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- 5503 Diagnostic role of transient elastography in patients with autoimmune liver diseases: A systematic review and meta-analysis
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Diagnostic role of transient elastography in patients with autoimmune liver diseases: A systematic review and meta-analysis

Hong Chen, Yue Shen, Sheng-Di Wu, Qin Zhu, Cheng-Zhao Weng, Jun Zhang, Mei-Xia Wang, Wei Jiang

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Abstract

BACKGROUND

Noninvasive methods have been developed to detect fibrosis in many liver diseases due to the limits of liver biopsy. However, previous studies have focused primarily on chronic viral hepatitis and nonalcoholic fatty liver disease. The diagnostic value of transient elastography for autoimmune liver diseases (AILDs) is worth studying.

AIM

To compare the diagnostic accuracy of imaging techniques with serum biomarkers of fibrosis in AILD.

METHODS

The PubMed, Cochrane Library and EMBASE databases were searched. Studies evaluating the efficacy of noninvasive methods in the diagnosis of AILDs [autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC)] were included. The summary area under the receiver operating characteristic curve (AUROC), diagnostic odds ratio, sensitivity and specificity were used to assess the accuracy of these noninvasive methods for staging fibrosis.

RESULTS

A total of 60 articles were included in this study, and the number of patients with AIH, PBC and PSC was 1594, 3126 and 501, respectively. The summary AUROC

of transient elastography in the diagnosis of significant fibrosis, advanced fibrosis and cirrhosis in patients with AIH were 0.84, 0.88 and 0.90, respectively, while those in patients with PBC were 0.93, 0.93 and 0.91, respectively. The AUROC of cirrhosis for patients with PSC was 0.95. However, other noninvasive indices (aspartate aminotransferase to platelet ratio index, aspartate aminotransferase/alanine aminotransferase ratio, fibrosis-4 index) had corresponding AUROCs less than 0.80.

CONCLUSION

Transient elastography exerts better diagnostic accuracy in AILD patients, especially in PBC patients. The appropriate cutoff values for staging advanced fibrosis and cirrhosis ranged from 9.6 to 10.7 and 14.4 to 16.9 KPa for PBC patients.

Key Words: Liver stiffness; Serum parameter; Liver fibrosis; Noninvasive diagnosis; Transient elastography; Autoimmune liver disease

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Core Tip: Onset of autoimmune liver diseases is frequently insidious, and immune cell infiltration and continuous inflammation drive hepatic fibrosis, which gradually progresses to cirrhosis, causing poorer long-term outcomes. Liver biopsy as the reference standard is an invasive procedure. Thus, repeated biopsies are difficult to implement. Consequently, appropriate noninvasive methods are essential to dynamically monitor the degree of liver fibrosis. Our meta-analysis compared the diagnostic accuracy of imaging techniques with serum biomarkers of fibrosis in autoimmune liver diseases.

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INTRODUCTION

The incidence of autoimmune liver diseases (AILDs), including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and multiple overlap syndromes, a group of autoimmune diseases associated with the liver and bile duct is increasing[1,2]. Onset is frequently insidious, with nonspecific symptoms. Immune cell infiltration and continuous inflammation drive hepatic fibrosis, which gradually progresses to cirrhosis, causing poorer long-term outcomes in patients[3-5]. Accordingly, accurate identification of high-risk patients for such conditions is essential in clinical care to guide timely treatment and delay disease progression.

For years, liver biopsy has been recognized as the reference standard for the assessment of liver fibrosis. However, biopsy area restrictions, sampling errors, and interobserver variability may affect the diagnostic accuracy[6,7]. Moreover, because biopsy is an invasive procedure with potentially hazardous complications ranging from pain to more severe events and even death, many patients are reluctant to undergo repeat biopsies[8,9]. Consequently, an increasing number of studies have focused on noninvasive methods to identify the ideal approach for dynamically monitoring the degree of liver fibrosis[10].

In recent years, some noninvasive methods, including biochemical tests and imaging techniques, have been widely developed, including the aspartate aminotransferase to platelet ratio index (APRI), aspartate aminotransferase/alanine aminotransferase (ALT) ratio (AAR), fibrosis-4 index (FIB-4), red cell distribution width to platelet ratio (RPR), Mac-2 binding protein (M2BP), platelet count to spleen diameter (PC/SD) ratio, transient elastography (TE), shear wave elastography (SWE), acoustic radiation force impulse (ARFI), magnetic resonance spectroscopy (MRS) and magnetic resonance elastography (MRE). Previous studies have validated that elastography is a reliable method with a diagnostic accuracy higher than that of blood tests for staging liver fibrosis in chronic viral hepatitis[11-13], nonalcoholic fatty liver disease[14] and AIH[15]; however, no studies have explored the diagnostic accuracy of noninvasive methods for the other two types of AILDs (PBC and PSC).

Therefore, the present meta-analysis aimed to compare the diagnostic accuracy of biochemical tests and imaging techniques for detecting liver fibrosis in patients with AILD, determine whether the same noninvasive methods show different diagnostic values in the three types of AILDs and recommend appropriate cutoff values for different fibrosis stages.

MATERIALS AND METHODS

Literature search strategy

Studies on the diagnosis of AILD published between January 2006 and December 2022 were searched in PubMed, Cochrane Library and EMBASE databases using the following keywords: AIH, PSC, PBC, liver fibrosis, TE, SWE, MRE, APRI, FIB-4 and AAR. The detailed search strategy is presented in [Supplementary Table 1](#).

Study selection criteria

Original studies that fulfilled the following criteria were enrolled: (1) Studies with patient populations with AIH, PBC or PSC with discrete data that could be separately extracted from the mixed liver disease study cohort; (2) Studies in which liver biopsy was used as the gold standard to assess fibrosis based on the Metavir score or another score that could be converted to the Metavir score; (3) Studies assessing the performance and utility of APRI, AAR, FIB-4, RPR, M2BP, ARFI, PC/SD ratio, TE, SWE, MRE or MRS for staging liver fibrosis; and (4) Studies directly reporting the true-positive, false-positive, false-negative and true-negative values or provided data by which they could be calculated to allow the construction of a 2×2 table for each test.

The following studies were excluded: (1) Studies exploring the prognostic value of liver stiffness measurement (LSM) for patients with AILD; (2) Animal experiments, reviews, protocols, guidelines, case reports or meta-analyses; (3) Studies on liver fibrosis due to other etiologies, including nonalcoholic fatty liver disease, chronic hepatitis B, or chronic hepatitis C; and (4) Studies without sufficient data for further analysis or with the same or overlapping group of participants.

Data extraction and quality assessment

Two investigators (Chen H and Shen Y) independently evaluated the eligibility and quality of the included studies and extracted the data. Any disagreements were resolved by a senior researcher (Wu SD). We collated the following parameters in Microsoft Excel 2010: authors; year of publication; country; study period and design; pathological type; diagnostic methods; sample size; patient characteristics [age, sex, body mass index (BMI), ALT level, treatment condition]; quality of liver biopsy; and performance of the index test, including cutoff values, sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operating characteristic curve (AUROC). Two reviewers (Chen H and Shen Y) independently assessed the risk of bias using the Quality Assessment of Diagnostic Accuracy Studies-2 tool[16].

Data synthesis and statistical analysis

According to the Metavir, Batts-Ludwig and Scheuer scores, liver fibrosis was classified into five stages (F0, F1, F2, F3 and F4), whereas there were seven stages according to the Ishak score. Given that Shiha *et al*[17] proposed that an Ishak score of 3 corresponds to METAVIR score of F2, significant fibrosis (SF), advanced fibrosis (AF) and cirrhosis were defined as stages F2-F4, F3-F4, and F4, respectively. For the data analysis, we constructed 2×2 contingency tables with true-positive, false-positive, false-negative and true-negative values based on data directly extracted from the original studies or calculated from indirect variables (sensitivity, specificity and sample size). A bivariate random effects model was subsequently applied to calculate the diagnostic test accuracy variables, including summary sensitivity, summary specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio (DOR) with their associated 95% confidence intervals (95% CIs). We also performed meta-analyses using hierarchical models to produce summary ROC curves, from which we obtained summary AUROC values to evaluate the diagnostic accuracy of the different noninvasive methods. The method was considered to have excellent accuracy if the summary AUROC value was above 0.90, moderate accuracy if it was greater than 0.80, and poor accuracy if it was less than 0.80[18].

The heterogeneity was assessed using multiple methods. Spearman's correlation coefficient was calculated to evaluate the threshold heterogeneity of the included studies, whereas Cochran's Q and I^2 values were used to assess nonthreshold heterogeneity. If an I^2 value $> 50\%$ or $P < 0.05$ indicated distinct statistical heterogeneity, a random effects model was used to combine the data. A fixed effect model was chosen when the I^2 value $\leq 50\%$ or $P \leq 0.05$. However, the number of original studies was sufficient to perform a meta-regression to explore the potential heterogeneity of certain index tests. In addition, we conducted a subgroup analysis according to the sample size, treatment conditions and cutoff value. Deeks' funnel plots were used to evaluate the possible publication bias. The meta-analysis was performed using Stata 12.0, Reviewer Manager Version 5.3 and Meta-Disc Version 1.4.

RESULTS

Characteristics of the included studies and patients

The study selection process is illustrated in [Figure 1](#). A total of 1386 studies were retrieved through our search strategy, of which 427 were excluded as duplicates and 602 were removed following the screening of titles, abstracts and reviews. The remaining 355 potentially eligible studies were selected for further evaluation. Of these, 60 articles were included in the evaluation and analysis. Among them, 22, 29 and 6 studies were regarding AIH, PBC and PSC, respectively (2 studies focused on both AIH and PBC[19,20], while 1 study focused on both PBC and PSC[21]). In total, they included 11 noninvasive index tests. The basic characteristics of the included studies are presented in [Table 1](#). We selected articles published between 2006 and 2022, of which 46 (76.7%) were published between 2016 and 2022. There were 31 (51.7%) retrospective studies, 17 (28.3%) prospective studies, 10 (16.7%) unknown studies and 2 studies with both designs. Most

Table 1 Characteristics of studies included in this study

No.	Ref.	Country	Disease	Study time	Study design	Diagnostic model ¹	Sample size	Mean age in yr	Sex, F/M	Mean BMI in kg/m ²	Mean, ALT in IU/mL	Treatment condition	Scoring system	Interval
1	Youssef <i>et al</i> [40], 2013	Egypt	AIH	NA	Retrospective	5	16	NA	NA	NA	NA	NA	Metavir	NA
2	Kim <i>et al</i> [41], 2014	Korea	AIH	2008-2014	Retrospective	5	47	NA	41/6	NA	NA	NA	Metavir	NA
3	Abdollahi <i>et al</i> [42], 2015	Iran	AIH	2011-2013	NA	1, 2, 3	80	34.75	51/29	NA	106.49	NA	Ishak	NA
4	Harrison <i>et al</i> [43], 2016	United Kingdom	AIH	2013-2015	Prospective	5	27	56	25/2	NA	21	Post	Ishak	The same day
5	Hartl <i>et al</i> [44], 2016	Germany	AIH	2007-2010	Prospective	5	34	53	28/6	NA	48.5	Post	Scheuer	Within 3 mo
	Hartl <i>et al</i> [44], 2016	Germany	AIH	2008-2015	Retrospective	5	60	52	50/10	NA	35	Post	Scheuer	Within 4 mo
6	Nishikawa <i>et al</i> ⁴⁵ , 2016	Japan	AIH	2005-2015	Prospective	1, 2, 3, 11	84	64	69/15	NA	57.5	Pre	Scheuer	NA
7	E Anastasiou <i>et al</i> [46], 2016	Germany	AIH	2008-2013	Retrospective	1, 2, 3, 5	53	47.3	31/22	NA	606.42	Pre 35 + post 18	Metavir	Within 3 wk
8	Piwczyńska <i>et al</i> [47], 2016	Poland	AIH	NA	Prospective	4	46	14.5	33/13	NA	NA	NA	Batts-Ludwig	NA
9	Sheptulina <i>et al</i> [48], 2016	Russian	AIH	2008-2014	Prospective	1, 2, 3, 9	76	40	65/11	25	54.4	Pre 22 + post 54	Metavir	Within 7 d
10	Guo <i>et al</i> [29], 2017	China	AIH	2012-2017	Retrospective	1, 3, 5	108	46.54	88/20	23.52	146.51	NA	Metavir	Within 3 d
11	Paranagua-Vezozzo <i>et al</i> [49], 2016	Brazil	AIH	2012-2015	Prospective	4, 5	33	NA	28/5	28.6	NA	Post	Metavir	The same day
12	Puustinen <i>et al</i> [50], 2017	Finland	AIH	NA	Prospective	8	12	42.8	10/2	NA	28.5	NA	Metavir	Within 1 mo
13	Wang <i>et al</i> [22], 2017	China	AIH	2007-2015	Retrospective	1, 2, 3, 7	36	51.6	NA	27.7	217.4	Pre 17 + post 19	Metavir	Within 3 mo
14	Xu <i>et al</i> [51], 2017	China	AIH	2014-2016	Prospective	1, 3, 5	100	45	81/19	NA	131.5	Pre	Metavir	The same day
15	Zeng <i>et al</i> [52], 2017	China	AIH	2011-2016	Prospective	6	62	45.6	NA	21.6	78.5	Pre	Metavir	3 d
16	Liu <i>et al</i> [53], 2019	China	AIH	2008-2018	Retrospective	2, 3	45	54.29	37/8	NA	NA	NA	Metavir	The same day

17	Park <i>et al</i> [19], 2019	South Korea	AIH PBC	2014-2017	NA	4	49	56	42/7	23.7	163	NA	Metavir	The same day
							41	55.3	35/6	25.5	45	NA		
18	Li <i>et al</i> [54], 2020	China	AIH	2010-2019	Retrospective	1, 2, 3, 10	72	54	64/8	NA	137.55	Post	Metavir	NA
19	Wang <i>et al</i> [55], 2020	China	AIH	2016-2019	Retrospective	1, 3, 10	119	52.5	99/20	NA	81.6	Pre	Scheuer	Within 7 d
20	Xing <i>et al</i> [30], 2020	China	AIH	2016-2019	Retrospective	1, 3, 6	103	54	81/22	22.5	163	NA	Scheuer	Within 7 d
21	Janik <i>et al</i> [31], 2021	Poland	AIH	2015-2020	Prospective	6	63	37	15/48	23.9	130	Post	Batts-Ludwig	Within 3 mo
22	Zachou <i>et al</i> [20], 2021	Greece	AIH PBC	2009-2016	Retrospective	5	78	57	54/24	NA	68	Pre 47 + post 31	Metavir	The same day
							56	52	48/8	NA	47	Pre 37 + post 19		
23	Ferronato <i>et al</i> [56], 2022	Italy	AIH	NA	Retrospective	1, 2, 3	122	59	90/32	NA	481.8	Pre	Ishak	Within 23 d
24	Soh <i>et al</i> [57], 2022	Korea	AIH	2014-2021	Retrospective	6	69	59.7	60/9	NA	187.1	Pre 44 + post 25	Metavir	The same day
25	Nyblom <i>et al</i> [58], 2006	Sweden	PBC	1976-2000	Retrospective	2	121	54	NA	NA	189.9	NA	Metavir	NA
26	Gómez-Domínguez <i>et al</i> [59], 2008	Spain	PBC	NA	Prospective	5	80	54	64/16	NA	NA	Post	Metavir	Within 9 mo
27	Alempijević <i>et al</i> [60], 2009	Serbia	PBC	2006	NA	1, 2	112	53.88	104/8	NA	NA	Post	Scheuer	Within 1 wk
28	Ferrara <i>et al</i> [61], 2009	Italy	PBC	NA	NA	1, 3	248	52	233/15	NA	NA	NA	Scheuer	The same day
29	Su <i>et al</i> [62], 2009	China	PBC	1985-2006	Retrospective	2	46	53.3	34/12	NA	140.6	NA	Scheuer	Within 1 mo
30	Floreani <i>et al</i> [63], 2011	Italy	PBC	2009	NA	5	114	58	96/24	24	44	NA	Metavir	Within 6 mo
31	Corpechot <i>et al</i> [64], 2012	France	PBC	2004-2010	Prospective	5	103	56	87/16	23.9	76	Post	Metavir	Within 9 mo
32	Zhang <i>et al</i> [34], 2014	China	PBC	2011-2013	NA	4	56	45	46/10	NA	NA	NA	Batts-Ludwig	Within 3 d
33	Sheptulina <i>et al</i> [21], 2015	Russian	PBC PSC	2008-2014	Retrospective	9	82	54.5	78/4	NA	NA	NA	Metavir	NA
						3	22	38	6/16	NA	NA	NA		NA
34	Umemura <i>et al</i> [65], 2015	Japan	PBC	1981-2014	Retrospective	11	137	57	111/26	NA	41	Post	Metavir	The same day

35	Nishikawa <i>et al</i> [66], 2016	Japan	PBC	2005-2014	Prospective	1, 3, 11	57	59	49/8	NA	35	Pre	Scheuer	NA
36	Olmez <i>et al</i> [67], 2016	Turkey	PBC	1995-2013	Retrospective	1, 3	40	49.6	40/0	NA	54.5	NA	Scheuer	Within 1 wk
37	Wang <i>et al</i> [68], 2016	China	PBC	2010-2015	Retrospective	1, 3, 10	73	52.4	62/11	NA	89.3	Pre	Ludwing and Scheuer	The day before
38	Koizumi <i>et al</i> [23], 2017	Japan	PBC	2012-2015	Prospective	1, 2, 3, 5	44	60.5	41/3	NA	65.9	Post	Metavir	Within 1 wk
39	Wang <i>et al</i> [69], 2017	China	PBC	2009-2016	Retrospective	1, 3	261	52	230/31	NA	NA	NA	Metavir	NA
40	Jiang <i>et al</i> [70], 2018	China	PBC	2009-2015	Retrospective	3, 10	77	62.4	64/13	NA	81.2	Pre	Scheuer	NA
41	Kamal <i>et al</i> [71], 2018	Netherlands	PBC	1979-2010	Retrospective	1, 2, 3	85	50	75/10	NA	NA	NA	Ishak	NA
42	Meng <i>et al</i> [72], 2018	China	PBC	2013-2017	Retrospective	1, 3, 10	94	51.02	NA	NA	116.58	Pre	Ludwing and Scheuer	Within 1 wk
43	Milovanović <i>et al</i> [73], 2018	Serbia	PBC	2009-2011	Prospective	1, 2, 5	122	57.4	NA	NA	50.8	Post	Metavir	Within 1 mo
44	Wang <i>et al</i> [74], 2018	China	PBC	2010-2016	Retrospective	1, 3, 10	58	53.3	51/7	NA	90.4	Pre	Ludwing and Scheuer	Within 1 wk
45	Jiang <i>et al</i> [75], 2020	China	PBC	2008-2018	Prospective	1, 2, 3, 10	78	52	71/7	NA	NA	Pre 39 + post 39	Scheuer	Within 2 wk
	Jiang <i>et al</i> [75], 2020	China b	PBC	2008-2018	Retrospective	1, 3, 10	40	51	35/5	NA	NA	Pre 20 + post 20	Scheuer	Within 2 wk
46	Joshita <i>et al</i> [76], 2020	Japan	PBC	2015-2019	NA	5, 11	74	64	62/12	NA	48	Pre	Scheuer	The same day
47	Rossi <i>et al</i> [77], 2020	Italy	PBC	NA	NA	5	92	NA	NA	NA	NA	NA	Scheuer	Within 1 mo
48	Yan <i>et al</i> [32], 2020	China	PBC	2016-2019	Retrospective	1, 2, 3, 6	157	53	136/21	22.2	72	NA	Scheuer	NA
49	Cristoferi <i>et al</i> [78], 2021	Italy	PBC	2006-2019	Prospective	1, 5	126	52	114/12	22.3	52.8	Pre	Batts-Ludwig	Within 12 wk
50	Fujinaga <i>et al</i> [79], 2021	Japan	PBC	2000-2019	Retrospective	1, 3, 11	102	61	89/13	NA	68.4	Pre	Scheuer	NA
51	Manesis <i>et al</i> [80], 2021	Greece	PBC	2010-2018	Retrospective	6	53	62.6	46/7	25.7	30	Pre 30 + post 23	Scheuer	Within 3 mo
52	Osman <i>et al</i> [33], 2021	United States	PBC	2007-2019	Retrospective	5	63	60.95	NA	NA	31.2	NA	Batts-Ludwig	Within 1 yr

53	Avcioglu <i>et al</i> [81], 2022	Turkey	PBC	2008-2020	Retrospective	7	98	60.21	NA	NA	36.4	NA		
54	Garrido <i>et al</i> [82], 2022	Portugal	PBC	2010-2021	NA	5	79	52	NA	NA	NA	Pre 40 + post 39	Batts-Ludwig	Within 2 mo
55	Corpechot <i>et al</i> [83], 2014	France	PSC	2005-20210	Prospective	5	59	40.7	24/35	NA	145.7	Post	Metavir	Within 6 mo
56	Bowlus <i>et al</i> [84], 2016,	France	PSC	NA	NA	5	56	43	22/34	NA	255	NA	Ishak	NA
57	Eaton <i>et al</i> [85], 2016	United States	PSC	2007-2013	Retrospective	1, 7	266	46.12	81/185	26	48	Pre	Batts-Ludwig	Within 1 yr
58	Ehlken <i>et al</i> [86], 2016	Germany	PSC	2006-2014	Retrospective	5	62	38	63/77	NA	38	NA	Scheuer	NA
59	Krawczyk <i>et al</i> [87], 2017	Poland	PSC	2014-2016	Prospective	5	30	33	12/18	NA	50	NA	Metavir	NA
60	Umetsu <i>et al</i> [88], 2018	Japan	PSC	2007-2016	Retrospective	1, 2, 3, 11	28	14	8/20	NA	56.5	NA	Batts-Ludwig	The same day

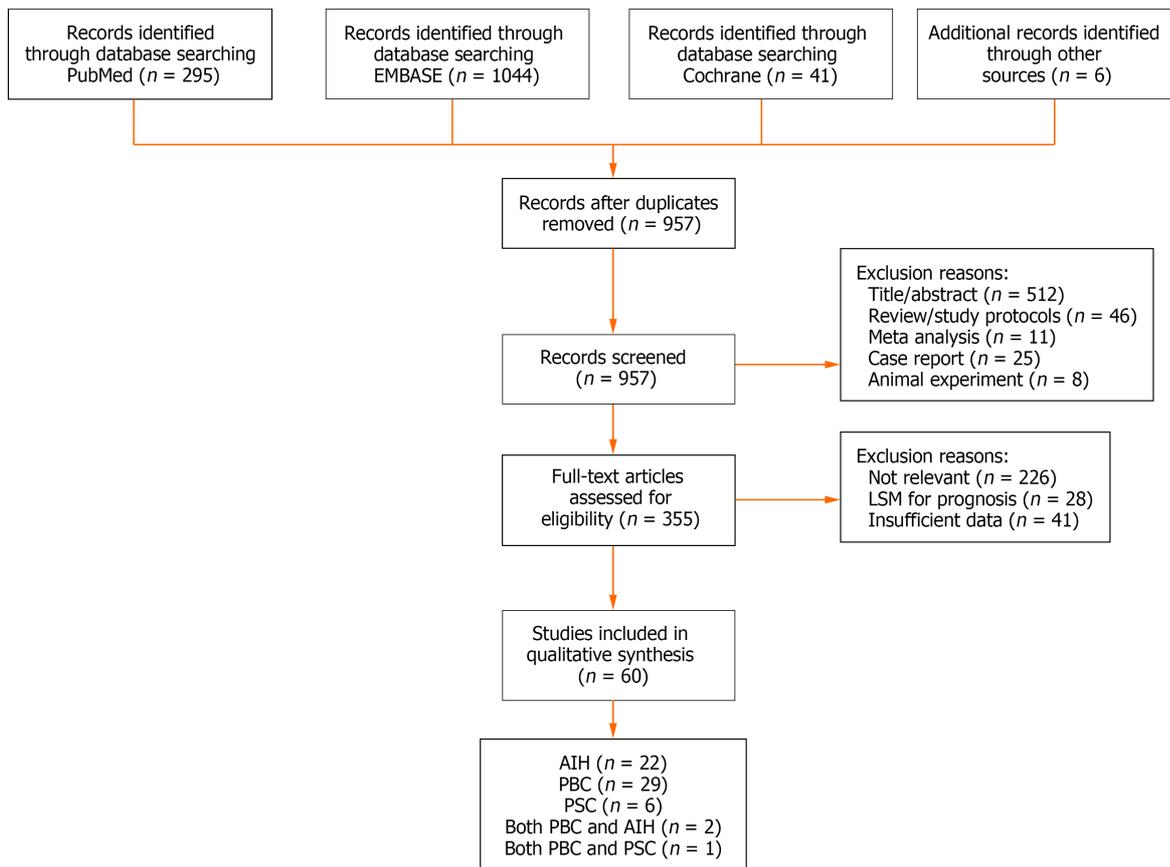
¹Diagnostic models are represented by the following numbers: 1 = Aspartate aminotransferase to platelet ratio index; 2 = caspartate aminotransferase to alanine aminotransferase ratio; 3 = Fibrosis-4 index; 4 = Acoustic radiation force impulse; 5 = Transient elastography; 6 = Shear wave elastography; 7 = Magnetic resonance elastography; 8 = Magnetic resonance spectroscopy; 9 = Platelet count to spleen diameter ratio; 10 = Red cell distribution width to platelet ratio ; 11 = Mac-2-binding protein. AIH: Autoimmune hepatitis; ALT: Alanine aminotransferase; BMI: Body mass index; F: Female; M: Male; NA: Not available; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.

included studies were conducted in Asia (28 studies) or Europe (24 studies). A total of 27 studies utilized the Metavir score, 8 studies used the Batts-Ludwig score, 17 studies used the Scheuer score, 5 studies used the Ishak score, and 3 studies used the Ludwig-Scheuer score.

A total of 1594, 3126 and 501 patients with AIH, PBC, and PSC, respectively, were included to analyze the diagnostic performance of noninvasive methods in staging liver fibrosis. Most patients with AIH and PBC were female (72.4% and 87.6%, respectively). In contrast, patients with PSC were predominantly male (73.7%). The average ages of patients with AIH, PBC and PSC were 47.0, 55.2 and 41.5 years, respectively. Patients with AIH (160.29 IU/mL) had higher ALT levels than patients with PBC (69.81 IU/mL).

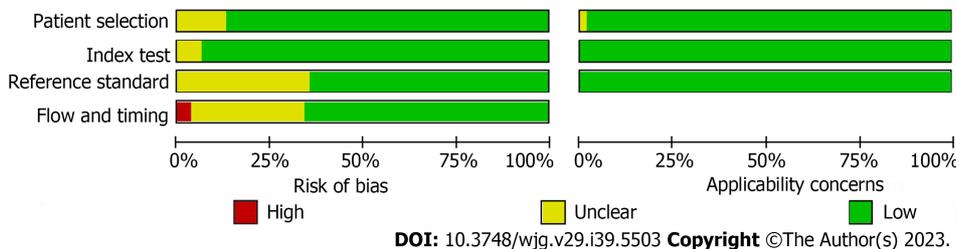
Quality assessment of the included studies

The results of the quality assessment based on the Quality Assessment of Diagnostic Accuracy Studies-2 scale for all 60 eligible studies are shown in [Figure 2](#) and [Supplementary Figure 1](#). Regarding patient selection, eight studies had an unclear risk of bias owing to the lack of information on whether patients were enrolled randomly or consecutively. Regarding the index test, four studies were determined to have an unclear risk of bias because the results of the index test were interpreted without blinded information on the results of the reference standard. Likewise, 22 studies were regarded as having an unclear risk of bias because the results of the reference standard were interpreted without blinded information regarding the results of the index test. In terms of flow and timing, two studies were considered high-risk because not every subject received a reference standard, while 19 studies were considered unclear risk because of an



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Figure 1 Flowchart of study identification and selection process. AIH: Autoimmune hepatitis; LSM: Liver stiffness measurement; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.



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Figure 2 Quality assessment of included studies by Quality Assessment of Diagnostic Accuracy Studies-2. Risk of bias and applicability concerns graph.

unknown time interval between the index and reference tests.

Performance of noninvasive methods in diagnosing SF (F ≥ 2)

Diagnosis of SF for AIH: Fifteen studies (n = 1001) evaluated eight noninvasive methods for detecting SF in patients with AIH. Of these, five (n = 459), two (n = 129), five (n = 459), nine (n = 523) and three (n = 234) studies focused on APRI, AAR, FIB-4, TE and SWE separately, whereas only one study each utilized the ARFI, PC/SD ratio and RPR.

The APRI had moderate summary sensitivity (exceeding 70%) with poor summary specificity (less than 50%), whereas the FIB-4 had the opposite result (Table 2). Interestingly, TE had a relatively greater diagnostic performance than the other laboratory tests, with summary sensitivity and specificity values of 0.82 and 0.73, respectively, and cutoff values ranging from 5.8–7.0 KPa. The summary sensitivity of SWE (0.89; 95%CI: 0.83–0.93) was significantly higher than that of the other six noninvasive methods and slightly greater than that of TE (0.83; 95%CI: 0.78–0.87).

Diagnosis of SF for PBC: Thirteen studies (n = 1389) evaluated nine noninvasive methods for diagnosing SF in patients with PBC. Among them, four (n = 584), three (n = 323), three (n = 462), two (n = 87), five (n = 446) and two (n = 210) studies focused on APRI, AAR, FIB-4, ARFI, TE and SWE, respectively; however, only one study each utilized the PC/SD ratio, MRE and M2BP.

Table 2 Summary sensitivities, specificities, positive likelihood ratio and negative likelihood ratio of noninvasive methods at various diagnostic thresholds for prediction of significant fibrosis, advanced fibrosis and cirrhosis in autoimmune liver diseases patients

Disease	Diagnostic model/Stage	Cutoff values	No. of patients (n)	Summary sensitivity	Summary specificity	Summary PLR	Summary NLR
AIH	APRI						
	SF	0.27-0.70	2 (195)	0.80 (0.72-0.86)	0.35 (0.23-0.48)	1.46 (0.55-3.89)	0.36 (0.061-2.09)
		0.88-1.55	3 (264)	0.74 (0.68-0.80)	0.51 (0.38-0.63)	1.52 (1.18-1.96)	0.50 (0.36-0.69)
	AF	0.38-0.90	4 (379)	0.86 (0.81-0.90)	0.48 (0.41-0.56)	1.60 (1.18-2.15)	0.33 (0.24-0.47)
		1.12-3.40	6 (538)	0.80 (0.72-0.86)	0.35 (0.23-0.48)	0.57 (0.51-0.64)	0.68 (0.62-0.73)
	Cirrhosis	0.55-1.81	3 (330)	0.65 (0.56-0.74)	0.47 (0.40-0.54)	1.49 (0.93-2.39)	0.62 (0.46-0.83)
		1.85-2.00	3 (213)	0.70 (0.57-0.81)	0.73 (0.65-0.79)	2.48 (1.75-3.52)	0.42 (0.28-0.62)
	AAR						
	SF	0.72-0.93	2 (129)	0.67 (0.57-0.77)	0.68 (0.49-0.83)	2.22 (1.32-3.72)	0.46 (0.23-0.90)
	AF	0.76-1.18	7 (532)	0.61 (0.54-0.68)	0.72 (0.66-0.77)	2.01 (1.59-2.53)	0.58 (0.46-0.73)
	Cirrhosis	0.94-1.40	3 (213)	0.61 (0.47-0.74)	0.83 (0.76-0.88)	3.31 (1.96-5.59)	0.49 (0.36-0.69)
	FIB-4						
	SF	1.95-2.90	3 (303)	0.64 (0.58-0.71)	0.71 (0.61-0.81)	2.20 (1.48-3.27)	0.50 (0.38-0.65)
		3.20-5.07	2 (156)	0.60 (0.51-0.69)	0.77 (0.60-0.90)	2.66 (1.44-4.92)	0.52 (0.39-0.69)
	AF	1.75-2.37	6 (476)	0.66 (0.59-0.72)	0.63 (0.57-0.69)	2.05 (1.56-2.70)	0.40 (0.20-0.81)
		3.21-5.60	5 (486)	0.47 (0.41-0.54)	0.73 (0.67-0.79)	1.83 (1.24-2.71)	0.68 (0.50-0.92)
	Cirrhosis	2.21-3.40	5 (440)	0.75 (0.67-0.82)	0.56 (0.50-0.62)	2.06 (1.53-2.77)	0.37 (0.19-0.71)
		6.44	1 (103)	0.68	0.64	1.88	0.51
	TE						
	SF	5.80-7.00	7 (423)	0.83 (0.78-0.87)	0.73 (0.65-0.80)	2.89 (2.23-3.76)	0.23 (0.12-0.42)
		9.10-10.05	2 (100)	0.77 (0.67-0.86)	0.94 (0.70-1.00)	7.65 (1.66-35.32)	0.18 (0.02-1.47)
	AF	8.18-9.00	3 (286)	0.80 (0.72-0.87)	0.80 (0.73-0.86)	4.09 (2.64-6.33)	0.24 (0.17-0.35)
		10.40-12.10	4 (174)	0.73 (0.60-0.83)	0.93 (0.86-0.97)	7.67 (2.89-20.31)	0.27 (0.12-0.61)
	Cirrhosis	11.00-12.67	4 (213)	0.89 (0.82-0.94)	0.88 (0.81-0.93)	6.89 (4.38-10.85)	0.14 (0.09-0.23)
	16.00-19.00	3 (147)	0.88 (0.74-0.96)	0.97 (0.92-0.99)	22.08 (5.35-91.22)	0.16 (0.08-0.33)	
2D-SWE							
SF	8.20-10.00	3 (234)	0.89 (0.83-0.93)	0.72 (0.59-0.83)	3.25 (1.67-6.32)	0.17 (0.11-0.28)	
AF	12.20-15.80	3 (234)	0.82 (0.73-0.89)	0.79 (0.72-0.86)	3.92 (2.79-5.52)	0.24 (0.13-0.44)	
Cirrhosis	14.30-19.30	4 (297)	0.83 (0.74-0.90)	0.86 (0.81-0.91)	5.85 (4.09-8.37)	0.21 (0.13-0.34)	
PBC	APRI						
	SF	0.26-1.20	4 (584)	0.84 (0.80-0.87)	0.63 (0.56-0.70)	1.98 (1.54-2.55)	0.34 (0.23-0.51)
	AF	0.3.0-0.75	8 (858)	0.62 (0.57-0.68)	0.54 (0.50-0.58)	1.39 (1.09-1.79)	0.68 (0.48-0.98)
		0.93-2.00	7 (731)	0.73 (0.68-0.78)	0.68 (0.64-0.72)	2.68 (1.80-3.97)	0.46 (0.36-0.58)
	Cirrhosis	0.65-1.39	6 (852)	0.75 (0.67-0.83)	0.51 (0.48-0.55)	2.19 (1.38-3.50)	0.31 (0.10-0.99)
	AAR						
	SF	0.92-1.00	3 (323)	0.69 (0.61-0.76)	0.56 (0.48-0.63)	1.61 (1.33-1.95)	0.52 (0.31-0.87)
	AF	0.81-1.01	5 (559)	0.54 (0.47-0.62)	0.73 (0.68-0.77)	2.15 (1.52-3.03)	0.63 (0.44-0.91)
	Cirrhosis	1.00-1.10	4 (407)	0.81 (0.70-0.90)	0.77 (0.72-0.82)	4.55 (1.98-10.49)	0.28 (0.10-0.79)
	FIB-4						

	SF	1.39-3.90	3 (462)	0.85 (0.81-0.89)	0.77 (0.69-0.83)	2.89 (2.10-3.98)	0.26 (0.10-0.66)
	AF	2.05-2.63	7 (865)	0.77 (0.72-0.81)	0.57 (0.53-0.61)	1.95 (1.51-2.52)	0.31 (0.16-0.61)
		2.81-4.60	6 (431)	0.63 (0.55-0.71)	0.80 (0.75-0.85)	3.25 (1.78-5.94)	0.49 (0.30-0.81)
	Cirrhosis	2.05-4.60	6 (852)	0.87 (0.80-0.93)	0.61 (0.58-0.65)	2.79 (1.92-4.07)	0.16 (0.05-0.52)
	TE						
	SF	5.90-8.80	4 (402)	0.81 (0.76-0.85)	0.95 (0.89-0.98)	10.51 (2.03-54.36)	0.23 (0.12-0.44)
		16.00	1 (44)	0.94	0.81	4.90	0.07
	AF	6.75-7.60	4 (377)	0.80 (0.73-0.86)	0.81 (0.76-0.86)	4.19 (2.35-7.46)	0.19 (0.05-0.79)
		9.60-10.70	3 (317)	0.91 (0.84-0.95)	0.82 (0.77-0.87)	5.68 (2.55-12.69)	0.12 (0.07-0.21)
		11.90-17.90	3 (180)	0.75 (0.60-0.86)	0.94 (0.88-0.97)	11.76 (2.29-60.48)	0.22 (0.06-0.80)
	Cirrhosis	11.40-14.40	3 (256)	0.84 (0.69-0.93)	0.94 (0.90-0.97)	13.46 (7.66-23.65)	0.19 (0.10-0.38)
		15.60-25.10	3 (227)	0.90 (0.74-0.98)	0.93 (0.89-0.96)	22.8 (0.81-639.69)	0.12 (0.04-0.34)
	RPR						
	AF	0.10-0.14	4 (362)	0.49 (0.40-0.58)	0.89 (0.84-0.92)	4.27 (2.22-8.22)	0.59 (0.47-0.74)
	M2BP						
	AF	1.00-1.40	4 (370)	0.68 (0.59-0.77)	0.80 (0.75-0.85)	4.26 (1.82-9.96)	0.32 (0.14-0.75)
PSC	TE						
	SF	8.80	2 (121)	0.76 (0.62-0.87)	0.88 (0.79-0.95)	6.34 (3.25-12.37)	0.29 (0.18-0.46)
	AF	9.60	3 (177)	0.82 (0.70-0.91)	0.83 (0.75-0.89)	4.75 (2.21-10.19)	0.15 (0.02-1.04)
	Cirrhosis	13.70-14.40	4 (207)	0.82 (0.68-0.91)	0.89 (0.83-0.94)	7.46 (3.74-14.88)	0.25 (0.15-0.43)

2D-SWE: Two-dimensional shear wave elastography; AAR: Aspartate aminotransferase to alanine aminotransferase ratio; AF: Advanced fibrosis; AIH: Autoimmune hepatitis; APRI: Aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis-4 index; M2BP: Mac-2-binding protein; NLR: Negative likelihood ratio; PLR: Positive likelihood ratio; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; RPR: Red cell distribution width to platelet ratio; SF: Significant fibrosis; TE: Transient elastography.

As shown in Table 2, the APRI and FIB-4 index had relatively good summary sensitivities of 0.84 and 0.85, respectively, with mild summary specificities of 0.63 and 0.77, respectively. The corresponding values for sensitivity and specificity of the AAR were poor (0.69, 0.56). In contrast, both the summary sensitivity (0.81; 95%CI: 0.76–0.85) and specificity (0.95; 95%CI: 0.89–0.98) of TE were significantly higher than those of the other five noninvasive methods for predicting SF with cutoff values ranging from 5.9–8.8 KPa.

Furthermore, Table 3 shows that the summary DORs of APRI, FIB-4 and TE were 3.9 (95%CI: 2.1–7.3), 5.1 (95%CI: 3.1–8.5) and 16.8 (95%CI: 8.8–32.2), respectively, in patients with AIH, while the summary DORs of APRI and TE were 6.3 (95%CI: 3.5–11.2) and 74.5 (95%CI: 12.2–455.5), respectively, in patients with PBC. Additionally, the summary AUROC value of TE in patients with PBC (0.93, 95%CI: 0.91–0.95) was relatively higher than that of TE in patients with AIH (0.84, 95%CI: 0.80–0.87) but significantly higher than that of FIB-4 (0.74) and APRI (0.67) in patients with AIH and APRI (0.77) in patients with PBC (Table 3 and Figure 3).

Performance of noninvasive methods in diagnosing AF ($F \geq 3$)

Diagnosis of AF for AIH: Twenty studies ($n = 1435$) evaluated 11 noninvasive methods for detecting AF in patients with AIH. Among them, 10 ($n = 917$), 7 ($n = 532$), 11 ($n = 962$), 7 ($n = 460$), 3 ($n = 234$) and 2 ($n = 191$) studies focused on APRI, AAR, FIB-4, TE, SWE and RPR, respectively; however, only one study each utilized the ARFI, MRS, PC/SD ratio, MRE and M2BP methods.

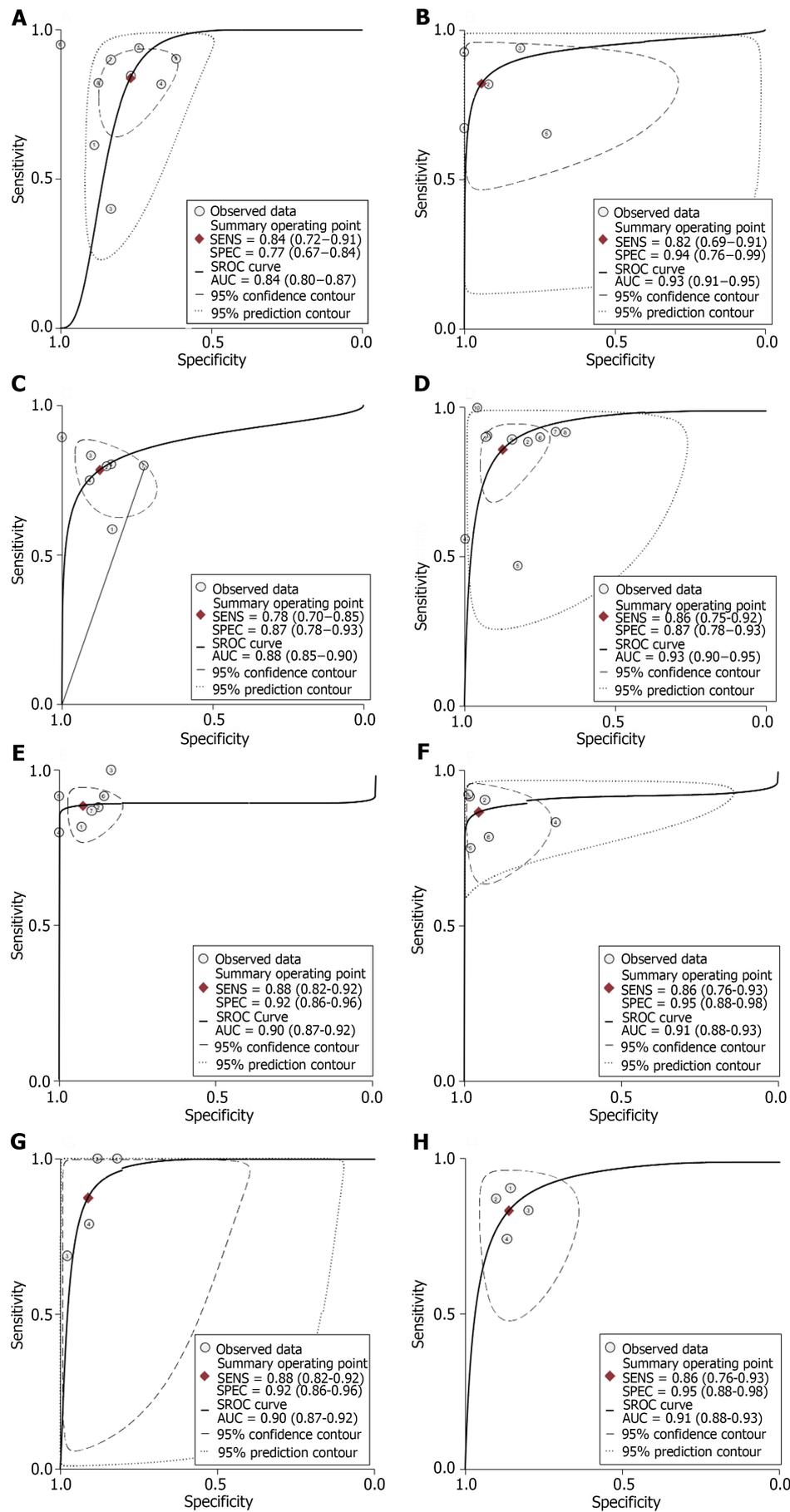
As shown in Table 2, with a cutoff value of 8.2–9.0 KPa, both the summary sensitivity and specificity exceeded 80% when TE was used for predicting AF, whereas with a cutoff value of 10.4–12.1 KPa, there was a better summary specificity (0.93; 95%CI: 0.86–0.97) with a mild summary sensitivity (0.73; 95%CI: 0.60–0.83). Regarding SWE, MRE and the PC/SD ratio, the summary sensitivity and specificity also exceeded 80%. The specificity of MRE was 1.00, but only one study assessed it[22]. For AAR and FIB-4 index, there was a relatively modest summary specificity (< 0.80) and poor summary sensitivity (< 0.60).

Diagnosis of AF for PBC: Twenty-eight studies ($n = 2737$) evaluated 11 noninvasive methods for detecting AF in patients with PBC. Of these, 15 ($n = 1589$), 6 ($n = 559$), 13 ($n = 1296$), 2 ($n = 97$), 10 ($n = 874$), 5 ($n = 362$), 4 ($n = 370$) and 2 ($n = 210$) studies were focused on APRI, AAR, FIB-4, ARFI, TE, RPR, M2BP and SWE, respectively. Only one study each utilized the methods of MRE and RLR.

Table 3 Summary area under the receiver operator curve and diagnostic odds ratio of noninvasive methods for prediction of significant fibrosis, advanced fibrosis and cirrhosis in autoimmune liver diseases patients

Disease	Diagnostic model/Stage	No. of studies (patients)	AUROC (95%CI)	DOR (95%CI)
AIH	APRI			
	SF	4 (383)	0.67 (0.63-0.71)	3.87 (2.1-7.3)
	AF	10 (917)	0.71 (0.67-0.75)	3.85 (2.8-5.3)
	Cirrhosis	6 (543)	0.71 (0.67-0.75)	3.77 (2.2-6.4)
	FIB-4			
	SF	5 (459)	0.74 (0.70-0.78)	5.11 (3.1-8.5)
	AF	11 (962)	0.73 (0.69-0.76)	4.04 (2.4-6.8)
	Cirrhosis	6 (543)	0.72 (0.68-0.76)	5.48 (2.4-12.6)
	TE			
	SF	9 (523)	0.84 (0.80-0.87)	16.83 (8.8-32.2)
	AF	7 (460)	0.88 (0.85-0.90)	25.14 (9.7-65.3)
	Cirrhosis	7 (415)	0.90 (0.87-0.92)	91.77 (40.1-201.2)
	AAR			
	AF	6 (410)	0.73 (0.69-0.77)	4.94 (3.2-7.8)
PBC	2D-SWE			
	Cirrhosis	4 (297)	0.91 (0.89-0.94)	30.68 (15.7-59.9)
	APRI			
	SF	4 (584)	0.77 (0.73-0.80)	6.27 (3.5-11.2)
	AF	15 (1589)	0.70 (0.66-0.74)	3.67 (2.3-5.9)
	Cirrhosis	6 (852)	0.83 (0.79-0.86)	14.55 (1.9-113.8)
	FIB-4			
	AF	13 (1296)	0.79 (0.75-0.82)	7.13 (4.0-12.8)
	Cirrhosis	6 (852)	0.88 (0.85-0.91)	29.79 (5.9-150.3)
	TE			
	SF	5 (446)	0.93 (0.91-0.95)	74.45 (12.2-455.5)
	AF	10 (880)	0.93 (0.90-0.95)	41.84 (19.3-91.0)
	Cirrhosis	6 (483)	0.91 (0.88-0.93)	134.83 (33.0-551.8)
	AAR			
AF	6 (559)	0.74 (0.70-0.78)	4.13 (2.0-8.6)	
Cirrhosis	4 (407)	0.88 (0.84-0.90)	25.29 (9.0-70.9)	
RPR				
AF	4 (362)	0.53 (0.49-0.58)	7.98 (4.0-15.8)	
M2BP				
AF	4 (370)	0.86 (0.82-0.88)	13.17 (4.1-42.4)	
PSC	TE			
	Cirrhosis	4 (207)	0.95 (0.93-0.97)	70.59 (15.4-322.7)

2D-SWE: Two-dimensional shear wave elastography; 95%CI: 95% confidence interval; AAR: Aspartate aminotransferase to alanine aminotransferase ratio; AF: Advanced fibrosis; AIH: Autoimmune hepatitis; APRI: Aspartate aminotransferase to platelet ratio index; AUROC: Area under the receiver operator curve; DOR: Diagnostic odds ratio; FIB-4: Fibrosis-4 index; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; RPR: Red cell distribution width to platelet ratio; SF: Significant fibrosis; TE: Transient elastography.



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Figure 3 The summary receiver operating characteristic curve plots of transient elastography in autoimmune liver disease patients. A and

B: Transient elastography (TE) for detecting significant fibrosis in autoimmune hepatitis (AIH, A) and primary biliary cholangitis (PBC, B) patients; C and D: TE for detecting advanced fibrosis in AIH (C) and PBC (D) patients; E-G: TE for detecting cirrhosis in AIH (E), PBC (F) and primary sclerosing cholangitis (G) patients; H: Shear wave elastography for detecting cirrhosis in AIH patients. AUC: Area under the curve; SENS: Sensitivity; SPEC: Specificity; SROC: Summary receiver operating characteristic.

As shown in **Table 2**, TE had a good summary sensitivity and specificity (0.91, 0.82) with a cutoff value of 9.6–10.7 KPa, while RPR and M2BP had good summary specificity (0.89 and 0.80, respectively) with poor summary sensitivity (0.49 and 0.68, respectively). Regardless of the cutoff values, the summary sensitivities and specificities of the AAR, APRI and FIB-4 were less than 0.80.

Furthermore, **Table 3** shows that the summary DORs of AAR, APRI, FIB-4 and TE were 4.9 (95%CI: 3.2–7.8), 3.9 (95%CI: 2.8–5.3), 4.0 (95%CI: 2.4–6.8) and 25.1 (95%CI: 9.7–65.3), respectively, in patients with AIH and 4.1 (95%CI: 2.0–8.6), 3.7 (95%CI: 2.3–6.0), 7.1 (95%CI: 4.0–12.8) and 41.8 (95%CI: 19.3–91.0), respectively, in patients with PBC. Moreover, the summary DORs of RPR and M2BP in patients with PBC were 8.0 (95%CI: 4.0–15.8) and 13.2 (95%CI: 4.1–42.4), respectively. As shown in **Table 3** and **Figure 3**, the summary AUROC value of TE for detecting AF was 0.88 (95%CI: 0.85–0.90) and 0.93 (95%CI: 0.90–0.95) in patients with AIH and PBC, respectively. The value of M2BP was 0.86 (95%CI: 0.82–0.88) in patients with PBC, whereas the summary AUROC values for AAR, APRI and FIB-4 were less than 0.80 in both patients with AIH and PBC, and the value for RPR in patients with PBC was less than 0.60.

Performance of noninvasive methods in diagnosing cirrhosis (F = 4)

Diagnosis of cirrhosis for AIH: Sixteen studies ($n = 1076$) evaluated ten noninvasive methods for detecting cirrhosis in patients with AIH. Of these, six ($n = 543$), three ($n = 213$), six ($n = 543$), two ($n = 82$), seven ($n = 415$) and four ($n = 297$) studies focused on APRI, AAR, FIB-4, ARFI, TE and SWE, respectively. Only one study each utilized the PC/SD ratio, MRE, RPR and M2BP.

As shown in **Table 2**, the summary sensitivities and specificities of APRI and FIB-4 were less than 75%, and those of AAR were 0.61 and 0.83, respectively. Moreover, the summary sensitivity and specificity of TE (cutoff value ranging from 11.0–12.7 KPa) were significantly higher for predicting cirrhosis, with 0.89 (95%CI: 0.82–0.94) and 0.88 (95%CI: 0.81–0.93), respectively, while the summary sensitivity and specificity of SWE (0.83, 0.86) were close to those of TE. Surprisingly, the summary specificity dramatically rose to 0.97 (95%CI 0.92–0.99) with a cutoff value ranging from 16.0–19.0 KPa.

Diagnosis of cirrhosis for PBC: Sixteen studies ($n = 1568$) evaluated nine noninvasive methods for detecting cirrhosis in patients with PBC. Among them, six ($n = 852$), four ($n = 407$), six ($n = 852$), six ($n = 483$), two ($n = 210$) and two ($n = 194$) studies focused on APRI, AAR, FIB-4, TE, SWE and M2BP, respectively. However, only one study utilized the ARFI and MRE methods.

As listed in **Table 2**, the summary sensitivities of APRI, AAR and FIB-4 for predicting cirrhosis were 0.75, 0.81 and 0.87, respectively, and their corresponding summary specificities were 0.51, 0.77 and 0.61, respectively. In contrast, TE had higher summary sensitivity (0.90; 95%CI: 0.74–0.98) and specificity (0.93; 95%CI: 0.89–0.96) with a cutoff value ranging from 15.6–25.1 KPa.

Diagnosis of cirrhosis for PSC: Four studies ($n = 207$) evaluated TE as a predictor of cirrhosis in patients with PSC. Because the diagnosis of PSC does not rely on liver biopsy, few related studies have been conducted. As listed in **Table 2**, the summary sensitivity and specificity of TE were 0.82 (95%CI: 0.68–0.91) and 0.89 (95%CI: 0.83–0.94), respectively.

Furthermore, **Table 3** shows that the summary DORs of APRI and FIB-4 were 3.8 (95%CI: 2.2–6.4) and 5.5 (95%CI: 2.4–12.6) in patients with AIH and 14.6 (95%CI: 1.9–113.8) and 29.8 (95%CI: 5.9–150.3) in patients with PBC. In addition, the summary DOR of TE was highest in patients with PBC, with values of 91.8 (95%CI: 40.1–201.2), 134.8 (95%CI: 33.0–551.8) and 70.6 (95%CI: 15.4–322.7) in patients with AIH, PBC and PSC, respectively. The summary AUROC values of TE for detecting cirrhosis in patients with AIH, PBC and PSC were 0.90 (95%CI: 0.87–0.92), 0.91 (95%CI: 0.88–0.93) and 0.95 (95%CI: 0.93–0.97), respectively, while the summary AUROC values for APRI and FIB-4 were less than 0.80 in patients with AIH and 0.90 in patients with PBC (**Table 3** and **Figure 3**).

Methodological heterogeneity, subgroup analysis and publication bias

As shown in **Table 4**, threshold heterogeneity was observed only in APRI F2 in both patients with AIH and PBC, whereas nonthreshold heterogeneity was observed in most groups (**Figure 4**, **Supplementary Figures 2 and 3**). Because meta-regression to explore the source of heterogeneity requires the number of original studies to exceed 10, we only conducted a meta-regression for AF in patients with AIH and PBC. The heterogeneity of APRI, FIB-4 and TE accuracy was mainly affected by the cutoff value with regard to specificity, whereas FIB-4 and TE were affected by sample size with regard to sensitivity, according to the meta-regression analysis (**Supplementary Figure 4**).

Subgroup analyses of TE according to sample size, cutoff value and treatment status are shown in **Table 5**. Because of the limited data, we only conducted an analysis for posttreatment combined with original data for pretreatment (**Supplementary Table 2**).

Deeks' funnel plot of these noninvasive methods was generated to assess publication bias. There was a publication bias for APRI in detecting SF ($P = 0.06$) and cirrhosis ($P = 0.08$) in patients with PBC but not in other methods for detecting SF, AF and cirrhosis (**Figure 5**, **Supplementary Figure 5**). Moreover, no publication bias was observed for any noninvasive method in patients with AIH (**Figure 5**, **Supplementary Figure 6**).

Table 4 Heterogeneity of all the included studies

			Threshold heterogeneity		Non-threshold heterogeneity		
			<i>r</i>	<i>P</i> value	<i>I</i> ² (%)	<i>P</i> value	
AIH	TE	SF	0.176	0.651	82.9	0	
		AF	-0.429	0.337	93.8	0	
		Cirrhosis	0.321	0.482	56.59	0.03	
	APRI	SF	1.0	0	62.34	0.05	
		AF	0.717	0.02	71.94	0	
		Cirrhosis	0.714	0.111	90.93	0	
	FIB-4	SF	0.70	0.188	46.81	0.11	
		AF	0.627	0.039	98.29	0	
		Cirrhosis	-0.029	0.957	88.98	0	
	AAR	AF	0.857	0.014	36.46	0.16	
	SWE	Cirrhosis	0	1.0	61.97	0.05	
	PBC	TE	SF	-0.10	0.873	99.99	0
AF			0.195	0.590	100	0	
Cirrhosis			-0.726	0.027	93.77	0	
APRI		SF	1.0	0	99.9	0	
		AF	0.209	0.454	100	0	
		Cirrhosis	-0.657	0.156	100	0	
FIB-4		AF	0.418	0.156	100	0	
		Cirrhosis	0.029	0.957	100	0	
AAR		AF	0.60	0.208	96.05	0	
		Cirrhosis	0.40	0.60	95.37	0	
M2BP		AF	0	1.0	99.24	0	
RPR		AF	0	1.0	94.49	0	
PSC		TE	Cirrhosis	0.80	0.20	50.07	0.11

AAR: Aspartate aminotransferase to alanine aminotransferase ratio; AF: Advanced fibrosis; AIH: Autoimmune hepatitis; APRI: Aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis-4 index; M2BP: Mac-2-binding protein; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; RPR: Red cell distribution width to platelet ratio; SF: Significant fibrosis; SWE: Shear wave elastography; TE: Transient elastography.

DISCUSSION

In our review, a total of 60 studies (including 1594, 3126 and 501 patients with AIH, PBC and PSC, respectively) were included to evaluate the diagnostic accuracy of noninvasive methods for predicting SF, AF and cirrhosis in patients with AILDs. TE had excellent accuracy with summary AUROC values of 0.93, 0.93 and 0.91 for SF, AF and cirrhosis, respectively, in patients with PBC, while TE had a moderate to excellent accuracy of 0.84, 0.88 and 0.90, respectively, in patients with AIH. Moreover, the summary AUROC was 0.95 for cirrhosis in patients with PSC. In contrast, other noninvasive methods, such as AAR, APRI, FIB-4 and RPR, had poor accuracy, with summary AUROC values of < 0.80. In addition, the pooled sensitivity and specificity of TE were higher than those of the other noninvasive methods. Our results indicated that LSM using TE had a better diagnostic performance for staging hepatic fibrosis in AILDs, especially in patients with PBC. Moreover, our results showed that TE had mostly higher specificity and relatively low sensitivity for the diagnosis of AILDs. Koizumi *et al*[23] found that TE had high sensitivity and relatively low specificity for the diagnosis of PBC. However, the optimal cutoff values were higher and the range was wider than those in other studies, indicating that different optimal cutoff values may have an effect on diagnostic accuracy.

Meta-regression analysis is a reliable method for screening heterogeneity. In our study, the sample size, cutoff values, prevalence of SF and scoring system provided heterogeneity in summarizing the test results, consistent with previous studies[24,25]. We conducted subgroup analyses based on the sample size and cutoff values. Our results revealed that TE had a better predictive effect in a larger sample of patients with PBC. LSM by TE is the best surrogate marker for staging in SF and AF with a cutoff ranging from 6.4–9.1 KPa and 9.0–11.0 KPa, respectively, in patients with AIH and staging in

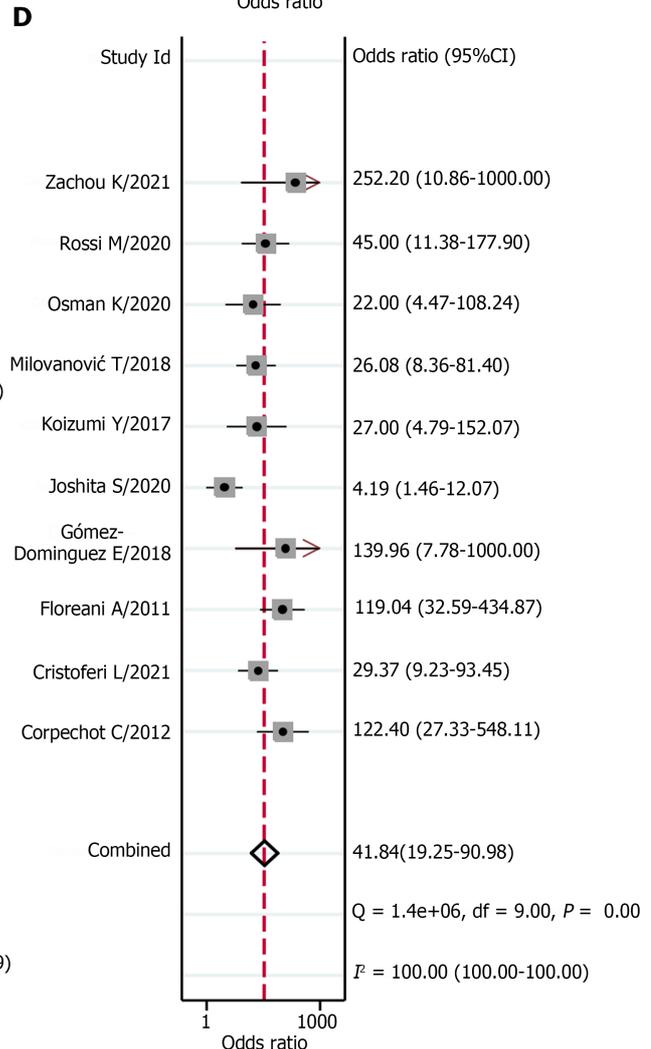
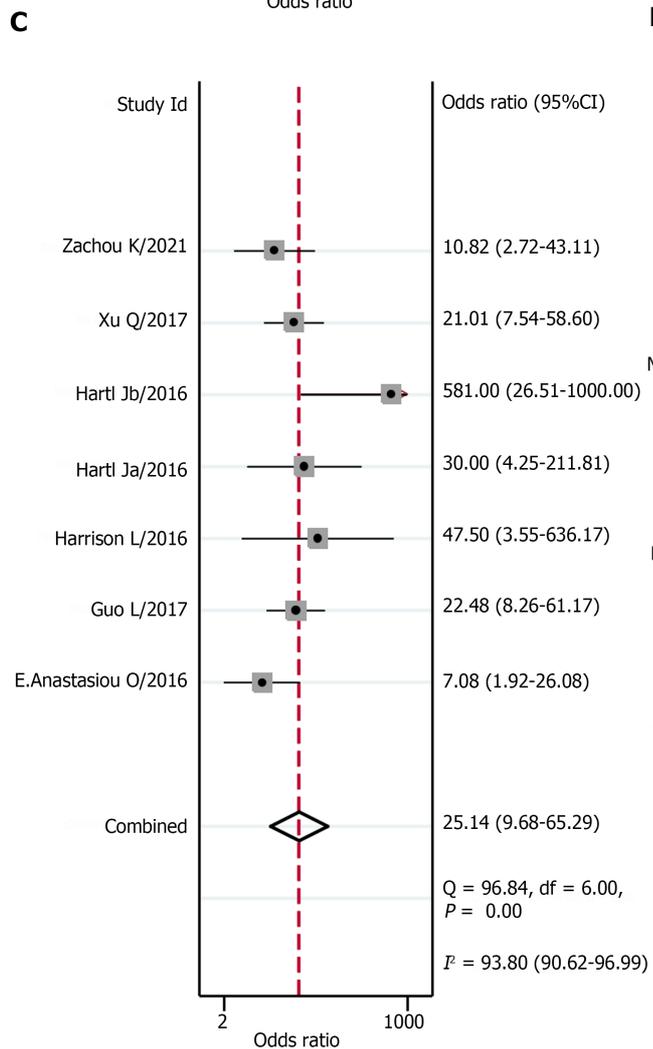
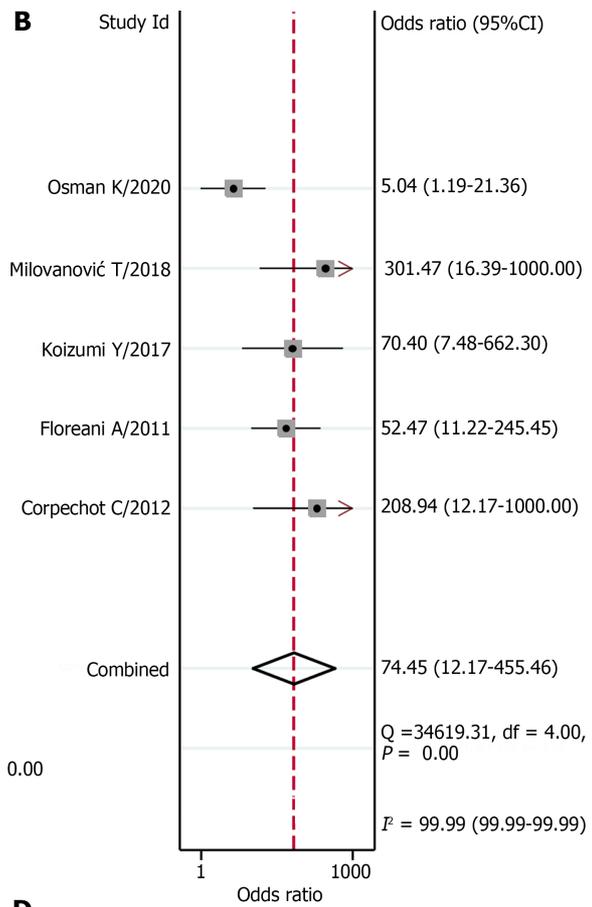
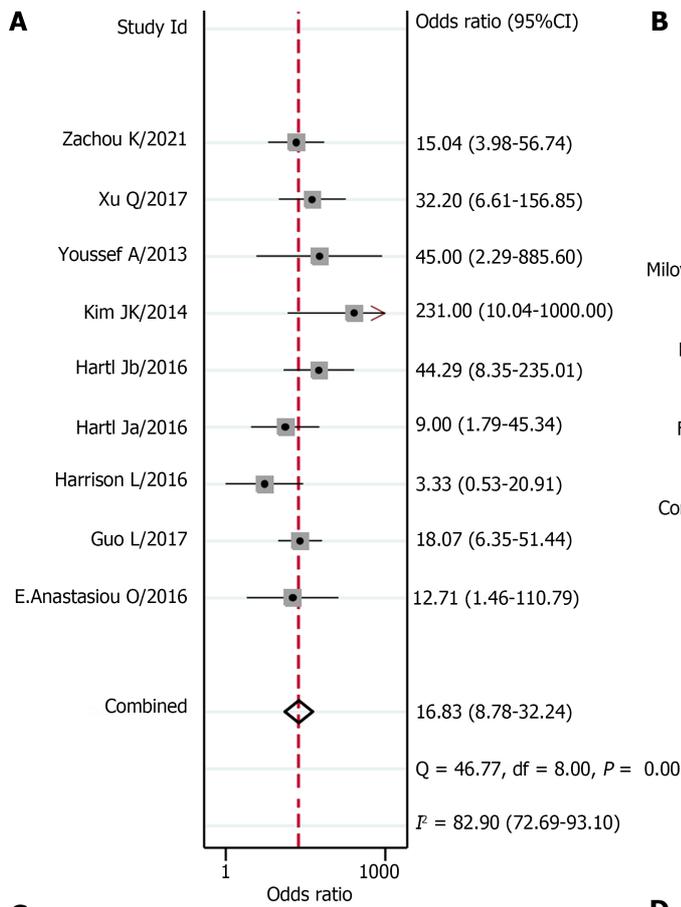
Table 5 Subgroup analysis of sample size and treatment status in prediction of significant fibrosis, advanced fibrosis and cirrhosis in autoimmune hepatitis and primary biliary cholangitis patients

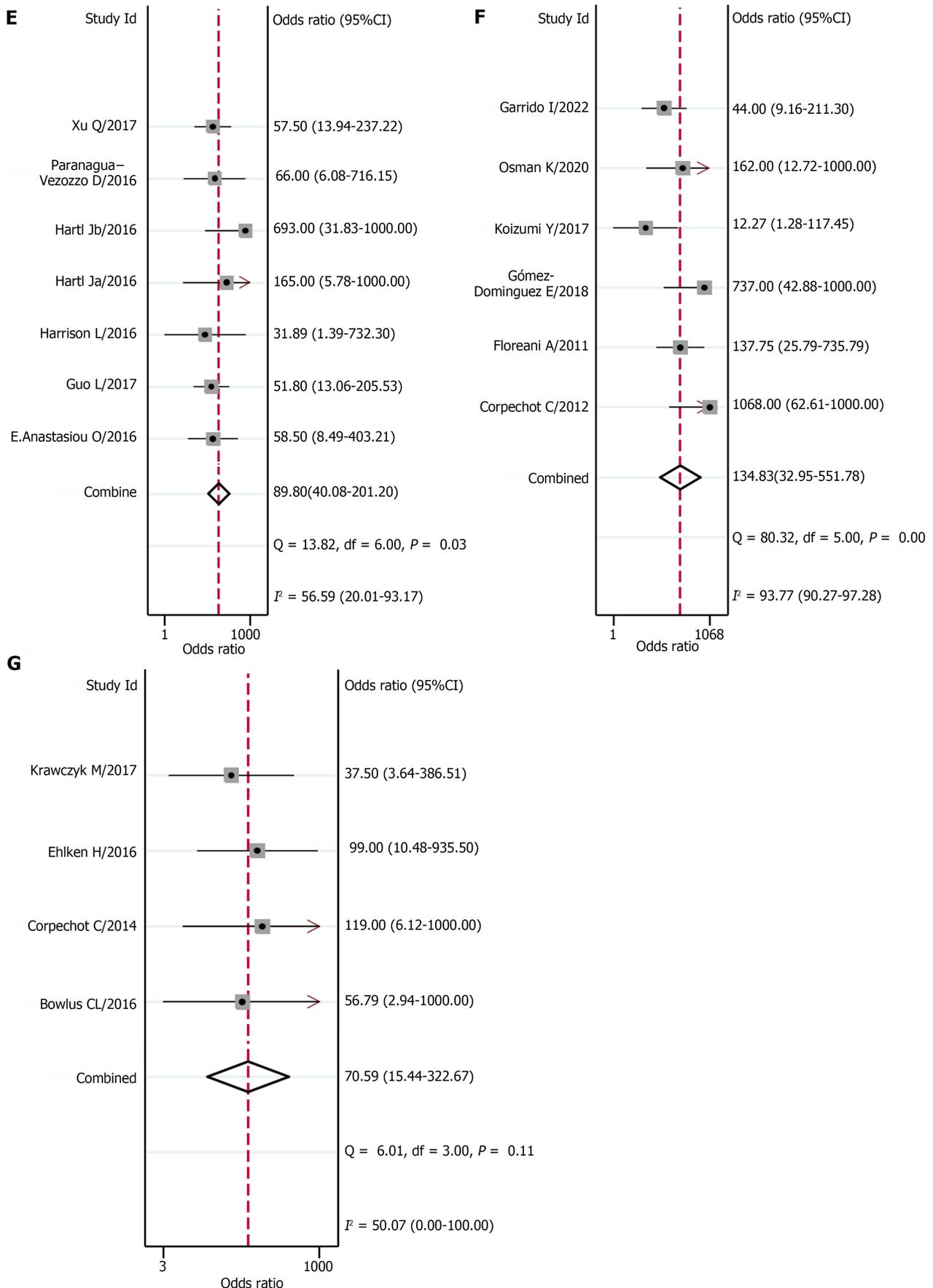
Disease	Parameter	Stage	Subgroup	Sensitivity (95%CI)	Specificity (95%CI)	AUROC (95%CI)
AIH	Sample size	SF	$n < 50$	0.83 (0.55-0.95)	0.82 (0.65-0.92)	0.85 (0.82-0.88)
			$n > 50$	0.84 (0.73-0.91)	0.77 (0.63-0.87)	0.87 (0.84-0.90)
		AF	$n < 50$	0.78 (0.54-0.91)	0.91 (0.78-0.96)	0.92 (0.89-0.94)
			$n > 50$	0.78 (0.68-0.86)	0.87 (0.73-0.94)	0.88 (0.84-0.90)
		Cirrhosis	$n < 50$	0.90 (0.65-0.98)	0.92 (0.74-0.98)	0.96 (0.94-0.97)
			$n > 50$	0.88 (0.82-0.93)	0.93 (0.86-0.96)	0.92 (0.89-0.94)
	Treatment status	SF	Post	0.78 (0.44-0.94)	0.76 (0.60-0.86)	0.79 (0.75-0.82)
		AF	Post	0.83 (0.66-0.93)	0.96 (0.84-0.99)	0.93 (0.91-0.95)
		Cirrhosis	Post	0.91(0.77-0.97)	0.97 (0.73-1.00)	0.94 (0.91-0.95)
	Cutoff value	SF	5.80-6.27	0.87 (0.81-0.92)	0.69 (0.60-0.77)	0.86 (0.83-0.89)
			6.40-9.10	0.82 (0.75-0.88)	0.89 (0.74-0.96)	0.92 (0.89-0.94)
		AF	9.00-11.00	0.83 (0.69-0.91)	0.92 (0.73-0.98)	0.88 (0.85-0.91)
			8.18-12.10	0.77 (0.71-0.83)	0.85 (0.80-0.89)	0.88 (0.85-0.90)
		Cirrhosis	11.00-12.67	0.89 (0.82-0.94)	0.88 (0.81-0.93)	0.92 (0.94-0.96)
11.00-19.00			0.88 (0.82-0.93)	0.92 (0.88-0.95)	0.90 (0.87-0.92)	
PBC	Sample size	SF	$n < 100$	0.81 (0.48-0.95)	0.78 (0.60-0.89)	0.82 (0.79-0.86)
			$n > 100$	0.83 (0.68-0.92)	0.98 (0.74-1.00)	0.97 (0.95-0.98)
		AF	$n < 100$	0.90 (0.85-0.94)	0.88 (0.78-0.94)	0.91 (0.88-0.93)
			$n > 100$	0.81 (0.64-0.91)	0.88 (0.75-0.94)	0.91 (0.88-0.93)
		Cirrhosis	$n < 100$	0.82 (0.67-0.91)	0.94 (0.80-0.99)	0.86 (0.82-0.89)
			$n > 100$	0.91 (0.76-0.97)	0.97 (0.90-0.99)	0.94 (0.92-0.96)
	Treatment status	SF	Post	0.89 (0.70-0.97)	0.98 (0.41-1.00)	0.97 (0.95-0.98)
		AF	Post	0.85 (0.68-0.94)	0.92 (0.63-0.99)	0.93 (0.91-0.95)
		Cirrhosis	Post	0.90 (0.71-0.97)	0.96 (0.74-1.00)	0.94 (0.92-0.96)
	Cutoff value	AF	6.75-7.60	0.80 (0.73-0.86)	0.81 (0.76-0.86)	0.88 (0.85-0.91)
			9.60-10.70	0.91 (0.84-0.95)	0.82 (0.77-0.87)	0.92 (0.89-0.94)
			11.90-17.90	0.75 (0.60-0.86)	0.94 (0.88-0.97)	0.93 (0.91-0.95)
		Cirrhosis	11.40-14.40	0.84 (0.69-0.93)	0.94 (0.90-0.97)	0.96 (0.94-0.97)
			14.40-16.90	0.88 (0.72-0.97)	0.99 (0.96-1.00)	0.99 (0.98-1.00)

95%CI: 95% confidence interval; AF: Advanced fibrosis; AIH: Autoimmune hepatitis; AUROC: Area under the receiver operator curve; PBC: Primary biliary cholangitis; SF: Significant fibrosis.

AF and cirrhosis with a cutoff ranging from 9.6–10.7 KPa and 14.4–16.9 KPa, respectively, in patients with PBC.

Several previous studies have demonstrated that inflammation in the liver (reflected by elevated ALT levels)[26] and extrahepatic cholestasis (reflected by total bilirubin)[27] may increase the stiffness value, causing a decrease in the diagnostic accuracy of TE, whereas ALT and bilirubin levels decline after treatment. Because a limited number of studies have reported results for the ALT subgroup, we only conducted a subgroup analysis of treatment conditions, which showed that the diagnostic accuracy for staging liver fibrosis was comparable between pretreatment and posttreatment in patients with both PBC and AIH. In other words, this may indicate that ALT levels have no significant effect on diagnostic accuracy. Meanwhile, two scoring systems [International Autoimmune Hepatitis Group (IAIHG) 1999 and IAIHG 2008] proposed by Granito *et al*[28] for the diagnosis of AIH are not interchangeable. According to our subgroup analysis regarding diagnostic criteria, the IAIHG 2008 showed diagnostic accuracy comparable to that of the IAIHG 1999 in distinguishing patients with AIH (Supplementary Tables 3 and 4). However, due to the limited number of studies, further investigation is required to confirm these results.

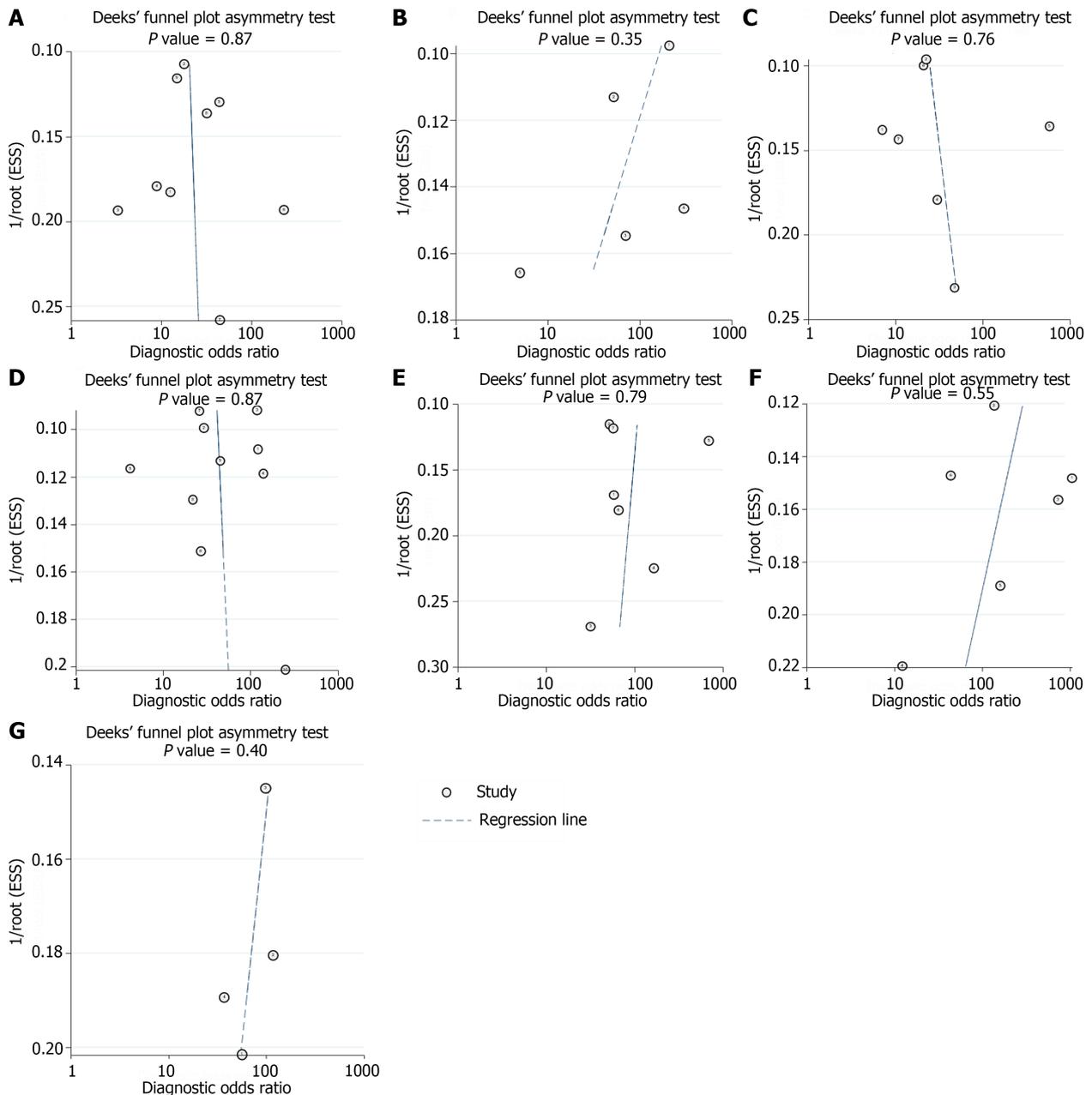




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Figure 4 Forest plots of diagnostic odds ratio of transient elastography in autoimmune liver disease patients. A and B: Transient elastography (TE) for detecting significant fibrosis in autoimmune hepatitis (AIH, A) and primary biliary cholangitis (PBC, B) patients, respectively; C and D: TE for detecting

advanced fibrosis in AIH (C) and PBC (D) patients; E-G: TE for detecting cirrhosis in AIH (E), PBC (F) and primary sclerosing cholangitis (G) patients. 95%CI: 95% confidence interval.



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Figure 5 Deeks' funnel plot asymmetry test for publication bias of transient elastography in autoimmune liver disease patients. A and B: Transient elastography (TE) for detecting significant fibrosis in autoimmune hepatitis (AIH, A) and primary biliary cholangitis (PBC, B) patients; C and D: TE for detecting advanced fibrosis in AIH (C) and PBC (D) patients; E-G: TE for detecting cirrhosis in AIH (E), PBC (F) and primary sclerosing cholangitis (G) patients.

In addition, some studies have shown that other imaging technologies, including two-dimensional-SWE (2D-SWE)[29-32], MRE[22,33] and ARFI[19,34], also perform well in staging liver fibrosis (Supplementary Table 5). Further, 2D-SWE had excellent accuracy, with a summary AUROC of 0.91 for cirrhosis in patients with AIH (Table 3). In comparison, our findings indicated that 2D-SWE and ARFI had good accuracy with higher sensitivity, specificity and AUROC for AF and cirrhosis in patients with PBC, while the AUROC of MRE was higher in patients with AIH. Interestingly, compared with TE, 2D-SWE produces a two-dimensional grayscale image so that interference from the gallbladder, ascites and large tubular structures in the liver can be effectively avoided. However, the number of studies on 2D-SWE, MRE and ARFI included in our analysis was small. Indeed, the diagnostic accuracies of 2D-SWE and MRE require further studies with larger sample sizes to determine the best method for staging fibrosis in patients with AILDs.

However, the overlap syndrome, one of the AILDs, also deserves attention because it exhibits significantly higher rates of various complications, progresses to cirrhosis more rapidly and has a poor treatment response to ursodeoxycholic acid [35,36]. Hence, the development of noninvasive methods is beneficial for this disease. Wu *et al*[37] reported that the AUROCs of TE for SF, AF and cirrhosis were 0.837, 0.910 and 0.996, respectively. Yan *et al*[38] reported that the AUROCs of SWE were 0.91, 0.97 and 0.96, respectively. These results show that noninvasive imaging techniques have excellent accuracy for overlap syndrome, although more studies are required for further validation.

Our study had some limitations. First, we only included studies published in the English language; therefore, a language bias may have influenced the results. Second, we did not consider the confounding factors such as obesity, whereas a previous study proposed that a high BMI may reduce the efficiency of ultrasound-based elastography techniques in detecting fibrosis[39]. However, only a limited number of studies have provided sufficient data to conduct subgroup analyses to explore the potential impact of BMI on the diagnostic effects. Third, it is unknown whether ALT level is responsible for the difference in the diagnosis of TE between patients with AIH and PBC due to a lack of sufficient data. Moreover, the treatment conditions before inclusion in the study were unknown, and the lack of pretreatment studies made it impossible to compare the effects of treatment on outcomes. Finally, the number of studies on SWE, MRE and ARFI was inadequate to compare the effects of these imaging technologies and TE.

CONCLUSION

In conclusion, LSM using TE had better diagnostic performance for staging hepatic fibrosis in patients with AILDs compared to other serum biomarkers, especially in patients with PBC. The appropriate cutoff value for staging in AF and cirrhosis ranged from 9.6 to 10.7 KPa and 14.4 to 16.9 KPa, respectively, for patients with PBC. Additional recommended optimal cutoff values warrant further investigation to provide a better reference for clinical applications.

ARTICLE HIGHLIGHTS

Research background

Noninvasive criteria are needed for autoimmune liver diseases (AILDs) to assess liver fibrosis stage for prognosis and treatment decisions.

Research motivation

Results of individual diagnostic test accuracy studies assessing the diagnostic accuracy of transient elastography (TE) for the diagnosis of AILD appear promising. However, previous systematic review and meta-analyses have focused primarily on other liver diseases, which is still lacking in AILD.

Research objectives

To compare the diagnostic accuracy of imaging techniques with serum biomarkers of fibrosis in AILD.

Research methods

The PubMed, Cochrane and EMBASE databases were searched for literature. The Quality Assessment of Diagnostic Accuracy Studies-2 tool was used to evaluate the quality. Meta-Disc 1.4 and STATA 12.0 software were used to analyze the combined statistics: sensitivity; specificity; positive likelihood ratio; negative likelihood ratio; diagnostic odds ratio; and area under the curve fitted to the total receiver operating characteristic curve (AUROC).

Research results

A total of 60 studies were included in the meta-analysis. The AUROC curve values were 0.93, 0.93 and 0.91 for significant fibrosis, advanced fibrosis and cirrhosis, respectively, in primary biliary cholangitis patients, while the AUROC curve values were 0.84, 0.88 and 0.90, respectively, in autoimmune hepatitis patients.

Research conclusions

TE is a reliable method for diagnosis in AILD patients, especially in primary biliary cholangitis patients. The appropriate cutoff value for staging advanced fibrosis and cirrhosis ranged from 9.6 to 10.7 KPa and 14.4 to 16.9 KPa, respectively.

Research perspectives

We propose a suitable diagnostic threshold for TE in PBC patients. However, future prospective multicenter studies with TE and histopathology protocol are required to validate our results.

FOOTNOTES

Author contributions: Jiang W conceived and designed the study; Chen H and Shen Y contributed to acquiring the data; Wang MX and

Weng CZ contributed statistical analysis support; Chen H, Shen Y, Wu SD and Zhu Q contributed to analysis and interpretation of the data; Chen H wrote the manuscript; Wu SD and Zhang J contributed to manuscript revision; All authors read and approved the submitted version and are accountable for all aspects of the work.

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