Exploration of Digestive Diseases

Open Exploration

Open Access Review

Liver and spleen stiffness measurement in the prediction of hepatocellular carcinoma in chronic liver disease

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Academic Editor: Chiara Raggi, University of Florence, Italy

Received: February 8, 2024 **Accepted:** May 22, 2024 **Published:** August 21, 2024

Cite this article: Fichera A, Fraquelli M. Liver and spleen stiffness measurement in the prediction of hepatocellular carcinoma in chronic liver disease. Explor Dig Dis. 2024;3:344–61. https://doi.org/10.37349/edd.2024.00055

Abstract

One of the primary complications of cirrhosis and portal hypertension is the occurrence of hepatocellular carcinoma (HCC), which is among the most common malignancies worldwide. There is limited availability of predictive non-invasive markers for primary HCC development in compensated advanced chronic liver disease (cACLD) patients. The reference standard method of assessing prognosis for cACLD patients, beyond liver fibrosis assessed by histology, is the measurement of the hepatic venous pressure gradient (HVPG). HVPG ≥ 10 mmHg is associated with an increased risk of HCC in these patients. However, these methods are expensive and invasive and are available only at referral centers. In the last decade, several studies have focused on the evaluation of several, simple, non-invasive tests (NITs) as predictors of HCC development. Among these methods, attention has particularly been paid to the elastographic techniques for the assessment of liver and spleen stiffness. We have reviewed the current literature about vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE), and other ultrasound-based elastographic techniques (e.g., SWE) in predicting primary HCC occurrence and recurrence. Despite promising results, the overall heterogeneity resulting from the variability in the populations analyzed, the differences in the elastographic techniques used, the design and methodological quality of the available studies, prevented us from drawing definite conclusions on the liver and spleen stiffness role for predicting HCC occurrence and recurrence in chronic liver disease patients.

Keywords

Hepatocellular carcinoma (HCC), magnetic resonance elastography (MRE), non-invasive diagnosis, shear-wave elastography (SWE), vibration-controlled transient elastography (VCTE)

Introduction

In people with chronic liver disease (CLD), the most common type of primary liver cancer is hepatocellular carcinoma (HCC), which represents the fourth most common cause of cancer-related deaths. Many studies

have pointed out that in 90% of cases HCC occurs in patients with chronic liver diseases [1] and cirrhosis represents the strongest risk factor for its occurrence [2, 3].

This is the reason why several studies have investigated liver stiffness measurement (LSM) as assessed by vibration-controlled transient elastography (VCTE) or other elastographic techniques implemented on standard ultrasound machines (for example, shear wave elastography, SWE) or magnetic resonance elastography (MRE). These studies have aimed at assessing the predictive role of liver and spleen stiffness measurement (SSM) in evaluating the risk of HCC development in patients with chronic liver disease of various etiologies.

SSM has widened with VCTE over the last decade. The spleen, differently from the liver, is involved in the hemodynamic modifications due to portal hypertension (PH) even at higher values of portal pressure. The degree of PH is closely associated with spleen stiffness even at hepatic venous pressure gradient (HVPG) values above 10–12 mmHg.

Recently, several studies [4–6] have shown the excellent performance of SSM in predicting clinically significant liver events such as the presence of oesophageal varices and the risk of cirrhosis-related complications, including ascites, variceal bleeding, encephalopathy, and HCC.

This paper aims to offer a comprehensive narrative review of the available literature on the role of liver and spleen stiffness in predicting primary HCC occurrence and tumor recurrence in patients with chronic liver disease of various etiologies.

Methods

The following databases were searched until December 2023: MEDLINE via PubMed, Embase, Scopus, and Cochrane. The search strategy was developed according to repeatable patterns, ensuring the high quality of the obtained results. The databases search strategy consisted of using both medical subject heading keywords and free terms that ensured search repeatability in the various databases (Supplementary material).

We decided to exclude the studies assessing the predictive role of serological non-invasive tests (NITs) for HCC occurrence and recurrence as beyond the scope of our review, whereas we included the studies assessing the combination of elastographic techniques and serological tests.

On account that liver damage and fibrosis progression are strongly related to the cause of the underlying hepatic disease, we analyzed the studies according to their etiology.

Results

For better comprehension of the results we decided to summarize the findings of the primary studies according to the etiology of the underlying liver disease and according to the elastographic technique used to assess LSM or SSM.

