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Can liver ultrasound elastography predict the risk of hepatocellular carcinoma recurrence after radiofrequency ablation? A systematic review and meta-analysis.

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Abstract

Purpose: The role of liver stiffness (LS) on ultrasound elastography in the prediction of hepatocellular carcinoma (HCC) recurrence after treatment with radiofrequency ablation (RFA) is still unclear. Our aim was to perform a systematic review and meta-analysis to assess whether LS can predict the recurrence of HCC after RFA.

Materials and methods: Medline via PubMed, Embase, Scopus, and Cochrane Library databases, and abstracts of international conference proceedings were searched up to June 30, 2020. Cohort studies were included if they assessed the association between LS values measured by ultrasound elastography before RFA and HCC recurrence.

Results: 9 studies including 1373 patients with HCC treated by RFA, 643 of whom developed HCC recurrence, were identified. The mean value of LS before RFA was significantly higher in patients who developed HCC recurrence than in those who did not (weighted mean difference=11.98 kPa, 95%CI: 7.60-16.35, I2=63.8%). There was a significant positive association between LS value and HCC recurrence both at univariate (unadjusted HR=1.03, 95%CI: 1.00-1.07, I^2=72.7%) and multivariate analysis (adjusted HR=1.03, 95%CI: 1.02-1.04, I^2=0). Patients with LS value ≥13-14 kPa or >1.5 m/s have a higher risk of both HCC recurrence (unadjusted HR=2.18, 95%CI: 1.46-3.25, I^2=49.7%; adjusted HR=2.41, 95%CI: 1.53-3.79, I^2=0) and overall mortality (adjusted HR=4.38; 95%CI: 2.33-8.25, I^2=0) in comparison with those with LS below these cutoffs.

Conclusion: Liver ultrasound elastography appears to be a reliable tool to predict HCC recurrence and overall survival after RFA. This technique may be useful for the management of patients with HCC treated by RFA.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and a major cause of morbidity and mortality in patients with chronic liver disease [1]. Recently, the implementation of active surveillance strategies has led to a significant increase in the diagnosis of HCC. Liver transplantation, surgical resection, and radiofrequency ablation (RFA) are therapeutic options that can be offered to patients with HCC with curative intent [2]. Radiofrequency ablation is a percutaneous treatment comparable to surgical resection in terms of overall survival [3], with a lower rate of serious adverse events [4]. However, HCC recurrence is significantly higher in patients who underwent RFA, and this remains a major challenge for the long-term survival of these patients [4]. Recurrence of HCC has been reported in at least 60% of patients at 5 years after RFA treatment [6].

The degree of liver fibrosis plays a relevant pathogenetic role in liver carcinogenesis and severe liver fibrosis is an important risk factor for the development of HCC [2].Liver ultrasound elastography techniques including transient elastography (TE), two-dimensional-shear wave elastography (2D-SWE) and acoustic radiation force impulse imaging (ARFI) are non-invasive, simple and reproducible tools to evaluate the degree of liver fibrosis through the measurement of liver stiffness (LS) in patients with chronic liver disease, from viral to metabolic disease [7, 8]. In the last years, ultrasound elastography has been largely used to identify patients with liver fibrosis [7], cirrhosis and those with portal hypertension [8] and their complications [9, 8]. In addition, ultrasound elastography has been shown to predict the risk of HCC occurrence [10] in patients with chronic liver disease and HCC recurrence after liver surgery [11, 12].

However, whether liver ultrasound elastography can predict HCC recurrence and overall survival in patients treated by RFA is still unclear. There are limited and inconsistent data on the

association between LS measurement by ultrasound elastography and the risk of HCC recurrence after RFA.

A better knowledge of the role of liver ultrasound elastography in the prediction of clinical outcomes in patients with HCC who undergo RFA may help improving the management and follow-up after treatment of these patients. The aim of this study was to perform a systemic review and meta-analysis to evaluate whether LS measurement by ultrasound elastography before RFA for HCC can predict the recurrence of HCC in patients with chronic liver disease. The secondary outcome was to determine if liver stiffness measurement can predict overall survival.

