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ORIGINAL ARTICLE

Use of liver stiffness measurement for HCC risk stratification in metabolic dysfunction–associated steatotic liver disease

Binu V. John[1,2] | Dustin R. Bastaich[1,3] | Yangyang Deng[1,4] | Amit G. Singal[5] | Bassam Dahman[1,3,6] | on behalf of the Veterans Analysis of Liver Disease (VALID) group of investigators

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Miami VA Medical System, Miami, Florida, USA

[2]Division of Digestive Health and Liver Diseases, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida, USA

[3]Department of Biostatistics, Virginia Commonwealth University, Richmond, Virginia, USA

[4]Department of Biostatistics, Johns Hopkins University, Baltimore, Maryland, USA

[5]Division of Digestive and Liver Diseases, Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[6]Department of Health Policy, Virginia Commonwealth University, Richmond, Virginia, USA

Correspondence
Binu V. John, University of Miami Miller School of Medicine, Division of Gastroenterology and Hepatology, Department of Medicine, 1201 NW 16th St, Miami VA Health System, Miami, FL 33125, USA.
Email: binu.john@miami.edu

Abstract

Background and Aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) is the fastest-rising cause of HCC. A third of MASLD-HCC occur in the absence of cirrhosis, but tools to predict MASLD-HCC are lacking. Our study aimed to examine whether liver stiffness measurement (LSM) is associated with HCC risk in MASLD, identify if LSM thresholds can predict HCC risk, and identify patients for cost-effective HCC surveillance.

Approach and Results: We conducted a retrospective study of the Veterans Analysis of Liver Disease (VALID) cohort and included patients with MASLD who underwent transient elastography between May 27, 2014, and June 1, 2023. HCC incidence rates were calculated, and we fit multivariable Cox proportional models to study the association of LSM with HCC risk. Among 30,414 participants with MASLD followed over 69,974 person-years (PY), HCC risk increased by 18% with every 5 kPa increase in LSM (subdistribution hazard ratio: 1.18, 95% CI: 1.14–1.21). The annual incidence of HCC per 100 PY was 0.34 (0.24–0.49) with LSM 10–14.9, 0.45 (0.27–0.76) with LSM 15–19.9, 0.78 (0.50–1.20) for LSM 20–24.9, and 0.94 (0.68–1.29) per 100 PY with LSM $\geq$25 kPa. In patients with MASLD without cirrhosis or clinically significant portal hypertension, diabetes, and an LSM of $\geq$10 kPa, annual HCC rates were 0.46 per 100 PY (0.29–0.78), which is above the previously described threshold for cost-effectiveness for HCC surveillance.

Conclusions: LSM is associated with HCC risk in MASLD. HCC surveillance should be considered in noncirrhotic MASLD with diabetes and LSM of $\geq$10 kPa.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AIC, Akaike information criterion; AUDIT-C, alcohol use disorders identification test concise; CSPH, clinically significant portal hypertension; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; PY, person-years; sHR, subdistribution hazard ratio; TE, transient elastography; VALID, Veterans Analysis of Liver Disease; VHA, Veterans Health Administration.

Amit G. Singal and Bassam Dahman are co-senior authors.

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Keywords: cost-benefit analysis, cost-effectiveness analysis, diabetes mellitus, elasticity imaging techniques, HCC, humans, liver neoplasms, NAFLD, portal hypertensionl fibrosis, United States, Veterans

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD) affects ~38% of the population worldwide and is the fastest-rising cause of HCC in the United States.[1–3] Society guidelines recommend HCC surveillance in patients with MASLD cirrhosis, given a sufficient annual HCC risk of 1–1.5 per 100 person-years (PY).[4,5] However, owing to the potential for HCC development in the absence of cirrhosis, and the high prevalence of MASLD in the general population, screening for HCC in noncirrhotic MASLD represents challenges.[6] HCC incidence is much lower in patients with MASLD without cirrhosis, varying from as low as 0.008 per 100 patient-years among US Veterans, to 0.062 per 100 patient-years in a population-based study of residents in Minnesota.[6,7] The American Association for the Study of Liver Diseases (AASLD) guidelines do not recommend surveillance in those with noncirrhotic MASLD, given insufficient annual HCC risk below the 0.4 per 100 PY threshold for cost-effectiveness.[5,8] Experts have identified a critical need to develop risk stratification models/biomarkers in patients with MASLD to predict HCC risk.[6]

Liver stiffness measurement (LSM) using transient elastography (TE) has established its place in clinical practice as a point-of-care test to stratify the risk of portal hypertension and hepatic decompensation. The Baveno VII conference has recommended classifying patients with chronic liver disease (CLD) using LSM on TE.[9] An LSM <10 kPa rules out compensated advanced CLD, while an LSM >25 kPa or LSM >20 kPa with platelet count $<150\times10^9$/mL is consistent with clinically significant portal hypertension (CSPH). Studies have shown a direct association between LSM and composite liver-related outcomes of HCC, decompensation, transplant, and liver-related death.[10,11]

However, there is limited data on the association between HCC risk and LSM in MASLD. Given that HCC risk is higher with greater degrees of fibrosis, LSM offers a potential noninvasive method to predict HCC risk.[12]

Our study aimed to examine whether LSM on TE is associated with the risk of HCC in patients with MASLD. A secondary aim was to examine if a threshold of LSM can be used to predict annual HCC risk >0.4 per 100 PY, to identify patients with noncirrhotic MASLD for HCC surveillance.[8,12]

METHODS

Study design

We conducted a retrospective cohort study using the Veterans Analysis of Liver Disease (VALID) cohort from the Veterans Health Administration (VHA) Corporate Data Warehouse.[13–15] The VA central Institutional review board and research and development committee at the Miami Veterans Affairs medical center approved the study and waived the requirement for informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Inclusion and exclusion criteria

Eligibility criteria included patients aged 18 years or older who underwent a TE for a clinical indication of MASLD between May 27, 2014, and June 1, 2023, from the VALID cohort.[15–17] This cohort included 4.3 million Veterans in the VHA, including 2.5 million Veterans with either an ICD-9 or -10 code for CLD or at least 2 abnormal ALT levels (>40 IU/mL in males and >31 IU/mL in females) 6 months apart. An additional 1.8 million randomly selected individuals were included with no documented CLD and normal liver enzymes but engaged with care in the VHA.[14–16]

Steatotic liver disease was diagnosed with controlled attenuation parameter >288 dB/m on TE, or steatosis on abdominal imaging (ultrasound, CT, or MRI), identified using natural language processing.[12] Patients with alternative etiologies of CLD, including viral hepatitis and other CLD, were excluded. We excluded patients with elevated alcohol use disorders identification test concise (AUDIT-C) scores ≥4 in males and ≥3 in females, or an ICD-9 or -10 criteria for alcohol-associated disorder in the 5 years preceding the TE, to exclude participants with MASLD and increased alcohol intake (MetALD).[1,15] Patients with steatotic liver disease who had at least 1 cardiometabolic risk factor and absence of harmful alcohol use were considered to have MASLD.[1] We defined MASLD (and excluded MetALD) based on their documented absence of alcohol use, and the presence of cardiometabolic risk factors up to 5 years before the development of steatosis. Therefore, we did not consider patients with

their first documented alcohol use after TE to have MetALD.

