GASTROENTEROLOGY 2008;134:960–974

Performance of Transient Elastography for the Staging of Liver Fibrosis: A Meta-Analysis

MIREEN FRIEDRICH–RUST,* MEI–FANG ONG,‡ SWANTJE MARTENS,‡ CHRISTOPH SARRAZIN,* JOERG BOJUNGA,* STEFAN ZEUZEM,* and EVA HERRMANN‡

*Department of Internal Medicine I, J. W. Goethe-University Hospital, Frankfurt, Germany; and the ‡Faculty of Medicine, Internal Medicine-Biomathematics, Saarland University, Homburg, Germany

CME exam on page 1238.

Background & Aims: **Transient elastography has been studied in a multitude of liver diseases for the staging of liver fibrosis with variable results. A meta-analysis was performed to assess the overall performance of transient elastography for the diagnosis of liver fibrosis and to analyze factors influencing the diagnostic accuracy.** ***Methods:*** **Literature databases and international conference abstracts were searched. Inclusion criteria were as follows: evaluation of transient elastography, liver biopsy as reference, and assessment of the area under the receiver operating characteristic curve (AUROC). The meta-analysis was performed using the random-effects model for the AUROC, summary receiver operating curve techniques, as well as meta-regression approaches.** ***Results:*** **Fifty studies were included in the analysis. The mean AUROC for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis were 0.84 (95% confidence interval [CI], 0.82–0.86), 0.89 (95% CI, 0.88–0.91), and 0.94 (95% CI, 0.93–0.95), respectively. For the diagnosis of significant fibrosis a significant reduction of heterogeneity of the AUROC was found when differentiating between the underlying liver diseases ($P < .001$). Other factors influencing the AUROC were the scoring system used and the country in which the study was performed. Age, body mass index, and biopsy quality did not have a significant effect on the AUROC.** ***Conclusions:*** **Transient elastography can be performed with excellent diagnostic accuracy and independent of the underlying liver disease for the diagnosis of cirrhosis. However, for the diagnosis of significant fibrosis, a high variation of the AUROC was found that is dependent on the underlying liver disease.**

Liver fibrosis is a common pathway for a multitude of liver injuries. Viral, autoimmune, hereditary, metabolic, and toxin-mediated liver disease can result in hepatocellular dysfunction, expansion of extracellular matrix with distortion of hepatic architecture, portal hypertension, and, finally, cirrhosis.[1] A precise estimation of the degree of liver fibrosis is important for estimation of prognosis, surveillance, and treatment decisions in patients with chronic liver disease.[2,3] At present, liver biopsy still most commonly is used as the reference standard for the assessment of liver fibrosis. However, it is an invasive method that is associated with patient discomfort and in rare cases with serious complications.[4] In addition, the accuracy of liver biopsy is limited as a result of intraobserver and interobserver variability and sampling errors.[5]

Therefore, a lot of research has been focused on the evaluation of noninvasive methods for the assessment of liver fibrosis. The different approaches include routine hematologic and biochemical tests; serum surrogate fibrosis markers and panels; extracellular matrix markers and panels; and specialized tests for liver function, glycomics, proteomics, radiologic imaging, and transient elastography (FibroScan; Echosens, Paris, France).

In the past few years an increasing number of studies have evaluated transient elastography for the diagnosis of liver fibrosis in a multitude of liver diseases.

We performed a meta-analysis to assess the overall performance of transient elastography for the diagnosis of liver fibrosis and to analyze the heterogeneity between the available studies.

Materials and Methods

Transient Elastography

Transient elastography is a novel method. The first clinical data from transient elastography were published in 2002. Transient elastography is performed with an ultrasound transducer probe mounted

Abbreviations used in this paper: ASH, alcoholic steatohepatitis; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; DANA, difference of the mean of advanced and the mean of nonadvanced fibrosis stages; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; QUADAS, The Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews; SROC, summary ROC.

0016-5085/08/$34.00
doi:10.1053/j.gastro.2008.01.034

on the axis of a vibrator. A vibration transmitted from the vibrator toward the tissue induces an elastic shear wave that propagates through the tissue. These propagations are followed by pulse-echo ultrasound acquisitions and their velocity is measured, which is related directly to tissue stiffness. The harder the tissue, the faster the shear wave propagates.[6] Up to 10 successful acquisitions are performed routinely on each patient and the examination lasts about 5–10 minutes. The success rate is calculated automatically by the machine as the ratio of the number of successful acquisitions over the total number of acquisitions. According to the manufacturer's recommendations, only transient elastography results obtained with 10 valid measurements and with a success rate of at least 60% are considered reliable. However, recent publications have suggested that 3 valid measurements could be performed with the same results as 10 valid measurements for cirrhosis diagnosis, but the minimum number for significant and advanced fibrosis is unknown.[7] The quality assessment using the success rates varied between studies, with a range from 30% to 65%. Ten valid measurements and a success rate of at least 60% can be achieved in 90%–96% of examinations. Transient elastography can be learned easily and has a high intraobserver (96%–98%) and interobserver (89%–98%) agreement.[8]

Literature Search

A systematic literature search was performed to evaluate the performance of transient elastography for the diagnosis of liver fibrosis in chronic liver disease. Sources searched included the following.

- Electronic databases from 2002 to April 2007: Pub Med, EMBASE, and CENTRAL on The Cochrane Library using a search strategy derived from literature.[9,10] Terms used were "FibroScan," "transient elastography," "elastography and liver," "liver stiffness," "liver fibrosis."
- Citation database Web of Science from 2002 to April 2007 (Institute of Scientific Information) was searched using the same terms shown earlier.
- Relevant websites and conference abstract books: American Association for the Study of the Liver, European Association for the Study of the Liver, Digestive Disease Week, Liver Transplantation, Asian Pacific Association for the Study of the Liver, Conference on Retroviral and Opportunistic Infections, Interscience Conference on Antimicrobial Agents and Chemotherapy, and International Symposium on Ultrasonic Imaging and Tissue Characterization were searched for conference proceedings and abstracts (2002–April 2007).
- Authors of full-length articles and authors who presented their studies at the earlier-mentioned conferences were contacted via e-mail to obtain relevant data that were missing.
- Reference lists from relevant articles.

Inclusion Criteria

Studies were included if they met the following criteria: they evaluated transient elastography; they used liver biopsy as a reference standard; they used a comparable liver biopsy staging system: METAVIR, Ishak, Brunt, Ludwig's, Knodell, Desmet, and Scheuer; they assessed the diagnostic accuracy (area under the receiver operating characteristic curve [AUROC]) for fibrosis stage $F \geq 2$, $F \geq 3$, or $F = 4$ according to METAVIR or a comparable staging system; and/or they assessed sensitivity, specificity, positive predictive value, or negative predictive value for the diagnosis of a fibrosis stage based on some cut-off point for liver stiffness.

Exclusion Criteria

Studies were excluded if they met the following criteria: they did not evaluate transient elastography; they did not use liver biopsy as a reference test; they used a fibrosis staging system not comparable with METAVIR; they did not report data on diagnostic accuracy (AUROC), sensitivity, or specificity for any fibrosis stage; they were reviews, corresponding letters, or editorials not reporting own results; they were abstracts with data that have been published as full-length articles in the meantime; or they were abstracts that obviously presented data of the same study at different meetings (same study group, same patient population, identical study design, same number of patients, or increased number of patients). In this case the most recent abstract was included in this analysis.

Data extraction was undertaken by one reviewer (M.F.R.) and checked by a second reviewer (M.F.O.). Disagreements were resolved by discussion and analysis of the data.

Data Analysis

Data and results of the included studies are presented in Tables 1–3.

To analyze whether the underlying liver disease has an influence on the AUROC values, the studies were divided into 3 groups: studies examining hepatitis C virus (HCV)-infected patients only, studies examining a patient population of different liver diseases including HCV, and studies without HCV patients. This group selection was chosen because most studies examining a single liver disease considered HCV.