HBV: studies assessing LSM with VCTE

The worldwide prevalence of chronic hepatitis B virus (HBV) infection is estimated at around 400 million individuals [7]. The annual incidence of progression from chronic hepatitis to cirrhosis ranges from 2.1% to 6% and is influenced by older age, lack of viral suppression, and the co-infection with hepatitis C virus (HCV)/hepatitis D virus (HDV) [8]. Overall, the progression to liver cirrhosis and HCC is estimated to reach 40% of subjects with chronic HBV infection [9].

Assuming the need for a reliable non-invasive evaluation of liver fibrosis, Seo et al. [10] have demonstrated with a multivariate analysis that LSM value was an independent predictor of HCC occurrence [hazard ratio (HR): 1.041, $p < 0.001$], while histology was not ($p > 0.05$).

Taking into account other NITs for fibrosis staging, the study by Chon et al. [11] demonstrated a higher diagnostic accuracy of baseline LSM [area under the receiver operating curve (AUROC) 0.789] compared to APRI (AUROC 0.729) and FIB-4 (AUROC 0.744) in the prediction of HCC occurrence during follow-up.

Less satisfactory results were found in the study by Wang et al. [12] in which LSM had AUROC 0.636 with a proposed cut-off value of 21.5 kPa, (Sens 55.6%, Spec 64.2%). In addition, liver stiffness variations during follow-up were not demonstrated to be associated with HCC occurrence (Table 1).

HCV: studies assessing LSM with VCTE

It is estimated that HCC develops late, almost after 20 years from HCV infection, during the cirrhosis stage of the disease [23, 24]. Due to its worldwide diffusion, HCV is the leading cause of HCC occurrence in the setting of liver cirrhosis [25]. The natural history of HCV infection has been revolutionized by the antiviral therapy with direct antiviral agent (DAA); however, in patients with advanced liver fibrosis, the risk of HCC development remains high [26] even if in sustained virological response (SVR).

The study by Wang et al. [27] showed at multivariate analysis, that patients with baseline liver stiffness values > 24 kPa and between 12–24 kPa held higher risk of HCC development (HR 24.6, 95% CI 2.7–220.4, p = 0.004 and HR 11.7, 95% CI 1.3–105.2, p = 0.028) in comparison to those with LSM < 12 kPa. Furthermore, during follow-up LSM values persistently > 12 kPa carried a higher risk to develop HCC compared with those with LSM < 12 kPa.

In the study by Nakagomi et al. [28] baseline liver stiffness predicted the cumulative risk of HCC occurrence until 10 years. In detail, at enrollment, values of LSM ≤ 5 kPa, 5.1–10 kPa, 10.1–15 kPa, 15.1–20 kPa, 20.1–25 kPa, and > 25 kPa were associated with a progressively higher risk of 1.8%, 4.8%, 7.3%, 11.9%, 16.9%, and 22.7% of developing HCC at 1, 2, 3, 5, 7, and 10 years, respectively (Table 2).

HCV: studies assessing LSM with MRE

Promising results come from the application of MRE in the prediction of HCC occurrence.

In the study by Kumada et al. [39], a total of 537 viremic patients with HCV were evaluated at baseline with MRE. During follow-up, the patients received DAA treatment obtaining SVR. During the median follow-up of 43.8 months, those patients with baseline MRE value > 4.5 kPa (adjusted HR 7.301) showed higher rates of HCC occurrence and MRE resulted to be independently associated with HCC development at multivariate analysis.

Conversely, Tamaki et al. [40] evaluated 346 patients with SVR in prediction of HCC occurrence. In their study, MRE was compared to other NITs such as FIB-4. LSM ≥ 3.75 kPa was shown to be an independent predictive factor for HCC occurrence (HR 3.51, 95% CI 1.24–9.99) at multivariate analysis. In the patients with LSM ≥ 3.75 kPa the development of HCC was 6.6%, 11.9%, and 14.5% at 1/2/3-year, respectively. The AUROC analysis for LSM resulted in 0.661, 0.724, and 0.743 at 1, 2 and 3 years, respectively.

In a further study, Kumada et al. [41] evaluated patients with HCV-related chronic liver disease at baseline (viremic) with MRE and SWE (LOGIQ S8 GE Healthcare) in the prediction of HCC occurrence. Their study found a good accuracy of both methods in the prediction of HCC at 5 years of follow-up. More in detail, LSM-MRE > 4.5 kPa showed a time-dependent AUROC 0.808 and LSM-SWE > 11.7 kPa showed a time-dependent AUROC 0.826 for the development of HCC (Table 3).

