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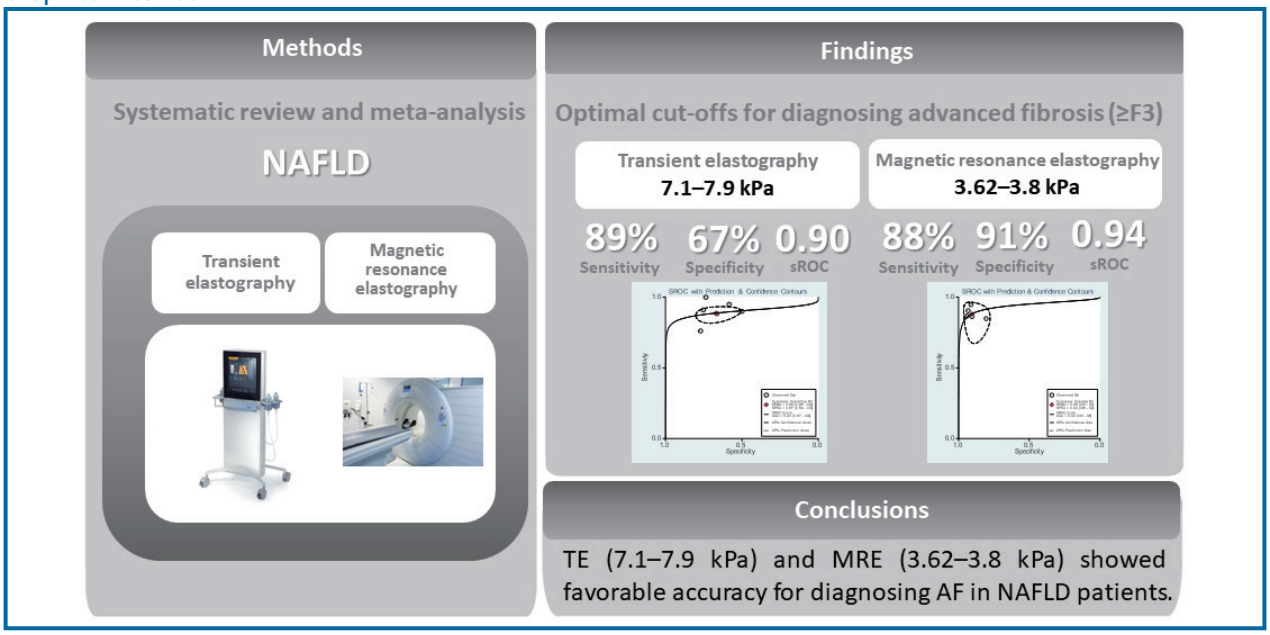
Original Article

Optimal cut-offs of vibration-controlled transient elastography and magnetic resonance elastography in diagnosing advanced liver fibrosis in patients with nonalcoholic fatty liver disease: A systematic review and meta-analysis

Young Eun Chon[1,*], Young-Joo Jin[2,*], Jihyun An[3], Hee Yeon Kim[4], Miyoung Choi[5], Dae Won Jun[6], Mi Na Kim[7,8], Ji Won Han[9], Han Ah Lee[10], Jung Hwan Yu[2], and Seung Up Kim[7,8]

[1]Department of Gastroenterology, CHA Bundang Medical Center, CHA University, Seongnam; [2]Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon; [3]Department of Gastroenterology and Hepatology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri; [4]Department of Internal Medicine, College of Medicine, Bucheon St. Mary's Hospital, The Catholic University of Korea, Seoul; [5]Division of Health Technology Assessment Research, National Evidence-Based Healthcare Collaborating Agency (NECA), Seoul; [6]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul; [7]Department of Internal Medicine, Yonsei University College of Medicine, Seoul; [8]Yonsei Liver Center, Severance Hospital, Seoul; [9]Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul; [10]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

Graphical Abstract



Study Highlights

- The vibration-controlled transient elastography and magnetic resonance elastography with the suggested cut-offs (7.1–7.9 kPa and 3.62–3.8 kPa, respectively) showed favorable accuracy for diagnosing advanced fibrosis in patients with nonalcoholic fatty liver disease. This result will serve as a basis for clinical guidelines for non-invasive tests and differential diagnosis of advanced fibrosis.

Background/aims: Opinions differ regarding vibration-controlled transient elastography and magnetic resonance elastography (VCTE/MRE) cut-offs for diagnosing advanced fibrosis (AF) in patients with non-alcoholic fatty liver disease (NAFLD). We investigated the diagnostic performance and optimal cut-off values of VCTE and MRE for diagnosing AF.

Methods: Literature databases, including Medline, EMBASE, Cochrane Library, and KoreaMed, were used to identify relevant studies published up to June 13, 2023. We selected studies evaluating VCTE and MRE regarding the degree of liver fibrosis using liver biopsy as the reference. The sensitivity, specificity, and area under receiver operating characteristics curves (AUCs) of the pooled data for VCTE and MRE for each fibrosis stage and optimal cut-offs for AF were investigated.

Results: A total of 19,199 patients from 63 studies using VCTE showed diagnostic AUC of 0.83 (95% confidence interval: 0.80–0.86), 0.83 (0.80–0.86), 0.87 (0.84–0.90), and 0.94 (0.91–0.96) for ≥F1, ≥F2, ≥F3, and F4 stages, respectively. Similarly, 1,484 patients from 14 studies using MRE showed diagnostic AUC of 0.89 (0.86–0.92), 0.92 (0.89–0.94), 0.89 (0.86–0.92), and 0.94 (0.91–0.96) for ≥F1, ≥F2, ≥F3, and F4 stages, respectively. The diagnostic AUC for AF using VCTE was highest at 0.90 with a cut-off of 7.1–7.9 kPa, and that of MRE was highest at 0.94 with a cut-off of 3.62–3.8 kPa.

Conclusions: VCTE (7.1–7.9 kPa) and MRE (3.62–3.8 kPa) with the suggested cut-offs showed favorable accuracy for diagnosing AF in patients with NAFLD. This result will serve as a basis for clinical guidelines for non-invasive tests and differential diagnosis of AF. **(Clin Mol Hepatol 2024;30(Suppl):S117-S133)**

Keywords: Non-alcoholic fatty liver disease; Meta-analysis; Advanced fibrosis; Vibration-controlled transient elastography; Magnetic resonance elastography

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and the most common chronic liver disease affecting 25–40% of the worldwide population.[1,2] Most patients remain asymptomatic for long periods; however, some patients slowly progress to cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC).[3]

The degree of liver fibrosis is the critical determinant of the long-term prognosis of patients with NAFLD, such as the development of liver-related events, death, and HCC.[4,5] Liver biopsy (LB) is the gold standard for identifying and staging liver fibrosis in patients with NAFLD.[5,6] However, LB

Corresponding author : **Seung Up Kim**
Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1944, Fax: +82-2-393-6884, E-mail: ksukorea@yuhs.ac
https://orcid.org/0000-0002-9658-8050

Jung Hwan Yu
Department of Internal Medicine, Inha University School of Medicine, 27, Inhang-ro, Jung-gu, Incheon 22332, Korea
Tel: +82-32-890-3414, Fax: +82-32-863-1333, E-mail: junghwan0081@naver.com
https://orcid.org/0000-0001-5672-038X

*Young Eun Chon and Young-Joo Jin contributed equally as co-first authors.

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Abbreviations:

AF, advanced fibrosis; AST, aspartate aminotransferase; AUC, area under the receiver operating characteristics curve; BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; LB, liver biopsy; LS, liver stiffness; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NITs, non-invasive tests; ROC, receiver operating characteristics; sROC, summary ROC curves; VCTE, vibration-controlled transient elastography

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is invasive and carries infrequent but fatal risk of complications such as bleeding or pneumothorax, and has sampling and intra- and inter-observer variability in pathological reporting.[7,8] Therefore, in the clinical setting, clinicians should essentially have alternative tests for LB that can estimate the long-term prognosis of patients with NAFLD. In particular, clinicians are interested in the critical point at which patients begin to deteriorate and should be referred to a liver specialist. Growing evidence shows advanced fibrosis (AF) is a turning gate for increased risk of liver-related events.[9-11]

Various non-invasive tests (NITs) have been developed to stratify the risk of individual patients according to the presence of AF.[6,11,12] Serum markers are generally simple and inexpensive and can be easily used in the clinical setting; however, caution is required in interpretation as they can be affected by patient's systemic condition. In contrast, the diagnostic accuracy of liver stiffness (LS) measurement using vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE) for liver fibrosis in patients with NAFLD is higher than that of other serum markers; based on research published so far, diagnostic area under receiver operating characteristics (ROC) curves (AUCs) for AF is 0.65–0.98 for VCTE,[13-30] and 0.83–0.93 for MRE.[31-34] Several meta-analyses have analyzed the cut-off ranges for AF using VCTE, yielding a range of 6.8–13.6 kPa.[32,35-38] However, some of the studies are outdated, with only a small number of papers included,[35,36] and recent papers published after 2023 have not been included in any meta-analysis.[32,35-38] Moreover, all these papers showed wide cut-off ranges for AF to demonstrate optimal cut-off. In meta-studies that investigated the cut-off of AF using MRE in NAFLD, the value ranged widely from 2.43 to 5.97 kPa.[32,39-41]

Therefore, this study, including the most recent studies, comprehensively analyzed the diagnostic performance of VCTE and MRE in patients with NAFLD and investigated the optimal cut-off values of VCTE and MRE for diagnosing AF.

MATERIALS AND METHODS

This meta-analysis was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement.[42] The study protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews with registration number CRD42024539470.

Search and eligibility criteria

We searched Medline, EMBASE, Cochrane Library, and KoreaMed for relevant articles published up to June 13, 2023. The Patient/Intervention/Comparison/Outcomes used for this study were as follows: P, NAFLD; I, VCTE or MRE; C, LB; and O, AF. We used Medical Subject Heading terms and combined them with free-text words where applicable, according to the databases. The search words (NAFLD, VCTE, MRE, LB, and liver fibrosis-related index words), search strategy, and subsequent results are listed in Supplementary Table 1. Inclusion criteria were as follows: (1) adult patients with NAFLD (≥18 years), (2) adequate description of VCTE or MRE procedures, (3) reliable diagnostic AUC and available cut-off values of VCTE or MRE at least one fibrosis stage, (4) LB as the reference standard for liver fibrosis assessment, (5) interval less than 6 months between LB and VCTE/MRE, and (6) availability of all parameters including true positive, false positive, true negative, and false negative rates. Exclusion criteria were as follows: (1) duplications, (2) articles with only conference abstracts or articles for which the full text was not available, (3) no human subjects, and (4) language not written in English or Korean. The search process was conducted by a professional statistician (M.C.).

Data extraction and quality and bias assessment

Two independent experts in the field of NAFLD (Y.E.C. and H.Y.K.) reviewed relevant titles and abstracts. In cases where it was difficult to decide on inclusion or exclusion, or any discrepancy between the two reviewers was resolved by further discussion with third reviewers (D.W.J. or S.U.K.). Variables collected for meta-analysis included methods of NIT (VCTE or MRE), authors, publication year, study region, study design, number of patients, mean age, sex, mean body mass index (BMI), presence of diabetes mellitus, and fibrosis stages. The data of AUC, test performance parameters, and cut-off values for each liver fibrosis stage

using VCTE and MRE were recorded. The quality of studies was assessed independently using the Quality Assessment of Diagnostic Accuracy Studies tool-2 in pairs, and disagreements were resolved by consensus with the third review author. Publication bias was assessed using a funnel plot.

Statistical analysis

We calculated the pooled diagnostic accuracy (sensitivity, specificity, and AUC) using the weighted mean of the transformed diagnostic accuracy using a bivariate random-effect model.[43] A two-tailed $P<0.05$ was defined as significant. Statistical heterogeneity was evaluated using I^2 values, and I^2 values of 50% and 75% indicated moderate and high degrees of heterogeneity, respectively. Review Manager software version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and STATA statistical package (release 15.1; Stata, College Station, TX, USA) were used for statistical analyses.