Because the fibrosis staging system used to classify the histology varied, scoring systems using scores from 0 to 4 for fibrosis staging (METAVIR, Desmet and Scheuer, Knodell, Brunt, Ludwig's) were pooled for the overall calculation of the mean AUROC. The influence of the

Table 1. Characteristics of Studies Evaluating the Performance of Transient Elastography for the Diagnosis of Liver Fibrosis

Study	Type	Country	No.	No. for analysis[a]	Exclusion failure, %		Mean age, y	% Male
					FS(reason)	LB(reason)		
Sandrin et al[6]	Original	France	91	67	5	21 (<10 pt)	48	61
Ziol et al, 2005[26]	Original	France	327	251	7 (SR < 60%, VM < 10)	16 (<10 pt)	48	61
Castera et al, 2005[17]	Original	France	193	183	5.5 (SR < 60%, VM < 10)	N/R	51	57
Foucher et al, 2005[27]	Original	France	758	354	N/R (SR < 60%, VM < 5)	N/R (<10 pt)	50	58
Coletta et al, 2005[18]	Original	Italy	40	40	N/R	N/R	44	55
de Ledinghen et al, 2006[20]	Original	France	77	72	N/R (SR < 30%, VM < 5)	6.5 (<10 pt, <7 mm length)	42	72
Corpechot et al, 2006[19]	Original	France	101	95	2 (SR < 60%, VM < 10)	4	57	26
Carrion et al, 2006[16]	Original	Spain	135	124 (169[b])	1 (SR < 60%)	1	60	66
Gomez-Dominguez et al, 2006[23]	Original	Spain	103	94	5 (SR < 60%, VM < 10)	4	49	57
Ganne-Carrie et al, 2006[22]	Original	France	1257	775	9 (SR < 50%, VM < 8)	10 (<10 mm length)	49	65
Erhardt et al, 2006[21]	Original	Germany	147	135	8 (SR < 60%, VM < 6)	0	52	63
Nahon et al, 2006[24]	Original	France	142	142	N/R (SR < 60%, VM < 10)	N/R	46	61
Takeda et al, 2006[28]	Original	Japan	287	287	N/R	N/R	58	43
Posthouwer et al, 2007[25]	Original	The Netherlands	63/124	63	N/R (SR < 40%, VM < 10)	N/R	44	N/R
Kettaneh et al, 2007[7]	Original	France	935	560	8.5	37 (15 mm length)	48	62
Marin et al, 2007[52]	Abstract	Spain	110	47	N/R	N/R	N/R	N/R
Blanc et al, 2007[31]	Abstract	Italy	508	136	7 (SR < 65%)	N/R	N/R	N/R
Gaia et al, 2007[43]	Abstract	Italy	124	78 46	N/R	N/R	N/R	N/R
Nahon et al, 2007[54]	Abstract	France	126	105	11 (VM < 8)	6 (<10 mm length)	54	75
Nguyen-Khac et al, 2007[55]	Abstract	France	61	61	N/R	N/R	51	75
Miailhes et al, 2007[53]	Abstract	France	31	31	N/R (SR < 60%, IQR < 30%)	N/R	43	77
Vergara et al, 2007[62]	Abstract	Spain	101	101	N/R	N/R	N/R	N/R
Chang et al, 2007[34]	Abstract	Singapore	35	33	6	0	43	N/R
Servin-Abad et al, 2006[61]	Abstract	United States	39	39	N/R	N/R	52	44
Gomez-Dominguez et al, 2006[45]	Abstract	Spain	64	54	N/R	N/R	56	8
Baldaia et al, 2006[29]	Abstract	Portugal	105	105	N/R	N/R (<10 mm length)	44	74
Serejo et al, 2006[60]	Abstract	Portugal	158	60	N/R	N/R	N/R	N/R
Beaugrand et al, 2006[63]	Abstract	France	639	494	9 (VM < 8)	13 (<10 pt, <10 mm length)	49	65
Rigamonti et al, 2006[59]	Abstract	Italy	78	73	5 (SR < 65%, VM < 10)	N/R	53	77
Lewin et al, 2006[50]	Abstract	France	54	54	N/R	N/R	N/R	N/R
Fraquelli et al, 2006[42]	Abstract	Italy	200	196	2 (VM < 10)	N/R	N/R	59
Corradi et al, 2006[38]	Abstract	Italy	36	36	N/R	N/R	N/R	N/R
Kim et al, 2006[48]	Abstract	Korea	47	47	N/R	N/R	46	23
Coco et al, 2006[37]	Abstract	Italy	256	181	N/R	N/R	N/R	N/R
de Ledinghen et al, 2006[40]	Abstract	France/United States	129	129	N/R	N/R	54	N/R
Laharie et al, 2006[49]	Abstract	France	292	60	8	N/R	54	69
Jeon et al, 2006[46]	Abstract	Korea	47	47	N/R	N/R	N/R	64
Castera et al, 2006[33]	Abstract	France	412	252	4.5	N/R	52	56
Rigamonti et al, 2006[58]	Abstract	Italy	42	31	11 (SR < 50%, VM < 10)	N/R	53	74
Khokhar et al, 2005[47]	Abstract	United States	175	175	N/R	N/R	N/R	N/R
Coco et al, 2005[36]	Abstract	Italy	241	228	2	3	N/R	N/R
Castera et al, 2005[32]	Abstract	France and Belgium	111	111	N/R	N/R	53	51
Pares et al, 2005[57]	Abstract	Spain	150	150	N/R	N/R	60	8
Ganne-Carrie et al, 2005[44]	Abstract	France	1345	891	16 (SR < 50%, VM < 10)	18 (<10 mm length)	47	63
De Ledinghen et al, 2005[39]	Abstract	France	104	25	N/R	N/R	11	47
Barrault et al, 2005[30]	Abstract	France	30	30	N/R	N/R	56	83
Marcellin et al, 2005[51]	Abstract	France	220	170	5 (VM < 8)	17 (<10 pt)	N/R	N/R
Foucher et al, 2005[41]	Abstract	France	363	363	N/R	N/R	51	60
Chanteloup et al, 2004[35]	Abstract	France	456	456	N/R	N/R	53	56
Palau et al, 2003[56]	Abstract	France	120	96	4	16	N/R	N/R

AIH, autoimmune hepatitis; FS, FibroScan; HBV, hepatitis B virus infection; IQR, interquartile; LB, liver biopsy; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cirrhosis; post-Tx, posttransplantation; PSC, primary sclerosing cholangitis; pt, portal tracts; SR, success rate; VM, valid FibroScan measurements.
[a]Number of patients suitable for analysis, excluding patient with failed transient elastography measurement or liver biopsy.
[b]There were 167 biopsies performed at different time points together with FS in 124 patients.

different staging systems on the mean AUROC was analyzed separately. The Ishak score, using a scale from 0 to 6, was transferred into METAVIR with Ishak F ≥ 3 assigned to METAVIR F ≥ 2, Ishak F ≥ 4 assigned to METAVIR F ≥ 3, and Ishak F ≥ 5 assigned to METAVIR F = 4, respectively.

The meta-analysis was performed using the random-effects model (DerSimonian and Laird estimator)[11] for

Table 2. Histology Distribution and Quality of Studies Evaluating the Performance of Transient Elastography

