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Original Article

Diagnostic accuracy of vibration-controlled transient elastography for staging liver fibrosis in autoimmune liver diseases: A systematic review and meta-analysis

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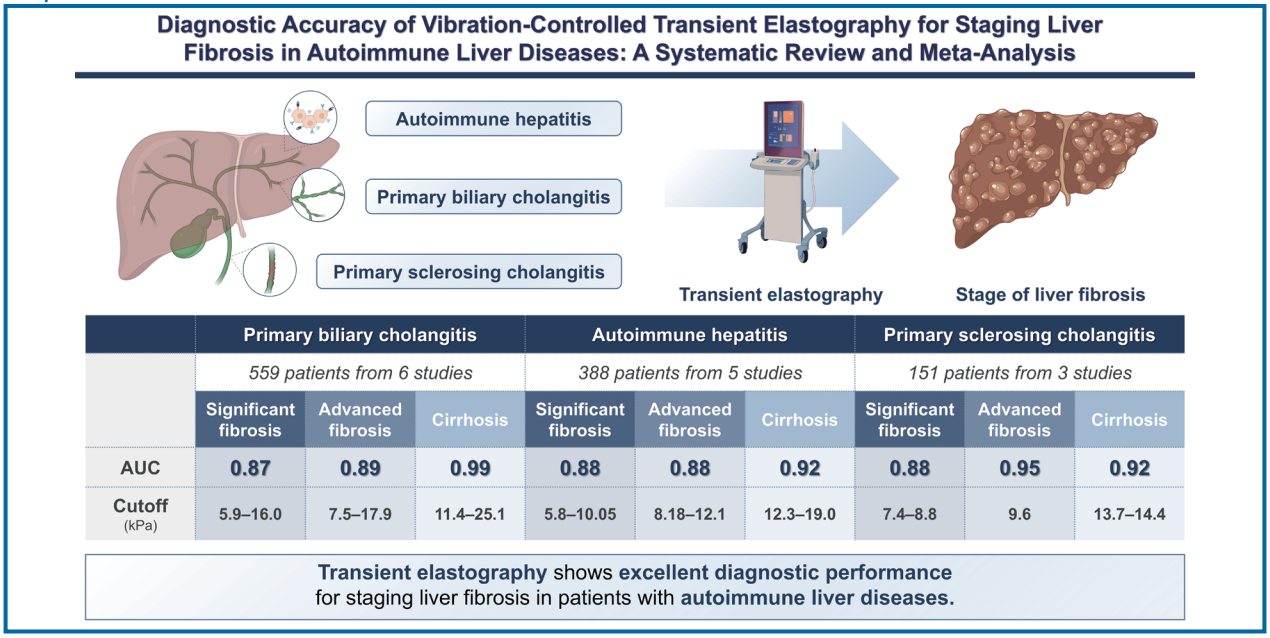
Graphical Abstract



	Primary biliary cholangitis			Autoimmune hepatitis			Primary sclerosing cholangitis		
	559 patients from 6 studies			*388 patients from 5 studies*			*151 patients from 3 studies*		
	Significant fibrosis	Advanced fibrosis	Cirrhosis	Significant fibrosis	Advanced fibrosis	Cirrhosis	Significant fibrosis	Advanced fibrosis	Cirrhosis
AUC	0.87	0.89	0.99	0.88	0.88	0.92	0.88	0.95	0.92
Cutoff (kPa)	5.9–16.0	7.5–17.9	11.4–25.1	5.8–10.05	8.18–12.1	12.3–19.0	7.4–8.8	9.6	13.7–14.4

Transient elastography shows **excellent diagnostic performance** for staging liver fibrosis in patients with **autoimmune liver diseases.**

Study Highlights

- This systematic review and meta-analysis evaluated the diagnostic performance of VCTE for staging fibrosis in patients with autoimmune liver diseases.
- The study demonstrated excellent diagnostic accuracy of transient elastography, with summary AUC values exceeding 0.85 across all degrees of fibrosis in patients with primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis.
- VCTE is a simple and reliable tool for evaluating and monitoring fibrosis associated with autoimmune liver diseases.

Background/Aims: The assessment of liver fibrosis is crucial for managing autoimmune liver diseases such as primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis (PSC). However, data on the efficacy of noninvasive tests for these diseases are limited. This meta-analysis evaluated the diagnostic accuracy of vibration-controlled transient elastography (VCTE) for staging fibrosis in patients with autoimmune liver disease.

Methods: Searches were conducted in PubMed, Embase, CINAHL, Web of Science, and Cochrane Library databases to assess the diagnostic accuracy of VCTE against histology as the reference standard in adult patients with autoimmune liver disease. The summary area under the curve (sAUC) and diagnostic odds ratio were calculated for significant fibrosis (SF), advanced fibrosis (AF), and cirrhosis, according to liver biopsy.

Results: Fourteen articles were included, comprising 559 PBC patients from six studies, 388 AIH patients from five studies, and 151 PSC patients from three studies. VCTE demonstrated good performance for fibrosis staging in PBC, AIH, and PSC. In PBC, sAUCs of VCTE were 0.87, 0.89, and 0.99 for staging SF, AF, and cirrhosis, respectively. In AIH, the sAUCs were 0.88, 0.88, and 0.92, respectively, while in PSC, they were 0.88, 0.95, and 0.92, respectively. The cutoff values for AF were 7.5–17.9 kPa in PBC, 8.18–12.1 kPa in AIH, and 9.6 kPa in PSC.

Conclusions: VCTE shows high diagnostic accuracy for staging liver fibrosis in patients with autoimmune liver diseases. This non-invasive method serves as a valuable tool for the evaluation and monitoring of fibrosis in these lifelong diseases. **(Clin Mol Hepatol 2024;30(Suppl):S134-S146)**

Keywords: Liver fibrosis; Transient elastography; Autoimmune disease; Noninvasive test

INTRODUCTION

Primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis (PSC) are the three major forms of autoimmune liver disease, which differ according to their histopathological features and clinical phenotypes.[1-3] PBC involves non-suppurative, destructive cholangitis of the small interlobular bile ducts, AIH is characterized by interface hepatitis with a direct immune attack on hepatocytes, and PSC is marked by obliterative fibrosis and stricturing of the medium-sized intra- and extrahepatic bile ducts. Reports indicate meaningful changes in disease epidemiology, with an increasing incidence and prevalence of AIH and PSC in Europe and a rising prevalence of PBC across Europe, North America, and the Asia-Pacific region.[4-7] All three disorders have a progressive course with

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Abbreviations:

AIH, autoimmune hepatitis; ALT, alanine transaminase; AUC, area under the curve; LSM, liver stiffness measurement; METAVIR, Meta-analysis of Histological Data in Viral Hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; sAUC, summary AUC; sROC, summary receiver operating characteristic; VCTE, vibration-controlled transient elastography

fibrosis that, if untreated, develops into cirrhosis and liver failure requiring liver transplantation.

The evaluation of liver fibrosis is fundamental in managing autoimmune liver diseases and serves both diagnostic and prognostic purposes. An accurate assessment of fibrosis stages helps determine the severity and extent of the disease, which is crucial for deciding on treatment strategies and predicting disease progression.[8-11] Monitoring changes in liver fibrosis during treatment is essential, and a decrease in fibrosis can indicate effective therapeutic intervention, while progression may signal a need for treatment modification. Therefore, a regular and precise assessment of liver fibrosis is imperative to optimize patient outcomes in autoimmune liver diseases.

Liver biopsy has long been considered the gold standard for assessing liver fibrosis in autoimmune liver diseases.[12] However, this method has notable limitations, including its invasive nature, risk of complications such as bleeding and pain, and potential sampling errors due to the heterogeneous distribution of fibrosis.[12-14] In response, noninvasive tests, especially vibration-controlled transient elastography (VCTE), have gained prominence as safer alternatives that can be repeated regularly to monitor the degree of liver fibrosis. However, the current literature evaluating the role of VCTE in autoimmune liver diseases reveals inconsistencies and limitations.[15,16] Most studies included a small number of patients and presented a diverse range of cutoff values for diagnostic thresholds. Additionally, some studies have suggested that the reliability of these tests may vary based on treatment duration or patient condition.

These gaps underscore the need for comprehensive evaluations. Our study aims to systematically review and analyze the performance of transient elastography in this context. This approach will help clarify the role of noninvasive tests in the management of autoimmune liver diseases, potentially leading to improved diagnostic and monitoring strategies.

MATERIALS AND METHODS

This study adhered to the standard guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension Statement on Diagnostic Test Accuracy (PRISMA-DTA). The protocol for this systematic review is available at PROSPERO: CRD42024568147.

Eligibility criteria

Any study types that reported diagnostic performance of VCTE for staging liver fibrosis on patients with PBC, AIH, or PSC were eligible for inclusion in this meta-analysis. Studies that directly reported true-positive, false-positive, false-negative, and true-negative values, or reported data via which these values could be calculated to construct a 2×2 table for each test were included. Only full-text articles published in English in peer-reviewed journals were included. Duplicates, letters, conference proceedings, and meeting abstracts were excluded.

Exclusion criteria

Studies were excluded if they met the following criteria: (i) included patients with overlap syndrome; (ii) did not specify disease types within autoimmune liver diseases; and (iii) lacked sufficient data to calculate predictive performance measures.