RESULTS

Characteristics of included studies

A total of 2,815 records were initially retrieved through database research (Medline: 1,103; EMBASE: 1,577; Cochrane Library: 111; and KoreaMed: 24). After removing duplicates, 2,171 records remained. We obtained 217 eligible records from the first article selection process after excluding 1,947 records by abstract and title screening. After excluding more articles during the second article selection process, 72 articles were included for the final analysis. Figure 1 depicts the study selection flow chart. Table 1 shows the characteristics of the 72 included articles. Studies were conducted in various countries across the world (at least from 19 countries worldwide). Thirty-eight studies were from Western countries, 29 were from Eastern countries, and five were global studies. Among the 72 studies, 63 and 14 articles dealt with diagnostic accuracy of liver fibrosis using VCTE[13,15-21,23-28,30,44-90] and MRE,[16,26,48,75,87,91-99] respectively. Five articles measured both VCTE and

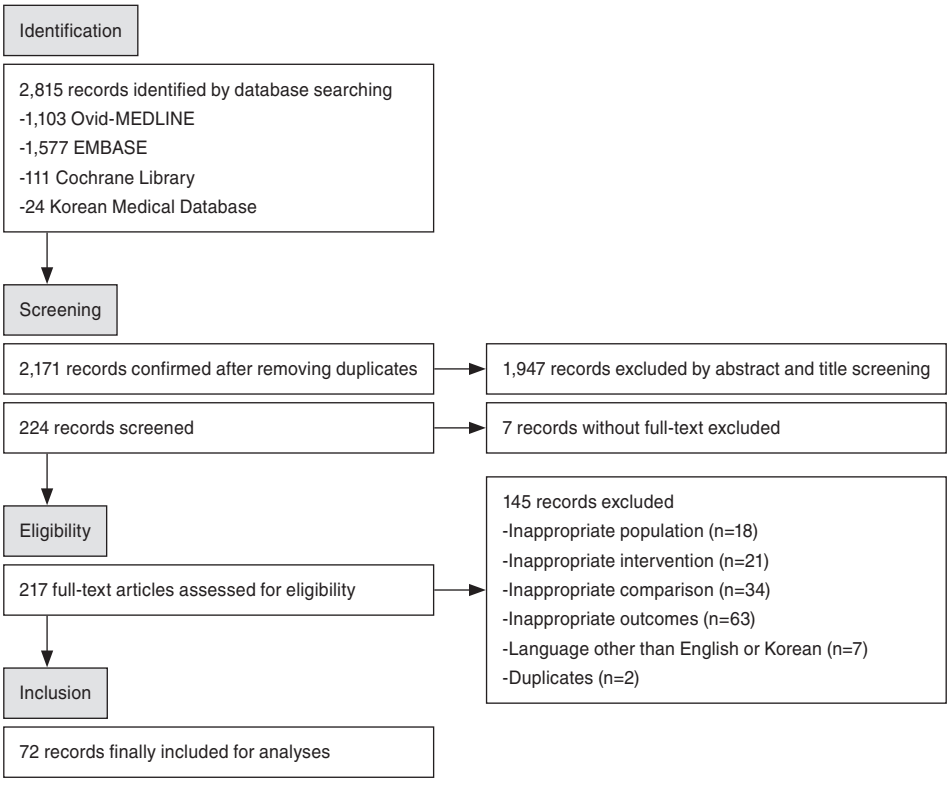

Figure 1. Flow chart of study selection.

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Table 1. Characteristics of the included studies

Author	Year	Region	Study design	Patients, n	Age, years	Male, %	BMI, kg/m^2	Diabetes mellitus, %	Fibrosis stage for analyses
VCTE									
Argalia et al.[44]	2022	Italy	CS, SS	50	52.2	64	29.4	NR	≥F1, ≥F2, ≥F3, F4
Barsamian et al.[45]	2020	France	CS, SS	108	41	21	43	24	≥F1, ≥F2, ≥F3
Chan et al.[15]	2015	Malaysia	CS, SS	101	50.5	54.4	29.3	52.4	≥F1, ≥F2, ≥F3, F4
Chan et al.[46]	2017	Malaysia, Hongkong	CS, SS	57	50.1	49	39.2	NR	≥F1, ≥F2, ≥F3, F4
Gaia et al.[17]	2011	Italy	CS, SS	72	48	72.2	27.5	NR	≥F1, ≥F2, ≥F3, F4
Garteiser et al.[47]	2021	France	CS, SS	152	42	16	44.1	21	≥F1, ≥F2
Imajo et al.[48]	2022	Japan	CS, SS	231	61	52.7	27.1	61.7	≥F1, ≥F2, ≥F3, F4
Kim et al.[49]	2022	Korea	CS, SS	60	50.9	45.9	29.9	61.7	≥F1, ≥F2, ≥F3, F4
Kumar et al.[19]	2013	India	CS, SS	120	39.1	75	26.1	16.6	≥F1, ≥F2, ≥F3, F4
Lee et al.[50]	2016	Korea	CS, SS	183	40.6	60.7	27.9	14.2	≥F1, ≥F2, ≥F3, F4
Leong et al.[51]	2020	Malaysia	CS, SS	100	57.1	46	30.8	NR	≥F1, ≥F2, ≥F3, F4
Lupsor et al.[21]	2010	Netherlands	CS, SS	72	42	70.8	28.7	NR	≥F1, ≥F2, ≥F3
Okajima et al.[52]	2017	Japan	CS, SS	163	55.8	48.5	27.2	NR	≥F1, ≥F2, ≥F3
Park et al.[26]	2017	US	CS, SS	104	50.8	43.3	30.4	27.9	≥F1, ≥F2, ≥F3, F4
Sharpton et al.[53]	2021	US	CS, SS	114	55	45.6	31.2	NR	≥F1, ≥F2, ≥F3, F4
Shi et al.[54]	2020	China	CS, SS	158	48.9	30.4	25.9	26.6	≥F1, ≥F2, ≥F3, F4
Shima et al.[55]	2020	Japan	CS, SS	278	57.8	48.2	27.5	58.6	≥F1, ≥F3
Siddiqui et al.[56]	2019	US	CS, SS	393	51	32	34.4	44	≥F1, ≥F2, ≥F3, F4
Yang et al.[57]	2021	China	CS, SS	91	40	50.5	29.1	71.4	≥F1, ≥F2, ≥F3, F4
Yoneda et al.[58]	2008	Japan	CS, SS	97	51.8	41.2	26.6	NR	≥F1, ≥F2, ≥F3, F4
Boursier et al.[59]	2023	France	CS, MS	1,051	58	60	31	49.8	≥F2, F4
Cardoso et al.[60]	2020	Brazil	CS, SS	81	54.2	26	32.8	60	≥F2
Cassinotto et al.[61]	2016	France	CS, MS	291	56.7	59.1	32.1	52.6	≥F2, ≥F3, F4
Chang et al.[62]	2023	US	CS, MS	1,370	56.6	44.5	34.2	38.0	≥F2, ≥F3, F4
Chang et al.[63]	2019	Singapore	CS, MS	51	49.4	55.6	23.9	NR	≥F2, F4
Eddowes et al.[64]	2019	UK	CS, MS	373	54	55	33.8	50	≥F2, ≥F3, F4
Eilenberg et al.[65]	2021	Austria	CS, SS	170	42	35.4	44.4	28.2	≥F2, ≥F3
Ergelen et al.[66]	2015	Turkey	CS, SS	87	45.8	49.4	30.6	NR	≥F2, ≥F3
Furlan et al.[16]	2020	US	CS, SS	62	50	42	34.8	35	≥F2
Garg et al.[18]	2018	India	CS, SS	76	39.3	23.3	46.2	NR	≥F2, ≥F3
Inadomi et al.[67]	2020	Japan	CS, SS	200	59.5	48	28.1	50.3	≥F2, ≥F3
Jafarov et al.[68]	2020	Turkey	CS, SS	139	49	59	32.9	64	≥F2, ≥F3
Lee et al.[23]	2022	Korea	CS, SS	539	56	47.5	26.9	36.2	≥F2, ≥F3, F4
Lee et al.[69]	2019	Korea	CS, SS	184	44.6	69	29.3	37.5	≥F2
Lee et al.[70]	2022	Korea	CS, SS	251	44	52.6	28.6	46.6	≥F2, ≥F3, F4
Lee et al.[20]	2017	Korea	CS, SS	94	55.5	43.6	27.1	39.4	≥F2, ≥F3, F4
Mendoza et al.[71]	2022	Switzerland	CS, SS	104	53.4	58.7	30.9	47.1	≥F2, ≥F3, F4
Myers et al.[72]	2010	Canada	CS, MS	20	NR	NR	NR	NR	≥F2, ≥F3, F4
Myers et al.[73]	2012	Canada	CS, MS	276	50	63	30	NR	≥F2, F4
Naveau et al.[24]	2014	France	CS, SS	100	42.5	19	41.3	15	≥F2, ≥F3

Table 1. Continued

Author	Year	Region	Study design	Patients, n	Age, years	Male, %	BMI, kg/m^2	Diabetes mellitus, %	Fibrosis stage for analyses
Nogami et al.[74]	2022	Japan	CS, SS	163	59.7	52.8	28.5	61.3	≥F2, ≥F3, F4
Oeda et al.[25]	2020	Japan	CS, MS	137	NR	NR	NR	NR	≥F2, ≥F3, F4
Ooi et al.[75]	2018	Australia	CS, SS	182	44	24.7	45.1	27.1	≥F2
Petta et al.[27]	2011	Italy	CS, SS	146	44.1	71	29.1	14	≥F2, ≥F3
Taibbi et al.[76]	2021	Italy	CS, SS	56	54.7	58.7	29.4	39.1	≥F2, ≥F3
Vali et al.[77]	2023	Europe	CS, MS	632	51.2	58	34.1	42	≥F2
Wong et al.[78]	2019	France, Hongkong	CS, MS	496	54	42.7	30.4	60.5	≥F2, ≥F3, F4
Wong et al.[30]	2010	France, Hongkong	CS, MS	246	51	54.9	28	36.2	≥F2, ≥F3, F4
Yu et al.[79]	2021	China	CS, SS	85	58	40	29.7	100	≥F2, ≥F3, F4
Petta et al.[28]	2019	Global	CS, MS	968	50.1	62.9	29.3	37	≥F3
Tovo et al.[80]	2019	Brazil	CS, MS	104	55.3	26	33	64.4	≥F3
Kosick et al.[81]	2021	Canada	CS, MS	407	48.5	54	32.3	30	≥F3
Boursier et al.[14]	2016	France	CS, MS	452	55.9	60	31.1	46.7	≥F3
Sanyal et al.[82]	2023	Global	CS, MS	1,434	55	50.8	31.7	50.4	≥F3, F4
Armandi et al.[83]	2023	Turkey	LS, SS	96	49.5	62.2	28.4	30.6	≥F3
Noureddin et al.[84]	2023	US	CS, MS	548	58	35	33.3	53	≥F3, F4
Petta et al.[85]	2017	Global	CS, MS	761	50.9	60.2	29.6	54.7	≥F3
Petta et al.[86]	2015	Italy	CS, MS	321	44.7	69.5	28.5	17.8	≥F3
Anstee et al.[13]	2019	US	CS, MS	3,202	58	38	NR	60	≥F3
Troelstra et al.[87]	2021	Netherlands	CS, SS	37	49	62	33.2	43	≥F3
Seki et al.[88]	2017	Japan	CS, SS	171	57.1	50.3	27.7	NR	≥F3
Labenz et al.[89]	2018	Germany	CS, MS	261	51	52.5	30.9	29.9	≥F3
Pavlides et al.[90]	2017	UK	CS, SS	71	53.4	43	32.7	35	F4
MRE									
Costa-Silva et al.[91]	2018	Brazil	CS, SS	49	53.8	14.3	32.2	NR	≥F1, ≥F2, ≥F3, F4
Cui et al.[92]	2016	US	CS, SS	125	48.9	45.6	31.8	26	≥F1, ≥F2, ≥F3, F4
Imajo et al.[93]	2016	Japan	CS, SS	142	57.5	57	28.1	71	≥F1, ≥F2, ≥F3, F4
Imajo et al.[48]	2022	Japan	CS, SS	231	61	52.7	27.1	61.7	≥F1, ≥F2, ≥F3, F4
Kim et al.[94]	2020	Korea	CS, SS	47	51	34	28.3	NR	≥F1, ≥F2, ≥F3
Loomba et al.[95]	2014	US	CS, SS	117	50.1	43.6	32.4	34.2	≥F1, ≥F2, ≥F3, F4
Park et al.[26]	2017	US	CS, SS	104	50.8	43.3	30.4	27.9	≥F1, ≥F2, ≥F3, F4
Zhang et al.[96]	2022	US	CS, SS	100	51.8	46	31.6	NR	≥F1, ≥F2, ≥F3, F4
Furlan et al.[16]	2020	US	CS, SS	62	50	42	34.8	35	≥F2
Inada et al.[97]	2022	Japan	CS, SS	105	65	44.8	27.5	50.5	≥F2
Nogami et al.[74]	2022	Japan	CS, SS	163	55.8	48.5	27.2	NR	≥F2, ≥F3, F4
Troelstra et al.[87]	2021	Netherlands	CS, SS	37	49	62	33.2	43	≥F3
Cui et al.[98]	2015	US	CS, SS	102	51.3	58.8	31.7	25.5	≥F3
Loomba et al.[99]	2016	US	CS, SS	100	50.2	44	32.1	33	≥F3

VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography; CS, cross-sectional study; LS, longitudinal study; SS, single center study; MS, multicenter study; BMI, body mass index; NR, not recorded.

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MRE.[16,26,48,74,87] Of the 63 VCTE-related studies, the mean age of the participants was 50.8 years, 49.3% were male, their mean BMI was 31.5 kg/m^2, and diabetes mellitus was present in 43.0%. Of the 14 VCTE-related studies, the mean age of the participants was 53.3 years, 45.5% were male, mean BMI was 30.6 kg/m^2, and diabetes mellitus was present in 40.8%. Since cut-offs for single to all fibrosis stages were presented in one paper, articles were used multiple times for analyses if they contained cut-offs for various liver fibrosis stages. Quality and bias risk assessment results are listed in Supplementary Figure 1, and most included studies were of good quality.