Diagnosis	Mean BMI	METAVIR and other scoring systems, %					Mean or median length of LB (fragmentation)
		F = 0	F = 0–1	F = 2	F = 3	F = 4	
HCV	N/R	7	40	25	21	14	N/R
HCV, HCV/HIV, HCV/HBV	24	0.4	35	35	11	19	18
HCV	25	0	26	29	20	25	17 (2)
HCV, HBV, HCV/HIV, NASH, ASH, PBC, other	25	N/R	31	28	14	27	16.5
HCV	21	7.5	65	22.5	12.5	0	20
HCV/HIV	22	N/R	39	31	7	23	20
PBC, PSC	N/R	N/R	40	23	21	16	17 (2)
HCV post-Tx	25	24	58	24	9	9	N/R
HCV, PBC, AIH, ASH	N/R	0	18	44	21	17	N/R
HCV, HBV, HCV/HIV, NASH, ASH, PBC, other	N/R	N/R	N/R	N/R	N/R	15	17
HCV, HBV, NASH, ASH, PBC, other	26	16	31	22	14	33	N/R
HCV	N/R	0	31	32	10	27	15.8
HCV	N/R	17.4	57	24	6	13	N/R
HCV	N/R	6	54	24	13	9	33
HCV	25	N/R	50	26	14	10	21
NAFLD	26	36	76	11	6.5	6.5	N/R
HCV	N/R	N/R	N/R	N/R	N/R	N/R	N/R
HCV, HBV	N/R	5	47	22	4	27	N/R
NASH	N/R	33	50	22	19	9	N/R
ASH	27	0	8	18	26	48	N/R
ASH	N/R	15	34	25	25	16	12
HBV/HIV	22	N/R	36	32	(F3–F4: 32%)		18
HCV/HIV	N/R	N/R	N/R	N/R	N/R	37	N/R
HBV	26	20	66	(F2–F3: 14%)		20	N/R
HCV, HBV, ASH, other	N/R	2.6	13	36	25.5	25.5	N/R
PBC	N/R	N/R	N/R	N/R	N/R	N/R	N/R
HCV, HBV	N/R	N/R	19	51	12	18	19
HCV	N/R	N/R	(F0–F2: 70%)		(F3–F4: 30%)		N/R
HCV	25	6	45	31	10	14	N/R
HCV, HBV, PBC, PSC, other	N/R	N/R	53	14	N/R	N/R	35
HCV	N/R	2	57	15	9	19	N/R
Different causes	N/R	N/R	N/R	N/R	N/R	N/R	N/R
HCV post-Tx	N/R	0	67	22	8	3	N/R
HCV, HBV, HCV/HBV, NAFLD, PBC, other	24	0	19	36	33	12	24
HCV, HBV	N/R	N/R	N/R	N/R	N/R	N/R	N/R
NASH	30	N/R	50	21	9	20	N/R
ASH	25	N/R	N/R	N/R	N/R	N/R	N/R
HCV, HBV	N/R	8	23	32	30	15	N/R
HCV	N/R	N/R	24	36	20	20	19
post-Tx with HCV, HBV, other	24	N/R	71		(F2–F4: 29%)		N/R
HCV, HBV, ASH, NASH	N/R	N/R	(F0–F2: 39%)		11	49	N/R
HCV, HBV	N/R	N/R	N/R	N/R	N/R	N/R	N/R
HCV	N/R	N/R	25	27	23	25	N/R
PBC	N/R	0	56	25.3	13.3	5.3	N/R
HCV, HBV, ASH, hemochromatosis, other	24	N/R	N/R	N/R	N/R	N/R	N/R
HCV, HBV, cystic fibrosis and others, children only	N/R	N/R	32	16	24	28	N/R
HCV, ASH, other	N/R	N/R	N/R	N/R	N/R	N/R	N/R
HBV	N/R	6	42	30	14	14	N/R
HCV, HBV, ASH, other	N/R	N/R	31	28	14	27	N/R
HCV, HBV, NASH, ASH, hemochromatosis, other	N/R	N/R	N/R	N/R	N/R	21	N/R
HCV	N/R	N/R	N/R	N/R	N/R	N/R	N/R

the AUROC with straightforward extensions to meta-regression and summary ROC (SROC) techniques. The AUROC was known in all included studies (see inclusion criteria) and the standard error of the single studies could be determined or approximated from the available data, especially using the 95% confidence intervals (CIs). The random-effects model incorporated heterogeneity of studies in the analysis of the overall efficacy of transient elastography in the different studies. The method estimated the magnitude of the heterogeneity and assigned a greater variability to the estimate of the overall mean AUROC. Studies with a larger sample size and therefore a smaller standard error received more weight when calculating the mean AUROC. The reason for heterogeneity between studies was analyzed in regard to the effect of different factors (underlying liver disease, staging system used, country where the study was performed, publication as abstract vs full-length article, mean body mass index [BMI], mean age, fibrosis stage, sex distribution, mean or median length of liver biopsy specimen, proportion of liver biopsy failure, proportion of FibroScan failure, as well as the quality criteria described later) on the AUROC. Nevertheless, in contrast to testing continuous factors, the asymptotic foundation of testing categoric factors may become problematic if only part of the heterogeneity can be explained by the respective factor.

Table 3. Results of Studies Evaluating the Performance of Transient Elastography for the Diagnosis of Liver Fibrosis

	METAVIR and other scoring systems F ≥ 2				METAVIR and other scoring systems F ≥ 3				METAVIR and other scoring systems F = 4			
Study	AUROC	Cut-off value, kPa	Sensitivity, %	Specificity, %	AUROC	Cut-off value, kPa	Sensitivity, %	Specificity, %	AUROC	Cut-off value, kPa	Sensitivity, %	Specificity, %
Sandrin et al, 2003	0.88				0.91				0.99			
Ziol et al, 2005	0.79	8.8	56	91	0.91	9.6	86	85	0.97	14.6	86	96
Castera et al, 2005	0.83	7.1	67	89	0.90	9.5	73	91	0.95	12.5	87	91
Foucher et al, 2006	0.80	7.2	64	85	0.90	12.5	65	95	0.96	17.6	77	97
Coletta et al, 2005	1.00	8.74	100	100		9.6						
de Ledinghen et al, 2006	0.72	4.5	93	18	0.91				0.97	11.8	100	93
Corpechot et al, 2006	0.92	7.3	84	87	0.95	9.8	91	90	0.96	17.3	93	95
Carrion et al, 2006	0.90	8.50	90	81	0.93				0.98	12.50	100	87
Gomez-Dominguez et al, 2006	0.74	5.00	94	33	0.72	11	58	89	0.94	16.00	89	96
Ganne-Carrie et al, 2006									0.95	11.7	91	87
Erhardt et al, 2006					0.91				0.94	13.0	90	82
Nahon et al, 2006	0.68				0.78				0.89			
Takeda et al, 2006	0.81				0.88				0.88			
Posthouwer et al, 2007	0.87	7.1	72	85	0.89	9.5	71	90				
Kettaneh et al, 2007	0.79				0.89				0.91			
Marin et al, 2007	0.83				0.88				0.97			
Blanc et al, 2007	0.80				0.91				0.95			
Gaia et al, 2007	0.84				—				0.90			
	0.84				0.74				0.98			
Nahon et al, 2007					0.96				0.90			
Nguyen-Khac et al, 2007									0.94	19	90	81
Miailhes et al, 2007	0.79				0.73							
Vergara et al, 2007	0.88	7.2							0.95	14.6		
Chang et al, 2007		11.8	90	78		14.5	86	92				
Servin-Abad et al, 2006					0.84	13.1	69	95	0.87			
Gomez-Dominguez et al, 2006					0.89				0.95			
Baldaia et al, 2006					0.92	8.29	90	97				
Serejo et al, 2006	0.79	5.43	78	67	0.96	8.18	95	93	0.98	10.08	93	93
Beaugrand et al, 2006	0.84	7.50	67	87	0.93				0.96	10.2	99	85
Rigamonti et al, 2006	0.93	7.80	92		0.97	12	87					
Lewin et al, 2006	0.87				0.92							
Fraquelli et al, 2006	0.84	7.9	71	84	0.87	10.3	76	90	0.90	11.93	90	98
Corradi et al, 2006	0.94	11.2	92	88								
Kim et al, 2006	0.77	7.35	79	88	0.93	8.85	95	78	0.81	15.10	80	78

Therefore, we interpret significant test results as a reduction of heterogeneity and also provide CIs from a random-effects model for different categories. Furthermore, we studied the influence of the difference of the mean of advanced and the mean of nonadvanced fibrosis stages (DANA) on the mean AUROC and the adjusted AUROC according to the quality of liver biopsy.[12,13]

To assess the quality of the studies included in the meta-analysis, the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Review (QUADAS) questionnaire was used (Supplementary Table 1; see Supplementary Table 1 online at www.gastrojournal.org). Items were rated as yes, no, or unclear. The impact of the fulfillment of the individual QUADAS items on the diagnosis of liver fibrosis was analyzed.[14] Item 3 (appropriate reference standard) was rated as unclear if no data on the length of the liver biopsy specimen or portal tracts were given. Item 9 was rated as

Table 3. Continued

Study	METAVIR and other scoring systems F ≥ 2				METAVIR and other scoring systems F ≥ 3				METAVIR and other scoring systems F = 4			
	AUROC	Cut-off value, kPa	Sensitivity, %	Specificity, %	AUROC	Cut-off value, kPa	Sensitivity, %	Specificity, %	AUROC	Cut-off value, kPa	Sensitivity, %	Specificity, %
Coco et al, 2006	0.85	8.30							0.87	14.00		
de Ledinghen et al, 2006	0.86	8.75	81	78								
Lahaire et al, 2006									0.96	14.50		
Jeon et al, 2006					0.79				0.86	11.45	86	78
Castera et al, 2006									0.95			
Rigamonti et al, 2006	0.84	7.30	83									
Khokhar et al, 2005					0.92	14	77	90				
Coco et al, 2005		8.30	89	75					0.95	14.00	78	98
Castera et al, 2005	0.82				0.90				0.93			
Pares et al, 2005	0.80				0.86				0.93			
Ganne-Carrie et al, 2005									0.93	10.20	90	85
										14.60	73	94
de Ledinghen et al, 2005	0.91								0.88			
Barrault et al, 2005					0.80							
Marcellin et al, 2005	0.81				0.92				0.90			
Foucher et al, 2005	0.79	8.60			0.89	13.0			0.95	17.60		
Chanteloup et al, 2004	0.79				0.89				0.93	17.00		
Palau et al, 2003	0.89								0.98			

unclear if the staging system was given, but no inclusion criteria concerning the length of the liver biopsy or the number of portal tracts.