Index test and reference standard

The primary index test was VCTE, performed using FibroScan (Echosens, Paris, France). Liver biopsy served as the reference standard for staging liver fibrosis according to the Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) scoring system or other pathological scoring systems that are convertible to the METAVIR score. The diagnostic accuracy of the index tests was assessed across the following dichotomized groups: F0-1 vs. F2-4, F0-2 vs. F3-4, and F0-3 vs. F4. Significant fibrosis, advanced fibrosis, and cirrhosis were defined as stages F ≥2, F ≥3, and F4, respectively, based on liver biopsy scoring systems.

Search strategy and selection criteria

An experienced medical librarian conducted a systematic literature search of all publications in PubMed, EMBASE, Cochrane Library, CINAHL, and Web of Science from the inception of each database up to May 24, 2023. Reference lists of related systematic reviews and the included studies were manually searched to identify additional studies. A

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detailed search strategy and query terms are presented in Supplementary Table 1.

The search results were imported into an online platform for systematic review management (Covidence, www.covidence.org), and duplicates were automatically removed. At least two researchers (JA, YEC, and GK) independently screened all titles and abstracts identified during the searches. Full manuscripts of potentially relevant studies, as selected by each reviewer, were scrutinized using predefined criteria. Any discrepancies were resolved through discussion and consensus, or with the involvement of an additional reviewer.

Data extraction

We extracted the study information, including the author, publication year, sample size, study period, country of study, and study design. For the index test and reference standard, we recorded the biopsy system classification, patients per fibrosis stage, the time interval between liver biopsy and the index test, and the performance of the index test (sensitivity, specificity, positive predictive value, negative predictive value, area under the receiver operating curve, and cutoff values). The data necessary for calculating the true positives, false positives, true negatives, and false negatives were extracted. In cases where this information was not explicitly provided in the study, values were computed based on the reported diagnostic test sensitivity, specificity, and prevalence.

Additional summary data such as participant characteristics (age, sex, diagnostic criteria for autoimmune liver diseases, baseline alanine transaminase [ALT] level, body mass index, and treatment status) were also extracted. All the data are publicly available or computable from individual studies. A summary of the included studies is presented in Table 1 and Supplementary Table 2.

Quality assessment

The risk of bias in the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, which encompasses four domains: patient selection, index test, reference standard, and flow and timing.[15] Two investigators (JA and GK) independently assessed the risk of bias for the included studies and performed evaluations in duplicate. Any discrepancies were resolved through discussion and consensus with additional investigators.

Data synthesis and statistical analysis

True-positive, true-negative, false-positive, and false-negative values for significant fibrosis, advanced fibrosis, and cirrhosis were calculated based on the sensitivity, specificity, and sample size of patients in each original study. Summary area under the curve (sAUC), sensitivity, and specificity with 95% confidence intervals (CI) were calculated as the effect measures. For index tests for staging liver fibrosis with a sufficient number of original studies, hierarchical models, including the hierarchical summary receiver operating characteristic model and the bivariate model, were used to evaluate diagnostic accuracy, considering the correlation between sensitivity and specificity.

The I^2 statistic was calculated to assess the heterogeneity of the diagnostic accuracy of each noninvasive method by measuring the proportion of the overall variation attributable to between-study heterogeneity. The Cochrane Q test was used to statistically evaluate heterogeneity. An I^2 value >50% or a *P*-value <0.05 was considered to represent substantial heterogeneity.

All analyses were conducted using R version 4.3.1, with R packages including meta, metafor, and mada, Review Manager (RevMan) Version 5.3, and MedCalc Statistical Software version 22.03.

RESULTS

Study selection and characteristics

Figure 1 shows a flowchart of the study selection process. From 3,619 articles initially identified and imported into Covidence from electronic database searches, 2,042 article titles and abstracts of potentially relevant studies were screened after removing duplicates. Of these, 80 met the eligibility criteria for the full-text assessment. We examined the references in the relevant systematic reviews but identified no new records because all references were already included in our database search results. Of the 80 studies, 66 were excluded based on the exclusion criteria.

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

Disease	Author (year)	Region	Study period	Study design	Sample size	Mean age (years)	Female (%)	Mean ALT (IU/L)	Mean BMI (kg/m^2)	Treatment status	Scoring system	Interval
PBC	Gómez-Dominguez et al.[19] (2008)	Spain	NA	Prospective	55	54	80.0	NA	NA	Post-treatment	Metavir	Within 9 months
	Floreani et al.[18] (2011)	Italy	2009	NA	120	58.0	93.0	44.0	24.0	NA	Metavir	Within 6 months
	Corpechot et al.[17] (2012)	France	2004–2010	Prospective	103	56.0	84.5	76	23.9	Post-treatment	Metavir	Within 9 months
	Koizumi et al.[20] (2017)	Japan	2012–2015	Prospective	44	60.5	93.2	65.9	NA	Post-treatment	Metavir	Within 1 weeks
	Milovanović et al.[21] (2018)	Serbia	2009–2011	Prospective	122	57.4	NA	50.8	NA	Post-treatment	Metavir	Within 1 months
	Osman et al.[22] (2021)	USA	2007–2019	Retrospective	63	60.95	NA	31.2	NA	NA	Batts-Ludwig	Within 1 year
AIH	Hartl et al.[25] (2016)	Germany	2007–2010	Prospective	34	53.0	82.0	48.5	NA	Post-treatment	Desmet & Scheuer	Within 3 months
	Hartl et al.[25] (2016)	Germany	2008–2015	Retrospective	60	52.0	82.0	35.0	NA	Post-treatment	Desmet & Scheuer	Within 4 months
	Anastasiou et al.[23] (2016)	Germany	2008–2013	Retrospective	53	47.3	58.5	606.4	NA	Pre-treatment: 35 Post-treatment: 18	Metavir	4 (2–17) days
	Xu et al.[27] (2017)	China	2014-2016	Prospective	100	45.0	81.0	131.5	NA	Pre-treatment	Metavir	Same day
	Guo et al.[24] (2017)	China	2012–2017	Retrospective	108	46.5	81.5	146.5	23.52	NA	Metavir	3 days
	Paranaguá-Vezozzo et al.[26] (2023)	Brazil	2012–2015	Prospective	33	37.9	84.8	NA	28.6	Post-treatment	Metavir	Same day
PSC	Corpechot et al.[28] (2014)	France	2005–2010	Prospective	66	40.7	40.7	145.7	NA	Post-treatment	Metavir	Within 4 months
	Krawczyk et al.[30] (2017)	Poland	2014–2016	Prospective	30	33	40.0	50.0	NA	NA	Metavir	NA
	Ehlken et al.[29] (2019)	Germany	2006–2014	Retrospective	62	38	40.0	38.0	NA	NA	Scheuer	NA

ALT, alanine aminotransferase; BMI, body mass index; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; NA, not assessed.

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Finally, 14 articles were included in the meta-analysis, comprising the following diseases: PBC (559 patients in 6 studies),[17-22] AIH (388 patients in 5 studies),[23-27] and PSC (151 patients in 3 studies).[28-30]

The characteristics of the included studies are summarized in Table 1. The number of publications is expected to range from 2008 to 2023. Most of the studies were conducted in Europe (71.4%).

Methodological quality and risk of bias results

The methodological quality of the studies assessed using the QUADAS-2 tool is summarized in Supplementary Figure 1. In terms of patient selection, four studies presented an unclear risk of bias owing to insufficient information on whether patients were enrolled randomly or consecutively. Overall, the risk of bias across studies was relatively low.

Diagnostic performance of VCTE in hepatic fibrosis for PBC

Six studies comprising 559 patients with PBC were included in the meta-analysis.[17-22] The majority of these studies (5 out of 6; 83.3%) were conducted prospectively[17,19-22] and predominantly included female patients, as shown in Table 1. Four studies were conducted in Europe at different centers,[17-19,21] one in the USA,[22] and one in Japan.[20] In terms of treatment, four studies included patients undergoing PBC treatment,[17,19-21] while two studies did not specify the treatment status.[18,22] The original data on the number of patients and cutoff values across the degrees of fibrosis for each study are listed in Supplementary Table 2.

