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Original Article

Non-invasive prediction of post-sustained virological response hepatocellular carcinoma in hepatitis C virus: A systematic review and meta-analysis

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Graphical Abstract
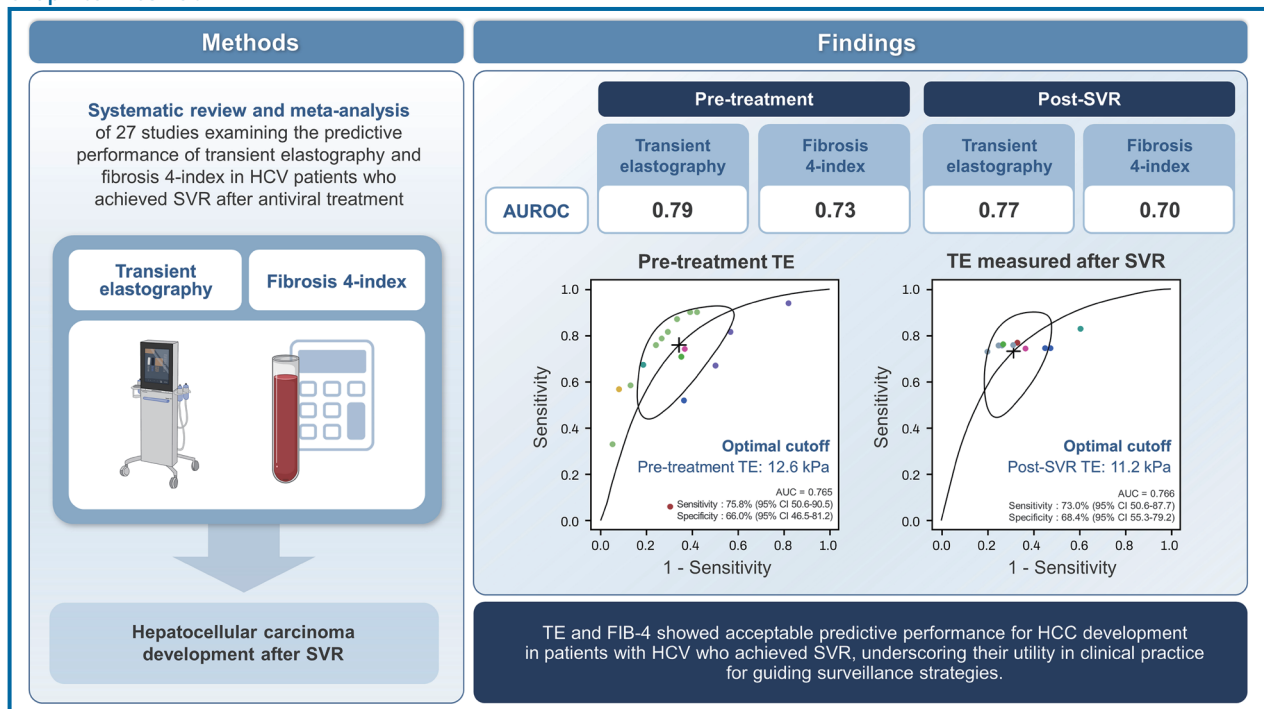
Study Highlights
- This systematic review and meta-analysis explores the predictive performance of VCTE and FIB-4 for HCC development after SVR in patients with HCV infection.
- It includes data from 27 studies, encompassing 169,911 patients, revealing that both pre-treatment VCTE and FIB-4 offer acceptive predictive performance for HCC development after SVR, with optimal cut-off values identified for early detection.
- The identified optimal cut-off values for predicting HCC after SVR are 12.6 kPa for pre-treatment VCTE and 11.2 kPa for VCTE measured after the SVR, with FIB-4 >3.25 also showing high predictive accuracy.
- These results affirm the importance of VCTE and FIB-4 in clinical practice, enabling targeted surveillance strategies for HCV patients achieving SVR, thus facilitating early intervention for those at risk of developing HCC.

Backgrounds/Aims: Despite advances in antiviral therapy for hepatitis C virus (HCV) infection, hepatocellular carcinoma (HCC) still develops even after sustained viral response (SVR) in patients with advanced liver fibrosis or cirrhosis. This meta-analysis investigated the predictive performance of vibration-controlled transient elastography (VCTE) and fibrosis 4-index (FIB-4) for the development of HCC after SVR.

Methods: We searched PubMed, MEDLINE, EMBASE, and the Cochrane Library for studies examining the predictive performance of these tests in adult patients with HCV. Two authors independently screened the studies' methodological quality and extracted data. Pooled estimates of sensitivity, specificity, and area under the curve (AUC) were calculated for HCC development using random-effects bivariate logit normal and linear-mixed effect models.

Results: We included 27 studies (169,911 patients). Meta-analysis of HCC after SVR was possible in nine VCTE and 15 FIB-4 studies. Regarding the prediction of HCC development after SVR, the pooled AUCs of pre-treatment VCTE >9.2–13 kPa and FIB-4 >3.25 were 0.79 and 0.73, respectively. VCTE >8.4–11 kPa and FIB-4 >3.25 measured after SVR maintained good predictive performance, albeit slightly reduced (pooled AUCs: 0.77 and 0.70, respectively). The identified optimal cut-off value for HCC development after SVR was 12.6 kPa for pre-treatment VCTE. That of VCTE measured after the SVR was 11.2 kPa.

Conclusions: VCTE and FIB-4 showed acceptable predictive performance for HCC development in patients with HCV who achieved SVR, underscoring their utility in clinical practice for guiding surveillance strategies. Future studies are needed to validate these findings prospectively and validate their clinical impact. **(Clin Mol Hepatol 2024;30(Suppl):S172-S185)**

Keywords: Vibration-controlled transient elastography; Fibrosis 4-index; Hepatitis C virus; Hepatocellular carcinoma; Prediction

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Abbreviations:

AUC, area under the curve; CI, confidence interval; DAAs, direct-acting antivirals; FIB-4, fibrosis 4-index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LS, liver stiffness; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; sROC, summary receiver operating characteristic; SVR, sustained viral response; VCTE, vibration-controlled transient elastography

INTRODUCTION

Hepatitis C virus (HCV) is a significant cause of hepatocellular carcinoma (HCC), accounting for 8.2–12.0% of HCC cases in South Korea and contributing to 34% of HCC cases in the United States.[1,2] The majority of HCV-related HCC cases are preceded by cirrhosis, because HCV is an RNA virus that does not integrate into the host's genome, making it less likely to be the primary initiator of tumorigenesis.[3] Although cases of HCC have been documented in individuals with minimal or no fibrosis, most HCV-related HCC are observed in patients with advanced fibrosis or cirrhosis, with an annual incidence rate of 2–4% in HCV-related cirrhosis.[4,5]

Regarding HCV-related HCC, treating existing HCV infections is the most effective way to prevent the development of HCC. Previously, achievement of sustained virological response (SVR) with interferon (IFN) decreased the risk of HCC.[6] In the last decade, direct-acting antivirals (DAAs) have emerged as the standard treatment for HCV infection due to their remarkable effectiveness.[7] Although SVR achieved with DAA therapy has been found to reduce HCC risk by >70%, HCC still develops in a substantial proportion of patients, especially among those with advanced fibrosis or cirrhosis and patients who have other oncogenic factors in the post-SVR period.[8]

Therefore, it is crucial to identify patients at risk of developing HCC, necessitating continuous surveillance while also identifying those who can safely terminate their follow-up monitoring. The recommendations for HCC surveillance vary across guidelines for HCV patients in the post-SVR period with advanced fibrosis (METAVIR score F3) or cirrhosis (METAVIR score F4).[9,10] Since non-invasive surrogates such as vibration-controlled transient elastography (VCTE) or the Fibrosis-4 index (FIB-4) are currently used to assess the fibrotic burden, it is clinically important to establish the criteria of these non-invasive surrogates for selecting candidates for surveillance of HCC after SVR. Moreover, antiviral therapy can improve liver damage, potentially decreasing the risk of HCV-related HCC development.[11,12] Therefore, dynamic changes in non-invasive surrogates in the post-SVR period should be considered in the risk assessment of HCC development after SVR.

This meta-analysis explored the performance and optimal cut-off values of VCTE and FIB-4, measured before and after SVR, in predicting HCC development among patients with HCV.

MATERIALS AND METHODS

This study followed the preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy guidelines (Supplementary Table 1).

Eligibility

We included studies that examined VCTE-based liver stiffness (LS) or FIB-4 measured before and after achieving SVR with antiviral therapy in patients with HCV. For this analysis, only studies involving patients with HCV who achieved SVR after antiviral therapy were included. Studies published in peer-reviewed journals in any language were considered if they met the following criteria: i) included adults aged ≥18 years with HCV; ii) provided data for at least 10 patients; and iii) reported estimates for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) for predicting HCC development after SVR.

Exclusion criteria

Studies were excluded if they met the following criteria: i) included patients with coinfection with hepatitis B virus and/or HIV, ii) included patients who did not receive antiviral therapy for HCV, iii) comprised individuals with a history of HCC or liver transplantation, and iv) lacked sufficient data to calculate predictive performance measures. In cases where the studies had missing data or did not report predictive performance, specifically for patients with HCV within a mixed cohort of patients with liver disease, the corresponding author was contacted via email to request the necessary information or results. Studies were excluded if no responses were received within 28 days.

Search strategy and selection process

A comprehensive web-based literature search of PubMed/MEDLINE, EMBASE, and CENTRAL (Cochrane Library) was systematically performed for articles pub-

lished until June 30th, 2023 (see Supplementary Table 2 for specific search terms). The search was performed collaboratively by an experienced medical librarian (CHJ) and a hepatologist (HAL). Additionally, the reference lists of the included studies were manually searched to identify further relevant research.