Duplicate reports and clinical notes that incorporated incomplete elastography findings without documentation of LSM and LSM IQR, TE with <10 documented valid LSM measurements, and those exams with an IQR $>30\%$ were excluded. In addition, we excluded participants for whom LSM was obtained after HCC diagnosis.

Variables

Patient demographics (including age, sex, and self-reported race/ethnicity), and measurements (including body mass index, diabetes mellitus, AUDIT-C score, smoking status, and lab results) were extracted closest to the baseline (date of TE) for all participants. Vibration-controlled TE (FibroScan; Echosens) was used to measure the LSM. Only the first eligible TE study was included among participants with multiple exams.[12] LSM was extracted from the CDW from a national templated note, which lists the variables of interest in a standardized format. In addition, we extracted reports that did not use the national templated note using natural language processing, as described.[12,15] The LSM, measured in kilo Pascals (kPa), was categorized into participants LSM <10, 10–14.9, 15–19.9, 20–24.9, and ≥ 25.[9]

We defined CSPH as an LSM ≥ 25 kPa or an LSM ≥ 20 and a platelet count $<150\times10^9$/L.[9] The diagnosis of cirrhosis was based on ICD-9/10 codes of cirrhosis and/or portal hypertension.

HCC was based on ICD-9 code 155.0 or ICD-10 code C22.0, shown to have a high positive predictive value in the veteran population (Supplemental Table S1, http://links.lww.com/HEP/K244).[18]

Participants were followed up until the development of HCC, liver transplant, death, or the date of data extraction cutoff (June 1, 2023).

Statistical analysis

Descriptive statistics of baseline characteristics were compared using Wilcoxon rank-sum tests to compare the distribution of continuous variables or chi-squared tests for binary and categorical variables. *p* values were calculated using Kruskal-Wallis tests to compare the distributions of continuous variables across the LSM groups, and chi-squared tests to compare the distributions of binary and categorical variables across the groups. Annual HCC rates were calculated.

To evaluate the association of LSM and other demographic and baseline characteristics with the time to develop HCC, we estimated the subdistribution hazard ratios (sHR) by fitting multivariable Cox proportional hazards models using the Fine-Gray method with liver transplantation and death as competing risks, adjusted for the following a priori selected variables that are known to be associated with HCC risk: age,[19] sex,[19] race/ethnicity,[20] body mass index,[21] diabetes mellitus,[21] and smoking status.[22]

We evaluated this association using the continuous LSM (every 5 kPa) in one model and at 5 kPa categorical intervals of LSM in another. We also performed a sensitivity analysis by repeating the above analysis after excluding veterans who developed HCC within 6 months of LSM. In addition, in patients with MASLD without cirrhosis, we performed transformation regression procedures on the models to fit splines of liver stiffness based on increments of 1 kPa to identify patients with HCC risk above the threshold for cost-effective HCC surveillance.

To study HCC risk in patients with MASLD and without cirrhosis, we did a subgroup analysis by excluding patients with ICD-9/10 codes of cirrhosis, portal hypertension, or ascites, those with LSM ≥ 25 kPa by itself, or with LSM >20 kPa and platelet count below 150×10^9/mL. However, if patients with ascites had no other evidence of portal hypertension but had ICD-9/10 codes for intra-abdominal malignancy or heart failure, they were retained. We chose a cutoff of LSM of 20 kPa to identify cirrhosis based on previously published data from a prospective study of patients with LSM and liver biopsies in 1 of 4 randomized controlled trials.[23] In this study, the median LSM of patients with biopsy-proven metabolic dysfunction-associated steatohepatitis with stage 3 fibrosis was 16.6 kPa (IQR: 9.7, 17.3) while the median LS for biopsy-proven cirrhosis was 21.1 (IQR: 14.2, 29.3).

We aimed to identify subgroups with noncirrhotic MASLD who had HCC rates above the threshold for cost-effective HCC surveillance.[8]

We used the variables known to be associated with HCC or identified on the multivariable analysis, namely LSM (<10, 10–14.9, 15–19.9, 20–24.9 kPa, and ≥ 25 kPa), age (<60 and ≥ 60), diabetes, and sex. Because there were few women in several categories of LSM, we calculated combined rates for males and females. We then calculated annual HCC rates (with 95% CI) to identify HCC rates associated with combinations of these risk factors.

RESULTS

Study population

In total, 72,116 participants in the VALID cohort underwent TE for any indication during the study period (Figure 1). Of these, we excluded 33,561 with liver diseases other than MASLD. Of the remaining 38,555 participants, 5729 with missing documentation of LSM