When we evaluated the diagnostic performance of VCTE for hepatic fibrosis, the pooled sensitivity was 0.86 (95% CI, 0.78–0.91), the pooled specificity was 0.92 (95% CI, 0.83–0.96), and the pooled AUC was 0.95 (0.90–1.00) with a pooled diagnostic odds ratio of 54.71 (27.84–107.52), as depicted in Supplementary Figure 2. Further analysis according to the stages of liver fibrosis (Table 2) revealed that for predicting significant fibrosis (≥F2), four studies with 330 patients were included. Within the cutoff range of 5.9–16.0 kPa, the diagnostic accuracy showed a sensitivity of 0.76 (0.64–0.85), a specificity of 0.92 (0.72–0.98), an sAUC of 0.87 (0.80–0.94), and a diagnostic odds ratio of 34.20. For advanced fibrosis (≥F3), six studies involving 507 patients were included in the meta-analysis. Within the cutoff

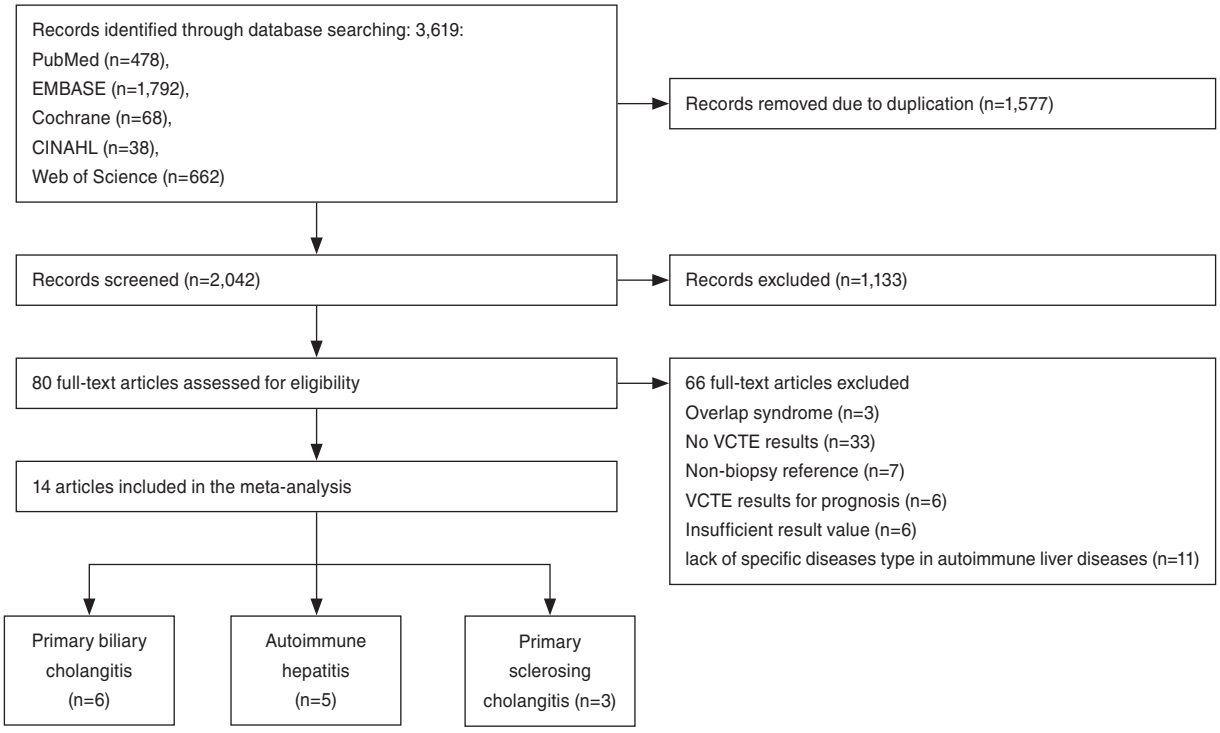

Figure 1. Flow diagram of study screening and selection. VCTE, vibration-controlled transient elastography.

Table 2. Summary diagnostic performance of VCTE for the detection of fibrosis stages in autoimmune liver diseases

Disease	Fibrosis stage	Cut-off range (kPa)	No. of studies	No. of patients	sAUC	I^2 (*P*-value)	sSe (95% CI)	I^2 (*P*-value)	sSp (95% CI)	I^2 (*P*-value)	DOR (95% CI)	I^2 (*P*-value)
PBC	≥F2	5.9–16.0	4	330	0.87 (0.80–0.94)	66% (0.03)	0.76 (0.64–0.85)	68% (0.03)	0.92 (0.72–0.98)	0% (0.60)	34.20 (7.05–165.84)	64% (0.04)
	≥F3	7.5–17.9	6	507	0.89 (0.85–0.94)	56% (0.05)	0.88 (0.78–0.94)	64% (0.02)	0.87 (0.73-0.95)	77% (<0.01)	53.62 (25.44–113.02)	10% (0.35)
	F4	11.4–25.1	5	385	0.99 (0.96–1.00)	0% (0.81)	0.92 (0.78–0.97)	0% (0.85)	0.95 (0.79–0.99)	84% (<0.01)	119.32 (24.22–587.87)	39% (0.16)
AIH	≥F2	5.8–10.05	5	388	0.88 (0.84–0.92)	0% (0.53)	0.81 (0.72–0.88)	64% (0.02)	0.80 (0.71–0.87)	0% (0.80)	21.15 (11.04–40.51)	0% (0.69)
	≥F3	8.18–12.1	5	388	0.88 (0.83–0.93)	57% (0.04)	0.77 (0.68–0.83)	37% (0.16)	0.88 (0.81–0.93)	0% (0.96)	18.57 (10.69–32.26)	37% (0.16)
	F4	12.3–19.0	5	388	0.92 (0.88–0.96)	0% (0.45)	0.87 (0.78–0.92)	0% (0.96)	0.93 (0.86–0.97)	0% (0.99)	65.54 (30.54–140.70)	0% (0.68)
PSC	≥F2	7.4–8.8	2	121	0.88 (0.82–0.95)	28% (0.24)	0.78 (0.67–0.85)	15% (0.28)	0.88 (0.74–0.95)	0% (0.91)	20.24 (6.48-63.25)	0% (0.58)
	≥F3	9.6	2	121	0.95 (0.90–1.00)	0% (0.73)	0.90 (0.78–0.96)	0% (0.73)	0.86 (0.76–0.92)	19% (0.27)	77.93 (19.66–308.94)	0% (0.72)
	F4	13.7–14.4	3	151	0.92 (0.84–0.99)	61% (0.08)	0.79 (0.64-0.89)	0% (0.79)	0.93 (0.84–0.97)	25% (0.27)	82.04 (17.40–298.24)	0% (0.78)

VCTE, vibration-controlled transient elastography; sAUC, summary area under the curve; sSe, summary sensitivity; sSp, summary specificity; CI, confidence interval; DOR, diagnostic odds ratio; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis.

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range of 7.5–17.9 kPa, the sensitivity was 0.88 (0.78–0.94), the specificity was 0.87 (0.73–0.95), the sAUC was 0.89 (0.85–0.94) and the diagnostic odds ratio was 53.62. For cirrhosis (F4), five studies involving 385 patients were identified. Within the cutoff range of 11.4–25.1 kPa, the sensitivity was 0.92 (0.78–0.97), the specificity was 0.95 (0.79–0.99), the sAUC was 0.99 (0.96–1.00), and the diagnostic odds ratio was 119.32. The summary point estimate of the mean, with a 95% confidence region for each fibrosis stage, is shown in Figure 2.

Diagnostic performance of VCTE in hepatic fibrosis for AIH

Five studies comprising 388 patients with AIH were included in the meta-analysis.[23-27] The studies predominantly included female patients with mean ages ranging from 37.9 to 53 years, as shown in Table 1. Two studies were con-