Furthermore, a SROC was calculated from all studies in which sensitivity and specificity were known for at least one cut-off level using a weighted linear model according to Littenberg and Moses.[15] The weights were chosen according to sample size. Such a weighting scheme also was used for the assessment of the influence of the chosen cut-off levels for liver stiffness on sensitivity and specificity (where reported). In general, sensitivity should decrease and specificity should increase with increasing cut-off levels. Nevertheless, heterogeneity between the studies may disturb this general trend.

Results

The literature search yielded 56 full-length articles and 123 abstracts that evaluated transient elastography. They were read in full. Fifty studies were included in the meta-analysis according to the inclusion and exclusion criteria. In detail, these were 15 full-length articles[6,7,16–28] and 35 abstracts.[29–63]

The patient characteristics and study results varied between studies and are shown in Tables 1 and 3.

The fibrosis staging system used to classify the histology varied. Thirty-six studies used METAVIR score, 5 studies used Ishak score, 3 studies used Desmet and Scheuer score, 1 study used Knodell score (viral hepatitis and mixed hepatopathies), 3 studies used Brunt score (for nonalcoholic steatohepatitis [NASH] and alcoholic steatohepatitis [ASH]), and 2 studies used Ludwig's classification (for primary biliary cirrhosis [PBC] and primary sclerosing cholangitis [PSC]).

Reasons for study exclusion were as follows: article currently in press and not available for analysis yet (1%); liver biopsy was not used as a reference test (50%); liver biopsy was used as a reference, but the publication/abstract did not report data on the diagnostic accuracy (AUROC), sensitivity, or specificity for any fibrosis stage (19%); liver biopsy was used and data on the AUROC were reported, but a fibrosis staging system that was not comparable with METAVIR was used (3%); a publication/abstract was a review, corresponding letter, or editorial not reporting own results (15%); an abstract fulfilled the inclusion criteria, but the data presented have been published as a full-length article in the mean time, in this case the full-length article was included only (8%); an abstract fulfilled the inclusion criteria, but presented data of the obviously same study at different meetings and was not yet published as a full-length article. In this case the most recent abstract was included (4%).

Detailed information on the reason why full-length articles were excluded is given in Supplementary Table 2 (see Supplementary material online at www.gastrojournal.org). From the 88 excluded abstracts, the detailed infor-

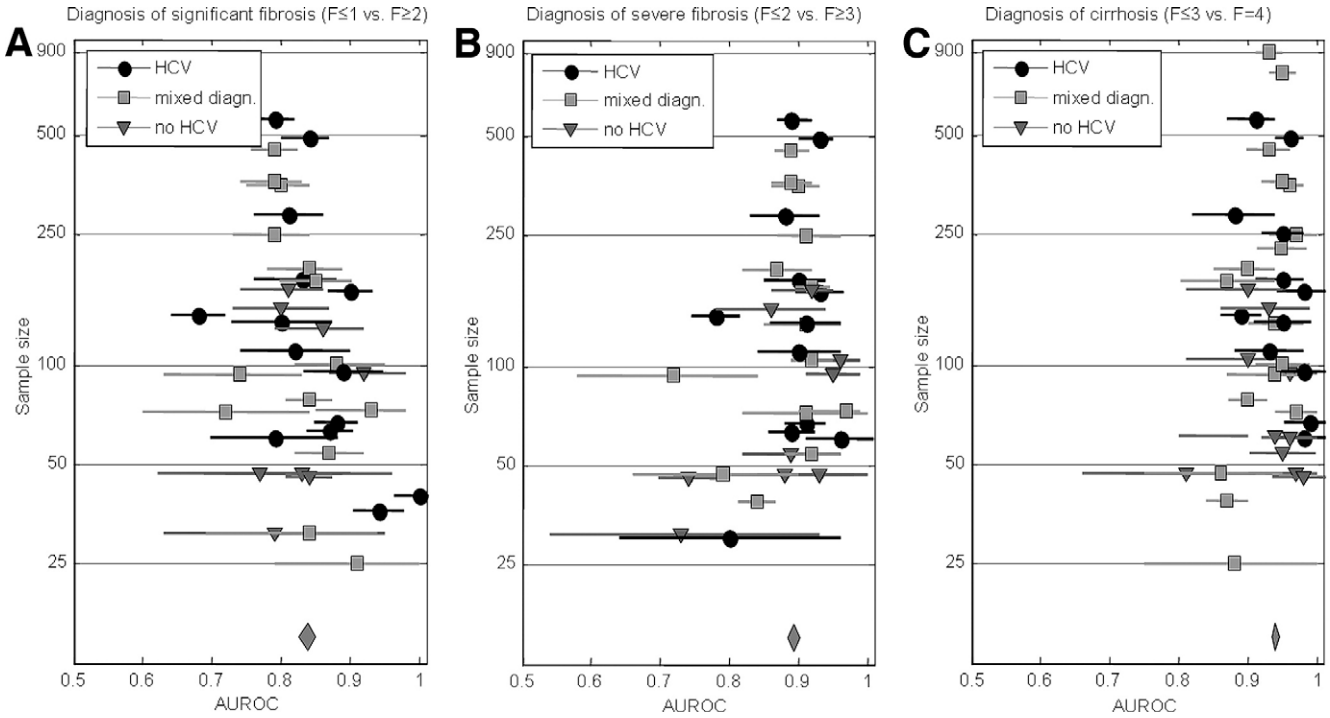

Figure 1. Forest plot from meta-analysis of AUROC values using a random-effects model for fibrosis stages (*A*) F ≤ 1 vs F ≥ 2, (*B*) F ≤ 2 vs F ≥ 3, and (*C*) F ≤ 3 vs F = 4. The distribution is shown according to the sample size. The length of the horizontal line represents the 95% CI, ●, AUROC of the studies examining HCV-infected patients only, ■, AUROC of the studies examining a patient population of different liver diseases including HCV, ▲, AUROC of the studies without HCV patients, and ♦, overall mean AUROC with 95% confidence bounds.

mation of selected abstracts with liver biopsy only is given in Supplementary Table 3 (see supplementary material online at www.gastrojournal.org). Abstracts that were published as full-length articles or that were presented at a more recent meeting are not listed.

Results for the Diagnosis of Significant Fibrosis: F0/1 Vs F2/3/4

Thirty-five studies reported data on the AUROC for significant fibrosis (fibrosis stage F ≥ 2). The mean AUROC (random-effects) for the diagnosis of significant fibrosis was 0.84 (95% CI, 0.82–0.86) (Figure 1 *A*). The adjusted AUROC, which corrects for liver biopsy quality, was 0.91.

The best results were shown in a study analyzing patients with hepatitis C infection and normal transaminase levels in which two thirds of patients had METAVIR fibrosis stage F0/1.