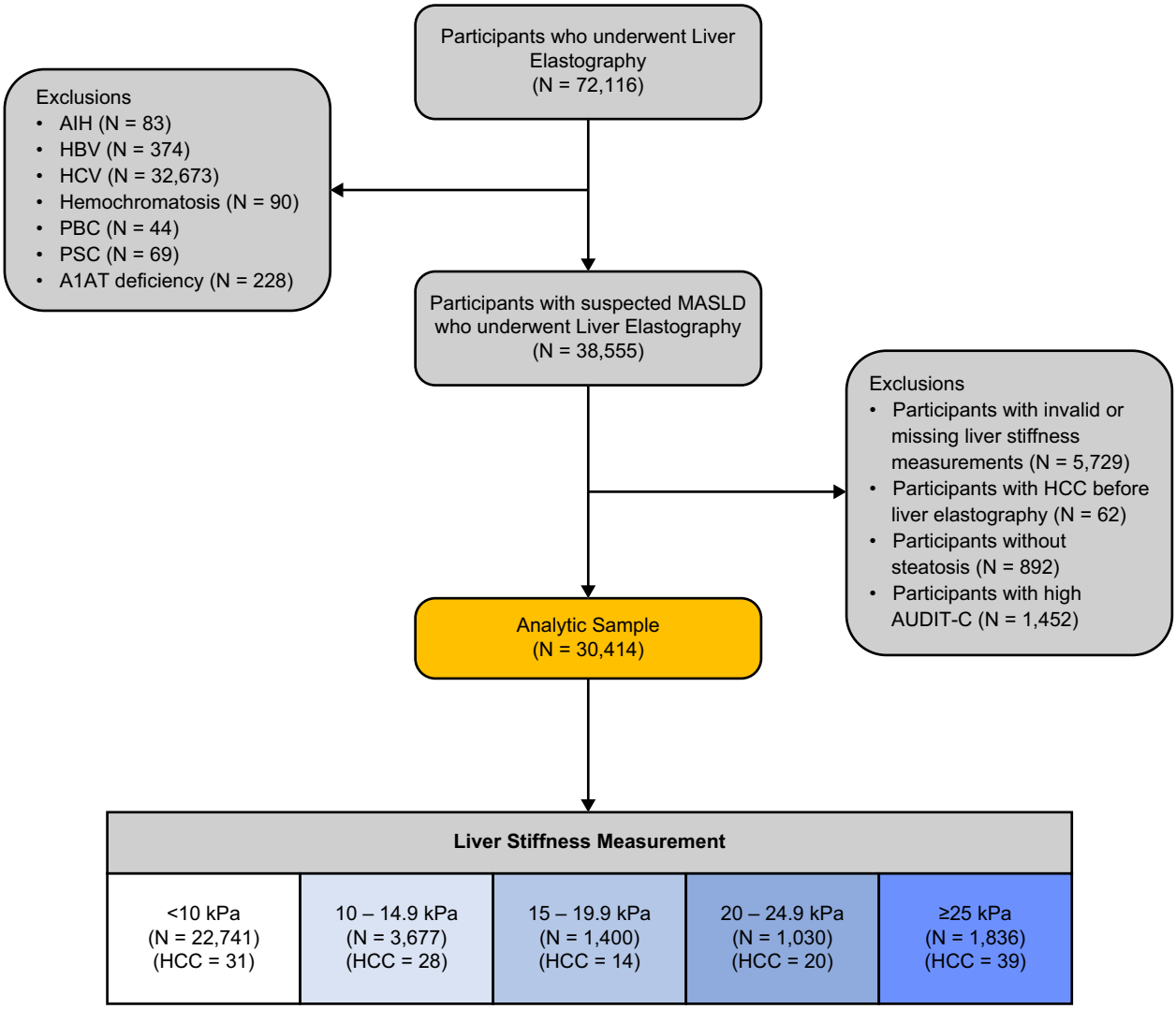

FIGURE 1 Identification of participants with MASLD who underwent liver elastography. Abbreviations: AIH, autoimmune hepatitis; AUDIT-C, alcohol use disorders identification test concise; MASLD, metabolic dysfunction–associated steatotic liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosis cholangitis .

and IQR, IQR $<30\%$, or <10 valid measurements, 62 with HCC before TE, 892 with no steatosis identified on abdominal imaging (using natural language processing) or TE, and 1452 who had an elevated AUDIT-C in the 5 years preceding TE (potential MetALD) were excluded.[17]

Baseline characteristics of included participants

Of the 30,414 remaining eligible participants, the median age was 48.2 years (IQR: 19.1), and 91.6% were male. The sample was racially diverse, including 47.6% non-Hispanic White, 22.2% Hispanic, and 12.4% Black. The median body mass index was 32.1 (IQR: 7.2), with 93.9% being obese or overweight, 24.9% having diabetes mellitus, and 4.3% with cirrhosis (Table 1).

The majority of participants had LSM <10 kPa ($n=22{,}471$); others had LSM 10–14.9 ($n=3677$), 15–19.9 kPa ($n=1400$), 20–24.9 ($n=1030$), and ≥ 25 kPa ($n=1836$).

Comparison of baseline characteristics of Veterans who met the inclusion criteria ($n=30{,}414$), with 465,588 patients with MASLD in the VALID cohort who did not undergo TE, is shown in Supplemental Table S2, http://links.lww.com/HEP/K244. Patients who underwent TE were younger (48.2 vs. 61.2 y), more likely to be Hispanic (22.2% vs. 6.7%), and less likely to be White (47.6% vs. 60.2%), more likely to be diabetic (24.9% vs. 22.9%), obese (65.4% vs. 55.4%), and evaluated by a hepatology provider (68.0% vs. 19.3%). Patients with a high Charlson comorbidity index ≥ 3 were less likely to be referred for TE (36.5% vs. 47.4%).

TABLE 1 Baseline characteristics of participants with MASLD in the analytic sample

