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Original Article

ORIGINAL ARTICLE

Diagnostic performance of elastography on liver fibrosis in antiviral treatment-naive chronic hepatitis B patients: a meta-analysis

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Abstract

Background: This study aimed to assess the performance of transient elastography (TE), two-dimensional shear wave elastography (2D-SWE), and magnetic resonance elastography (MRE) for staging significant fibrosis and cirrhosis in untreated chronic hepatitis B (CHB) patients.
Methods: Pubmed, Embase, Web of Science, and Cochrane Library were searched for terms involving CHB, TE, 2D-SWE, and MRE. Other etiologies of chronic liver disease, previous treatment in patients, or articles not published in SCI journals were excluded. Hierarchical non-linear models were used to evaluate the diagnostic accuracy of TE, 2D-SWE, and MRE. Heterogeneity was explored via analysis of threshold effect and meta-regression.
Results: Twenty-eight articles with a total of 4,540 untreated CHB patients were included. The summary areas under the receiver-operating characteristic curves (AUROCs) using TE, 2D-SWE, and MRE for predicting significant fibrosis (SF) were 0.84, 0.89, and 0.99, respectively. The AUROC values of TE, 2D-SWE, and MRE for staging cirrhosis were 0.9, 0.94, and 0.99, respectively. Based on the meta-analysis of studies with head-to-head comparison, 2D-SWE is superior to TE (0.92 vs 0.85, $P < 0.01$) in staging significant fibrosis.
Conclusion: TE, 2D-SWE, and MRE express acceptable diagnostic accuracies in staging significant fibrosis and cirrhosis in untreated CHB patients. 2D-SWE outperforms TE in detecting significant fibrosis in treatment-naive people with hepatitis B virus.

Key words: chronic hepatitis B; elasticity imaging techniques; liver fibrosis

Introduction

Despite the availability of effective drug interventions that reduce or prevent complications in most cases, chronic hepatitis B (CHB) remains a major public health issue worldwide that poses a significant health burden [1]. As the causative agent of CHB, human hepatitis B virus (HBV) is a hepatotropic DNA virus

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that can trigger acute and chronic hepatitis, contributing to HBV-related cirrhosis and even hepatocellular carcinoma [2]. Due to the lack of early signs in patients with HBV-related compensated cirrhosis, liver biopsy in the asymptomatic population is inadequate, and early diagnosis of HBV-related cirrhosis is not easy [3]. In the majority of cases, at the time of inpatient visits, the disease tends to progress to a decompensated period. Patients tend to suffer from various serious or even fatal complications, namely esophageal-gastric varices bleeding, refractory ascites, and hepatocellular carcinoma [4]. Several avenues point out that the progression of liver fibrosis can be halted or even reversed by early diagnosis, dynamic assessment, and effective intervention that blocks persistent damage to the liver [5]. Hence, early detection of fibrosis and effective intervention of the related etiology are extremely fundamental to improve the prognosis of patients with chronic liver disease (CLD) [6].

Liver biopsy is the gold standard for assessing hepatitis and fibrosis. However, invasiveness, sampling error, and interobserver variations limit its clinical application [7]. More researchers have focused on non-invasive methods to accurately assess liver fibrosis. Imaging techniques such as transient elastography (TE), 2D shear wave elastography (2D-SWE), and magnetic resonance elastography (MRE) have been proven to assess fibrosis efficiently and precisely in CHB patients. TE, also known as FibroScan, has been recommended by the World Health Organization for assessing fibrosis and has become widely present in clinical practice [8]. 2D-SWE is a well-validated device ultrasonographic elastography technique with various strengths such as offering a more precise region of interest (ROI) and monitoring blood-flow alterations for high-quality measurements. Growing evidence has revealed that 2D-SWE is a favorable choice for staging fibrosis in CHB patients [9]. MRE is another elastography technique that utilizes a modified phase-contrast imaging sequence to estimate fibrosis via shear waves within the whole liver. Thus far, MRE has been considered the most accurate non-invasive method to assess liver fibrosis in CLD with great reliability and reproducibility [10].

These three imaging techniques have been proven to exhibit promising results for the quantification of liver fibrosis with considerable accuracy. Dong *et al.* [11] concluded that MRE and 2D-SWE are excellent tools for staging fibrosis in patients with CHB. Nevertheless, they also included studies regardless of whether the patients were receiving antiviral treatment or not. Indeed, there is an urgent need to stage fibrosis for treatment-naive people with HBV. Given that CHB is a dynamic disease, persons who are not receiving treatment need be assessed regularly to determine whether to initiate antiviral treatment. If the biopsy specimen shows significant fibrosis in patients with elevated HBV-DNA levels, antiviral treatment is recommended based on the American Association for the Study of Liver Diseases (AASLD) 2018 Hepatitis B Guidance [12].

The AASLD suggests that adults with compensated cirrhosis and low-level viremia (<2000 IU/mL) be treated with antiviral treatment to reduce the risk of decompensation, regardless of the alanine transaminase (ALT) level [12]. To better tune the timing of antiviral treatment, we conduct a meta-analysis to investigate the diagnostic performance of TE, 2D-SWE, and MRE for staging significant fibrosis and cirrhosis in treatment-naive people with HBV.

Materials and methods

This study was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [13]. The protocol was registered with PROSPERO (CRD42021248023).

Articles search strategy

The specific search strategy is listed in Supplementary Table 1. Four authorized online databases, namely Pubmed, Embase, the Web of Science, and the Cochrane Library (-01/02/2021) were screened utilizing the following words: hepatitis B, liver fibrosis, FibroScan, transient elastography, shear wave elastography, and MRE.

Eligibility criteria

The following situations were considered as the inclusion criteria: (i) the accuracies of 2D-SWE, TE, and MRE for discriminating liver fibrosis in CHB patients were investigated; (ii) the specific liver fibrosis stage of each patient was biopsy-proven; (iii) the sensitivity, specificity, and number of patients in each fibrosis stage could be extracted to create a 2×2 table of test performance; (iv) at least 50 patients were enrolled in each investigation; and (v) the original articles need to be published in English and could be screened in SCI journals.