Pooled diagnostic performance of VCTE for fibrosis stages

In a meta-analysis of 19,199 patients from 63 studies using VCTE as an intervention, 20 studies were included for the diagnosis of F1,[15,17,19,21,26,44-58] 48 for the diagnosis of ≥F2 (significant fibrosis),[15-21,23-27,30,44-54,56-79] 53 for the diagnosis of ≥F3 (AF),[13-15,17-21,23-28,30,44-46,48-58,61,62,64-68,70-72,74,76,78-89] and 34 for the diagnosis of F4 (cirrhosis).[15,17,19,20,23,25,26,30,44,46,48-51,53,54,56-59,61-64,70-74,78,79,82,84,90] The diagnostic AUC for ≥F1, ≥F2, ≥F3, and F4 fibrosis stages was 0.83 (95% confidence interval [CI]: 0.80–0.86), 0.83 (95% CI: 080–0.86), 0.87 (95% CI: 0.84–0.90), and 0.94 (95% CI: 0.91–0.96), respectively (Table 2). The summary ROC curves (sROC) of VCTE to assess each fibrosis stage is depicted in Figure 2. The sensitivity and specificity for each fibrosis stage according to sROC were F1 (0.78 and 0.75), F2 (0.79 and 0.74), F3 (0.81 and 0.79), and F4 (0.88 and 0.89), respectively. Forest plots of sensitivity and specificity estimates from VCTE studies for assessing each fibrosis stage are shown in Supplementary Figure 2. The cut-off ranges for each fibrosis stage ≥F1, ≥F2, ≥F3, and F4 were 5.0–9.6 kPa, 4.8–16.4 kPa, 7.1–14.1 kPa, and 6.9–20.1 kPa, respectively (Table 2). Supplementary Figure 3 shows funnel plots of VCTE-related studies for each stage, and publication bias was documented regarding results for the F2 and F3 stages.

Pooled diagnostic performance of MRE for fibrosis stages

In a meta-analysis of 1,484 patients from 14 studies using MRE as an intervention, eight studies were included for the diagnosis of F1,[26,48,91-96] 11 for the diagnosis of ≥F2,[16,26,48,74,91-97] 12 for the diagnosis of ≥F3,[26,48,74,87,91-96,98,99] and eight for the diagnosis of F4.[26,48,74,91-93,95,96] The diagnostic AUC for ≥F1, ≥F2, ≥F3, and F4 fibrosis stages was 0.89 (95% CI: 0.86–0.92), 0.92 (95% CI: 0.89–0.94), 0.89 (95% CI: 0.86–0.92), and 0.94 (95% CI: 0.91–0.96), respectively (Table 2). Figure 3 shows the sROC with the corresponding sensitivity and specificity (F1 [0.78 and 0.87], F2 [0.85 and 0.86], F3 [0.85 and 0.89], and F4 [0.88 and 0.89]), respectively, of MRE to assess each fibrosis stage. Forest plots of sensitivity and specificity estimates from studies of MRE for assessing each fibrosis stage are depicted in

Table 2. Pooled diagnostic performance of VCTE and MRE for assessing fibrosis stages in patients with NAFLD

Cut-off range, kPa		Studies, n	AUC (95% CI)	Sensitivity (95% CI)	I^2, % (95% CI)	Specificity (95% CI)	I^2, % (95% CI)
VCTE							
≥F1	5.0–9.6	20	0.83 (0.80–0.86)	0.78 (0.72–0.82)	88.1 (83.9–92.3)	0.75 (0.68–0.81)	83.5 (77.1–89.9)
≥F2	4.8–16.4	48	0.83 (0.80–0.86)	0.79 (0.74–0.82)	95.2 (94.5–96.0)	0.74 (0.70–0.78)	92.3 (90.9–93.7)
≥F3	7.1–14.1	53	0.87 (0.84–0.90)	0.81 (0.78–0.84)	87.2 (84.6–89.9)	0.79 (0.76–0.82)	90.0 (88.0–91.9)
F4	6.9–20.1	34	0.94 (0.91–0.96)	0.91 (0.85–0.94)	89.6 (86.8–92.3)	0.87 (0.84–0.89)	92.8 (91.1–94.4)
MRE							
≥F1	2.5–3.14	8	0.89 (0.86–0.92)	0.78 (0.67–0.86)	84.5 (74.9–94.1)	0.87 (0.74–0.94)	88.1 (81.3–95.0)
≥F2	2.77–4.14	11	0.92 (0.89–0.94)	0.85 (0.78–0.90)	79.5 (68.0–91.0)	0.86 (0.78–0.92)	83.3 (74.4-92.2)
≥F3	2.3–4.8	12	0.89 (0.86–0.92)	0.85 (0.80–0.88)	0.0 (0.0–87.5)	0.89 (0.85–0.92)	61.8 (37.9-85.8)
F4	3.35–6.7	8	0.94 (0.91–0.96)	0.88 (0.79–0.93)	0.0 (0.0–96.1)	0.89 (0.83–0.92)	84.1 (74.2-94.0)

VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; AUC, area under receiver operating characteristics curves; CI, confidence interval.

Supplementary Figure 4. The cut-off ranges for each fibrosis stage F≥1, F≥2, F≥3, and F4 were 2.5–3.14 kPa, 2.77–4.14 kPa, 2.3–4.8 kPa, and 3.35–6.7 kPa, respectively. Supplementary Figure 5 shows funnel plots of MRE-related studies for each stage, and publication bias was documented in the F1 and F3 stages.

Optimal cut-off values of VCTE and MRE for diagnosing AF

Considering the significant clinical importance of diagnosing AF accurately, we further analyzed the diagnostic performances of VCTE and MRE according to the sub-

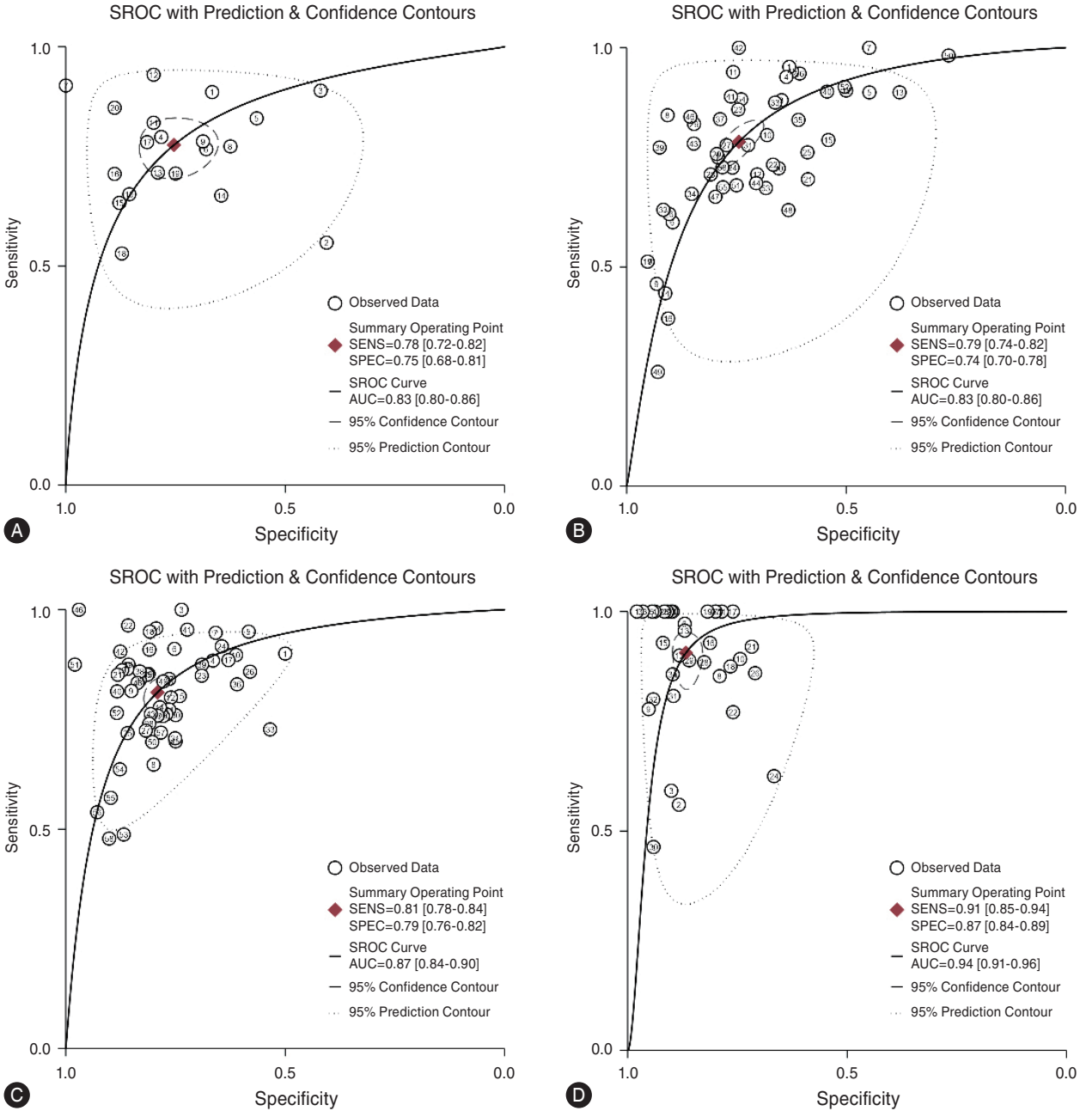

Figure 2. Summary of receiver operating characteristics curves of vibration-controlled transient elastography for assessing fibrosis stages (A) ≥F1, (B) ≥F2, (C) ≥F3, and (D) F4. ROC, receiver operating characteristics; sROC, summary ROC curves; AUC, area under the receiver operating characteristics curve.

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groups of cut-off ranges. Among 53 VCTE-related studies analyzed for determining cut-offs for AF, five cut-offs from four studies were used in duplicate; thus, 58 VCTE-related studies (including duplicates) presented the cut-off values for AF. Characteristics of the studies used for determining AF cut-offs are depicted in Supplementary Table 2. Twenty-seven (26.6%) of the studies were Western studies, including 50.4% male participants, with 51.3 years mean age, 31.1 kg/m^2 mean BMI, and diabetes mellitus was present in 44.6%. The cut-off values for six, 33, 13, and six studies were 7.1–7.9 kPa, 8.0–9.9 kPa, 10.0–11.9 kPa, and 12.0–14.1 kPa, respectively, demonstrating pooled diagnostic

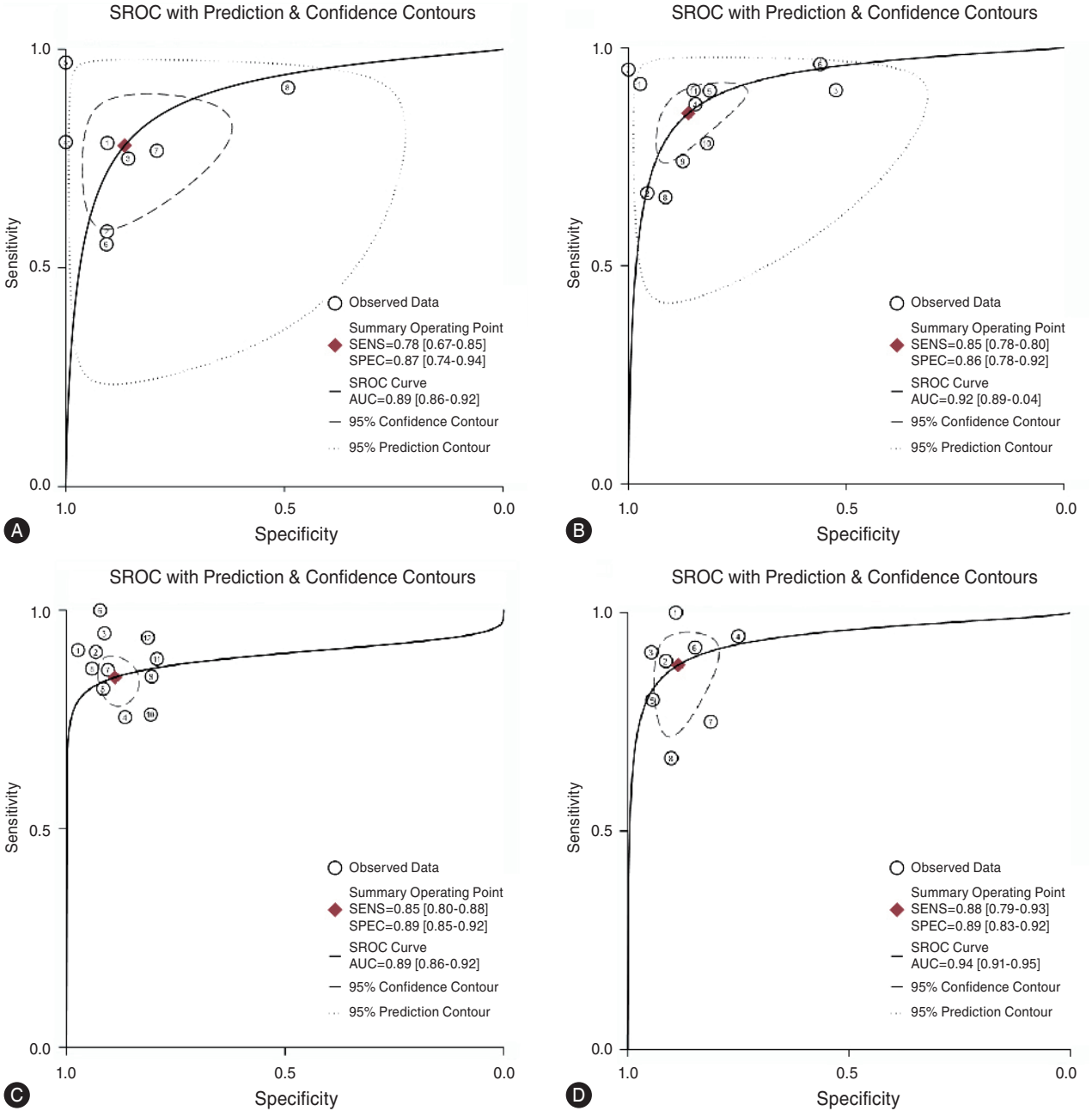

Figure 3. Summary of receiver operating characteristics curves of magnetic resonance elastography for assessing fibrosis stages (A) ≥F1, (B) ≥F2, (C) ≥F3, and (D) F4. ROC, receiver operating characteristics; sROC, summary ROC curves; AUC, area under the receiver operating characteristics curve.