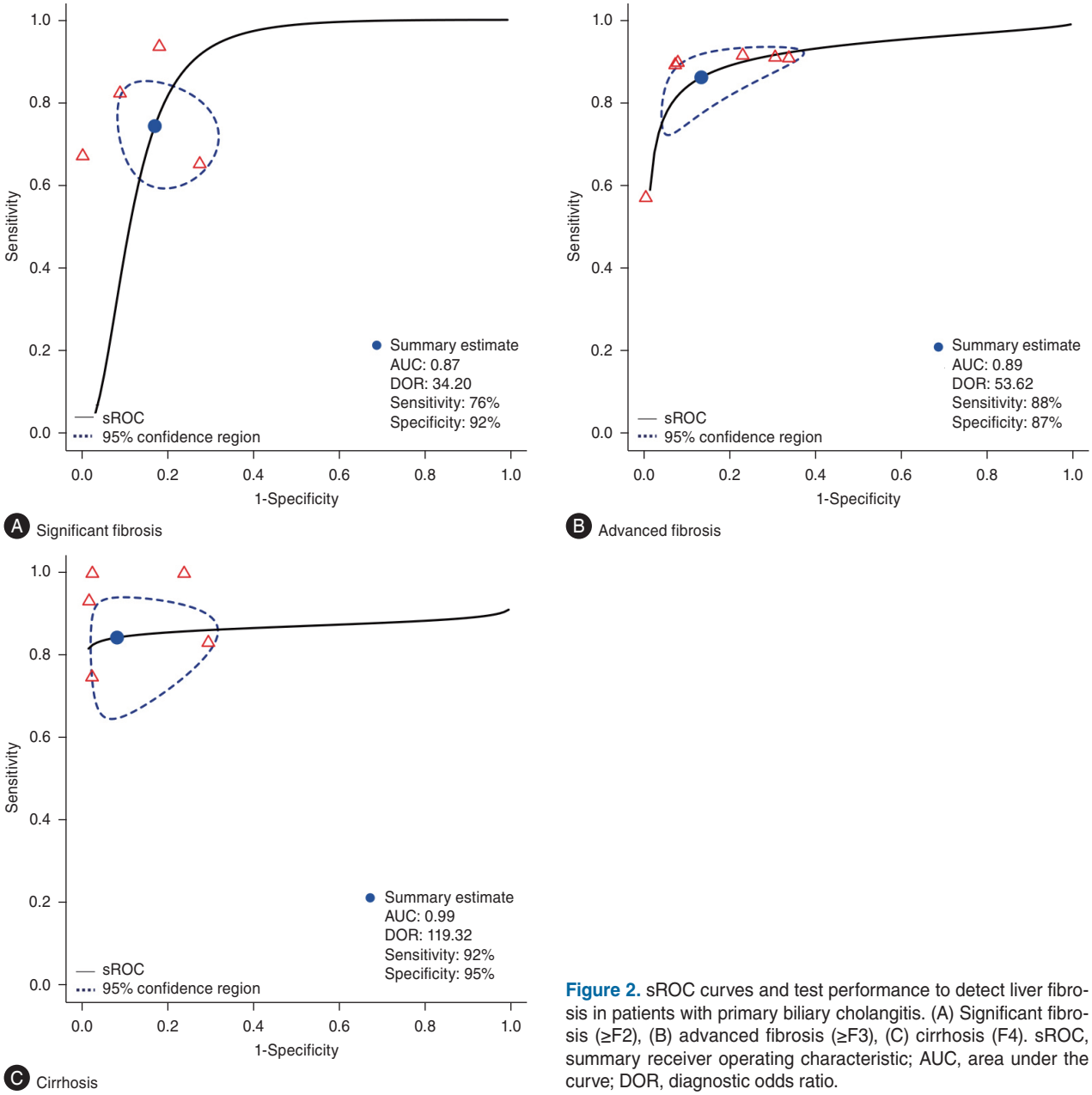

Figure 2. sROC curves and test performance to detect liver fibrosis in patients with primary biliary cholangitis. (A) Significant fibrosis (≥F2), (B) advanced fibrosis (≥F3), (C) cirrhosis (F4). sROC, summary receiver operating characteristic; AUC, area under the curve; DOR, diagnostic odds ratio.

ducted in Europe,[23,25] two in Asia,[24,27] and one in Latin America.[26] Patients receiving immunosuppressive treatments for AIH were included in three studies.[23,25,26]

A summary of the diagnostic performance of VCTE for the detection of the fibrosis stages in AIH is presented in Table 2 and Figure 3. The pooled sensitivity was 0.81 (0.76–0.85), the pooled specificity was 0.89 (0.85–0.93), the pooled AUC was 0.90 (0.88–0.92), and the pooled diagnostic odds ratio was 25.98 (17.97–37.56), as presented in Supplementary Figure 3. For diagnosing significant fibrosis (≥F2), five studies involving 388 patients were analyzed. Within the cutoff range of 5.8–10.05 kPa, the diagnostic accuracy showed a sensitivity of 0.81 (0.72–0.88), specificity of 0.80 (0.71–0.87), an sAUC of 0.88 (0.84–0.92), and a diagnostic odds ratio of 21.15. For advanced fibrosis (≥F3), five studies with 388 patients were included. Within the cutoff range of 8.18–12.1 kPa, the sensitivity was 0.77 (0.68–0.83), specificity was 0.88 (0.81–0.93), the

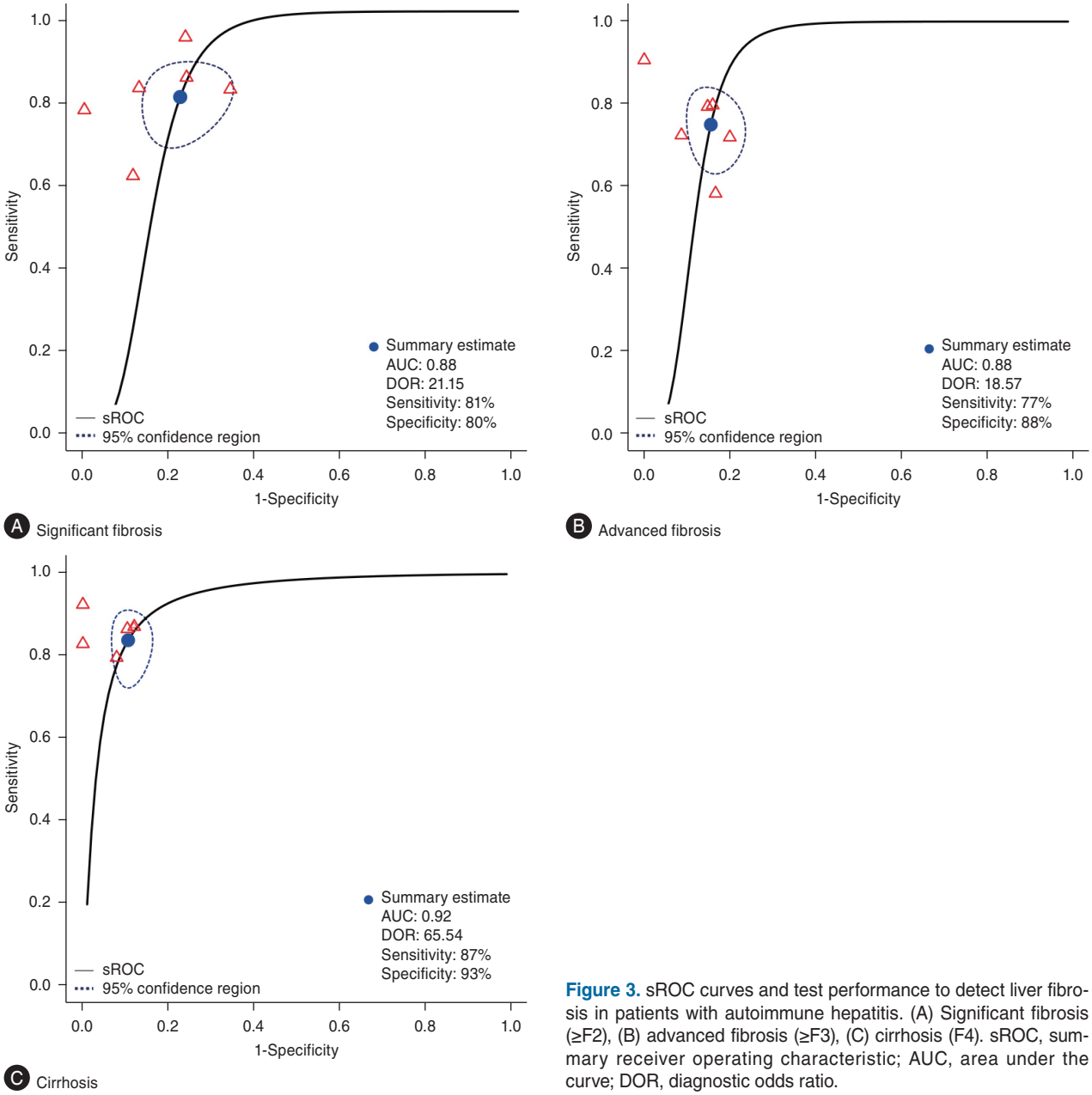

Figure 3. sROC curves and test performance to detect liver fibrosis in patients with autoimmune hepatitis. (A) Significant fibrosis (≥F2), (B) advanced fibrosis (≥F3), (C) cirrhosis (F4). sROC, summary receiver operating characteristic; AUC, area under the curve; DOR, diagnostic odds ratio.

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sAUC was 0.88 (0.83–0.93), and the diagnostic odds ratio was 18.57. For cirrhosis (F4), five studies involving 388 patients were analyzed. Within the cutoff range of 12.3–19.0 kPa, the sensitivity was 0.87 (0.78–0.92), the specificity was 0.93 (0.86–0.97), the sAUC was 0.92 (0.88–0.96), and the diagnostic odds ratio was 65.54.

Diagnostic performance of VCTE in hepatic fibrosis for PSC

Three studies comprising 151 patients with PSC were included in this meta-analysis (Table 1). All studies were conducted in Europe and two were performed prospectively.[28-30] The number of patients included in each study ranged from 30 to 62. One study enrolled patients undergoing treatment for PSC,[28] whereas others did not present the treatment status.

The diagnostic performance of VCTE for hepatic fibrosis was evaluated, yielding a pooled sensitivity of 0.81 (0.75–0.87), a pooled specificity of 0.90 (0.84–0.94), and a pooled AUC of 0.93 (0.89–0.96) with a pooled diagnostic odds ratio of 42.97 (20.22–91.36), as depicted in Supplementary Figure 4. When analyzed according to the stages of liver fibrosis (Table 2), two studies involving 121 patients with significant fibrosis (≥F2) were analyzed. At the cutoff value of 8.8 kPa, the sensitivity was 0.78 (0.67–0.85), specificity was 0.88 (0.74–0.95), sAUC was 0.88 (0.82–0.95), and diagnostic odds ratio was 20.24. For advanced fibrosis (≥F3), two studies with 121 patients were included. At the cutoff value of 9.6 kPa, the sensitivity was 0.90 (0.78–0.96), specificity was 0.86 (0.76–0.92), sAUC was 0.95 (0.90–1.00), and diagnostic odds ratio was 77.93. For cirrhosis (F4), three studies with 151 patients were analyzed. Within the cutoff range of 13.7–14.4 kPa, the sensitivity was 0.79 (0.64–0.89), the specificity was 0.93 (0.84–0.97), the sAUC was 0.92 (0.84–0.99), and the diagnostic odds ratio was 82.04.

DISCUSSION

Clinical practice and research present an increasing need to reduce the reliance on liver biopsies to assess hepatic fibrosis in autoimmune liver diseases. In this study, we conducted a systematic review and meta-analysis of 16 studies involving 1,053 patients, categorizing and examining each type of autoimmune liver disease to summarize the evidence for the diagnostic accuracy of VCTE in the non-invasive diagnosis of liver fibrosis. By including only original articles in our meta-analysis, we ensured high-quality peer-reviewed evidence, thereby enhancing the validity and reliability of our findings. Our results suggest VCTE's excellent diagnostic performance in staging liver fibrosis in patients with autoimmune liver disease.