The following situations were considered as the exclusion criteria: (i) the original articles did not focus on the diagnostic performance of TE, 2D-SWE, or MRE; (ii) special types of work such as patent, book section, case report, reply, letter, commentary, conference abstracts, review, or meta-analysis were excluded; (iii) studies on children or animals; (iv) insufficient data to create a 2×2 table of test performance; (v) patients were co-infected with other viral hepatitis or HIV; (vi) patients were diagnosed as CLD triggered by other etiologies such as alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and autoimmune liver disease; (vii) patients had already received antiviral treatment, hepatectomy, or liver transplant before biopsy or imaging tests; (viii) patients were identified as having hepatic carcinoma before TE, 2D-SWE, MRE, or liver biopsy; (ix) unclear interval between imaging tests and liver biopsy or unclear liver biopsy size.

Identification of liver fibrosis

Significant fibrosis and cirrhosis were identified as stages F2–F4 and F4, respectively, using the corresponding scoring systems such as Scheuer, Ishak, Metavir, Batts-Ludwig, and Knodell.

Data acquirement

Two experienced researchers (M.L. and S.W.) were first invited to screen the online databases and make preliminary selections. The eligibility and quality of each article were screened by each investigator. Two researchers then extracted the targeted data separately. Basic characteristics, technical characteristics of the included studies, as well as the diagnostic performance of these three non-invasive approaches were summarized in our predesigned forms.

Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was employed to conduct the evaluation of the quality of the included studies. The results of the QUADAS evaluation were visualized through Review Manager 5.3 (The Cochrane Collaboration). A third investigator (X.W.) was then invited to assess the discrepancies between the two

researchers. The variation between the investigators was resolved through a discussion.

Data synthesis and statistical analysis

The demographic characteristic of the included patients were presented as mean with standard deviation or median with interquartile range. The number of true positives, false positives, false negatives, and true negatives was calculated based on the reported population in each biopsy-proven fibrosis stage. Then the summary positive and negative likelihood ratios and area under the receiver-operating characteristic curve (AUROC) were calculated according to the corresponding formulas. For meta-analysis, the pooled sensitivity and specificity were presented with midas and metannif modules in Stata 16.0 (StataCorp LP) [14]. The summary diagnostic odds ratios were calculated utilizing a Der-Simonian and Laird random effects model with a corresponding test of heterogeneity. Hierarchical non-linear models including the hierarchical summary receiver operating characteristic (HSROC) model and the bivariate model were used in our study to evaluate the diagnostic accuracy. The non-threshold heterogeneity was presented with the Q-I^2 statistic in the forest plots. An I^2 value of >50% was regarded as a threshold for determining substantial statistical heterogeneity [15]. The pairwise comparisons of the AUROC values were conducted through the DeLong test [16]. A P-value < 0.05 was considered to indicate statistically significant differences.

Publication bias

Deeks' funnel plots were generated by Stata 16.0 with the "midas" command and a "mylabels" package for the evaluation of publication bias of the included studies. $P < 0.05$ was considered to indicate the existence of publication bias.

Exploration of heterogeneity

As different cut-off values were adopted in individual studies, the threshold effect was evaluated via spearman correlation analysis of the sensitivity and the specificity using MetaDisc 1.4. Meta-regression analyses were used to evaluate the influence of seven characteristics of individual studies on the AUROC, namely the location of the study population (Asia vs Europe), study design (prospective vs retrospective cohort study), mean biopsy length (<20 vs ≥20 mm), mean ALT (<5 vs ≥5 upper limit of normal), liver biopsies scoring system (Metavir vs non-Metavir), the interval between biopsy and imaging test (<3 vs ≥3 months), and study quality (all question score yes vs one or more questions scored no or unclear).

Results

Characteristics and the quality of the retrieved studies

The flow diagram of the study selection is presented in Figure 1. A total of 4,190 records were retrieved utilizing our primary search strategies, among which 3,609 articles were identified after duplications were removed. After excluding the studies that did not fulfill the eligibility criteria, 28 studies were ultimately included, which are listed in the Supplementary materials. The overall prevalence of significant fibrosis and cirrhosis was 64.1% and 20.3%, respectively. Tables 1 and 2 offer the basic and technical characteristics of the included studies, respectively. Finally, 4,540 subjects (mean age, 42.3 years; 67.2% male) were included. Because of the high hepatitis B prevalence in China, the majority of the included studies were from Asia (90%). In addition to 7 (25%) retrospective studies, 21 (75%) studies were based on a prospective design. Regarding the QUADAS-2 score, 5 (17.9%) studies scored 14 points, and 16 (57.1%), 6 (21.4%), and 1 (3.5%) study scored 13, 12, 11, and 10 points, respectively (Supplementary Table 2 and Supplementary Figure 1).

Diagnosing significant fibrosis

Twenty-three studies (3,879 untreated patients) focused on the diagnostic performance of TE, 2D-SWE, and MRE for staging significant fibrosis. Specifically, 16 (3,244 patients), 6 (827 patients), and 5 (408 patients) studies investigated TE, 2D-SWE, and MRE. Figure 2 and Table 3 demonstrate the diagnostic performance of these three methods for staging significant fibrosis. The pooled sensitivity and specificity of TE were 0.76 [95% confidence interval (CI), 0.72–0.79] and 0.79 (95% CI, 0.75–0.83), respectively. As shown in Figure 3, the summary AUROC of TE was 0.84 (95% CI, 0.81–0.87). Regarding 2D-SWE, the pooled sensitivity and specificity were 0.84 (95% CI, 0.80–0.88) and 0.84 (95% CI, 0.76–0.89). The AUROC was 0.89 (95% CI, 0.86–0.92). The overall diagnostic performance of MRE is 95% sensitivity, 96% specificity, and 99% accuracy, at cut-off values that ranged from 2.47 to 4.07 kpa.

Diagnosing cirrhosis

Twenty-six studies (with 4,441 treatment-naive CHB patients) investigated these three non-invasive methods for the prediction of cirrhosis. Nineteen (3,806 patients), five (773 patients), and five (408 patients) items focused on the TE, 2D-SWE, and MRE, respectively, for diagnosing cirrhosis. Figure 4 and Table 3 summarize the diagnostic performance of these three methods for staging cirrhosis. The pooled sensitivity and specificity of TE were 0.84 (95% CI, 0.78–0.88) and 0.84 (95% CI, 0.80–0.88). As shown in Figure 3, the summary AUROC of TE was 0.90 (95% CI, 0.88–0.93). Regarding 2D-SWE, the pooled sensitivity and specificity were 0.91 (95% CI, 0.82–0.96) and 0.89 (95% CI, 0.84–0.92). The AUROC of 2D-SWE was 0.94 (95% CI, 0.92–0.96). The overall diagnostic performance of MRE is 96% sensitivity, 96% specificity, and 99% accuracy, at cut-off values that ranged from 3.46 to 6.87 kpa.

