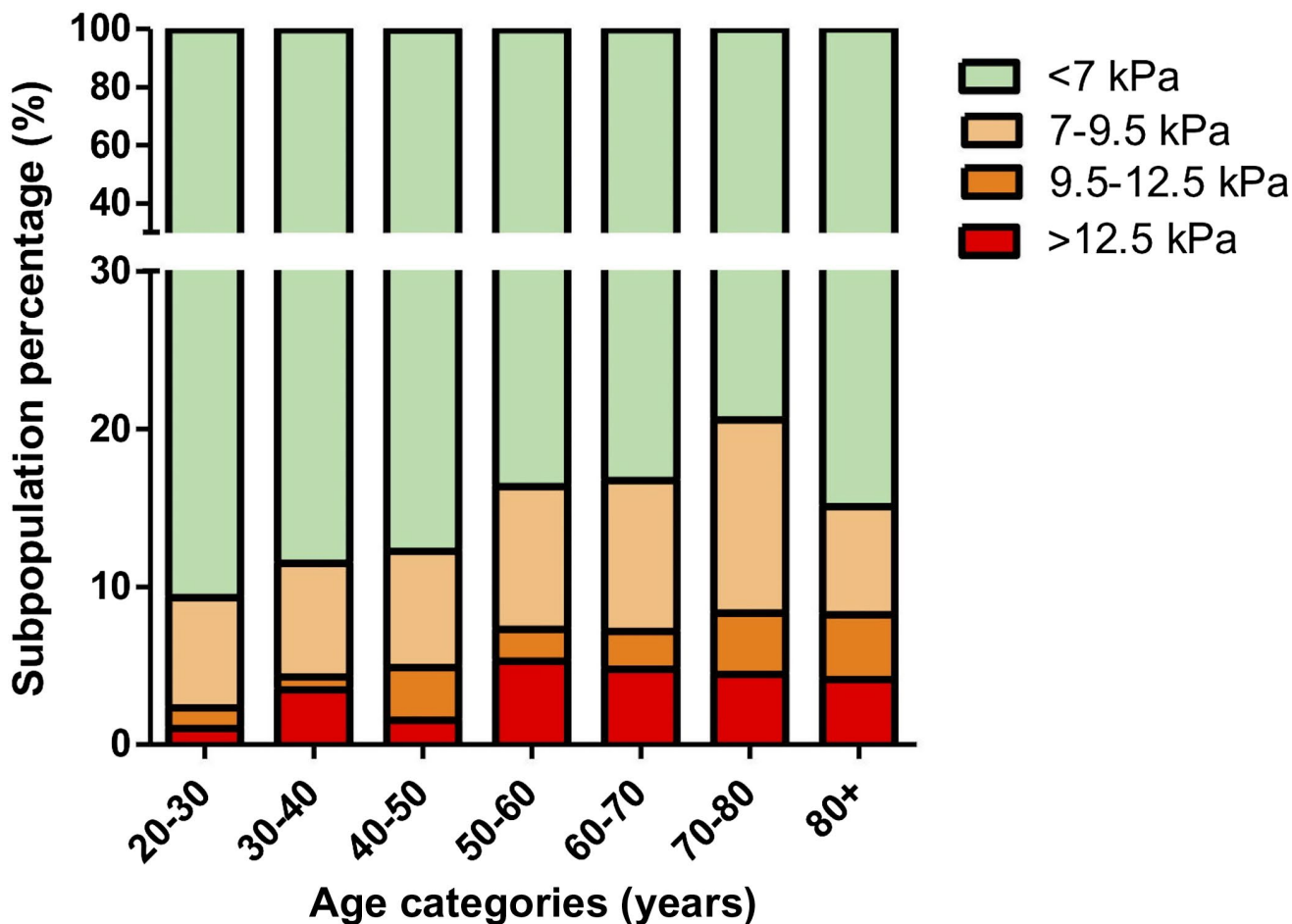


FIG. 1. Prevalence of increased liver stiffness by age. The proportions of the US population with LSM <7.5, 7.5-9.5, 9.5-12.5, and ≥ 12.5 kPa are plotted in each age group from 20 to 80 years and above.

