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ORIGINAL RESEARCH

HCC Is the Predominant Liver-Related Event in MASLD: 2-Step Non-Invasive Algorithms to Stratify Risk in Non-Cirrhotic Patients

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Background & Aims: Hepatocellular carcinoma (HCC) may develop in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) even in the absence of cirrhosis. Whether the risk of HCC in non-cirrhotic MASLD is substantial to justify surveillance, and which patients may benefit, remains unclear.

Methods: Post-hoc analysis conducted on a prospective MASLD cohort. All participants underwent baseline liver stiffness measurement (LSM) using SuperSonic Imagine (SSI) two-dimensional shear wave elastography (2D-SWE) and were surveilled every 6–12 months. Exclusion criteria were less than 6 months follow-up, unavailable LSM-SSI, prior HCC. Primary outcome was HCC, with hepatic decompensation and portal vein thrombosis (PVT) as competing risks. To improve risk stratification, LSM-SSI optimized cut-offs were applied: <7.4 kPa to rule-out advanced fibrosis, ≥15.6 kPa to rule-in cirrhosis, based on recent meta-analytic data, and were integrated in different risk stratification algorithms.

Results: Among 352 patients with a median follow-up of 31 (14.1–57.8) months, 257 (73%) had LSM-SSI <7.4 kPa, 67 (19%) between 7.4–15.6 kPa, and 28 (8%) ≥15.6 kPa. During follow-up, 9 (2.6%) developed HCC, 6 (1.7%) decompensation, 2 (0.6%) PVT. No events occurred in patients with LSM-SSI <7.4 kPa. In the 7.4–15.6 kPa group, HCC and decompensation occurred in 3 (4.5%) and 1 (1.5%), respectively. For non-cirrhotic patients (LSM-SSI <15.6 kPa), LSM-SSI was significantly associated with HCC risk (HR 1.542, p<0.0001). Following multivariate analysis, independent HCC predictors were: LSM-SSI (HR 1.052, 95% CI 1.030–1.075, p<0.001), type 2 diabetes mellitus (HR 4.555, 95% Ci 1.091–19.012, p=0.038), and gamma-glutamyl transferase (HR 1.004, 95% CI 1.001–1.006, p=0.003). A two-step non-invasive algorithm combining LSM-SSI and the PLEASE score yielded 100% negative predictive value and 89.5% accuracy in identifying patients for HCC surveillance.

Conclusion: HCC is the leading liver-related complication in non-cirrhotic MASLD. LSM-SSI <7.4 kPa effectively excludes high-risk patients. A two-step algorithm further enhances risk stratification and surveillance precision.

Keywords: MASLD, hepatocellular carcinoma, ultrasound elastography, 2D-SWE, liver imaging

Impact and Implications

- HCC emerges as the most frequent liver-related complication in MASLD —surpassing hepatic decompensation and challenging current paradigms of disease progression.
- We identified a clinically actionable liver stiffness threshold (<7.4 kPa by 2D-SWE) below which the risk of HCC is negligible, potentially reducing unnecessary surveillance in low-risk patients.
- Conversely, patients with LSM ≥7.4 kPa, particularly those with type 2 diabetes and elevated GGT, are at significantly higher risk of HCC, as confirmed by multivariate analysis—allowing for targeted monitoring.

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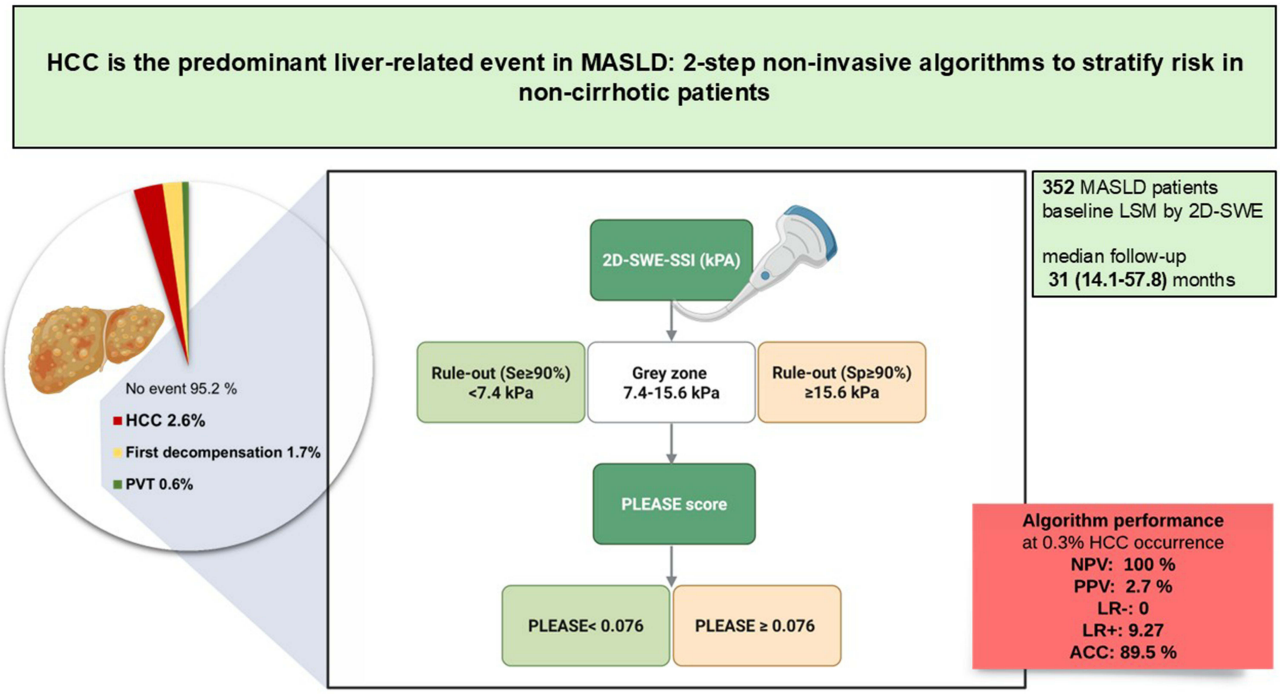
Graphical Abstract



- To enhance clinical applicability, we developed two-step risk stratification algorithms (eg, LSM-SSI combined with the validated PLEASE score), achieving excellent diagnostic accuracy and a 100% negative predictive value—providing a practical, evidence-based tool to guide more efficient and sustainable HCC surveillance in MASLD.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) progresses to metabolic dysfunction-associated steatohepatitis (MASH) in up to 20% of cases.[1] Among those, around 10% eventually develop cirrhosis.[2] Over time, cirrhosis leads to severe complications, which may represent the most frequent long-term clinical outcomes in this population. Nevertheless, 23% to 50% of hepatocellular carcinoma (HCC) cases linked to MASLD arise in non-cirrhotic livers.[3–8] This paradox positions MASLD as a significant cause of HCC even in the absence of cirrhosis, challenging traditional paradigms of liver cancer development. In these non-cirrhotic cases, HCC is often diagnosed at a more advanced stage, with larger tumors and poorer clinical outcomes, due to the lack of clinical features identifying patients requiring surveillance.[8] This pattern underscores the challenges in early detection and emphasizes the urgent need for improved surveillance strategies.[9]

In cirrhotic MASLD, an annual HCC incidence of 1.5% is considered the minimum threshold for cost-effective surveillance.[10,11] The global burden of MASLD, affecting approximately 38% of the adult population above 48 years,[12] renders widespread HCC surveillance impractical and cost-ineffective, differently from the decompensating events which only occur in patients with cirrhosis.[13,14] Although a threshold of 0.5% per year has been proposed for non-cirrhotic liver patients in general,[15] a specific threshold for non-cirrhotic MASLD is still to be established.[16] Accurately identifying the subset of non-cirrhotic MASLD patients who would benefit from HCC surveillance remains a complex and unresolved challenge.[17]

Fibrosis progression is the main driver of HCC onset in chronic liver diseases.[18] Nevertheless, emerging evidence supports the existence of an alternative carcinogenic pathway in MASLD, distinct from the classical fibrosis–cirrhosis–

HCC sequence.[13] Populations at increased risk for MASLD-HCC include males, Hispanics, older adults, and individuals with features of metabolic syndrome (MS). Additional contributing factors may involve moderate to high alcohol intake, tobacco use, elevated liver enzymes, and genetic predisposition.[13,18,19]

Several models are currently emerging to stratify patients according to their risk of developing HCC. Among them, the PLEASE (Platelet, Elastography, Age, Sex, Etiology) score has been recently proposed to assess HCC risk in individuals with advanced chronic liver disease (ACLD).[20] Scoring systems and prediction models are promising, particularly when validated across diverse clinical settings and when their risk strata is linked to tailored surveillance strategies.[21] In non-cirrhotic MASLD, comprehensive and individualized HCC risk assessment remains essential; however, the target population for surveillance must still be more clearly defined.[17]

Accordingly, the primary aims of this study were[1] to investigate the incidence of liver-related complications occurring during follow-up in a real-world cohort of MASLD patients, with a special focus on those without cirrhosis, and[2] to search for a combination of variables able to identify patients with non-cirrhotic MASLD at higher risk of developing HCC deserving surveillance.

Patients and Methods

Study Design

This study presents a post-hoc analysis of a consecutive prospective cohort of MASLD patients evaluated at a third-level hepatology center in Bologna, Italy. The cohort included patients referred from primary care (general practitioners, diabetologists, or obesity clinics) for further assessment, based on consistent evidence of hepatic steatosis (confirmed by imaging or biopsy), associated metabolic risk factors, or abnormal liver function tests, according to the EASL Guidelines.[22] Patients were included if seen between October 2014, and February 2023 [time of availability of SuperSonic equipment to measure liver stiffness], with the last follow-up recorded on January 30, 2024, in order to guarantee a minimal possible follow-up of one year even for the most recent patients.