HCV: studies assessing LSM with SWE

The study by Gyotoku et al. [42] assessed shear-wave velocity (LOGIQ E9 multi-purpose GE Healthcare) at baseline, at the end of DAA therapy, at 12 and 24 weeks after treatment for purposes of evaluating its diagnostic accuracy in HCC prediction. Their study showed a greater accuracy of shear wave velocity at 24 weeks with AUROC 0.86 as compared to baseline (AUROC 0.80), end of treatment (AUROC 0.74), and at 12 weeks after SVR (AUROC 0.72). The authors found that the patients with HCC had baseline SWE values higher than those who did not develop primary liver cancer: 1.86 ± 0.20 m/s (1.52–2.26) *vs.* 1.58 ± 0.26 m/s (1.03–2.56) (p = 0.0036).

The study by Hamada et al. [43] evaluated the diagnostic accuracy of LSM-SWE (SuperSonic Imagine S.A., France) in the prediction of HCC development in HCV-SVR patients. This study showed an AUROC 0.93 with an optimal LSM cut-off value ≥ 11 kPa (Sens 75%, Spec 95%) (Table 4).

Table 1. Studies (*n* = 13) evaluating liver stiffness by VCTE and HCC occurrence in HBV patients. Composite model comprising VCTE

Author & year	Region	Virological status	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Jung et al., 2011 [13]	Korea	Mixed	1,130	50.2	31	57	5	8	-	-	-	-	-	-	-
Chon et al., 2012 [11]	Korea	Mixed	1,126	50.2	30.7	63	5.5	-	0.789	-	-	-	-	-	-
Kim et al., 2012 [14]	Korea	No therapy at baseline	128	52.5	27.8	14	11	≥ 19	0.722	61.1	86.2	-	-	4.36	0.45
Kim et al., 2013 [15]	Korea	Mixed	1,250	50	30.7	56	4.5	-	0.802	-	-	-	-	-	-
Wong et al., 2014 [16]	China	Mixed	1,555	46 ± 12	69	55	3.5	≥ 11	0.89	87.9		-	99.4	-	-
Kim et al., 2015 [17]	Korea	Mixed	2,876	46.1	48.9	52	1.8	≥ 13	-	-	-	-	-	-	-
Bihari et al., 2016 [18]	Asia	Mixed	964	38.6 ± 14.6	-	14	1.4	-	0.767*	-	-	-	-	-	-
Seo et al., 2016 [10]	Asia	No therapy at baseline	381	44.1 ± 12.3	48.1	34	8.9	-	0.745	-	-	-	-	-	-
Jeon et al., 2017 [19]	Korea	Mixed	540	51.5	54.1	81	15	≥ 13	0.598	-	-	-	-	-	-
Li et al., 2017 [20]	China	Viral suppression	1,200	40–59	-	156	13	≥ 9.7	-	-	-	-	-	-	-
Izumi et al., 2019 [21]	Japan	Mixed	377	-	27	23	6	≥ 6.2	0.79520	73.9	82.2	21.3	98	4.11	0.31
Wang et al., 2019 [12]	Taiwan, China	Viral suppression	257	52.6	45.6	27	10	≥ 21.5	0.636	55.6	64.2	-	-	1.5	0.68
Lee et al., 2021 [22]	Korea	Viral suppression	880	53.1	24	81	9	≥ 6.4	-	-	-	-	-	-	-

*: composite outcome; VCTE: vibration-controlled transient elastography

Table 2. Studies (*n* = 13) evaluating liver stiffness by VCTE and HCC occurrence in patients with HCV