Comparison of diagnostic performance between TE and 2D-SWE

Regarding the direct comparison of TE and 2D-SWE for staging significant fibrosis or cirrhosis, the sizes of the included studies are significantly unbalanced. Hence, we were interested in three studies with head-to-head comparison of TE and 2D-SWE in detecting significant fibrosis [17–19]. A total of 537 untreated CHB patients were included in the further meta-analysis. As presented in Table 4, 2D-SWE is more precise than TE in detecting significant fibrosis (AUROCs, 0.92 vs 0.85, $P < 0.01$). We did not further compare the diagnostic performance of MRE or 2D-SWE with TE given the significantly unbalanced sizes of the studies and the lack of articles with head-to-head comparison.

Heterogeneity and publication bias

Non-threshold heterogeneity was observed in TE, 2D-SWE, and MRE for detecting significant fibrosis and cirrhosis (Supplementary Table 3). A meta-regression analysis can only be conducted in groups of >10 studies with complete data to examine the methodological heterogeneity. In groups of >10 studies, heterogeneity existed when TE was used for staging

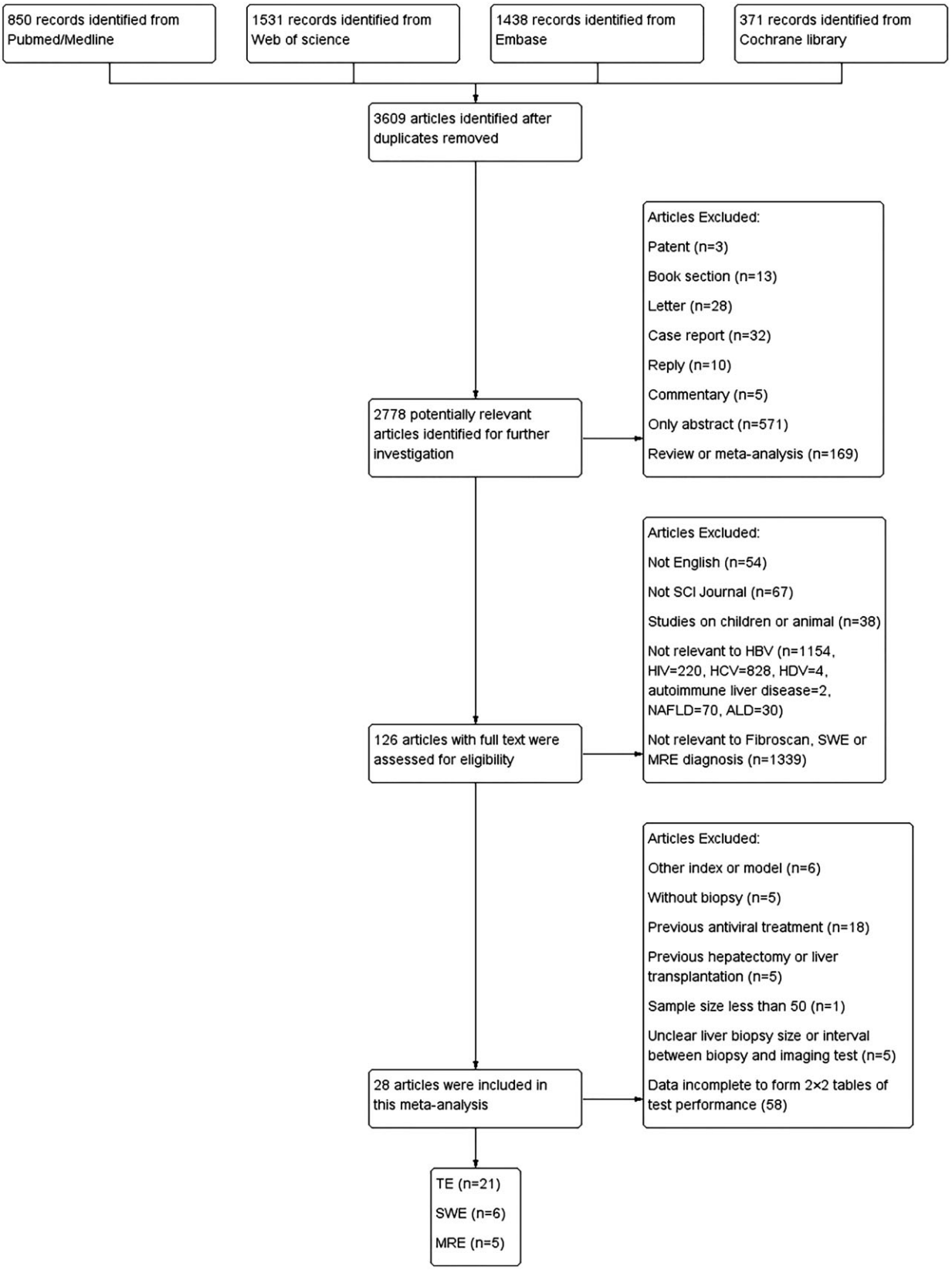

Figure 1. Flow diagram of the study selection.

