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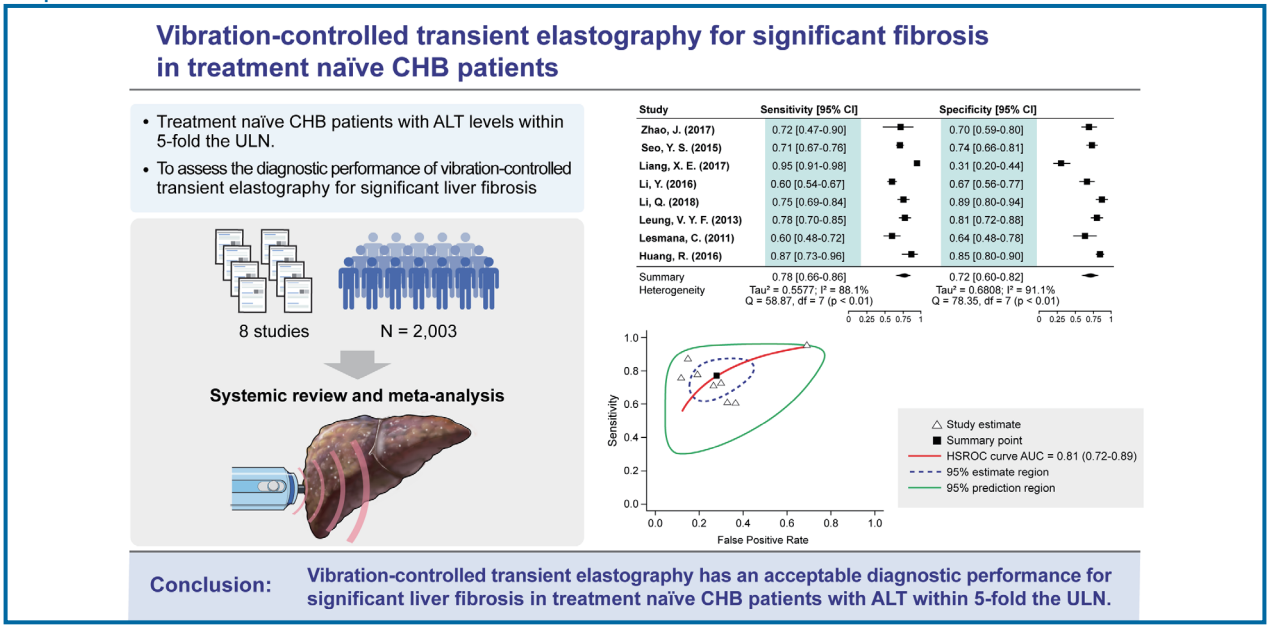
Original Article

Vibration-controlled transient elastography for significant fibrosis in treatment-naïve chronic hepatitis B patients: A systematic review and meta-analysis

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Graphical Abstract



Study Highlights

- Accurate diagnosis of significant liver fibrosis is more important for patients with chronic hepatitis B who do not meet the current criteria for antiviral treatment.
- Our study demonstrated that VCTE performs well to diagnose significant liver fibrosis in antiviral treatment-naïve chronic hepatitis B patients with serum alanine transaminase levels within 5-fold the upper limit of normal.
- VCTE seems to be a useful noninvasive tool for diagnosis of significant liver fibrosis in antiviral treatment-naïve chronic hepatitis B patients.

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Backgrounds/Aims: Accurate diagnosis of significant liver fibrosis in patients with chronic hepatitis B (CHB) is crucial when determining whether to initiate antiviral treatment (AVT). We conduct a meta-analysis to assess the diagnostic performance of vibration-controlled transient elastography (VCTE) for significant liver fibrosis in AVT-naïve CHB patients with serum alanine transaminase (ALT) levels within 5-fold the upper limit of normal (ULN).

Methods: The Ovid-Medline, EMBASE, Cochrane, and KoreaMed databases were searched to identify studies that compared the performance of VCTE and liver biopsy (reference standard) when diagnosing significant liver fibrosis (≥F2) in AVT-naïve CHB patients with ALT within 5-fold the ULN. A hierarchical summary receiver operating characteristic curve (HSROC) and bivariate model were performed to evaluate the diagnostic performance of VCTE in the meta-analysis.

Results: Eight studies (2,003 patients) were included. The summary sensitivity and specificity for diagnosis of significant liver fibrosis were 0.78 (95% confidence interval [CI], 0.66–0.86) and 0.72 (95% CI, 0.60–0.82), respectively. The HSROC for the diagnosis of significant liver fibrosis was 0.81 (95% CI, 0.72–0.86). The optimal cut-off value of VCTE for diagnosis of significant liver fibrosis was 7.7 kPa with a sensitivity of 0.64 (95% CI, 0.50–0.76) and specificity of 0.83 (95% CI, 0.72–0.90).