Ethical Approval

The study was conducted in compliance with the Declaration of Helsinki, Istanbul, and Good Clinical Practice guidelines. It received approval from the Institutional Ethical Committee of IRCCS Sant'Orsola-Malpighi University Hospital in Bologna, Italy (BOMASH study, 0044335/2024). Informed consent was obtained and signed by each alive participant.

Patients, Inclusion, and Exclusion Criteria

Patients were eligible for inclusion if they met the following criteria:

- Diagnosis of MASLD according to the updated definition.[23]
- No other known causes of liver disease, including viral hepatitis, autoimmune liver diseases, cholestatic disorders, alcohol-related liver disease, inherited conditions (alpha-1 antitrypsin deficiency, hemochromatosis, Wilson disease), drug-induced liver injury, and vascular liver disorders.[23]
- Age ≥18 years.
- Availability of semiquantitative grading of liver steatosis via ultrasound (US),[4]
- Availability of a reliable baseline LSM-SSI measurement.
- Comprehensive clinical and laboratory evaluation at baseline.

Exclusion criteria included:

- Presence of HCC at or prior to enrollment.
- Presence of hepatic decompensation at or prior to enrollment.
- Absence of a reliable baseline LSM-SSI measurement.
- Follow-up duration of less than 6 months.

Patients with missing data were excluded from the analysis. The patient flow is illustrated in Figure S1.

Baseline Demographic, Clinical, and Laboratory Data Collection

The inclusion period began with the first LSM-SSI performed as part of a comprehensive multiparametric US evaluation at baseline. Demographic and clinical data were systematically collected for each patient, including laboratory parameters such as blood count, coagulation profile, electrolytes, renal and liver function tests, inflammatory markers, and lipid and glycemic profiles. Lifestyle factors were documented, including alcohol consumption, smoking status, and body mass index (BMI).

Clinical Outcomes and Follow-Up

The endpoints were the development of HCC diagnosed according to the EASL clinical practice guidelines,[24,25] the development of the first decompensation event (ascites, variceal bleeding, overt hepatic encephalopathy) according to the BAVENO VII guidelines,[26] or the development of portal vein thrombosis (PVT). Follow-up assessments were conducted every 6 months in patients with cirrhosis and every 12 months in non-cirrhotic patients, in line with institutional protocols.

Liver Stiffness Measurement Using Two-Dimensional Shear Wave Elastography with the SuperSonic Imagine Ultrasound System (LSM-SSI)

Ultrasound Examination

LSM-SSI was performed by experienced ultrasound operators using the Aixplorer ultrasound system (SuperSonic Imagine SA, Aix-en-Provence, France). Patients were examined in a fasting state, placed supine with the abducted right upper limb. The operator selected the region of interest using B-mode ultrasound, avoiding large vascular structures and targeting an area at least 15 mm below the liver capsule through a right intercostal space. An adequate SWE color map with complete and homogeneous filling was acquired, followed by image capture for stiffness measurement using the Q-box tool. The Stability Index (SI) was calculated for each acquisition, aiming for values ≥0.90. For each patient, at least five reliable measurements were obtained during neutral respiratory apnea, and their median and interquartile range (IQR) was reported in kilopascals (kPa). Measurement reliability was defined according to the latest EFSUMB Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography.[27]

Optimized LSM-SSI Cut-off Values for Advanced Fibrosis (≥F3) and Cirrhosis (F4)

Optimized LSM-SSI cut-off values, derived from our recently published meta-analysis[28] and adapted for the SuperSonic Imagine ultrasound system, were applied as follows: <7.4 kPa to exclude advanced fibrosis (≥F3), and ≥15.6 kPa to confirm cirrhosis (F4). These thresholds were used to stratify the study population, highlighting fibrosis stage as the most significant predictor of clinical events in MASLD.[29]

Other HCC Risk Stratification Scores

PLEASE Score

To evaluate the risk of HCC occurrence in patients with non-cirrhotic MASLD, we calculated the recently developed PLEASE score[20] using the online tool available at https://www.medizin.uni-muenster.de/en/med-b/please-calculator.html.

Additional non-invasive risk stratification scores, using predefined thresholds according to guidelines,[22] were also calculated, with detailed methodologies provided in the Supplementary Materials.

Assessment of Additional Clinical Events During Follow-Up

The occurrence of dysplastic nodules (DN), clinically significant portal hypertension (CSPH), portal vein thrombosis (PVT), and major adverse cardiovascular events (MACE) were also assessed during follow-up, with definitions of these conditions provided in the Supplementary Materials.

Statistical Analysis

Continuous variables were assessed for normality using the Kolmogorov–Smirnov test. Based on their distribution, the data were summarized as either the median with the first and third quartiles (Q1-Q3) or the mean with the standard deviation (SD). Categorical variables were presented as counts and percentages. To compare means between two groups, we applied the independent samples *t*-test, with Levene's test used to assess homogeneity of variances. When the assumptions for parametric tests were not met, the Mann–Whitney *U*-test was employed as a non-parametric alternative. For categorical variables, the Chi-square test (χ^2) was used, or Fisher's Exact Test for smaller sample sizes. The Kruskal–Wallis test was applied to compare more than two independent groups with ordinal or non-normally distributed data. Competing risks regressions based on Fine and Gray's proportional sub-hazards models were performed to identify risk factors for HCC occurrence, with results expressed as sub-hazard ratios (sHRs) and 95% confidence intervals (CIs) for each predictor. The competing risk events for HCC occurrence included the first decompensation event—defined by the Baveno VII consensus as ascites, variceal bleeding, or hepatic encephalopathy[26] - and the occurrence of portal vein thrombosis (PVT), if initially detected by ultrasound. Subsequently, we conducted univariable and multivariable Cox proportional hazards models without accounting for competing risks. Variables significantly associated with HCC occurrence in the univariable analyses were then entered into the multivariable model, and the optimal model was ultimately identified using a backward elimination procedure. Follow-up ended with the diagnosis of HCC, the occurrence of a competing risk event (first decompensation event or PVT), or patient censoring at the last available follow-up. PVT presence was confirmed by a CT scan. A receiver operating characteristic (AUROC) curve analysis was conducted to assess the predictive performance of continuous parameters. The Youden Index was applied to identify optimal cut-off values, while additional cut-off points were established based on pre-defined sensitivity (Se) and specificity (Sp) criteria. The Kaplan-Meier method was used to illustrate and compare the cumulative incidence functions of HCC in MASLD by LSM-SSI category. The cumulative incidence of HCC was calculated, accounting for decompensation and the occurrence of portal vein thrombosis (PVT) as competing risk events. The Log rank test and Gray's test were used to assess group differences for survival and HCC cumulative incidence. To evaluate the performance of various predictors and two-step algorithms for predicting HCC onset in MASLD at different pre-set occurrence,[30] key metrics were assessed, including sensitivity (Se), specificity (Sp), negative predictive value (NPV), positive predictive value (PPV), negative likelihood ratio (LR-), positive likelihood ratio (LR+), and accuracy (Acc). The algorithms were tested for the following HCC occurrence rates: 0.3% (retrieved in our non-cirrhotic population, <15.6 kPa), 0.5% (surveillance proposed for non-cirrhotic liver patients in general,[15] 0.8% (retrieved in our overall population), and 2% (suitable for a high risk scenario).[30] The evaluations were conducted using both optimized and previously reported cut-off values[20,22] across different strategies. The added value of a second examination for patients with indeterminate results or those falling within the "grey zone" was also examined.

All statistical tests were two-sided, with a significance level set at $p < 0.05$. Analyses were performed using STATA 18 or R software (version 4.3.2).

Results

Patients' Characteristics

Following the application of the study criteria, 352 patients were included in the final study population (Figure S1).

Baseline population characteristics are detailed in Tables 1 and S1. The median age of the cohort was 58.2 (IQR: 48.5–66) years, with 191 (54%) male participants. The median body mass index (BMI) was 29.1 (IQR: 26.4–31.7) kg/m^2. Type 2 diabetes mellitus (T2DM) and arterial hypertension (HTA) were present in 94 patients (27%) and 241 patients (68%) at baseline, respectively. The cohort had a median LSM-SSI of 6.2 (IQR: 5.2–7.7) kPa. A total, of 257 patients (73%) had LSM-SSI values below 7.4 kPa, while 95 (27%) had values above this threshold. Patients with LSM-SSI > 7.4 kPa were significantly older, with a median age of 64.2 (IQR: 58.8–70.3) vs 56 (IQR: 45.2–63.2) years, had a higher prevalence of T2DM, 54.7% vs 42%, and HTA 82.1% vs 63%, as well as higher median blood glucose levels 125 (IQR: 90–149) mg/dL vs 100 (IQR: 84–108) mg/dL. The complete comparison is presented in Tables 1 and S1.