Table 1. Basic characteristics of the included studies

Study	Region	Imaging	Design	Center	Subject	Study period	Mean age (years)	Male (%)	BMI (kg/m^2)	ALT (U/L)	ALT ≥ 5ULN excluded	HBeAg (+) (%)	HBV-DNA (log IU/mL)	QUADAS-2
Cardoso 2012	France	TE	Retrospective	Single	202	2006–2008	49	60	24.4 ± 3.5	92 (40–112)	Yes	24	4.9 ± 1.9	14
Gaia 2011	Italy	TE	Prospective	Single	70	2007–2009	44	71.4	24.3 (16.7–33.1)	70 (13–464)	No	NA	Detectable	13
Hennedige 2017	Singapore	MRE	Retrospective	Single	63	2009–2012	50.1	69.8	24.9 ± 4.0	NA	No	NA	NA	13
Jekarl 2018	Korea	TE	Retrospective	Single	151	2011–2013	44.6	66.9	NA	2.08 ± 2.67	Yes	NA	6.4 ± 2.4	12
Leung 2013	China	TE, 2D-SWE	Prospective	Single	226	2011–2012	48.8	65	24.2 (21.6–27.3)	69 (37.5–105)	No	100	5.6 ± 3.1	12
Li 2018	China	TE	Retrospective	Single	118	2013–2015	37	62.8	22.5 (20.4–24.2)	39 ± 16	Yes	66	5.4 (3.2–7.5)	12
Liu 2019	China	2D-SWE	Prospective	Single	123	2016–2018	36.3	49.6	20.5 ± 2.2	33.5 ± 22.3	Yes	60.2	6.67 (4.5–8.09)	12
Liu 2015	China	TE	Prospective	Single	108	2011–2012	40.1	75	22 ± 3	53.2 (8–270)	No	NA	NA	11
Park 2019	Korea	2D-SWE, MRE	Retrospective	Single	63	2013–2018	50.8	58.7	23.4 ± 3.4	44 ± 20.8	Yes	55.6	5.78 ± 1.64	12
Seo 2015	Korea	TE	Retrospective	15 centers	567	2006–2014	45	66.7	23.8 (22.1–25.7)	48 (35–56)	Yes	NA	NA	13
Shi 2014	China	MRE	Prospective	Single	113	2012–2013	42	42.5	21.7 (17.8–32.6)	NA	No	NA	Detectable	14
Trembling 2014	Italy	TE	Prospective	Single	182	NA	46	71	NA	110.3 ± 103.4	No	29.1	NA	14
Venkatesh 2014	Singapore	MRE	Prospective	Single	63	2009–2011	50	69.8	24.82 ± 3.97	71.75 ± 101.8	No	NA	NA	13
Wu 2015	China	MRE	Prospective	Single	106	2011–2013	59	48.7	NA	NA	No	NA	NA	13
Yao 2020	China	TE, 2D-SWE	Retrospective	Single	54	2013–2015	36.7	76	23.9 (21.9–25)	50.4 (28.8–129.2)	No	61	4.8 (2.7–6.3)	14
Zeng 2014	China	2D-SWE	Prospective	Single	104	2011–2012	37.2	78.8	22.1 ± 3.4	43 (28–74)	No	NA	Detectable	13
Zeng 2017	China	TE, 2D-SWE	Prospective	Single	257	2013–2015	36.7	77.4	21.7 (19.7–23.9)	42 (28.3–67.8)	No	NA	NA	13
Zhang 2015	China	TE	Retrospective	Single	180	2011–2013	36.43	77.2	24.36 ± 3.52	93.88 ± 116.82	No	NA	4.62 ± 2.69	13
Osakabe 2011	Japan	TE	Prospective	Single	51	2005–2009	51	36.8	NA	34 (20.3–80)	No	32.5	4.6 (3–7)	13
Cho 2011	Korea	TE	Prospective	Single	121	2006–2009	39.1	66.9	23.9 ± 3.0	167.0 ± 197.9	No	NA	Detectable	13
Kim BK 2012	Korea	TE	Prospective	Single	194	2008–2010	46.7	61.3	23.4 ± 2.8	58.4 ± 27.1	No	NA	NA	13
Kim SU 2012	Korea	TE	Prospective	Single	150	2007–2009	41.9	71.3	23.2 ± 2.8	74.1 ± 98.3	No	NA	NA	13
Kumar 2013	India	TE	Prospective	Single	200	2009–2011	37.6	79.5	24.2 ± 3.7	44 (9–320)	No	40.5	5.65 (3.33–8.82)	13
Zhao 2017	China	TE	Prospective	Single	99	2014–2015	37.7	64.6	23.87 ± 3.42	46.73 ± 30.19	Yes	NA	NA	12
Shen 2019	China	TE	Prospective	Single	593	2014–2015	37	63.7	NA	NA	Yes	59.5	NA	14
Kim DY 2009	Korea	TE	Prospective	Single	91	2005–2006	42.5	79.2	25.3 ± 1.3	45.1 ± 23.4	No	58.5	NA	13
Kim SU 2009	Korea	TE	Prospective	Single	130	2006–2007	40	80.2	23.8 ± 4.6	46 ± 24	No	59.3	50.5% detectable	13
Chan 2009	China	TE	Prospective	Single	161	2006–2008	45	76	24 ± 4	93 ± 78	No	43	6.5 ± 1.7	13

Values are presented as mean ± standard deviation or median (range/interquartile range).

ALT, alanine transaminase; BMI, body mass index; MRE, magnetic resonance elastography; NA, not available; QUADAS, Quality Assessment of Studies of Diagnostic Accuracy Studies; 2D SWE, 2D shear wave elastography; TE, transient elastography; ULN, upper limit of normal.

Table 2. Technical characteristics of imaging and histological examination

Study	Imaging	Instrument detail	Scoring system	Interval	Length (mm)
Cardoso 2012	TE	M probe (1–6 MHz)	Metavir	<1 day	≥15
Gaia 2011	TE	M probe (1–6 MHz)	Metavir	<6 months	≥20
Hennedige 2017	MRE	1.5T (60 Hz); 2D-GRE sequence	Metavir	<6 months	≥15
Jekarl 2018	TE	M probe (1–6 MHz)	Knodell	<1 day	≥20
Leung 2013	TE, 2D-SWE	M probe (1–6 MHz); SC6-1 probe (1–6 MHz)	Metavir	<1 year	≥15
Li 2018	TE	M probe (1–6 MHz)	Metavir	<1 week	≥15
Liu 2019	TE	M probe (1–6 MHz)	Metavir	<1 day	15–19
Liu 2015	2D-SWE	SC6-1 probe (1–6 MHz)	Scheuer	<1 day	≥15
Park 2019	2D-SWE, MRE	SC6-1 probe (1–6 MHz); 3 T (unclear frenquency), unclear sequence	Metavir	<2 weeks	≥10
Seo 2015	TE	M probe (1–6 MHz)	Batts and Ludwig	<3 months	15–30
Shi 2014	MRE	1.5T (60 Hz); 2D-GRE sequence	Metavir	23 days	14 ± 7
Trembling 2014	TE	M probe (1–6 MHz)	Metavir	<1 day	≥20
Venkatesh 2014	MRE	1.5T (60 Hz); 2D-GRE sequence	Metavir	<6 months	≥18
Wu 2015	MRE	1.5T (60 Hz); 2D-GRE sequence	Metavir	<3months	≥10
Yao 2020	TE, 2D-SWE	M probe (1–6 MHz); SC6–1 probe (1–6 MHz)	Ishak	<1 month	≥20
Zeng 2014	2D-SWE	SC6-1 probe (1–6 MHz)	Metavir	<3 days	≥15
Zeng 2017	TE, 2D-SWE	M probe (1–6 MHz); SC6-1 probe (1–6 MHz)	Metavir	<3 days	≥15
Zhang 2015	TE	M probe (1–6 MHz)	Scheuer	<3 days	≥15
Osakabe 2011	TE	M probe (1–6 MHz)	Metavir	<1month	≥15
Cho 2011	TE	M probe (1–6 MHz)	Metavir	<1 day	≥15
Kim BK 2012	TE	M probe (1–6 MHz)	Batts and Ludwig	<1 day	≥20
Kim SU 2012	TE	M probe (1–6 MHz)	Laennec	<1 day	≥15
Kumar 2013	TE	M probe (1–6 MHz)	Metavir	<1 week	≥15
Zhao 2017	TE	M probe (1–6 MHz)	Metavir	<1 day	≥15
Shen 2019	TE	M probe (1–6 MHz)	Metavir	<1 week	≥15
Kim DY 2009	TE	M probe (1–6 MHz)	Metavir	<1 day	≥10
Kim SU 2009	TE	M probe (1–6 MHz)	Metavir	<1 day	≥15
Chan 2009	TE	M probe (1–6 MHz)	Metavir	<1 month	≥15