AUCs of 0.90 (95% CI: 0.87–0.92; sensitivity: 0.89; specificity: 0.67), 0.87 (95% CI: 0.00–1.00; sensitivity: 0.83; specificity: 0.77), 0.87 (95% CI: 0.84–0.90; sensitivity: 0.80; specificity: 0.84), and 0.79 (95% CI: 0.75–0.82; sensitivity: 0.55; specificity: 0.88), respectively (Table 3).

Among 12 MRE-related studies that presented the cut-off values for AF, eight (66.7%) were Western studies, including 45.8% male participants, with 52.6 years mean age, 30.5 kg/m^2 mean BMI, and diabetes mellitus was present in 40.3% (Supplementary Table 2). Three, five, and four studies had cut-off values of 2.3–2.99 kPa, 3.62–3.8 kPa, and 3.9–4.8 kPa, respectively. Due to the insufficient number of studies, pooled AUC calculation was not possible for the group with cut-offs of 2.3–2.99 kPa. The pooled diagnostic AUC for five studies with cut-off values of 3.62–3.8 kPa and four studies with cut-off values of 3.9–4.8 kPa were 0.94 (95% CI: 0.91–0.96; sensitivity: 0.88; specificity: 0.91) and 0.93 (95% CI: 0.91–0.95; sensitivity: 0.83; specificity: 0.91), respectively (Table 3).

DISCUSSION

This comprehensive systematic review and meta-analysis of 72 pertinent studies demonstrated that VCTE and MRE are reliable tools for assessing the degree of liver fibrosis in patients with NAFLD. In addition, VCTE (7.1–7.9 kPa) and MRE (3.62–3.8 kPa) with the suggested cut-offs showed favorable performance for diagnosing AF in patients with NAFLD. The outcomes of our study carry important clinical significance as they can aid clinicians in deciding on the management of patients with NAFLD by providing an accurate prediction of AF.

Our study has some important implications. First, to the best of our knowledge, this systematic review and meta-analysis is the most comprehensive, large-scale, and accurate study for assessing liver fibrosis using VCTE and MRE in patients with NAFLD. Compared to LB, the pooled AUC of VCTE and MRE for assessing each liver fibrosis stage was 0.83–0.94 and 0.89–0.94, respectively. The diagnostic performance for VCTE was comparable to the results of previous meta-analyses, showing similar pooled AUC of 0.76–0.99 and a trend toward higher AUC values with the F3 and F4 stages than with the F1 and F2 stages.[32,35-38] Similarly, the diagnostic performance for MRE was comparable to that of previous studies at 0.87–0.95.[32,39-41] In contrast, this study dealt with the most recently updated papers published until mid-2023. We attempted to reduce heterogeneity by excluding studies including patients with alcoholic fatty liver disease or other chronic viral hepatitis, those on pediatric patients, and those without LB results as a reference standard. Although NAFLD can co-exist with increased alcohol intake, we wanted to clarify that the main driver of the disease is a metabolic factor. Besides, as children and adults NAFLD have different histopathological features, studies for children should be conducted separately.

Second, this study can serve as the basis for clinical

Table 3. Summary diagnostic performance of VCTE and MRE for detecting advanced fibrosis in patients with NAFLD according to cut-off ranges

Cut-off range, kPa	Studies, n	Patients, n	AUC (95% CI)	Sensitivity (95% CI)	I^2, % (95% CI)	Specificity (95% CI)	I^2, % (95% CI)
VCTE							
7.1–7.9	6	1,895	0.90 (0.87–0.92)	0.89 (0.85–0.91)	35.9 (0.0–94.7)	0.67 (0.59–0.74)	88.8 (81.4–96.3)
8.0–9.9	33	11,862	0.87 (0.00–1.00)	0.83 (0.80–0.86)	75.0 (66.6–83.4)	0.77 (0.74–0.80)	88.9 (86.0–91.9)
10.0–11.9	13	2,195	0.87 (0.84–0.90)	0.80 (0.76–0.84)	40.1 (0.9–79.3)	0.84 (0.79–0.88)	77.1 (65.0–89.3)
12.0–14.1	6	1,256	0.79 (0.75–0.82)	0.55 (0.49–0.61)	25.7 (0.0–90.4)	0.88 (0.84–0.90)	32.5 (0.0–93.7)
MRE							
2.3–2.99	3	241	Cannot be synthesized				
3.62–3.8	5	607	0.94 (0.91–0.96)	0.88 (0.81–0.93)	0.0 (0.0–100.0)	0.91 (0.86–0.94)	64.1 (29.3–98.8)
3.9–4.8	4	439	0.93 (0.91–0.95)	0.83 (0.73–0.89)	22.2 (0.0–100.0)	0.91 (0.85–0.95)	34.3 (0.0–100.0)

VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; AUC, area under receiver operating characteristics curves; CI, confidence interval.

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guidelines for diagnosing and managing AF in patients with NAFLD through VCTE. According to the 2023 American Association for the Study of the Liver Disease practical guidance on the clinical assessment and management of NAFLD, if AF is suspected, improvement of patient prognosis by referring the patients to a high-grade institution capable of specialized treatment given by a gastroenterologist or hepatologist is recommended.[6] According to the algorithm for assessing the risk of patients with NAFLD in this guidance, LS measured by VCTE 8 kPa at a primary medical institution is recommended as a cut-off to rule out AF. The suggested cut-offs to diagnose AF in previous meta-analyses were 8.0–10.4 kPa in the study by Kwok et al.[35], 6.95–12.85 kPa in the study by Hashemi et al.[36], 6.8–12.9 kPa in the study by Selvaraj et al.[32], 9.75 kPa in the study by Cao et al.[37], and 9.68 kPa in the study by Mózes et al.[38]. Similarly, the suggestion of LS 8 kPa to rule out AF is documented in the European Association for the Study of the Liver Clinical Practice Guidelines on NITs 2021 updates.[12] In our study, diagnostic performance was highest when the cut-off for AF was set at 7.1–7.9 kPa, slightly lower value than 8 kPa. This study confirms the accuracy of VCTE for assessing each fibrosis stage in patients with NAFLD and suggests that the cut-off value of 7.1–7.9 kPa is the optimal benchmark to rule out AF. These findings are expected to serve as the basis for newly established Korean NIT guidelines 2024.

Third, our result suggested a useful cut-off for diagnosing AF using MRE in patients with NAFLD. MRE is recommended as the most accurate imaging test to diagnose liver fibrosis at higher-level institutions when patients are referred due to suspicion of AF. The pooled AUC of MRE for diagnosing AF in our study was high at 0.89 but slightly lower than those from other meta-analyses. Selvaraj et al.[32], Xiao et al.[40], Liang et al.[41], and Liang et al.[39] reported the AUC of MRE for diagnosing AF to be 0.92, 0.96, 0.92, and 0.94, respectively. The cut-off values of MRE for AF show a wide range at 2.99–4.80 kPa, 3.62–4.8 kPa, 3.53 (3.40–3.66) kPa, and 2.43–5.97 kPa in the study by Selvarai et al.[32], Xiao et al.[40], Liang et al.[41], and Liang et al.[39], respectively. Although the cut-off range of our study was also wide (2.3–4.80 kPa), we further sub-grouped the studies according to the cut-off levels and calculated the pooled AUCs for each group. Compared with studies with an AF cut-off set at 3.9–4.8 kPa, studies with an AF cut-off value of 3.62–3.8 kPa showed higher AUC at 0.94. This narrowing the AF cut-off range of MRE may be clinically helpful for clinicians to put more effort into preventing complications of cirrhosis and to perform regular HCC surveillance for patients whose cut-offs were beyond that specific point.

Lastly, detecting AF through NIT according to the suggested F3 cut-offs from this meta-analysis may provide a practical guide for primary care and tertiary hospital physicians in clinical settings. AF in patients with NAFLD is known to be an important surrogate for liver-related complications, liver-related mortality, and overall mortality.[9-11] Since NAFLD is a disease with high prevalence, primary care physicians often encounter many patients with NAFLD and consider performing liver blood tests, patients' metabolic and environmental risk factors evaluation, and history of liver disease assessments collectively. As the negative predictive value of LS assessed with VCTE is known to be high in patients with NAFLD,[12,30] patients with LS <7.1–7.9 kPa with none to minimal risk factors or history of liver disease may have a very low risk of cirrhotic complications and HCC and can be safely managed by primary physicians. At the tertiary center, hepatologists use NITs to monitor disease progression, predict future liver-related complications, and make treatment decisions. According to our results, if LS is assessed with VCTE >7.1–7.9 kPa or MRE with >3.62–3.8 kPa, there is a high probability of F3 disease being present. However, as the positive predictive value of VCTE for diagnosing AF in NAFLD is known to be higher than that in viral chronic hepatitis,[12] and the positive predictive value in this meta-analysis varied from 0.39 to 0.84, there is a chance of overestimation of the degree of liver fibrosis in patients who have been referred to tertiary hospitals with suspicion of AF. Therefore, to predict liver-related complications more accurately and perform proper treatment interventions in these patients, combinations of NITs are often considered and are under active investigation. The FibroScan-aspartate aminotransferase (AST) score combining VCTE and AST levels,[100] and the magnetic resonance imaging-AST score combining MRE and AST levels to detect AF showed AUC of 0.8 and 0.9, respectively.[101] The MRE combined with fibrosis-4 index showed an AUC of 0.90 for detecting significant fibrosis in patients with NAFLD.[102] As a lot of research is being conducted on TE- or MRE-based combination NITs, meta-analysis should be considered in the future.

There are some limitations to our study. First, the application of the diagnostic performance obtained from the LB-based patient cohort to the NAFLD population with a low prevalence of AF or cirrhosis portends generalization error. Second, as the number of enrolled studies is small for the currently proposed cut-off for MRE, further validation of the appropriate cut-off value for AF appears to be necessary. Third, we could not consider confounding factors such as sex, BMI, presence of diabetes mellitus, or probe types, which may affect diagnostic accuracy. Fourth, we did not simultaneously measure or adjust steatosis to diagnose fibrosis. Lastly, publication bias was present in assessing some liver fibrosis stages.

In summary, VCTE (7.1–7.9 kPa) and MRE (3.62–3.8 kPa) with the suggested cut-offs showed favorable accuracy for diagnosing AF in patients with NAFLD. This result will serve as a basis for clinical guidelines for NITs and will be clinically useful to rule out AF. Future studies with a combination of NITs or the addition of genetic biomarkers in NAFLD may provide more accurate data on disease progression and treatment decisions.