Methods

We performed a systematic review and meta-analysis following the recommendations of the Cochrane Collaboration Group [13].

Search strategy and study selection

We searched MEDLINE via PubMed, Ovid Embase, Scopus and the Cochrane Library databases up to 30th June 2020. The electronic search of literature was carried out using the following keywords: “liver stiffness”, “elastography”, “transient elastography”, “ultrasound elastography”, “hepatocellular carcinoma”, “HCC”, “liver neoplasm”, “radiofrequency ablation”. The search strategies are reported in Supplemental 1. In addition, we searched electronically and by hand abstracts of the conference proceedings of European Association for the Study of the Liver, American Association for the Study of Liver Diseases, Asian Pacific Association for the Study

of the Liver. We also searched the references lists of the included studies and relevant published reviews. We did not restrict for language or publication status.

Two authors performed the initial selection on the basis of titles and abstracts. Subsequently, they carried out a full text assessment of potentially relevant publications, with any disagreement resolved through discussion or arbitration by a third reviewer.

For the inclusion in the review, we selected studies if they met the following pre-specified criteria: cohort studies that evaluated the association between liver stiffness value measured by ultrasound elastography and HCC recurrence in patients with HCC treated by RFA. Liver ultrasound elastography should be performed before RFA using any techniques in accordance with manufacturer's instructions and reliability criteria [7]. The diagnosis of HCC should be based either on dynamic imaging studies, including computed tomography or magnetic resonance imaging, according to criteria of international guidelines or histology on tumor biopsy. The indications for RFA treatment should be the following: single nodule ≤ 2 cm, single or 2-3 nodules ≤3 cm not suitable for surgery, or, in selected patients, nodules >3 cm, or >3 nodules. We excluded studies that did not meet the inclusion criteria or whether essential information was missing and could not obtained by the authors.

Data extraction and quality assessment

Two authors extracted independently relevant data regarding the publication, study methods and results using a standardized data extraction form. In addition, the following items were extracted from each study, when available: study design, country, inclusion and exclusion criteria, number of participants, mean age and gender, main etiology of liver disease, proportion of patients with cirrhosis, previous treatment for HCC, duration of follow-up, number of patients with HCC

recurrence after RFA, type (local or distant) of HCC recurrence, overall survival of patients after RFA treatment, ultrasound elastography technique and equipment, parameters and values of liver stiffness before RFA, variables included in multivariate analyses for the prediction of HCC recurrence or overall survival. When multiple articles for a single study were found, the latest publication was considered and supplemented, if necessary, with data from the previous publications.

Two authors independently assessed the risk of bias of the included studies using the QUIPS (Quality In Prognosis Studies) tool (Supplemental 2) [14]. Any disagreements were resolved through discussion and, if necessary, arbitration by a third reviewer. The QUIPS-file, with the key list for our study's topic, is available from the author on request. The overall study quality was rated as low, moderate, high risk of bias.[15]

Statistical analysis

We pooled mean differences with 95% confidence intervals (CI) of LS values measured before RFA for HCC between patients with HCC recurrence and those without recurrence using the weighted mean difference (WMD). For studies that did not report the mean LS value, we calculated mean and standard deviation (SD) using median and interquartile range according to the McGrath method [16].

Using the univariate and multivariate Cox proportional hazard ratios (HRs) with 95%CI for the LS value, we calculated the pooled univariate and multivariate HRs of HCC recurrence. We also calculated a pooled multivariate HR of overall survival after RFA. We used a random effect model to pool data. The heterogeneity between the studies was assessed using the Q test and the I^2 statistic; we considered an I^2 value >50% as suggestive for substantial heterogeneity [17].