Given that advanced histological stages are consistently associated with poor prognosis in PBC,[9,31] the assessment of fibrosis is crucial for risk stratification and management. As liver biopsy is no longer recommended for diagnostic purposes,[32] VCTE has become the preferred method for detecting fibrosis.[33] Recent studies have revealed that changes in liver stiffness measurement (LSM) assessed by VCTE are strongly and independently associated with the risk of severe clinical events.[17,34] In conjunction with biochemical response criteria, LSM by VCTE may help identify patients who need second-line therapy with recent US Food and Drug Administration approval.[35] Our meta-analysis shows the high diagnostic accuracy of VCTE, with sAUC values exceeding 0.85 across all degrees of fibrosis, supporting its role in evaluating and risk-stratifying patients with PBC and tailoring their monitoring accordingly. Although one Japanese study[20] reported higher cutoff values for staging fibrosis than other studies (Supplementary Table 2), a cut-off value range of 9.9–10.7 kPa for LSM by VCTE appears to be appropriate for ruling-in advanced fibrosis in PBC. This range is consistent with the cut-off value of 10 kPa proposed by the European guidelines.[33]

In the context of AIH, our meta-analysis confirmed that LSM by VCTE correlates positively with the histological fibrosis stage and can detect fibrosis stages noninvasively with high accuracy, with sAUC values above 0.85. Although VCTE cannot currently substitute biopsy, particularly at diagnosis, this method provides a valuable tool for monitoring disease activity during treatment in patients with AIH.[2,36] Hepatic inflammation is a recognized confounding factor that can cause the overestimation of liver stiffness, regardless of the fibrosis stage.[33] One study included in our meta-analysis demonstrated that VCTE's diagnostic performance improved after six months of immunosuppressive treatment, suggesting that its accuracy in assessing fibrosis may increase with prolonged therapy.[25] The VCTE cutoff

value for detecting advanced fibrosis in AIH is approximately 10 kPa. However, further research is needed to establish precise cutoff values that consider treatment duration and hepatic inflammation.

Several retrospective studies have demonstrated that baseline liver fibrosis and changes in liver stiffness are associated with clinical outcomes in PSC.[28,29,37] However, only three studies with a small number of patients that evaluated the diagnostic performance of VCTE for detecting liver fibrosis were included in this meta-analysis, despite a comprehensive search. This may be because liver biopsy, the reference standard for our meta-analysis, is not routinely performed in PSC patients because of its invasive nature and limited diagnostic value. Our results indicate that LSM using VCTE is independently associated with histological fibrosis stage, demonstrating high diagnostic performance for detecting advanced fibrosis and cirrhosis, with sAUC values over 0.90. Although liver stiffness values need careful interpretation due to the risk of overestimating fibrosis in patients with increased serum bilirubin from extrahepatic bile duct stenosis,[3,33] cutoff values of 9.6 kPa for advanced fibrosis and 14.4 kPa for cirrhosis appear to be appropriate in PSC. These findings should be confirmed in larger independent cohorts.

Several limitations of this study should be noted when interpreting the data. First, we did not have access to the original studies' data; therefore, we could not perform an individual patient data meta-analysis to properly assess potentially relevant effect modifiers such as ALT or bilirubin levels, body mass index, disease duration, and treatment duration. Second, insufficient data and the limited number of studies made it impossible to compare the effects of treatment on the diagnostic performance of VCTE. Further studies are needed to examine the effect of autoimmune liver disease therapy on liver fibrosis.

In conclusion, VCTE exhibits a high diagnostic accuracy for the assessment of fibrosis in patients with autoimmune liver diseases. As a simple and reliable noninvasive method, VCTE can be an effective tool for evaluating and monitoring fibrosis associated with these chronic conditions. Further large-scale studies are necessary to establish precise cutoff values for VCTE in this patient population.

Authors' contribution

Conception: Jihyun An, Young Eun Chon, Ji Won Han, Young-Joo Jin. Study design: Jihyun An, Young Eun Chon, Ji Won Han, Young-Joo Jin. Data analysis and interpretation: Jihyun An, Young Eun Chon, Miyoung Choi, Young-Joo Jin, Gunho Kim, Mi Na Kim, Ji Won Han and Dae Won Jun. Review of the results: Jihyun An, Young Eun Chon, Ji Won Han, Young-Joo Jin, Gunho Kim, Mi Na Kim, Ji Won Han, Hee Yeon Kim, Han Ah Lee, Jung Hwan Yu, Young Eun Chon, Seung Up Kim, Dae Won Jun. Drafting of the manuscript: Jihyun An. Overall Study Oversight and Guarantor of Manuscript: Ji Won Han and Young-Joo Jin. 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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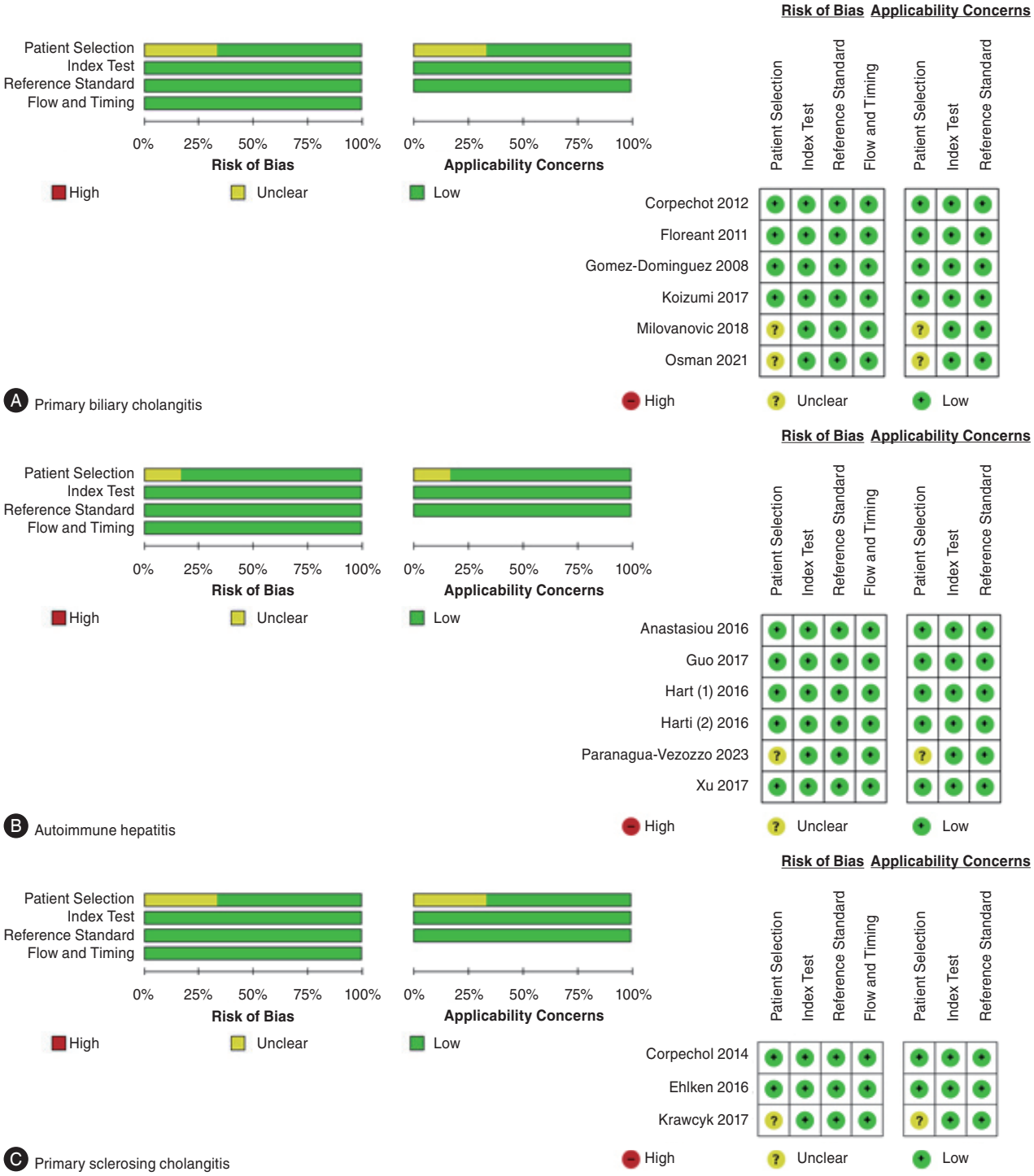

Supplementary Figure 1. Risk-of-bias graph for included studies.