Authors' contribution

All authors take responsibility for the data integrity and the accuracy of the data analyses. YE Chon, Y-J Jin, HY Kim, JH Yu, and SU Kim were responsible for the conception and design of the study; YE Chon, Y-J Jin, HY Kim, M Choi, DW Jun, MN Kim, JW Han, HA Lee, JH Yu, J An, and SU Kim were responsible for the acquisition, analysis, and interpretation of data, and drafting the manuscript. M Choi performed the statistical analyses. All authors approved the final version of the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

SUPPLEMENTARY MATERIAL

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

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Supplementary Table 1. Searching strategies and subsequent results

Ovid MEDLINE

Search date: 2023. 06. 13			
	N	**Search words**	**Results**
P	1	exp Non-alcoholic Fatty Liver Disease/ OR (Non-alcoholic Fatty Liver Disease OR NAFLD OR Steatohepatitis, Nonalcoholic OR (fatty liver adj2 (non-alcoholic or nonalcoholic))).tw,kw	34,331
I	2	exp Elasticity Imaging Techniques/ OR (Fibroscan or fibrosis stating or transient elastography or TE or vibration controlled transient elastography or Tissue Elasticity or Elasticity Imaging or Sonoelastography or VCTE or magnetic resonance elastography or elastrograph* or MRE).tw,kw.	56,523
P&I	3	1 AND 2	1,871
O-Liver Cirrhosis, fibrosis	4	exp Liver Cirrhosis/ or (cirrhosis or liver fibros* or hepatic fibros* or fibros*).tw,kw.	368,551
	5	3 AND 4	1,612
SIGN Filter (Diagnostic Accuracy)	6	exp "Sensitivity and Specificity"/ OR (sensitivity OR specificity OR ((pre-test or pretest) adj probability) OR post-test probability OR predictive value* OR predictive value* OR likelihood ratio* or predict* or diagnos* or accuracy).tw,kw.	6,051,576
Total	7	5 AND 6	1,103

Embase

Search date: 2023. 06. 13			
	N	**Search words**	**Results**
P	1	'nonalcoholic fatty liver'/exp OR ('nonalcoholic fatty liver' OR NAFLD OR 'Steatohepatitis, Nonalcoholic' OR ('fatty liver' NEAR/2 (non-alcoholic or nonalcoholic))):ab,ti,kw	74,675
I	2	'elastography'/exp OR (Fibroscan or 'fibrosis stating' or 'transient elastography' or TE or 'vibration controlled transient elastography' or 'Tissue Elasticity' or 'Elasticity Imaging' or Sonoelastography or VCTE or 'magnetic resonance elastography' or elastrograph* or MRE):ab,ti,kw	90,299
P&I	3	#1 AND #2	6,005
O-Liver Cirrhosis, fibrosis	4	'liver cirrhosis'/exp or (cirrhosis or 'liver fibros*' or 'hepatic fibros*' or fibros*):ab,ti,kw	601,505
	5	#3 AND #4	5,160
SIGN Filter (Diagnostic Accuracy)	6	'sensitivity and specificity'/exp OR (sensitivity OR specificity OR ((pre-test or pretest) NEAR probability) OR 'post-test probability' OR 'predictive value*' OR 'predictive value*' OR 'likelihood ratio*' OR predict* or diagnos* or accuracy):ab,ti,kw	8,098,674
	7	#5 AND #6	3,525
Total	8	#7 AND ('article'/it OR 'article in press'/it OR 'review'/it OR 'short survey'/it)	1,577

Cochrane library

Search date: 2023. 06. 13			
	N	**Search words**	**Results**
P	1	[mh "Non-alcoholic Fatty Liver Disease"] OR ("Non-alcoholic Fatty Liver Disease" OR NAFLD OR "Steatohepatitis, Nonalcoholic" OR ("fatty liver" NEAR/2 (non-alcoholic or nonalcoholic))):ab,ti,kw	4,103
I	2	[mh "Elasticity Imaging Techniques"] OR (Fibroscan or "fibrosis stating" or "transient elastography" or TE or "vibration controlled transient elastography" or "Tissue Elasticity" or "Elasticity Imaging" or Sonoelastography or VCTE or "magnetic resonance elastography" or elastrograph* or MRE):ab,ti,kw	6,228
P&I	3	#1 AND #2	462

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Supplementary Table 1. Continued

Search date: 2023. 06. 13			
	N	**Search words**	**Results**
O-Liver Cirrhosis, fibrosis	4	[mh "Liver Cirrhosis, Biliary"] or (cirrhosis or "liver fibros*" or fibrosing):ab,ti,kw	12,040
Total	5	#3 AND #4	111

KoreaMed

Search date: 2023. 06. 13			
	N	**Search words**	**Results**
P	1	("Non-alcoholic Fatty Liver Disease"[MH]) OR ("Non-alcoholic Fatty Liver Disease"[ALL] OR "NAFLD"[ALL] OR "Steatohepatitis, Nonalcoholic"[ALL] OR ("fatty liver"[ALL] AND ("non-alcoholic"[ALL] or "nonalcoholic"[ALL])))	656
I	2	("Elasticity Imaging Techniques"[MH]) OR ("Fibroscan"[ALL] or "fibrosis stating"[ALL] or "transient elastography"[ALL] or "TE"[ALL] or "vibration controlled transient elastography"[ALL] or "Tissue Elasticity"[ALL] or "Elasticity Imaging"[ALL] or "Sonoelastography"[ALL] or "VCTE"[ALL] or "magnetic resonance elastography"[ALL] or "elastrography"[ALL] or "MRE"[ALL])	912
P&I	3	1 AND 2	38
O-Liver Cirrhosis, fibrosis	4	("Liver Cirrhosis"[MH]) OR ("cirrhosis"[ALL] or "liver fibrosis"[ALL] or "fibrosing"[ALL])	2,790
Total	5	3 AND 4	24

Supplementary Table 2. Characteristics of the studies used for diagnosing advanced fibrosis cut-offs

Author	Year	Region	Cut-off for advanced fibrosis, kPa	Study design	Patients, n	Age, years	Male, %	BMI, kg/m^2	Diabetes mellitus, %
VCTE									
Argalia et al.[44]	2022	Italy	8.8	CS, SS	50	52.2	64	29.4	NR
Barsamian et al.[45]	2020	France	8.7	CS, SS	108	41	21	43	24
Chan et al.[15]	2015	Malaysia	8.0	CS, SS	101	50.5	54.4	29.3	52.4
Chan et al.[46]	2017	Malaysia, Hongkong	11.5	CS, SS	57	50.1	49	39.2	NR
Gaia et al.[17]	2011	Italy	8.0	CS, SS	72	48	72.2	27.5	NR
Imajo et al.[48]	2022	Japan	9.7	CS, SS	231	61	52.7	27.1	61.7
Kim et al.[49]	2022	Korea	11.9	CS, SS	60	50.9	45.9	29.9	61.7
Kumar et al.[19]	2013	India	9.0	CS, SS	120	39.1	75	26.1	16.6
Lee et al.[50]	2016	Korea	9.0	CS, SS	183	40.6	60.7	27.9	14.2
Leong et al.[51]	2020	Malaysia	9.0	CS, SS	100	57.1	46	30.8	NR
Lupşor et al.[21]	2010	Netherlands	9.28	CS, SS	72	42	70.8	28.7	NR
Okajima et al.[52]	2017	Japan	10.0	CS, SS	163	55.8	48.5	27.2	NR
Park et al.[26]	2017	US	7.3	CS, SS	104	50.8	43.3	30.4	27.9
Sharpton et al.[53]	2021	US	8.7	CS, SS	114	55	45.6	31.2	NR
Shi et al.[54]	2020	China	10.8	CS, SS	158	48.9	30.4	25.9	26.6
Shima et al.[55]	2020	Japan	9.9	CS, SS	278	57.8	48.2	27.5	58.6
Siddiqui et al.[56]	2019	US	8.6	CS, SS	393	51	32	34.4	44
Yang et al.[57]	2021	China	8.3	CS, SS	91	40	50.5	29.1	71.4
Yoneda et al.[58]	2008	Japan	9.8	CS, SS	97	51.8	41.2	26.6	NR
Cassinotto et al.[61]	2016	France	8.2	CS, MS	291	56.7	59.1	32.1	52.6
Cassinotto et al.[61]	2016	France	12.5	CS, MS	291	56.7	59.1	32.1	52.6
Chang et al.[62]	2023	US	9.7	CS, MS	1,370	56.6	44.5	34.2	38.0
Eddowes et al.[64]	2019	UK	14.1	CS, MS	373	54	55	33.8	50
Eddowes et al.[64]	2019	UK	7.1	CS, MS	373	54	55	33.8	50
Eddowes et al.[64]	2019	UK	9.7	CS, MS	373	54	55	33.8	50
Eilenberg et al.[65]	2021	Austria	12.6	CS, SS	170	42	35.4	44.4	28.2
Ergelen et al.[66]	2015	Turkey	9.9	CS, SS	87	45.8	49.4	30.6	NR
Garg et al.[18]	2018	India	12.45	CS, SS	76	39.3	23.3	46.2	NR
Inadomi et al.[67]	2020	Japan	11.45	CS, SS	200	59.5	48	28.1	50.3
Jafarov et al.[68]	2020	Turkey	11.0	CS, SS	139	49	59	32.9	64
Lee et al. [23]	2022	Korea	8.3	CS, SS	539	56	47.5	26.9	36.2
Lee et al.[70]	2022	Korea	9.8	CS, SS	251	44	52.6	28.6	46.6
Lee et al.[20]	2017	Korea	8.0	CS, SS	94	55.5	43.6	27.1	39.4
Mendoza et al.[71]	2022	Switzerland	9.7	CS, SS	104	53.4	58.7	30.9	47.1
Myers et al.[72]	2010	Canada	10.3	CS, MS	20	NR	NR	NR	NR
Naveau et al.[24]	2014	France	7.6	CS, SS	100	42.5	19	41.3	15
Nogami et al.[74]	2022	Japan	10.0	CS, SS	163	59.7	52.8	28.5	61.3
Oeda et al.[25]	2020	Japan	10.8	CS, MS	137	NR	NR	NR	NR
Petta et al.[27]	2011	Italy	8.75	CS, SS	146	44.1	71	29.1	14

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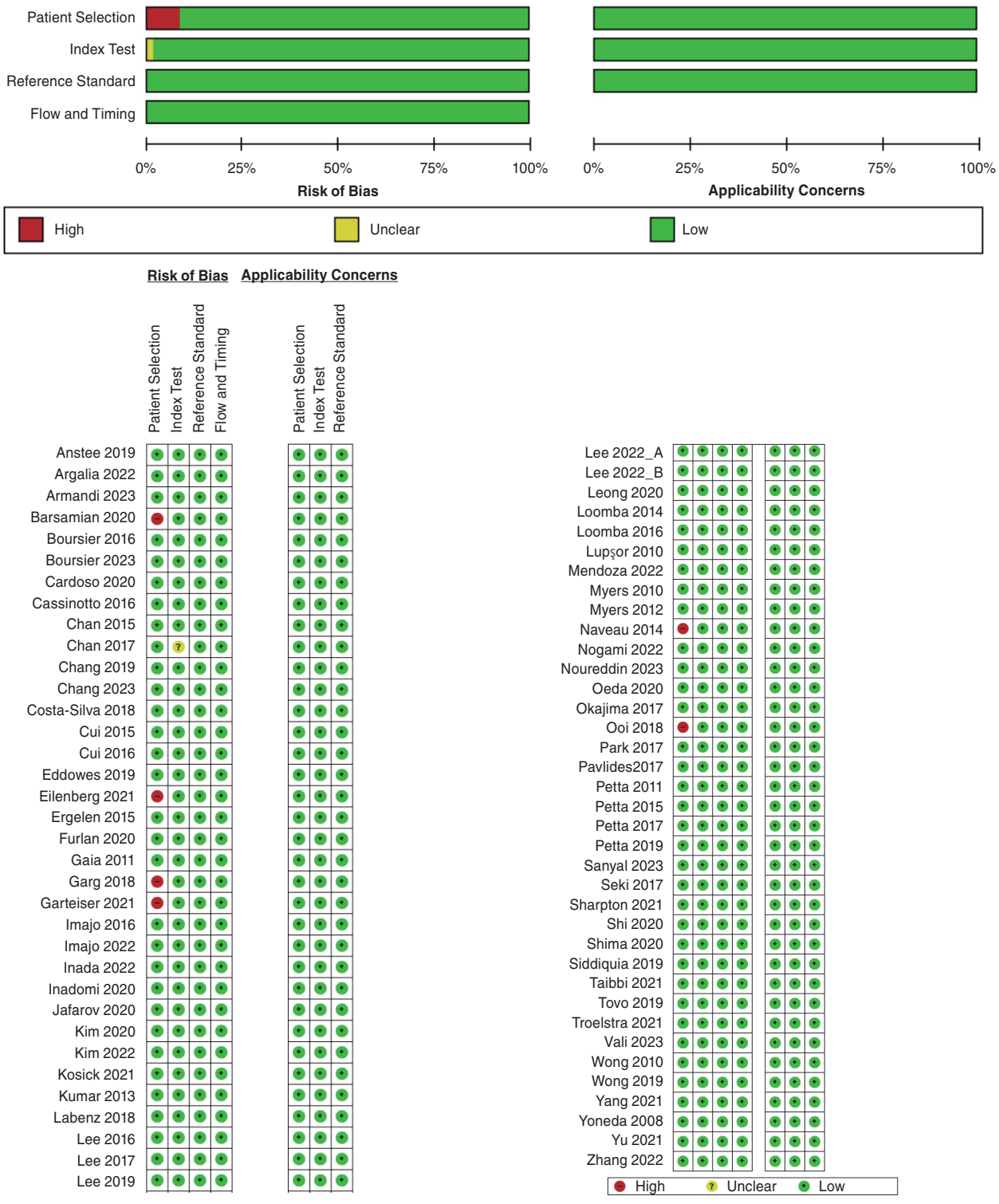
Supplementary Table 2. Continued