Table 1 Baseline Characteristics of the Population Stratified by Subgroups

Variable	LSM-SSI <7.4 kPa (n=257, 73%)	LSM-SSI 7.4–15.6 kPa (n=67, 19%)	LSM-SSI >15.6 kPa (n=28, 8%)
Follow-up; months, median (Q1-Q3)	31 (14.1–57.8)	35.2 (18–58.3)	32.6 (15.9–61.1)
Demographic and clinical data			
Age; years, median (Q1-Q3)	58.2 (48.5–66)	63.4 (56.6–70.1)	66.4 (59.4–71.3)
Male n (%)	142 (55)	36 (54)	13[45]
Body mass index; kg/m^2, median (Q1-Q3)	29.1 (26.4–31.7)	29.7 (27.1–33.3)	30.8 (28–31.5)
Metabolic risk factors			
Diabetes n (%)	42 (16)	31 (46)	21 (75)
Arterial hypertension n (%)	163 (63)	56 (84)	22 (79)
Blood glucose; mg/dL, median (Q1-Q3)	100 (84–108)	111 (87–128)	156 (95–208)
Total cholesterol; mg/dL, median (Q1-Q3)	196 (171–225)	190 (165–210)	167 (140–203)
LDL cholesterol; mg/dL, median (Q1-Q3)	120 (9–148)	115 (83–151)	108 (61–176)
HDL cholesterol; mg/dL, median (Q1-Q3)	51 (42–61)	49 (36–59)	46 (32–67)
Triglycerides; md/dL, median (Q1-Q3)	151 (89–197)	150 (88–206)	138 (73–240)
Liver function			
Total bilirubin; mg/dL, median (Q1-Q3)	0.8 (0.5–1)	0.9 (0.4–1.2)	0.9 (0.5–1.5)
Aspartate aminotransferase; IU/L, median (Q1-Q3)	32 (21–42)	37 (23–56)	48 (25–73)
Aalanine transaminase; IU/L, median (Q1-Q3)	44 (22–56)	45 (22–74)	45 (22–80)
Albumin; g/dL, median (Q1-Q3)	4.2 (4–4.5)	4.2 (4–4.5)	4 (3.4–4.2)
International normalized ratio; median (Q1-Q3)	1.02 (1–1.08)	1.05 (1–1.11)	1.17 (1.06–1.22)
Gamma-glutamyl transferase; IU/L, median (Q1-Q3)	35 (23–65)	42 (26–71)	112 (63–150)
Platelets ×10^3/μL, median (Q1-Q3)	241 (197–285)	227 (174–272)	120 (82–181)
Ultrasound			
Steatosis grade			
I n (%)	51 (20)	19 (28)	12 (43)
II n (%)	115 (45)	19 (28)	12 (43)
III n (%)	91 (35)	29 (44)	4 (14)
Events			
De novo HCC n (%)	0	3 (4.5)	6 (21.4)
First decompensation n (%)	0	1 (1.5)	5 (17.9)
PVT n (%)	0	0	2 (7.1)
De novo CSPH n (%)	0	4 (6)	9 (32.1)

(*Continued*)

Table 1 (Continued).

Variable	LSM-SSI <7.4 kPa (n=257, 73%)	LSM-SSI 7.4–15.6 kPa (n=67, 19%)	LSM-SSI >15.6 kPa (n=28, 8%)
De novo dysplastic nodules n (%)	0	3 (4.5)	2 (7.1)
MACE n (%)	18 (7)	7 (10.4)	3 (10.7)

Abbreviations: %, percentage; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; IU/L, international units per liter; kPa, kilopascals; kg/m^2, kilograms per square meter; I mild, II moderate; III, severe; LSM, liver stiffness measurement; MACE, major cardiovascular events; mg/dL, milligrams per deciliter; n, number; PVT, portal vein thrombosis; Q1, first quartile; Q3, third quartile; SD, standard deviation; SSI, SuperSonic Imagine; µL, microliters.

Follow-Up, Liver-Related Complications, and HCC Incidence Rates

The median follow-up duration for the entire cohort was 31 months (IQR: 14.1–57.8). During follow-up, 9 patients (2.6%) developed HCC, 6 (1.7%) experienced a first decompensation event, and 2 (0.6%) developed portal vein thrombosis (PVT). No patient with a baseline LSM-SSI <7.4 kPa developed liver-related clinical outcomes. Conversely, among patients with LSM-SSI ≥7.4 kPa, the following event rates were observed: 9.5% (9 patients) developed HCC, and 6.3% (6 patients) experienced a first decompensation event, including 5 cases of grade II ascites and 1 case of overt hepatic encephalopathy. One patient concurrently developed both HCC and a new decompensation episode (ascites). Additionally, 2.1% (2 patients) developed de novo PVT, with one case coinciding with HCC diagnosis. De novo dysplastic nodules were observed exclusively in patients with LSM-SSI ≥7.4 kPa, with a global occurrence of 5.3% (5 patients). Similarly, 13.7% (13 patients) developed de novo clinically significant portal hypertension (CSPH), identified by gastroesophageal varices on upper endoscopy or collateral circulation on cross-sectional imaging (Table 1).

Regarding MACE, 10.5% (10 patients) with LSM-SSI ≥7.4 kPa experienced events, compared to 7% (18 patients) among those with LSM-SSI <7.4 kPa (Table 1). Baseline LSM-SSI values among patients who developed MACE ranged from 3.7 to 28.8 kPa, with events occurring regardless of fibrosis severity (Table 1).

The median time to HCC occurrence was 22.6 months (IQR: 12.3–40.8). Nine patients with MASLD developed HCC over 1128 PY of follow-up, resulting in an annual incidence rate of 0.8 per 100 PY. When patients with LSM-SSI between 7.4–15.6 kPa were considered only, the HCC incidence rate increased to 1.3 per 100 PY. When patients with LSM-SSI ≥15.6 kPa (F4) were excluded, the HCC incidence rate in the subgroup <15.6 kPa decreased to 0.3 per 100 PY. Additional incidence rates are reported in Table S2.

Kaplan–Meier estimates for HCC occurrence by LSM-SSI categories are presented in Figure 1. Figure S2A–C show the Kaplan–Meier curves for the first decompensation event, MACE, and onset of CSPH, respectively, stratified by LSM-SSI categories.

Competing-Risk Regression Analysis for HCC Occurrence

Univariate analysis identified age (HR 1.075, 95% CI 1.030–1.121, p=0.001), white blood cells (HR 0.999, 95% CI 0.998–0.999, p=0.013), platelets (HR 0.987, 95% CI 0.975–0.997, p=0.020), aspartate aminotransferase (HR 1.023, 95% CI 1.005–1.041, p=0.011), gamma glutamyl transferase (HR 1.004, 95% CI 1.001–1.006, p=0.001), alkaline phosphatase (HR 1.009, 95% CI 1.005–1.011, p=0.000), total bilirubin (HR 2.147, 95% CI 1.154–3.990, p=0.016), international normalized ratio (HR 3.873, 95% CI 1.188–12.619, p=0.025), blood glucose (HR 1.008, 95% CI 1.004–1.012, p=0.000), T2DM (HR 4.952, 95% 1.236–19.835, p=0.024), LSM-SSI (HR 1.052, 95% CI 1.027–1.076, p<0.0001) as independent risk factors for HCC occurrence in MASLD in the overall cohort. Multivariate analysis identified LSM-SSI (HR 1.052, 95% CI 1.030–1.075, p<0.001), T2DM (HR 4.555, p=0.038), and gamma-glutamyl transferase (HR 1.004, p=0.003) as independent predictors for HCC occurrence in our MASLD overall cohort (Table 2).

The results of the univariable and multivariable Cox proportional hazards models, conducted without accounting for competing risk events, are presented in Table S3.

Table S4 presents a comparison of the performance of various scores and clinical and laboratory variables in predicting HCC occurrence in MASLD.

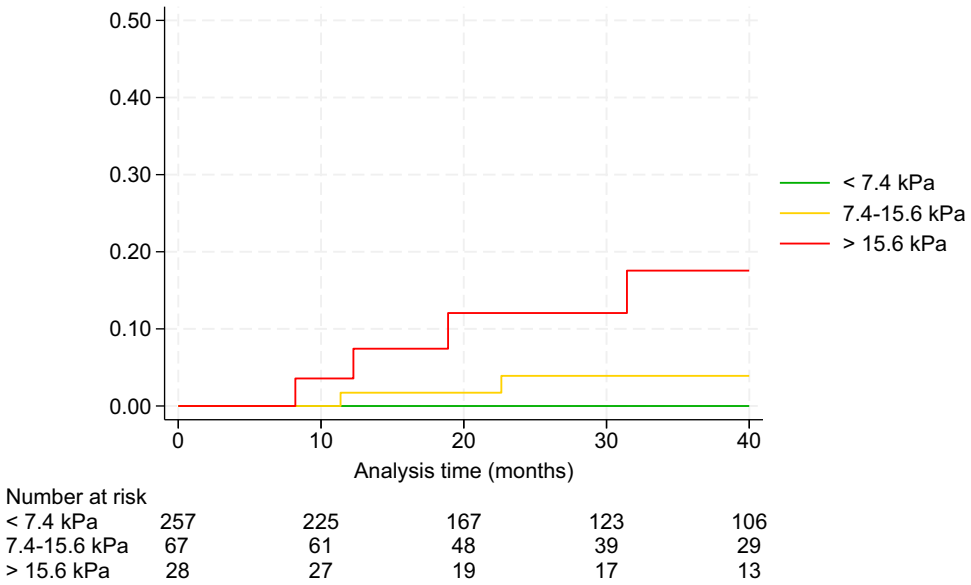


Figure 1 Kaplan-Meyer estimates for HCC occurrence by LSM-SSI categories.
Notes: A significant difference in HCC-free survival (time to HCC) was observed among the three groups, log-rank $\chi^2(2) = 37.35$, $p < 0.001$).
Abbreviations: HCC, hepatocellular carcinoma; kPa, kilopascals; LSM, liver stiffness measurement; SSI, SuperSonic Imagine.