Conclusions: Our study demonstrated that VCTE has an acceptable diagnostic performance for significant liver fibrosis in AVT-naïve CHB patients with ALT within 5-fold the ULN. **(Clin Mol Hepatol 2024;30(Suppl):S106-S116)**

Keywords: Chronic hepatitis B; Significant liver fibrosis; Vibration-controlled transient elastography; Antiviral treatment-naïve

INTRODUCTION

Liver fibrosis is a main risk factor for progression to liver cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis B (CHB).[1] Thus, accurate diagnosis of the liver fibrosis stage and timely initiation of effective intervention are crucial to improve the prognosis of patients with CHB. A longitudinal study of untreated CHB patients indicated that 7.4% of patients had progression of fibrosis stage during a median of 3.3 years of follow-up.[2] Indeed, regular assessment of liver fibrosis is required for patients with CHB who are not currently receiving antiviral treatment (AVT) to determine whether AVT should be initiated.[3,4]

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Abbreviations:

ALT, alanine aminotransferase; AVT, antiviral treatment; CHB, chronic hepatitis B; CI, confidence interval; HSROC; hierarchical summary receiver operating characteristic curve; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography

Although liver biopsy remains the gold standard for diagnosis of liver fibrosis, its invasiveness, sampling variability, and inter-observer variations limit its clinical application.[5,6] Vibration-controlled transient elastography (VCTE) has been widely recommended as a noninvasive tool to assess liver fibrosis efficiently and precisely in patients with chronic liver disease, and has shown acceptable diagnostic accuracy.[7-9] Cumulative evidence indicates that the diagnostic performance of VCTE was also acceptable in patients with CHB.[10-13]

The diagnosis of significant liver fibrosis is more important for patients with CHB who do not meet the serum alanine aminotransferase (ALT) criterion for initiation of AVT. According to current guidelines, AVT can be initiated when significant inflammation or bridging fibrosis/cirrhosis is diagnosed, even if the ALT level does not meet the criteria.[14-17] While several meta-analyses have previously been conducted in patients with CHB,[11-13] the analyses included studies regardless of whether the patients were receiving antiviral treatment or not. In addition, since the elevated ALT level more than 5-fold the upper limit of normal (ULN) can overestimate the value of VCTE,[18,19] the exclusion of these patients could provide a more accurate assessment of the diagnostic performance of VCTE.

Accordingly, we conducted a meta-analysis to assess the diagnostic performance of VCTE for significant liver fibrosis in AVT-naïve CHB patients with serum ALT levels within 5-fold the ULN.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the methodological recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[20] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement.[21]

Search strategy

A systematic literature search was performed to identify studies assessing the diagnostic performance of VCTE for significant liver fibrosis in patients with CHB. The Ovid-Medline, EMBASE, Cochrane, and KoreaMed electronic databases were searched in June 2023. The search terms used to identify studies were as follows: (1) hepatitis B virus or hepatitis B or chronic hepatitis B or CHB; and (2) fibroscan or transient elastography or TE or vibration controlled transient elastography or VCTE.

Eligibility criteria

Studies were included according to the following criteria: (1) patients with CHB were enrolled in the study; (2) liver biopsy was performed as the reference standard to stage fibrosis; and (3) the data were sufficient to calculate true-positive, false-positive, true-negative, and false- negative results for patients with fibrosis stage of ≥F2.

The exclusion criteria were as follows: (1) the articles did not focus on the diagnostic performance of VCTE; (2) special types of publications, such as patent, book section, case report, reply, letter, commentary, conference abstracts, review, or meta-analysis were excluded; (3) insufficient data to create a 2×2 table of test performance; (4) patients were diagnosed with chronic liver disease triggered by other etiologies such as alcoholic liver disease, non-alcoholic fatty liver disease, and autoimmune liver disease; (5) patients had already received AVT before undergoing biopsy or VCTE; and (6) patients had ALT more than 5-fold the ULN.

Identification of liver fibrosis

Significant liver fibrosis was identified as stage 2 to 4 fibrosis (F2–F4), using the corresponding scoring systems such as Metavir, Batts-Ludwig, and Scheuer.

Cut-off value for normal ALT

The ULN for ALT levels was defined as 40 IU/L in accordance with the values provided in the reimbursement criteria of South Korea,[22] and by the European Association for the Study of the Liver[16] and Asian Pacific Association for the Study of the Liver.[17]

Study selection and data extraction

The selection of individual studies and data extraction were performed independently by two authors (MNK and JWH). Any disagreements regarding study selection or

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data extraction were resolved by a third author (DWJ). The basic and technical characteristics of the included studies and data regarding the diagnostic performance of VCTE were summarized in predesigned forms. Additionally, the necessary data for calculating true positives, false positives, true negatives, and false negatives were extracted. In cases where this information was not explicitly provided in the study, these values were computed based on the reported diagnostic test sensitivity, specificity, and prevalence.

Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was employed to evaluate the quality of the included studies.[23] The authors worked in pairs to independently assess the quality of selected studies, disagreements were addressed by consensus with the participation of a third reviewer (MC). The results of the QUADAS evaluation were visualized using Review Manager 5.3 (The Cochrane Collaboration).

Publication bias

A funnel plot was generated using the 'mada' and 'meta' packages in R version 4.3.1 to evaluate publication bias of the included studies. Egger's test was used to evaluate funnel plot asymmetry.

Data synthesis and statistical analyses

The numbers of true positives, false positives, false negatives, and true negatives were calculated based on the reported population in biopsy-proven fibrosis stage. A hierarchical summary receiver operating characteristic curve (HSROC) and bivariate models were used to evaluate the diagnostic accuracy. Summary estimates of sensitivity and specificity were calculated using a bivariate random effects model. Study-specific estimates of sensitivity, specificity, and corresponding 95% confidence intervals (CI) were generated and graphically illustrated in a forest plot. The heterogeneity of the threshold effect was presented with the Q-I^2 statistic in a forest plot. We assessed statistical heterogeneity for threshold effects using I^2 and the Cochrane Q test. We assessed statistical heterogeneity for threshold effects using I^2 and the Cochrane Q test. These statistics were represented within a forest plot.

We used a linear mixed-effects model to analyze multiple-thresholds data from the individual studies, as recently proposed in the "diagmeta" package in R. The multiple-

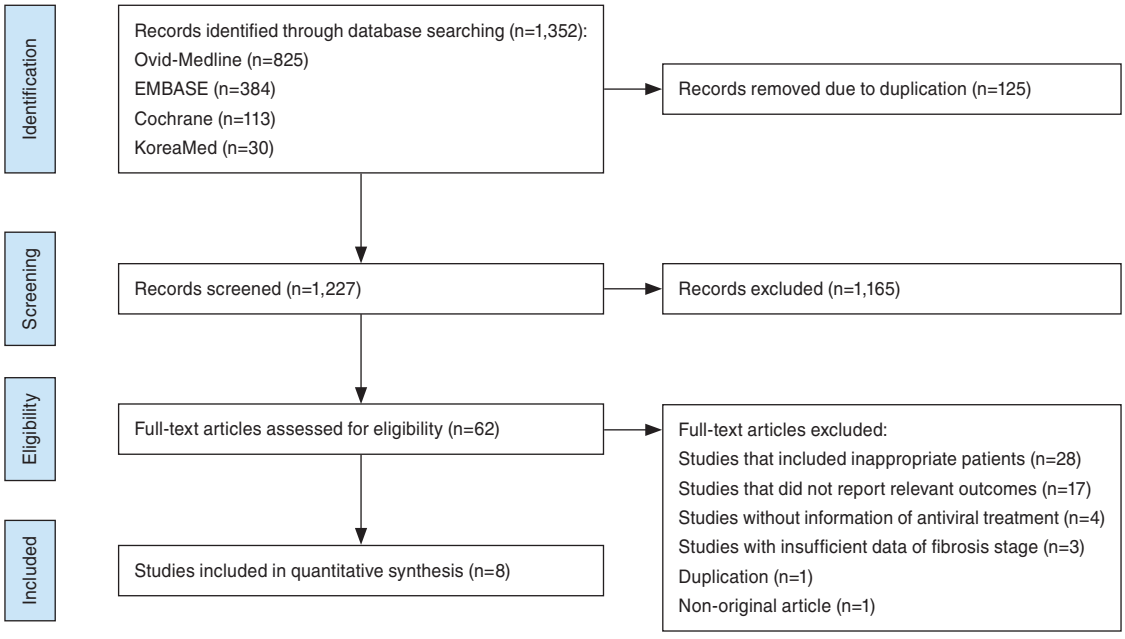


Figure 1. The flow diagram of the studies included in the meta-analysis.

thresholds model is a multilevel random-effects model that enables the calculation of summarized sensitivities and specificities of different cut-off points, and the calculation of the predictive values, given the prevalence of the target condition of interest.[24,25] Funnel plot was generated by 'mada', 'meta' packages in R for the evaluation of publication bias. Egger's test evaluated funnel plot asymmetry. *P*-value <0.05 was considered to indicate the existence of publication bias.

All statistical analyses were performed using R for Window (Version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study selection

A flow diagram of our study selection process is presented in Figure 1. A total of 1,352 records were retrieved utilizing our primary search strategy, of which 125 were excluded due to duplication. In addition, 1,165 other irrelevant articles were excluded based on the titles and abstracts. After excluding the studies that did not fulfill the eligibility criteria, eight studies were finally selected.