Parameters	Total n = 30,414	< 10 kPa n = 22,471	10–14.9 kPa n = 3677	15–19.9 kPa n = 1400	20–24.9 kPa n = 1030	≥ 25 kPa n = 1836	*p*
Sex, N (%)							***< 0.0001***
Male	27,872	20,441 (91)	3425 (93.2)	1307 (93.4)	967 (93.9)	1732 (94.3)	
Female	2542	2030 (9.0)	252 (6.9)	93 (6.6)	63 (6.1)	104 (5.7)	
Age, median (IQR)	48.2 (19.1)	46.7 (20.1)	51.0 (17.8)	52.2 (17.1)	52.3 (15.6)	53.3 (15.0)	***< 0.0001***
Race/ethnicity, N (%)							***< 0.0001***
White	14,489	10,210 (45.4)	1914 (52.1)	744 (53.1)	559 (54.3)	1062 (57.8)	
Black	3785	3146 (14.0)	329 (9.0)	102 (7.3)	78 (7.6)	130 (7.1)	
Hispanic/Latino	6756	5124 (22.8)	765 (20.8)	306 (21.9)	219 (21.3)	342 (18.6)	
Other/Unknown	5384	3991 (17.8)	669 (18.2)	248 (17.7)	174 (16.9)	302 (16.5)	
BMI, median (IQR)	32.1 (7.2)	31.6 (6.8)	33.5 (7.7)	33.6 (8.0)	34.1 (8.9)	33.3 (8.4)	***< 0.0001***
BMI class, N (%)							***< 0.0001***
Normal/underweight (≤ 24.9)	1808	1391 (6.2)	176 (4.8)	76 (5.4)	54 (5.2)	111 (6.1)	
Overweight (25–29.9)	8722	7069 (31.5)	756 (20.6)	280 (20.0)	202 (19.6)	415 (22.6)	
Obese (≥ 30)	19,884	14,011 (62.4)	2745 (74.7)	1044 (74.6)	774 (75.2)	1310 (71.4)	
Diabetes, N (%)	7577	4634 (20.6)	1201 (32.7)	526 (37.6)	432 (41.9)	784 (42.7)	***< 0.0001***
Current/former Smoker, N (%)	15,173	10,923 (48.6)	1921 (52.2)	757 (54.1)	554 (53.8)	1018 (55.5)	***< 0.0001***
Cirrhosis, N (%)	1302	126 (0.6)	209 (5.7)	256 (18.3)	216 (21.0)	495 (27.0)	***< 0.0001***
Time from elastography to HCC in years, median (IQR)	1.0 (2.1)	0.6 (1.4)	1.0 (1.7)	0.5 (2.8)	1.0 (1.9)	1.3 (2.1)	*0.2839*
Time from elastography to HCC, death, or end of the study, in years, median (IQR)	1.9 (2.5)	1.9 (2.4)	1.8 (2.4)	1.7 (2.4)	2.1 (2.7)	1.8 (2.4)	***< 0.0001***
Elastography parameters, median (IQR)							
LSM	6.7 (5.2)	5.8 (2.5)	11.9 (2.3)	17.1 (2.4)	22.3 (2.0)	37.3 (27.8)	***< 0.0001***
LSM IQR	1.1 (1.8)	0.9 (0.9)	2.0 (1.5)	3.0 (2.3)	3.8 (3.0)	6.6 (6.1)	***< 0.0001***
LSM IQR percentage (%)	14 (10)	14 (10)	15 (10)	16 (12)	17 (11)	17 (14)	***< 0.0001***
CAP score	317 (87)	310 (86)	337.5 (74)	339.5 (80)	341 (95)	330 (102)	***< 0.0001***
Diagnosis of steatosis, N (%)							
CAP score ≥ 288 dB/m	17,442	12,345 (54.9)	2463 (67.0)	950 (67.9)	604 (58.6)	1080 (58.8)	***< 0.0001***
Steatosis on imaging	14,994	10,333 (46.0)	1214 (33.0)	450 (32.1)	426 (41.4)	756 (41.2)	***< 0.0001***
Cardiometabolic criteria, N (%)							
Hypertension	18,199	12,783 (56.9)	2463 (67.0)	983 (70.2)	723 (70.2)	1247 (67.9)	***< 0.0001***
Hypertriglyceridemia	11,580	8041 (35.8)	1615 (43.9)	671 (47.9)	476 (46.2)	777 (42.3)	***< 0.0001***
Low HDL	11,065	7497 (33.4)	1575 (42.8)	648 (46.3)	503 (48.8)	842 (45.9)	***< 0.0001***

Lab results at time of elastography, median (IQR)						
ALT (IU/mL)	42.0 (42.0)	40.0 (40.0)	50.0 (48.0)	51.0 (47.0)	46.0 (45.0)	45.0 (42.0)	***<0.0001***
AST (IU/mL)	31.0 (24.0)	29.0 (20.0)	37.0 (30.0)	41.0 (32.0)	40.0 (32.0)	46.0 (37.0)	***<0.0001***
Platelet count ($\times 10^9$/L)	215.0 (88.0)	223.0 (84.0)	202.0 (85.0)	187.0 (86.0)	181.0 (87.0)	161.0 (92.0)	***<0.0001***
Creatinine (mg/dL)	1.0 (0.3)	1.0 (0.3)	1.0 (0.3)	1.0 (0.4)	1.0 (0.4)	1.0 (0.4)	***<0.0001***
Total bilirubin (mg/dL)	0.6 (0.4)	0.6 (0.5)	0.6 (0.4)	0.7 (0.4)	0.7 (0.4)	0.8 (0.6)	***<0.0001***

Note: Other race included Asian, Native American/Alaska Native, Native Hawaiian, Pacific Islander, and 2 or more races. Statistical method/test applied: chi-square test (categorical variables); Wilcoxon median test (continuous variables). Values in bold denote statistical significance ($p < 0.05$).
Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease.

HCC incidence rates in patients with MASLD, stratified by LSM

Over a total follow-up of 69,963.8 PY, 132 patients developed HCC. The median time from baseline to HCC diagnosis was 1.0 years (IQR: 2.1).

The annual HCC incidence rate was 0.06 per 100 PY (95% CI: 0.04–0.08) among 22,471 participants with LSM < 10 kPa, 0.34 (95% CI: 0.24–0.49) with LSM 10–14.9, 0.45 (95% CI: 0.27–0.76) with LSM 15–19.9, 0.78 (95% CI: 0.50–1.20) for LSM 20–24.9, and 0.94 (95% CI: 0.69–1.29) per 100 PY with LSM ≥ 25 kPa (Table 2).

Association of LSM and HCC in MASLD

On multivariable analysis using the continuous LSM, with liver transplantation and death as a competing risk, the likelihood of HCC in patients with MASLD (including those with and without cirrhosis) was 18% higher with every 5 kPa increase in LSM (sHR: 1.18, 95% CI: 1.14–1.21, $p < 0.0001$). Other factors associated with HCC included older age and diabetes mellitus. Males had an increased HCC risk, but the association was not statistically significant (Table 3).

Compared with the reference group with LSM < 10 kPa, the sHR of HCC was 4.31 (95% CI: 2.56–7.25) for LSM 10–14.9; 5.26 (95% CI: 2.77–9.96) for patients with LSM 15–19.9, 8.56 (95% CI: 4.73–15.50) for LSM ≥ 20–24.9 kPa, and 9.98 (95% CI: 6.06–16.42) for LSM ≥ 25 kPa (Table 3 and Figure 2). In addition, age (sHR: 1.70, 95% CI: 1.43–2.03) and diabetes mellitus (sHR: 2.80, 95% CI: 1.95–4.00) were associated with an increased risk of HCC, while male sex trended toward an increased risk but was not statistically significant (sHR: 2.05, 95% C:I 0.65–6.45, Table 3).

Sensitivity analysis—HCC incidence rates in patients with MASLD excluding HCC within 6 months of baseline

In a sensitivity analysis, excluding participants who developed HCC or died within 6 months of TE, annual rates of HCC increased with higher LSM (Supplemental Table S3, http://links.lww.com/HEP/K244) from 0.03 per 100 PY (95% CI: 0.02–0.05) among participants with LSM < 10 kPa, 0.26 (0.17–0.39) with LSM 10–14.9, 0.23 (0.11–0.47) with LSM 15–19.9, 0.51 (0.29–0.87) with LSM 20–24.9, and 0.70 (95% CI 0.49–1.01) per 100 PY with LSM ≥ 25 kPa, respectively (Supplemental Table S3, http://links.lww.com/HEP/K244). The likelihood of HCC in patients with MASLD was 20% higher with every 5 kPa increase in LSM (sHR: 1.20, 95% CI: 1.16–1.24; Supplemental Table S4, http://links.lww.com/HEP/K244) after adjusting for the same variables as the primary analysis.