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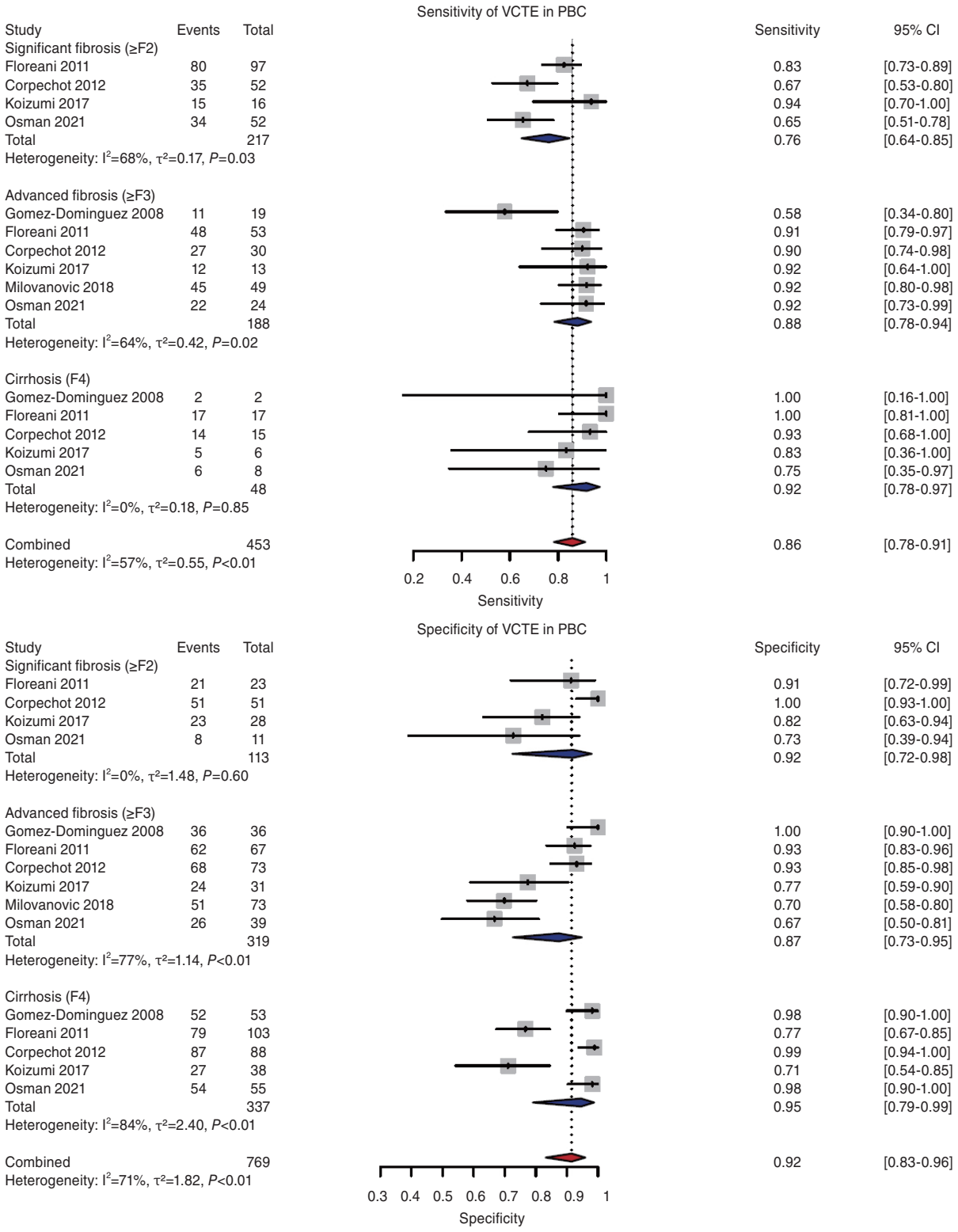
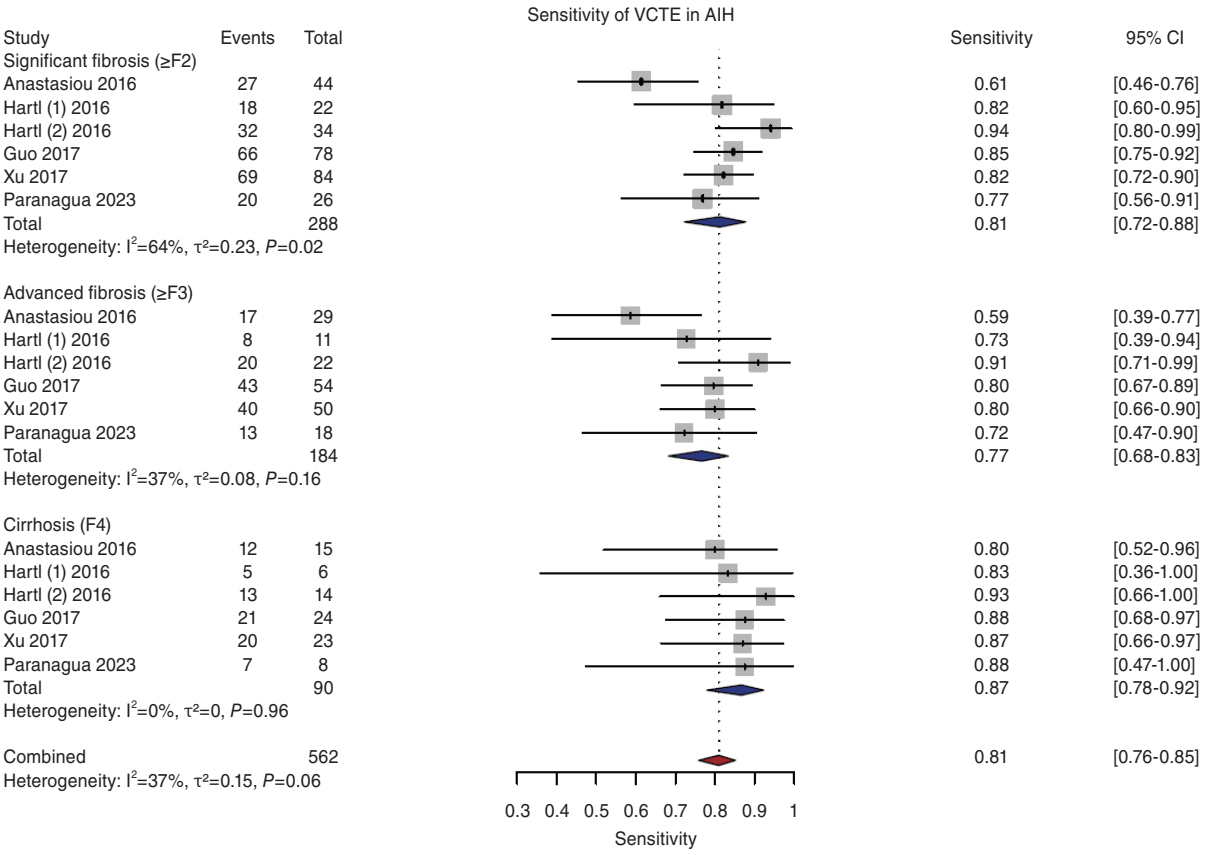


Supplementary Figure 2. Forest plots of pooled sensitivity and specificity in included studies with primary biliary cholangitis (PBC).



Supplementary Figure 3. Forest plots of pooled sensitivity and specificity in included studies with autoimmune hepatitis (AIH).