Study characteristics

The characteristics of the included studies are described in Table 1.[26-33] These studies were published between 2011 and 2018. All the studies were conducted in Asian countries and had a cross-sectional design.

Diagnostic performance of VCTE for significant liver fibrosis

Eight studies (comprising 2,003 AVT-naïve CHB patients) evaluated the diagnostic performance of VCTE for significant liver fibrosis. The sensitivity was 0.60–0.95, and specificity was 0.31–0.88. The summary sensitivity and specificity were 0.78 (95% CI, 0.66–0.86) and 0.72 (95% CI, 0.60–0.82), respectively (Fig. 2). As shown in Figure 3, the summary HSROC was 0.81 (95% CI, 0.72–0.86).

A subgroup analysis was conducted for CHB patients with serum ALT levels within 2-fold the ULN. The summary

Table 1. Characteristics of the studies included in the meta-analysis

Study	Region	Study period	Design	Subjects (n)	Age (years)[a]	Male (%)	Alanine aminotransferase (IU/mL)[a]	HBV DNA[a]	Fibrosis stage (%)				
									F0	F1	F2	F3	F4
Lesmana et al.[26] (2011)	Indonesia	2008–2010	Cross-sectional	117	40.6	53.8	47.6	6.1 (log_{10} copies/mL)	2.6	35	38.5	20.5	3.4
Leung et al.[27] (2013)	China	2011–2012	Cross-sectional	226	48.8	65	69	5.6 (log IU/mL)	17	23	25	20	15
Seo et al.[28] (2015)	Korea	2006–2014	Cross-sectional	567	45	66.7	48	NA	28.4		26.8	24.3	20.5
Huang et al.[29] (2016)	China	2010–2013	Cross-sectional	263	33.5	60.8	44.1	NA	6.5	78.7	9.5	4.2	1.1
Li et al.[30] (2016)	China	2013–2015	Cross-sectional	307	40.4	73.3	38.8	4.67 (log_{10} copies/mL)	27.7		54.1	10.8	7.5
Liang et al.[31] (2017)	China	NA	Cross-sectional	236	30.8	79.7	71.5	NA	3	24.6	32.6	22	17.8
Zhao et al.[32] (2017)	China	NA	Cross-sectional	99	37.7	64.6	46.7	NA	NA	81.8	18.2	NA	NA
Li et al.[33] (2018)	China	2013–2015	Cross-sectional	188	37	62.8	39	5.4 (log_{10} copies/mL)	5.9	44.1	28.7	6.4	14.9

[a]Variables are expressed as mean or median.
HBV, hepatitis B virus; NA, not applicable.

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Study	TP	FP	FN	TN	Total	≥F2	Cutoff	Sensitivity [95% CI]	Specificity [95% CI]
Zhao, J. (2017)	13	24	5	57	99	18	7.04	0.72 [0.47-0.90]	0.70 [0.59-0.80]
Seo, Y. S. (2015)	289	42	117	119	567	406	7.80	0.71 [0.67-0.76]	0.74 [0.66-0.81]
Liang, X. E. (2017)	163	45	8	20	236	171	5.50	0.95 [0.91-0.98]	0.31 [0.20-0.44]
Li, Y. (2016)	134	28	88	57	307	222	6.20	0.60 [0.54-0.67]	0.67 [0.56-0.77]
Li, Q. (2018)	71	11	23	83	188	94	6.50	0.76 [0.66-0.84]	0.88 [0.80-0.94]
Leung, V. Y. F. (2013)	106	17	30	73	226	136	6.90	0.78 [0.70-0.85]	0.81 [0.72-0.89]
Lesmana, C. (2011)	44	16	29	28	117	73	5.85	0.60 [0.48-0.72]	0.64 [0.48-0.78]
Huang, R. (2016)	34	33	5	191	263	39	8.00	0.87 [0.73-0.96]	0.85 [0.80-0.90]
Summary								0.78 [0.66-0.86]	0.72 [0.60-0.82]
Heterogeneity:								Tau^2=0.5577, I^2=88.1%	Tau^2=0.6083, I^2=91.1%
								Q=58.87, df=7 (*P*<0.01)	Q=78.38, df=7 (*P*<0.01)