Sub-group analyses were designed to explore the following sources of heterogeneity: study design (prospective vs retrospective), country, number of participant centers (single vs multi center study), ultrasound elastography technique, type of HCC recurrence, HCC-treatment naïve status and methodological quality of the included studies. Publication bias was investigated using the Egger test. A p-value of less than 0.05 was considered statistically significant. All analyses were carried out using STATA statistical software (Stata Corp., College Station, TX, USA).

Results

The electronic search identified 207 records after duplicates were removed, of which 29 full-text articles were assessed for eligibility [18–46]. Of these, 4 were excluded because of different target condition (i.e. lesions other than HCC or treatments other than RFA) [26, 37, 38, 43], 2 evaluated LS by magnetic resonance elastography [19, 22] and 14 for other reasons (Fig. 1) [18, 20, 21, 23, 25, 27, 29–31, 36, 40–42, 45]. Finally, a total of 9 studies [24, 28, 32–35, 39, 44, 46] were included in the meta-analysis.

Study characteristics

The nine included studies involved a total of 1373 patients with HCC who underwent RFA, of whom 643 developed HCC recurrence during the follow-up.

Tab. 1 shows the characteristics of the included studies. The mean age of patients ranged from 58.2 [44] to 69.1 years [32] and the proportion of men from 62% [32] to 83% [28]. Five studies were carried out in South Korea [28, 33–35, 46], one in Japan [24], one in China [44], one in Taiwan [32], and one in France [39]. Seven studies [24, 28, 32, 34, 39, 44, 46] were performed in a single center, while two [33, 35] were multicenter studies. Six studies had a retrospective

design [28, 33–35, 39, 44] and three were prospective [24, 32, 46]. The most common etiology of chronic liver disease was hepatitis B virus in six studies [32–35, 44, 46], hepatitis C virus in one study [24] and alcohol use in one study [39], while in one study [28] the etiology of liver disease was not reported. The proportion of patients with cirrhosis ranged from 53% [34] to 100% [39]. Six studies [28, 32, 35, 39, 44, 46] included only patients naïve to HCC-treatment, two studies [33, 34] enrolled also patients previously treated for HCC and one [24] did not provide any information. Regarding LS measurement, six studies [24, 28, 33, 35, 39, 46] used TE (Fibroscan, Echosens, Paris, France), two [34, 44] 2D-SWE (Aixplorer, Supersonic Imagine, France) and one [32] ARFI (Acuson S2000, Siemens, Germany). Of the studies with TE, one [46] used also ARFI. In all studies, but one that used meter per second (m/s) [32], the value of LS was reported in kilopascal (kPa). The median follow-up of patients after RFA treatment ranged from 12 [24] to 56 [39] months and the HCC recurrence rate from 26.7% [44] to 64.8% [39]. Five studies [34, 35, 39, 44],[32] included both local and distant HCC recurrence, while four studies [24, 28, 33, 46] considered only distant HCC recurrence.

Of the 9 selected studies, five [24, 28, 33, 35, 46] reported mean or median LS value before RFA in patients with HCC recurrence and in those without, seven the unadjusted [24, 28, 32, 39] or adjusted [28, 35, 46] HR for HCC recurrence using LS value as continuous variable and eight the unadjusted [28, 32, 34, 44, 46] or adjusted [32, 33, 44] HR for HCC recurrence using an LS cutoff value; in addition, four studies [32–34, 44] reported the adjusted HR for overall survival after RFA. In the multivariate analyses, the studies adjusted for a variable number of relevant confounders including demographic factors (i.e. age and gender), etiology of liver disease, presence of cirrhosis, laboratory variables indicating liver function reserve (i.e. albumin level,

platelet count, prothrombin time), tumor factors (i.e. tumor size and number and alpha-fetoprotein level), antiviral treatment and previous anti-HCC treatment history.

Tab. 2 shows the results of the assessment of the methodological quality of the included studies. All studies, but one that was at "moderate risk" of bias [46], were at "high risk" of bias. In particular, most studies were at high risk of bias in the selection of participants, mainly because they did not enroll a random or consecutive sample of patients. In addition, most studies did not adjust for all potential confounding factors, and half of the studies did not report the rate of patients with unfeasible LS measurement.