TABLE 2 Incidence rates of HCC by liver stiffness measurement in participants with MASLD, including those with and without cirrhosis, with liver transplantation as a competing risk

Event	# patients	Person-years	# event (%)	HCC per 100 PY
Total	30,414	69,963.84	132 (0.43)	—
Liver stiffness, kPa				
<10	22,471	51,904.39	31 (0.14)	0.06 (0.04, 0.08)
10–14.9	3677	8226.22	28 (0.76)	0.34 (0.24, 0.49)
15–19.9	1400	3111.73	14 (1.00)	0.45 (0.27, 0.76)
20–24.9	1030	2574.96	20 (1.94)	0.78 (0.50, 1.20)
≥25	1836	4146.54	39 (2.12)	0.94 (0.69, 1.29)

Abbreviation: MASLD, metabolic dysfunction–associated steatotic liver disease.

TABLE 3 Risk of liver cancer by categories of liver stiffness measurement among participants with MASLD, including those with and without cirrhosis

	Categorical LSM		Continuous LSM	
Parameters	**sHR (95% CI)**	***p***	**sHR (95% CI)**	***p***
Number of patients	30,414		30,414	
Number of liver cancer cases	132		132	
LSM continuous	—	—	1.18 (1.14, 1.21)	***<0.0001***
LSM category, kPa				
<10	Reference		—	—
10–14.9	4.31 (2.56, 7.25)	***<0.0001***	—	—
15–19.9	5.26 (2.77, 9.96)	***<0.0001***	—	—
20–24.9	8.56 (4.73, 15.50)	***<0.0001***	—	—
≥25	9.98 (6.06, 16.42)	***<0.0001***		
Age at elastography	1.70 (1.43, 2.03)	***<0.0001***	1.76 (1.49, 2.09)	***<0.0001***
Sex				
Female	Reference		Reference	
Male	2.05 (0.65, 6.45)	0.2206	2.16 (0.69, 6.81)	*0.1877*
Race/ethnicity				
White	Reference		Reference	
Black	0.81 (0.40, 1.61)	*0.5385*	0.66 (0.33, 1.31)	*0.2380*
Hispanic/Latino	0.99 (0.63, 1.58)	*0.9774*	0.99 (0.62, 1.57)	*0.9510*
Other/Unknown	1.34 (0.86, 2.10)	*0.2003*	1.37 (0.87, 2.15)	*0.1763*
BMI				
Normal underweight (≤24.9)	Reference		Reference	
Overweight (25–29.9)	0.68 (0.36, 1.28)	*0.2337*	0.65 (0.35, 1.22)	*0.1777*
Obese (≥30)	0.51 (0.28, 0.92)	***0.0266***	0.56 (0.31, 1.03)	*0.0615*
Diabetes				
No	Reference		Reference	
Yes	2.80 (1.95, 4.00)	***<0.0001***	3.35 (2.33, 4.82)	***<0.0001***
Current/former smoker				
No	Reference		Reference	
Yes	1.22 (0.87, 1.73)	*0.3267*	1.22 (0.86, 1.72)	*0.2725*
AIC	***2354.48***		***2410.65***	

Bold and italicized values are statistical significance $p < 0.05$.
Abbreviations: AIC, Akaike information criterion; BMI, body mass index; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; sHR, subdistribution hazard ratio.

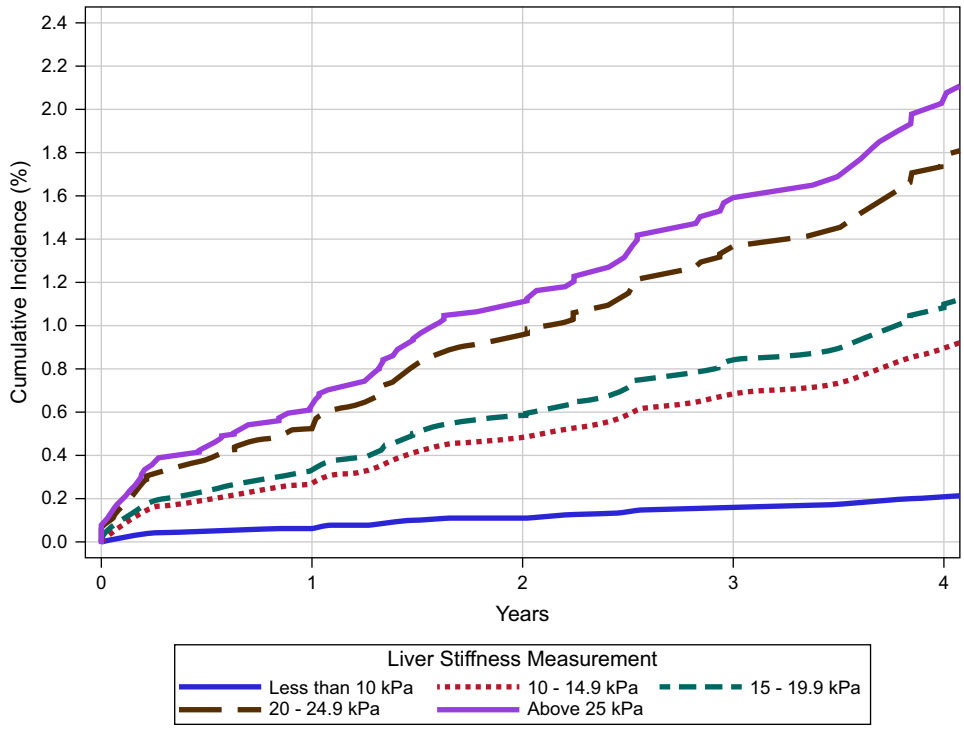

FIGURE 2 Cumulative incidence rate of HCC in patients with MASLD by categories of liver stiffness measurement (Fine-Gray method). Abbreviation: MASLD, metabolic dysfunction–associated steatotic liver disease.

When examining HCC incidence by LSM categories, compared with the reference group with LSM < 10 kPa, the sHR of HCC was 6.21 (95% CI: 3.25–11.87) for LSM 10–14.9; 5.14 (95% CI: 2.14–12.37) for LSM 15–19.9, 10.39 (95% CI: 4.91–22.02) for patients with LSM 20–24.9, and 14.52 (95% CI: 7.75–27.20) for LSM ≥ 25 kPa excluding participants who developed HCC within 6 months of LSM (Supplemental Table S4, http://links.lww.com/HEP/K244).

