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[ARTICLE TITLE]

Results presentation

Graphic presentation of the results

Author Last Name, et al.

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Estimation of liver fibrosis using elastography in cholestatic diseases: systematic review and meta-analysis

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ABSTRACT

Introduction: staging fibrosis extent in liver disease is highly relevant for appropriate management. Liver biopsy remains the reference standard for assessment, but noninvasive methods such as elastography are becoming increasingly accurate and relevant. However, evidence regarding elastography in cholestatic diseases is lower than in other etiologies.

Methods: we searched MEDLINE, EMBASE and Web of Science for publications on the diagnostic accuracy of transient elastography and sonoelastography in cholestatic diseases (PBC and PSC) using biopsy as the reference standard. A systematic review and meta-analysis of the results was then carried out.

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Results: a total of 13 studies were included. Using transient elastography in PBC sensitivity and specificity were estimated to be 0.76 and 0.93; 0.88 and 0.9; and 0.91 and 0.95 for ≥ F2, ≥ F3 and = F4, respectively. For sonoelastography in PBC sensitivity and specificity estimates were 0.79 and 0.82; 0.95 and 0.86; and 0.94 and 0.85 for ≥ F2, ≥ F3 y = F4, respectively. In PSC, transient elastography had a sensivity and specificity of 0.76 and 0.88; 0.91 and 0.86; and 0.71 and 0.93 for ≥ F2, ≥ F3 and = F4, respectively.

Conclusion: elastography has adequate diagnostic accuracy in the assessment of fibrosis stages in cholestatic liver diseases.

Keywords: Elastography. Ultrasonidos. Hepatic fibrosis. Transient elastography. Primary biliary cholangitis. Primary sclerosing cholangitis.

INTRODUCTION

Diagnosing and staging fibrosis extent in liver disease is important for managing the condition properly as it is directly associated with disease prognosis and complications development (1). Liver biopsy is the reference standard method for diagnosing and staging fibrosis extent. However, this is an invasive technique not exempt of potentially serious complications (1 %) (2,3), with both inter- and intra-observer variability (1,4,5). Furthermore, heterogeneous fibrosis distribution may lead to obtaining a non-representative sample (1,4,5).

Because of this, non-invasive tests for assessing liver fibrosis are becoming increasingly popular as well as increasingly used in routine clinical practice (6). Among non-invasive tests, elastography plays a significant role in diagnosing and staging liver fibrosis (6,7), and among elastography techniques, transient elastography (TE) and ultrasound-guided techniques, SWE and ARFI carry more weight in clinical practice (6,7).

Among chronic liver conditions, autoimmune cholestatic diseases have been less studied regarding elastographic assessment. Primary biliary cholangitis (PBC) is an uncommon autoimmune cholestatic disease characterized by non-suppurative, granulomatous, lymphocytic small-duct cholangitis (8). Primary sclerosing cholangitis

(PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis that destroy intra- and extra-hepatic bile ducts, which leads to cirrhosis (9).

Evidence is scarcer on the usefulness of elastography for PBC and PSC, but higher liver stiffness scores are reportedly associated with poorer prognosis (7,9).

Given the growing use of elastography methods for the staging and follow-up of patients with chronic liver disease, as well as the lack of consensus and evidence regarding said usefulness in the setting of autoimmune cholestatic conditions, we decided to perform a systematic review and meta-analysis of the current data on this class of diseases and on their study using elastographic methods, specifically TE and sonoelastography.

MATERIAL AND METHODS

The study was conducted according to the PRISMA 2020 guidelines as described in the following sections.

Literature search

A literature search of the medical databases PubMed (MEDLINE), EMBASE and Web of Science from their onset to the present time. The following terms were used — (primary biliary cholangitis), (primary biliary cirrhosis), (primary sclerosing cholangitis), (elastography), (ARFI), (shear wave or 2D-SWE), (FibroScan or transient elastography), (acoustic radiation force impulse), (magnetic resonance elastography).

The search strategy was as follows: (primary biliary cholangitis OR primary biliary cirrhosis OR primary sclerosing cholangitis) AND (elastography OR ARFI OR shear wave OR fibroscan OR acoustic radiation force impulse OR magnetic resonance elastography) NOT review[Publication Type] NOT meta analysis [Publication Type].

Experts in the field were asked to identify additional publications.

Study selection

Two independent reviewers (ALJ and NMC) read the abstracts of the candidate articles, and the full text was collected where an abstract was unavailable. The articles were read and compliance with inclusion criteria was independently verified. Disagreements

were solved by a third independent researcher (MGG). Primary studies reporting data required for the meta-analysis were identified and included.

Inclusion/exclusion criteria

Inclusion criteria were as follows: studies in patients with PBC or PSC; if patients with other liver etiologies were also included, the data of those with PBC and PCS had to be available separately; the elastographic diagnostic methods used had to be TE, 2D-SWE, ARFI; studies had to compare results versus liver biopsy as gold standard; both prospective and retrospective studies were included that were written in English or Spanish.