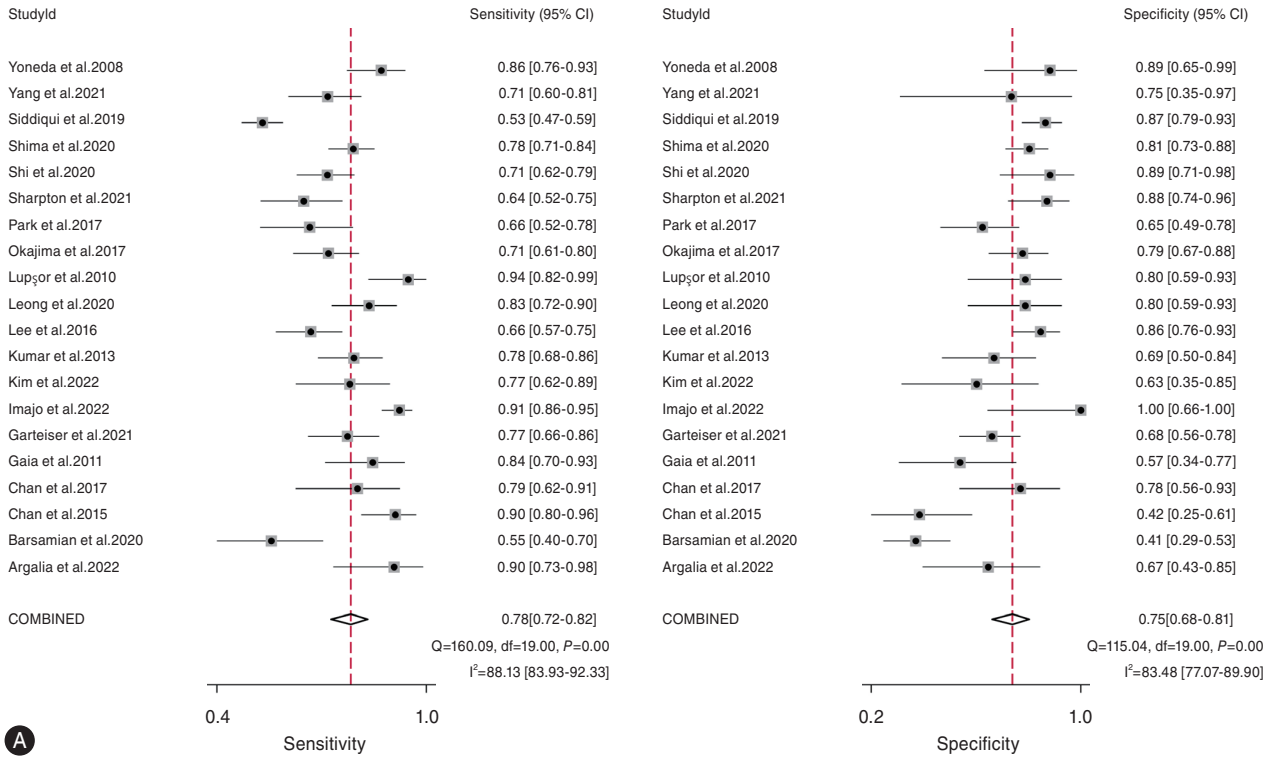
Author	Year	Region	Cut-off for advanced fibrosis, kPa	Study design	Patients, n	Age, years	Male, %	BMI, kg/m^2	Diabetes mellitus, %
Taibbi et al.[76]	2021	Italy	8.5	CS, SS	56	54.7	58.7	29.4	39.1
Wong et al.[78]	2019	France, Hongkong	10.0	CS, MS	496	54	42.7	30.4	60.5
Wong et al.[78]	2019	France, Hongkong	10.0	CS, MS	496	54	42.7	30.4	60.5
Wong et al.[30]	2010	France, Hongkong	7.9	CS, MS	246	51	54.9	28	36.2
Yu et al.[79]	2021	China	13.8	CS, SS	85	58	40	29.7	100
Petta et al.[28]	2019	Global	7.9	CS, MS	968	50.1	62.9	29.3	37
Petta et al.[28]	2019	Global	9.6	CS, MS	968	50.1	62.9	29.3	37
Tovo et al.[80]	2019	Brazil	7.9	CS, MS	104	55.3	26	33	64.4
Kosick et al.[81]	2021	Canada	8.4	CS, MS	407	48.5	54	32.3	30
Boursier et al.[14]	2016	France	8.7	CS, MS	452	55.9	60	31.1	46.7
Sanyal et al.[82]	2023	Global	9.2	CS, MS	1434	55	50.8	31.7	50.4
Armandi et al.[83]	2023	Turkey	9.4	LS, SS	96	49.5	62.2	28.4	30.6
Noureddin et al.[84]	2023	US	9.6	CS, MS	548	58	35	33.3	53
Petta et al.[85]	2017	Global	9.6	CS, MS	761	50.9	60.2	29.6	54.7
Petta et al.[86]	2015	Italy	9.6	CS, MS	321	44.7	69.5	28.5	17.8
Anstee et al.[13]	2019	US	9.9	CS, MS	3,202	58	38	NR	60
Troelstra et al.[87]	2021	Netherlands	9.9	CS, SS	37	49	62	33.2	43
Seki et al.[88]	2017	Japan	10.0	CS, SS	171	57.1	50.3	27.7	NR
Labenz et al.[89]	2018	Germany	12.0	CS, MS	261	51	52.5	30.9	29.9
MRE									
Costa-Silva et al.[91]	2018	Brazil	4.39	CS, SS	49	53.8	14.3	32.2	NR
Cui et al.[92]	2016	US	3.62	CS, SS	125	48.9	45.6	31.8	26
Imajo et al.[93]	2016	Japan	4.8	CS, SS	142	57.5	57	28.1	71
Imajo et al.[48]	2022	Japan	3.9	CS, SS	231	61	52.7	27.1	61.7
Kim et al.[94]	2020	Korea	4.34	CS, SS	47	51	34	28.3	NR
Loomba et al.[95]	2014	US	3.64	CS, SS	117	50.1	43.6	32.4	34.2
Park et al.[26]	2017	US	2.99	CS, SS	104	50.8	43.3	30.4	27.9
Zhang et al.[96]	2022	US	2.77	CS, SS	100	51.8	46	31.6	NR
Nogami et al.[74]	2022	Japan	3.78	CS, SS	163	55.8	48.5	27.2	NR
Troelstra et al.[87]	2021	Netherlands	2.3	CS, SS	37	49	62	33.2	43
Cui et al.[98]	2015	US	3.64	CS, SS	102	51.3	58.8	31.7	25.5
Loomba et al.[99]	2016	US	3.8	CS, SS	100	50.2	44	32.1	33

VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography; CS, cross-sectional study; LS, longitudinal study; SS, single center study; MS, multicenter study; BMI, body mass index; NR, not recorded.

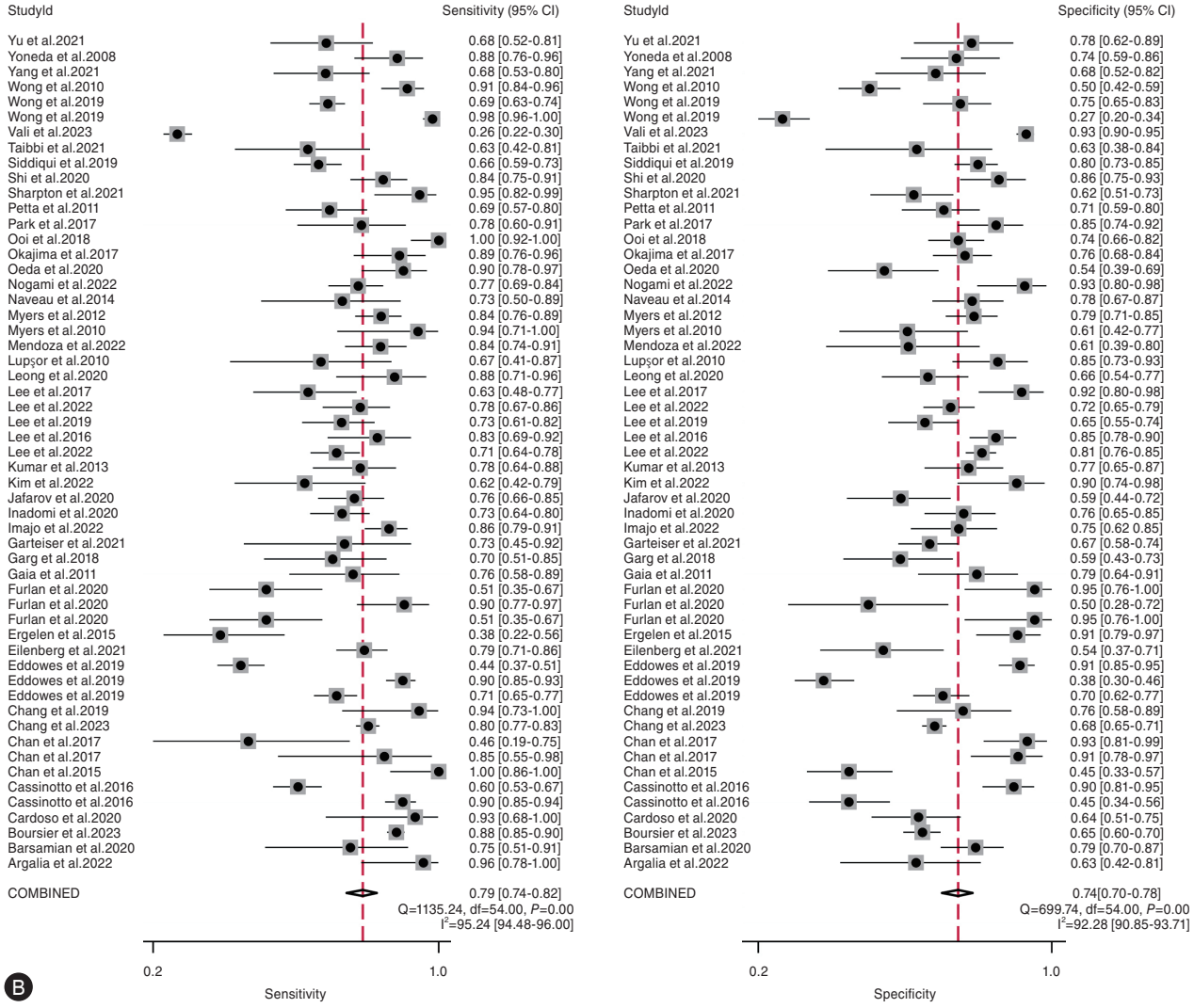


Supplementary Figure 1. Summary of quality and risk of bias assessment.

 https://doi.org/10.3350/cmh.2024.0392

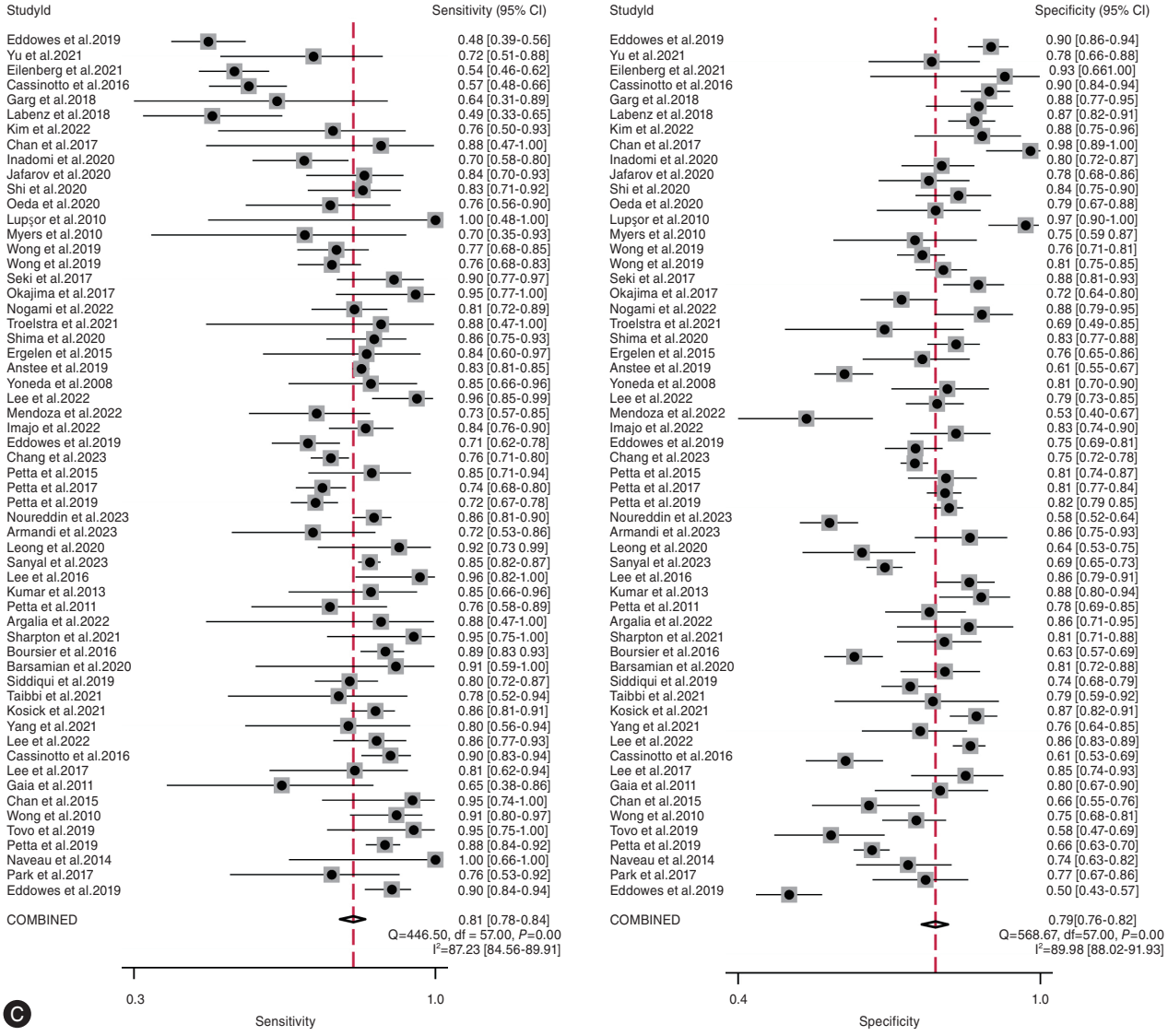


Supplementary Figure 2. Forrest plots of VCTE for assessing fibrosis stages (A) ≥F1, (B) ≥F2, (C) ≥F3, and (D) F4. VCTE, vibration-controlled transient elastography.