GRE, gradient-recalled echo; MRE, magnetic resonance elastography; 2D-SWE, 2D shear wave elastography; TE, transient elastography.

fibrosis. Results of the meta-regression are presented in Tables 5 and 6. The diagnostic accuracy was not affected by the following factors when TE was used for staging significant fibrosis and cirrhosis: study design ($P = 0.18$ and 0.87), classification criteria ($P = 0.5$ and 0.21), region ($P = 0.4$ and 0.49), interval between biopsy and imaging test ($P = 0.55$ and 0.32), obviously abnormal ALT ($P = 0.9$ and 0.94), liver biopsy length ($P = 0.33$ and 0.71), and QUADAS-2 score ($P = 0.10$ and 0.94). There was no evidence of publication bias for TE, 2D-SWE, and MRE for staging fibrosis (Supplementary Figure 2).

Discussion

In this study, we performed a systematic review and meta-analysis, which included 28 (4,540 patients) articles to investigate the diagnostic performance of TE, 2D-SWE, and MRE for liver fibrosis in treatment-naive people with HBV. Our results showed that the overall mean prevalence of significant fibrosis and cirrhosis was 64.1% and 20.3%, respectively, in untreated CHB patients. A previous meta-analysis has revealed that the mean incidence of significant fibrosis and cirrhosis was 45% and 9.4% in NAFLD patients [20], suggesting a higher incidence rate of fibrosis in CHB patients. Once an untreated CHB patient is diagnosed as having cirrhosis or histologically confirmed as having significant fibrosis with an elevated HBV-DNA level, antiviral treatment is recommended [12]. There is an increasing clinical need to better tune the timing of antiviral treatment given the increasing prevalence of CHB worldwide.

Among the non-invasive methods in this review, both elastography based on ultrasound or magnetic resonance imaging express acceptable accuracy. For staging significant fibrosis, the summary AUROC values of TE, 2D-SWE, and MRE were 0.84, 0.89, and 0.99, respectively. Based on the further head-to-head comparison, we also confirmed that 2D-SWE outperformed TE is staging significant fibrosis (0.92 vs 0.85, $P < 0.01$), which is similar to a previous meta-analysis that focused on the direct comparison of TE and 2D-SWE for fibrosis in chronic viral hepatitis [21]. An almost similar trend was observed in patients with chronic hepatitis C [22]. Nevertheless, no significant difference was observed between 2D-SWE and TE in staging significant fibrosis in NAFLD [23]. It is well known that obesity and overweight are associated with higher rates of NAFLD. We speculated that the drop in diagnostic accuracy of 2D-SWE may be correlated with an evident unreliable results rate observed in obese patients, which is even higher than TE [24].

It is quite evident that MRE expresses extremely high accuracy. The diagnostic accuracy of MRE for staging significant fibrosis and cirrhosis was both >0.95 using AUROC at cut-off values of 2.47–4.07 and 3.46–6.87 kpa, which is also consistent with previous findings in patients with CLD [25, 26]. However, it is of less reliability to compare the diagnostic performance of TE and MRE since the sizes of the included studies are significantly unbalanced. Regarding the direct comparison of 2D-SWE and MRE, only one study with head-to-head comparison revealed that MRE is more precise than 2D-SWE for staging significant fibrosis [27], indicating that MRE is a more reliable technique to