Validation of PLEASE Score for HCC in Non-Cirrhotic MASLD

The predictive performance of the PLEASE score for HCC occurrence was indicated by an AUROC of 0.94 [0.92–0.97] for the whole population and 0.80 [0.70–0.87] for those with LSM-SSI ≥7.4 kPa. For the entire cohort, using our proposed rule-out (Se>90%) cut-off of 0.076, the PLEASE score showed Se=100%, Sp=89.21%, PPV=19.6%, NPV=100%. By applying our proposed rule-in cut-off (Sp>90%) of 0.152, the PLEASE score exhibited a Se=55.6%, Sp=95.9%, PPV=26.3%, and NPV=98.8%, respectively.

Table 2 Univariate and Multivariate Competing-Risk Analysis for HCC Occurrence in MASLD

Variables						
	Univariate Analysis			**Multivariate Analysis**		
n=352	**Sub-Hazard Ratio**	**95% CI**	**p-Value**	**Sub-Hazard Ratio**	**95% CI**	**p-Value**
Demographics						
Age (years)	1.075	1.030–1.121	**0.001**			
Age > 60 years	5.069	1.054–24.360	**0.043**			
Age > 65 years	8.850	0.952–82.184	0.055			
Gender (female/male)	0.901	0.244–3.329	0.876			
Body mass index (kg/m2)	1.119	1.019–1.227	**0.018**			
Obesity (yes/no)	1.514	0.389–5.888	0.550			
Weist circumference (cm)	1.042	1.010–1.075	**0.009**			
Arterial hypertension	3.732	0.455–30.599	0.220			
Alcohol intake (units/week)	1.040	0.976–1.107	0.220			
Tabacco use (never/former/curent)	2.039	0.936–4.437	0.073			

(*Continued*)

Table 2 (Continued).

Variables						
	Univariate Analysis			Multivariate Analysis		
n=352	Sub-Hazard Ratio	95% CI	p-Value	Sub-Hazard Ratio	95% CI	p-Value
Laboratory data						
Hemoglobin (g/dL)	0.712	0.472–1.072	0.104			
White blood cells (count×10^3/μL)	0.999	0.998–0.999	**0.013**			
Platelets (×10^3/μL)	0.987	0.975–0.997	**0.020**			
Aalanine transaminase (IU/L)	0.992	0.973–1.011	0.427			
Aspartate aminotransferase (IU/L)	1.023	1.005–1.041	**0.011**			
Gamma glutamyltransferase (IU/L)	1.004	1.001–1.006	**0.001**	1.004	1.001–1.006	**0.003**
Alkaline phosphatase (IU/L)	1.009	1.005–1.011	**0.000**			
Total bilirubin (mg/dL)	2.147	1.154–3.990	**0.016**			
International normalized ratio	3.873	1.188–12.619	**0.025**			
Total serum proteins (g/dL)	2.281	0.664–7.827	0.190			
Albumin (g/dL)	0.368	0.102–1.319	0.125			
Total cholesterol (mg/dL)	0.999	0.984–1.013	0.859			
LDL cholesterol (mg/dL)	1.010	0.999–1.019	0.061			
HDL cholesterol (mg/dL)	1.009	0.975–1.043	0.607			
Triglycerides (md/dL)	0.989	0.974–1.003	0.151			
Blood glucose (mg/dL)	1.008	1.004–1.012	**0.000**			
Glycated Hemoglobin	1.027	1.001–1.053	**0.041**			
Type 2 diabetes mellitus	4.952	1.236–19.835	**0.024**	4.555	1.091–19.012	**0.038**
Creatinine (mg/dL)	0.002	0.000–0.068	**0.001**			
Na (mmol/L)	0.948	0.722–1.243	0.701			
K (mmol/L)	0.192	0.032–1.118	0.066			
AFP μg/L	1.213	0.667–2.202	0.527			
Other aspects						
Physical activity	0.662	0.281–1.561	0.347			
MASLD criteria						
At least 3 criteria fulfilled	1.009	0.257–3.960	0.990			
At least 4 criteria fulfilled	1.374	0.348–5.421	0.650			
Ultrasound						
Baseline 2D-SWE SSI (kPa)	1.052	1.027–1.076	**<0.001**	1.052	1.031–1.075	**<0.001**
2D-SWE SSI out/grey/in	8.205	3.693–18.226	**<0.001**			

(*Continued*)

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Table 2 (Continued).

Variables						
	Univariate Analysis			Multivariate Analysis		
n=352	Sub-Hazard Ratio	95% CI	p-Value	Sub-Hazard Ratio	95% CI	p-Value
2D-SWE SSI ≥15.6 kPa	17.763	4.596–68.651	**<0.001**			
Grey zone	1.997	0.494–8.073	0.332			
HRI	0.396	0.047–3.300	0.392			
Steatosis grade (I/II/III)	0.795	0.285–2.212	0.661			
Scores						
MAF-5	1.431	1.155–1.772	**0.001**			
FIB-4	1.143	1.053–1.239	**0.001**			
PLEASE score (continuous)	3119.142	173.833–55,967.76	**<0.001**			
PLEASE score (points)	3.0189	1.616–5.638	**0.001**			
ANTICIPATE	1.626	1.396–1.895	**<0.001**			
ANTICIPATE-NASH	2.116	1.593–2.812	**<0.001**			

Note: bold - statistically significant.

Abbreviations: %, percentage; 2D-SWE, two dimensional shear wave elastography; AFP, alfafetoprotein; CI, confidence interval; cm, centimeters; CFIB-4, fibrosis 4 index; g/dL, grams per deciliter; HCC, hepatocellular carcinoma; HRI, hepatorenal index; IU/L, international units per liter; K, potassium; kg/m^2, kilograms per square meter; MASLD, metabolic dysfunction-associated steatotic liver disease; mmHg, millimeters mercury; n, number; Na, sodium; SSI, SuperSonic Imagine; µL, microliter.

Clinical Algorithms for HCC Surveillance in Patients with MASLD

The diagnostic performance of FIB-4, LSM-SSI, the PLEASE score, and our multivariate model were first assessed individually using standardized cut-off values to rule out (sensitivity >90%) and rule in (specificity >90%) HCC, across predefined HCC occurrence scenarios of 0.3%, 0.8%, and 2%.

Based on the diagnostic performance of each individual score, two-step algorithms were developed and tested to enhance HCC risk stratification. In the first step, standardized thresholds were applied to rule out HCC (sensitivity >90%), identify high-risk individuals (specificity >90%), and define a "grey zone" of indeterminate cases. A second stratification step was applied within this grey zone to refine risk assessment and improve diagnostic accuracy. All possible single and sequential combinations of these approaches were systematically evaluated to determine the most effective strategy. The diagnostic performance of the algorithms across different pre-test HCC occurrence scenarios (0.3%, 0.5%, 0.8%, and 2%) is summarized in Tables 3, 4, and S5, with an overview illustrated in Figure 2 and a clinical interpretation in Figure 3.

At a predefined HCC occurrence of 0.3%, a FIB-4 value <1.3 effectively ruled out HCC occurrence, with a Se=88.9% and a NPV=99.9%, outperforming the age-adapted FIB-4 ≥2.0 strategy in patients aged ≥65 years (Table 3). In the same setting, LSM-SSI <7.4 kPa ruled out HCC with perfect Se (100%) and NPV (100%), and demonstrated superior overall accuracy compared to FIB-4 (75.6% vs 64.5%). Similarly, the PLEASE score, using a proposed rule-out threshold of <0.076 (Se >90%), matched the performance of LSM-SSI <7.4 kPa (Se=100%, NPV=100%), and achieved an accuracy of 89.2% (Table 3).

In rule-in scenarios using standard thresholds (eg, FIB-4 ≥2.67, LSM-SSI ≥15.6 kPa), the diagnostic performance was modest. FIB-4 ≥2.67 yielded a Sp=91% and a PPV=2.5%, while LSM-SSI ≥15.6 kPa showed a Se=93.6% and a PPV=3.0%.

When non-invasive tests (NITs) were integrated into two-step algorithms to enhance diagnostic accuracy and improve risk stratification, the combination of LSM-SSI (<7.4 kPa, ≥15.6 kPa) with a PLEASE score <0.076 achieved excellent rule-out performance (Se =100%, NPV=100%) and a high overall accuracy (Acc=89.5%). This algorithm outperformed other tested combinations, such as FIB-4 (<1.3 and ≥2.67) followed by LSM-SSI <7.4 kPa (Se=88.9%, NPV=100%, Acc=81.8%), or FIB-4 followed by PLEASE score <0.076 (Se=88.9%, NPV=100%, Acc=86.6%). This trend remained consistent across higher HCC occurrence scenarios, including 0.8% (Table 4) and 2% (Table S5).