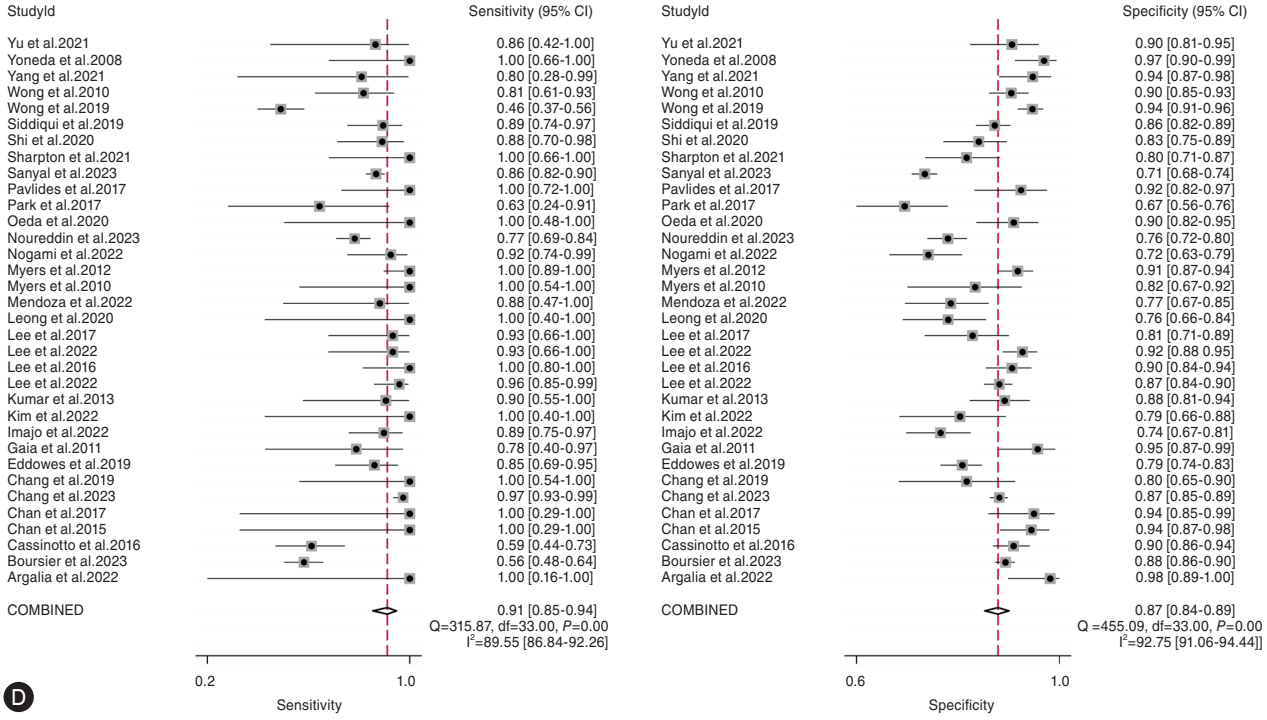
Supplementary Figure 2. Continued.

 https://doi.org/10.3350/cmh.2024.0392

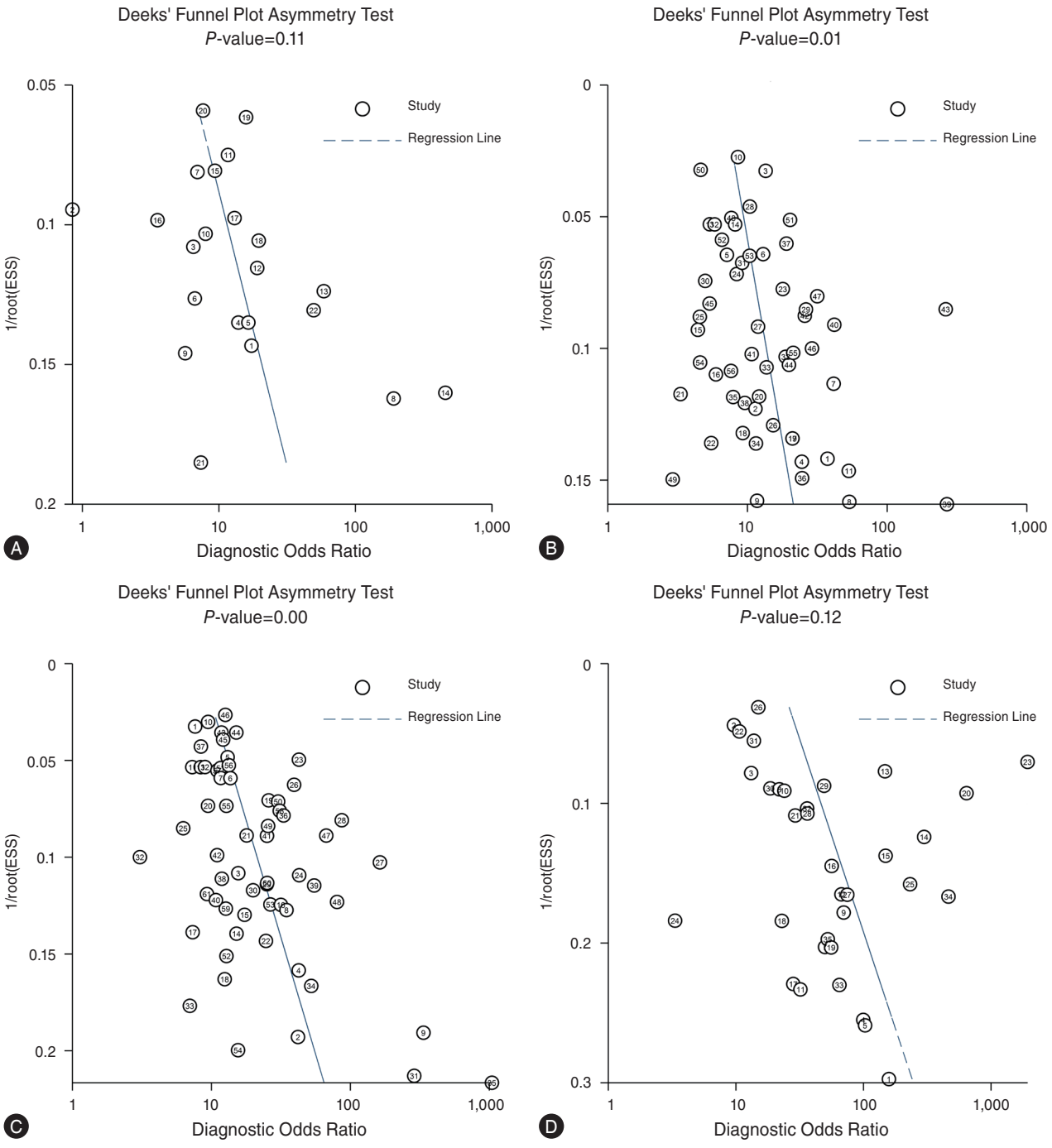


C

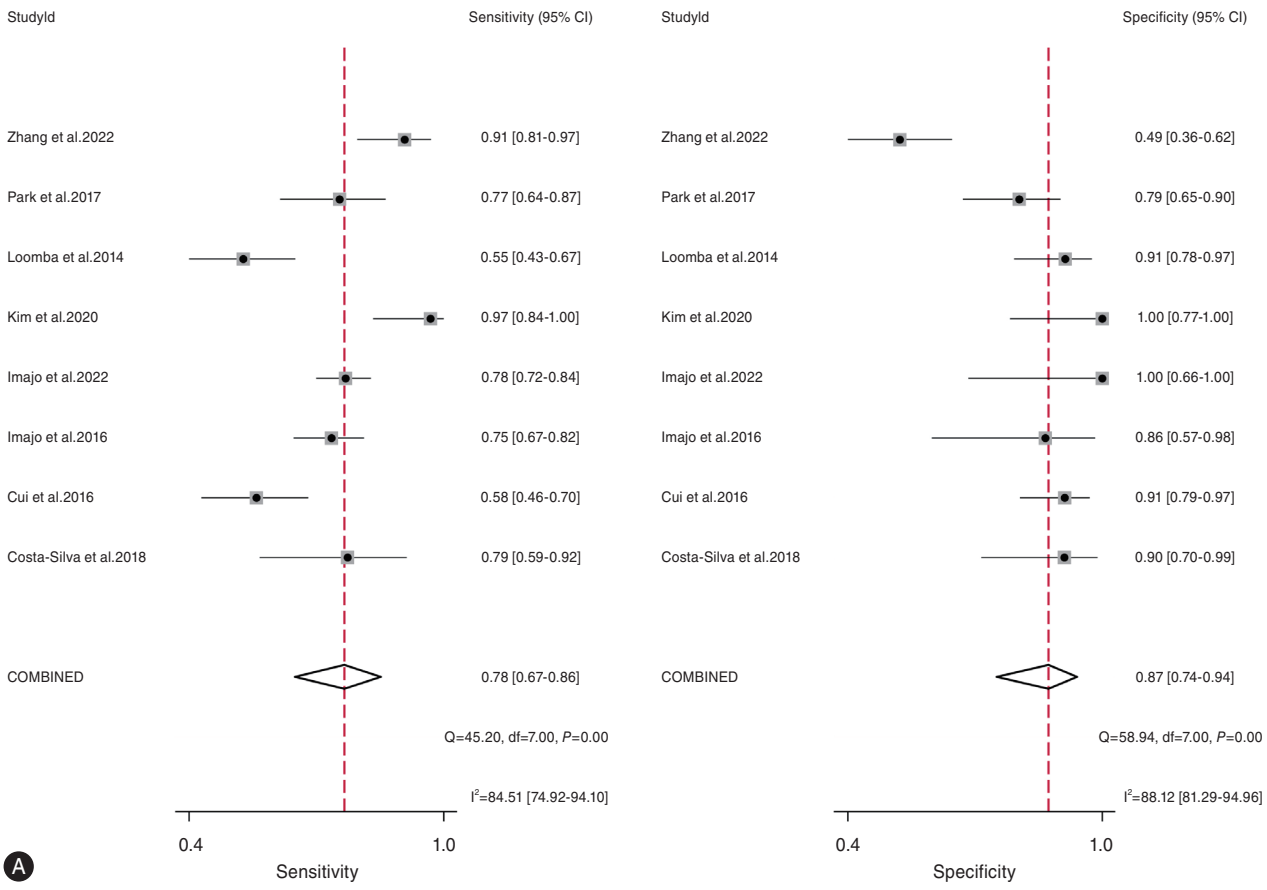
Supplementary Figure 2. Continued.



Supplementary Figure 2. Continued.

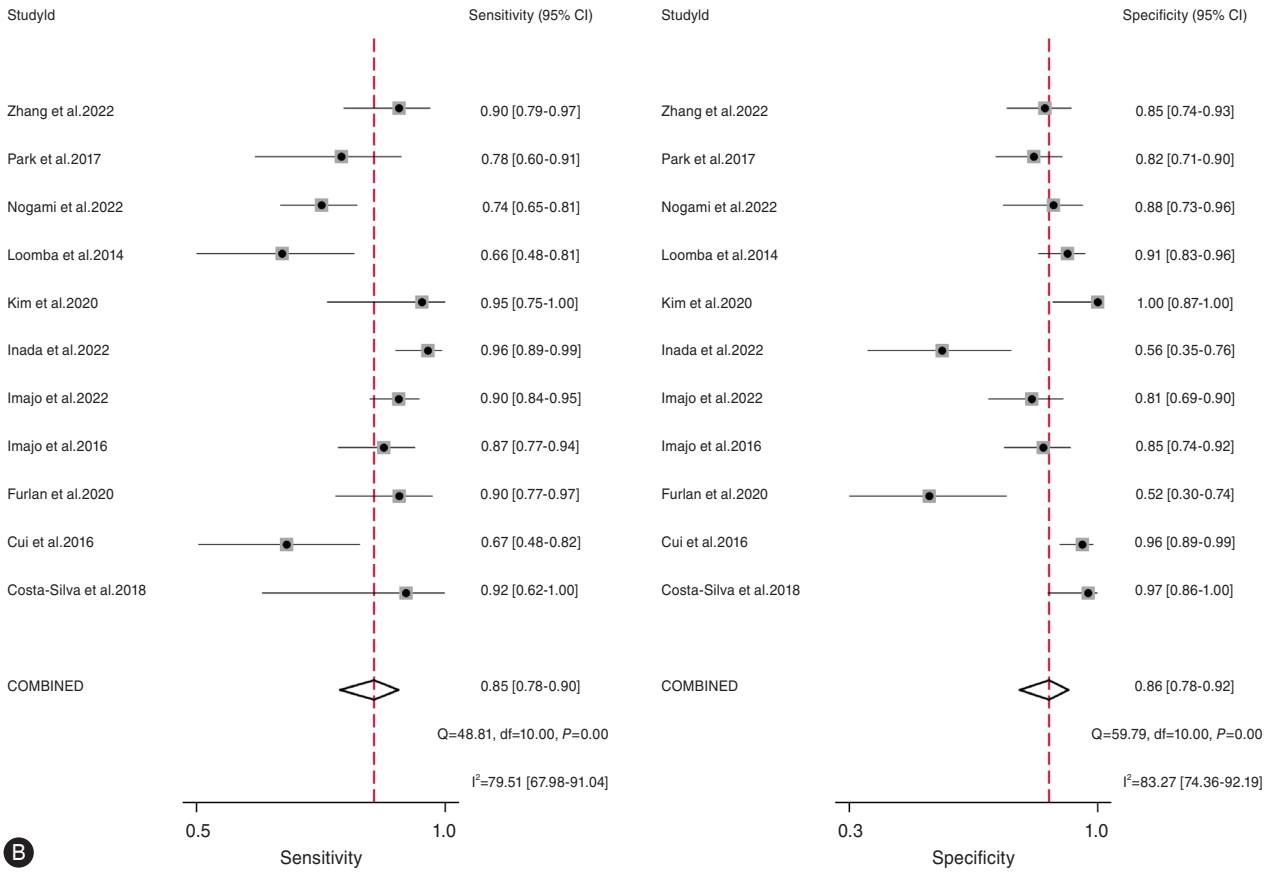


Supplementary Figure 3. Funnel plots of VCTE for assessing fibrosis stages (A) ≥F1, (B) ≥F2, (C) ≥F3, and (D) F4. VCTE, vibration-controlled transient elastography.