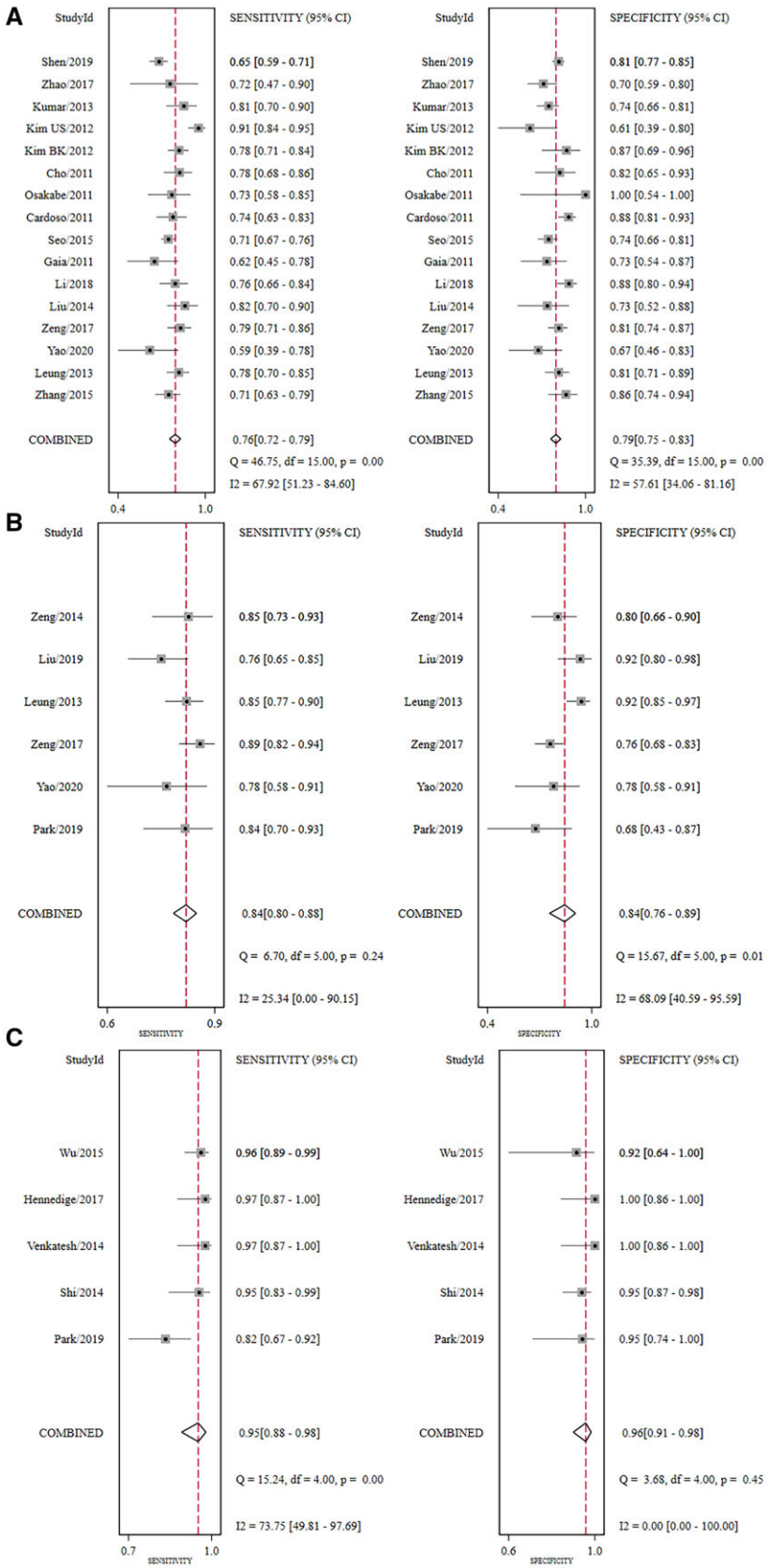

Figure 2. Forest plots of transient elastography (A), 2D shear wave elastography (B), and magnetic resonance elastography (C) in detecting significant fibrosis.

Table 3. Pooled sensitivity and specificity of TE, 2D-SWE, and MRE for staging fibrosis by bivariate analysis

Imaging	No. of studies (no. of patients)	Cut-off values	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	AUROC (95% CI)
Staging significant fibrosis							
TE	16 (3,244)	6–8.8	0.76 (0.72–0.79)	0.79 (0.75–0.83)	3.65 (3.08–4.32)	0.31 (0.26–0.36)	0.84 (0.81–0.87)
2D-SWE	6 (827)	6.73–9.05	0.84 (0.80–0.88)	0.84 (0.76–0.89)	5.15 (3.47–7.66)	0.19 (0.15–0.24)	0.89 (0.86–0.92)
MRE	5 (408)	2.47–4.07	0.95 (0.88–0.98)	0.96 (0.91–0.98)	24.94 (10.14–61.3)	0.06 (0.02–0.13)	0.99 (0.97–0.99)
Staging cirrhosis							
TE	19 (3,806)	8–14.1	0.84 (0.78–0.88)	0.84 (0.80–0.88)	5.1 (4.13–6.30)	0.19 (0.14–0.26)	0.90 (0.88–0.93)
2D-SWE	5 (773)	9.5–11.8	0.91 (0.82–0.96)	0.89 (0.84–0.92)	7.97 (5.61–11.32)	0.1 (0.04–0.21)	0.94 (0.92–0.96)
MRE	5 (408)	3.46–6.87	0.96 (0.85–0.99)	0.96 (0.92–0.98)	25.68 (11.28–58.47)	0.04 (0.01–0.16)	0.99 (0.98–1.00)

AUROC, area under the receiver-operating characteristic curve; CI, confidence interval; MRE, magnetic resonance elastography; 2D-SWE, 2D shear wave elastography; TE, transient elastography.

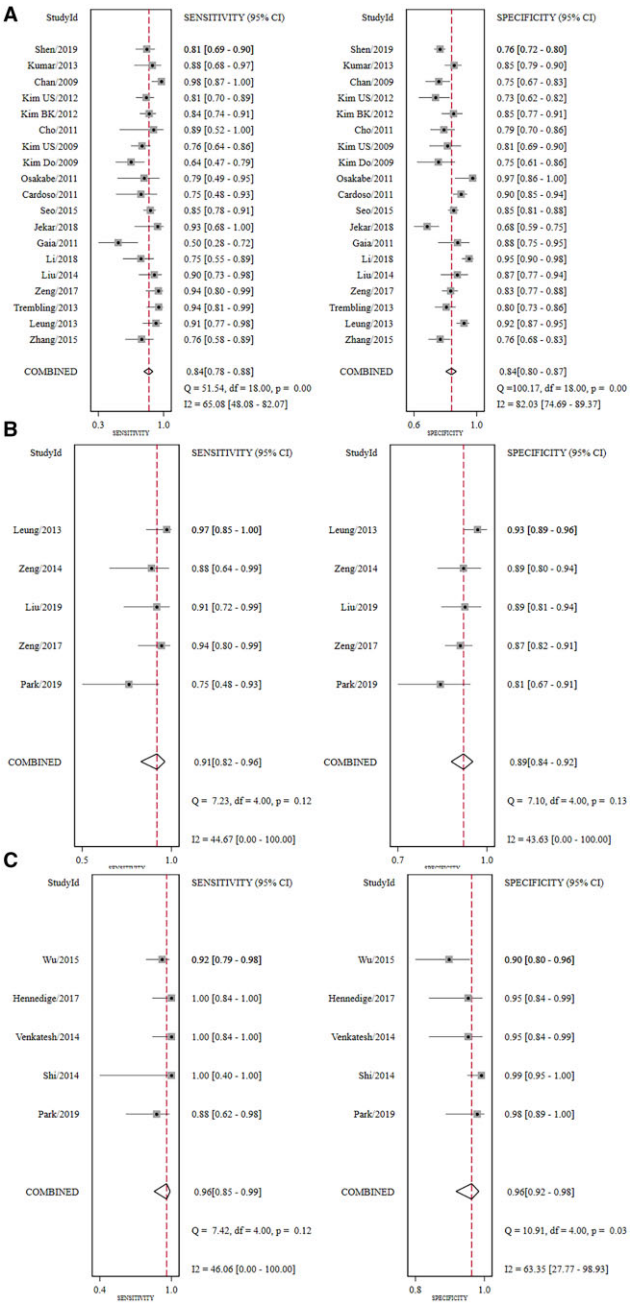

Figure 3. Forest plots of transient elastography (A), 2D shear wave elastography (B), and magnetic resonance elastography (C) in detecting cirrhosis.