LSM cutoffs for cost-effective HCC surveillance in patients with noncirrhotic MASLD

Over a total follow-up of 66,574.31 PY, 83 patients without an established diagnosis of cirrhosis developed HCC. The annual rates of HCC increased with higher LSM levels and was 0.06 per 100 PY (95% CI: 0.04–0.09) among patients with LSM < 10 kPa and were 0.29 (0.19–0.43), 0.16 (95% CI: 0.06–0.43), 0.45 (95% CI: 0.23–0.87), and 0.61 (95% CI: 0.38–0.99) per 100 PY with increasing LSM categories (10–14.9, 5–19.9, 20–24.9, and ≥ 25 kPa, respectively; Supplemental Table S5, http://links.lww.com/HEP/K244).

We defined LSM thresholds that correspond to HCC incidence rates at which HCC surveillance in patients without a prior diagnosis of cirrhosis would be cost-effective. LSM ≥ 19.2 kPa corresponded to an annual incidence rate ≥ 0.4 per 100 PY (Figure 3), and LSM ≥ 24.4 kPa (95% CI: 19.6–31.3) corresponded to an HCC incidence rate ≥ 1.0 per 100 PY.

Subgroups of patients with MASLD without cirrhosis or CSPH for cost-effective HCC surveillance

We applied a more stringent definition of cirrhosis and CSPH to identify subgroups with noncirrhotic MASLD for cost-effective HCC surveillance, by restricting this analysis to patients without cirrhosis or CSPH or TE. We examined if the variables chosen a priori as predictors of HCC risk, namely LSM (< 10, 10–14.9, 15–19.9 and 20–24.9 kPa), age (< 60 and ≥ 60), diabetes, and sex, can be used to identify patients with noncirrhotic MASLD requiring surveillance. Our findings indicate that patients with noncirrhotic MASLD with diabetes and an LSM of ≥ 10 kPa had annual HCC rates of 0.46 per 100 PY (95% CI: 0.29–0.78), which is above the previously described threshold for cost-effectiveness (Table 4 and Figure 4). The annual rates were 0.48 per 100 PY (95% CI: 0.29–0.78) for males with diabetes and LSM ≥ 10 kPa, but nonestimable for females with diabetes and LSM ≥ 10 kPa due to low events. Within this group of male patients with noncirrhotic MASLD, diabetes, and LSM ≥ 10 kPa, patients with age < 60 (HCC rates 0.44 per 100 PY, 95% CI: 0.25–0.78) and age > 60 years (HCC rates 0.49 per

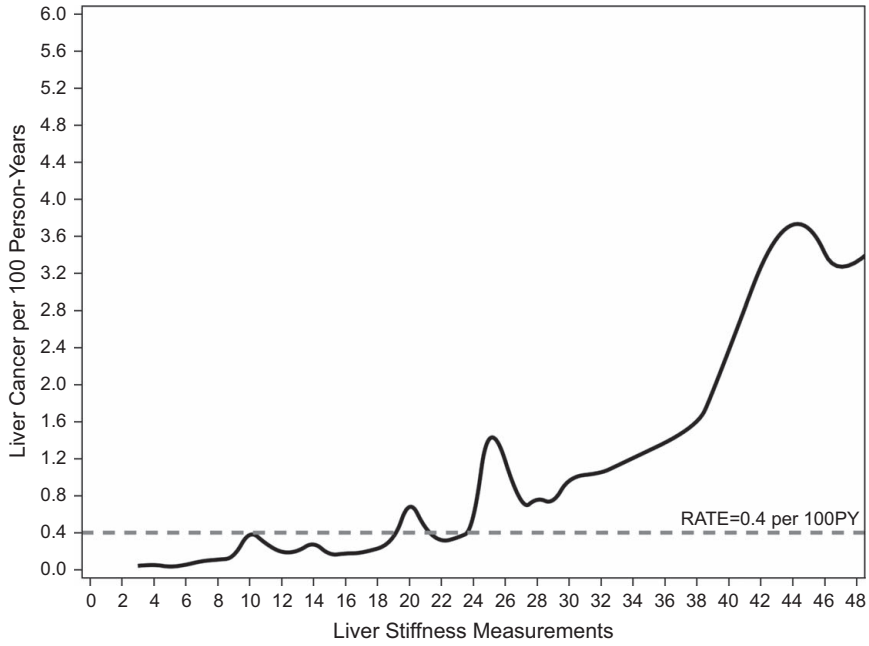

FIGURE 3 Splines created using transformation regression procedures showing rates of HCC (per 100 person-years) per increments of 1 kPa in liver stiffness measurement, among veterans with MASLD without cirrhosis. Abbreviation: MASLD, metabolic dysfunction–associated steatotic liver disease.

100 PY, 95% CI: 0.18–1.31) had HCC rates above the threshold for cost-effective surveillance. However, among patients with noncirrhotic MASLD without diabetes, annual HCC rates were <0.4 per 100 PY in all groups, regardless of sex or LSM.

HCC incidence rates in patients with MASLD, stratified by fibrosis-4 scores

Of 30,288 participants with available Fib-4 over a total follow-up of 69,635.5 PY, 131 patients developed HCC

TABLE 4 Identification of subgroups of patients with MASLD without cirrhosis or clinically significant portal hypertension with annual rates of HCC that meet the cost-effectiveness threshold for surveillance

Parameter	# patients	HCC per 100 PY
Total	26,872	0.09 (0.07, 0.11)
Categories		
LSM ≥ 10 and diabetes	1433	0.46 (0.28, 0.74)
Subcategories		
LSM ≥ 10 and diabetes male	1353	0.48 (0.29, 0.78)
LSM ≥ 10 and diabetes female	80	NE
LSM ≥ 1, diabetes, and age <60 y	1110	0.44 (0.25, 0.78)
LSM ≥ 10, diabetes, and age >60 y	323	0.49 (0.18, 1.31)
LSM: <10, male, age <60, and diabetes	3370	0.09 (0.04, 0.18)
LSM: <10, male, age <60, and no diabetes	13,588	0.03 (0.02, 0.06)
LSM: <10, male, age ≥ 60, and diabetes	875	0.32 (0.15, 0.66)
LSM: <10, male, age ≥ 60, and no diabetes	2492	0.14 (0.07, 0.28)
LSM: 10–14.9, male, age <60, and diabetes	795	0.52 (0.28, 0.98)
LSM: 10–14.9, male, age <60, and no diabetes	1731	0.11 (0.04, 0.29)
LSM: 10–14.9, male, age ≥ 60, and diabetes	241	0.67 (0.25, 1.79)
LSM: 10–14.9, male, age ≥ 60, and no diabetes	458	0.39 (0.15, 1.04)
LSM: 20–24.9, male, age <60, and diabetes	110	0.61 (0.15, 2.43)
LSM: 20–24.9, male, age <60, and no diabetes	188	NE

Note: Other subcategories with no occurrence of HCC are excluded from this table.
Abbreviations: LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease.