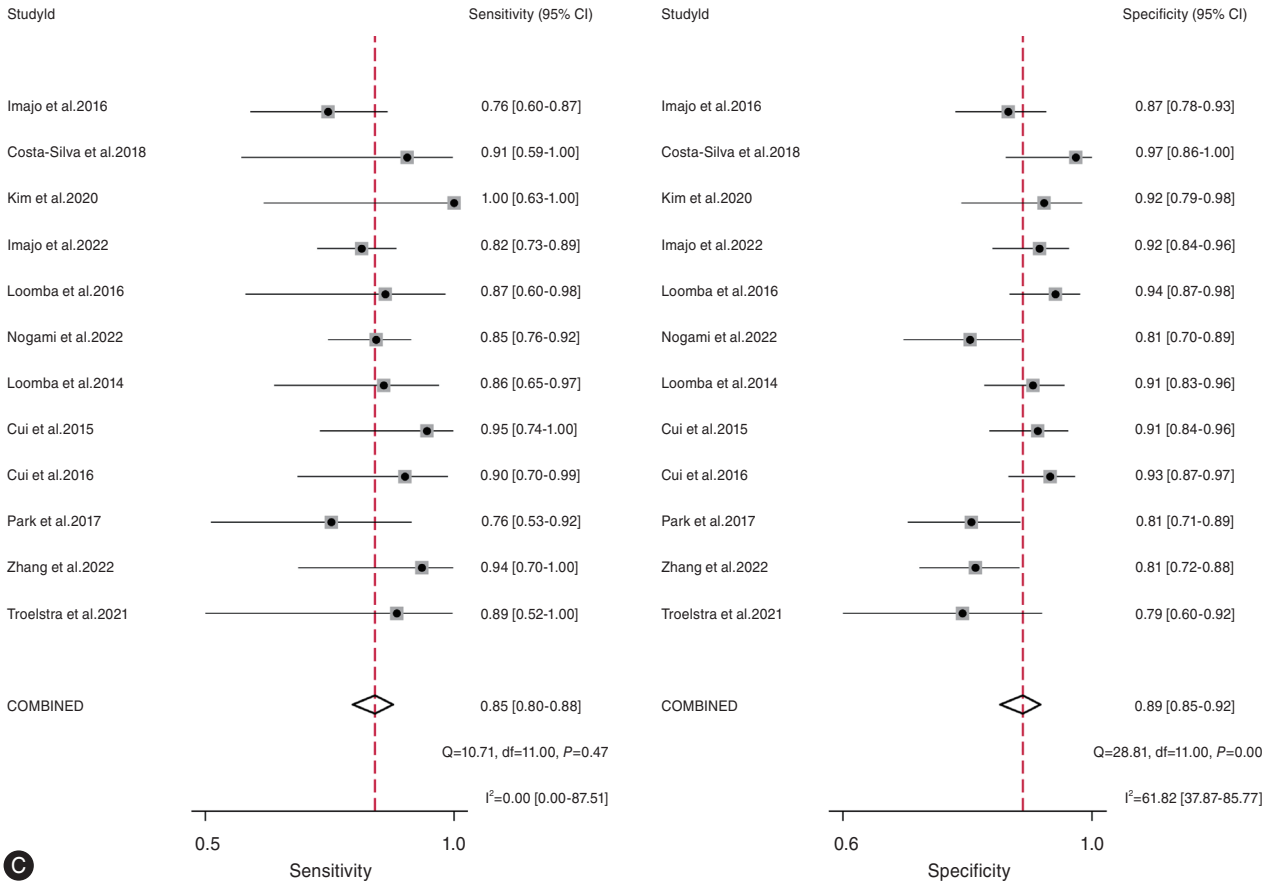
Supplementary Figure 4. Forrest plots of MRE for assessing fibrosis stages (A) ≥F1, (B) ≥F2, (C) ≥F3, and (D) F4. MRE, magnetic resonance elastography.

 https://doi.org/10.3350/cmh.2024.0392



B

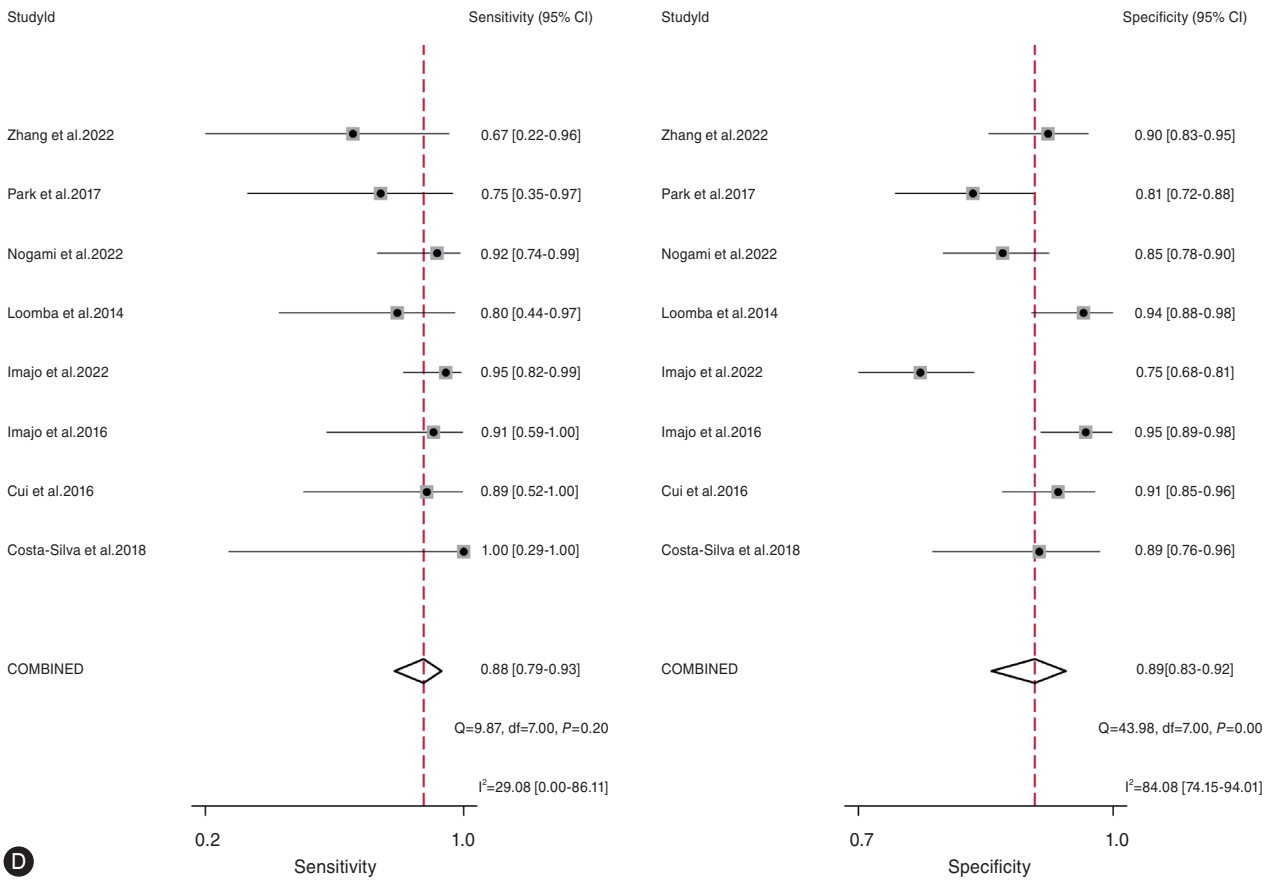
Supplementary Figure 4. Continued.



C

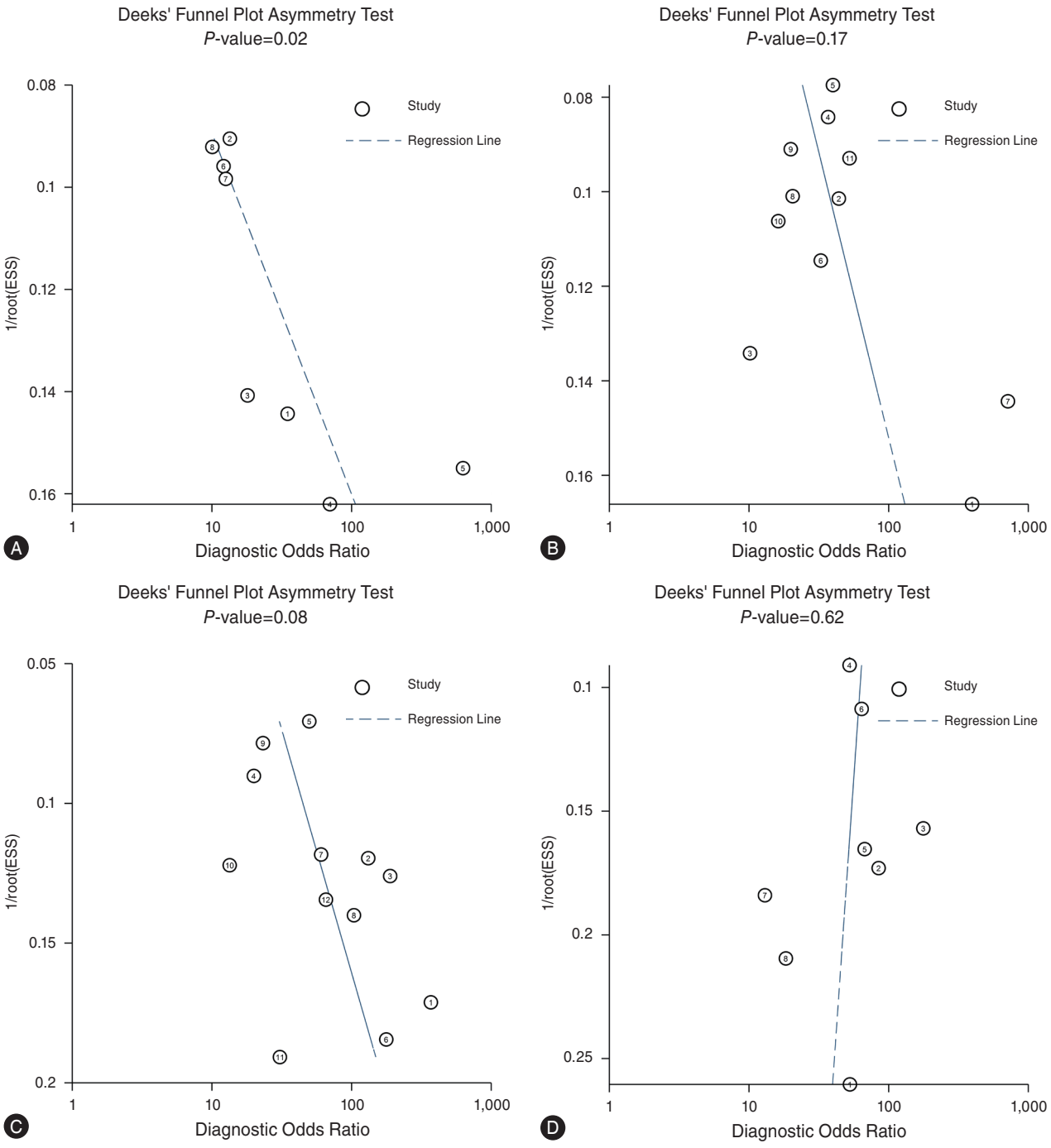
Supplementary Figure 4. Continued.

 https://doi.org/10.3350/cmh.2024.0392



D

Supplementary Figure 4. Continued.



Supplementary Figure 5. Funnel plots of MRE for assessing fibrosis stages (A) ≥F1, (B) ≥F2, (C) ≥F3, and (D) F4. MRE, magnetic resonance elastography.

 https://doi.org/10.3350/cmh.2024.0392