Liver stiffness value and HCC recurrence after RFA for HCC

Five studies, with a total of 634 patients and 308 cases of HCC recurrence after RFA, reported mean or median LS value before treatment in patients with and without HCC recurrence; three studies reported the mean value of LS, while two reported the median value with interquartile range which was used to calculate mean and SD. All five studies performed ultrasound elastography using TE.

The overall mean value of LS was significantly higher in patients who developed HCC recurrence after RFA than in those who did not with a pooled WMD of LS of 11.98 (95%CI: 7.60-16.35) kPa. There was substantial heterogeneity between the studies (I^2=63.8%) (Fig. 2, Supplemental 3). No publication bias was found (p=0.52).

Sub-group analyses showed that previous treatment for HCC was a possible source of heterogeneity between the studies. After the exclusion of the study with patients previously treated for HCC [33] and the study [24] not providing data on a possible previous treatment of HCC, the sub-group analysis of the three studies including only patients naïve to HCC treatment

confirmed the association between LS values and HCC recurrence (WMD:15.33, 95%CI: 12.56-18.10) with no heterogeneity between the studies (I^2=0%).

Six studies assessed the association between LS value used as continuous variable and the risk of HCC recurrence using Cox proportional regression analyses. All studies measured LS with TE, except for one [32] that used ARFI.

Pooling data from the four studies [24, 28, 32, 39] that reported unadjusted HRs, including a total of 507 patients with 268 cases of HCC recurrence, at univariate analysis there was a positive association between LS value and HCC recurrence with a borderline statistical significance; the pooled unadjusted HR was 1.03 (95%CI:1.00-1.07). There was substantial heterogeneity between the studies (I^2=72.7%) (Fig. 3a, Supplemental 4). The result did not change when we considered only studies with LS value in kPa (unadjusted HR:1.03, 95%CI: 1.00-1.06, I^2=72.9%).

Pooling data from the three studies [28, 35, 46] that reported adjusted HRs, including a total of 426 patients with 206 cases of HCC recurrence, after adjustment the association between LS value and HCC recurrence was statistically significant with a pooled adjusted HR of 1.03 (95%CI: 1.02-1.04). There was no heterogeneity between the studies (I^2=0%) (Fig. 3b, Supplemental 4).

Six studies [28, 32–34, 44, 46] assessed the risk of HCC recurrence according to a predetermined cut-off value of LS. Five studies measured LS with TE [28, 33, 34, 46] or 2D-SWE [34] and used a cutoff value ranging from 13 to 14 kPa, while one study used ARFI [32] and a cutoff of 1.5 m/s.

Pooling data from five studies [28, 32, 33, 44, 46], the overall cumulative recurrence of HCC after RFA was higher in patients with LS value above 13-14 kPa or 1.5 m/s (38.8%, 185/477) than in those with LS value below these cut-offs (18%, 50/278).

At univariate analysis, pooling data from five studies [28, 32, 34, 44, 46] including a total of 778 patients with 309 cases of HCC recurrence, the risk of HCC recurrence was significantly higher in patients with LS ≥ 13-14 kPa or > 1.5 m/s than in those with LS value below these cut-offs; the pooled unadjusted HR was 2.18 (95%CI: 1.46-3.25). There was moderate heterogeneity between the studies (I^2=49.7%) (Fig. 4a, Supplemental 5). The sub-group analysis of the four studies [28, 32, 44, 46] including only patients naïve to HCC treatment confirmed the association between these cutoff values of LS and the risk of HCC recurrence (unadjusted HR: 2.64, 95%CI: 1.88-3.70) with no heterogeneity among the studies (I^2=0).