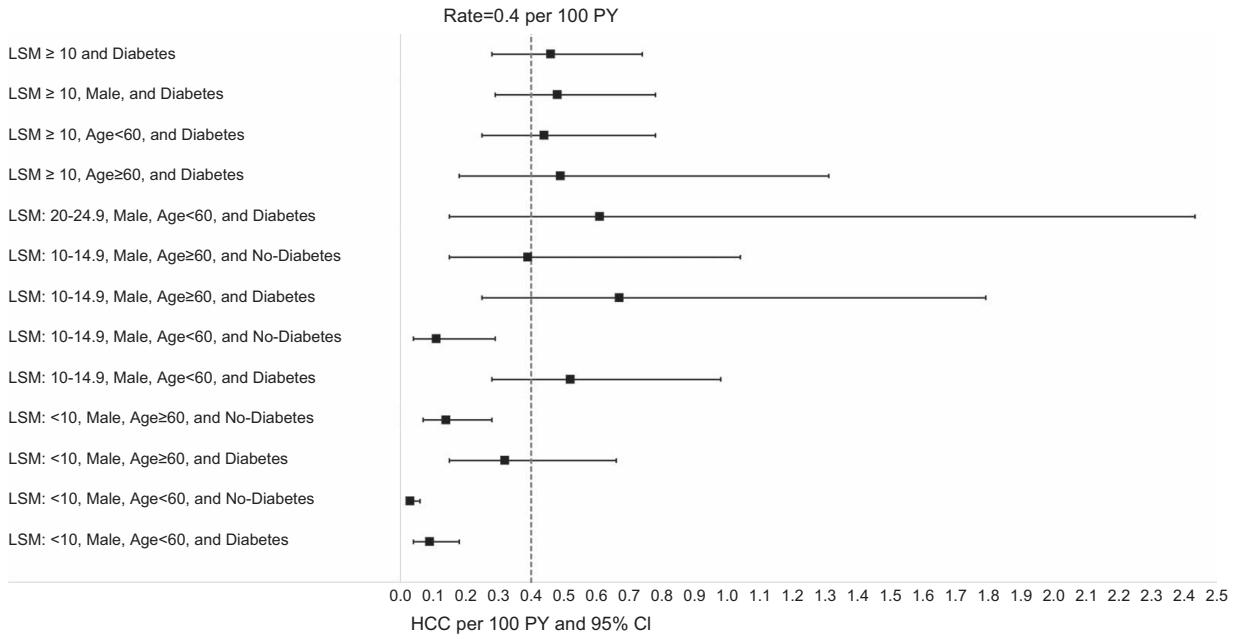

FIGURE 4 Annual HCC rates of subgroups of patients with MASLD without cirrhosis or clinically significant portal hypertension. Abbreviation: MASLD, metabolic dysfunction–associated steatotic liver disease.

(Supplemental Table S6, http://links.lww.com/HEP/K244). The annual HCC incidence rate was 0.08 per 100 PY (95% CI: 0.06–0.11) among 19,125 participants with low Fib-4 (defined as Fib-4 <1.3 for patients <65 y and <2.0 for age ≥ 65), 0.21 (95% CI: 0.16–0.29) with low intermediate cutoff (Fib-4 above low cutoff and up to 2.67), 0.68 (95% CI: 0.43–1.10) for patients with high intermediate cutoff (Fib-4 2.67–3.25), and 1.01 (95% CI: 0.73–1.39) per 100 PY for patients with Fib-4 ≥ 3.25.

Combining fibrosis-4 and LSM as a 2-step stratification to estimate HCC incidence rates

We examined a 2-step stratification by first excluding patients with a low Fib-4, and then using LSM to stratify HCC risk (Supplemental Table S7, http://links.lww.com/HEP/K244). In this analysis, we first excluded patients with low Fib-4 (<1.3 for patients <65 y, <2.0 for patients ≥ 65 y). These data showed that after excluding patients with a low Fib-4, an LSM of 10–14 kPa was associated with an HCC rate of 0.44 (95% CI: 0.28–0.70), an LSM of 15–19.9 kPa with an HCC rate of 0.69 (95% CI: 0.40–1.19), 20–24.9 kPa with an HCC rate of 1.07 (95% CI: 0.68, 1.70), and an LSM >25 kPa with an HCC rate of 0.99 (0.70, 1.40), all above the threshold of 0.4 per 100 PY for cost-effective HCC surveillance. This is in contrast to when patients with low Fib-4 were retained, HCC rates were above 0.4 per 100 PY only among patients with an LSM of 15–19.9 kPa or greater (Table 2).

Comparison of model performance of clinical, Fib-4, and LSM-based models

To assess if the addition of LSM improved the model, we compared the Akaike information criterion (AIC) of the models with and without LSM. A model examining the relationship of LSM with HCC without any clinical variables had an AIC of 2558.93, while one that included clinical variables without LSM improved the AIC to 2455.72. Combining LSM categories with clinical variables significantly improved the AIC to 2354.48 (Likelihood ratio test $p<0.0001$).

Among patients who had LSM and Fib-4 available, the AIC of the model with clinical variables and Fib-4 was 2393.8. A model with clinical variables and LSM improved the AIC to 2339.4, while adding both Fib-4 and LSM to clinical variables produced the best performing model (AIC = 2,332.4, $p=0.007$).

DISCUSSION

HCC surveillance represents a major challenge in patients with MASLD due to the well-recognized occurrence of HCC in the absence of cirrhosis. MASLD HCC is associated with a more advanced tumor stage at diagnosis and a lower possibility of receiving a liver transplant.[24] Our data indicate a linear association between HCC incidence and LSM in patients with MASLD. Among patients with noncirrhotic MASLD without CSPH, LSM was able to help identify a subgroup of patients with HCC incidence rates above the threshold

for cost-effectiveness for surveillance—patients with diabetes and LSM ≥ 10.