Study selection

The search results were imported into an online platform for systematic review management (Covidence; Veritas Health Innovation, Melbourne, Australia; www.covidence. org), where duplicates were automatically eliminated. Initially, titles and abstracts were screened to identify potentially relevant papers, and a full-text assessment of eligibility was conducted. Two researchers independently screened titles, abstracts, and full papers. Any disagreements were resolved through a consensus among the researchers; if a consensus could not be reached, a senior team member made the final decision. In cases where multiple reports from the same study existed, the most comprehensive or recent publication was selected based on consensus among the reviewers.

Data extraction

Two researchers independently extracted data using a standardized data extraction form. Any disagreements were resolved by consensus or, if necessary, consultation with a senior member of the review team. The data included study characteristics (country, year of publication, and study type), patient characteristics (age, sex, and laboratory findings), viral factors (HCV genotype and HCV RNA levels), number of HCC cases, type of antiviral therapy (IFN or DAAs), timing of non-invasive surrogates, and predictive performance of non-invasive surrogates (including cut-off values, sensitivity, specificity, PPV, NPV, and AUC). Additionally, the necessary data for calculating the true positives, false positives, true negatives, and false negatives were extracted. In cases where this information was not explicitly provided in the study, the values were computed based on the reported diagnostic test sensitivity, specificity, and prevalence. The database search for this study commenced on June 1, 2023, and the article review process was completed on September 26, 2023.

Methodological quality assessment

Two independent reviewers assessed the risk of bias and the relevance of the study findings to the review question using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[13] Disagreements were resolved through consensus between the reviewers whenever possible. If a consensus could not be reached, a third member of the review team made the final decision.

Evaluation of predictive accuracy

Tables containing performance indices data were extracted and reconstructed to assess the performance of non-invasive surrogates in predicting the development of HCC after SVR. Sensitivity, specificity, PPV, NPV, positive likelihood ratio (PLR), and negative likelihood ratio (NLR), along with their respective 95% confidence intervals (CIs), were calculated based on study-specific estimates. Graphical descriptive analysis of the included studies was conducted using forest plots.

A meta-analysis was conducted when three or more studies with adequate information were available for the same non-invasive surrogate at the same measurement period. In cases where multiple cut-off values were reported, studies were categorized into specific ranges of cut-off values for meta-analysis. A bivariate logit-normal random effects model was employed to estimate mean sensitivity, mean specificity, and their respective variances and covariances. Summary receiver operating characteristic (sROC) curves were created, including 95% CIs, which indicates that the 'true value' would typically be within this region 95% of the time, based on the available data. The 95% CIs corresponding to the summary AUC values were estimated using 500 bootstrap iterations.

A linear mixed-effects model was used to analyze data from individual studies reporting more than two cut-offs.[14,15] This model allows for the calculation of summary sensitivities and specificities across different cut-offs as well as the determination of PPV and NPV based on the prevalence of the target condition. Sensitivity and specificity were aggregated at each recommended cut-off to generate a multiple-threshold sROC curve. Furthermore, the PPV and NPV were derived, and the cut-offs necessary to meet the minimum acceptable criteria were identified. The statistical

software R, utilizing the mada and diagmeta packages (Version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria), was used for all analyses.

RESULTS

Search results

Out of the 3,263 articles initially identified and imported into Covidence from electronic database searches, 2,600 articles were screened after removing duplicates. From these, 64 articles were selected for full-text review based on electronic searches, with an additional three articles

identified through manual searching of the reference lists. Ultimately, 27 studies (26 full-text reports and one conference abstract) were included in the meta-analysis, as depicted in Figure 1.

Study characteristics

The characteristics of the TE[8,16-23] and FIB-4[15,16,22-40] studies included in the systematic review are summarized in Table 1. Eleven single-center and 16 multicenter studies were included. The meta-analysis included 17 studies from Asia and 10 from non-Asian regions, comprising seven prospective cohort studies and 20 retrospective studies. Three studies evaluated both the VCTE and FIB-4.
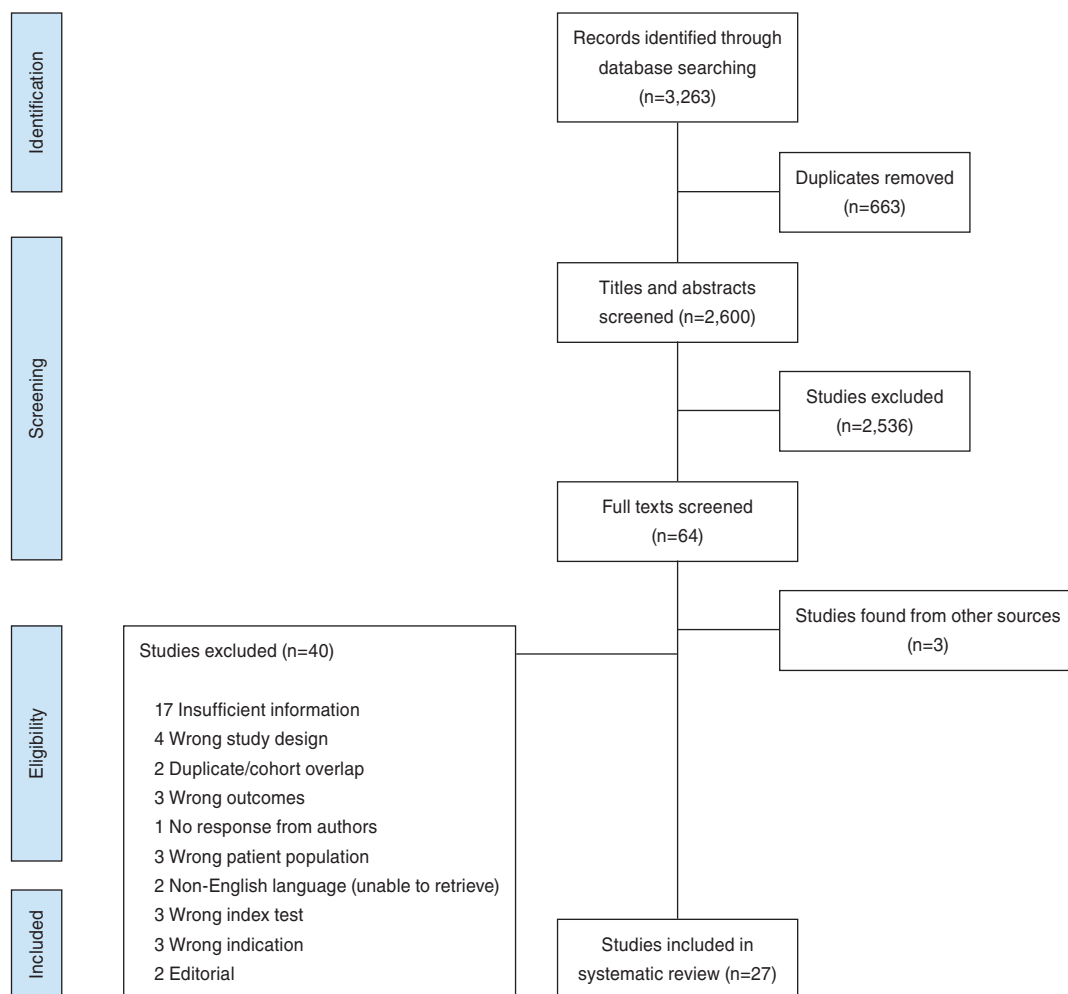
Figure 1. PRISMA flow diagram of studies included in meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

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Table 1. A summary of studies included in the systematic literature review and meta-analysis

Reference	Publication year	Country	Study design	Number of patients	Number of HCCs	Treatment	Test	Time of measurement	Cutoff
Sohn et al.[23]	2024	South Korea	Multicenter, retrospective	1,248	34	DAA	VCTE	Pre-treatment	14.5 kPa
								SVR12	14.5 kPa
Nakai et al.[19]	2022	Japan	Multicenter, retrospective	567	30	DAA	VCTE	Pre-treatment	9.2 kPa
							VCTE	SVR24	8.4 kPa
Pons et al.[8]	2020	Spain	Multicenter, prospective	572	25	DAA	VCTE	Pre-treatment	20.0 kPa
							VCTE	SVR48	10.0 kPa
Rinaldi et al.[20]	2019	Italy	Multicenter, prospective	258	35	DAA	VCTE	Pre-treatment	27.8 kPa
Wang et al.[21]	2016	Taiwan	Single center, retrospective	376	21	IFN	VCTE	Pre-treatment	12.0 kPa
Liu et al.[17]	2023	Taiwan	Single center, retrospective	466	40	DAA	VCTE	Pre-treatment	12.0 kPa
							VCTE	SVR	10.0 kPa
							FIB-4	Pre-treatment	4.6
							FIB-4	SVR	3.7
Kuo et al.[16]	2022	Taiwan	Single center, retrospective	697	28	DAA	VCTE	Pre-treatment	11.0 kPa
							FIB-4	SVR	3.6
Morisco et al.[18]	2021	Italy	Multicenter, prospective	687	26	DAA	VCTE	Pre-treatment	20.0 kPa
Ciancio et al.[24]	2023	Italy	Single center, prospective	1,000	71	DAA	FIB-4	Pre-treatment	3.25
Zou et al.[25]	2022	China	Single center, retrospective	701	27	DAA	FIB-4	Pre-treatment	3.25
Ideno et al.[26]	2023	Japan	Single center, retrospective	690	71	DAA	FIB-4	Pre-treatment	3.25
Kumada et al.[27]	2022	Japan	Single center, retrospective	1,384	51	DAA, IFN	FIB-4	Pre-treatment	3.25
Azzi et al.[28]	2022	France	Multicenter, prospective	3,531	153	DAA	FIB-4	SVR	3.25
Caviglia et al.[29]	2022	Italy	Single center, retrospective	575	57	DAA	FIB-4	SVR	3.38
Tada et al.[30]	2022	Japan	Multicenter, retrospective	3,058	107	DAA	FIB-4	SVR	3.25
Ampuero et al.[31]	2022	Spain	Multicenter, prospective	1,054	56	DAA	FIB-4	Pre-treatment	3.25
Tahata et al.[32]	2021	Japan	Multicenter, prospective	1,473	52	DAA	FIB-4	Pre-treatment	3.25
Kumada et al.[33]	2021	Japan	Single center, retrospective	1,352	55	DAA, IFN	FIB-4	Pre-treatment	1.50
Matsumae et al.[34]	2023	Japan	Multicenter, prospective	524	24	DAA	FIB-4	Pre-treatment	2.625
Myojin et al.[35]	2022	Japan	Multicenter, retrospective	964	50	DAA	FIB-4	Pre-treatment	3.25
Ide et al.[36]	2019	Japan	Multicenter, prospective	2,552	70	DAA	FIB-4	Pre-treatment	4.6