After adjustment, pooling data from three studies [32, 33, 44] including a total of 557 patients with 196 cases of HCC recurrence, we found that LS value ≥ 13-14 kPa or 1.5 m/s was an independent predictor of the risk of HCC recurrence; the pooled adjusted HR was 2.41 (95%CI: 1.53-3.79). There was no heterogeneity between the studies (I^2=0) (Fig. 4b, Supplemental 5). The results did not change when we considered only studies that measured LS in kPa both in univariate (unadjusted HR: 2.26, 95%CI: 1.31-3.92, I^2=62.2%) and multivariate analyses (adjusted HR: 3.02, 95%CI: 1.53-5.96, I^2=0).

Liver stiffness value and overall survival after RFA for HCC

Four studies [32–34, 44], including 691 patients treated with RFA for HCC, reported the overall survival of patients during the follow-up according to a predetermined cut-off value of LS. Three

studies measured LS with TE [33] or 2D-SWE [34, 44] and used a cutoff value ranging from 13 to 14 kPa, while one [32] used ARFI with a cutoff of 1.5 m/s.

Pooling data from these studies, the overall cumulative mortality was 29.8% (137/460) in patients with LS ≥ 13-14 kPa or > 1.5 m/s and 11.3% (26/231) in those with an LS value below these cut-offs. After adjustment, a value of LS ≥ 13-14 kPa or 1.5 m/s was an independent predictor of an increased risk of death after RFA for HCC; the pooled adjusted HR was 4.38 (95%CI: 2.33-8.25). There was no heterogeneity between the studies (I^2=0%) (Fig. 5, Supplemental 6).

Discussion

This meta-analysis included 9 studies that assessed whether liver stiffness measurement by ultrasound elastography can predict the risk of HCC recurrence in patients with HCC treated by RFA. Pooled analyses showed an independent positive association between LS value and HCC recurrence; the higher LS value was associated with the higher risk of HCC recurrence. Patients with LS value above a cutoff of 13-14 kPa or 1.5 m/s have a 2-fold higher risk of HCC recurrence after RFA. In addition, we found that liver stiffness value can predict overall survival in these patients.

The association between the LS value and HCC recurrence was expected as the risk of HCC recurrence increases with the increasing degree of fibrosis and elastography measures the degree of fibrosis[2]. This association seems to be independent from other factors as it resulted statistically significant in the multivariate analyses after adjustment from other risk factors for HCC recurrence including tumor factors and liver function reserve. We found that a value ≥ 13-14 kPa was associated with a two times risk of HCC recurrence after RFA. The value of 13-14

Kpa is similar to the cutoff value of 12-15 kPa that indicates the presence of advanced stage of liver fibrosis or cirrhosis (); this may partially explain our result aspatients with liver cirrhosis have generally bad prognosis and increased risk of HCC. We also found that LS values measured by ultrasound elastography can predict overall survival in patients with HCC treated by RFA; patients with LS values above 13-14 kPa have a 4-fold higher risk of death during the follow-up after RFA. Similar to HCC recurrence, this finding seems to be independent from other factors associated with overall survival, including age, tumor burden and antiviral treatment. Unfortunately, we could not stratify for the causes of mortality and we could not assess the specific survival related to HCC recurrence. The increased mortality of patients with LS value above 13-14 kPa is likely to be due not only to the increased risk of HCC but also to the status of advanced liver fibrosis, that is associated with poorer liver function and higher risk of portal hypertension and its complications [2]. In fact, the value of 13-14 kPa is very close to the cut-off value for the diagnosis of portal hypertension [47].

To our knowledge, this is the first meta-analysis that has evaluated the role of liver ultrasound elastography in the prediction of HCC recurrence and overall survival after RFA treatment. A strength of this review is the comprehensive literature search without restriction on the language or type of publication, which minimized the risk of missing studies. Furthermore, the test for publication bias was not statistically significant, thus minimizing the risk that unpublished studies may affect our results. Another strength is the use of an appropriate tool for the evaluation of the methodological quality of the studies.