Table 3 Performance of Various Clinical Algorithms for HCC in MASLD at 0.3% Pre-Set HCC Occurrence

ALGORITHM	Cut-Off Values	HCC Pre-Set Occurrence (0.3%)										
		TP	FN	FP	TN	Se	Sp	NPV	PPV	LR-	LR+	ACC
FIB-4 (rule-out)	FIB-4: **<1.3**	8	1	124	219	88.9	63.8	99.9	0.7	0.17	2.46	64.5
	FIB-4: **<1.3** or **<2** (age adapted)	7	2	100	243	77.8	70.7	99.9	0.8	0.31	2.67	71.0
LSM-SSI kPa (rule-out)	LSM-SSI: **<7.4** (rule-out F3)	9	0	86	257	100	74.9	100	1.2	0	3.99	75.6
	LSM-SSI: **<9** (rule-out F4)	8	1	56	287	88.9	83.7	100	1.6	0.13	5.44	83.8
PLEASE score (rule-out)	PLEASE: **<0.076**	9	0	38	305	100	88.9	100	2.6	0	9.03	89.2
	PLEASE: **<4**	4	5	23	320	44.4	93.3	99.8	2	0.6	6.63	92.0
Multivariate score (rule-out)	Multivariate score: **<2.299**	9	0	106	237	100	69.1	100	1	0	3.24	69.9
FIB-4 (rule-in)	FIB-4: ≥**2.67**	7	2	31	312	77.8	91	99.9	2.5	0.24	8.61	90.6
LSM-SSI kPa (rule-in)	LSM-SSI: ≥**15.6** (rule-in F4)	6	3	22	321	66.7	93.6	99.9	3	0.36	10.39	92.9
	LSM-SSI: ≥**14** (rule-in F3)	6	3	27	316	66.7	92.1	99.9	2.5	0.36	8.47	91.5
PLEASE score (rule-in)	PLEASE: ≥**0.152** (continuous)	5	4	15	328	55.6	95.6	99.9	3.7	0.46	12.7	94.6
	PLEASE: ≥**4** (points)	4	5	23	320	44.4	93.3	99.8	2	0.6	6.63	92.0
Multivariate score (rule-in)	Multivariate score: ≥**19.402**	5	4	10	333	55.6	97.1	99.9	5.4	0.46	19.06	96.0
FIB-4 - LSM-SSI kPa (rule-out F3)	FIB-4: **<1.3** and ≥**2.67** LSM-SSI: **<7.4**	8	1	63	280	88.9	81.6	100	1.4	0.14	4.84	81.8
FIB-4 - LSM-SSI kPa (rule-out F4)	FIB-4: **<1.3** and ≥**2.67** LSM-SSI: **<9**	7	2	56	287	77.8	83.7	99.9	1.4	0.27	4.76	83.5
FIB-4 - PLEASE	FIB-4: **<1.3** and ≥**2.67** PLEASE: **<0.076**	8	1	46	297	88.9	86.6	100	2	0.13	6.63	86.6
	FIB-4: **<1.3** and ≥**2.67** PLEASE: **<4**	7	2	38	305	77.8	88.9	99.9	2.1	0.25	7.02	88.6
FIB-4 - Multivariate score	FIB-4: **<1.3** and ≥**2.67** Multivariate score: **<2.299**	8	1	68	275	88.9	80.2	100	1.3	0.14	4.48	80.4
LSM-SSI kPa (rule-out F3) - PLEASE	LSM-SSI: **<7.4** and ≥**15.6** PLEASE: **<0.076**	9	0	37	306	100	89.2	100	2.7	0	9.27	89.5
	LSM-SSI: **<7.4** and ≥**15.6** PLEASE: **<4**	7	2	27	316	77.8	92.1	99.9	2.9	0.24	9.88	91.8
LSM-SSI kPa (rule-out F3) - Multivariate score	LSM-SSI: **<7.4** and ≥**15.6** Multivariate score: **<2.299**	9	0	53	290	100	84.5	100	1.9	0	6.47	84.9
PLEASE - LSM-SSI kPa (rule-out F3)	PLEASE: **<0.076** and ≥**0.152** LSM-SSI: **<7.4**	9	0	33	310	100	90.4	100	3	0	10.39	90.6

(*Continued*)

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Table 3 (Continued).

ALGORITHM	Cut-Off Values	HCC Pre-Set Occurrence (0.3%)										
		TP	FN	FP	TN	Se	Sp	NPV	PPV	LR-	LR+	ACC
PLEASE - LSM-SSI kPa (rule-out F4)	PLEASE: **<0.076** and ≥**0.152** LSM-SSI: **<9**	8	1	29	314	88.9	91.5	100	3.1	0.12	10.51	91.5
PLEASE - Multivariate score	PLEASE: **<0.076** and ≥**0.152** Multivariate score: **<2.299**	9	0	28	315	100	91.8	100	3.6	0	12.25	92.0
Multivariate score - LSM-SSI kPa (rule-out F3)	Multivariate score: **<2.299** and ≥**19.402** LSM-SSI:**<7.4**	9	0	54	289	100	84.3	100	1.9	0	6.35	84.7
Multivariate score - LSM-SSI kPa (rule-out F4)	Multivariate score: **<2.299** and ≥**19.402** LSM-SSI:**<9**	8	1	47	296	88.9	86.3	100	1.9	0.13	6.49	86.4
Multivariate score - PLEASE	Multivariate score: **<2.299** and ≥**19.402** PLEASE: **<0.076**	9	0	29	314	100	91.5	100	3.4	0	11.83	91.8
	Multivariate score: **<2.299** and ≥**19.402** PLEASE: **<4**	6	3	22	321	66.7	93.6	99.9	3	0.36	10.39	92.9

Note: green - rule-out cut-off, red - rule-in cut-off.

Abbreviations: ACC, accuracy; F3, advanced fibrosis; F4, cirrhosis; FIB-4, fibrosis 4 index; FN, false negatives; FP, false positives; HCC, hepatocellular carcinoma; kPa, kilopascals; LR, negative likelihood ratio; LR+, positive likelihood ratio; LSM, liver stiffness measurement; NPV, negative predictive value; PLEASE, (platelet elastography age sex etiology) score; PPV, positive predictive value; Se, sensitivity; Sp, specificity; SSI, SuperSonic Imagine; TN, true negatives; TP, true positives; %, percentage.

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Table 4 Performance of Various Clinical Algorithms for HCC in MASLD at 0.8% Pre-Set HCC Occurrence

ALGORITHM	Cut-off Values	HCC pre-set occurrence (0.8%)										
		TP	FN	FP	TN	Se	Sp	NPV	PPV	LR-	LR+	ACC
FIB-4 (rule-out)	FIB-4: **<1.3**	8	1	124	219	88.9	63.8	99.9	1.9	0.17	2.46	64.5
	FIB-4: **<1.3** or **<2** (age adapted)	7	2	100	243	77.8	70.8	99.7	2.1	0.31	2.67	71.0
LSM-SSI kPa (rule-out)	LSM-SSI: **<7.4** (rule-out F3)	9	0	86	257	100	74.9	100	3.1	0	3.99	75.6
	LSM-SSI: **<9** (rule-out F4)	8	1	56	287	88.9	83.7	99.9	4.2	0.13	5.44	83.8
PLEASE score (rule-out)	PLEASE: **<0.076**	9	0	38	305	100	88.9	100	6.8	0	9.03	89.2
	PLEASE: **<4**	4	5	23	320	44.4	93.3	99.5	5.1	0.6	6.63	92.0
Multivariate score (rule-out)	Multivariate score: **<2.299**	9	0	106	237	100	69.1	100	2.5	0	3.24	69.9
FIB-4 (rule-in)	FIB-4: ≥**2.67**	7	2	31	312	77.8	91	99.8	6.5	0.24	8.61	90.6
LSM-SSI kPa (rule-in)	LSM-SSI: ≥**15.6** (rule-in F4)	6	3	22	321	66.7	93.6	99.7	7.7	0.36	10.39	92.9
	LSM-SSI: ≥**14** (rule-in F3)	6	3	27	316	66.7	92.1	99.7	6.4	0.36	8.47	91.5
PLEASE score (rule-in)	PLEASE: ≥**0.152** (continuous)	5	4	15	328	55.6	95.5	99.6	9.3	0.46	12.7	94.6
	PLEASE: ≥**4** (points)	4	5	23	320	44.4	93.3	99.5	5.1	0.6	6.63	92.0
Multivariate score (rule-in)	Multivariate score: ≥**19.402**	5	4	10	333	55.6	97.1	99.6	13.3	0.46	19.06	96.0
FIB-4 - LSM-SSI kPa (rule-out F3)	FIB-4: **<1.3** and ≥**2.67** LSM-SSI: **<7.4**	8	1	63	280	88.9	81.6	99.9	3.8	0.14	4.84	81.8
FIB-4 - LSM-SSI kPa (rule-out F4)	FIB-4: **<1.3** and ≥**2.67** LSM-SSI: **<9**	7	2	56	287	77.8	83.7	99.8	3.7	0.27	4.76	83.5
FIB-4 - PLEASE	FIB-4: **<1.3** and ≥**2.67** PLEASE: **<0.076**	8	1	46	297	88.9	86.6	99.9	5.1	0.13	6.63	86.6
	FIB-4: **<1.3** and ≥**2.67** PLEASE: **<4**	7	2	38	305	77.8	88.9	99.8	5.4	0.25	7.02	88.6
FIB-4 - Multivariate score	FIB-4: **<1.3** and ≥**2.67** Multivariate score: **<2.299**	8	1	68	275	88.9	80.2	99.9	3.5	0.14	4.48	80.4
LSM-SSI kPa (rule-out F3) - PLEASE	LSM-SSI: **<7.4** and ≥**15.6** PLEASE: **<0.076**	9	0	37	306	100	89.2	100	7	0	9.27	89.5
	LSM-SSI: **<7.4** and ≥**15.6** PLEASE: **<4**	7	2	27	316	77.8	92.1	99.8	7.4	0.24	9.88	91.8
LSM-SSI kPa (rule-out F3) - Multivariate score	LSM-SSI: **<7.4** and ≥**15.6** Multivariate score: **<2.299**	9	0	53	290	100	84.5	100	5	0	6.47	84.9
PLEASE - LSM-SSI kPa (rule-out F3)	PLEASE: **<0.076** and ≥**0.152** LSM-SSI: **<7.4**	9	0	33	310	100	90.4	100	7.7	0	10.39	90.6

(*Continued*)

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Table 4 (Continued).