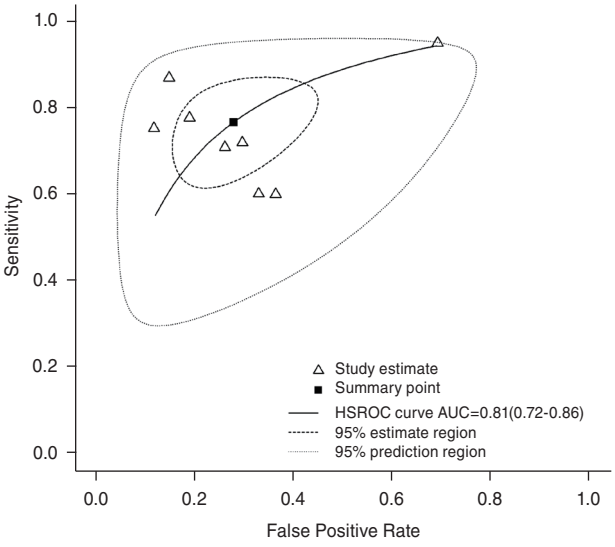


Figure 2. The forest plot of vibration-controlled transient elastography for the diagnosis of significant liver fibrosis. CI, confidence interval.

Figure 3. The hierarchical summary receiver operating characteristic curve of vibration-controlled transient elastography for diagnosis of significant liver fibrosis. HSROC; hierarchical summary receiver operating characteristic curve; AUC, area under the curve.

sensitivity and specificity were 0.74 (95% CI, 0.59–0.85) and 0.82 (95% CI, 0.70–0.89), respectively (Supplementary Fig. 1). As shown in Supplementary Figure 2, the summary HSROC was 0.83 (95% CI, 0.66–0.92).

Optimal cut-off value of VCTE for the diagnosis of significant liver fibrosis

The optimal cutoff value of VCTE for the diagnosis of significant liver fibrosis was identified using the data from six studies that provided a single cut-off value and two studies that each provided two cut-off values. The cut-off values ranged from 5.5 to 8.0 kPa in the previous studies. The optimal cut-off value for VCTE was 7.7 kPa with a sensitivity of 0.64 (95% CI, 0.50–0.76) and specificity of 0.83 (95% CI, 0.72–0.90). With this cut-off value of VCTE, the area under the receiver operating characteristic curve (AUC) was 0.78 (95% CI, 0.67–0.86).

Methodological quality

The results of quality assessment of the included studies using the QUADAS-2 tool are shown in Supplementary Figure 3. All the studies had low risk of bias.

Publication bias

The results of publication bias analysis are shown in the funnel plot (Supplementary Fig. 4). Application of Egger's test revealed that significant publication bias was not found in the included studies (*P*=0.356).

DISCUSSION

In this study, we performed a systematic review and meta-analysis, which included eight studies (comprising 2,003 AVT-naïve CHB patients) to investigate the diagnostic performance of VCTE for significant liver fibrosis in AVT-naïve CHB patients with ALT within 5-fold the ULN. The summary sensitivity, specificity, and HSROC of VCTE for diagnosis of significant liver fibrosis were 0.78, 0.72, and 0.81, respectively. In addition, we identified the optimal cut-off value of VCTE as 7.7 kPa for diagnosis of significant liver fibrosis in these patients.

Several guidelines recommend that AVT can be considered in CHB patients with elevated HBV-DNA levels who do not have ALT levels that are sufficiently elevated to meet

the AVT initiation criteria if the patients have significant inflammation or bridging fibrosis/cirrhosis.[14-17] A recent meta-analysis reported that the pooled proportion of significant fibrosis was 32% in AVT-naïve CHB patients with ALT within the ULN.[34] Another meta-analysis demonstrated that 48% of AVT-naïve CHB patients with ALT levels 1- to 2-fold greater than the ULN had significant liver fibrosis.[35] Given that there is a substantial proportion of significant liver fibrosis among AVT-naïve CHB patients with normal or minimally elevated ALT levels, the diagnosis of significant liver fibrosis in these patients is crucial due to an increasing clinical need to better align the timing of AVT with CHB.

Numerous studies have validated the high diagnostic accuracy of VCTE for significant fibrosis and cirrhosis across various liver disease including viral hepatitis, compared to the gold standard of liver biopsy.[7-9] VCTE has advantages of its non-invasiveness, the ease of use, and ability to provide immediate results, which make it particularly useful in routine clinical practice and for monitoring disease progression or response to therapy.[36]

While VCTE was initially studied in patients with chronic hepatitis C,[37,38] it has also been proven to be useful in patients with CHB, with evidence largely drawn from studies conducted in Asian countries where CHB is prevalent. Several meta-analyses reported that the summary AUC of VCTE for the diagnosis of significant fibrosis in patients with CHB ranged from 0.81 to 0.86.[11,13,39] However, the previous meta-analyses included individual studies of patients at various stages of CHB, including those receiving AVT, which did not allow for an accurate assessment of the performance of VCTE specifically in AVT-naïve patients.