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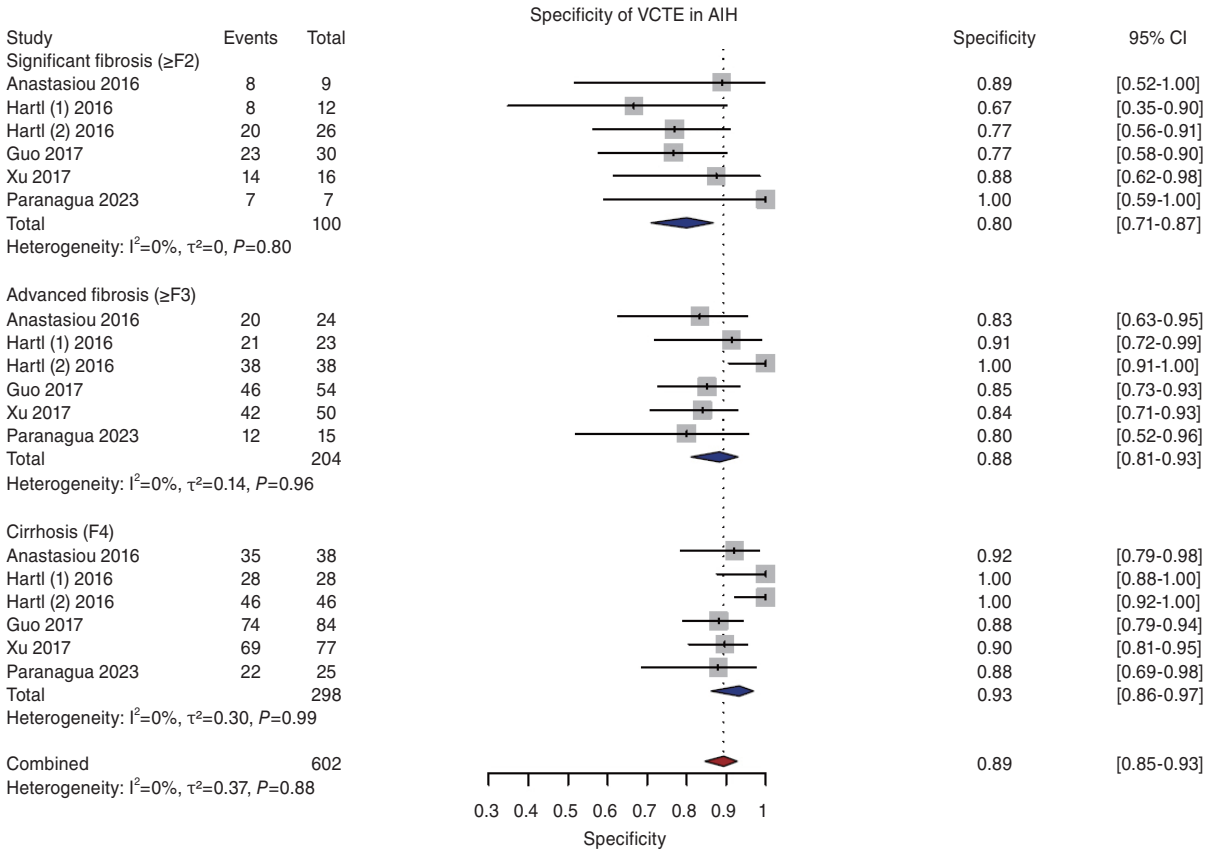
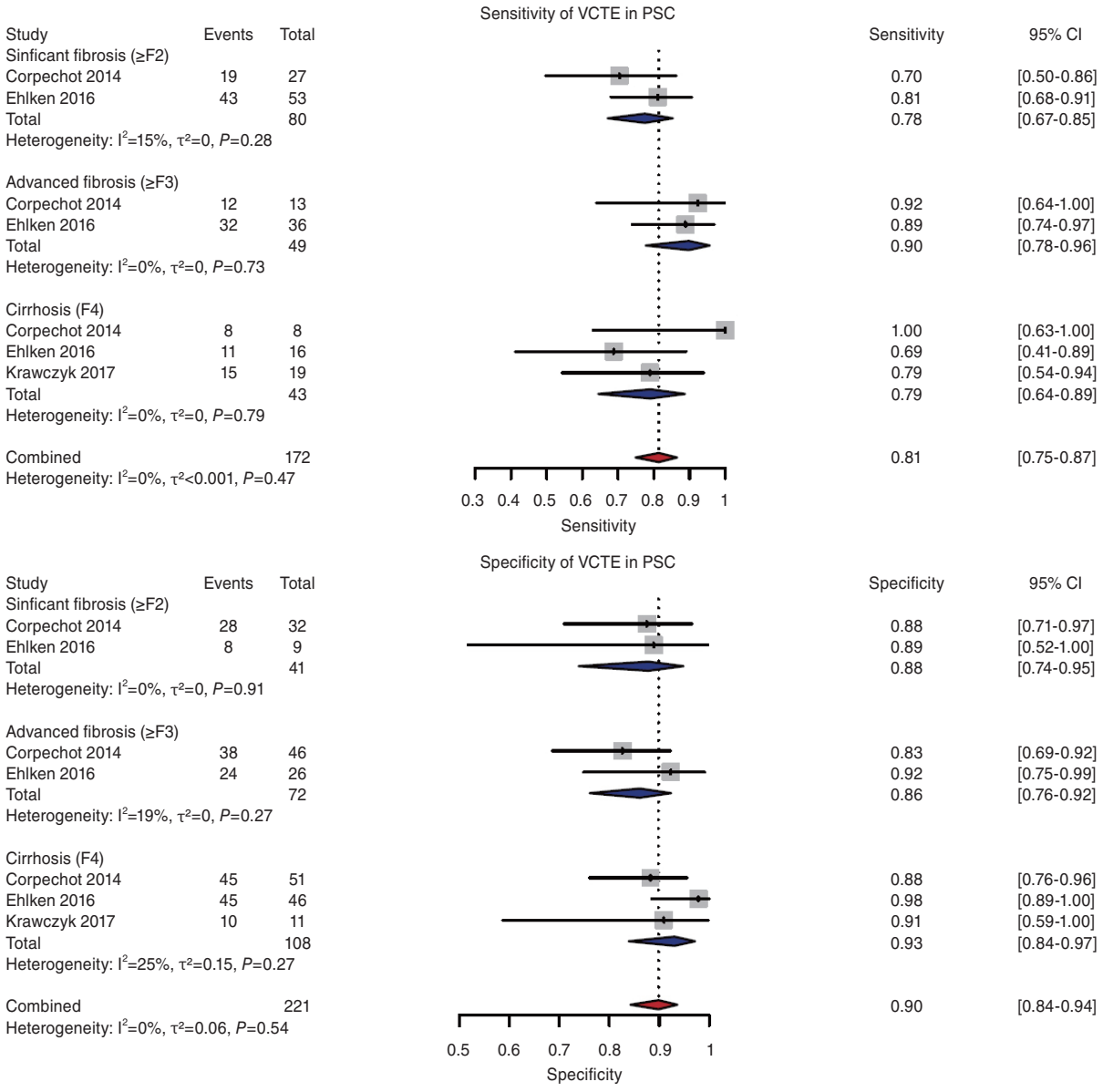


Supplementary Figure 3. Continued.



Supplementary Figure 4. Forest plots of pooled sensitivity and specificity in included studies with primary sclerosing cholangitis (PSC).

Supplementary Table 1. Search strategies

PubMed

No.	Search Query	Results
#1	"Hepatitis, Autoimmune"[Mesh]	4,324
#2	Autoimmune[TW] AND (Hepatitis[TW] OR Hepatitides[TW] OR "liver diseas*"[TW])	14,620
#3	AIH[TW]	3,202
#4	"Cholangitis, Sclerosing"[Mesh]	4,633
#5	"liver cirrhosis, biliary"[Mesh]	8,710
#6	"primary biliary cirrhos*"[TW] OR "primary biliary cholangit*"[TW] OR "Primary sclerosing cholangitis"[TW] OR "biliary liver cirrhosis"[TW]	13,951
#7	"overlap syndrome*"[TW]	2,906
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	32,055
#9	non-invasiv*[TW] OR noninvasiv*[TW]	240,882
#10	"APRI"[TW] OR "aspartate aminotransferase to platelet ratio index"[TW] OR "AST to platelet ratio index"[TW]	2,209
#11	"fibrosis-4"[TW] OR "fibrosis-4 index"[TW] OR "FIB-4"[TW]	2,801
#12	Fibrotest*[TW]	415
#13	"aspartate aminotransferase/alanine aminotransferase ratio"[TW] OR "aspartate aminotransferase alanine aminotransferase ratio"[TW] OR AAR[TW] OR "AST/ALT ratio"[TW]	2,115
#14	"Elasticity Imaging Techniques"[Mesh]	11,583
#15	"Elasticity Imag*"[TW] OR elastograp*[TW]	16,846
#16	"FibroScan"[TW] OR "transient elastograp*"[TW] OR TE[TW]	35,806
#17	"vibration controlled transient elastograp*"[TW] OR VCTE[TW] OR FibroMeter[TW] OR FMVCTE[TW]	499
#18	"shear wave elastograp*"[TW] OR SWE[TW]	4,312
#19	"magnetic resonance elastograp*"[TW] OR "MR elastograp*"[TW] OR MRE[TW]	3,556
#20	"Acoustic Radiation Force Impuls*"[TW] OR ARFI[TW]	1,173
#21	"Platelet count to spleen diameter ratio"[TW] OR "PC/SD"[TW]	41
#22	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	291,447
#23	#8 AND #22	694
#24	#23 NOT (animals[Mesh:noexp] NOT (animals[Mesh:noexp] AND humans[Mesh]))	682
#25	#24 NOT ("Review"[ptyp] OR "Systematic Review"[ptyp] OR "Meta-Analysis"[ptyp] OR Review*[TI] OR Meta-Analys*[TI] OR "Systematic Literature*"[TI] OR Autobiography[ptyp] OR Bibliography[ptyp] OR Biography[ptyp] OR pubmed books[filter] OR Comment[ptyp] OR Dataset[ptyp] OR Dictionary[ptyp] OR Editorial[ptyp] OR Electronic Supplementary Materials[ptyp] OR Interview[ptyp] OR Legislation[ptyp] OR News[ptyp] OR Newspaper Article[ptyp] OR Retracted Publication[sb] OR Retraction of Publication[sb] OR Technical Report[ptyp] OR Letter[ptyp])	513
#26	#25 AND ("1950/01/01"[PDAT] : "2023/05/31"[PDAT]) AND (English[Lang])	478

EMBASE

No.	Search Query	Results
#1	'autoimmune liver disease'/exp OR 'autoimmune hepatitis'/exp	17,262
#2	(Autoimmune NEAR/6 (Hepatitis OR Hepatitides OR 'liver diseas*')):ab,ti,kw	17,134
#3	AIH:ab,ti,kw	6,385
#4	'primary biliary cirrhosis'/exp OR 'primary sclerosing cholangitis'/exp	22,039
#5	'biliary cirrhosis'/exp	5,201