ALGORITHM	Cut-off Values	HCC pre-set occurrence (0.8%)										
		TP	FN	FP	TN	Se	Sp	NPV	PPV	LR-	LR+	ACC
PLEASE - LSM-SSI kPa (rule-out F4)	PLEASE: **<0.076** and ≥**0.152** LSM-SSI: **<9**	8	1	29	314	88.9	91.5	99.9	7.8	0.12	10.51	91.5
PLEASE - Multivariate score	PLEASE: **<0.076** and ≥**0.152** Multivariate score: **<2.299**	9	0	28	315	100	91.8	100	9	0	12.25	92.0
Multivariate score - LSM-SSI kPa (rule-out F3)	Multivariate score: **<2.299** and ≥**19.402** LSM-SSI:**<7.4**	9	0	54	289	100	84.3	100	4.9	0	6.35	84.7
Multivariate score - LSM-SSI kPa (rule-out F4)	Multivariate score: **<2.299** and ≥**19.402** LSM-SSI:**<9**	8	1	47	296	88.9	86.3	99.9	5	0.13	6.49	86.4
Multivariate score - PLEASE	Multivariate score: **<2.299** and ≥**19.402** PLEASE: **<0.076**	9	0	29	314	100	91.5	100	8.7	0	11.83	91.8
	Multivariate score: **<2.299** and ≥**19.402** PLEASE: **<4**	6	3	22	321	66.7	93.6	99.7	7.7	0.36	10.39	92.9

Note: green - rule-out cut-off, red - rule-in cut-off.

Abbreviations: ACC, accuracy; F3, advanced fibrosis; F4, cirrhosis; FIB-4, fibrosis 4 index; FN, false negatives; FP, false positives; HCC, hepatocellular carcinoma; kPa, kilopascals; LR, negative likelihood ratio; LR+, positive likelihood ratio; LSM, liver stiffness measurement; NPV, negative predictive value; PLEASE, (platelet elastography age sex etiology) score; PPV, positive predictive value; Se, sensitivity; Sp, specificity; SSI, SuperSonic Imagine; TN, true negatives; TP, true positives; %, percentage.

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2D-SWE-SSI			
LSM-SSI (kPa) (n=352 pts, 9 HCC)	**Rule-out (Se ≥90%) < 7.4 kPa**	**Best cut-off (Youden) 12.4 kPa**	**Rule-in (Sp ≥90%) 15.6 kPa**
Diagnostic test results			
True positive (TP)	9	8	6
False positive (FP)	86	29	22
True negative (TN)	257	315	321
False Negative (FN)	0	1	3
Operating characteristics (study incidence = 0.8% [95% CI]			
Sensitivity (95%n CI)	100 (66.4-100)	88.9 (51.8-99.7)	66.7 (29.9-92.5)
Specificity (95%n CI)	74.9 (70.0-79.4)	91.6 (88.1-94.3)	93.6 (90.4-95.9)
PPV (95% CI)	3.1 (2.6-3.7)	7.8 (5.3-11.4)	7.7 (4.3-13.4)
NPV (95% CI)	100	99.9 (99.4-100)	99.7 (99.3-99.9)
LR-positive (95% CI)	3.99 (3.32-4.79)	10.54 (6.94-16.01)	10.39 (5.63-19.20)
LR-negative (95% CI)	0	0.12 (0.02-0.77)	0.36 (0.14-0.90)
AUROC (95% CI)	0.87 (0.85-0.90)	0.90 (0.79-1.00)	0.80 (0.64-0.97)
2D-SWE-SSI + PLEASE score two-step algorithm overall performance			

Diagnostic test results	
True positive (TP)	9
False positive (FP)	37
True negative (TN)	306
False Negative (FN)	0
Operating characteristics (study incidence = 0.8% [95% CI]	
Sensitivity (95%n CI)	100 (66.4-100)
Specificity (95%n CI)	89.2 (85.4-92.3)
PPV (95% CI)	7 (5.2-9.2)
NPV (95% CI)	100
LR-positive (95% CI)	9.27 (6.84-12.57)
LR-negative (95% CI)	0
AUROC (95% CI)	0.95 (0.93-0.96)

Figure 2 Diagnostic accuracy of LSM-SSI for HCC occurrence (kPa).
Abbreviations: 2D-SWE, two-dimensional shear wave elastography; AUROC, area under the ROC curve; CI, confidence interval; HCC, hepatocellular carcinoma; kPa, kilopascals; LR, negative likelihood ratio; LR+, positive likelihood ratio; LSM, liver stiffness measurement; n, number; NPV, negative predictive value; PPV, positive predictive value; pts, patients; SSI, SuperSonic Imagine.

Discussion

In our cohort of MASLD patients, hepatocellular carcinoma (HCC) emerged as the most prevalent liver-related event, with an incidence rate of 0.8 per 100 person-years in the overall cohort. This surpassed the incidence of both first hepatic decompensation events and portal vein thrombosis. Among the subgroup with liver stiffness measurement (LSM-SSI) values ranging from 7.4 to 15.6 kPa, the HCC incidence rate was higher at 1.3 per 100 person-years, approaching the 1.5% threshold, for which HCC surveillance is generally recommended across all liver disease etiologies.[31,32] This findings underscore the importance of establishing effective HCC surveillance strategies in MASLD and highlights the distinct clinical course of this condition compared to other chronic liver disease etiologies.[33–35] Recent guidelines emphasize that patients with MASLD and advanced fibrosis, but without cirrhosis, are at higher risk of developing HCC.[21] However, routine HCC surveillance is not currently recommended for non-cirrhotic MASLD due to insufficient supporting evidence.[21]

Nevertheless, etiology-specific surveillance could support more personalized approaches by distinguishing between low-risk and high-risk patients. A study from the ITALICA Study Group highlighted the challenge of delayed HCC diagnosis in MASLD, as HCC is often detected at more advanced stages and may occur in the absence of cirrhosis.[8] Timely detection of MASLD-HCC during its often-prolonged asymptomatic phase is critical to improve treatment decision-making and expand the range of available therapeutic options.[8,17]

Cost-effectiveness analyses suggest that HCC surveillance is justified when the annual incidence reaches at least 1.5%, regardless of the underlying etiology,[31,32] as mentioned above. However, recent modeling studies have shown that

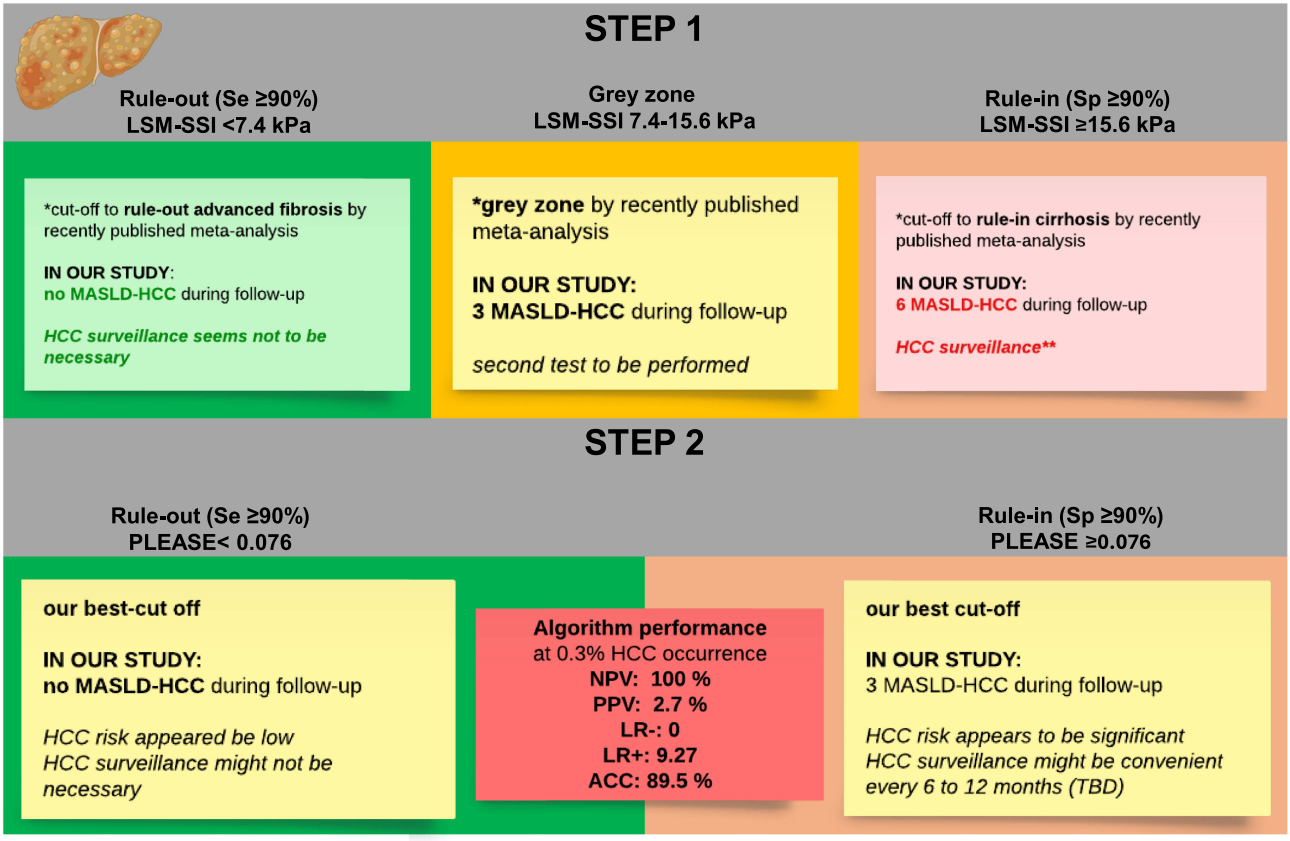

Figure 3 Interpretation and synthesis of the two-step risk stratification algorithm based on LSM-SSI and the PLEASE score.
Abbreviations: ACC, accuracy; HCC, hepatocellular carcinoma; kPa, kilopascals; LR, likelihood ratio; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; NPV, negative predictive value; PLEASE (score), Platelet, Elastography-SSI, Age, Sex, Etiology (score); PPV, positive predictive value; Se, sensitivity; Sp, specificity; SSI, SuperSonic Imagine; TBD, to be determined.