A significant reduction of heterogeneity ($P < .001$) was found when differentiating between the underlying liver diseases, with a mean AUROC of 0.85 (95% CI, 0.80–0.89) for studies examining HCV-infected patients only, 0.83 (95% CI, 0.80–0.86) for studies examining a patient population with different liver diseases including HCV, and 0.84 (95% CI, 0.81–0.87) for studies without HCV patients. In addition, a significant reduction of heterogeneity ($P < .001$) was found when accounting for different staging systems (AUROC of 0.83, 95% CI, 0.80–0.86 for METAVIR; AUROC of 0.84, 95% CI, 0.81–0.88 for Brunt; AUROC of 0.86, 95% CI, 0.75–0.98 for Ludwig's; AUROC of 0.81, 95% CI, 0.77–0.86 for Scheuer; AUROC of 0.94, 95% CI, 0.90–0.98 for Knodell; and AUROC of 0.88, 95% CI, 0.79–0.97 for Ishak). Interestingly, part of the heterogeneity also was explained by the countries where the studies were performed ($P < .001$), with a mean AUROC of 0.82 (95% CI, 0.79–0.85) in France, of 0.82 (95% CI, 0.74–0.90) in France/Belgium, of 0.86 (95% CI, 0.80–0.93) in France/United States, of 0.88 (95% CI, 0.83–0.93) in Italy, of 0.81 (95% CI, 0.76–0.86) in Japan, of 0.77 (95% CI, 0.64–0.91) in Korea, of 0.79 (95% CI, 0.70–0.88) in Portugal, of 0.84 (95% CI, 0.78–0.90) in Spain, and of 0.87 (95% CI, 0.84–0.90) in The Netherlands.

No significant difference in the AUROC was found between abstracts and full-length articles. Analyzing quantitative factors (where available) showed no significant effect of DANA on the AUROC (Figure 2 *A*, Supplementary Table 5; see supplementary material online at www.gastrojournal.org). Analogously, age, BMI, percentage of males, biopsy specimen length, proportion of liver biopsies, and FibroScan failure did not have an effect on the mean AUROC.

The SROC analysis showed no significant deviation from symmetry, which corresponds to a threshold independent diagnostic odds ratio ($P = .13$; Figure 3 *A* and

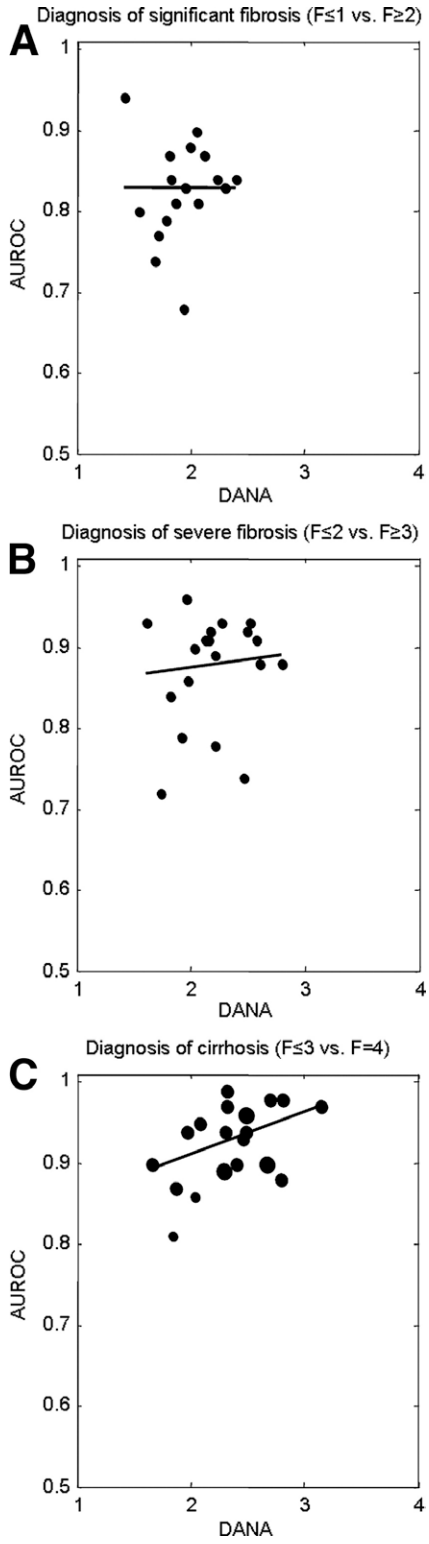

Figure 2. The AUROC according to DANA. The size of the dots is derived from the respective DerSimonian and Laird[11] type of weights for each study and the line showed a meta-regression fit.

D). Cut-off levels of liver stiffness (kPa) values with respective sensitivity and specificity were available in 17 studies for prediction of fibrosis stage F ≥ 2. We evaluated the dependence of sensitivity and specificity on the respective cut-off levels, but heterogeneity between the studies did not allow decisive conclusions on cut-off levels corresponding to the optimal sensitivity and specificity of the SROC curve (Figure 4 *A* and *D*).

Results for the Diagnosis of Severe Fibrosis: F0/1/2 Vs F3/4

Thirty-five studies reported data on the AUROC for severe fibrosis (fibrosis stage F ≥ 3). The mean AUROC (random-effects) for the diagnosis of severe fibrosis was 0.89 (95% CI, 0.88–0.91) (Figure 1 *B*).

No significant difference in the AUROC was found between the different underlying liver diseases, between the different countries where the studies were performed, and between abstracts and full-length articles. However, a significant reduction of heterogeneity was found when differentiating between studies using different staging systems ($P < .001$).

Analyzing quantitative factors (where available) showed a slight significant influence of BMI on the AUROC ($P = 0.05$). No significant effect of DANA (Figure 2 *B*, Supplementary Table 4; see supplementary material online at www.gastrojournal.org), as well as of age, percentage of males, biopsy specimen length, proportion of liver biopsies, and FibroScan failure on the AUROC was found.

Cut-off levels of liver stiffness (kPa) with respective sensitivity and specificity were available in 13 studies for METAVIR stage F ≥ 3 (Figure 4 *B* and *E*). The SROC analysis showed a symmetric ascending slope of 0.25 ($P < .001$) (Figure 3 *B*).

Results for the Diagnosis of Cirrhosis: F0/1/2/3 Vs F4

Thirty-eight studies reported data on the AUROC for fibrosis stage F = 4. The mean AUROC (random-effects) for the diagnosis of F = 4 (cirrhosis) was 0.94 (95% CI, 0.93–0.95) (Figure 1 *C*). The adjusted AUROC, which corrects for liver biopsy quality, was 0.99.

No significant difference in AUROC was found between the different underlying liver diseases. A slightly significant reduction of heterogeneity was found when differentiating between studies using different staging systems ($P < .05$).

However, part of the heterogeneity also was explained by the countries where the studies were performed ($P < .001$) with a mean AUROC of 0.95 (95% CI, 0.94–0.96) in France, 0.93 (95% CI, 0.88–0.98) in France/Belgium, 0.94 (95% CI, 0.90–0.98) in Germany, 0.93 (95% CI, 0.90–0.96) in Italy, 0.88 (95% CI, 0.82–0.94) in Japan, 0.84 (95% CI, 0.76–0.92) in Korea, 0.98 (95% CI, 0.94–1.0) in Portugal, 0.96 (95% CI, 0.94–0.98) in Spain, and 0.87 (95% CI, 0.84–0.90) in the United States. No significant difference was found between abstracts and full-length articles. Analyzing quantitative factors (where available) showed a slight effect of DANA on the AUROC (1-sided