In addition, liver stiffness (LS) improvement during AVT does not necessarily correlate with cirrhosis improvement in histology or imaging modality for several reasons. First, LS reflects the physical properties of the liver and can improve relatively quickly during antiviral therapy, whereas histological changes in fibrosis take longer to manifest. Second, decline in LS during antiviral therapy is a combination of resolution of hepatic inflammation, and regression of fibrosis. Finally, in cases of severe fibrosis or cirrhosis, irreversible changes may have occurred, where LS shows some improvement but histological fibrosis and cirrhosis remain.[40,41]

A recent meta-analysis reported the acceptable diagnostic performance of VCTE for significant fibrosis particularly in AVT-naïve CHB patients.[10] The analysis of 23 studies (comprising 3,879 AVT-naïve CHB patients) demonstrated that the pooled sensitivity and specificity of VCTE were 0.76 and 0.79, respectively. The summary AUC of VCTE was 0.84. However, the study included patients with ALT more than 5-fold the ULN. Elevated ALT levels have been reported to overestimate the value of VCTE.[18,19,42,43] Kim et al.[44] found that value of VCTE tended to increase with ALT levels. In addition, higher ALT levels were found to contribute to the discordance of diagnostic results between VCTE and liver biopsy.[45] Thus, several previous studies excluded patients with ALT levels more than 5-fold the ULN to investigate the diagnostic performance of VCTE in CHB.[46,47] In consideration of these points, the recent European Association for the Study of the Liver guideline suggested an algorithm for the use of VCTE in patients with ALT within 5-fold the ULN.[48]

Thus, our study focused on the diagnostic performance of VCTE for significant liver fibrosis in AVT-naïve CHB patients with ALT within 5-fold the ULN. Our results indicated that VCTE showed acceptable performance for the diagnosis of significant liver fibrosis, with a summary sensitivity of 0.78 and summary specificity of 0.72; these values were similar to those reported in similar pervious meta-analyses (ranges of sensitivity 0.73–0.81 and specificity 0.66–0.82).[10-13] The HSROC of VCTE for diagnosis of significant liver fibrosis was 0.81 (95% CI, 0.72–0.86). The HSROC is beneficial in the meta-analysis of diagnostic tests by joint analysis of sensitivity and specificity while accounting for the potential imperfections in the sensitivity and specificity of the reference test. This comprehensive approach incorporates both within-study and between-study variability, allowing for robust and reliable results that simpler models might not provide.[49]

However, a HSROC value of 0.81, along with sensitivity values of 0.78 and specificity values of 0.72 respectively, indicates a moderate level of accuracy in diagnosing significant liver fibrosis. While this reflects reasonably good diagnostic performance similar to previous meta-analyses, the relative lower accuracy noted by the reviewer could be due to several factors. First, previous studies reported that VCTE performed better for diagnosis of advanced liver fibrosis (F3 and F4) compared to significant fibrosis,[12,13] due to more pronounced changes in LS associated with severe fibrosis and cirrhosis.[50] Second, different studies might use

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various thresholds to define significant liver fibrosis, affecting the pooled diagnostic accuracy. Third, the relatively small sized cohorts and subsequent small number of F2 stage patients in the included studies could impact the overall accuracy.

We also identified the optimal cut-off value of VCTE for diagnosis of significant liver fibrosis, which was reported to be 7.7 kPa. Based on the descriptive statistics of included studies, the cut-off values for diagnosis of significant liver fibrosis ranged from 5.5 to 8.0 kPa. In two previous meta-analyses, the reported cut-off value of VCTE were 7.2 and 7.25 kPa for diagnosis of significant liver fibrosis,[11,12] which were similar to that found in our study. The high specificity of the VCTE cut-off value identified in our study is advantageous to reduce the likelihood of false-positive results, which in turn minimizes the risk of unnecessary AVT. However, the relative low sensitivity of the cut-off values raises concerns about the potential to miss significant liver fibrosis in some patients. It is imperative in clinical practice to adopt a comprehensive approach to patient evaluation for significant liver fibrosis, taking into account the limitations of VCTE sensitivity at this cut-off value.

The main strengths of our meta-analysis are comprehensive search strategy and strict inclusion criteria. However, there are several limitations to be discussed. First, most of the included studies selected cut-off values based on the AUC instead of employing pre-specified values, which may increase the diagnostic accuracy of VCTE for diagnosis of significant liver fibrosis in patients with CHB. Second, sufficient sensitivity analyses and evaluation of biases beyond publication bias were not conducted due to the small number of included studies. This limitation can affect the generalizability and reliability of the findings. Future research should include a larger number of studies to enable more comprehensive sensitivity analyses and thorough assessment of various biases. Third, all the included studies were conducted on Asian population, particularly in China, limiting the generalizability of this study. Fourth, the included studies were retrospective in nature, which may have introduced bias and limits determinations of causal inference. Finally, a meta-analysis of CHB patients restricted to those with ALT 1- to 2-fold greater than the ULN might be more helpful for deciding AVT initiation in accordance with current treatment guidelines. However, there were no studies specifically investigating this patient group. Instead, we conducted a subgroup analysis including three studies with CHB patients with serum ALT levels within 2-fold the ULN. The results were similar to the main findings. However, due to the small number of included studies in this subgroup analysis, caution is needed in interpreting these results as there is a potential for bias.