an annual HCC incidence of approximately 0.8% may also be cost-effective for initiating surveillance, even when accounting for potential harms such as high false-positive rates and the need for additional diagnostic procedures.[36]

As previously reported, the benefits of HCC screening remain uncertain for MASLD patients with a low annual incidence, such as 0.4%.[36] This finding aligns with previous studies that assessed HCC incidence or composite liver-related events (LREs), using vibration-controlled transient elastography (VCTE).[37–43] Recent evidence suggests that individuals with significant or advanced fibrosis, combined with additional risk factors, may benefit from cost-effective HCC surveillance strategies.[36] Consistently, our univariate and multivariate analyses identified LSM-SSI, among other variables (T2DM, and GGT) as independent predictors of HCC. Moreover, LSM-SSI demonstrated a progressively increasing risk trajectory for HCC occurrence on Kaplan–Meier analysis (Figure 1), in alignment with previous findings reported for vibration-controlled transient elastography (VCTE).[44]

Emerging concerns about the potential harms of surveillance—such as false positives leading to unnecessary testing and patient anxiety—have raised important questions regarding the overall value of HCC surveillance in MASLD.[45,46] In response, our study aimed to refine the criteria for identifying patients who may not require surveillance, achieving excellent negative predictive values (NPVs).

In our cohort, LSM-SSI outperformed FIB-4 in guiding HCC surveillance decisions, demonstrating superior rule-out capability and higher overall diagnostic accuracy. We found that HCC surveillance is unnecessary in MASLD patients with LSM-SSI <7.4 kPa (rule-out ≥F3), for at least around 3 years, time at which patients could be reassessed. Furthermore, we proposed a two-step algorithm based on LSM-SSI and PLEASE score, which achieved a negative predictive value (NPV) of 100% and an overall accuracy of 89.5% in identifying patients who should avoid HCC surveillance, assuming a predefined HCC occurrence of 0.3% (Table 3).

We also developed and tested similar algorithms combining various available tools—including FIB-4, the PLEASE score, LSM-SSI, and our multivariate model (LSM-SSI, GGT, T2DM)—to assess their performance under different clinical conditions and HCC occurrence assumptions. These strategies aim to provide clinicians with practical, adaptable tools for real-world decision-making, tailored to varying risk profiles and surveillance settings. Such an approach may prove both feasible and acceptable for implementation in the MASLD population.[17] Since elastography modules are now integrated into most modern ultrasound systems, 2D-SWE offers substantial potential for evaluating patients with MASLD in both primary and tertiary care settings;[47] in this context, LSM-SSI emerges a promising alternative to VCTE-based LSM.

While PPV increased with higher HCC occurrence—reaching up to 20% at a 2% pre-set occurrence rate (Tables 3, 4, S4)—the PPV remained relatively low overall. For this reason, we recommend using these algorithms primarily to identify individuals who do not require HCC surveillance. This is a critical consideration, especially given the widespread prevalence of MASLD, which affects more than one-third of the global adult population above 48 years.[12] Conversely, to better define the subgroup of patients most likely to benefit from HCC surveillance, future studies are needed in larger cohorts with more reported HCC events. Such studies would support improved PPV, maintain diagnostic accuracy, and enhance the performance of algorithms for disease confirmation.

Many at-risk individuals may remain unidentified until advanced stages of MASLD. Our proposed two-step non-invasive algorithms offer a practical approach to bridge this gap by combining readily available biochemical scores with two-dimensional ultrasound–based fibrosis assessment. This modality has the potential to become more widely accessible in the future as standardization progresses, offering a feasible alternative to other liver stiffness measurement techniques.[48] Unlike existing risk models that often rely on single metrics or are not routinely applicable in everyday practice,[49–51] our approach enables flexible and scalable risk stratification tailored to the tests available in different clinical settings.

Limitations and Strengths

The limitations of this study stem from its post-hoc nature and monocentric design. Importantly, the threshold of elastography we defined may not apply to all other elastographic ultrasound methods. Nevertheless, its strength lies in the use of a prospective consecutive cohort of 352 patients, retrospectively evaluated, all of whom underwent standardized LSM-SSI evaluation using the same ultrasound system (SuperSonic Aixplorer), thereby ensuring data consistency and measurement reliability. In developing the algorithm, standardized cut-off values derived from previously published studies were applied, enhancing the robustness and reproducibility of the model. While the algorithms show promise, external validation in independent populations would be necessary to ensure broader applicability. Interestingly, our cohort included a lower proportion of patients with elevated LSM, compared to prior studies,[20] which may reflect a more representative group of the entire MASLD population. Nevertheless, our cohort consisted of 352 patients from a single-center experience, of whom 9 (2.6%) developed HCC during follow-up. This limited number of events may have reduced the statistical power of our analysis and should be taken into consideration when interpreting the findings. External validation would further support the generalizability and clinical applicability of our proposed algorithms.

Conclusions

HCC represents the most common liver-related complication in non-cirrhotic MASLD.

As supporting evidence expands and the method becomes further standardized, two-dimensional shear wave elastography (2D-SWE) is increasingly becoming more available in clinical practice and has the potential to make a meaningful contribution to HCC risk stratification in MASLD. An LSM-SSI value <7.4 kPa (rule-out ≥F3) reliably identifies patients at negligible risk of developing HCC, for whom routine surveillance may be safely omitted. In contrast, patients with LSM-SSI ≥7.4 kPa, particularly those with additional risk factors such as T2DM or elevated GGT, may benefit from regular HCC surveillance. To support clinical decision-making, a two-step algorithm combining LSM-SSI with the PLEASE score demonstrated excellent rule-out performance and high overall accuracy, offering a practical tool for real-time risk stratification. This personalized approach reduces unnecessary examinations in low-risk individuals while enhancing the efficiency of surveillance in higher-risk groups. Future validation in larger and more diverse populations will be crucial to confirm its widespread implementation and to further optimize HCC surveillance strategies in MASLD.

Abbreviations

%, percentage; 2D-SWE, two-dimensional shear wave elastography; AASLD, American Association for the Study of Liver Diseases; ACLD, advanced chronic liver disease; Acc, accuracy; AFP, alpha-fetoprotein; BMI, body mass index; FIB-4, fibrosis-4 index; CI, confidence interval; cm, centimeters; CSPH, clinically significant portal hypertension; DN, dysplastic nodules; Df, degree of freedom; EASL, European Association for the Study of the Liver; F3, advanced fibrosis; F4, cirrhosis; FN, false negatives; FP, false positives; g/dL, grams per deciliter; GGT, gamma-glutamyltransferase (IU/L); HCC, hepatocellular carcinoma; HRI, hepatorenal index; HS, hazard ratio; HTA, arterial hypertension; IU/L, international units per liter; IQR, interquartile range; kPa, kilopascals; K, potassium; kg, kilograms; kg/m^2, kilograms per square meter; LR-, negative likelihood ratio; LR+, positive likelihood ratio; LSM, liver stiffness measurement; MACE, major adverse cardiovascular events; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; mg/dL, milligrams per deciliter; mmHg, millimeters of mercury; MS, metabolic syndrome; n, number; Na, sodium; NPV, negative predictive value; PVT, portal vein thrombosis; PLEASE score, Platelet, Elastography-SSI, Age, Sex, Etiology; PPV, positive predictive value; PY, person-years; Q1, first quartile; Q3, third quartile; SD, standard deviation; Se, sensitivity; SI, stability index; Sp, specificity; SSI, SuperSonic Imagine; SWE, shear wave elastography; T2DM, type 2 diabetes mellitus; χ^2 - chi-square statistic.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Madalina-Gabriela Indre and Bernardo Stefanini are co-first authors for this study. Silvia Ferri and Federico Ravaioli are co-last authors for this study. Prof. Dr. Francesco Tovoli reports personal fees from Roche, AstraZeneca, BMS, outside the submitted work. Prof. Dr. Fabio Piscaglia reports personal fees from Astrazeneca, BMS, Bracco, IPSEN, MSD, Novonordisk, Roche, EISAI, and SIEMENS Healthineers, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Friedman SL. Fat, fibrosis, and the future: navigating the maze of MASLD/MASH. *J Clin Invest*. 2025;135(7). doi:10.1172/JCI186418
2. Sheka AC, Adeyi O, Thompson J, Hameed B, Crawford PA, Ikramuddin S. Nonalcoholic Steatohepatitis: a Review. *JAMA*. 2020;323(12):1175–1183. doi:10.1001/jama.2020.2298
3. Dyson J, Jaques B, Chattopadyhay D, et al. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. *J Hepatol*. 2014;60(1):110–117. doi:10.1016/j.jhep.2013.08.011
4. Mittal S, Sada YH, El-Serag HB, et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. *Clin Gastroenterol Hepatol*. 2015;13(3):594–601.e1. doi:10.1016/j.cgh.2014.08.013
5. Villanueva A. Hepatocellular Carcinoma. *N Engl J Med*. 2019;380(15):1450–1462. doi:10.1056/NEJMra1713263
6. Stine JG, Wentworth BJ, Zimmet A, et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. *Aliment Pharmacol Ther*. 2018;48(7):696–703. doi:10.1111/apt.14937
7. Ioannou GN. Epidemiology and risk-stratification of NAFLD-associated HCC. *J Hepatol*. 2021;75(6):1476–1484. doi:10.1016/j.jhep.2021.08.012
8. Piscaglia F, Svegliati-Baroni G, Barchetti A, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. *Hepatology*. 2016;63(3):827–838. doi:10.1002/hep.28368
9. Xiang J, Li Y, Mei S, et al. Novel diagnostic and therapeutic strategies based on PANoptosis for hepatocellular carcinoma. *Cancer Biol Med*. 2025;22(8):928–939. doi:10.20892/j.issn.2095-3941.2025.0150
10. Sarasin FP, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. *Am J Med*. 1996;101(4):422–434. doi:10.1016/S0002-9343(96)00197-0
11. Ningarhari M, Mourad A, Delacôte C, et al. Benefits of tailored hepatocellular carcinoma screening in patients with cirrhosis on cancer-specific and overall mortality: a modeling approach. *Hepatol Commun*. 2022;6(10):2964–2974. doi:10.1002/hep4.2059
12. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology*. 2023;77(4):1335–1347. doi:10.1097/HEP.0000000000000004
13. Tovoli F, Ferri S, Piscaglia F. Hepatocellular carcinoma in non alcoholic fatty liver disease. *Curr Pharm Des*. 2020;26(32):3909–3914. doi:10.2174/1381612826666200429093648