Studies in animals, studies in children, articles with incomplete information, and systematic reviews and meta-analyses were excluded, as were conference communications, combined studies, studies not comparing results to liver biopsy, and studies combining patients with different liver disease causes.

Study quality assessment

All studies meeting the inclusion criteria were analyzed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS2) list. This tool is comprised of 4 domains: patient selection, index test, reference standard, and patient flow. All domains are assessed for bias risk, and the first three domains also for applicability.

Data extraction

Two reviewers (NMC and ALJ) independently extracted the required information from the original studies. Data were collected from each study regarding type of elastography used, number of patients, etiology of cholestatic disease (PBC or PSC), sensitivity, specificity, positive predictive value, negative predictive value (all this with a 95 % confidence interval), and area under the curve for the various fibrosis stages in the various types of liver disease. Cut-off values were also collected for the different fibrosis stages.

Statistical analysis

Average sensitivity and specificity values were estimated using a bivariate hierarchical model (10). When the number of studies was lower than 4 or the bivariate model had convergence issues, said average values were estimated by a univariate random-effects model. Heterogeneity among studies from the bivariate model was described by means of logit variances, and from I^2 statistics (11) when the univariate model was used. The MetaDiSc 2.0 software was used for the analysis online.

RESULTS

A total of 185, 79, and 232 potentially eligible articles were found in PubMed, Embase, and WoS, respectively. After evaluation and duplicate removal 61 articles had their titles and abstracts reviewed. Of these, 25 full articles were reviewed, and finally 16 articles met all inclusion/exclusion criteria, 3 of them being excluded because of incomplete data (Fig. 1).

Study quality and applicability were assessed using the QUADAS 2, as described in the Material and Methods section. The results of the analysis are listed in table 1.

The characteristics of the different studies that were finally included are listed in table 2.

TE in PBC

For the diagnosis of significant fibrosis (equal to or higher than F2) using transient elastography (TE), a sensitivity of 0.76 (95 % CI; 0.63-0.85) and a specificity of 0.93 (95 % CI; 0.70-0.99) were estimated, with a heterogeneity index (I^2) of 51 % (Fig. 2).

For the diagnosis of severe fibrosis (equal to or higher than F3) using transient elastography a sensitivity of 0.89 (95 % CI; 0.80-0.94) and a specificity of 0.89 (95 % CI; 0.77-0.95) were estimated, with a heterogeneity index (I^2) of 0 % (Fig. 2).

As regards the diagnosis of cirrhosis (F4) a sensitivity of 0.91 (95 % CI; 0.77-0.97) and a specificity of 0.95 (95 % CI; 0.82-0.99) were estimated, with a heterogeneity index (I^2) of 36 % (Fig. 2).

Table 3 lists the sensitivity and specificity values, positive and negative predictive values, and cut-off values for each fibrosis stage in the studies assessed.

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TE in PSC

For the diagnosis of significant fibrosis (equal to or higher than F2) using transient elastography (TE) in patients with PSC, a sensitivity of 0.76 (95 % CI; 0.63-0.85) and a specificity of 0.88 (95 % CI; 0.78-0.94) were estimated, with a heterogeneity index (I^2) of 0 % (Fig. 3).

Regarding the diagnosis of severe fibrosis using TE in patients with PSC, a sensitivity of 0.91 (95 % CI; 0.75-0.97) and a specificity of 0.86 (95 % CI; 0.78-0.92) were obtained, with a heterogeneity index (I^2) of 0 % for sensitivity and 11 % for specificity (Fig. 3).

For the diagnosis of cirrhosis in these patients, a sensitivity of 0.71 (95 % CI; 0.45-0.88) and a specificity of 0.93 (95 % CI; 0.84-0.97) were estimated, with a heterogeneity index of (I^2) of 0 % for sensitivity and 25 % for specificity (Fig. 3).

Table 4 lists the sensitivity and specificity values, positive and negative predictive values, and cut-off values for each fibrosis stage in the studies assessed regarding PSC.

Ultrasound-guided methods in PBC

For the diagnosis of significant fibrosis (equal to or higher than F2) using ultrasound-guided methods in patients with PBC, a sensitivity of 0.79 (95 % CI; 0.72-0.85) and a specificity of 0.83 (95 % CI; 0.73-0.89) were obtained, with a heterogeneity index (I^2) of 0 % (Fig. 4).

Regarding the diagnosis of severe fibrosis (equal to or higher than F3), values of 0.91 (95 % CI; 0.82-0.96) and 0.87 (95 CI; 0.77-0.92) were obtained for sensitivity and specificity, respectively, with a heterogeneity index (I^2) of 0 % (Fig. 4).

Finally, for the diagnosis of cirrhosis (F4) using ultrasound-guided methods, a sensitivity of 0.95 (95 % CI; 0.81-0.99) and a specificity of 0.85 (95 % CI; 0.68-0.94) were obtained, with a heterogeneity index (I^2) of 0 % for sensitivity and 87 % for specificity (Fig. 4).

Table 5 lists the sensitivity and specificity values, positive and negative predictive values, and cut-off values for each fibrosis stage in the studies that assessed ultrasound-guided methods for PBC.

DISCUSSION

Non-invasive methods, which include the various elastography methods, are increasingly useful and applicable in our setting for prognostic assessment regarding diagnosis, and during the follow-up of most chronic liver conditions (6,7). Their usefulness has been extensively documented and validated particularly for liver conditions with a viral or alcohol-related etiology (7,28-32), with a recent increase in studies on non-alcoholic metabolic disease (33,34). However, in the setting of cholestatic liver conditions evidence is significantly lower, although results obtained from individual studies are positive (12-26).

In this systematic review and meta-analysis we identified and assessed 13 studies in the literature comparing elastography (whether transient or sonoelastography) with liver biopsy in patients with cholestatic liver diseases (primary biliary cholangitis and primary sclerosing cholangitis). Sensitivity and specificity for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis were good in patients with either disease using either method. As for mild fibrosis, the results obtained were not evaluable since few studies reported complete data in this respect.

This implies that elastographic methods are useful to estimate prognosis at diagnosis and during the follow-up of patients with cholestatic liver disease, particularly of patients with PBC.

Regarding study quality assessment with the QUADAS-2 tool, only two of the studies included in the systematic review showed a low bias risk in all domains, which suggests that only these two studies may be considered to have a low bias risk (27). Furthermore, publications are scarce for this group of diseases, especially so in the case of primary sclerosing cholangitis, hence the total number of studies where results could be collected from was limited.

In addition to their limited number, while statistical heterogeneity indices are favorable to results, the studies are highly heterogeneous in terms of methodology. The number of assessed patients is also scarce in these studies, likely due to the fact that these conditions are uncommon in routine practice.

We could not assess the diagnostic accuracy or ultrasound-guided elastography for PSC since no studies were found that met both the inclusion and exclusion criteria.

Furthermore, since data are not available from the studies in the meta-analysis, more accurate cutt-offs could not be estimated for each fibrosis stage in the conditions under study.

CONCLUSION

To conclude, overall elastography, both transient elastography for PSC and ultrasound-guided elastography for PBC, is fairly capable of diagnosing significant fibrosis (>/= F2), severe fibrosis (>/= F3) and cirrhosis (F4). However, the number of studies available is limited. Therefore, further studies are needed to validate and strengthen these results.

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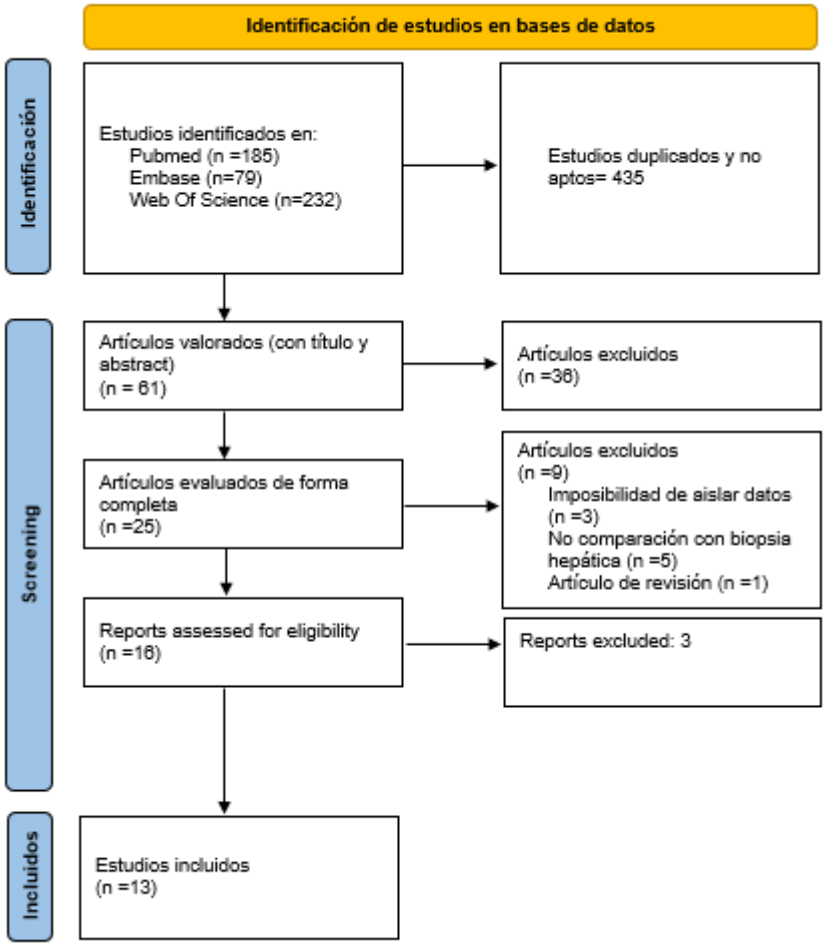
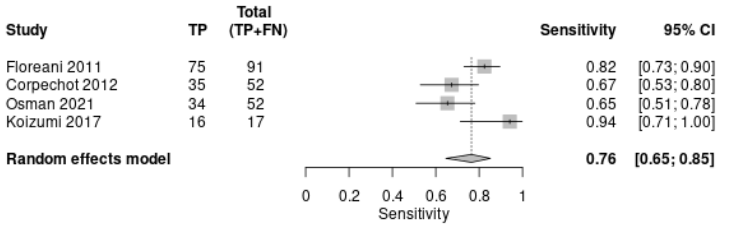
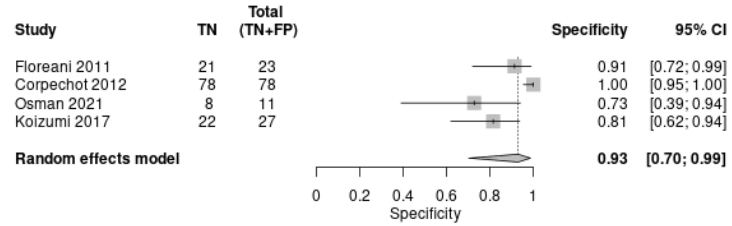


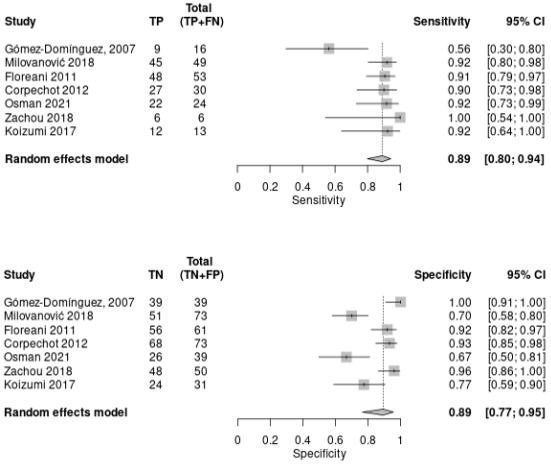
Figure 1. Review flow and study inclusion flow chart.

A


Study
TP
Total (TP+FN)
Sensitivity
95% CI
Floreani 2011 75 91 0.82 [0.73; 0.90]
Corpechot 2012 35 52 0.67 [0.53; 0.80]
Osman 2021 34 52 0.65 [0.51; 0.78]
Koizumi 2017 16 17 0.94 [0.71; 1.00]
Random effects model 0.76 [0.65; 0.85]
0 0.2 0.4 0.6 0.8 1
Sensitivity


Study
TN
Total (TN+FP)
Specificity
95% CI
Floreani 2011 21 23 0.91 [0.72; 0.99]
Corpechot 2012 78 78 1.00 [0.95; 1.00]
Osman 2021 8 11 0.73 [0.39; 0.94]
Koizumi 2017 22 27 0.81 [0.62; 0.94]
Random effects model 0.93 [0.70; 0.99]
0 0.2 0.4 0.6 0.8 1
Specificity

B


Study
TP
Total (TP+FN)
Sensitivity
95% CI
Gómez-Domínguez, 2007 9 16 0.56 [0.30; 0.80]
Milovanović 2018 45 49 0.92 [0.80; 0.98]
Floreani 2011 48 53 0.91 [0.79; 0.97]
Corpechot 2012 27 30 0.90 [0.73; 0.98]
Osman 2021 22 24 0.92 [0.73; 0.99]
Zachou 2018 6 6 1.00 [0.54; 1.00]
Koizumi 2017 12 13 0.92 [0.64; 1.00]
Random effects model 0.89 [0.80; 0.94]
0 0.2 0.4 0.6 0.8 1
Sensitivity

Study
TN
Total (TN+FP)
Specificity
95% CI
Gómez-Domínguez, 2007 39 39 1.00 [0.91; 1.00]
Milovanović 2018 51 73 0.70 [0.58; 0.80]
Floreani 2011 56 61 0.92 [0.82; 0.97]
Corpechot 2012 68 73 0.93 [0.85; 0.98]
Osman 2021 26 39 0.67 [0.50; 0.81]
Zachou 2018 48 50 0.96 [0.86; 1.00]
Koizumi 2017 24 31 0.77 [0.59; 0.90]
Random effects model 0.89 [0.77; 0.95]
0 0.2 0.4 0.6 0.8 1
Specificity

C

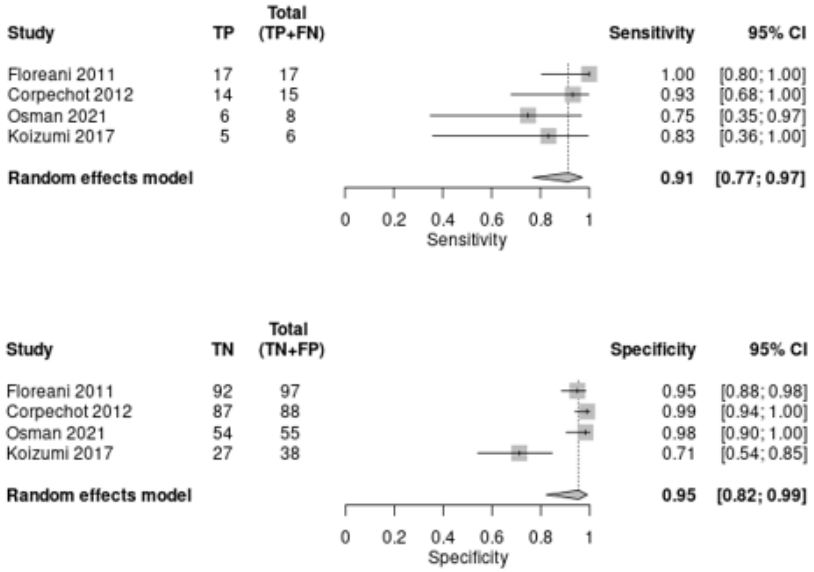
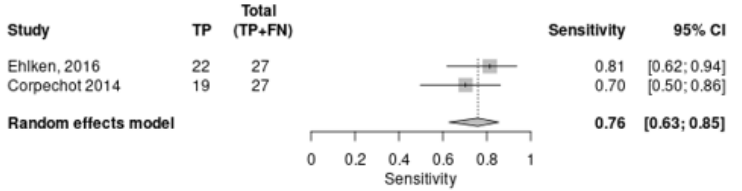
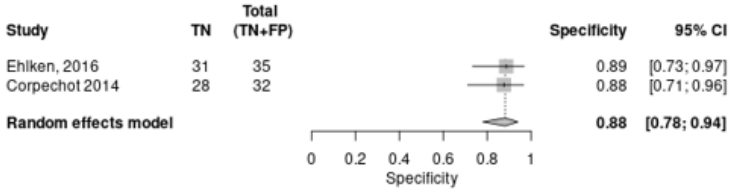


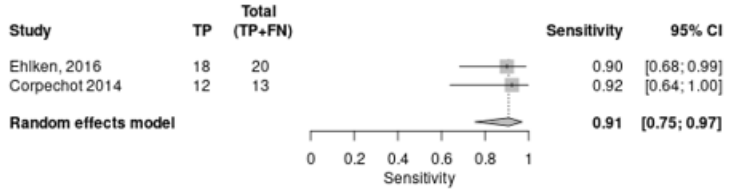
Figure 2. Forest plots showing the sensitivity and specificity of TE for the diagnosis of A: significant fibrosis (>/= F2) in patients with PBC; B: severe fibrosis (>/= F3) in patients with PBC; C: cirrhosis (F4) in patients with PBC.

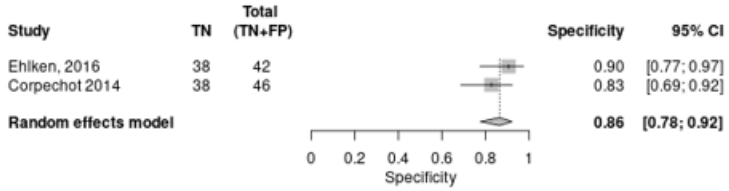
A


Study
TP
Total (TP+FN)
Sensitivity
95% CI
Ehlken, 2016 22 27 0.81 [0.62; 0.94]
Corpechot 2014 19 27 0.70 [0.50; 0.86]
Random effects model 0.76 [0.63; 0.85]
0 0.2 0.4 0.6 0.8 1
Sensitivity


Study
TN
Total (TN+FP)
Specificity
95% CI
Ehlken, 2016 31 35 0.89 [0.73; 0.97]
Corpechot 2014 28 32 0.88 [0.71; 0.96]
Random effects model 0.88 [0.78; 0.94]
0 0.2 0.4 0.6 0.8 1
Specificity

B


Study
TP
Total (TP+FN)
Sensitivity
95% CI
Ehlken, 2016 18 20 0.90 [0.68; 0.99]
Corpechot 2014 12 13 0.92 [0.64; 1.00]
Random effects model 0.91 [0.75; 0.97]
0 0.2 0.4 0.6 0.8 1
Sensitivity


Study
TN
Total (TN+FP)
Specificity
95% CI
Ehlken, 2016 38 42 0.90 [0.77; 0.97]
Corpechot 2014 38 46 0.83 [0.69; 0.92]
Random effects model 0.86 [0.78; 0.92]
0 0.2 0.4 0.6 0.8 1
Specificity

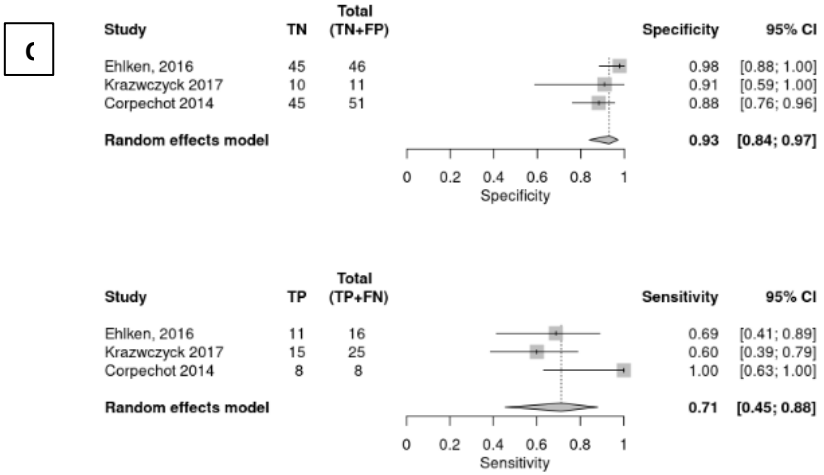
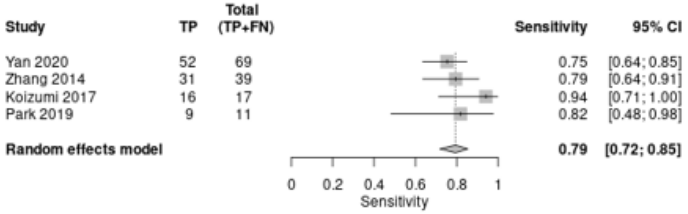
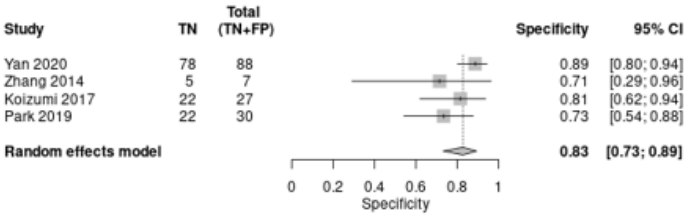


Figure 3. Forest plots showing the sensitivity and specificity of TE for the diagnosis of significant fibrosis (>/= F2), severe fibrosis (>/= F3) and cirrhosis (F4) in patients with PSC.

A


Study
TP
Total (TP+FN)
Sensitivity
95% CI
Yan 2020 52 69 0.75 [0.64; 0.85]
Zhang 2014 31 39 0.79 [0.64; 0.91]
Koizumi 2017 16 17 0.94 [0.71; 1.00]
Park 2019 9 11 0.82 [0.48; 0.98]
Random effects model 0.79 [0.72; 0.85]
0 0.2 0.4 0.6 0.8 1
Sensitivity

B


Study
TN
Total (TN+FP)
Specificity
95% CI
Yan 2020 78 88 0.89 [0.80; 0.94]
Zhang 2014 5 7 0.71 [0.29; 0.96]
Koizumi 2017 22 27 0.81 [0.62; 0.94]
Park 2019 22 30 0.73 [0.54; 0.88]
Random effects model 0.83 [0.73; 0.89]
0 0.2 0.4 0.6 0.8 1
Specificity

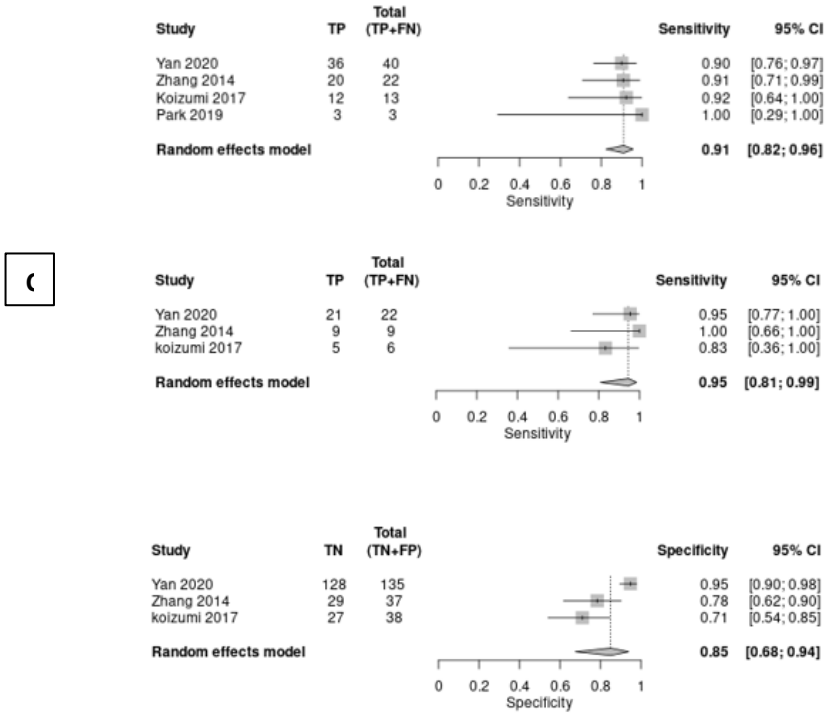


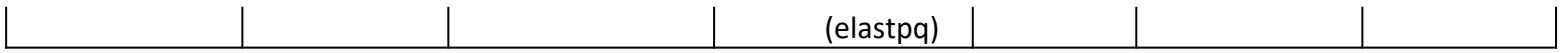
Figure 4. Forest plots showing the sensitivity and specificity of ultrasound-guided elastography methods for the diagnosis of significant fibrosis (>/= F2), severe fibrosis (>/= F3) and cirrhosis (F4) in patients with PBC.

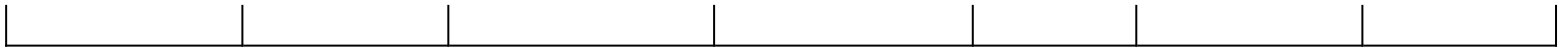
Table 1. QUADAS-2

	Probability of BIAS				Applicability of results		
	Patient selection	**Index test**	**Reference standard**	**Flow**	**Patient selection**	**Index test**	**Reference standard**
Gomez-Dominguez, 2007	High	High	Low	High	Low	Low	Low
Koizumi, 2017	High	High	Low	High	Low	Low	Low
Milovanovic, 2018	High	High	Low	High	Low	Low	Low
Zachou, 2020	Low	Low	Low	Low	Low	Low	Low
Corpechot, 2014	Low	Low	Low	High	Low	High	Low
Krawczyk, 2017	High	Low	High	High	High	Low	Low
Ehlken, 2016	Low	High	High	Low	Low	Low	Low
Floreani, 2011	Low	High	Low	High	Low	Low	Low
Osman, 2021	High	High	High	High	Low	High	Low
Corpechot, 2012	Low	High	Low	High	Low	Uncertain	Low
Zhang, 2014	Low	Low	Low	Low	Low	Low	Low
Yan, 2020	High	Low	High	High	Low	Low	Low
Park, 2019	Low	Low	Low	Low	Low	Low	Low

Table 2. Study characteristics

Author, publication year	Country	Study design	Elastography technique	Mean age	No. of parcipants	Etiology
Ehlken, 2016	Germany	Retrospective	Fibroscan	38	62	PSC
Gómez-Domínguez, 2007	Spain	Prospective	Fibroscan	56	55	PBC
Milovanović, 2018	Serbia	Prospective	Fibroscan	57	122	PBC
Floreani, 2011	Italy	Prospective	Fibroscan	58	114	PBC
Corpechot, 2012	France	Prospective	Fibroscan	56	103	PBC
Osman, 2021	USA	Retrospective	Fibroscan	60	63	PBC
Zachou, 2020	Greece	Prospective	Fibroscan	52	56	PBC
Krawczyk, 2017	Poland	Prospective	Fibroscan	33	30	PSC
Zhang, 2014	China	Prospective	ARFI	45	56	PBC
Yan, 2020	China	Retrospective	2D SWE	53	157	PBC
Coperchot, 2014	France	Prospective	Fibroscan	40	66	PSC
			2D SWE	60		
Koizumi, 2017	Japan	Prospective	Fibroscan		44	PBC
Park, 2019	Korea	Prospective	ARFI	55	41	PBC


(elastpq)



			ARFI (elastpq)			

Table 3. Sensitivity (S), specificity (Sp), positive and negative predictive value (PPV & NPV), and fibrosis stage cut-off values in transient elastography studies in PBC

Author, publication year	**No. of participants**	**Value F2 kPa**	**AUROC* ≥ F2 (95 % CI)**	**S F ≥ 2**	**Sp F ≥ 2**	**PPV F ≥ 2**	**NPV F ≥ 2**	**Value F3 kPa**	**AUROC ≥ F3 (95 % CI)**	**S F ≥ 3**	**Sp F ≥ 3**	**PPV F ≥ 3**	**NPV F ≥ 3**	**Value F4 kPa**	**AUROC F4 (95 % CI)**	**S F4**	**Sp F4**	**PPV F4**	**NPV F4**
Gomez-Dominguez, 2007	55							14.7	0.86 (0.72-0.94)	56 %	100 %	100 %	83 %	15.6	0.96 (0.87-0.99)	88 %	98 %	88 %	98 %
Milovanović, 2018	122							9.9	0.804 (0.659-0.95)	91, 70 %	69, 20 %								
Floreani, 2011	114	5.9	0.87	82 %	92 %	97 %	59 %	7.6	0.88	90 %	92 %	90 %	92 %	11.4	0.99	99 %	94 %	77 %	100 %
Corpechot, 2012	103	8.8	0.91	67 %	100 %	100 %	75 %	10.7	0.95	90 %	93 %	84 %	96 %	16.9	0.99	93 %	99 %	93 %	99 %
Osman, 2021	63	7	0.65 (0.52-0.77)	65 %	73 %	90 %	28 %	7.5	0.73 (0.6-0.83)	92 %	67 %	60 %	92 %	14.4	0.94 (0.85-0.98)	75 %	98 %	75 %	96 %
Zachou, 2020	56							11.9		100 %	96 %	75 %	100 %						
Koizumi, 2017	44	16	0.92 (0.8-0.97)	94.1 %	80.8 %			17.9	0.91 (0.79-0.97)	92.3 %	76.7 %			25.1	0.91 (0.69-0.98)	83.3 %	70.7 %		

*AUROC: area under the ROC curve. **CI: confidence interval.

Table 4. Sensitivity (S), specificity (Sp), positive and negative predictive value (PPV & NPV), and fibrosis stage cut-off values in transient elastography studies in PSC

Author, publication year	No. of participants	Value F2 kPa	AUROC ≥ F2 (95 % CI)	S F ≥ 2	Sp F ≥ 2	PPV F ≥ 2	NPV F ≥ 2	Value F3 kPa	AUROC ≥ F3 (95 % CI)	S F ≥ 3	Sp F ≥ 3	PPV F ≥ 3	NPV F ≥ 3	Value F4 kPa	AUROC F4 (95 % CI)	SF4	S F4 LCI	S F4 UCI	Sp F4	PPV F4	NPV F4
Ehlken, 2016	62	8.8	0.91 (0.82-0.99)	81.50 %	88.60 %	84.60 %	86.10 %	9.6	0.95 (0.89-1)	90 %	90.50 %	81.80 %	95 %	14.4	0.978 (0.93-1)	68.80 %	46 %	91.50 %	97.80 %	91.70 %	90 %
Krawczyk, 2017	30													13.7	0.9 (0.8-1)	78 %	52 %	93 %	90 %		
Coperchot, 2014	66	8.6	0.84	72 %	89 %	85 %	78 %	9.6	0.93	93 %	83 %	61 %	98 %	14.4	0.95	100 %			88 %	56 %	100 %

*AUROC: area under the ROC curve. **CI: confidence interval.

Table 5. Sensitivity (S), specificity (Sp), positive and negative predictive value (PPV & NPV), and fibrosis stage cut-off values in ultrasound-guided elastography studies in PBC

Author, publication year	**No. of participants**	**Value F2**	**AUROC ≥ F2 (95 % CI)**	**S F ≥ 2**	**Sp F ≥ 2**	**PPV F ≥ 2**	**NPVF ≥ 2**	**ValueF 3**	**AUROC ≥ F3**	**S F ≥ 3**	**Sp F ≥ 3**	**PPV F ≥ 3**	**NPV F ≥ 3**	**Value F4**	**AUROC = F4**	**S F4**	**Sp F4**	**PPV F4**	**NPV F4**
Zhang, 2014	56	1.51 m/s	0.83 (0.72-0.94)	80 %	77 %	89 %	62 %	1.79 m/s	0.93 (0.86-0.99)	91 %	82 %	77 %	93 %	2.01 m/s	0.91 (0.83-0.99)	100 %	79 %	47 %	100 %
Yan, 2020	157	10.7 kPa	0.88 (0.82-0.94)	75 %	89 %	84 %	82 %	12.2 kPa	0.97 (0.94-1)	90 %	94 %	84 %	96 %	14.1 kPa	0,99 (0.97-1)	96 %	95 %	76 %	99 %
Koizumi, 2017	44	2.74 m/s	0.92 (0.79-0.97)	94.1 %	88.5 % %			3.45 m/s	0.95 (0.81-0.99)	92.3 %	83.3 %			5.32 m/s	0.97 (0.87-0.99)	95.2 %	89.2 %		
Park, 2019	41	5.56 kPa	0.81 (0.65-0.91)	81.8 0 %	73.3 0 %	52.9 0 %	91.70 %	6.04 kPa	0.91 (0.78-0.98)	100 %	81.6 0 %	30 %	100 %						

*AUROC: area under the ROC curve. **CI: confidence interval.