Table 1. Continued

Reference	Publication year	Country	Study design	Number of patients	Number of HCCs	Treatment	Test	Time of measurement	Cutoff
Nagaoki et al.[37]	2020	Japan	Single center, retrospective	298	29	DAA, IFN	FIB-4	Pre-treatment	5.0
Hiraoka et al.[38]	2019	Japan	Multicenter, retrospective	1,069	22	DAA	FIB-4	SVR24	3.25
Ioannou et al.[39]	2019	US	Multicenter, retrospective	48,135	1,509	DAA, IFN	FIB-4	Pre-treatment	3.25
Kramer et al.[15]	2022	US	Multicenter, retrospective	92,567	3,247	DAA	FIB-4	Pre-treatment	3.25/1.45
Ogawa et al.[22]	2020	Japan	Single center, retrospective	290	16	DAA	FIB-4 / VCTE	SVR12 / SVR12	3.25 / 10.0 kPa
Tamaki et al.[40]	2021	Japan	Multicenter, retrospective	3,823	148	DAA	FIB-4	SVR24, 48	3.25

HCC, hepatocellular carcinoma; DAA, direct acting antiviral; VCTE, vibration-controlled transient elastography; IFN, interferon; FIB-4, fibrosis-4 index; SVR, sustained viral response; kPa, kilopascal; SVR12, 12 weeks after SVR; SVR24, 24 weeks after SVR; SVR48, 48 weeks after SVR.

Study quality

The methodological quality of the studies assessed using the QUADAS-2 tool is summarized in Supplementary Figure 1. None of the studies exhibited a high risk of bias.

Patient characteristics

In total, 169,911 patients with HCV infection who achieved SVR with antiviral therapy were included in this meta-analysis. Supplementary Table 3 describes the characteristics of the patients in the studies included in the meta-analysis. The mean and median age ranged from 54.1 to 69.0 years. LS measured using VCTE had a mean or median range of 7.1–25.5 kPa, whereas FIB-4 had a mean or median range of 1.86–3.98.

Predictive performance of VCTE for HCC development after SVR

The predictive performances of VCTE and FIB-4 for HCC development after achieving SVR were evaluated. The pooled predictive AUC of a pre-treatment VCTE (eight studies) was 0.73, with a sensitivity of 65.7%, specificity of 69.5%, PLR of 2.22, and NLR of 0.48 (Table 2, Supplementary Fig. 2A). The pooled risk ratio of pre-treatment VCTE (nine studies) was 3.88 (95% CI 2.21–18.16) for HCC development after SVR (Table 3, Supplementary Fig. 3A). When limited to a pre-treatment VCTE cut-off of 9.2–13 kPa (five studies), the predictive performance improved, with a pooled diagnostic AUC of 0.79, sensitivity of 75.1%, specificity of 71.7%, PLR of 2.67, and NLR of 0.39. The cut-off 9.2–13.0 kPa of pre-treatment VCTE (six studies) had a pooled risk ratio of 4.56 (95% CI 3.05–6.81) for HCC development after SVR (Table 3).

For the VCTE measured after SVR (six studies with a cut-off range of 8.4–11 kPa), the pooled predictive AUC was 0.77, with a sensitivity of 76.6%, specificity of 63.9%, PLR of 2.20, and NLR of 0.37 (Table 2, Supplementary Fig. 2B). The pooled risk ratio of VCTE measured after SVR (seven studies) was 3.93 (95% CI: 2.17–7.11) (Table 3, Supplementary Fig. 3B).

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Table 2. The diagnostic performance of vibration-controlled transient elastography and FIB-4 in chronic hepatitis C patients with sustained virological response

Test	Time of measurement	Cutoff	Number of studies	Number of patients	Number of HCCs	AUC	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
VCTE	Pre-treatment	Total (9.2–27.8 kPa)	8	4,871	239	0.73	65.7 (45.5–0.81)	69.5 (56.8–79.8)	2.22 (1.65–2.99)	0.48 (0.28–0.85)
		9.2–13 kPa	5	3,354	153	0.79	75.1 (61.9–84.9)	71.7 (50.3–86.3)	2.67 (1.85–3.86)	0.39 (0.29–0.51)
	After SVR	Total (8.4–11 kPa)	6	3,840	171	0.77	76.6 (69.3–82.6)	63.9 (51.5–74.7)	2.20 (1.62–3.00)	0.37 (0.28–0.49)
FIB-4	Pre-treatment	Total (1.45–5)	15	154,408	5,386	0.72	73.4 (66.1–79.6)	60.5 (52.7–67.8)	1.88 (1.67–2.11)	0.50 (0.45–0.56)
		3.25	13	86,435	4,330	0.73	70.9 (62.4–78.1)	64.9 (55.5–73.3)	2.05 (1.73–2.43)	0.48 (0.42–0.55)
		3.25–5.0	5[a]	40,534	3,339	0.66	73.3 (63.2–81.5)	52.4 (42.3–62.3)	1.56 (1.34–1.81)	0.50 (0.40–0.63)
	After SVR	Total (2.73–3.7)	9	14,757	605	0.71	61.6 (55.0–67.8)	73.7 (66.9–79.6)	2.34 (1.98–2.77)	0.55 (0.50–0.60)
		3.25	7	13,019	480	0.70	57.9 (50.2–65.2)	75.4 (68.0–81.6)	2.37 (1.89–2.85)	0.58 (0.51–0.65)

HCC, hepatocellular carcinoma; AUC, area under the receiver operating characteristic; CI, confidence interval; FIB-4, fibrosis-4 index; SVR, sustained virological response; VCTE, vibration-controlled transient elastography; kPa, kilopascal.
[a]Studies including only patients with liver cirrhosis.

Table 3. Risk ratio for predicting the occurrence of hepatocellular carcinoma in chronic hepatitis C patients who achieved sustained viral response

Test	Time of measurement	Cutoff	Number of studies	Number of patients	Number of HCCs	I² (%)	P-value	Risk ratio	95% CI
VCTE	Pre-treatment	Total (8.4–27.8 kPa)	9	6,744	324	88.0	<0.01	3.88	2.21–18.16
		9.2–13.0 kPa	6	4,347	188	3.1	0.39	4.56	3.05–6.81
		17.3–27.8 kPa	3	1,343	80	0.0	0.40	4.68	2.21–9.90
	After SVR	Total (8.4–11 kPa)	7	4,238	190	60.0	0.02	3.93	2.17–7.11
FIB-4	Pre-treatment	Total (1.45–5)	15	155,444	5,427	95.0	<0.01	2.30	1.64–3.10
		<3.25	2	64,521	898	77.2	0.03	4.14	0.94–18.19
		3.25	14	86,614	4,355	81.6	<0.01	2.45	1.68–3.13
		3.25–5.0	4	4,309	174	38.5	0.18	1.32	0.95–1.82
	After SVR	Total (2.73–3.7)	10	16,913	681	89.0	<0.01	2.22	1.62–3.03
		3.25	6	13,019	480	0.0	0.58	3.05	2.46–3.80
		3.25–3.7	3	1,738	125	0.0	0.81	3.00	2.03–4.44

HCC, hepatocellular carcinoma; CI, confidence interval; FIB-4, fibrosis-4 index; SVR, sustained virological response; VCTE, vibration-controlled transient elastography; kPa, kilopascal.

Predictive performance of FIB-4 for HCC development after SVR

The pooled predictive AUC of a pre-treatment FIB-4 (15 studies) was 0.72, with a sensitivity of 73.4%, specificity of 60.5%, PLR of 1.88, and NLR of 0.50 (Table 2, Supplementary Fig. 4A). In the risk ratio analysis, a pre-treatment FIB-4 (15 studies) had a pooled risk ratio of 2.30 (95% CI: 1.64–3.10) for HCC development after SVR (Table 3, Supplementary Fig. 5A). When limited to a pre-treatment FIB-4 cut-off of 3.25 (13 studies), the pooled predictive AUC was 0.73, with a sensitivity of 70.9%, specificity of 64.9%, PLR of 2.05, and NLR of 0.48, which was superior compared to those of higher cut-off values. The cut-off of 3.25 of a pre-treatment FIB-4 (14 studies) had a pooled risk ratio of 2.45 (95% CI: 1.68–3.13) for HCC development after SVR (Table 3).

For the FIB-4 measured after SVR (nine studies), the pooled diagnostic AUC was 0.71, with a sensitivity of 61.6%, specificity of 73.7%, PLR of 2.34, and NLR of 0.55 (Table 2, Supplementary Fig. 4B). The FIB-4 measured after the SVR (10 studies) had a pooled risk ratio of 2.22 (95% CI: 1.62–3.03) (Table 3, Supplementary Fig. 5B).

When limited to a FIB-4 measured after SVR cut-off of 3.25 in (six studies), the pooled predictive AUC was 0.70, with a sensitivity of 57.9%, specificity of 75.4%, PLR of 2.37, and NLR of 0.58. The FIB-4 measured after the SVR cut-off of 3.25 had a pooled risk ratio of 3.05 (95% CI: 2.46–3.80) (Table 3).

Optimal cut-off of VCTE to predict HCC development after SVR

The optimal VCTE cut-off for predicting HCC development after SVR was investigated in studies with multiple cut-off values (Fig. 2, Supplementary Fig. 6). For the pre-treatment VCTE (eight studies), the optimal cut-off for HCC was 12.6 kPa with a sensitivity of 75.8% and specificity of 66.0%. The optimal cut-off of VCTE measured after SVR for HCC development after SVR (six studies) was 11.2 kPa with a sensitivity of 73.0% and specificity of 68.4%.

DISCUSSION

The development of HCC after achieving SVR in patients
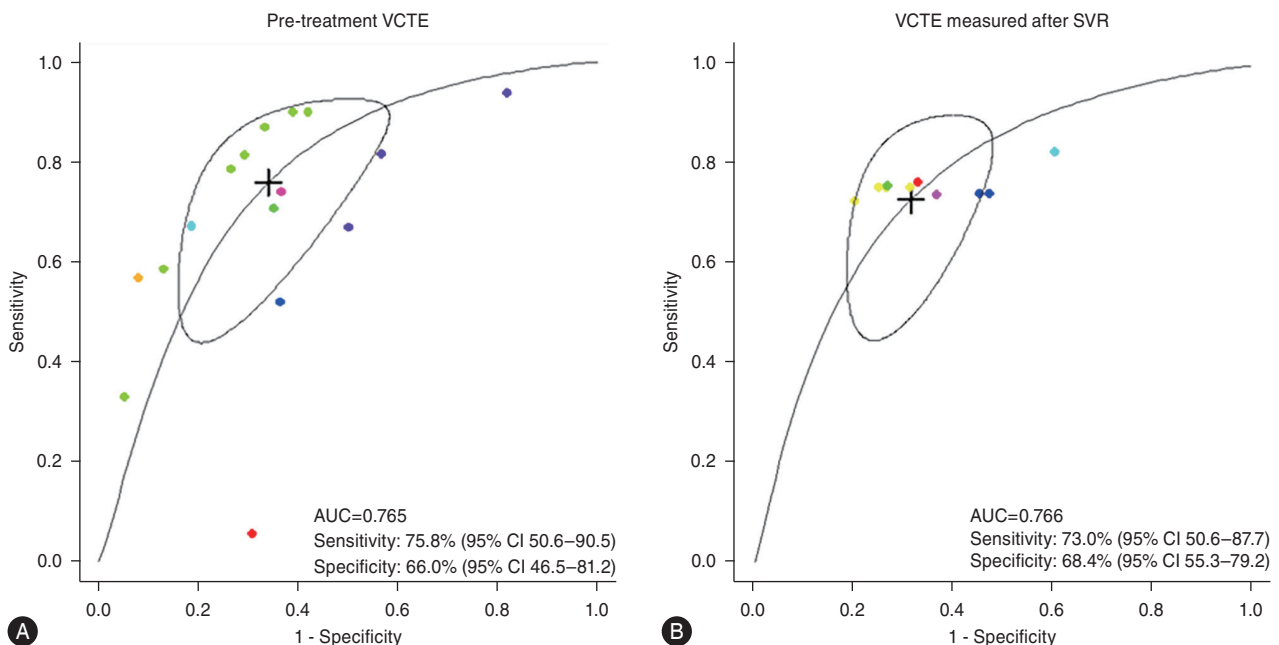
Figure 2. The performance of VCTE for predicting HCC after the achievement of SVR. Multiple-threshold sROC curve of pre-treatment VCTE (A) and VCTE measured after SVR (B). sSROC, summary receiver operating characteristic curve; VCTE, vibration-controlled transient elastography; SVR, sustained virological response; HCC, hepatocellular carcinoma; CI, confidence interval.

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with HCV infection has garnered significant attention owing to the evolving landscape of antiviral therapies, particularly with the advent of DAAs. Despite these advancements, HCC can still develop in a subset of patients after achieving an SVR, particularly in those with advanced liver fibrosis or cirrhosis, underscoring the need for effective predictive tools and surveillance strategies. This meta-analysis of 27 studies, including 169,911 patients, presented acceptable performance of VCTE and FIB-4 measured before and after SVR to predict HCC development after SVR in patients with HCV. These findings highlight the substantial role of non-invasive surrogates in identifying patients at increased risk of HCC development after SVR, emphasizing their utility in clinical practice for guiding surveillance strategies after SVR.

The results of this meta-analysis have profound implications for clinical practice. First, pre-treatment VCTE >9.2–13 kPa and FIB-4 >3.25 had pooled diagnostic AUC of 0.73 and 0.79, respectively, for the prediction of HCC after SVR. This indicates that the integration of VCTE and FIB-4 into the routine assessment of patients with HCV before antiviral therapy is required, which might facilitate the early identification of individuals with a non-invasive surrogate-based high fibrotic burden who require careful surveillance owing to the increased risk of post-SVR HCC development. Recent studies support these results;[15-17] however, the significance lies in the increased reliability of the predictive performance of non-invasive surrogates for HCC after SVR by conducting a systematic review and meta-analysis of the largest number of studies reported to date.

Second, VCTE and FIB-4 measured after SVR showed good performance in predicting HCC development after SVR. Although the predictive performance of VCTE and FIB-4 measured after SVR was slightly lower than that of pre-treatment VCTE and FIB-4, the pooled AUC values for VCTE and FIB-4 at both time points were maintained above 0.7, which underscores the dynamics of non-invasive surrogates and their clinical implications for HCC surveillance strategies during antiviral therapy for HCV. In a recent multicenter retrospective study that examined patients who achieved SVR following DAA therapy, those who experienced an increase in FIB-4 from baseline to 2 years after SVR had elevated HCC risks compared to those whose FIB-4 levels stabilized or declined after treatment.[15] In addition, two studies regarding the VCTE measured af-

ter SVR also showed acceptable predictive performance for HCC development after SVR.[17,19] Consequently, VCTE and FIB-4 measured after SVR can serve as important indicators for assessing HCC risk after SVR, emphasizing that dynamic assessment of non-invasive surrogates, rather than a single pre-treatment assessment, is essential for accurate identification of patients at increased risk of HCC after SVR. However, caution is needed when interpreting these non-invasive surrogate measurements after SVR because they do not precisely correlate with the fibrosis stage after SVR.[41]

Third, VCTE had higher diagnostic accuracy than FIB-4 before and after SVR, which may be because various systemic conditions, such as inflammation, abnormalities in other organs, or other acute illnesses, can influence FIB-4. In addition, the diagnostic accuracy of FIB-4 in assessing fibrotic burden has been reported to be low in young and older adults.[42,43] However, LS measured using VCTE can also be overestimated by intrahepatic inflammation.[44,45] Considering the high cost and limited accessibility of the test, FIB-4 is useful as a primary screening test for identifying high-risk groups for HCC after SVR in patients with HCV infection.

Fourth, to establish simplified and effective screening criteria for high-risk groups with HCC after SVR, various cut-off values were comprehensively analyzed to determine the optimal cut-off value. In this study, the optimal cut-off values for HCC were found to be 12.6 kPa for pre-treatment VCTE and 11.2 kPa for VCTE measured after SVR. However, the identified cut-off values were derived from the analysis of various studies with diverse clinical characteristics; therefore, further validation through multiple studies, especially prospective studies, is necessary. Currently, there are no established criteria for non-invasive surrogates to select patients in need of HCC surveillance. Moreover, considering that most patients with HCV infection do not undergo liver biopsy for fibrosis assessment, a simplified strategy may be helpful in clinical decision-making. Owing to insufficient data, we could not conduct an sROC analysis for an optimal FIB-4 cut-off. However, a meta-analysis showed that FIB-4 >3.25 measured before and after SVR was considered the most useful cut-off value in predicting HCC development after SVR. The identification of optimal cut-off values for VCTE and FIB-4 enhances the precision of risk stratification, enabling clinicians to tailor

surveillance and management strategies more effectively. The study findings support the use of simple, specific cut-off values, thereby enhancing the clinical utility of VCTE and FIB-4 in HCC surveillance after achieving SVR. Furthermore, this approach optimizes patient care and contributes to the efficient allocation of healthcare resources by focusing efforts on those most at risk.

Despite these robust findings, this study has some limitations. First, a substantial number of included studies were retrospective, potentially introducing bias and limiting causal inference. Second, heterogeneity in study design, patient characteristics, and diagnostic thresholds across the studies may have influenced the pooled estimates. Furthermore, the lack of standardized cut-off values for non-invasive surrogates underscores the need for further research to establish widely applicable thresholds. The generalizability of our findings is limited by the heterogeneity in patient characteristics across the included studies. The applicability of these findings to specific subgroups uncertain. Third, the variability in the follow-up duration and time of assessment of VCTE and FIB-4 may have influenced the generalizability of the results. Future research should aim to address these limitations through prospective studies with standardized methodologies and longer follow-up periods to validate the identified cut-off values and further refine the risk stratification models. Fourth, although VCTE and FIB-4 measured before and after SVR showed significant predictive performance, the clinical implications of the dynamic change in these tests on the risk of HCC development after SVR were not assessed. Further prospective studies assessing non-invasive surrogates, pre- and post-SVR, are needed to reveal the changes in the results of non-invasive tests and their clinical relevance to HCC development after SVR. Fifth, the inability to perform detailed sensitivity or subgroup analyses due to insufficient data and variability in the cut-off values used across studies is a notable limitation. Sixth, due to time constraints and limitations in accessible data, we couldn't perform individual participant data analysis, so there is a limitation in overcoming the diversity of participants included in the study. Seventh, although the cut-off value derived in this study aims to achieve the highest diagnostic accuracy, its application in clinical settings may have limitations, particularly concerning the NPV, which is essential for HCC surveillance. Eighth, although the likelihood of overlapping pa-

tients between the studies is small, there is a possibility of some patient overlap. This could potentially inflate the sample size and introduce bias, affecting the accuracy and validity of the meta-analysis results. Finally, considering the modest predictive accuracies of FIB-4 and VCTE in this study, exploring the integration of additional biomarkers with VCTE or FIB-4 could enhance the predictive performance for HCC development after SVR, offering a more comprehensive approach to patient management.

In conclusion, this systematic review and meta-analysis reinforces the importance of VCTE and FIB-4 in predicting the risk of HCC development after SVR in patients with HCV. These tools can guide the implementation of targeted surveillance strategies by identifying patients at an increased risk of HCC after SVR, ultimately facilitating the early detection and management of HCC. Future research for prospective validation of optimal cut-off values and the integration of non-invasive surrogates into clinical practice guidelines for HCC surveillance in patients with HCV who achieved SVR are needed.

Authors' contribution

HAL and YJK conceptualized and designed the study. HAL and HAL performed the statistical analyses. All the authors interpreted the findings. HAL and MNK drafted the manuscript. HAL, MNK, HAL, MC, JWH, and YJK critically revised the manuscript for important intellectual content. All authors provided their final approval for the version to be submitted.

Acknowledgements

Conflicts of Interest

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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Supplementary Table 1. PRISMA-DTA checklist

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	5
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	8
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	8
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	8
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	9

Supplementary Table 1. Continued

Page 1 of 2

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	10
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	10
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	10
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	13
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	15
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	16

Adapted from: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM; and the PRISMA-DTA Group. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: The PRISMA-DTA statement. JAMA 2018;319:388-396.

Supplementary Table 2. Electronic search strategy

Classification	Number	Search terms
Population	1	Hepatitis C, Chronic/ OR Hepatitis C/ OR (chronic hepatitis C or hepatitis C virus or hepatitis C).tw,kw
Intervention	2	(Fibroscan or fibrosis stating or transient elastography or TE or vibration controlled transient elastography or VCTE or fibrosis-4 or FIB-4).tw,kw.
P&I	3	1 AND 2
Outcome	4	Carcinoma, Hepatocellular/ OR Liver Neoplasms/ OR (Hepatocellular carcinoma or HCC or liver cancer).tw,kw.
P&I&O	5	3 AND 4
SIGN Filter	6	exp "Sensitivity and Specificity"/ OR (sensitivity OR specificity OR ((pre-test or pretest) adj probability) OR post-test probability OR predictive value* OR predictive value* OR likelihood ratio*).tw.
	7	AND 6

P, population; I, intervention; O, outcome; TE, transient elastography; VCTE, vibration controlled transient elastography; FIB-4, fibrosis-4 index; HCC, hepatocellular carcinoma.

Supplementary Table 3. Patient characteristics of included studies in the systematic literature review and meta-analysis

Reference	Male (%)	Age, years	AST (IU/L)	ALT (IU/L)	Baseline LS (kPa)	Baseline FIB-4	Genotype (%)
Kim et al.[a]	58.0	59.4 (51.7–68.8)	44 (27–75)	38 (22–73)	8.0 (5.6–14.0)	N/A	1 (52.0); 2 (46.0); 3 (1.0); 4 (0.5); 6 (0.5)
Nakai et al.[1]	45.7	66 (16–92)	40 (10–342)	38 (5–389)	7.1 (2.9–66.4)	2.72 (0.29–82.8)	1 (63.3); 2 (34.4); others (2.3)
Pons et al.[2]	49.3	63.7 (11.1)	N/A	103 (67)	20.2 (10.4)	N/A	1 (85.8); 2 (1.8); 3 (6.8); 4 (5.6)
Rinaldi et al.[3]	55.4	68 (61–74)	N/A	N/A	25.5 (18–35.6)	N/A	1 (76.7); 2 (18.6); 3 (3.2); 4 (1.6)
Wang et al.[4]	49.2	54.1±10.8	>40 (10.4%)	>40 (15.2%)	7.7 ± 6.1	N/A	1 (32.3); others (63.8)
Liu et al.[5]	42.0	65±11	N/A	77 (49–137)	13.4 (10.5–22.3)	3.98 (2.67–6.11)	1 (67.0); others (33.0)
Kuo et al.[6]	42.2	63.8±10.3	>40 (12.8%)	>40 (11.0%)	12.0±9.3	2.87±1.99	1 (56.5); 2 (38.9); other (4.6)
Morisco et al.[7]	54.8	64.1±11.7	N/A	N/A	19.2 (7.9)	N/A	1 (80.3); 2 (13.6); 3 (3.8); 4 (2.1); others (0.1)
Zou et al.[8]	24.5	56.7 (8.3)	N/A	N/A	N/A	>3.25 (39.0%)	N/A
Ideno et al.[9]	54.6	65 (24–90)	33.5 (7–367)	34 (9–436)	N/A	3.38 (0.4–5.38)	1 (68.8); 2 (29.9); others (1.3)
Kumada et al.[10]	49.0	62 (53–70)	21 (18–26)	15 (11–20)	N/A	1.86 (1.26–2.69)	1 (57.9); 2 (41.9); 3 (0.2)
Azzi et al.[11]	62.1	60.1 (10.5)	N/A	N/A	N/A	3.65 (3.41)	1 (68.9); 2 (4.6); 3 (12.6); 4 (12.3); others (1.7)
Caviglia et al.[12]	57.6	65 (57–77)	24 (20–29)	20 (16–25)	N/A	N/A	N/A
Tada et al.[13]	40.9	68 (59.4–76)	23 (19–28)	15 (12–21)	N/A	2.41 (1.65–3.45)	1 (72.0); 2 (27.4); others (0.6)
Ampuero et al.[14]	65.4	57.3±9.9	83±54	92±64	19.9±12.3	N/A	N/A
Tahata et al.[15]	41.7	69 (60–76)	39 (28–58)	38 (24–61)	N/A	N/A	1 (77.3); 2 (22.1); others (0.6)
Ide et al.[16]	39.3	64.6±11.9	51.0±35.6	51.8±45.5	N/A	3.86±3.22	1 (78.0); 2 (21.7); 1+2 (0.3)
Hiraoka et al.[17]	44.7	66.9±11.0	24.1±10.3	17.8±11.6	N/A	2.76±1.77	1 (71.1); 2 (28.9)
Kramer et al.[18]	96.4	61.5±7.6	N/A	N/A	N/A	<1.45 (41.9%); 1.45–3.25 (45.9%); >3.25 (11.5%)	1a (55.1); 1a/1b (3.26); 1b (21.45); 1–unknown (2.4); 2 (9.46); 3 (5.66); 4/5/6 (0.95)
Ogawa et al.[19]	42.4	66 (58–73)	36 (26–56)	32 (21–53)	7.5 (5.4–11.4)	N/A	1 (72.4); 2 (26.6)
Tamaki et al.[20]	42.4	67 (58–75)	23 (19–28)	16 (12–22)	N/A	2.31 (1.59–3.32)	N/A

Values as median (interquartile range) or mean±standard deviation.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; LS, liver stiffness; FIB-4, fibrosis-4 index; N/A, not available.
[a]Studies lacking data on the characteristics of the entire patient cohort were excluded.
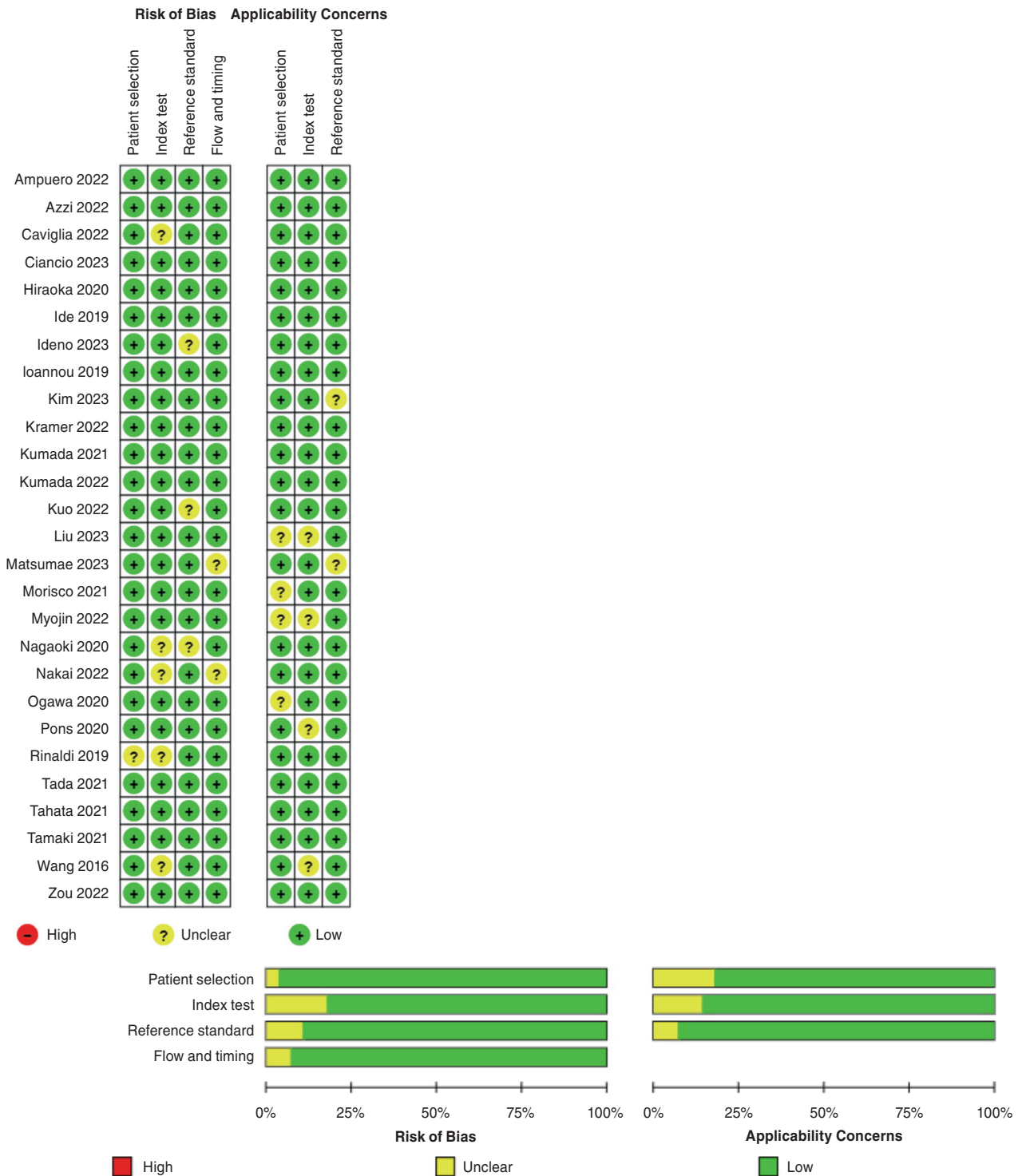
Supplementary Figure 1. Methodological quality summary of included studies. Red circles: high risk of bias, Yellow circles: unclear risk of bias, Green circles: low risk of bias.

Study	Threshold	TP	FP	FN	TN	Se [95% CI]	Sp [95% CI]
Nakai 2022	9.2	19	91	9	400	0.68 [0.49, 0.82]	0.81 [0.78, 0.85]
Pons 2020	20	13	199	12	348	0.52 [0.33, 0.70]	0.64 [0.60, 0.68]
Rinaldi 2019	27.8	25	78	10	144	0.71 [0.55, 0.84]	0.65 [0.58, 0.71]
Wang 2016	12	12	28	9	326	0.57 [0.37, 0.76]	0.92 [0.89, 0.94]
Liu 2023	12	33	241	7	184	0.82 [0.68, 0.91]	0.43 [0.39, 0.48]
	13	27	213	13	213	0.68 [0.52, 0.80]	0.50 [0.45, 0.55]
	10	38	348	2	77	0.95 [0.83, 0.99]	0.18 [0.15, 0.22]
Kuo 2022	11	21	244	7	424	0.75 [0.57, 0.87]	0.63 [0.60, 0.67]
Morisco 2021	20	1	166	25	375	0.04 [0.01, 0.19]	0.69 [0.65, 0.73]
Kim 2023	9.2	31	508	3	706	0.91 [0.77, 0.97]	0.58 [0.55, 0.61]
	10	31	471	3	743	0.91 [0.77, 0.97]	0.61 [0.58, 0.64]
	11	30	403	4	811	0.88 [0.73, 0.95]	0.67 [0.64, 0.69]
	12	28	356	6	858	0.82 [0.66, 0.92]	0.71 [0.68, 0.73]
	13	27	320	7	894	0.79 [0.63, 0.90]	0.74 [0.71, 0.76]
	20	20	157	14	1057	0.59 [0.42, 0.74]	0.87 [0.85, 0.89]
	27.8	11	61	23	1153	0.32 [0.19, 0.49]	0.95 [0.94, 0.96]

(A)

Study	Threshold	TP	FP	FN	TN	Se [95% CI]	Sp [95% CI]
Nakai 2022	8.4	23	23	7	360	0.77 [0.59, 0.88]	0.73 [0.69, 0.77]
Pons 2020	10	21	21	4	216	0.84 [0.65, 0.94]	0.39 [0.35, 0.44]
Liu 2023	10	30	30	10	233	0.75 [0.60, 0.86]	0.55 [0.50, 0.59]
	9.5	30	30	10	225	0.75 [0.60, 0.86]	0.53 [0.48, 0.58]
Kuo 2022	11	21	21	7	425	0.75 [0.57, 0.87]	0.64 [0.60, 0.67]
Ogawa 2020	10	11	11	3	188	0.79 [0.52, 0.92]	0.67 [0.61, 0.72]
Kim 2023	8.4	26	26	8	833	0.76 [0.60, 0.88]	0.69 [0.66, 0.71]
	9.5	26	26	8	892	0.76 [0.60, 0.88]	0.73 [0.71, 0.76]
	10	26	26	8	912	0.76 [0.60, 0.88]	0.75 [0.73, 0.77]
	11	25	25	9	971	0.74 [0.57, 0.85]	0.80 [0.78, 0.82]

(B)

Supplementary Figure 2. Forest plots of studies included in the diagnostic accuracy analysis for the prediction of HCC using VCTE measured at (A) pre-treatment and (B) after SVR. HCC, hepatocellular carcinoma; VCTE, vibration-controlled transient elastography; SVR, sustained virological response.

Study	logRR	SE(logRR)	Risk Ratio	RR	95%-CI	Weight (common)	Weight (random)
Nakai 2022	1.8450	0.5379		6.33	[2.21; 18.16]	0.0%	9.7%
Rinaldi 2019	1.1119	0.4710		3.04	[1.21; 7.65]	0.0%	10.6%
Wang 2016	1.8464	0.5699		6.34	[2.07; 19.36]	0.0%	9.3%
Liu 2023	1.1743	0.4829		3.24	[1.26; 8.34]	0.0%	10.5%
Kuo 2021	1.0396	0.4712		2.83	[1.12; 7.12]	0.0%	10.6%
Ogasawara 2020	2.2659	0.9431		9.64	[1.52; 61.22]	0.0%	5.4%
Morisco 2021	1.9741	0.6742		7.20	[1.92; 26.99]	0.0%	8.0%
Ampuero 2022	0.0198	0.0100		1.02	[1.00; 1.04]	99.7%	15.7%
Kim 2024	2.5111	0.6072		12.32	[3.75; 40.50]	0.0%	8.8%
Common effect model				1.02	[1.00; 1.05]	100.0%	-
Random effects model				3.88	[2.28; 6.59]	-	100.0%

Heterogeneity: I^2=88%, τ^2=0.4671, P<0.01

0.1　0.5　1　2　　10

A

Study	logRR	SE(logRR)	Risk Ratio	RR	95%-CI	Weight (common)	Weight (random)
Nakai 2022	1.8934	0.4931		6.64	[2.53; 17.46]	14.5%	14.8%
Pons 2020	1.1086	0.5526		3.03	[1.03; 8.95]	11.5%	13.5%
Liu 2023	0.4292	0.4248		1.54	[0.67; 3.53]	19.5%	16.5%
Ogasawara 2020	2.6319	0.6400		13.90	[3.96; 48.73]	8.6%	11.7%
Kuo 2022	1.0396	0.4712		2.83	[1.12; 7.12]	15.8%	15.3%
Ogawa 2020	0.4637	0.6809		1.59	[0.42; 6.04]	7.6%	10.9%
Kim 2024	2.0275	0.3948		7.59	[3.50; 16.47]	22.5%	17.3%
Common effect model				3.9	[2.72; 5.67]	100.0%	-
Random effects model				3.93	[2.17; 7.11]	-	100.0%

Heterogeneity: I^2=60%, τ^2=0.3757, P=0.02

0.1　0.5　1　2　　10

B

Supplementary Figure 3. Forest plots of studies included in the risk ratio analysis for the prediction of HCC using VCTE measured at (A) pre-treatment and (B) after SVR. HCC, hepatocellular carcinoma; VCTE, vibration-controlled transient elastography; SVR, sustained virological response.

Study	Threshold	TP	FP	FN	TN	Se [95% CI]	Sp [95% CI]
Liu 2023	4.6	23	162	17	264	0.58 [0.42, 0.71]	0.62 [0.57, 0.66]
Ciancio 2022	3.25	60	458	11	471	0.85 [0.74, 0.91]	0.51 [0.47, 0.54]
Zou 2022	3.25	17	256	10	418	0.63 [0.44, 0.78]	0.62 [0.58, 0.66]
Ideno 2022	3.25	67	252	10	361	0.87 [0.78, 0.93]	0.59 [0.55, 0.63]
Kumada 2022	3.25	21	217	30	1,116	0.41 [0.29,0.55]	0.84 [0.82, 0.86]
Ampuero 2022	3.25	44	504	12	494	0.79 [0.66, 0.87]	0.49 [0.46, 0.53]
Tahata 2021	3.25	41	561	11	860	0.79 [0.66, 0.88]	0.61 [0.58, 0.63]
Kumada 2021	1.5	53	852	2	445	0.96 [0.88, 0.99]	0.34 [0.32, 0.37]
Matsumae 2023	2.625	17	199	6	301	0.74 [0.54, 0.87]	0.60 [0.56, 0.64]
Myojin 2022	3.25	39	308	11	606	0.78 [0.65, 0.87]	0.66 [0.63, 0.69]
Ide 2019	4.6	59	915	4	547	0.94 [0.85, 0.98]	0.37 [0.35, 0.40]
Nagaoki 2020	5	20	122	9	147	0.69 [0.51, 0.83]	0.55 [0.49, 0.60]
Ioannou 2019	3.25	168	875	63	1145	0.73 [0.67, 0.78]	0.57 [0.55, 0.59]
	3.25	529	4,458	90	2,456	0.85 [0.82, 0.88]	0.36 [0.34, 0.37]
	3.25	168	1,762	203	14,718	0.45 [0.40, 0.50]	0.89 [0.89, 0.90]
	3.25	167	4,515	121	16,697	0.58 [0.52, 0.64]	0.79 [0.78, 0.79]
Kramer 2022	3.25	1,418	9,249	986	17,745	0.59 [0.57, 0.61]	0.66 [0.65, 0.66]
	1.45	561	29,138	282	33,188	0.67 [0.63, 0.70]	0.53 [0.53, 0.54]
Kim 2023	1.45	33	938	1	276	0.97 [0.85, 0.99]	0.23 [0.20, 0.25]
	1.5	33	914	1	300	0.97 [0.85, 0.99]	0.25 [0.22, 0.27]
	2.625	31	563	3	651	0.91 [0.77, 0.97]	0.54 [0.51, 0.56]
	3.25	29	415	5	799	0.85 [0.70, 0.94]	0.66 [0.63, 0.68]
	4.6	23	259	11	955	0.68 [0.51, 0.81]	0.79 [0.76, 0.81]
	5	20	235	14	979	0.59 [0.42, 0.74]	0.81 [0.78, 0.83]

(A)

Sensitivity axis: 0.29 0.64 0.99 Specificity axis: 0.20 0.55 0.90

Study	Threshold	TP	FP	FN	TN	Se [95% CI]	Sp [95% CI]
Liu 2023	3.7	24	124	16	302	0.60 [0.45, 0.74]	0.71 [0.66, 0.75]
Azzi 2022	3.25	74	478	79	2,900	0.48 [0.41, 0.56]	0.86 [0.85, 0.87]
Caviglia 2022	3.38	40	234	17	341	0.70 [0.57, 0.80]	0.59 [0.55, 0.63]
Tada 2022	3.25	72	829	35	2122	0.67 [0.58, 0.75]	0.72 [0.70, 0.74]
Kuo 2022	3.6	17	145	11	524	0.61 [0.42, 0.76]	0.78 [0.75, 0.81]
Hiraoka 2019	3.25	11	112	11	350	0.50 [0.31, 0.69]	0.76 [0.72, 0.79]
Ogawa 2020	3.25	11	124	5	150	0.69 [0.44, 0.86]	0.55 [0.49, 0.61]
Tamaki 2021	3.25	75	925	48	2,775	0.61 [0.52, 0.69]	0.75 [0.74, 0.76]
Kim 2023	3.25	19	220	15	994	0.56 [0.39, 0.71]	0.82 [0.80, 0.84]
	3.38	17	199	17	1,015	0.50 [0.34, 0.66]	0.84 [0.81, 0.86]
	3.6	17	170	17	1,044	0.50 [0.34, 0.66]	0.86 [0.84, 0.88]
	3.7	17	152	17	1,062	0.50 [0.34, 0.66]	0.87 [0.85, 0.89]

(B)

Sensitivity axis: 0.31 0.58 0.86 Specificity axis: 0.49 0.69 0.89

Supplementary Figure 4. Forest plots of studies included in the diagnostic accuracy analysis for the prediction of HCC using FIB-4 measured at (A) pre-treatment and (B) after SVR. HCC, hepatocellular carcinoma; FIB-4, fibrosis-4 index; SVR, sustained virological response.

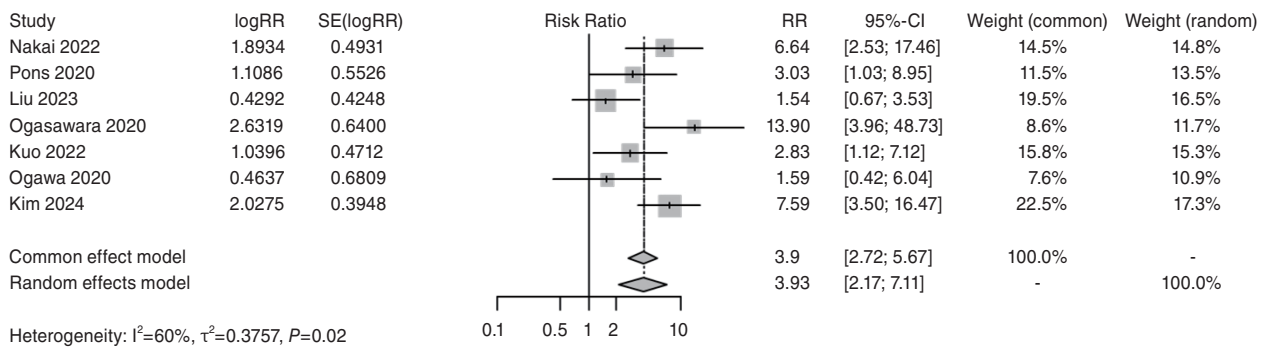| Study	logRR	SE(logRR)	Risk Ratio	RR	95%-CI	Weight (common)	Weight (random)
Nakai 2022	-0.6143	0.5058		0.54	[0.20; 1.46]	0.2%	3.9%
Liu 2023	0.0760	0.3545		1.08	[0.54; 2.16]	0.3%	5.0%
Ciancio 2022	-0.1985	0.4342		0.82	[0.35; 1.92]	0.2%	4.4%
Zou 2022	0.9203	0.4206		2.51	[1.10; 5.72]	0.2%	4.5%
Ideno 2022	-1.5051	0.7317		0.22	[0.05; 0.93]	0.1%	2.7%
Kumada 2022	1.4734	0.3481		4.36	[2.21; 8.63]	0.3%	5.0%
Ampuero 2022	0.8154	0.3768		2.26	[1.08; 4.73]	0.3%	4.8%
Tahata 2021	1.4462	0.4218		4.25	[1.86; 9.71]	0.2%	4.5%
Kumada 2021	2.3684	0.7350		10.68	[2.53; 45.10]	0.1%	2.7%
Myojin 2022	0.9895	0.3944		2.69	[1.24; 5.83]	0.3%	4.7%
Ide 2019	0.1133	0.0228		1.12	[1.07; 1.17]	76.6%	6.6%
Nagaoki 2020	0.6663	0.3807		1.95	[0.92; 4.11]	0.3%	4.8%
Ioannou 2019	1.0225	0.1905		2.78	[1.91; 4.04]	1.1%	6.0%
	0.7608	0.1288		2.14	[1.66; 2.75]	2.4%	6.3%
	1.6312	0.1324		5.11	[3.94; 6.62]	2.3%	6.3%
	1.2698	0.1338		3.56	[2.74; 4.63]	2.2%	6.3%
Kramer 2022	0.9123	0.0846		2.49	[2.11; 2.94]	5.6%	6.5%
	0.8198	0.0750		2.27	[1.96; 2.63]	7.1%	6.5%
Kim 2024	2.3372	0.4993		10.35	[3.89; 27.55]	0.2%	4.0%
Common effect model				1.37	[1.31; 1.42]	100.0%	-
Random effects model				2.30	[1.64; 3.10]	-	100.0%

Heterogeneity:I^2=95%, τ^2=0.3809, P<0.01

0.1 0.5 1 2 10

A

Study	logRR	SE(logRR)	Risk Ratio	RR	95%-CI	Weight (common)	Weight (random)
Nakai 2022	-0.0171	0.4268		0.98	[0.43; 2.27]	0.5%	6.5%
Liu 2023	0.9187	0.3644		2.51	[1.23; 5.12]	0.6%	7.5%
Azzi 2022	0.8548	0.2471		2.35	[1.45; 3.82]	1.4%	9.5%
Caviglia 2022	1.2149	0.2903		3.37	[1.91; 5.95]	1.0%	8.7%
Tada 2022	1.0616	0.2291		2.89	[1.85; 4.53]	1.6%	9.8%
Kuo 2022	1.1009	0.4177		3.01	[1.33; 6.82]	0.5%	6.7%
Hiraoka 2019	1.0567	0.4556		2.88	[1.18; 7.03]	0.4%	6.1%
Ogawa 2020	0.5423	0.7559		1.72	[0.39; 7.57]	0.1%	3.3%
Tamaki 2021	1.2179	0.1768		3.38	[2.39; 4.78]	2.7%	10.6%
Kim 2024	1.5839	0.3650		4.87	[2.38; 9.97]	0.6%	7.5%
Common effect model				1.23	[1.16; 1.30]	100.0%	-
Random effects model				2.22	[1.62; 3.03]	-	100.0%