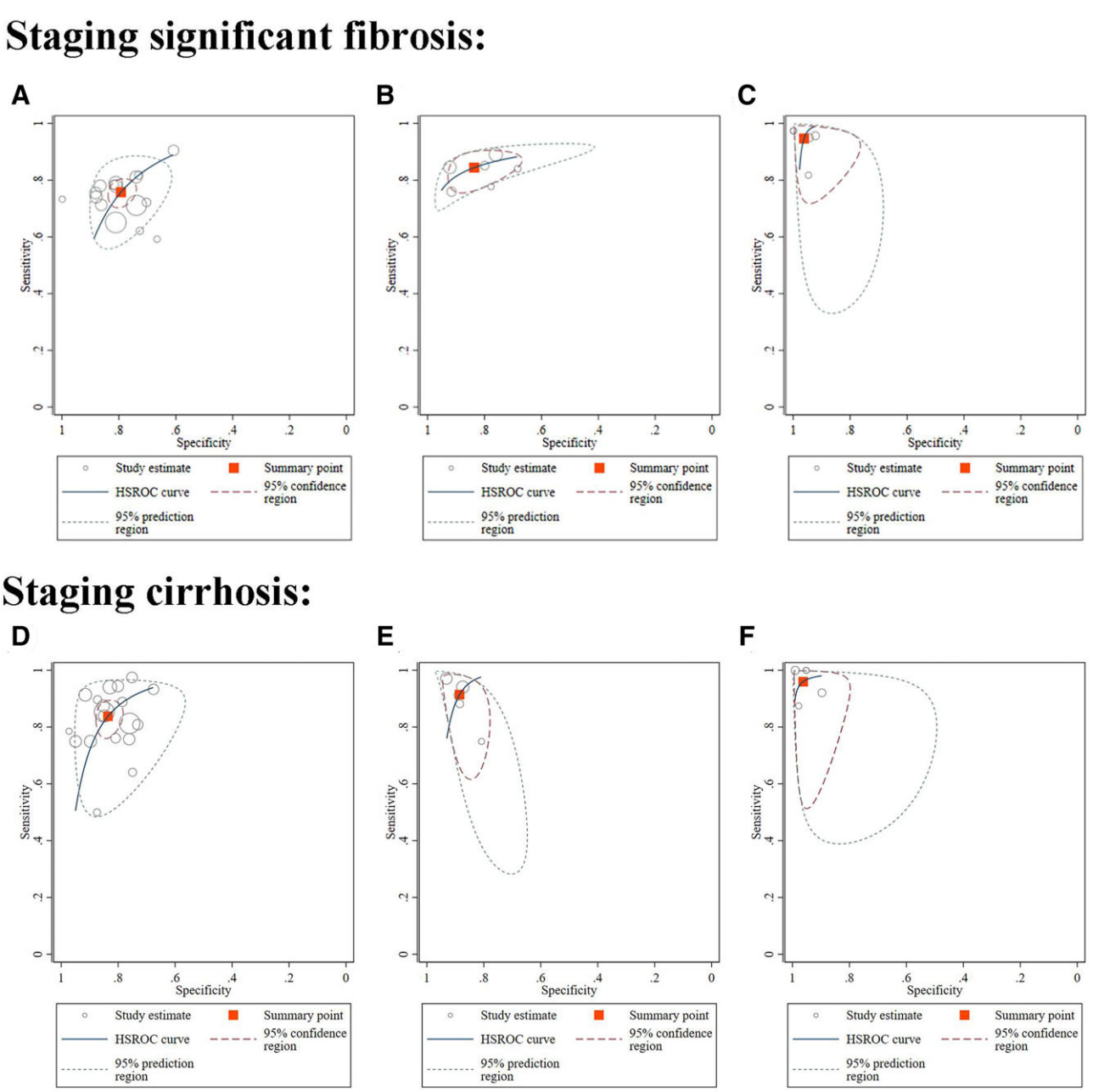

Figure 4. The HSROC plots of transient elastography, 2D shear wave elastography, and magnetic resonance elastography for sensitivity and specificity in detecting significant fibrosis [(A), (B), and (C), respectively] and cirrhosis [(D), (E), and (F), respectively].

Table 4. Meta-analysis of studies with head-to-head comparison of TE and 2D-SWE in staging significant fibrosis

Imaging	No. of studies (No. of patients)	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	AUROC (95% CI)	Diagnostic odds ratio (95% CI)
TE	3 (537)	0.77 (0.71–0.81)	0.80 (0.74–0.84)	3.76 (2.92–4.85)	0.29 (0.24–0.37)	0.85 (0.82–0.88)	12.17 (8.18–18.09)
2D-SWE	3 (537)	0.86 (0.81–0.90)	0.82 (0.77–0.86)	5.03 (3.81–6.64)	0.17 (0.13–0.23)	0.92 (0.90–0.94)	31.38 (19.30–51.01)

AUROC, area under summary receiver-operating characteristic; CI, confidence interval; MRE, magnetic resonance elastography; 2D-SWE, 2D shear wave elastography; TE, transient elastography.

Table 5. Results of meta-regression on transient elastography (TE) in detecting significant fibrosis

Covariate	No. of studies	Pooled sensitivity	P-value	Pooled sensitivity	P-value	Joint P-value
Study design			<0.01		<0.01	0.18
Prospective	11	0.78 (0.74–0.82)		0.78 (0.73–0.82)		
Retrospective	5	0.72 (0.65–0.78)		0.82 (0.77–0.87)		
Classification criteria			<0.01		<0.01	0.50
METAVIR score	11	0.75 (0.71–0.80)		0.80 (0.77–0.84)		
Non-METAVIR score	5	0.76 (0.70–0.83)		0.76 (0.68–0.83)		
Region			0.14		<0.01	0.40
Asia	14	0.76 (0.73–0.80)		0.79 (0.75–0.82)		
Not Asia	2	0.70 (0.57–0.82)		0.84 (0.76–0.92)		
ALT >5 ULN excluded			<0.01		<0.01	0.90
Yes	8	0.76 (0.71–0.81)		0.80 (0.75–0.85)		
No	8	0.75 (0.70–0.81)		0.79 (0.73–0.84)		
TE was performed within 3 months prior to biopsy			0.05		0.01	0.55
Yes	14	0.76 (0.72–0.80)		0.79 (0.76–0.83)		
No	2	0.73 (0.61–0.84)		0.79 (0.68–0.89)		
Specimen length (mm)			<0.01		<0.01	0.33
≥20	3	0.70 (0.60–0.81)		0.76 (0.65–0.87)		
<20	13	0.77 (0.73–0.81)		0.80 (0.76–0.83)		
QUADAS-2 = 14			<0.01		<0.01	0.10
Yes	3	0.67 (0.59–0.76)		0.82 (0.75–0.88)		
No	13	0.77 (0.74–0.81)		0.79 (0.75–0.83)		

QUADAS, Quality Assessment of Studies of Diagnostic Accuracy Studies; ULN, upper limit of normal.