In conclusion, our study demonstrated that VCTE has an acceptable diagnostic performance for significant liver fibrosis in AVT-naïve CHB patients with ALT within 5-fold the ULN.

Authors' contributions

Conception: Mi Na Kim, Dae Won Jun; Study design: Mi Na Kim, Dae Won Jun, Ji Won Han, Miyoung Choi; Data analysis and interpretation: Mi Na Kim, Jihyun An, Ji Won Han, Eun Hwa Kim, Dae Won Jun, Miyoung Choi; Review of the results: Mi Na Kim, Jihyun An, Eun Hwa Kim, Hee Yeon Kim, Han Ah Lee, Jung Hwan Yu, Young-Joo Jin, Young Eun Chon, Seung Up Kim, Dae Won Jun, Ji Won Han, Miyoung Choi; Drafting of the manuscript: Mi Na Kim; Overall study oversight and guarantor of the manuscript: Dae Won Jun, Ji Won Han, Miyoung Choi. All authors reviewed the paper and approved the final version.

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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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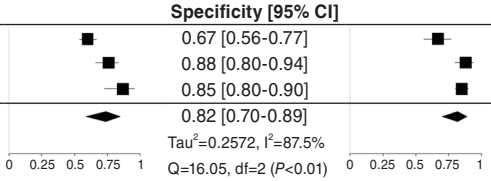
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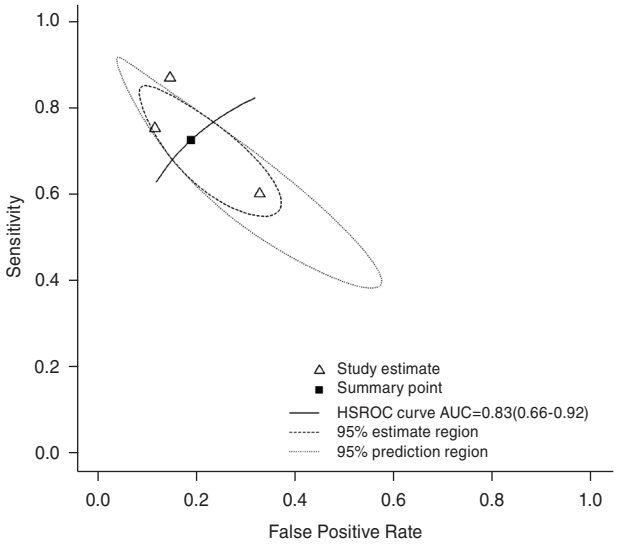
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Study	TP	FP	FN	TN	Total	≥F2	Cutoff	Sensitivity [95% CI]	Specificity [95% CI]
Li, Y. (2016)	134	28	88	57	307	222	6.20	0.60 [0.54-0.67]	0.67 [0.56-0.77]
Li, Q. (2018)	71	11	23	83	188	94	6.50	0.76 [0.66-0.84]	0.88 [0.80-0.94]
Huang, R. (2016)	34	33	5	191	263	39	8.00	0.87 [0.73-0.96]	0.85 [0.80-0.90]
Summary								0.74 [0.59-0.85]	0.82 [0.70-0.89]
Heterogeniety:								Tau^2=0.2592, I^2=85.4%	Tau^2=0.2572, I^2=87.5%
								Q=13.71, df=2 (*P*<0.01)	Q=16.05, df=2 (*P*<0.01)