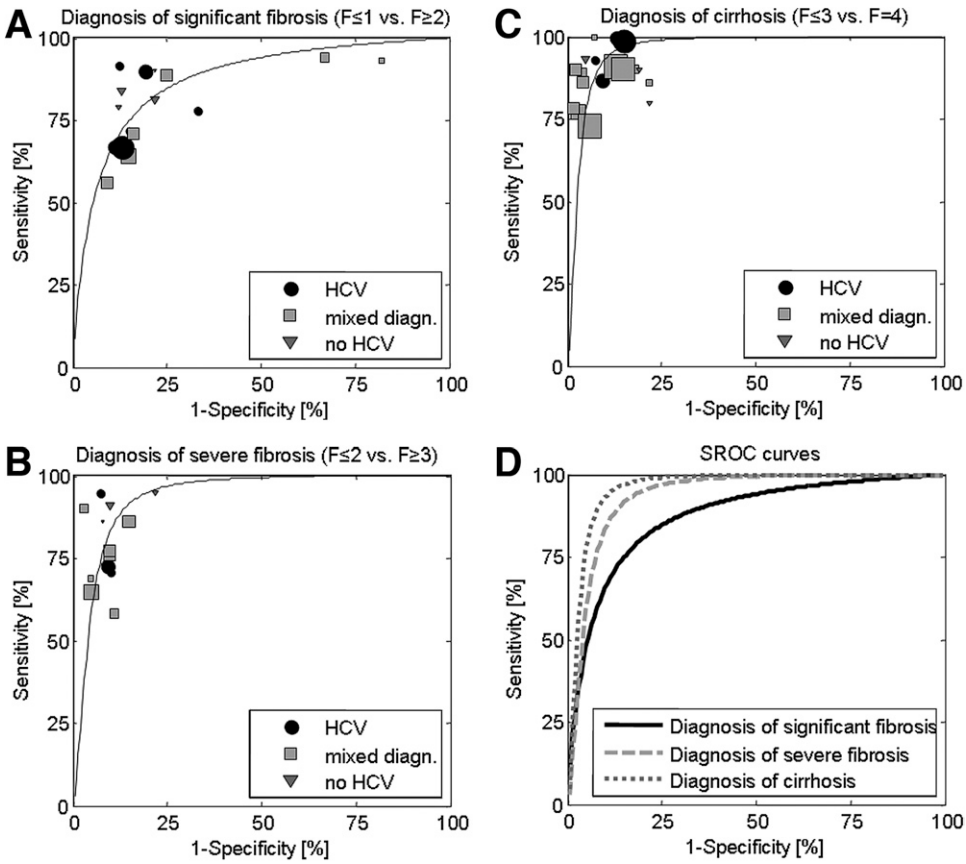

Figure 3. (*A*) SROC for F ≥ 2, (*B*) F ≥ 3, and (*C*) F = 4. The size of the dots for 1-specificity and sensitivity of the single studies in the ROC space is derived from the respective sample size. (*D*) SROC curves for different fibrosis stages are compared shown in the right lower panel. (*A–C*) ●, HCV; ■, mixed diagnosis; ▼, no HCV. (*D*) —, Diagnosis of significant fibrosis; – – –, diagnosis of severe fibrosis; - - -, diagnosis of cirrhosis.

$P = .044$; Figure 2 *C*, Supplementary Table 4; see supplementary material online at www.gastrojournal.org). Adjusting the AUROC according to the DANA effect and liver biopsy quality resulted in an AUROC of 0.99. Age, BMI, percentage of males, biopsy specimen length, proportion of liver biopsies, and FibroScan failure did not have an effect on the mean AUROC.

Cut-off levels of liver stiffness (kPa) with respective sensitivity and specificity were available in 17 studies for METAVIR stage F = 4 (Figure 4 *C* and *F*); in 1 study sensitivity and specificity were available for 2 different cut-off levels. The SROC analysis again showed a symmetric ascending slope of 0.29 ($P < .001$) (Figure 3 *C* and *D*).

Quality Assessment Using the QUADAS Questionnaire

Detailed information on the rating of items for each included study can be found in Supplementary Table 5 (see supplementary material online at www.gastrojournal.org). Item 14 (withdrawals) was always rated with yes because no withdrawals were expected in any study. The proportion of studies rated as yes, no, or unclear for each of the QUADAS items are shown in Figure 5.

A significant reduction of heterogeneity of the AUROC was found, accounting for different answers for selection criteria, appropriate reference standard, partial verification bias, reference execution details, test review bias, diagnostic review bias, and a number of uninterpretable results. Details are shown in Figure 5. However, the sum of all QUADAS items had no significant influence on the AUROC.

Discussion

The systematic literature search revealed 50 studies evaluating the diagnostic performance of transient elastography for the staging of liver fibrosis, which fulfilled the inclusion criteria and reported enough data to perform a meta-analysis. The aim of the systematic literature search was to include all relevant publications (including abstracts) with the main focus on the meta-analysis of the AUROC. A meta-analysis based on individual data was not the scope of the present study. Therefore, the power of this meta-analysis is certainly lower in comparison with large studies and studies including individual data.

Transient elastography performed best at differentiating cirrhosis vs no cirrhosis with a mean AUROC of 94%

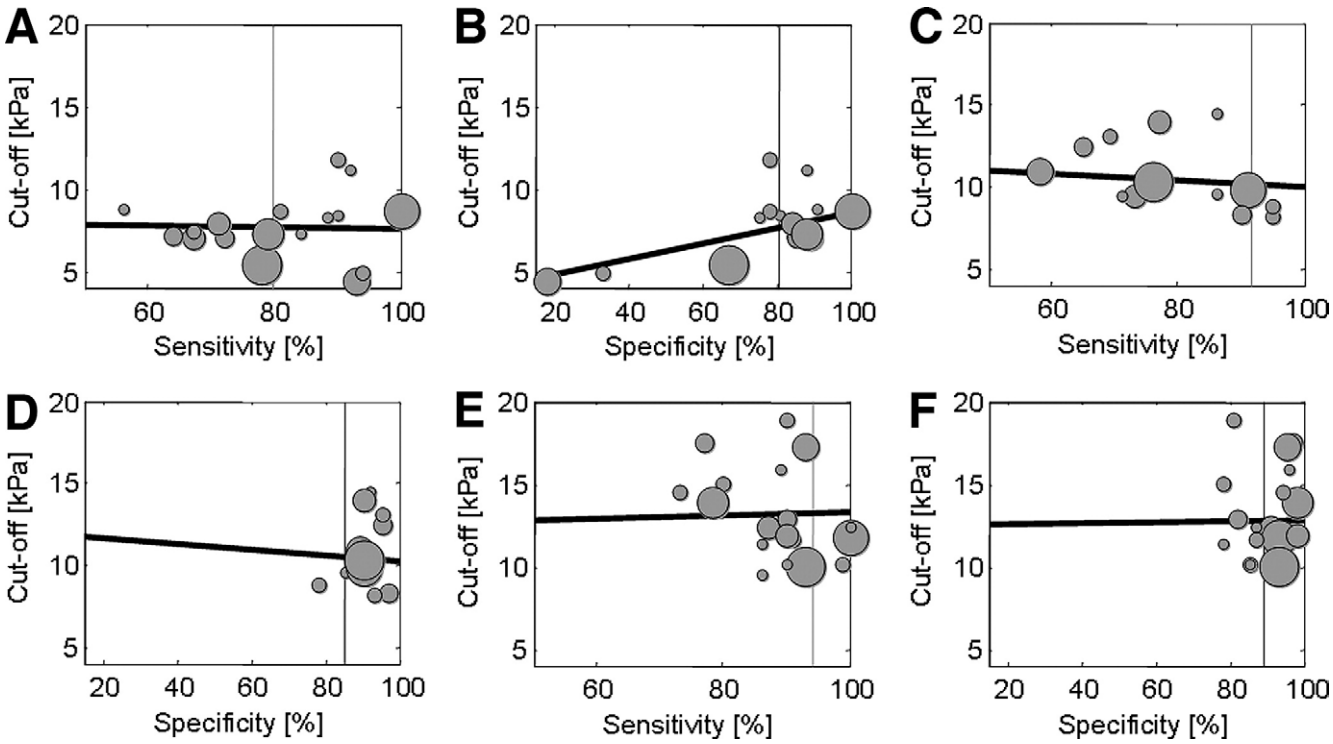

Figure 4. Sensitivity and specificity of respective cut-off values of the single studies for (*A* and *D*) F ≥ 2, (*B* and *E*) F ≥ 3, and (*C* and *F*) F = 4. The size of the dots is derived from the sample size of the single studies. Furthermore, the regression line with respect to a corresponding weighted linear regression is shown. The vertical line is drawn by calculation of the optimal sensitivity and specificity from the SROC. The crossing of both lines suggests the optimal cut-off value (F ≤ 1 vs F ≥ 2, 7.65 kPa; F ≤ 3 vs F = 4, 13.01 kPa).