Heterogeneity:I^2=89%, τ^2=0.2082, P<0.01

0.2 0.5 1 2 5
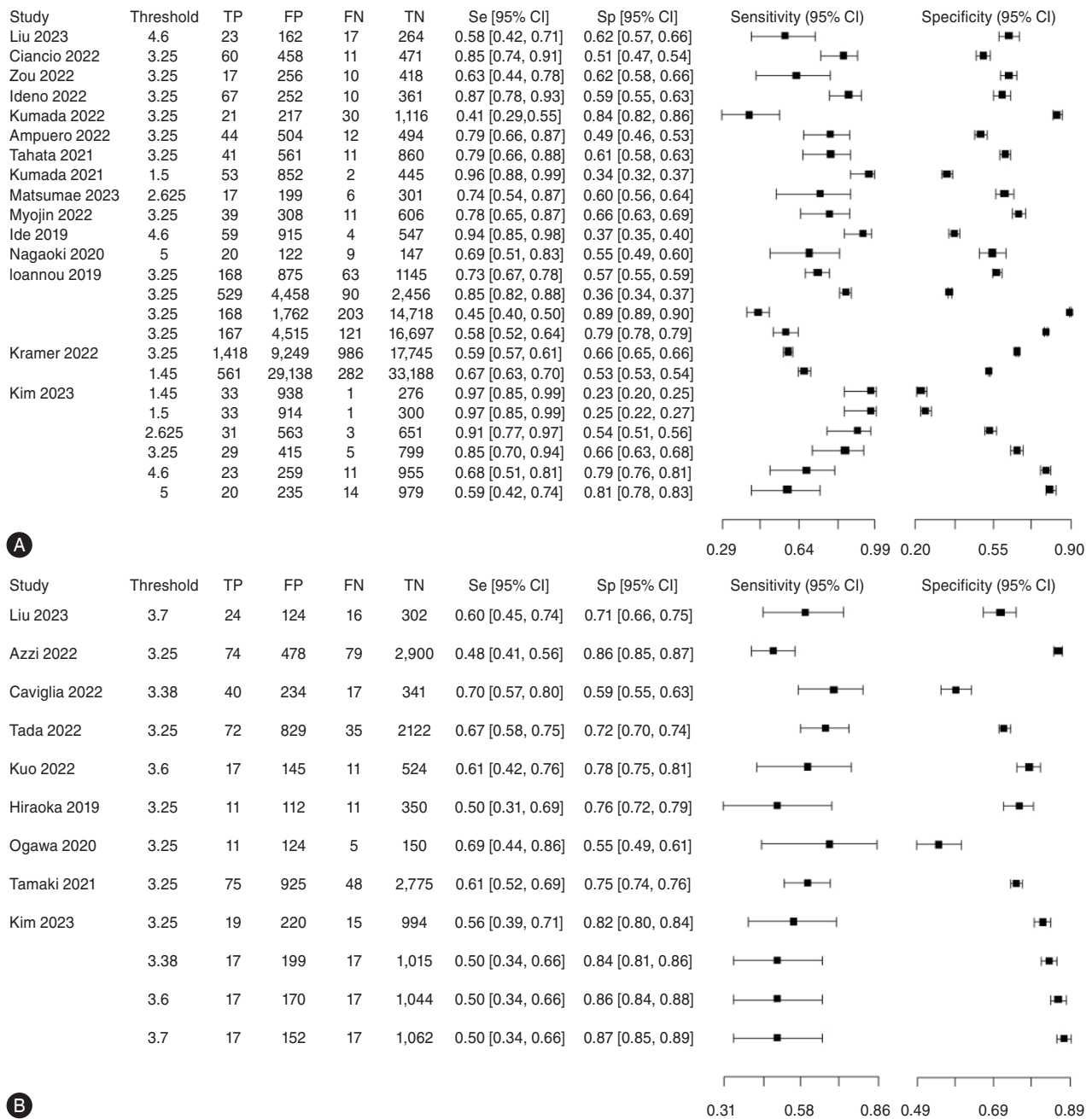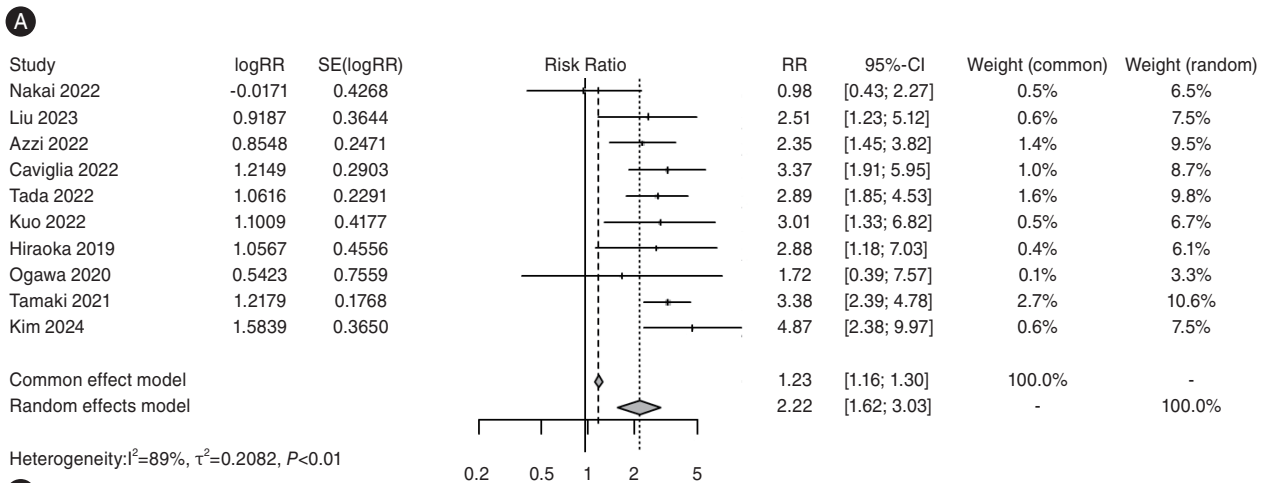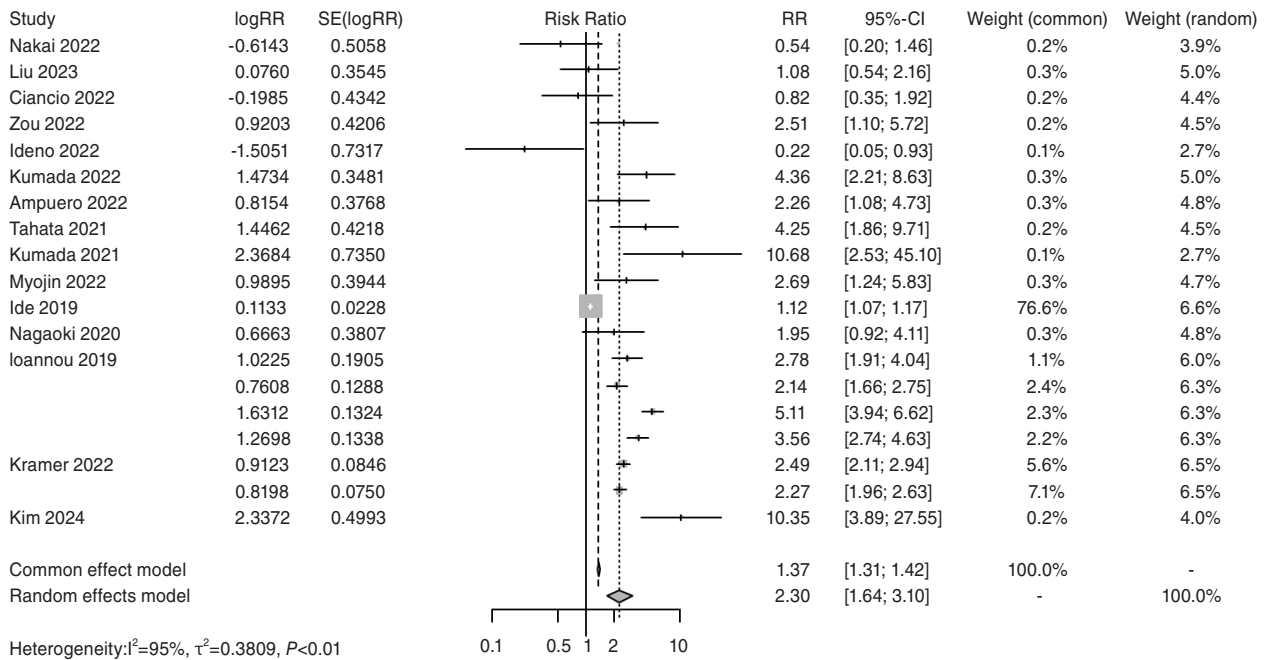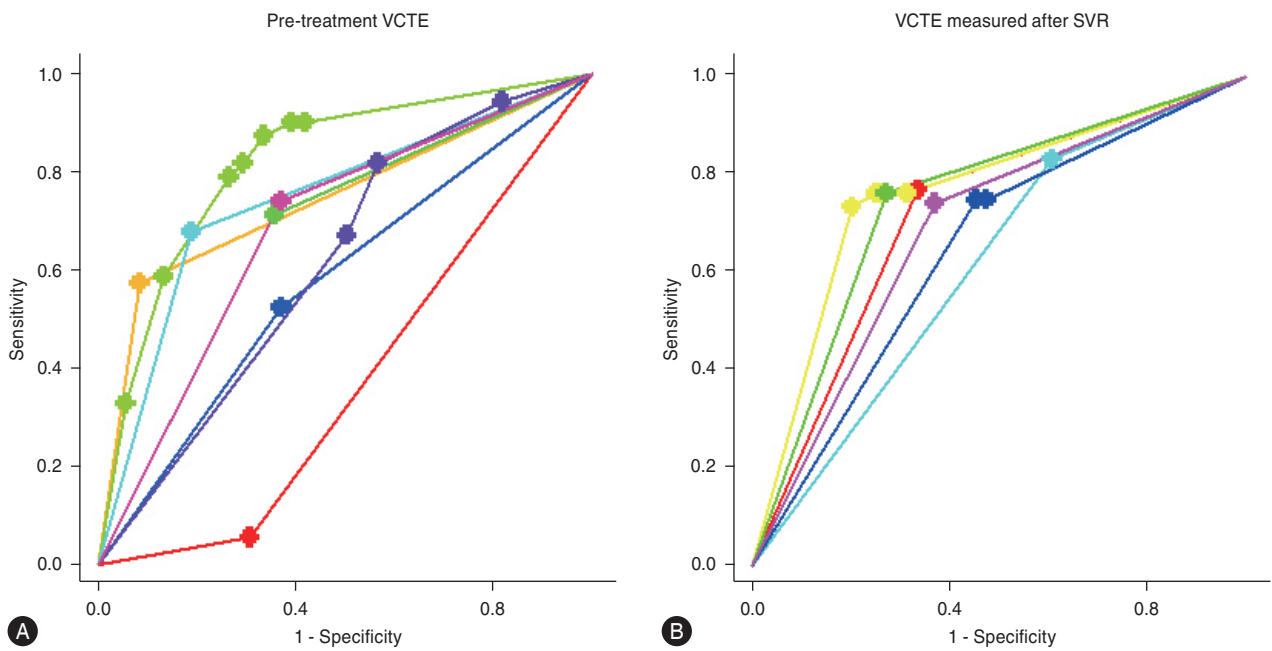
B

Supplementary Figure 5. Forest plots of studies included in the risk ratio analysis for the prediction of HCC using FIB-4 measured at (A) pre-treatment and (B) after SVR. HCC, hepatocellular carcinoma; FIB-4, fibrosis-4 index; SVR, sustained virological response.

Supplementary Figure 6. The performance of VCTE for predicting HCC after the achievement of SVR. Multiple-threshold ROC curves of pre-treatment VCTE (A) and VCTE measured after SVR (B). ROC, receiver operating characteristic curve; VCTE, vibration-controlled transient elastography; SVR, sustained virological response; HCC, hepatocellular carcinoma.

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