Table 6. Results of meta-regression on transient elastography (TE) in detecting cirrhosis

Covariate	No. of studies	Pooled sensitivity	P-value	Pooled sensitivity	P-value	Joint P-value
Study design						
Prospective	14	0.84 (0.79–0.90)	0.04	0.83 (0.79–0.87)	<0.01	0.87
Retrospective	5	0.82 (0.72–0.92)		0.85 (0.78–0.91)		
Classification criteria						
METAVIR score	14	0.84 (0.78–0.90)	0.01	0.85 (0.82–0.89)	<0.01	0.21
Non-METAVIR score	5	0.84 (0.76–0.93)		0.78 (0.71–0.86)		
Region						
Asia	16	0.85 (0.80–0.90)	0.44	0.83 (0.79–0.87)	<0.01	0.49
Not Asia	3	0.77 (0.62–0.93)		0.86 (0.79–0.94)		
ALT >5 ULN excluded						
Yes	5	0.83 (0.73–0.92)	0.01	0.84 (0.78–0.91)	<0.01	0.94
No	14	0.84 (0.78–0.90)		0.83 (0.79–0.87)		
TE was performed within 3 months prior to biopsy						
Yes	17	0.85 (0.80–0.89)	0.76	0.83 (0.79–0.86)	<0.01	0.32
No	2	0.75 (0.56–0.94)		0.91 (0.84–0.97)		
Specimen length						
≥20 mm	4	0.84 (0.73–0.94)	0.04	0.81 (0.72–0.89)	<0.01	0.71
<20 mm	15	0.84 (0.78–0.89)		0.84 (0.81–0.88)		
QUADAS-2 = 14						
Yes	3	0.85 (0.74–0.97)	0.13	0.83 (0.74–0.91)	<0.01	0.94
No	16	0.83 (0.78–0.89)		0.84 (0.80–0.88)		

QUADAS, Quality Assessment of Studies of Diagnostic Accuracy Studies; ULN, upper limit of normal.

aid in making clinical decisions to initiate antiviral treatment. Nevertheless, it is a retrospective, single-center analysis with a limited number of subjects (63 treatment-naive CHB patients). Further prospective studies are needed for head-to-head comparison between MRE and other imaging modalities in untreated CHB patients.

Venkatesh *et al.* [28] confirmed that normal liver stiffness measurement (LSM) assessed through MRE in the normal Asian population is highly reproducible. The results were not affected by age, sex, and body mass index (BMI). MRE can visualize the whole substantive organ without an accurate acoustic window, which is superior to TE [29]. A larger measurement area of the liver can effectively lower the sampling errors [30]. Ichikawa *et al.* [31] explained that TE can only conduct a unidirectional measurement, which is more likely to be interfered with by reflection waves and refraction waves. In terms of MRE, it evaluates 2D or even 3D displacement vectors. Additionally, compared with TE, MRE can generate better-quality figures with

compressional and continuous waves. Because MRE conducted with a gradient-recalled echo (GRE) sequence has been well validated in previous large cohorts of clinical studies [32], the commonly applied MRE technique is GRE-MRE [33]. Nevertheless, the conventional GRE-MRE technique tends to be technically deficient as the process of its imaging is easily susceptible to iron deposition. Hence, GRE-MRE is rather time-consuming and a more stringent breath hold by the patients is required [34]. To lower these barriers, the spin-echo-based echo planar imaging (SE-EPI) MRE sequence was developed. This novel sequence is less sensitive to the iron overload, thus contributing to shorter imaging time and a higher technical success rate [35]. Despite the promising advances, MRE is currently time-consuming and costly. Considering the high prevalence of CHB and the scarcity of MRE in Asian countries, there is still a long way to go in popularizing MRE for CHB patients on a large scale.

Compared with TE, easier access to the ROI with high-quality measurements with a colorful elasticity map would be accessible through 2D-SWE [36]. Moreover, the variation in blood flow can be monitored through 2D-SWE [37, 38]. As inspired by its advantages and indicated by the results in our article, 2D-SWE is a better choice to stage significant fibrosis than TE.

There are still limitations to this study. First, due to the incomplete data, our meta-regression analysis did not include factors such as obesity, ascites, and HBV-DNA, which may also be the sources of heterogeneity, thus affecting our ultimate conclusions [39]. Surprisingly, Petzold *et al.* [40] pointed out that parameters such as age, gender, and liver function indexes had no significant impact on LSM measured by 2D-SWE. It is worth noting that the LSM measured through TE tends to be affected by inflammation, congestion, and cholestasis [41], thus affecting our judgments. Second, this study did not take the financial cost, the convenience, or the success rate of examination into consideration. A cheaper and less time-consuming technique would lower the barrier for clinical applications [42]. Moreover, regarding 2D-SWE and MRE, although AUROCs are high, the number of studies on which these findings rely is rather small (six studies with 827 patients and five studies with 408 patients, respectively), limiting the persuasiveness of our conclusions. Therefore, more prospective and multicenter studies are needed.

Collectively, our current study confirms that TE, 2D-SWE, and MRE express acceptable diagnostic accuracies in staging fibrosis in untreated CHB patients. 2D-SWE outperformed TE in detecting significant fibrosis in treatment-naive people with HBV.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Author's contributions

All authors: data contribution, data interpretation, and critical review of the manuscript for important content. M.K.L., X.Y.W., and Y.L.: literature search and data extraction. M.K.L. and X.Y.W.: study quality assessment; M.K.L. and X.Y.W.: study design and data analysis. M.K.L.: drafting of the manuscript. Y.L. and B.W.: critical revision of the paper. B.W.: study conception and study supervision.

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Conflict of Interest

The authors declare that they do not have any conflict of interest.

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