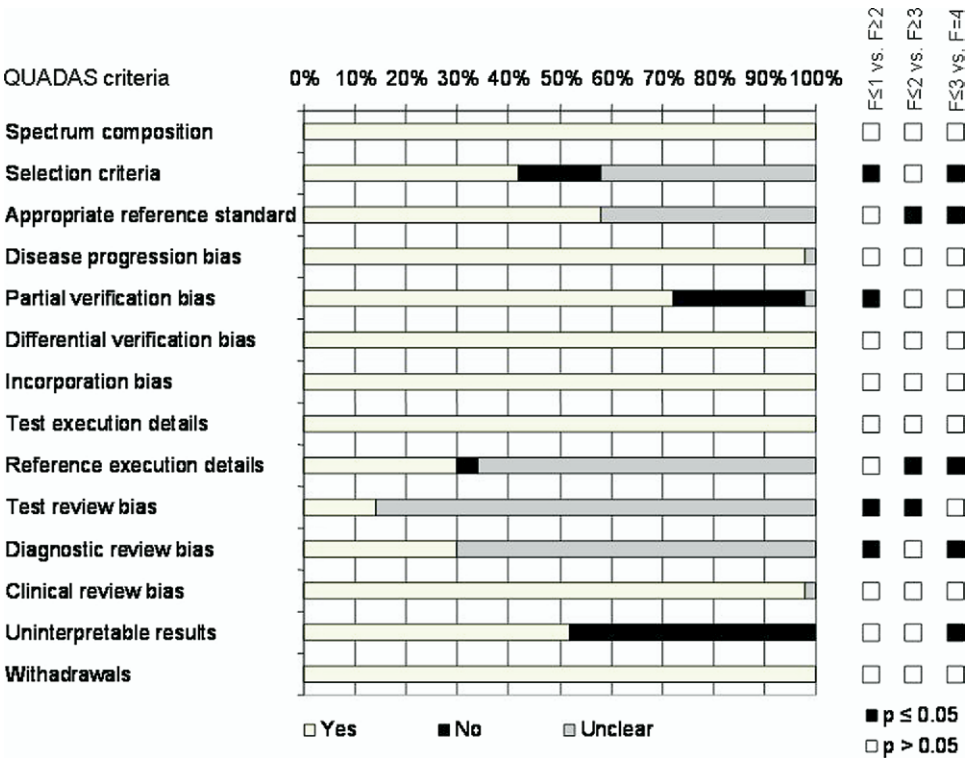

Figure 5. Proportion of studies rated as yes, no, or unclear for each of the QUADAS items. In the columns on the right it is indicated for each QUADAS item if a significant reduction of heterogeneity for the AUROC can be shown.

(95% CI, 0.93–0.95) and an adjusted AUROC of 99%. A diagnostic tool is defined as perfect if the AUROC is 100%, excellent if the AUROC is greater than 90%, and good if the AUROC is greater than 80%.[64,65] According to these results, transient elastography can be used in clinical practice as an excellent tool for the confirmation of cirrhosis when other clinical signs and examinations are nondecisive. In our view, a liver biopsy is not essential anymore to answer this question. Unfortunately, not enough information from the single studies was available to analyze in what percentage of patients the diagnosis of cirrhosis could have been made owing to overt clinical and biochemical signs of cirrhosis (low platelet count, low albumin level, increased international normalized ratio, sonographic signs of cirrhosis). The optimal cut-off value for the diagnosis of cirrhosis suggested from the SROC was 13.01 kPa.

The presence of significant fibrosis ($F \geq 2$) is considered a hallmark of a progressive liver disease. The highest aim of treatment is to cure the patient by resolving the underlying cause of liver disease (viral elimination in viral hepatitis, alcohol abstinence in ASH, weight loss in NASH, and immunosuppressant treatment in autoimmune hepatitis). Studies have shown that antiviral treatment of patients with chronic hepatitis C prolongs life, improves quality of life, and is cost effective.[66,67] However, treatment may be associated with severe side effects and the decision for treatment needs to be made on an individual basis. Patients with present fibrosis stage F2 and more already have shown a great progression of their liver disease and are at increased risk of developing cirrhosis with its sequelae (ie, esophageal varices, ascites, hepatic encephalopathy, and hepatocellular carcinoma). Therefore, patients with fibrosis stage F2 and more have a stronger indication for treatment as compared with patients with no or mild fibrosis (F0/1).[2,3,66]

The AUROC for $F \geq 2$ varied between the different studies with a range of 68%–100% and a mean AUROC of 84% (95% CI, 0.82–0.86) and an adjusted AUROC of 91%. For this indication, transient elastography alone cannot be used sufficiently in clinical practice. However, taking into account other clinical and diagnostic results, transient elastography can be a helpful tool for directing treatment decisions. The optimal cut-off value for the diagnosis of significant fibrosis suggested from the SROC was 7.65 kPa. However, because of the high heterogeneity caution must be taken when interpreting the results of different populations.

Compared with fibrosis biomarkers the disadvantage of transient elastography is the absence of a large control group to assess the limit of normal value (ie, blood donors). In addition, in studies using liver biopsy as a reference method, the number of patients without fibrosis (F0) is very small. Although transient elastography shows the best diagnostic accuracy for the differentiation of F0/1/2/3 and F4, the validated biomarkers are superior in differentiating F0 vs F1 vs F2. Studies thus have shown that the combination of transient elastography with biomarkers can further improve the diagnostic accuracy, especially for the diagnosis of significant fibrosis.[17,41]

Recently, a series of algorithms based on a sequential combination of noninvasive serum markers showed 93%–95% accuracy in the detection or exclusion of significant liver fibrosis and a reduction of 50% of liver biopsies in this subset of patients with HCV.[68] Further studies are needed to investigate if the inclusion of transient elastography in an algorithm with a combination of noninvasive serum markers may further reduce the number of liver biopsies needed. Transient elastography and the serum fibrosis marker FibroTest (BioPredictive, Paris, France) currently have been approved after an independent systematic review by the French Health authorities for the diagnosis of advanced fibrosis and cirrhosis in patients with HCV.

Significant heterogeneity was found between the single studies. Different possible reasons (qualitative and quantitative factors) for this heterogeneity were analyzed.

Discriminating between the underlying liver diseases led to a reduction of heterogeneity of AUROC for the differentiation of F0/1 vs F2/3/4. These results again support the use of transient elastography for the differentiation of cirrhosis vs no cirrhosis independent of the underlying liver disease, whereas caution needs to be taken for the interpretation of the differentiation of no/mild fibrosis from significant fibrosis.

The different scoring systems seem to have an impact on the heterogeneity of the studies and might be partially explained by the different underlying liver diseases that use different scoring systems. Not enough data were available to perform a multivariate analysis to analyze these coherences further.

For the diagnosis of significant fibrosis and cirrhosis a significant reduction of heterogeneity was observed when differentiating between the different countries where the studies were performed. This may be explained by different population groups and the quality criteria with respect to study conduction and result reporting. Because most of the studies were abstracts only, detailed information rarely was available. The mean/median length of the liver biopsy specimen was reported in 16 studies only. It ranged from 12 to 35 mm. However, in a subanalysis there was no significant influence of the length of the liver biopsy specimen on the AUROC. Most studies lack further information on the quality of the liver biopsy, ie, the number of fragmentations, the blinding of the pathologist, and the use of a central pathologist, and so forth. This certainly accounts for the heterogeneity between the studies. Nevertheless, assessment of quality by QUADAS items could not explain the heterogeneity between the studies sufficiently. Large international studies with satisfying high-quality criteria with respect to study

conduction and result reporting are awaited to overcome these discrepancies.

The predictive values of tests are known to be affected by disease prevalence and the distribution of fibrosis stages. However, the prevalence of extreme fibrosis stages described by DANA showed no or only slight influence on the AUROC in the present study (Figure 2, Supplementary Table 4; see Supplementary material online at www.gastrojournal.org). Obviously, the correlation of DANA with the AUROC in our meta-analysis was not as strong as in previous studies in the context with FibroTest[13,69] and as could be expected here (Figure 2, Supplementary Table 4; see supplementary material online at www.gastrojournal.org). This may have several reasons, especially additional reasons, for heterogeneity in our meta-analysis of FibroScan when compared with the published ones of FibroTest. Furthermore, the range of DANA that can vary between 1 and 4 is limited in our meta-regression here (Figure 2) and details on the prevalence of extreme fibrosis stages were not available in all included studies. Therefore, a multivariate analysis (eg, by the analysis of the DANA-adjusted AUROC with a reliable adjustment for DANA) was not possible here. This was a limitation of the present meta-analysis and the influence of differences in the prevalence of the fibrosis stages on AUROC should be examined in future analyses based on individual data.