A weakness of our meta-analysis is the paucity of the included studies; however, the overall sample size of patients was enough to allow for a relatively small uncertainty in the estimate of the association between the cutoff value of LS and HCC recurrence or overall survival, as shown

by the narrow confidence interval of the pooled adjusted HRs. Another weakness of our finding is the substantial heterogeneity between the studies when we evaluated pooled WMD of LS values and unadjusted HRs for HCC recurrence. However, after excluding studies with previous treatment for HCC, pooling data from studies with only patients naïve to HCC treatment the association between LS value and HCC recurrence remained statistically significant with no heterogeneity between the studies. Most important, when we pooled multivariate HRs for HCC recurrence and overall survival no heterogeneity between the studies was found. This would provide more strength to our estimates for the association between LS values and both HCC recurrence, especially in patients naïve to HCC treatment, and overall survival after RFA for HCC. Another weakness of our meta-analysis is the low methodological quality of the included studies. Most studies did not enroll a consecutive or random sample of subjects, thus introducing a possible selection bias. In addition, the majority of studies was retrospective and did not adjust for all potential confounding factors. For example, the antiviral treatment might reduce both HCC recurrence and mortality in patients with HBV- or HCV-related HCC after RFA [48, 49]. Unfortunately, none of the studies that assessed the risk for HCC recurrence and only two of the four studies that assessed overall survival adjusted for this confounder, and this may partially bias our estimates. However, we found that in patients with LS value above 13-14 kPa the pooled hazard for HCC recurrence and overall mortality was quite robust being 2.4 and 4.4, respectively; thus, it unlikely that the inclusion of antiviral treatment in the multivariate model would make null the association with these outcomes.

In conclusion, the results of this meta-analysis suggest that LS measurement by ultrasound elastography can predict the risk of HCC recurrence and overall survival after RFA treatment in patients with chronic liver disease, in particular in those naïve to HCC treatment. A cutoff value

of 13-14 kPa or 1.5 m/s could allow to identify patients at higher risk of HCC recurrence and mortality after RFA. As most of the studies included patients with virus-related liver disease, in particular HBV-related, no conclusions can be drawn for patients with other causes of chronic liver disease, such as non-alcoholic fatty liver disease, which is quickly becoming the predominant cause of liver disease worldwide. However, as the relationship between LS value and HCC recurrence largely depends on the degree of liver fibrosis, it is likely that the association between LS and HCC recurrence is valid regardless of the etiology of liver chronic disease. As most studies used TE, our findings are certainly applicable to this technique; however, our finding may be also valid for the 2D-SWE as there is a strong correlation between the two techniques in the measurement of LS [50]. As all, but one, studies were conducted in Asia, we think that our findings are certainly applicable to the Asian population.

Our findings would support the use of liver ultrasound elastography as a non-invasive tool to screening patients with HCC before RFA treatment in order to identify those at increased risk of developing HCC recurrence and worse overall survival. Ultrasound elastography may help clinicians for a better management of patients with HCC and may be useful for reducing liver cancer mortality; in fact, patients at high-risk of HCC recurrence could benefit from a closer follow-up, salvage liver transplantation or systemic therapies after RFA. However, how to adjust the management strategy of these patients according to the LS value should be further investigated. However, large well-designed high-quality studies are needed to confirm the role of liver ultrasound elastography in predicting the risk of HCC recurrence and overall survival in patients with HCC treated by RFA, in particular in Europe and America.

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Table 1 - Characteristics of the included studies

Study, Year	Country	Total patients, n.	Age mean, (SD)	Gender, male n, (%)	Liver cirrhosis n, (%)	Main etiology of liver disease, n, (%)	Antiviral treatment, n, (%)	HCC treatment -naïve	Elastography Technique and Equipment	HCC recurrence n, (%)	Death n, (%)	Follow-up, median (range)
Ikeda H, 2011 [28]	Japan	97	68.9 (8.5)	68 (64)	N/A	HCV, 92 (88)	N/A	N/A	TE, Fibroscan	55 (51.4)	N/A	12 (N/A)
Lee SH, 2015 [55]	South Korea	111	62.4 (9.5)	76 (69)	75 (68) 65 (87)	HBV, 71 (64)	58 (64.4)	No	TE, Fibroscan	47 (42.3)	18 (16.2)	22.4 (1.1–77.3)
Lee YR, 2017 [31]	South Korea	228	N/A	170 (75)	168 (74) 157 (94)	HBV, 149 (65)	131 (72)	Yes	TE, Fibroscan	125 (54.8)	37 (16.2)	24 (N/A)
Yoon JS, 2018 [33]	South Korea	120	N/A	91 (76)	90 (75) N/A	HBV, 87 (73)	76 (80.9)	Yes	TE, Fibroscan p-SWE, Siemens	51 (42.5)	3 (2.5)	21.9 (3-60)
Lee DH, 2018 [34]	South Korea	134	61.7 (8.3)	99 (73.9)	71 (53) 71(100)	HBV, 112 (83.6)	97 (72.4)	No	2D-SWE, Aixplorer	79 (59)	22 (16.4)	36 (N/A)
Kim R, 2019 [36]	South Korea	78	60.5 (9.6)	65 (83)	37 (53) 70 (89.7)	N/A	N/A	Yes	Transient elastography	30 (38.5)	N/A	15.6 (N/A)
Xie X, 2020 [40]	China	273	58.2 (2.1)	172 (68)	185 (68) 190 (70%)	HBV, 273 (100)	N/A	Yes	2D- SWE, Aixplorer	73 (26.7)	88 (33.2)	N/A
Rekik S, 2020 [38]	France	159	N/A	123 (77)	159 (100) 143 (90%)	Alcohol, 76 (48)	N/A	Yes	TE, Fibroscan	103 (64.8)	75 (47.2)	56 (N/A)
Lee PC, 2020 [37]	Taiwan	173	69.1 (11.6)	107 (62)	126 (73 173 (100)	HBV, 81 (47)	87 (50.3)	Yes	p-SWE, Siemens	80 (46.2)	38 (22)	27.7 (N/A)

2D-SWE: two-dimensional share wave elastography, CLD: chronic liver disease; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; N/A: not available; p-SWE: point share wave elastography, SD: standard deviation; SWE: share wave elastography, TE: transient elastography.

Table 2 - Risk of bias (RoB) ratings of the included studies assessed with the Quality in Prognostic Studies (QUIPS)-tool

	Bias Domains						
	Study participants	**Study Attrition**	**Prognostic Factor Measurement**	**Outcome Measurement**	**Study Confounding**	**Statistical Analysis and Reporting**	**Overall Risk**
Ikeda H, 2011 [28]	Moderate	Low	Moderate	Low	Moderate	Moderate	**High**
Lee SH, 2015 [55]	High	Low	Low	Low	Moderate	Moderate	**High**
Lee YR, 2017 [31]	High	Low	Low	High	Moderate	Low	**High**
Yoon JS, 2018 [33]	Moderate	Low	Low	Low	Moderate	Low	**Moderate**
Lee DH, 2018 [34]	High	Low	Low	High	Moderate	Moderate	**High**
Kim R, 2019 [36]	High	Low	Moderate	Low	High	Low	**High**
Xie X, 2020 [40]	High	Low	Moderate	High	Moderate	Moderate	**High**
Rekik S, 2020 [38]	High	Low	Moderate	High	Moderate	Moderate	**High**
Lee PC, 2020 [37]	Moderate	Low	Moderate	Moderate	Moderate	Moderate	**High**

Categorization of overall RoB on study level:
Low= at least 5 of the domains have low RoB and none has high RoB;
Moderate= At least 4 of the domains have low RoB and maximum of two have moderate RoB.
High= at least one domain has high RoB or ≥ 3 domains have moderate RoB.