14. Orci LA, Sanduzzi-Zamparelli M, Caballol B, et al. Incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. *Clin Gastroenterol Hepatol*. 2022;20(2):283–92.e10. doi:10.1016/j.cgh.2021.05.002
15. Bruix J, Sherman M. Management of Hepatocellular Carcinoma: an UpdateΔσ. *Hepatology*. 2011;53(3):1020–1022. doi:10.1002/hep.24199
16. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2018;68(2):723–750. doi:10.1002/hep.29913
17. Dobrow MJ, Hagens V, Chafe R, Sullivan T, Rabeneck L. Consolidated principles for screening based on a systematic review and consensus process. *Cmaj*. 2018;190(14):E422–e9. doi:10.1503/cmaj.171154
18. Taru MG, Lupsor-Platon M. Exploring opportunities to enhance the screening and surveillance of hepatocellular carcinoma in non-alcoholic fatty liver disease (NAFLD) through risk stratification algorithms incorporating ultrasound elastography. *Cancers*. 2023;15(16):4097. doi:10.3390/cancers15164097
19. Heath RD, Brahmbhatt M, Tahan AC, Ibdah JA, Tahan V. Coffee: the magical bean for liver diseases. *World J Hepatol*. 2017;9(15):689–696. doi:10.4254/wjh.v9.i15.689
20. Gu W, de Lédinghen V, Aubé C, et al. Hepatocellular cancer surveillance in patients with advanced chronic liver disease. *NEJM Evidence*. 2024;3(11):EVIDoa2400062. doi:10.1056/EVIDoa2400062
21. Sangro B, Argemi J, Ronot M, et al. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. *J Hepatol*. 2025;82(2):315–374.
22. Berzigotti A, Tsochatzis E, Boursier J, et al. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis–2021 update. *J Hepatol*. 2021;75(3):659–689.
23. Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology*. 2023;78(6):1966–1986.
24. Galle PR, Forner A, Llovet JM, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019
25. for Research EO. Liver EAftSot. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908–943. doi:10.1016/j.jhep.2011.12.001
26. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VII. Renewing consensus in portal hypertension. *J Hepatol*. 2022;76(4):959–974. doi:10.1016/j.jhep.2021.12.022
27. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (Long Version). *Ultraschall Med*. 2017;38(4):e16–e47. doi:10.1055/s-0043-103952
28. Indre MG, Leucuta DC, Lupsor-Platon M, et al. Diagnostic accuracy of 2D-SWE ultrasound for liver fibrosis assessment in MASLD: a multilevel random effects model meta-analysis. *Hepatology*. 2024;82:454–469. doi:10.1097/HEP.0000000000001190
29. Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med*. 2021;385(17):1559–1569. doi:10.1056/NEJMoa2029349
30. Yip TC-F, Lee HW, Lin H, et al. Prognostic performance of the two-step clinical care pathway in metabolic dysfunction-associated steatotic liver disease. *J Hepatol*. 2025;83(2):304–314. doi:10.1016/j.jhep.2025.01.014
31. Plaz Torres MC, Bodini G, Furnari M, et al. Surveillance for hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: universal or selective? *Cancers*. 2020;12(6):1422. doi:10.3390/cancers12061422
32. Díaz-González Á, Forner A. Surveillance for hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol*. 2016;30(6):1001–1010. doi:10.1016/j.bpg.2016.10.006
33. Bassegoda O, Olivas P, Turco L, et al. Decompensation in advanced nonalcoholic fatty liver disease may occur at lower hepatic venous pressure gradient levels than in patients with viral disease. *Clin Gastroenterol Hepatol*. 2022;20(10):2276–86.e6. doi:10.1016/j.cgh.2021.10.023
34. Piscaglia F, Salvatore V, Mulazzani L, et al. Differences in liver stiffness values obtained with new ultrasound elastography machines and Fibroscan: a comparative study. *Dig Liver Dis*. 2017;49(7):802–808. doi:10.1016/j.dld.2017.03.001
35. Paternostro R, Kwanten WJ, Hofer BS, et al. Hepatic venous pressure gradient predicts risk of hepatic decompensation and liver-related mortality in patients with MASLD. *J Hepatol*. 2024;81(5):827–836. doi:10.1016/j.jhep.2024.05.033
36. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-effectiveness of hepatocellular carcinoma surveillance: an assessment of benefits and harms. *Am J Gastroenterol*. 2020;115(10):1642–1649. doi:10.14309/ajg.0000000000000715
37. Braude M, Roberts S, Majeed A, et al. Liver stiffness (Fibroscan®) is a predictor of all-cause mortality in people with non-alcoholic fatty liver disease. *Liver Int*. 2023;43(1):90–99. doi:10.1111/liv.15415
38. Johnson AL, Hayward KL, Patel P, et al. Predicting liver-related outcomes in people with nonalcoholic fatty liver disease: the prognostic value of noninvasive fibrosis tests. *Hepatol Commun*. 2022;6(4):728–739. doi:10.1002/hep4.1852
39. Pons M, Rivera-Esteban J, Manzano R, et al. Non-invasive tests of liver fibrosis help in predicting the development of hepatocellular carcinoma among patients with NAFLD. *J Clin Med*. 2022;11(9):2466. doi:10.3390/jcm11092466
40. Boursier J, Hagström H, Ekstedt M, et al. Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events. *J Hepatol*. 2022;76(5):1013–1020. doi:10.1016/j.jhep.2021.12.031
41. Lee JS, Sinn DH, Park SY, et al. Liver stiffness-based risk prediction model for hepatocellular carcinoma in patients with nonalcoholic fatty liver disease. *Cancers*. 2021;13(18):4567.
42. Shili-Masmoudi S, Wong GL, Hiriart JB, et al. Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease. *Liver Int*. 2020;40(3):581–589. doi:10.1111/liv.14301
43. Lai JC-T, Yang B, Lee HW, et al. Non-invasive risk-based surveillance of hepatocellular carcinoma in patients with metabolic dysfunction-associated steatotic liver disease. *Gut*. 2025;74(12):2050–2057. doi:10.1136/gutjnl-2025-334981
44. Petta S, Sebastiani G, Viganò M, et al. Monitoring occurrence of liver-related events and survival by transient elastography in patients with nonalcoholic fatty liver disease and compensated advanced chronic liver disease. *Clin Gastroenterol Hepatol*. 2021;19(4):806–15.e5. doi:10.1016/j.cgh.2020.06.045
45. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. *PLoS Med*. 2014;11(4):e1001624. doi:10.1371/journal.pmed.1001624

46. Tzartzeva K, Obi J, Rich NE, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. *Gastroenterology*. 2018;154(6):1706–18.e1. doi:10.1053/j.gastro.2018.01.064
47. Ferraioli G, Barr RG, Berzigotti A, et al. WFUMB guideline/guidance on liver multiparametric ultrasound: part 1. update to 2018 guidelines on liver ultrasound elastography. *Ultrasound Med Biol*. 2024;50(8):1071–1087. doi:10.1016/j.ultrasmedbio.2024.03.013
48. John BV, Bastaich DR, Deng Y, Singal AG, Dahman B. Use of liver stiffness measurement for HCC risk stratification in metabolic dysfunction-associated steatotic liver disease. *Hepatology*. 2025. doi:10.1097/HEP.0000000000001498
49. Chalasani NP, Porter K, Bhattacharya A, et al. Validation of a novel multitarget blood test shows high sensitivity to detect early stage hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. 2022;20(1):173–82.e7. doi:10.1016/j.cgh.2021.08.010
50. Truong E, Gornbein JA, Yang JD, et al. MRI-AST (MAST) score accurately predicts major adverse liver outcome, hepatocellular carcinoma, liver transplant, and liver-related death. *Clin Gastroenterol Hepatol*. 2023;21(10):2570–2577.e1. doi:10.1016/j.cgh.2023.02.003
51. Fujiwara N, Kobayashi M, Fobar AJ, et al. A blood-based prognostic liver secretome signature and long-term hepatocellular carcinoma risk in advanced liver fibrosis. *Med*. 2021;2(7):836–50.e10. doi:10.1016/j.medj.2021.03.017