Supplementary Table 1. Continued

No.	Search Query	Results
#6	('primary biliary cirrhos*' OR "primary biliary cholangit*' OR "Primary sclerosing cholangitis' OR "biliary liver cirrhosis'):ab,ti,kw	21,837
#7	'overlap syndrome'/exp OR 'overlap syndrome*':ab,ti,kw	5,660
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	51,978
#9	(non-invasiv* OR noninvasiv*):ab,ti,kw	353,002
#10	('APRI' OR 'aspartate aminotransferase to platelet ratio index' OR 'AST to platelet ratio index'):ab,ti,kw	4,941
#11	('fibrosis-4' OR 'fibrosis-4 index' OR 'FIB-4'):ab,ti,kw	6,047
#12	Fibrotest*:ab,ti,kw	1,027
#13	('aspartate aminotransferase/alanine aminotransferase ratio' OR 'aspartate aminotransferase alanine aminotransferase ratio' OR AAR OR 'AST/ALT ratio'):ab,ti,kw	3,831
#14	'elastography'/exp	39,052
#15	('Elasticity Imag*' OR elastograp*):ab,ti,kw	22,886
#16	('FibroScan' OR 'transient elastograp*' OR TE):ab,ti,kw	54,825
#17	('vibration controlled transient elastograp*' OR VCTE OR FibroMeter OR FMVCTE):ab,ti,kw	1,043
#18	('shear wave elastograp*' OR SWE):ab,ti,kw	6,276
#19	('magnetic resonance elastograp*' OR 'MR elastograp*' OR MRE):ab,ti,kw	5,267
#20	('Acoustic Radiation Force Impuls*' OR ARFI):ab,ti,kw	2,042
#21	('Platelet count to spleen diameter ratio' OR 'PC/SD'):ab,ti,kw	76
#22	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	441,283
#23	#8 AND #22	2,202
#24	#23 NOT ('animal'/de NOT ('animal'/de AND 'human'/exp)) AND [english]/lim	2,121
#25	#24 NOT ([review]/lim OR [conference review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR Review*:ti OR Meta-Analys*:ti OR 'Systematic Literature*':ti)	1,792
#26	#25 AND ([english]/lim) AND [1966-2023]/py	1,792

Cochrane Library Trials

No.	Search Query	Results
#1	[mh "Hepatitis, Autoimmune"]	42
#2	(Autoimmune NEAR/6 (Hepatitis OR Hepatitides OR "liver diseas*")):ab,ti,kw	324
#3	AIH:ab,ti,kw	160
#4	[mh "Cholangitis, Sclerosing"]	127
#5	[mh "liver cirrhosis, biliary"]	363
#6	("primary biliary cirrhos*" OR "primary biliary cholangit*" OR "Primary sclerosing cholangitis" OR "biliary liver cirrhosis"):ab,ti,kw	340
#7	overlap syndrome*:ab,ti,kw	122
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	1,174
#9	(non-invasiv* OR noninvasiv*):ab,ti,kw	23,289
#10	("APRI" OR "aspartate aminotransferase to platelet ratio index" OR "AST to platelet ratio index"):ab,ti,kw	227
#11	("fibrosis-4" OR "fibrosis-4 index" OR "FIB-4"):ab,ti,kw	330
#12	Fibrotest*:ab,ti,kw	109
#13	("aspartate aminotransferase/alanine aminotransferase ratio" OR "aspartate aminotransferase alanine aminotransferase ratio" OR AAR OR "AST/ALT ratio"):ab,ti,kw	221

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Supplementary Table 1. Continued

No.	Search Query	Results
#14	[mh "Elasticity Imaging Techniques"]	216
#15	("Elasticity Imag*" OR elastograp*):ab,ti,kw	1,053
#16	("FibroScan" OR "transient elastograp*" OR TE):ab,ti,kw	5,594
#17	("vibration controlled transient elastograp*" OR VCTE OR FibroMeter OR FMVCTE):ab,ti,kw	53
#18	("shear wave elastograp*" OR SWE):ab,ti,kw	237
#19	("magnetic resonance elastograp*" OR "MR elastograp*" OR MRE):ab,ti,kw	184
#20	("Acoustic Radiation Force Impuls*" OR ARFI):ab,ti,kw	36
#21	("Platelet count to spleen diameter ratio" OR "PC/SD"):ab,ti,kw	1
#22	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	30,045
#23	#8 AND #22	68
#24	#23 with Publication Year from 1950 to 2023, in Trials	68

CINAHL

No.	Search Query	Results
S1	(MH "Hepatitis, Autoimmune")	582
S2	Autoimmune AND (Hepatitis OR Hepatitides OR "liver diseas*")	1,746
S3	AIH	736
S4	(MH "Cholangitis, Sclerosing")	637
S5	"liver cirrhosis, biliary"	1
S6	"primary biliary cirrhos*" OR "primary biliary cholangit*" OR "Primary sclerosing cholangitis" OR "biliary liver cirrhosis"	1,435
S7	"overlap syndrome*"	526
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	3,745
S9	non-invasiv* OR noninvasiv*	45,494
S10	"APRI" OR "aspartate aminotransferase to platelet ratio index" OR "AST to platelet ratio index"	483
S11	"fibrosis-4" OR "fibrosis-4 index" OR "FIB-4"	500
S12	Fibrotest*	57
S13	"aspartate aminotransferase/alanine aminotransferase ratio" OR "aspartate aminotransferase alanine aminotransferase ratio" OR AAR OR "AST/ALT ratio"	477
S14	"Elasticity Imag*"	106
S15	elastograp*	3,905
S16	"FibroScan" OR "transient elastograp*" OR TE	12,890
S17	"vibration controlled transient elastograp*" OR VCTE OR FibroMeter OR FMVCTE	84
S18	"shear wave elastograp*" OR SWE	1,500
S19	"magnetic resonance elastograp*" OR "MR elastograp*" OR MRE	783
S20	"Acoustic Radiation Force Impuls*" OR ARFI	428
S21	"Platelet count to spleen diameter ratio" OR "PC/SD"	7
S22	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	62,083
S23	S8 AND S22	117
S24	S23 Limiters - Published Date: 19500101-20230531; English Language; Human; Publication Type: Clinical Trial, Journal Article, Proceedings, Randomized Controlled Trial	38

Supplementary Table 1. Continued

Web of Science

No.	Search Query	Results
#1	TS=(Autoimmune AND (Hepatitis OR Hepatitides OR "liver diseas*"))	14,697
#2	TS=(AIH)	2,922
#3	TS=("primary biliary cirrhos*" OR "primary biliary cholangit*" OR "Primary sclerosing cholangitis" OR "biliary liver cirrhosis")	20,670
#4	TS="overlap syndrome*"	3,194
#5	#1 OR #2 OR #3 OR #4	35,279
#6	TS=(non-invasiv* OR noninvasiv*)	266,596
#7	TS=("APRI" OR "aspartate aminotransferase to platelet ratio index" OR "AST to platelet ratio index")	2,261
#8	TS=("fibrosis-4" OR "fibrosis-4 index" OR "FIB-4")	2,766
#9	TS=Fibrotest*	777
#10	TS=("aspartate aminotransferase/alanine aminotransferase ratio" OR "aspartate aminotransferase alanine aminotransferase ratio" OR AAR OR "AST/ALT ratio")	3,340
#11	TS=("Elasticity Imag*" OR elastograp*)	21,441
#12	TS=("FibroScan" OR "transient elastograp*" OR TE)	89,219
#13	TS=("vibration controlled transient elastograp*" OR VCTE OR FibroMeter OR FMVCTE)	502
#14	TS=("shear wave elastograp*" OR SWE)	8,059
#15	TS=("magnetic resonance elastograp*" OR "MR elastograp*" OR MRE)	7,029
#16	TS=("Acoustic Radiation Force Impuls*" OR ARFI)	1,764
#17	TS=("Platelet count to spleen diameter ratio" OR "PC/SD")	33
#18	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	376,272
#19	#5 AND #18	845
#20	#19 AND PY=(1983-2023) AND LANGUAGE:(English)	817
#21	#20 Refined by: DOCUMENT TYPES: (ARTICLE OR Procceding paper OR EARLY ACCESS OR Meeting Abstract)	662

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Supplementary Table 2. Detailed information regarding the number of patients and cut-off values for VCTE for staging liver fibrosis in studies included in the meta-analysis

Disease	Author (year)	Significant fibrosis (≥F2)		Advanced fibrosis (≥F3)		Cirrhosis (F4)	
		No. of patients	Cut-off value (kPa)	No. of patients	Cut-off value (kPa)	No. of patients	Cut-off value (kPa)
PBC	Gómez-Dominguez et al.[19] (2008)	-	-	16	14.7	-	15.6
	Floreani et al.[18] (2011)	88	5.9	50	7.6	17	11.4
	Corpechot et al.[17] (2012)	52	8.8	30	10.7	15	16.9
	Koizumi et al.[20] (2017)	17	16.0	13	17.9	6	25.1
	Milovanović et al.[21] (2018)	-	-	49	9.9	-	-
	Osman et al.[22] (2021)	52	7.0	24	7.5	8	14.4
AIH	Hartl et al.[25] (2016)	22	5.8	11	10.4	6	16.0
	Hartl et al.[25] (2016)	34	5.8	22	10.4	14	16.0
	Anastasiou et al.[23] (2016)	44	10.05	29	12.1	15	19.0
	Xu et al.[27] (2017)	84	6.45	50	8.75	23	12.5
	Guo et al.[24] (2017)	78	6.27	54	8.18	24	12.67
	Paranaguá-Vezozzo et al.[26] (2023)	26	6.3	18	8.7	8	12.3
PSC	Corpechot et al.[28] (2014)	32	7.4	15	9.6	9	14.4
	Krawczyk et al.[30] (2017)	-	-	-	-	19	13.7
	Ehlken et al.[29] (2019)	27 (43.5)	8.8	20 (32.3)	9.6	16 (25.8)	14.4

VCTE, vibration-controlled transient elastography; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis.