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Original Article

Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using vibration-controlled transient elastography: Systematic review and meta-analysis

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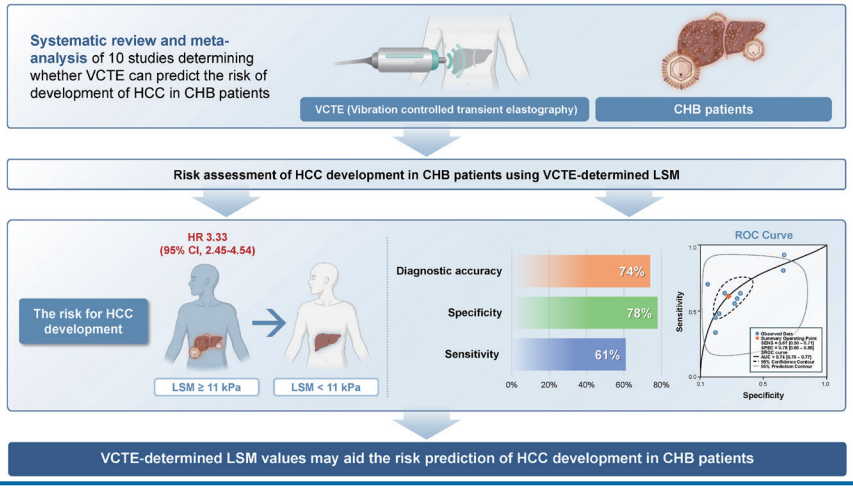
Graphical Abstract



Study Highlights

- The risk of HCC development was elevated in CHB patients with VCTE-determined LSM of ≥11 kPa.
- LSM of ≥ 11 kPa showed the sensitivity and specificity for predicting HCC development were 61% (95% CI, 50–71%) and 78% (95% CI, 66–86%), respectively, and the diagnostic accuracy was 0.74 (95% CI, 0.70–0.77).
- These findings suggest that VCTE-determined LSM values may aid the risk prediction of HCC development in CHB patients.
- VCTE can be used to identify CHB patients at elevated risk of HCC development and to facilitate the development of optimal HCC surveillance strategies in CHB patients.

Backgrounds/Aims: Liver stiffness measurement (LSM) using vibration-controlled transient elastography (VCTE) can assess fibrotic burden in chronic liver diseases. The systematic review and meta-analysis was conducted to determine whether LSM using VCTE can predict the risk of development of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients.

Methods: A systematic literature search of the Ovid-Medline, EMBASE, Cochrane, and KoreaMed databases (from January 2010 to June 2023) was conducted. Of the 1,345 individual studies identified, 10 studies that used VCTE were finally registered. Hazard ratios (HRs) and the 95% confidence intervals (CIs) were considered summary estimates of treatment effect sizes of ≥11 kilopascal (kPa) standard for HCC development. Meta-analysis was performed using the restricted Maximum Likelihood random effects model.

Results: Among the ten studies, data for risk ratios for HCC development could be obtained from nine studies. When analyzed for the nine studies, the HR for HCC development was high at 3.33 (95% CI, 2.45–4.54) in CHB patients with a baseline LSM of ≥11 kPa compared to patients who did not. In ten studies included, LSM of ≥11 kPa showed the sensitivity and specificity for predicting HCC development were 61% (95% CI, 50–71%) and 78% (95% CI, 66–86%), respectively, and the diagnostic accuracy was 0.74 (95% CI, 0.70–0.77).

Conclusions: The risk of HCC development was elevated in CHB patients with VCTE-determined LSM of ≥11 kPa. This finding suggests that VCTE-determined LSM values may aid the risk prediction of HCC development in CHB patients. **(Clin Mol Hepatol 2024;30(Suppl):S159-S171)**

Keywords: Liver stiffness measurement; Vibration-controlled transient elastography; Hepatocellular carcinoma; Chronic hepatitis B

INTRODUCTION

Chronic hepatitis B (CHB) is one of the leading causes of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) worldwide,[1-3] and LC is a major predictor of HCC development in patients with CHB.[3,4] Liver biopsy-based histological examination is the standard for diagnosing LC,[5] but liver biopsy cannot be easily performed in clinical practice settings due to the risk of sampling error, inter-observer variability, or invasiveness.[6-8] Considering the noninvasive nature and no risk of radiation exposure, ultrasonography (USG) is often used to diagnose LC in clinical practice.[9,10]

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Abbreviations:

AVT, antiviral therapy; CHB, chronic hepatitis B; CI, confidence interval; CLD, chronic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HRs, hazard ratios; IQR, interquartile range; kPa, kilopascals; LC, liver cirrhosis; LSM, liver stiffness measurement; M, median; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SROC, summary receiver operating characteristic; USG, ultrasonography; VCTE, vibration-controlled transient elastography

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However, USG may miss advanced fibrosis or an early-stage LC,[11] and thus, efforts are required to accurately and noninvasively diagnose advanced fibrosis or early-stage LC in CHB patients for the risk assessment of HCC development.

Liver stiffness measurements (LSMs), as determined by vibration-controlled transient elastography (VCTE), are a widely validated noninvasive method that accurately diagnoses advanced fibrosis or cirrhosis in patients with chronic liver disease (CLD).[12,13] In a previous meta-analysis, the degrees of VCTE-determined LSMs were reported to be associated with the risk of HCC development in patients with CLD,[14] but, the meta-analysis was limited by heterogeneous causes of CLD. In addition, of the studies analyzed, only a few focused on CHB patients.[14] Considering the heterogeneity of the previous meta-analysis, to evaluate the ability of VCTE to predict the risk of HCC development in CHB patients, it is necessary to exclude patients with other liver diseases and draw new conclusions in CHB patients. On the other hand, recent observational retrospective studies have shown that TE-determined LSMs are useful for predicting the risk of HCC development in CHB patients.[15,16] In addition, some prospective cohort studies also had similar results in CHB patients.[17,18] However, due to the retrospective natures[15,16] or cohort heterogeneities of the previous studies,[15-18] conclusions reached regarding the diagnostic ability of VCTE-determined LSMs to predict the risk of HCC development in CHB patients have been inconsistent. Moreover, the extent to which VCTE-determined LSMs reduce the risk of HCC development in CHB patients has not been fully established.

Therefore, we conducted a systematic review and a meta-analysis to determine whether LSM using VCTE can predict the risk of HCC development in CHB patients. For this purpose, we assessed the risk of HCC development using VCTE-determined LSMs and evaluated the diagnostic ability of VCTE-determined LSMs to predict HCC development in these patients.

MATERIALS AND METHODS

This systematic review was conducted according to the guidance provided by the Cochrane Handbook[19] and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] We have registered the protocol for this review on the PROSPERO website (CRD42024528604).

Study selection

To identify all relevant articles on the role of VCTE in predicting HCC development in CHB patients, a systematic literature search of the Ovid-Medline, EMBASE, Cochrane, and KoreaMed databases (from January 2010 to June 2023) was conducted with the help of an expert librarian. Medical subject terms used in the literature search included a combination of “liver”, “hepatitis B” and “stiff*”, “elastogra*,” “Fibroscan,” combined with “prognos*”, “predict*”, “cancer”, “HCC”. The search strategy is detailed in Supplementary Table 1. The titles and abstracts of studies identified during the search were independently reviewed by 2 authors (YJ Jin and HY Kim) to exclude studies that did not include the research-related question, based on pre-defined inclusion and exclusion criteria. Discrepancies in analytical study extraction were resolved by consensus. The full texts of the remaining studies were then reviewed in detail to identify whether they contained information directly related to the present study.

Eligibility criteria

Given the predictive goal of this systematic review, we included prospective and historical cohort studies. The study inclusion criteria were as follows: (1) VCTE was performed at the time of cohort entry in CHB patients, (2) systematically assessed the risk of HCC development in patients with no previous history of HCC, (3) had a follow-up period of at least 6 months for enrolled study subjects, and (4) reported on relevance measures (sensitivity, specificity, and hazard ratio [HR] of VCTE) for the prediction of HCC development or provided enough data to enable their calculation. The study exclusion criteria were as follows: (1) a conference, case series, case-control study, cross-sectional study, and review article; (2) studies conducted on subjects other than CHB patients; or (3) the provision of insufficient data on the relevance measures mentioned above; or (4) studies in which HCC was not diagnosed based on liver dynamic computed tomography, magnetic resonance imaging, or histologic confirmation were excluded. A flow-

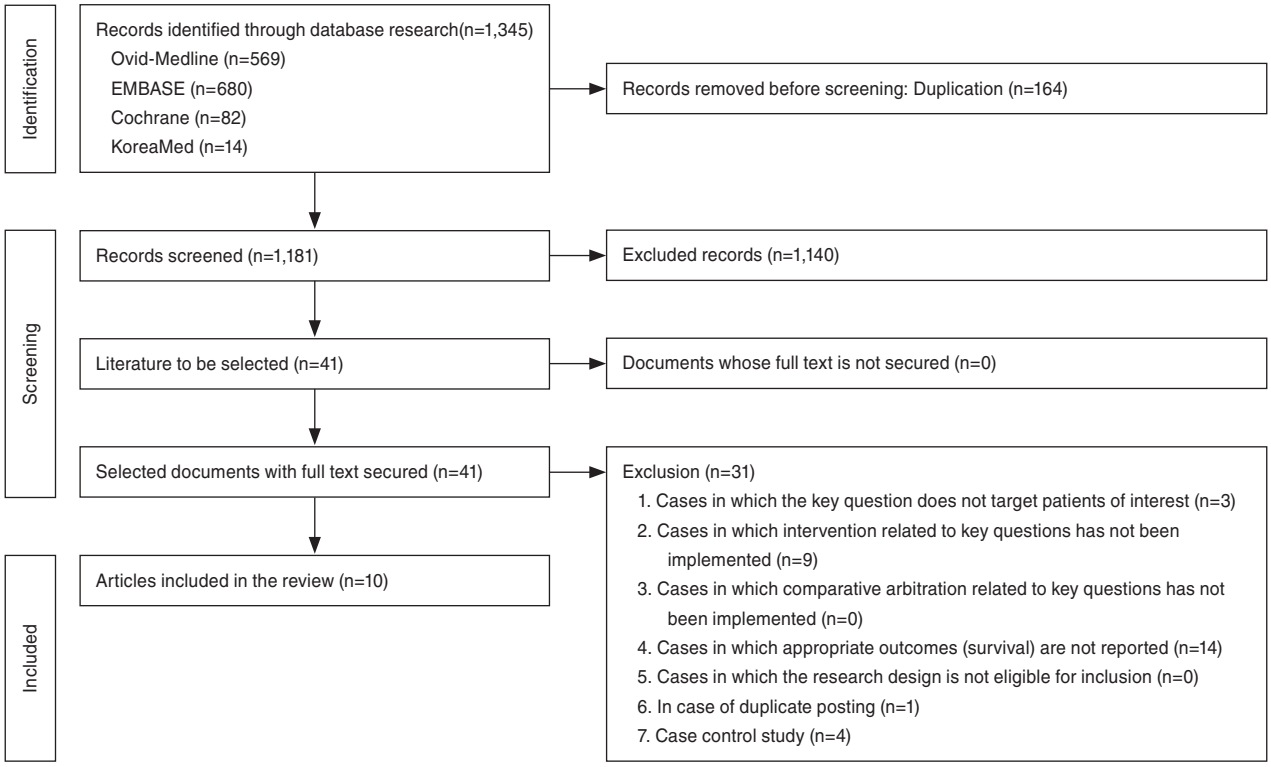

Figure 1. Flowchart showing the identification, screening, and inclusion process. Of the 1,345 individual studies identified, 10 studies were finally registered in the meta-analysis.

sheet of subject enrollment is provided in Figure 1.

Data extraction

The following data were extracted: (1) study characteristics: name of the primary author; research period/year of publication; country where the study was conducted; study design; follow-up period (median); (2) patient characteristics: age, sex, number of enrolled patients; etiology of CLD (viral hepatitis, other causes); TE values indicating liver fibrosis or cirrhosis stage; use of antiviral agents for CHB and information as to whether they were used in all patients or only in some patients who developed HCC or not; (3) exposure evaluation: the LSM technique, reported LSM failures and whether LSM was reported as a continuous or categorical variable; (4) outcomes assessment: HCC development; (5) statistical analysis: HR and 95% confidence interval (CI) with or without adjustment for confounders, or the sensitivity/specificity of LSM for HCC development; and (6) subgroup analysis according to study design method or frequency of antiviral drug use. In case of missing data that were important to the study results, the original authors were contacted directly to obtain additional relevant data where possible.

Quality assessment

Evaluation of the quality of diagnostic accuracy studies was performed by two study investigators (YJ Jin and HY Kim) independently, using the revised quality assessment of diagnostic accuracy studies (QUADAS-2).[21] The risk of bias was assessed in four key domains: patient selection, index test, reference standard, and flow and timing. Concerns about applicability were assessed in three key domains: patient selection, index test, and reference standard. Disagreements between two investigators (YJ Jin and HY Kim) during the quality assessment process were resolved through discussion and by a third opinion (M Choi).

Assessment of outcomes

The primary aim of the present study was to assess the

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prognostic usefulness of LSM for predicting HCC development in CHB patients. HCC was diagnosed based on liver dynamic computed tomography, magnetic resonance imaging, or histologic confirmation. Because heterogeneity among studies might have affected results, we performed subgroup analyses for two study-related variables: antiviral drug use (in all or some patients) and study design (retrospective versus prospective).

LSMs were obtained at the time of data enrolment in each study. LSM was expressed in kilopascals (kPa). LSM was repeated more than ten times with a success rate of ≥60% and the automatically calculated median value was recorded. LSM value was considered reliable if the interquartile range (IQR) value divided by the median (M) among valid results (IQR/M) was <0.3. The specific TE-determined LSM cutoff value that can identify histological cirrhosis has not yet been definitively defined in CHB patients. However, most previous studies have suggested that TE-determined LSM cutoffs of 11 to 13 kPa be used for diagnosing LC (F4 stage based on METAVIR score[22]).[23-27] Therefore, we used an LSM cutoff of 11 kPa to distinguish between the presence and absence of LC. The risk of HCC development and the diagnostic ability of TE-determined LSMs to predict the risk of HCC development were then determined using this cutoff.

Statistical analysis

HRs and 95% CIs were considered summary estimates of treatment effect sizes at an LSM cutoff of ≥11 kPa for HCC development. Meta-analysis was performed using the restricted Maximum Likelihood random effect model.[28] To assess the integration of diagnostic test accuracies obtained from each study, pooled sensitivity, pooled specificity, overall area under the curve (AUC) value, and confidence and prediction contours in summary receiver operating characteristic (SROC) curve space were calculated using the bivariate mixed effect model.[29]

To determine whether a dispersion existed among HRs, sensitivities, or specificities across studies, we used the I^2 statistic and Cochran's Q statistic, which are indexes of heterogeneity. A higher I^2 value indicates that heterogeneity across studies is more likely to exist. To explore potential sources of heterogeneity, subgroup analyses were conducted. The presence of publication bias was assessed by an Egger's asymmetry test[30] and adjusted by a trim-and-fill method.[31] Statistical significance was assessed at the 5% significance level. Statistical analysis was performed using STATA software version 18 (meta, midas, and metabias function; Stata Corporation, College Station, TX, USA).

RESULTS

Data acquisition

Of the 1,345 individual studies initially identified using the search strategy, 10 studies that met the study inclusion criteria were used in this meta-analysis (Fig. 1 and Table 1).[15-18,32-37] Three of these studies did not contain data on the risk of HCC development,[32-34] and thus, we contacted the authors directly and obtained data and could use them in the analysis. However, we could not obtain this data for one study, and therefore, this study was excluded from the analysis of the risk of HCC development.[18] In addition, in three of the ten studies on the meta-analysis of the diagnostic ability of HCC,[33,34,36] relevant data were obtained by directly contacting the authors. Thereafter, 10 studies, including these 3 studies,[33,34,36] were analyzed on the diagnostic ability of HCC.[15-18,32-37]

Characteristics of included studies

Table 1 shows the baseline characteristics of the enrolled ten studies, which included 18,150 CHB patients. All studies were published from 2010 to 2022 and used VCTE to obtain LSMs. All studies were conducted on the Asian population. Except for one study conducted in Hong Kong,[17] all nine studies were conducted in South Korea.[15,16,18,32-37] Regarding research methods, seven studies were retrospective cohort studies[15,16,32,34-37] and the remaining three were prospective cohort studies.[17,18,33] In four studies, all participants received antiviral therapy (AVT) for CHB,[15,16,35,36] and in the other six studies,[15,17,32-34,37] AVT was used in some patients. AVT consisted of oral antiviral drugs. Regarding LSM cutoffs, six studies used a cutoff of 13 kPa,[15,32-35,37] three[16-18] a cutoff of 12 kPa, and one[36] a cutoff of 11 kPa. Median follow-up periods ranged from 31 to 120 months.

Table 1. Baseline characteristics of the included studies

Studies	Year	Location	Design	Patients, n	Age, year (mean)	Male, n (%)	HBe Ag (-), n (%)	AVT, n (%)	TE cutoff, kPa	FU period, mo (median)	HCC, n	HR	95% CI
Kim et al.[32]	2015	S. Korea	Retro	2,876	46.1	1,775 (61.7)	1,868 (65)	1,559 (54.2)	≥13	48.9	52	3.305	1.083–10.086
Yoo et al.[15]	2021	S. Korea	Retro	9,300	47.5	5,474 (58.9)	6,525 (70.2)	5,066 (54.5)	≥13	60	48	2.064	1.534–2.77
Jung et al.[33]	2011	S. Korea	Pros	1,130	50.2	137 (69.5)	722 (63.9)	443 (39.2)	>13	30.7	57	3.07 (95% CI, 1.01–9.31; *P*=0.047) for LSM 8.1–13 kPa; 4.68 (95% CI, 1.40–15.64; P=0.012) for LSM 13.1–18 kPa; 5.55 (95% CI, 1.53–20.04; *P*=0.009) for LSM 18.1–23 kPa; and 6.60 (95% CI, 1.83–23.84; *P*=0.004) for LSM >23 kPa	
Wong et al.[17]	2014	Hong Kong	Pros	1035	46	661 (64)	779 (75)	390 (38)	>12	69	38	6.000	2.5–14.6
Kim et al.[34]	2014	S. Korea	Retro	170	45.3	103 (60.6)	125 (73.5)	82 (48.2)	>13	41	31	2.366	1.159–4.830
Kim et al.[35]	2016	S. Korea	Retro	1,079	49	696 (64.5)	509 (47.2)	1,079 (100)	>13	7 years	91	3.265	2.151–4.954
Lee et al.[36]	2020	S. Korea	Retro	1,511	49.7	989 (65.5)	716 (47.4)	1,511 (100)	≥11	10 years	143	6.090	3.89–9.55
Jeon et al.[37]	2017	S. Korea	Retro	540	51.5	355 (65.7)	320 (59.3)	185 (34.3)	<13	54.1	81	LSM<13 kPa, 0.462	0.251–0.850
Kim et al.[16]	2023	S. Korea	Retro	347	51	224 (64.6)	196 (56.5)	347 (100)	<12	110.4	49	LSM<12 kPa, aHR, 0.33	0.17–0.64
Kim et al.[18]	2014	S. Korea	Pros	162	51	99 (61.1)	73 (45.1)	162 (100)	>12	24	15 (decompensated LC, n=3)	AUROC=0.736	0.620–0.852; *P*=0.003

S. Korea, South Korea; Retro, retrospective; Pros, prospective; HBeAg, Hepatitis B envelop Antigen; AVT, antiviral therapy; VCTE, vibration-controlled transient elastography; kPa, kilopascal; FU, follow-up; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; LSM, liver stiffness measurement; AUROC, area under receiver operating characteristic; LC, liver cirrhosis.

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Quality of included studies

The risk of bias in most of the included studies was low to moderate for patient selection, index test, reference standard, and flow and timing. However, some studies were at high risk of bias because of possible selection bias at enrollment. Figure 2 shows the results of the overall quality assessment of the included studies using the QUADAS-2. Egger's test of asymmetry did not reveal significant publication bias, so the trim and fill method did not adjust the estimate (Supplementary Tables 2 and 3).

Risk of HCC

Among the ten studies, when analyzing nine studies that presented a risk ratio for HCC development[15-17,32-37] (Table 1), the HR for HCC development was high at 3.33 (95% CI, 2.45–4.54) in CHB patients with a VCTE-determined LSM of ≥11 kPa compared to patients who did not, and I^2 value (61.20%) presented in the Forrest plot was 61.20% (Fig. 3A). The Funnel plot visually shows no publication bias (Fig. 3B). By Egger's asymmetry test, it cannot be said that there is publication bias since the *P*-value of bias in the model is 0.270 (Supplementary Table 2). The corrected HR value (3.33) determined by the trim-and-fill method was the same as that obtained using the random effect model (Supplementary Table 3).

Considering the impact of AVT on HCC development in CHB patients, two meta-analyses were separately conducted on the risk of HCC development in three studies in which AVT was used in all (100%) patients[16,35,36] and in six studies in which AVT was used in some patients[15,17,32-34,37] (Supplementary Fig. 1A). As a result of meta-analyses of these two sets of studies, HRs for the HCC development in CHB patients with a VCTE-determined LSM of ≥11 kPa were 4.02 (95% CI, 2.57–6.29) and 2.95 (95% CI, 2.00–4.37), respectively (Supplementary Fig. 1A). Publication bias does not appear to exist in the Funnel plot (Supplementary Fig. 1B). In addition, considering the possibility of confounders that may arise in retrospective cohort studies, meta-analysis was performed on seven retrospective cohort studies[15,16,32,34-37] and two prospective cohort studies[17,33] with data on the occurrence of HCC, respectively (Supplementary Fig. 2A). As a result of a meta-analysis conducted on retrospective and prospective cohort studies, HRs for HCC development in CHB patients with a VCTE-determined LSM of ≥11 kPa were 2.98 (95% CI, 2.15–4.15) and 5.70 (95% CI, 3.25–10.01), respectively (Supplementary Fig. 2A). Publication bias does not appear to exist in the Funnel plot (Supplementary Fig. 2B).

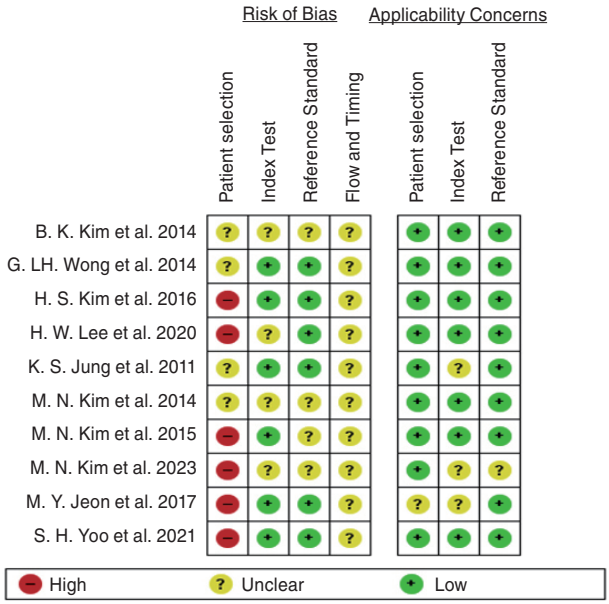

Figure 2. Quality assessment of enrolled studies using the revised QUADAS-2. The risk of bias was assessed in 4 key domains: patient selection, index test, reference standard, and flow and timing. Concerns about applicability were assessed in 3 key domains: patient selection, index test, and reference standard. QUADAS, quality assessment of diagnostic accuracy studies.

Analysis of diagnostic test metrics

All ten studies assessing the association between LSM of ≥11 kPa and HCC development were published as full-text literature. Meta-analysis was performed on the sensitivity and specificity of the ten studies for predicting HCC development (Fig. 4). In CHB patients with a VCTE-determined LSM of ≥11–13 kPa, the sensitivity and specificity for predicting HCC development were 61% (50–71%) and 78% (66–86%), respectively (Fig. 4A). The diagnostic AUC was 0.74 (95% CI, 0.70–0.77) (Fig. 4B).

DISCUSSION

In this meta-analysis, we analyzed the risk of HCC development by comparing CHB patients with LC (≥11 kPa)

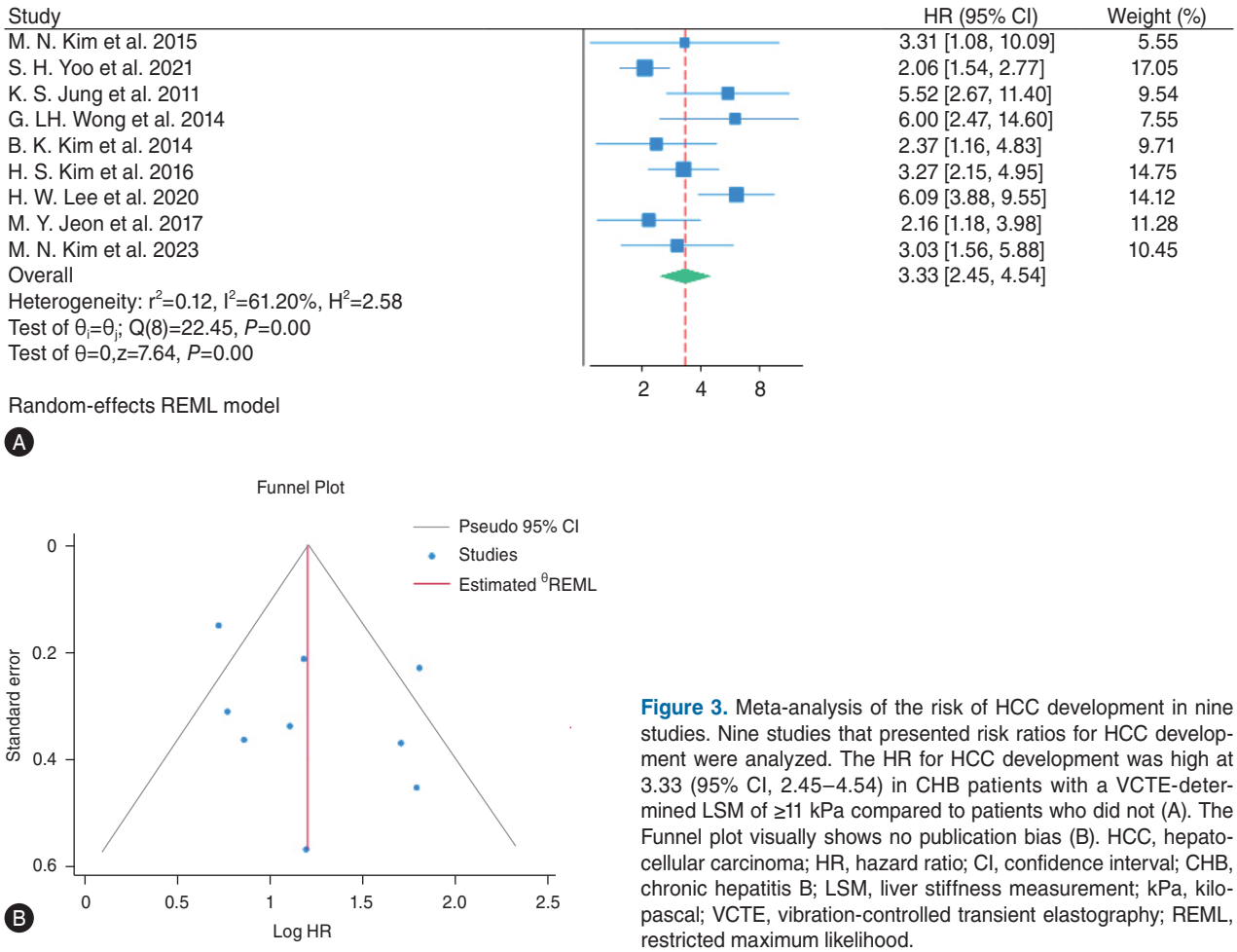

Figure 3. Meta-analysis of the risk of HCC development in nine studies. Nine studies that presented risk ratios for HCC development were analyzed. The HR for HCC development was high at 3.33 (95% CI, 2.45–4.54) in CHB patients with a VCTE-determined LSM of ≥11 kPa compared to patients who did not (A). The Funnel plot visually shows no publication bias (B). HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; CHB, chronic hepatitis B; LSM, liver stiffness measurement; kPa, kilopascal; VCTE, vibration-controlled transient elastography; REML, restricted maximum likelihood.

with those without LC (<11 kPa) using VCTE-determined LSM. In addition, the ability of VCTE to predict the risk of HCC development was analyzed using an LSM cutoff value of 11 kPa. The analysis confirmed that the risk of HCC development was higher in CHB patients with LC (≥11 kPa) based on VCTE-determined LSM. The present study is meaningful as the meta-analysis shows that VCTE-determined LSM helps predict the risk of HCC development in CHB patients. Although a previous meta-analysis reported that VCTE helped predict the risk of HCC development,[14] it was limited by heterogeneous causes of CLD. Given that the risk of HCC development varies depending on the cause of CLD,[3,38] heterogeneous causes of CLD could have confounded the interpretation of the results and there are limitations in fully applying the study results to CHB patients.[14] To avoid this heterogeneity, we focused on CHB patients and found that VCTE would be helpful clinically for the prediction of the risk of HCC development in CHB patients.

CHB is an important risk factor of HCC development,[1-3] and when LC is combined, the risk of HCC development is further increased. Therefore, to allow the implementation of optimal surveillance strategies that can modify the natural course of CHB, early, accurate, and noninvasive identification of CHB patients at high risk of HCC development is essential.[39] Interestingly, the present study showed that the risk of HCC development was greater in CHB patients with VCTE-determined LC. In addition, the specificity and diagnostic AUC of VCTE for predicting HCC development were acceptable, although sensitivity was relatively low. Therefore, in CHB patients with VCTE-determined diagnosis of LC, more careful follow-up is required for the detection of early HCC. However, caution is required when interpreting the VCTE-determined LSMs

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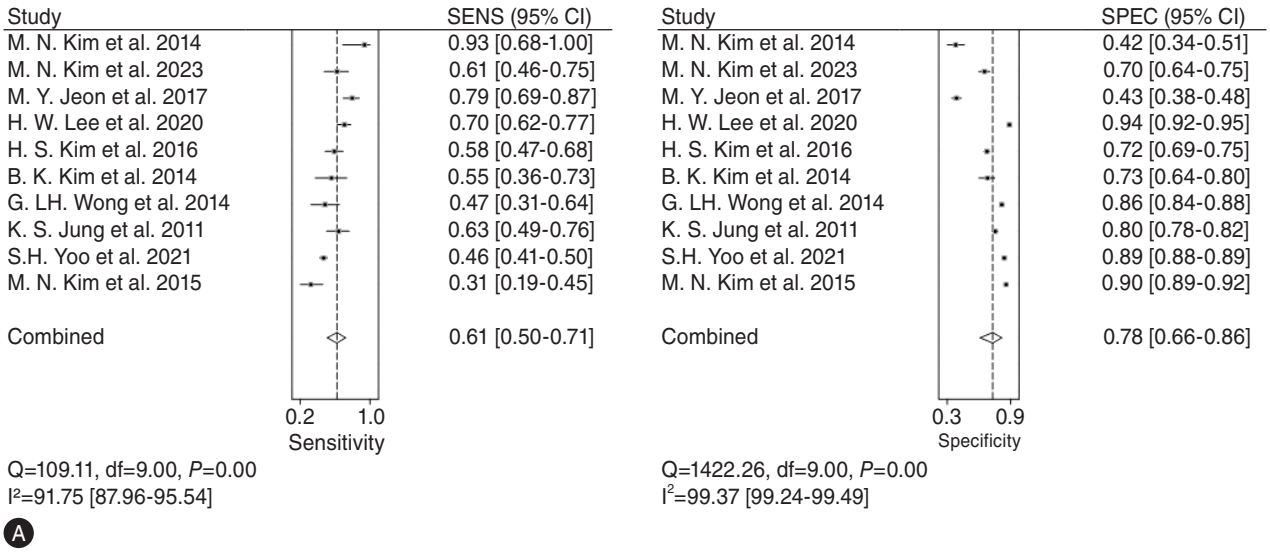

Figure 4. Analysis of diagnostic test metrics for HCC development. All ten studies included were analyzed. In CHB patients with a VCTE-determined LSM of ≥11–13 kPa, the sensitivity and specificity for predicting HCC development were 61% (50–71%) and 78% (66–86%), respectively (A). The diagnostic AUC was 0.74 (95% CI, 0.70-0.77) (B). SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating characteristic; HCC, hepatocellular carcinoma; CHB, chronic hepatitis B; LSM, liver stiffness measurement; VCTE, vibration-controlled transient elastography; AUC, area under the curve.

because they can be affected by intrahepatic inflammation, cholestasis, liver congestion, food intake, or excessive drinking.[40-43]

In the present study, to evaluate the prognostic role of VCTE-determined LSM in CHB patients, we estimated time-to-event analysis using HR for HCC development, which may better reflect the prognostic value than relative risk (RR), unlikely to a previous study.[14] Moreover, the value of HR in the present study was higher than that of RR in a previous study with regard to HCC development.[14] This result may be because, unlike a previous study,[14] the subjects enrolled in the present study were focused on CHB patients. Above all, due to the severe heterogeneity of a previous meta-analysis, the associated I^2 value was not presented in the Forrest plot, and statistical testing for funnel plot asymmetry to assess the publication bias was not also performed.[14] However, in the present study, heterogeneity was not observed based on the associated values of the heterogeneity tests presented in the Forrest plot. Moreover, publication bias was not also found based on the Funnel plot, an Eager's test, and a trim-and-fill method in the present study. Therefore, our results suggest that VCTE-determined LSM can be useful in predicting the risk of HCC development in CHB patients.

Considering the unmeasured potential heterogeneity among studies, we separately analyzed the risk of HCC development in two study sets in which AVT was administered to all patients and to some patients. For both study sets, in CHB patients with an LSM of ≥11 kPa, the HRs for HCC development were higher at 4.02 and 2.95, respectively, than those of patients with an LSM of <11 kPa. Interestingly, our results did not vary depending on the proportion of AVT. On the other hand, the risk of HCC development in the group in which AVT was administered to all patients was lower than that in the group in which AVT was used in some patients. Considering the impact of AVT on suppressing the HCC development,[44,45] this result was likely due to differences in hepatitis B virus (HBV) activities among patients. In other words, AVT for HBV would not have been used in some patients because the HBV activity was not high. In addition, in these patients included, low HBV activity itself probably resulted in a relatively low risk of HCC development. Therefore, the results of this study suggest that since patients who need AVT for HBV have a high risk of HCC development, there is an advantage in quickly selecting patients at high risk of HCC development using VCTE-determined LSMs. Moreover, based on the recently issued guidelines for the treatment of CHB,[46,47] additional meta-analysis is needed to predict the risk of HCC development in CHB patients with significant (≥F2) or advanced (≥F3) liver fibrosis using TE-determined LSMs.

In the present study, a meta-analysis was also conducted on the risk of HCC development according to the study design (retrospective or prospective cohort studies). It was consistently confirmed that the risk of HCC development was higher for an LSM of ≥11 kPa than one of <11 kPa. However, since the research design of the studies registered was not a randomized controlled trial (RCT), additional researches with RCT will be required on this topic in the future.

This study had several limitations. First, because the studies registered were not RCTs, heterogeneity of the enrolled patients among studies was unavoidable. Additional research will be needed on RCT studies in the future, but will not be easily conducted because of the long-term follow-ups required. Fortunately, neither an Egger's asymmetry test nor the trim-and-fill method detected publication bias, and subgroup analyses based on receipt of AVT or study design produced consistent results. However, heterogeneity may have arisen due to other unmeasured confounders that could not be completely ruled out. Second, all studies were conducted on Asian populations, which limits the generalizability of our results because HBV genotypes differ between races, and the associated risks of HCC development also differ. Nonetheless, given that South Korea is an HBV-endemic area, our results are expected to be helpful for the management of CHB patients. Third, the sensitivity of VCTE-determined LSMs for predicting HCC development was low. Therefore, based on our study results, VCTE could not be used to completely replace other methods (e.g., radiologic imaging or liver biopsy) for assessing the risk of HCC development but could be used to supplement other imaging test results. Fourth, some studies were conducted at the same research institution, and their data collection periods partially overlapped. This may have the limitation of data duplication. However, the data collection periods of the included studies were slightly different and inclusion criteria were slightly different for each study. In addition, the outcomes among these studies were somewhat different. Therefore, we cautiously believe that even if a meta-analysis is conducted excluding studies with overlapping research periods, there is a low possibility that there will be significant differences from the results of this meta-analysis. Moreover, despite the drawback of possible overlap in study populations, this study has the advantage of being the first meta-analysis for risk assessment of HBV-related HCC using VCTE. Nonetheless, validation through additional large-scale RCT studies is needed to strengthen the validity and reliability of the research results._Fifth, we could not obtain data on whether different CHB phases are associated with different cutoffs of LSM to predict HCC. Because the relationship between LSM and HCC risk across different phases of CHB may be important, future research is needed on this issue.

In conclusion, this meta-analysis shows that the risk of HCC development was elevated in CHB patients with TE-determined LSM of ≥11 kPa. This finding suggests that TE-determined LSM values may aid the risk prediction of HCC development in CHB patients. Moreover, we believe that VCTE can be used to identify CHB patients at elevated risk of HCC development and to facilitate the development of optimal HCC surveillance strategies in CHB patients. Furthermore, as this meta-analysis was performed on

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Asian patients, we suggest further studies be conducted in the other ethnic groups.

Authors' contribution

YJ Jin, HY Kim, M Choi, and SU Kim were responsible for the concept and design of the study, the data acquisition, analysis and interpretation of the data, and manuscript drafting. YJ Suh, CH Lee, and M Choi helped with the statistical analysis and data interpretation. JH Yu, MN Kim, JW Han, HA Lee, J An, YW Chon, and DW Jun helped with the data interpretation.

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Conflicts of Interest

The authors have no conflict of interest to declare.

SUPPLEMENTARY MATERIAL

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

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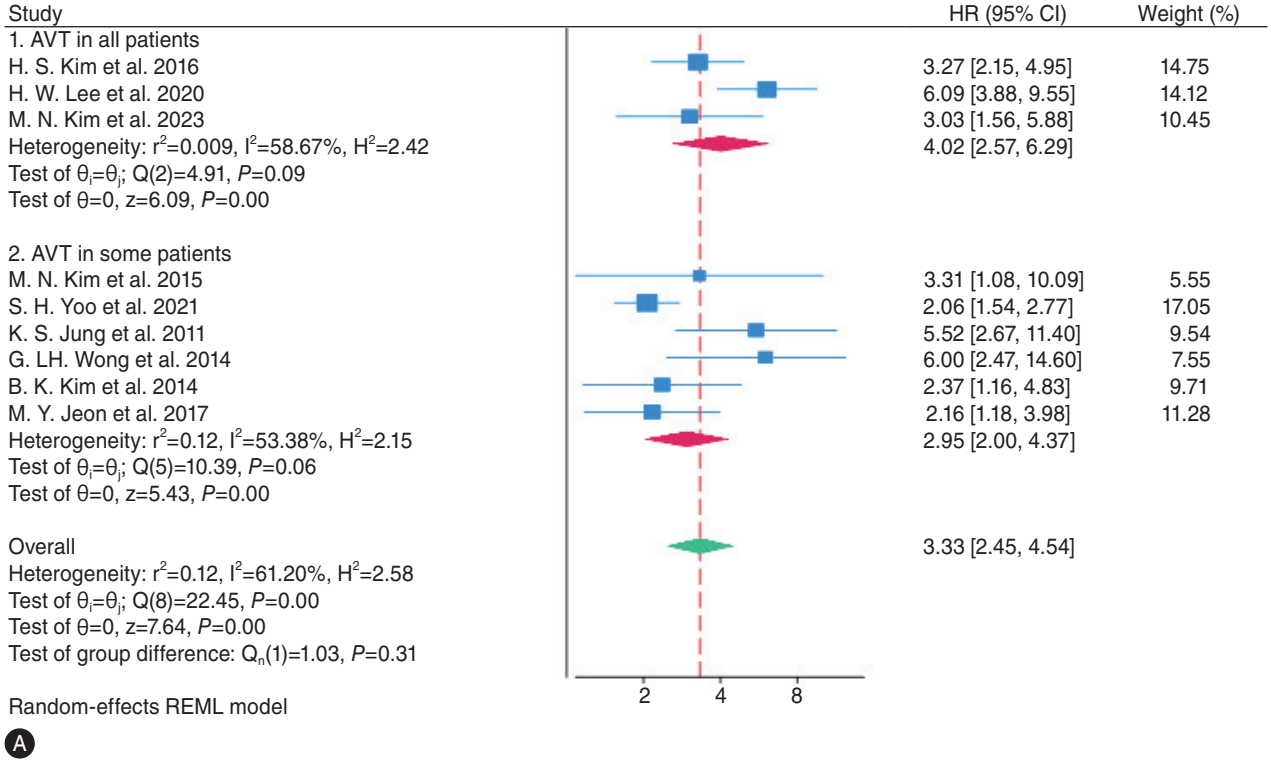

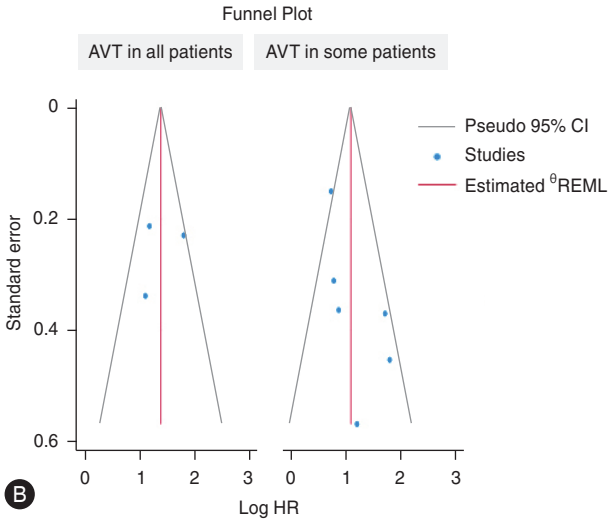

Supplementary Figure 1. Meta-analysis of the risk of HCC development according to the proportion of AVT use. Two meta-analyses were separately conducted on the risk of HCC development in three studies in which AVT was used in all (100%) patients and in six studies in which AVT was used in some patients (A). HRs for the HCC development in CHB patients with a VCTE-determined LSM of ≥11 kPa were 4.02 (95% CI, 2.57–6.29) and 2.95 (95% CI, 2.00–4.37), respectively (A). Publication bias does not appear to exist in the Funnel plot (B). HCC, hepatocellular carcinoma; AVT, antiviral therapy; CHB, chronic hepatitis B; LSM, liver stiffness measurement; HR, hazard ratio; CI, confidence interval; kPa, kilopascal; VCTE, vibration-controlled transient elastography; REML, restricted maximum likelihood.

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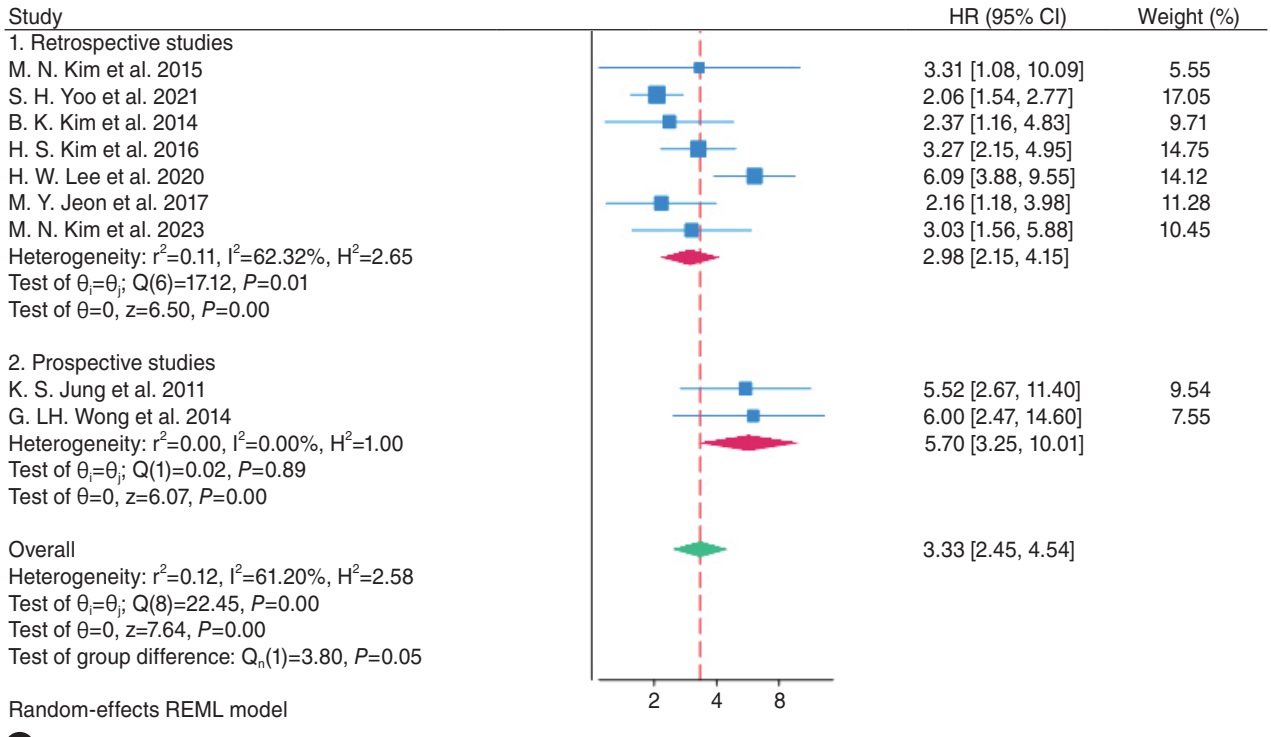

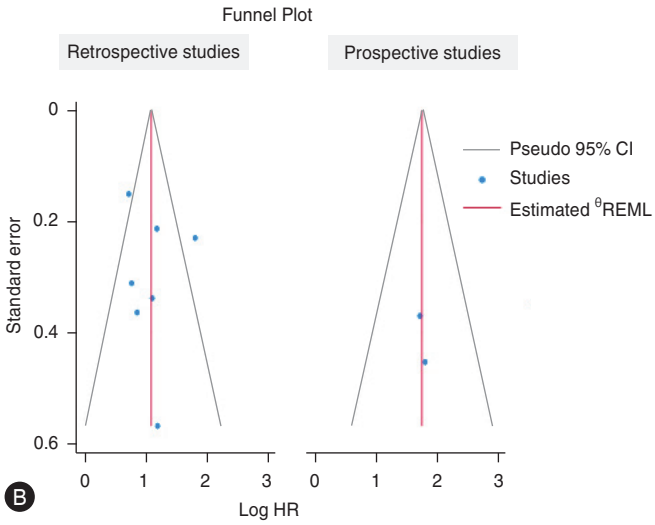

Supplementary Figure 2. Meta-analysis of the risk of HCC development according to the study design. A meta-analysis was performed on seven retrospective cohort studies and two prospective cohort studies that had data on the occurrence of HCC, respectively (A). HRs for HCC development in CHB patients with a VCTE-determined LSM of ≥11 kPa were 2.98 (95% CI, 2.15–4.15) and 5.70 (95% CI, 3.25–10.01), respectively (A). Publication bias does not appear to exist in the Funnel plot (B). HCC, hepatocellular carcinoma; CHB, chronic hepatitis B; LSM, liver stiffness measurement; HR, hazard ratio; CI, confidence interval; kPa, kilopascal; VCTE, vibration-controlled transient elastography; REML, restricted maximum likelihood.

Supplementary Table 1. Search strategy

Ovid Medline (R) 2010.1.1 to 2023. 06. 30

Search date: 2023. 06. 30

Category	N	Search terms	Results
P- common	1	Hepatitis B virus/ OR Hepatitis B/ OR (chronic hepatitis B or CHB or Hepatitis B virus or Hepatitis B or HBsAg or HBV* or CHV* or viral hepatitis).tw,kw.	125,607
I	2	(Fibroscan or (fibrosis adj2 staging) or elastogra*).tw,kw.	14,545
P&I	3	#1 AND #2	1,232
O-HCC	4	Carcinoma, Hepatocellular/ OR Liver Neoplasms/ OR (Hepatocellular carcinoma or HCC or cirrhosis or liver cancer).tw,kw.	306,165
O	5	"sensitivity and specificity"/ or roc curve/ or (diagnostic accuracy or diagnosis or sensitivity or specificity or probability or predict* or prognosis or cut-off or stiffness or LSM or risk stratification* or progress or prognos*).tw,kw.	5,708,522
P&I &O	6	#3 AND #4 AND #5	569

EMBASE 2010.1.1 to 2023. 06. 30

Search date: 2023. 06.30

Category	N	Search terms	Results
P- common	1	'hepatitis b virus'/exp OR 'hepatitis b'/exp OR ('chronic hepatitis B' or CHB or 'Hepatitis B virus' or 'Hepatitis B' or HBsAg or HBV* or CHV* or 'viral hepatitis'):ab,ti,kw	221,799
I	2	('Fibroscan' or (fibrosis NEAR/2 staging) or elastogra*):ab,ti,kw	26,977
	3	#1 AND #2	3,951
O-HCC	4	'liver cell carcinoma'/exp OR 'liver tumor'/exp OR ('liver cell carcinoma' or HCC or cirrhosis or 'liver tumor'):ab,ti,kw	506,919
O	5	'sensitivity and specificity'/exp or ('diagnostic accuracy' or diagnosis or sensitivity or specificity or probability or predict* or prognosis or cut-off or stiffness or LSM or risk stratification* or progress or prognos*):ab,ti,kw	2,106,471
P&I&O	6	#3 AND #4 AND #5	680

Cochrane library 2010.1.1 to 2023. 06. 30

Search date: 2023. 06. 30

Category	N	Search terms	Results
P- common	1	[mh "Hepatitis B virus"] OR [mh "Hepatitis B"] OR ('chronic hepatitis B' or CHB or 'Hepatitis B virus' or 'Hepatitis B' or HBsAg or HBV* or CHV* or 'viral hepatitis'):ab,ti,kw	15,794
I	2	("Fibroscan" or (fibrosis NEAR/2 staging) or elastogra*):ab,ti,kw	1,464
	3	#1 AND #2	278
O-HCC	4	[mh "Carcinoma, Hepatocellular"] OR [mh "Liver Neoplasms"] OR ("liver cell carcinoma" or HCC or cirrhosis or "liver tumor"):ab,ti,kw	17,285
O	5	[mh "Sensitivity and Specificity"] or ("diagnostic accuracy" or diagnosis or sensitivity or specificity or probability or predict* or prognosis or cut-off or stiffness or LSM or risk stratification* or progress):ab,ti,kw	386,613
P&I&O	6	#3 AND #4 AND #5	82

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Supplementary Table 1. Continued
KoreaMed 2010.1.1 to 2023. 06. 30

Search date: 2023. 06. 30

Search site	N	Search terms	Results
KoreaMed	1	(“Hepatitis B virus”[MH] OR “Hepatitis B”[MH]) OR (“chronic hepatitis B”[ALL] or “CHB”[ALL] or “Hepatitis B virus”[ALL] or “Hepatitis B”[ALL] or “HBsAg”[ALL] or “HBV”[ALL] or “CHV”[ALL] or “viral hepatitis”[ALL])	2,517
	2	(“Fibroscan”[ALL] or “fibrosis staging”[ALL] or “elastograpy”[ALL])	46
	3	(“Carcinoma, Hepatocellular”[MH]) OR (“Liver Neoplasms”[MH]) OR (“liver cell carcinoma”[ALL] or “HCC”[ALL] or “cirrhosis”[ALL] or “liver tumor”[ALL])	5,437
	4	(“Sensitivity and Specificity”[MH]) or (“diagnostic accuracy”[ALL] or “diagnosis”[ALL] or “sensitivity”[ALL] or “specificity”[ALL] or “probability”[ALL] or “predict”[ALL] or “prognosis”[ALL] or “cut-off”[ALL] or “stiffness”[ALL] or “LSM”[ALL] or “risk stratification”[ALL] or “progress”[ALL])	69,274
	5	#1 AND #2 AND #3 AND #4	14

Supplementary Table 2. Assessment of publication bias using an Egger's test for nine studies

Std.Eff	Coefficient	Std. error	t	P>|t|	95% CI
slope	0.692	0.379	1.82	0.111	–0.205 to 1.590
bias	1.710	1.427	1.20	0.270	–1.666 to 5.08

Number of studies=9.
Std. Eff, standardized effect size; Std.error, standard error; CI, confidence interval.

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Supplementary Table 3. Assessment of publication using a trim-and-fill test for nine studies

In all studies	Exponential (ES)	95% CI
Observed	3.334	2.449–4.540
Observed+Imputed	3.334	2.449–4.540

ES, effect size; CI, confidence interval.