Author & year	Region	SVR	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Masuzaki et al., 2008 [29]	Japan	-	265	-	8	85	32	≥ 25	0.805	-	-	-	-	-	-
Masuzaki et al., 2009 [30]	Japan	No	866	62.2 ± 11.3	36	77	8.9	≥ 25	-	-	-	-	-	-	-
Wang et al., 2013 [27]	Taiwan, China	Mixed	198	53.0 ± 11.2	47.8	10	5	≥ 12	-	-	-	-	-	-	-
Calvaruso et al., 2013 [31]	Italy	No	233	-	42 ± 18	20	8.5	≥ 21	0.73	70	60	-	-	1.75	0.5
Feier et al., 2013 [32]	Romania	No	184	62.23	-	72	39	≥ 38.5	0.68	51.7	90.4	86.1	61.8	5.2	0.5
Narita et al.,2014 [33]	Japan	No	151	62	24	9	5.9	≥ 14	-	-	-	-	-	-	-
Wang et al., 2016 [34]	Taiwan, China	SVR	278	54.1	91.2	18	6.5	≥ 12	0.781	55.6	91.9	-	-	0.7	0.5
D'Ambrosio et al., 2018 [35]	Italy	No	404	63	36	24	6	≥ 30	-	-	-	-	-	-	-
Degasperi et al, 2019 [36]	Italy	No	546	64	25	28	5	≥ 30	-	-	-	-	-	-	-
Nakagomi et al., 2019 [28]	Japan	No	1,146	63	79.2	190	16.5	-	-	-	-	-	-	-	-
Pons et al., 2020 [37]	Spain	SVR	572	63.7	33.6	25	4	-	-	-	-	-	-	-	-
Izumi et al, 2019 [21]	Japan	Mixed	419	-	30	32	7.6	≥ 8	0.80592	84.4	63.3	16.1	98	2.3	0.25
Rinaldi et al., 2019 [38]	Italy	SVR	258	68	24	35	13.5	≥ 27.8	0.691	72	65	-	-	2.05	0.4

SVR: sustained virological response; VCTE: vibration-controlled transient elastography

Table 3. Studies (*n* = 3) evaluating liver stiffness with MRE and HCC occurrence in patients with HCV

Author & year	Region	SVR	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Tamaki et al., 2019 [40]	Japan	SVR	346	68.2 ± 10	26.4 ± 7.9	24	7	-	-	-	-	-	-	-	-
Kumada et al., 2021 [39]	Japan	No	537	72	43.8	18	3	> 4.5	-	-	-	-	-	-	-
Kumada et al., 2022 [41]	Japan	No	525	72	60	21	4	> 4.5	0.808	77.8	81.6	-	-	4.3	0.26

SVR: sustained virological response

Table 4. Studies (*n* = 3) evaluating liver stiffness by SWE and HCC occurrence in patients with HCV

Author & year	Region	SVR	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Hamada et al., 2018 [43]	Japan	SVR	196	62	26	-	-	≥ 11	0.933	75	95	0.273	0.989	1.5	0.6
Gyotoku et al., 2022 [42]	Japan	SVR during FU	229	65.6	32.6 ± 19.5	8	3.5	-	0.86041	-	-	-	-	-	-
Kumada et al., 2022 [41]	Japan	No	525	72	60	21	4	> 11.7	0.826	78.6	82	-	-	4.3	0.26

SWE: shear wave elastography; SVR: sustained virological respons

HCV: studies assessing SSM with VCTE

Dajti et al. [44] evaluated the prediction of LSM and SSM for the diagnosis of HCC in patients with SVR. They found in univariate analysis that SSM SVR-24 was significantly associated with HCC development (HR 1.029, 95% CI 1.006–1.053, $p = 0.013$). At adjusted multivariate analysis, SSM SVR-24 showed HR 1.025 (95% CI 1.001–1.050, $p = 0.049$).

The SSM cut-off value defined in this study was 42 kPa (Sens 75%, Spec 61%, NPV 93.6%, PPV 24.2%) (Table 5).

Mixed etiology: studies assessing LSM with VCTE

The studies reported below include populations with different etiologies of liver disease, this fact has to be considered in the evaluation of liver stiffness diagnostic performance in prediction of HCC occurrence.

The study by Kuo et al. [45] evaluated 435 patients with HCV/HBV infection at different stages of liver disease. The AUROC of LSM in predicting HCC presence was 0.736. At multivariate analysis, liver stiffness proved to be an independent factor for HCC presence (odds ratio 1.07, 95% CI 1.05–1.09). LSM diagnostic performance was further stratified according to stiffness values < 12 kPa, 12–24 kPa, and > 24 kPa. In the prediction of HCC occurrence, LSM > 24 kPa showed 41.5% sensitivity and a higher level of specificity at 92.7%, as compared to the other cut-off values.

Many studies compared LSM and HVPG in the prediction of clinically significant liver-related events as a composite outcome.