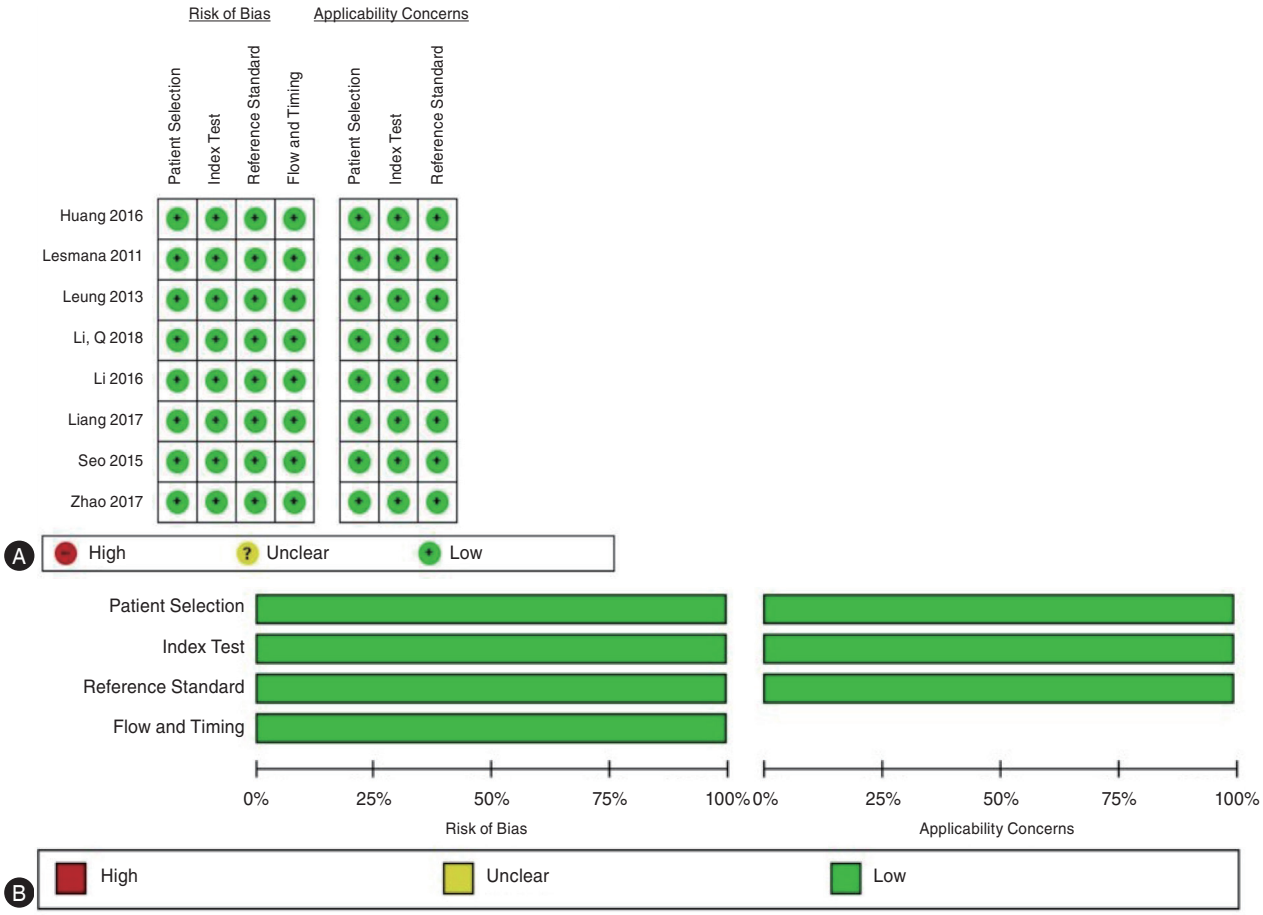


Supplementary Figure 1. The forest plot of vibration-controlled transient elastography for the diagnosis of significant liver fibrosis in a subgroup analysis of patients with serum alanine transferase levels within 2-fold the upper limit of normal. CI, confidence interval.

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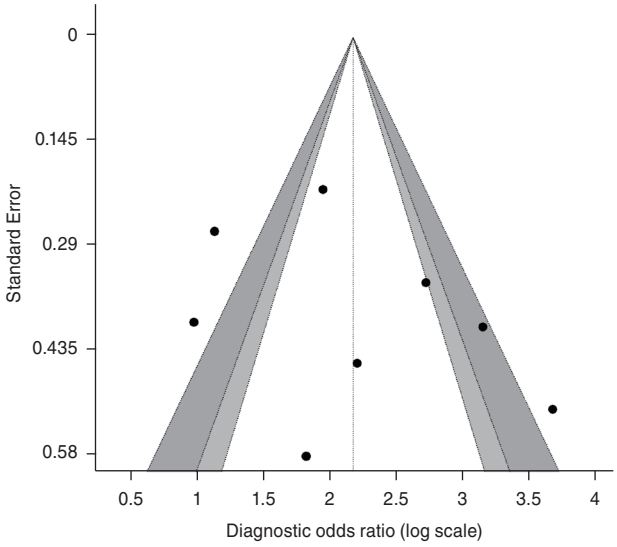


Supplementary Figure 2. The hierarchical summary receiver operating characteristic curve of vibration-controlled transient elastography for diagnosis of significant liver fibrosis in a subgroup analysis of patients with serum alanine transferase levels within 2-fold the upper limit of normal. HSROC; hierarchical summary receiver operating characteristic curve; AUC, area under the curve.



Supplementary Figure 3. The summary of methodological quality of nine studies according to the Quality Assessment of Diagnostic Studies-2 tool. (A) Overall and (B) study-level of bias.

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Supplementary Figure 4. The funnel plot used to assess publication bias.