While LFT and FIB-4 have been widely used in the risk stratification of patients with underlying liver disease, their performance in the general population is suboptimal as a screening test to identify LSM ≥ 9.5 (Supporting Table S2). A sex-specific low cutoff of LFT had a sensitivity of 68%, while a low FIB-4 cutoff of 1.0 had a sensitivity of 60% in identifying individuals with LSM ≥ 9.5 kPa. In comparison, a SODA-2B score of 3 and above had a sensitivity of 83.7% and a specificity of 57.9% in identifying LSM ≥ 9.5 kPa. A SODA-2B+LF score by the inclusion of abnormal LFT and FIB-4 ≥ 2.67 resulted in a moderate increase of sensitivity to 87.8% and a specificity of 54.3% (Supporting Table S2).

We tested how the SODA-2B score can be used to risk stratify an estimated 207.8 million US adults and

identify the estimated 11.6 million individuals with LSM ≥ 9.5 kPa, which is concerning for advanced liver fibrosis. If optimized sensitivity was needed, a SODA-2B score of 2 and above could effectively reduce the population needed for screening from 207.8 million to 144.7 million with a negative predictive value of 99.2% (Fig. 3A; Supporting Table S2). When we include abnormal LFT (1 point) and FIB-4 ≥ 2.67 (2 points) in SODA-2B-LF, the negative predictive value increased to 99.3% (Supporting Table S2). A subsequent VCTE test would identify 1 individual suspected of advanced fibrosis among approximately every 13 tested. If the SODA-2B cutoff was increased to 3 and above, the number needed for VCTE in this cost-aware model could decrease by more than one third from 144.7 million to 92.5 million, with a

TABLE 2. BACKGROUND CHARACTERISTICS OF THE US POPULATION BY LSM CATEGORIES

Characteristic	LSM Categories			P Value
	<7 kPa	7-9.5 kPa	≥9.5 kPa	
Observation number	3,797	415	298	
Population estimate*	178.4	17.7	11.6	
Age [†]	47.3 ± 14.7	50.7 ± 15.1	53 ± 13.9	<0.001
Sex				
Male [‡]	84.9 (47.6%)	10.4 (58.4%)	7.2 (61.9%)	0.004
Female	93.5 (52.4%)	7.4 (41.6%)	4.4 (38.1%)	
Race				
White	111.3 (62.4%)	11.1 (63.1%)	7.4 (64.0%)	0.4
Black	19.7 (11.0%)	2.3 (13.3%)	1.2 (10.7%)	
Hispanic	28.1 (15.7%)	2.9 (16.4%)	1.9 (16.1%)	
Asian	11.0 (6.2%)	0.5 (2.6%)	0.5 (3.9%)	
Others	8.4 (4.7%)	0.8 (4.5%)	0.6 (5.3%)	
Annual household income				
<\$20,000	17.9 (10.7%)	1.9 (11.1%)	1.5 (14.3%)	0.01
\$20,000-\$45,999	36.1 (21.6%)	5.5 (32.7%)	2.6 (24.3%)	
\$45,999-\$99,999	64.4 (38.6%)	5.9 (34.9%)	4.3 (40.1%)	
>\$100,000	48.6 (29.1%)	3.6 (21.3%)	2.3 (21.2%)	
Health Insurance				
Medicare	34.6 (19.4%)	4.5 (25.5%)	3.5 (30.2%)	0.001
Safety net insurance	29.4 (16.5%)	3.0 (17.1%)	1.8 (15.6%)	0.9
Military health care	7.3 (4.1%)	0.8 (4.6%)	0.6 (5.8%)	0.5
Government insurance	6.0 (3.3%)	0.5 (3.2%)	0.3 (2.9%)	0.9
Private insurance	104.7 (58.6%)	10.4 (58.8%)	7.7 (66.4%)	0.3
No insurance	0.03 (0%)	0 (0%)	0 (0%)	0.9
Comorbidities				
Diabetes	15.8 (8.2%)	3.8 (20.1%)	4.7 (32.5%)	<0.001
Hypertension	55.0 (29.2)	7.9 (40.7%)	8.5 (56.6%)	<0.001
Hyperlipidemia	59.9 (31.9%)	6.9 (35.2%)	6.5 (43.3%)	0.08
Coronary artery disease	6.1 (3.2%)	0.7 (3.9%)	1.3 (7.3%)	0.05
Stroke	5.1 (2.6%)	0.6 (2.6%)	0.7 (4.9%)	0.1
Congestive heart failure	2.5 (1.4%)	0.4 (2.4%)	0.7 (4.6%)	0.02
Chronic obstructive pulmonary disease	6.9 (3.5%)	1.0 (5.1%)	0.9 (6.4%)	0.1
Alcohol history (drinks/week)				
None	41.1 (23.1%)	4.6 (26.1%)	2.8 (23.7%)	0.5
<7 (women)/<14 (men)	47.1 (26.5%)	4.4 (25.0%)	2.3 (19.8%)	
7+ (women)/14+ (men)	83.7 (47.1%)	8.1 (45.5%)	6.0 (51.9%)	
Former heavy drinker	6.2 (3.4%)	0.6 (3.5%)	0.5 (4.6%)	
Smoking history				
Never smoker	105.4 (59.1%)	9.4 (53.2%)	5.9 (51.2%)	0.1
Past smoker	42.8 (24%)	5.2 (29.4%)	3.5 (30.8%)	
Current smoker	30.1 (16.8%)	3.0 (17.3%)	2.0 (17.9%)	
BMI (kg/m ²)				
<18.5	2.8 (1.6%)	0.2 (0.9%)	0.1 (0.3%)	<0.001
18.5-25	49.4 (27.9%)	2.9 (16.2%)	1.2 (8.8%)	
25-30	60.1 (33.9%)	4.0 (18.9%)	2.0 (13.5%)	
≥30	65.0 (36.6%)	13.1 (64.1%)	12.6 (77.3%)	

TABLE 2. Continued

Characteristic	LSM Categories			P Value
	<7 kPa	7-9.5 kPa	≥9.5 kPa	
Waist circumference (cm)	98 ± 13.1	108.8 ± 15.4	123.1 ± 18.1	<0.001
Laboratory findings				
ALT	17 (13-25)	21 (14-35)	19 (13-31)	0.001
AST	19 (16-23)	20 (16-28)	20 (16-26)	<0.001
ALP	75 (61-91)	76 (64-99)	81 (66-98)	0.3
Total bilirubin	0.4 (0.3-0.6)	0.4 (0.3-0.6)	0.4 (0.3-0.6)	0.4
Gamma-glutamyltransferase	18 (13-27)	24 (17-38)	24 (15-45)	<0.001
Ferritin	90 (42-167)	124 (60-210)	63 (29-140)	<0.001
Creatinine	0.8 (0.7-1.0)	0.9 (0.7-1.0)	0.8 (0.7-1.0)	<0.002
Positive HCV antibody	1.0 (0.5%)	0.2 (1.1%)	0.9 (7.8%)	<0.001
Positive HBsAg	0.4 (0.2%)	0.09 (0.5%)	0.05 (0.4%)	0.2

*All population estimates are shown as millions of individuals.

†Continuous variables reported as mean ± SD if normally distributed and median (IQR) if not normally distributed.

‡Categorical variables reported as population estimate in millions (% of LSM category).

decrease of negative predictive value to 98.0%, which was associated with the misclassification of 1.5 million individuals, representing 6.7% of the true positives (Fig. 3B; Supporting Table S2). In this model, VCTE was expected to identify 1 in every approximately 9 individuals suspected of advanced liver fibrosis. If the SODA-2B score cutoff was increased to 4 and above in a resource-limited scenario, the number needed for VCTE would decrease to 49.6 million while still capturing 6.9 million individuals with LSM ≥9.5 kPa, representing two thirds of the positive cases. In this scenario, 1 in every 7 individuals would test positive for advanced fibrosis by VCTE (Fig. 3C).

Discussion

Transient elastography is a widely used diagnostic test to quantitate the extent of liver fibrosis, a common pathway of CLD that leads to cirrhosis. Herein, we document the first population-wide estimates on the prevalence of elevated liver stiffness in the United States. These data provide much-needed evidence about the extensive burden of hepatic fibrosis in the United States and the feasibility of screening to detect it.

The prevalence of elevated liver stiffness increases with age and plateaus at age 50 years and beyond. Among those 50 years and older, 7.4 million (95%

CI 5.7 -9.2 million), accounting for 7.5%, had LSM ≥9.5 kPa. This observation was similar to that of Long and colleagues⁽⁹⁾ in the Framingham Heart Study and confirms a higher prevalence in the United States compared to some European countries. Interestingly, the prevalence of LSM ≥12.5 kPa, a cutoff indicating cirrhosis, peaked in the 50-60-year age group. This relatively higher burden may highlight both age-based screening efforts as well as the potential for an increased risk of death, resulting in a lower prevalence after this age. The prevalence of high liver stiffness in the population was higher than those with abnormal fasting glucose ≥126 mg/dL, highlighting the need and feasibility of a screening program.

Our study did not find a clear socioeconomic disparity among those with a high LSM compared to their counterparts. Household income and insurance type were largely similar across LSM groups. Conversely, those with a high LSM presented a higher rate of nonhepatic medical comorbidities and were more likely to report poor sleep, disabilities in basic activities of daily living, and poor general health. The reasons behind these associations are likely complex and could be largely driven by nonalcoholic fatty liver disease (NAFLD), the most common form of CLD. This study found higher odds of having LSM ≥9.5 kPa in participants who were diagnosed with

TABLE 3. CHARACTERISTICS ASSOCIATED WITH ELEVATED LIVER STIFFNESS ≥ 9.5 KPA

Characteristic	Univariate	P Value	Multivariate [†]	P Value
	OR (95% CI)*		OR (95% CI)	
Age [‡]	1.2 (1.2-1.3)	<0.001	1.2 (1.1-1.4)	0.08
Sex				
Male	Reference		Reference	
Female	0.6 (0.4-0.9)	0.02	0.6 (0.4-1.1)	0.1
Race				
White	Reference		Reference	
Black	0.9 (0.7-1.3)	0.6	0.8 (0.5-1.2)	0.2
Hispanic	1.0 (0.7-1.4)	0.9	1.5 (0.9-2.6)	0.1
Asian	0.7 (0.4-1.2)	0.1	2.0 (0.9-4.7)	0.09
Others	1.1 (0.5-2.4)	0.7	1.0 (0.4-2.0)	0.8
Comorbidities				
Diabetes	4.5 (2.9-7.2)	<0.001	2.0 (1.3-3.0)	0.004
Hypertension	3.0 (2.0-4.4)	<0.001	1.4 (0.8-2.5)	0.2
Hyperlipidemia	1.6 (1.0-2.6)	0.05	1.1 (0.6-2.0)	0.8
Alcohol history (drinks/week)				
None	1.3 (0.8-2.3)	0.2	1.2 (0.6-2.4)	0.4
<7 (women)/<14 (men)	Reference		Reference	
7+ (women)/14+ (men)	1.5 (0.9-2.3)	0.09	1.7 (1.1-2.5)	0.01
Former heavy drinker	1.8 (0.7-4.3)	0.1	0.7 (0.1-5.2)	0.7
Smoking history				
Never smoker	Reference		Reference	
Past smoker	1.4 (1.0-2.0)	0.04	0.9 (0.6-1.2)	0.3
Current smoker	1.2 (0.6-2.3)	0.5	1.0 (0.6-1.7)	0.9
BMI (kg/m ²)	1.2 (1.1-1.2)	<0.001	1.1 (1.0-1.1)	0.05
Waist circumference (cm)	1.1 (1.1-1.1)	<0.001	1.1 (1.0-1.1)	<0.001
Positive HCV RNA	14.2 (2.7-75.2)	0.004	36.2 (5.3-249.0)	0.001
Positive HBsAg	1.6 (0.4-6.3)	0.4	2.2 (0.5-9.6)	0.2

*Odds ratio calculated by logistic regression for elevated LSM ≥ 9.5 kPa.

[†]Adjusted model included age, sex, race comorbidities, alcohol consumption in the last year, smoking history, BMI, positive HCV RNA, and positive HBsAg.

[‡]Age in 10-year intervals.

diabetes (OR, 4.5; 95% CI, 2.9-7.2) and have higher BMI (OR, 1.2; 95% CI, 1.1-1.2), further supporting this potential etiology. Higher odds were also found in those with hepatic C and heavy drinking as expected associations between etiologies of CLD and LSM. The lack of association with former binge drinkers was potentially limited by a lack of power in this subgroup and a large CI.

This study suggests that if VCTE is to be used as a screening test for a precirrhotic state, its relatively low prevalence in the general public necessitates further refining the target population to a high-risk group to augment its diagnostic effectiveness.

LFT is still widely used as a screening for liver disease but is a poor indicator for increased liver

stiffness in both sensitivity and specificity. FIB-4, a well-studied fibrosis index, does not have a high sensitivity at an even low cutoff of 1.0, despite its significant association with elevated LSM based on the multivariate logistic regression model. We propose an easy to calculate SODA-2B score that does not require laboratory tests and provides superior risk stratification compared to LFT and FIB-4. SODA-2B incorporates age, sex, BMI, and behavioral and medical risk factors, information that should be available to primary care physicians at a physical examination without additional testing. Of note, in this optimized model, 3 out of 6 points are allocated to obesity and diabetes, factors associated with NAFLD. This reflects the additive nature of

TABLE 4. SODA-2B AND SODA-2B-LF SCORES

SODA-2B (0-6)	Sex: 1 point for male, 0 point for female Other liver risk factors: 1 point for any of the following: 2+ drinks per day, history of HBV or HCV Diabetes: 1 point for diagnosis or active treatment Age: 1 point for 50 years or older BMI: 2 points for obesity (BMI \geq 30)
SODA-2B-LF (0-9)	Abnormal LFT: 1 point for any of the following: ALT male \geq 44 U/L, ALT female \geq 32 U/L, AST \geq 40 U/L, or ALP \geq 120 U/L Elevated FIB-4: 2 points for FIB-4 \geq 2.67

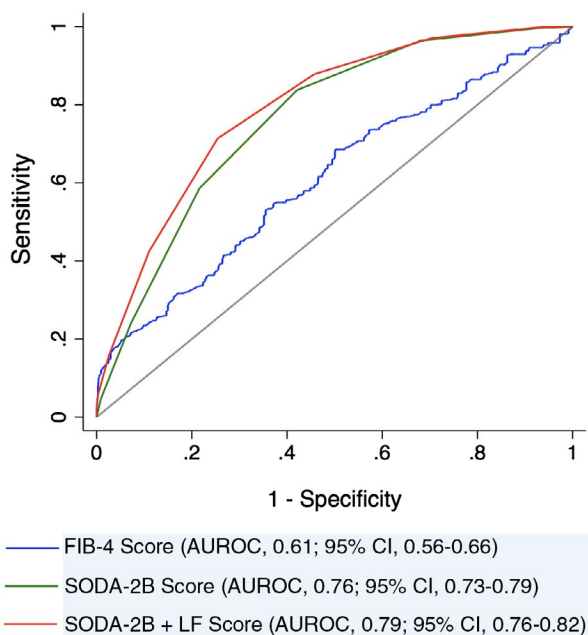


FIG. 2. Comparison of FIB-4, SODA-2B, and SODA-2B+LF in predicting high liver stiffness. ROC curves of FIB-4, SODA-2B, and SODA-2B+LF in predicting LSM \geq 9.5 kPa are compared. The AUROC of each model is shown at the bottom.

these risk factors in predicting a high liver stiffness. When the laboratory tests are available for LFT and FIB-4 score, they can be added to further improve the sensitivity with minimal loss of specificity (Supporting Table S2).