In the study by Robic et al. [46], LSM proved to be non-inferior to HVPG in the prediction of liver-related events (including HCC). Therefore, LSM could be considered a worthy alternative to invasive HVPG in the prediction of liver complications. In support of this, Pérez-Latorre et al. [47] have demonstrated the non-inferiority of VCTE (AUROC 0.85, 95% CI 0.73–0.97) compared to HVPG (AUROC 0.76, 95% CI 0.63–0.89) in the prediction of liver-related events (including HCC), in cirrhotic patients with HCV-HIV co-infection (Table 6).

Mixed etiology: studies assessing LSM with MRE

Lee et al. [54], evaluated 217 patients with various causes of liver disease at risk for HCC occurrence. At multivariate analysis, the authors found that LSM values obtained by MRE were predictive of HCC occurrence ($p < 0.001$, HR = 1.59 per unit, 95% CI 1.25–2.03). In addition, they identified LSM 4.4 kPa as a cut-off value able to predict the occurrence of HCC.

In the study by Ichikawa et al. [55] the predictive value of LSM-MRE was stratified based on three levels: LSM < 3 kPa, 3–4.7 kPa, or > 4.7 kPa. Patients have undergone MRE examinations at baseline and during follow-up. The authors subclassified patients into three groups according to sequential changes in liver stiffness: Group A (high LSM on the first MRE), Group C (low on both examinations), Group B (other combinations). This study showed that patients of Group A had a risk ratio of 1.018–6.030 ($p = 0.0028–0.0268$) for the development of HCC.

On the other hand, the previous case-control study by Anaparthy et al. [56] investigated the difference in LSM-MRE between cACLD patients with or without HCC. This study found no significant difference ($p = 0.7$) in LSM-MRE between individuals with HCC (6.3 ± 2.1 kPa) and patients without (6.1 ± 2.3 kPa) (Table 7).

Mixed etiology: studies assessing LSM with SWE

Kasai et al. [59] evaluated the predictive value of LSM-SWE (Aixplorer US system SuperSonic Imagine S.A.) for HCC in 273 patients with various etiologies of liver disease.

This case-control study found a significant difference in LSM value (22.65 ± 10.19 kPa) of patients with HCC and those without (12.67 ± 9.45 kPa) ($p < 0.0001$) (Table 8).

Table 5. Study evaluating spleen stiffness by VCTE and HCC occurrence in patients with HCV

Author & year	Region	SVR	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Dajti et al., 2021 [44]	Italy	SVR	140	63	41.5	20	14	≥ 42	0.682	75	61	24.2	93.6	1.92	0.41

SVR: sustained virological response; VCTE: vibration-controlled transient elastography

Table 6. Studies (*n* = 9) evaluating liver stiffness by VCTE and HCC occurrence in patients with mixed etiology

Author & year	Region	Etiology (%)	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Nahon et al., 2009 [48]	France	HCV 67 EtOH 33	265	-	-	66	26	-	-	-	-	-	-	-	-
Kuo et al., 2010 [45]	Taiwan, China	HCV 57 HBV 43	435	-	15	106	24	≥ 12	0.736	69.8	69.6	-	-	2.3	0.43
Robic et al., 2011 [46]	France	EtOH 38 HBV+ HCV 28 Others 34	100	56 ± 13	24	4	4	≥ 21.1*	0.837	81.6	75.9	68.9	86.3	3.37	0.23
Akima et al., 2011 [49]	Japan	HCV 85 HBV14 HBV + HCV 1	157	-	48	41	26	≥ 12.5	0.727	-	-	-	-	-	-
Klibansky et al., 2012 [50]	America-Israel	HCV 67.5 NAFLD 13.5 Others 19	667	51	28.07	16	2.3	≥ 10.5*	0.87	94.7	63	19.3	99.2	2.5	0.79
Salmon et al., 2012 [51]	France	HCV + HIV	244	46.8	31.2	21	8.7	≥ 12.5	-	-	-	-	-	-	-
Poynard et al., 2014 [52]	France	HCV 79 HIV 7 EtOH 14	3,927	49	144	84	2	-	0.86	-	-	-	-	-	-
Pérez-Latorre et al., 2014 [47]	Spain	HCV 40 HIV 60	60	-	42	7	12	≥ 40*	0.85	67	90	62	91	6.7	0.36
Adler et al., 2016 [53]	UK-Italy	HCV 50.7 NAFLD 10.2 Others 39.1	432	56 ± 13	31.1	41	9	≥ 20	-	-	-	-	-	-	-

*: composite outcome; NAFLD: non-alcoholic fatty liver disease; VCTE: vibration-controlled transient elastography

Table 7. Studies (*n* = 5) evaluating liver stiffness by MRE and HCC occurrence in patients with mixed etiology

Author & year	Region	Etiology (%)	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Anaparthy et al., 2011 [56]	USA	Viral 57 NAFLD 33 Others 10	90	64 ± 10 (pts with HCC)	-	30	33	-	-	-	-	-	-	-	-
Motosugi et al., 2013 [57]	Japan	HCV 65 Others 35	132	70.5	-	66	50	-	-	-	-	-	-	-	-
Lee et al., 2018 [54]	Japan	HBV 65.9 HCV 10.6 Others 23.5	217	59.7 ± 12.0	45.0 ± 17.6	33	15	≥ 4.4	-	-	-	-	-	-	-
Ichikawa et al., 2019 [55]	Japan	HCV 62 HBV 22 Others 16	161	-	-	47	29.2	-	-	-	-	-	-	-	-
Higuchi et al., 2022 [58]	Japan-USA	HCV 51.2 HBV 15.8 Others 33	2,373	68	33.6	99	4	-	-	-	-	-	-	-	-

NAFLD: non-alcoholic fatty liver disease

Table 8. Study evaluating liver stiffness by SWE and HCC occurrence in patients with mixed etiology

Author & year	Region	Etiology	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Kasai et al., 2015 [59]	Japan	Various, proportions not specified	273	-	-	89	33	-	0.791	-	-	-	-	-	-

SWE: shear wave elastography

NAFLD: studies assessing LSM with VCTE

Nowadays non-alcoholic fatty liver disease (NAFLD) represents the most frequent cause of liver disease worldwide with an estimated prevalence in the USA and Europe between 10% and 30% [60]. Many clinical conditions are associated with NAFLD: obesity, hyperlipidemia, hypertension, type-2 diabetes, and metabolic syndrome. NAFLD is defined as the presence of steatosis in more than 5% of hepatocytes. The histological spectrum varies and includes non-alcoholic fatty liver, steatohepatitis (NASH; steatosis with inflammation and hepatocyte ballooning) and advanced fibrosis which ultimately evolves in cirrhosis [61]. Patients whose liver disease progresses through stages are at major risk of liver-related complications, such as HCC development.

In the study by Shili-Masmoudi et al. [62], including 2,251 patients, LSM was showed to be at multivariate analysis an independent predictor of overall survival with an adjusted HR 2.85 (1.65–4.92), p = 0.0002. Moreover, patients with elevated baseline LSM had a major risk to develop cardiovascular and liver events. The study also showed that patients with HCC occurrence during follow-up had a higher level of baseline LSM, but no further data was provided.

The study by Lee et al. [63], including 2,666 patients, showed the high accuracy of a composite model including age, LSM, platelets (PLT) together with aspartate transaminase (AST) ≥ 34 IU/L in the prediction of HCC occurrence, with AUROC at 2, 3, and 5 years of 0.948, 0.947, and 0.939, respectively (Table 9).

NAFLD: studies assessing LSM with MRE

Ajmera et al. [64] evaluated 6 studies assessing LSM-MRE and the prediction of liver-related events and HCC occurrence. In this study, LSM-MRE ≥ 5kPa was found to be associated with a greater than 1.5% risk of HCC development per year thus supporting the use of this cut-off for HCC surveillance. Moreover, this study stratified patients for the risk of HCC development at 1 and 3 year/s based on the value of LSM-MRE values: < 5 kPa, 5–8 kPa, > 8 kPa, and found a risk of 0.1%–0.35%, 3.71%–5.25% and 3.61%–5.66%, respectively. The HRs for HCC development were 23.4 (95% CI 6.85–79.8, p < 0.001) for LSM > 5kPa and 33.8 (95% CI 8.94–127.7, p < 0.001) for LSM 5–8 kPa, compared to LSM < 5 kPa (Table 10).

Studies assessing LSM and SSM in the prediction of HCC recurrence after resection

HCC recurrence after curative treatment represents a strong predictor of poor prognosis. Thus, stratification of patients at risk for this condition, potentially improves outcomes [65].

Many studies have evaluated liver and SSM in the prediction of HCC recurrence after treatment.