These findings meet a critical need identified by many groups for the identification of patients with noncirrhotic MASLD who would benefit from HCC surveillance.[5,6] Prior studies have shown that non-Hispanic White individuals have the lowest HCC rates, whereas American Indian/Alaska native populations have the highest rates.[25] However, studies in MASLD without cirrhosis that examined clinical risk factors, including age, sex, race/ethnicity, and diabetes, among others, were unsuccessful in identifying a subgroup with high HCC risk. We believe that the addition of a noninvasive surrogate for fibrosis, namely LSM, improves the ability to risk-stratify patients better.

We identified that among patients in the entire cohort without an established diagnosis of cirrhosis, an LSM of 19.2 kPa corresponded to an HCC rate above 0.4 per 100 PY and an LSM ≥ 24.4 kPa to an HCC rate above 1.0 per 100 PY.

A prospective study of patients with MASLD with LSM and liver biopsies in 1 of 4 randomized controlled trials revealed that the median LSM of patients with biopsy-proven metabolic dysfunction-associated steatohepatitis with stage 3 fibrosis was 16.6 kPa (IQR: 9.7, 17.3) while the median LS for biopsy-proven cirrhosis was 21.1 (IQR: 14.2, 29.3).[23] Therefore, many patients with LSM above 19.2 kPa, and particularly above 24.4 kPa may have cirrhosis. However, these patients did not have a documented diagnosis of cirrhosis using imaging, laboratory tests, or liver biopsy criteria. Therefore, the use of LSM is helpful to predict HCC in these patients who did not otherwise have a diagnosis of cirrhosis and may not have otherwise undergone HCC surveillance.

LSM is a useful method for identifying patients requiring HCC surveillance because it is noninvasive, provides immediate results, and is already used in clinical practice among patients with MASLD.[23] Although LSM appears to be an important predictor of HCC in MASLD, and may reflect both underlying inflammation and fibrosis, future identification of molecular, genetic and/or biomarkers of inflammation may likely complement LSM and improve ways to personalize HCC surveillance in MASLD.[26]

Our studies corroborate others, who have described an association between LSM and HCC risk in MASLD.[27–30] In a study of 3133 participants with MASLD, investigators observed that LS ≥ 9.3 kPa was associated with HCC, but only 22 cases of HCC were observed.[27] In a study of 1039 patients with NAFLD with a histologic diagnosis of F3-F4 fibrosis and/or LSM > 10 kPa, baseline LSM was independently associated with HCC (HR: 1.03, 95% CI: 1.00–1.04).[29] Since participants with LSM < 10 kPa or biopsy-proven cirrhosis were excluded, the study was unable to estimate HCC risk in MASLD without compensated advanced CLD.

Our findings are also consistent with a recent paper by Lai et al,[30] who also described increasing HCC rates with LSM.[30] However, we identify a subgroup of patients without cirrhosis who would be eligible for HCC surveillance based on LSM cutoffs, which was not an aim of the paper by Lai et al.[30] We find similar associations of HCC rates with increments of Fib-4 as described by Lai et al. When using a 2-step approach, the use of LSM after excluding patients with a low Fib-4 appears to be helpful in identifying a lower LSM threshold of patients above 10–14.9 kPa for surveillance.

The data presented herein have relative strengths. Because the annual rate of HCC in MASLD without cirrhosis is low, studies exploring the association of LSM with HCC require sample sizes in the several thousands, and our cohort was adequately powered. Prior studies of HCC risk in noncirrhotic MASLD were limited to patients who underwent liver biopsy derived from tertiary referral centers, while this population-based cohort of Veterans with MASLD was identified without a tertiary center bias. Third, we included only patients who met the recently defined MASLD criteria with steatosis and cardiometabolic risk factors, which allows HCC risk stratification using the contemporary definition of MASLD.

Because of its retrospective nature, the study may have been affected by residual confounding due to unobserved differences, as well as potential selection bias in participants who were included in the study. Patients who underwent TE were younger, more likely to be Hispanic, obese, and diabetic, but these reflect real-world practice. Second, the Veteran cohort is predominantly male and has a higher prevalence of diabetes and obesity. Although over 2500 women were included in the cohort, most had low LSM values < 10 kPa. Therefore, further studies are needed in women with higher fibrosis levels to see if subgroups can be identified who would benefit from HCC surveillance. Third, survivor bias is a potential limitation since only participants who underwent LE and survived to develop HCC were included. However, the median time from LE to HCC was only 1 year because we included only the most recent TE for patients who had multiple exams, and deaths in the first year following TE were uncommon. Fourth, we acknowledge the short follow-up time from TE to HCC. The choice of the most recent LSM for patients with multiple exams was one of the reasons for the short follow-up. In addition, the vast majority of TE exams in the cohort were done between 2021 and 2023 as the Veterans Affairs expanded availability of TE throughout the country. Finally, we did not examine serial changes in LSM and HCC risk, but studies have shown that a single LSM is as good as serial changes in LSM to predict liver-related events.[31]

CONCLUSIONS

LSM is significantly associated with HCC risk and can add to risk stratification models for HCC in patients with MASLD. Patients with noncirrhotic MASLD with diabetes

and an LSM of $\geq$ 10 kPa have rates of HCC that are high enough to be considered for HCC surveillance.

DATA AVAILABILITY STATEMENT

The United States Department of Veterans Affairs (VA) places legal restrictions on access to veterans' health care data, including identifying data and sensitive patient information. The analytic data sets used in this study cannot leave the VA firewall without a Data Use Agreement. This limitation is consistent with those of other studies based on VA data. However, VA data are freely available to researchers behind the VA firewall, with an approved VA study protocol. For more information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center (VIReC) at Virec@Va.gov.

AUTHOR CONTRIBUTIONS

Binu V. John and Bassam Dahman had full access to all the data in the study and were responsible for the integrity of the data and the accuracy of the data analysis. Concept and design: Binu V. John. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Binu V. John. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: All authors. Obtained funding: Binu V. John. Administrative, technical, or material support: All authors. Supervision: Binu V. John, Amit G. Singal, and Bassam Dahman.

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CONFLICTS OF INTEREST

Binu V. John received grants paid to his institution from Exact Sciences, Takeda, Genentech, Gilead, and Glycotest. Amit G. Singal consults for FujiFilm, Exact Sciences, Helio Genomics, Curve Biosciences, Mursla, ImCare, Roche/Genentech, AstraZeneca, Eisai, and Boston Scientific. The remaining authors have no conflicts to report.

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ORCID

Binu V. John https://orcid.org/0000–0002–2002–9682

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