The design of an effective screening strategy has significant medical and economic implications. SODA-2B provides a reasonable tradeoff between sensitivity and positive detection rate by VCTE. Our data suggest that if maximal sensitivity is the goal, a SODA-2B score of 2 and above could capture 96.4% of positive cases at a positive detection rate of one

in 13 VCTEs. In a scenario where costs should be considered, an increase of SODA-2B cutoff to 3 and above can further reduce the number needed for VCTE, with a small loss in sensitivity to 83.7%. A further increase of the SODA-2B cutoff to 4 reduces the number by three fourths, with a higher loss in sensitivity to 58.6% and an increase in specificity from 57.9% to 78.4%. This final model is adjusted for scenarios where VCTE is limited.

Currently, there is no guideline for screening for advanced liver fibrosis in the general population in the United States. The latest guideline on the management of NAFLD by the American Association for the Study of Liver Diseases recommended keeping a high index of suspicion for those at high risk for advanced fibrosis by using clinical decision aids, such as FIB-4 or VCTE.⁽¹⁶⁾ Advanced liver fibrosis is a preclinical condition for cirrhosis, a disease associated with significant impairment to quality of life and risk of mortality.⁽¹⁷⁾ Our study shows that fibrosis is prevalent in the general population. Identifying these patients before the development of liver cirrhosis could allow for potential early interventions. Indeed, studies in North America, Asian, and Europe have shown that screening using transient elastography to identify patients with liver fibrosis before cirrhosis could be cost effective in the long run due to the high cost incurred to manage cirrhosis, its complications, and the loss of quality-adjusted life years.^(6,18) SODA-2B provides a combined risk-based model adjustable to a variety of clinical scenarios based on costs and sensitivity. This adaptability can augment the cost effectiveness of using VCTE as a screening strategy for advanced liver fibrosis. Options for disease-modifying pharmacotherapies and successful behavioral/lifestyle interventions on risk factors for CLD are rapidly evolving and, if successful, would require systematic screening to detect a largely subclinical process.

These data must be understood in the context of the study design. First, elevated LSM is typically but not always caused by advanced liver fibrosis. In NHANES data, only a small proportion of individuals with LSM \geq 9.5 kPa reported a history of congestive heart failure (5%) or chronic obstructive pulmonary disease (6%), conditions that can lead to hepatic congestion and stiffness unrelated to fibrosis (Table 2). We chose 9.5 kPa as the cutoff for advanced liver fibrosis based on the recent technical guideline by the American Gastroenterology Association.⁽¹²⁾ Among various types