The study by Marasco et al. [66] evaluated the diagnostic accuracy of LSM and SSM with VCTE in the prediction of HCC recurrence after resection in patients with chronic liver disease. They defined early recurrence and late recurrence considering HCC onset < 24 months from surgery and > 24 months, respectively. This study found that SSM > 70 kPa was associated with a higher recurrence rate with a statistical significance at multivariate analysis. Thus, the authors proposed a cut-off value of SSM > 70 kPa.

The wide use of MR during follow-up in patients with previous HCC to detect tumor reappearance, have led many clinicians to investigate the role of LSM-MR in the prediction of HCC recurrence. Cho et al. [67] evaluated 192 patients with HCC who underwent hepatic resection, radio-frequency ablation (RFA), or trans-arterial chemoembolization (TACE). Interestingly, this study found that higher values of LSM represented an independent risk factor for early tumor recurrence both in patients treated with RFA/resection and TACE. In the first group, a cut-off of LSM-MR > 4.5 kPa showed an HR = 2.95; 95% CI 1.26–6.94; p = 0.013; in the second group LSM-MR > 6 kPa they found an HR = 2.94; 95% CI 1.27–6.83; p = 0.012 (Table 11).

Table 9. Studies (*n* = 3) evaluating liver stiffness by VCTE and HCC occurrence in patients with NAFLD

Author & year	Region	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Izumi et al., 2019 [21]	Japan	258	-	30	33	13	≥ 5.4	0.69	93.9	35.1	17.5	97.5	1.43	2
Shili-Masmoudi et al., 2020 [62]	France/Asia/Australia	2,251	59.4	27	-	-	≥ 12	-	-	-	-	-	-	-
Lee et al., 2021 [63]	Korea	2,666	52	64.6	22	0.8	≥ 9.3	-	-	-	-	-	-	-

NAFLD: non-alcoholic fatty liver disease; VCTE: vibration-controlled transient elastography

Table 10. Study evaluating liver stiffness by MRE and HCC occurrence in patients with NAFLD

Author & year	Region	Patients (*n*)	Mean age (years)	F-U months	HCC (*n*)	Prevalence (%)	Proposed cut-off (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Ajmera et al., 2022 [64]	USA-Asia	2,018	57.84	50.4	69	-	≥ 5 kPa	-	-	-	-	-	-	-

NAFLD: non-alcoholic fatty liver disease

Table 11. Study evaluating SSM by VCTE and HCC recurrence in patients with mixed etiology

Author & year	Region	Patients (*n*)	Mean age (years)	F-U months	Etiology of liver disease (%)	Recurrent HCC	Proposed cut off (TE) (kPa)	AUROC	Sens (%)	Spec (%)	PPV	NPV	LR+	LR–
Marasco et al., 2019 [66]	Italy	157	62	24	HCV 56 HBV 19.8 EtOH 21 Others 3.2	66 (early) 27 (late)	SSM > 70	-	-	-	-	-	-	-

SSM: spleen stiffness measurement; VCTE: vibration-controlled transient elastography

Conclusions

The measurement of liver stiffness by VCTE, elastographic techniques implemented on standard ultrasound systems (e.g., SWE) or MR-elastography has recently emerged as a possible predictive marker for HCC.

Actually, this parameter is probably connected to fibrosis severity, inflammation, and indirectly PH, which are all involved in the pathogenesis of HCC.

Most of the studies evaluated in our review have shown a good predictive value of liver stiffness for HCC occurrence in patients with different chronic liver diseases.

Despite our decision to stratify studies by etiology in order to reduce heterogeneity, one should note that the cut-off values of LSM still varied greatly among the studies, according to the different techniques and methodology used (timing of measurement, experience of the operator, interpretation of results). Also, many studies [68] have compared the accuracy of different electrographic techniques in the estimation of liver fibrosis showing that ultrasound elastography advantagiously focuses on a larger region of interest (ROI) rather than transient elastography with the opportunity to perform concomitantly the evaluation of liver parenchyma and thus HCC detection. However, elastography as implemented on standard US devices needs expertise and training not required for VCTE, which currently remains the most popular elastographic technique. Additionally, despite slightly higher diagnostic accuracy estimates, MRE comes with some limitations, i.e., its low availability and higher costs.

Noteworthy, even within the same etiological group some studies evaluated patients with different virological status, thus making the proposed cut-off value less reliable. As an example, many studies assessed liver stiffness before the start of antiviral treatment in naïve patients, whereas others made the assessment during viral suppression, thus obtaining non-comparable results. In fact, in the former group, the presence of active necro-inflammation could have led to an overestimation of the actual liver fibrosis stage.

Thus, further studies are needed to validate these findings and better define the specific optimal cut-off values for each etiology and different diagnostic tools.

Moreover, different additional sources of heterogeneity should be considered when analyzing the studies' results. First of all, the studies differed in terms of study design: prospective with longitudinal evaluation of liver stiffness changes, retrospective, case-control.

Secondly, in terms of the population analyzed for different geographical origins, HCC prevalence, and clinical co-factors (prevalence of alcohol abuse, diabetes, etc.).

Furthermore, some studies assessed LSM combined with other variables, such as laboratory data, with the aim to create composite scores, thus preventing the estimation of the diagnostic accuracy of the single parameters.

Lastly, several prognostic models, including LSM as a predictor of HCC development, have been put forward and validated. However, different surveillance strategies according to different LSM risk categories have yet to be performed. In this respect, as showed in the study by Enomoto et al. [69], we should bear in mind that HCC can also occur in SVR patients in the absence of advanced fibrosis, thus making necessary the addition of other serum parameters in risk stratification of HCC occurrence.

Regarding the possible role of spleen stiffness assessment in the prediction of HCC occurrence PH is likely to be the cause of the correlation between increased SSM values and HCC development. When it comes to PH, the liver's altered blood flow and micro-circulation result in reduced oxygen supply to the tissue. Subsequently, the production of HIF (hypoxia-induced factor) and other cytokines is stimulated in dysplastic nodules due to this hypoxic environment [70]. The subsequent proliferation of new blood vessels and the progression of fibrosis favor the carcinogenesis process.

A few preliminary studies have directly addressed the role of SSM in HCC prediction, thus suggesting its promising use in HCC risk stratification.

Also, recent data has shown that SSM can predict tumor recurrence after surgical resection in HCC patients. Marasco et al. [66] have shown that the SSM value at multivariate analysis is the only independent predictor of late HCC recurrence after primary HCC resection.

Another possible role of liver and SSM regards the prediction of post-operative liver failure and overall survival in patients undergoing hepatic resection for HCC [71, 72] or RFA [73].

In conclusion, the main advantages of elastographic techniques, except for MRE, are that they are patient-friendly, largely available, fast to use, non-invasive, and easily repeatable. On the other hand, particularly for elastographic techniques implemented on standard US devices, results may vary according to the technique and device used, and this does not allow to obtain reproducible cut-off values. For this reason, the use of the same technique with the same device is recommended during a patient's follow-up. In addition, in order to obtain unbiased results future studies should be consecutive and designed for direct comparison of the different techniques (VCTE, 2D-SWE, and MRE) in the same population. Major efforts are still needed to identify specific cut-off values for different liver disease etiologies; in this regard, the longitudinal stiffness variations could add better stratification of HCC occurrence after the eradication [74, 75] or suppression of viral agents and during the course of liver disease, on account of concomitant factors that would possibly negatively impact on the hepatopathy course.

Future research should also focus on the use and validation of composite models including elastography and other NITs [76] with the aim of obtaining a better risk stratification of HCC occurrence. Very recently, Lin et al. [77] applied machine learning with artificial intelligence to develop a SMART-HCC score, which has demonstrated better diagnostic than conventional risk scores, with promising advances in HCC risk prediction.

Abbreviations

AUROC: area under the receiver operating curve

cACLD: compensated advanced chronic liver disease

DAA: direct antiviral agent

HBV: hepatitis B virus

HCC: hepatocellular carcinoma

HCV: hepatitis C virus

HR: hazard ratio

HVPG: hepatic venous pressure gradient

LSM: liver stiffness measurement

MR: magnetic resonance

MRE: magnetic resonance elastography

NAFLD: non-alcoholic fatty liver disease

NITs: non-invasive tests

PH: portal hypertension

RFA: radio-frequency ablation

SSM: spleen stiffness measurement

SVR: sustained virological response

SWE: shear wave elastography

VCTE: vibration-controlled transient elastography

Supplementary materials

The supplementary materials for this article are available at: https://www.explorationpub.com/uploads/Article/file/100555_sup_1.pdf.

Declarations

Author contributions

AF: Investigation, Writing—original draft. MF: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

The primary data for this review were sourced online from databases listed in the methods.

Funding

Not applicable.

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