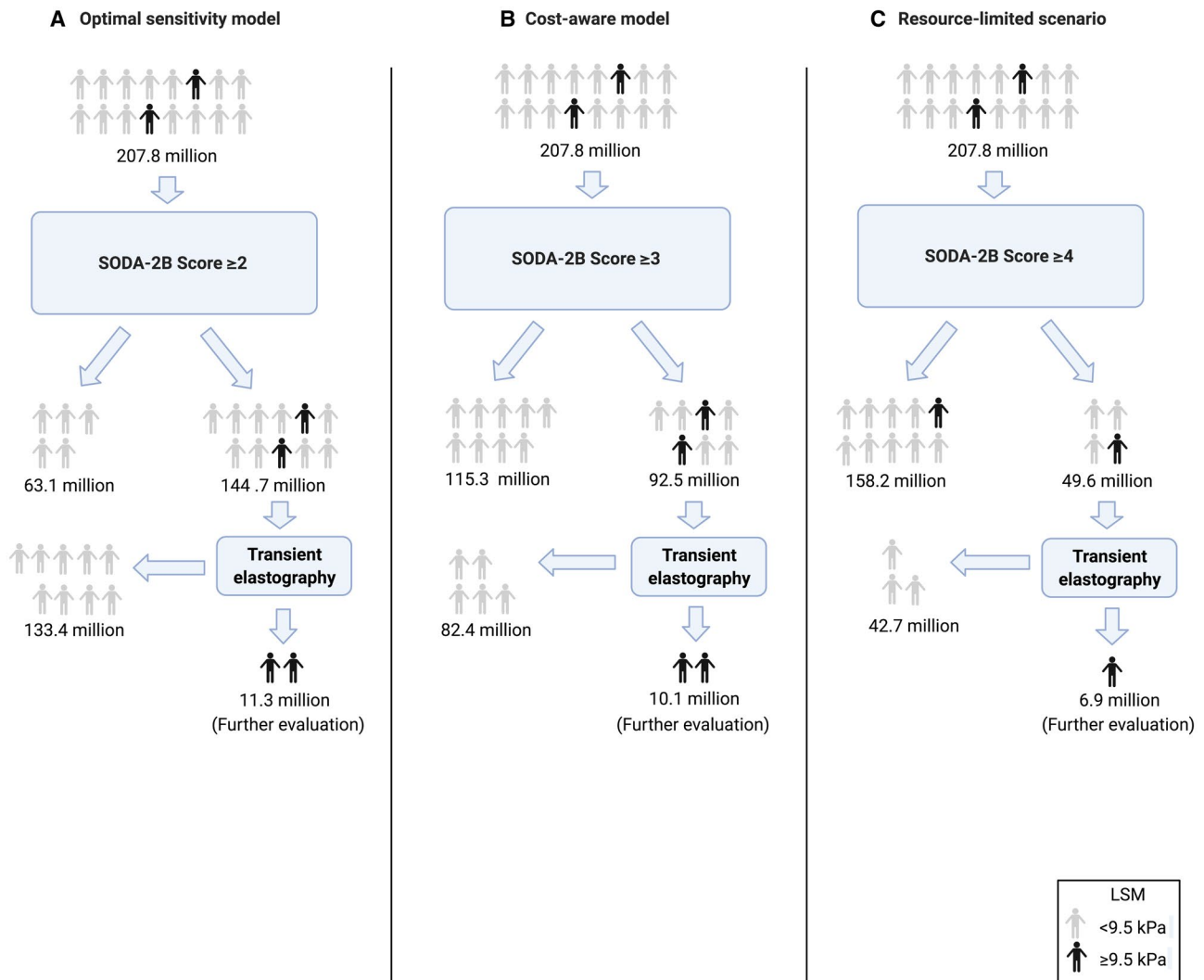


FIG. 3. Proposed screening strategy in different resource settings. Diagrams of three screening strategies and population estimates are shown. (A) Optimal sensitivity model uses SODA-2B score ≥ 2 as prescreening before VCTE. (B) Cost-aware model uses SODA-2B score ≥ 3 before VCTE. (C) Resource-limited model uses SODA-2B score ≥ 4 before VCTE. All population estimates are in millions.

of CLD, the LSM cutoff for stage 3 and above for NAFLD is the least standardized. An adjustment of LSM may change the estimate of the at-risk population but will not significantly alter the efficacy of SODA-2B. Similarly, epidemiologic studies have proposed a liver stiffness cutoff using other technologies, such as magnetic resonance elastography (MRE).⁽¹⁹⁾ Studies are required to calibrate cutoffs using technologies. Second, in a conventional model, the screening of CLDs relies heavily on LFT, a test that is age sensitive and has variable recommended cutoffs.^(12,13,20) The SODA-2B model de-emphasizes the need for

LFT. There is the ability to improve the precision of prediction by adopting an age-adjusted LFT. Third, missing data in NHANES impacts the accuracy of the population size estimates, although there is a lower proportion of missing data among the LSM strata. Those with incomplete VCTE examinations (including high IQR/median) were not captured in the study and could represent a significant at-risk group. These individuals may need further fibrosis evaluation with other modalities, such as MRE. Finally, the conclusions here are extrapolated from 4,510 subjects, using sampling weights in only one iteration of NHANES; the

accuracy of the population estimate would benefit from a continuation of this effort in future NHANES iterations. A larger sample size may allow us to examine the impact of physiological and pathologic states on LSM, such as menopause, bariatric surgery, and congestive heart failure. Future studies should also evaluate the cost effectiveness of VCTE-based fibrosis screening while using SODA-2B as a risk stratification tool.

A large number of US adults have elevated liver stiffness, which is concerning for advanced liver fibrosis. Although most standard risk factors demonstrate poor test characteristics on their own, a SODA-2B score shows improved performance compared to existing strategies to risk stratify individuals with elevated liver stiffness.

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Supporting Information

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