Most studies presented the AUROC as a measure of test performance. However, the AUROC has limitations and may not be the best way to present the diagnostic performance of a test. Unfortunately, SROC analysis showed significant dependence of the diagnostic odds ratios on the chosen threshold because of significant deviations from symmetry and different thresholds used in the single studies. Therefore, we did not perform a meta-analysis of diagnostic odds ratio.

The use of liver biopsy as a reference standard for the evaluation of noninvasive methods and markers has methodologic limitations that may influence the performance of these tests. The accuracy of liver biopsy is limited because of intraobserver and interobserver variability and sampling errors.[5] In a study on more than 10,000 virtual biopsy specimens Bedossa et al[5] showed that liver fibrosis stage is diagnosed correctly in only 65% of cases if the biopsy is at least 15 mm long, in 75% of cases if it is at least 25 mm long, and that the optimal size should be 40 mm. However, most biopsy specimens even at hepatology centers do not fulfill these optimal criteria.[70] Nevertheless, transient elastography cannot replace liver biopsy. Liver biopsy as compared with transient elastography gives additional information on the cause of liver injury (viral, hereditary, autoimmune liver disease), necroinflammatory activity, and steatosis. Also, it must be noted that transient elastography cannot be used for the staging of liver fibrosis in patients with acute hepatitis or hepatitis exacerbation because transient elastography measurements significantly overestimate the stage of liver fibrosis during alanine aminotransferase flare.[71]

Data analyzing the discordance of liver biopsy and the panel marker FibroTest showed that this discordance was highly attributed to biopsy in 5% and to the panel marker in 2% ($P = .03$).[70] The investigators concluded that these shortcomings of liver biopsy lead to underestimation of the diagnostic accuracy of noninvasive markers. That this also might apply to the underestimation of transient elastography was shown in another study analyzing the discordance of the panel marker FibroTest and transient elastography compared with liver biopsy. The investigators showed that this discordance was attributable to FibroTest failure in 12.4% and to transient elastography failure in 6.8%.[72] At present, a perfect gold standard for the evaluation of liver fibrosis is not available. Liver biopsy, FibroTest, and transient elastography remain imperfect reference methods. Therefore, specific methodology that is independent of a gold standard could be recommended to overcome these limitations at this time point.[73] Another possibility would be an optimization of the reference standard (eg, laparoscopic liver biopsy with a biopsy specimen from the left and right lobes of 20-mm length each). Only with an improved, comparable, and standardized reference standard can the true diagnostic performance of transient elastography be evaluated.

The ultimate validation of liver fibrosis as a marker of liver injury is its prognostic value in terms of morbidity and mortality. In a recently published study, the biomarker FibroTest was shown to have a 5-year prognostic value similar to that of liver biopsy.[74] However, transient elastography is still a novel method and 5-year follow-up studies are not available yet. Large, well-conducted, randomized trials with clearly defined end points (eg, assessing 5-year survival without HCV-related cirrhosis or complications related to liver disease such as liver-related death, liver transplantation, hepatic decompensation, variceal bleeding, hepatocellular carcinoma) are needed to compare transient elastography with liver biopsy and biochemical markers.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2008.01.034.

References

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41–52.
2. Strader DB, Wright T, Thomas DL, et al. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39:1147–1171.

3. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45: 507–539.
4. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495–500.
5. Bedossa P, Dargere D, Paradise V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449–1457.
6. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new non-invasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705–1713.
7. Kettaneh A, Marcellin P, Douvin C, et al. Features associated with success rate and performance of Fibroscan measurements for the diagnosis of cirrhosis in HCV patients: a prospective study of 935 patients. J Hepatol 2007;46:628–634.
8. Fraquelli M, Rigamonti C, Casazza G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007;56:968–973.
9. Deeks JJ. Systematic reviews of evaluation of diagnostic and screening tests. BMJ 2001;323:157–162.
10. Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis from Medline: analytical survey. BMJ 2004;328:1040.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
12. Poynard T, Halfon P, Castera L, et al. Variability of the area under the receiver operating characteristic curves in the diagnostic evaluation of liver fibrosis markers: impact of biopsy length and fragmentation. Aliment Pharmacol Ther 2007;25:733–739.
13. Poynard T, Halfon P, Castera L, et al. Standardization of ROC curve areas for diagnostic evaluation of liver fibrosis markers based on prevalences of fibrosis stages. Clin Chem 2007;53: 1615–1622.
14. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3:25.
15. Littenberg B, Moses LE. Estimating diagnostic accuracy from multiple conflicting reports: a new meta-analytic method. Med Decis Making 1993;13:313–321.
16. Carrion JA, Navasa M, Bosch J, et al. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Liver Transpl 2006;12:1791–1798.
17. Castera L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343–350.
18. Colletta C, Smirne C, Fabris C, et al. Value of two noninvasive methods to detect progression of fibrosis among HCV carriers with normal aminotransferases. Hepatology 2005;42:838–845.
19. Corpechot C, El Naggar A, Poujol-Robert A, et al. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. Hepatology 2006;43:1118–1124.
20. De Ledinghen V, Douvin C, Kettaneh A, et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. J Acquir Immune Defic Syndr 2006;41: 175–179.
21. Erhardt A, Lorke J, Vogt C, et al. [Transient elastography for diagnosing liver cirrhosis.] Dtsch Med Wochenschr 2006;131: 2765–2769.
22. Ganne-Carrie N, Ziol M, de Ledinghen V, et al. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. Hepatology 2006;44:1511–1517.
23. Gomez-Dominguez E, Mendoza J, Rubio S, et al. Transient elastography: a valid alternative to biopsy in patients with chronic liver disease. Aliment Pharmacol Ther 2006;24:513–518.
24. Nahon P, Thabut G, Ziol M, et al. Liver stiffness measurement versus clinicians' prediction or both for the assessment of liver fibrosis in patients with chronic hepatitis C. Am J Gastroenterol 2006;101:2744–2751.
25. Posthouwer D, Mauser-Bunschoten EP, Fischer K, et al. Significant liver damage in patients with bleeding disorders and chronic hepatitis C: non-invasive assessment of liver fibrosis using transient elastography. J Thromb Haemost 2007;5:25–30.
26. Ziol M, Handra-Luca A, Kettaneh A, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48–54.
27. Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55:403–408.
28. Takeda T, Yasuda T, Nakayama Y, et al. Usefulness of noninvasive transient elastography for assessment of liver fibrosis stage in chronic hepatitis C. World J Gastroenterol 2006;12:7768–7773.
29. Baldaia C, Serejo F, Marinho R, et al. Transient elastography in chronic hepatitis C—comparison between different noninvasive methods for liver fibrosis assessment. Hepatology 2006; 44(Suppl 1):276A.
30. Barrault C, Medkour F, Atanaiu C, et al. Non invasive assessment of liver graft fibrosis by transient elastography after liver transplantation. Hepatology 2005;42(suppl 1):485A–486A.
31. Blanc PL, Gabbuti A, Marino N, et al. Liver stiffness in chronic hepatitis C: will it modify the assessment of patients? J Hepatol 2007;46(suppl 1):S201A.
32. Castera L, Van hecke A, Trimoulet P, et al. Independent validation and comparison with FibroScan, FibroTest and liver biopsy of clinical glycomics for the non invasive assessment of liver fibrosis in chronic hepatitis C. Hepatology 2005;42(Suppl 1):436A.
33. Castera L, Foucher J, Le Bail B, et al. Prospective and independent validation of the Lok index for prediction of cirrhosis in patients with chronic hepatitis C: comparison with FibroScan, FibroTest and APRI. DDW 2006;(Abstract-ID: 552).
34. Chang J, Tan HH, Yew BS, et al. Transient elastography (FibroScan®) to assess hepatic fibrosis in Chinese with chronic hepatitis B. 17th Asian Pacific Association for the Study of Liver Conference 2007.
35. Chanteloup E, Foucher J, Castera L, et al. FibroScan® is a new non invasive method for the detection of cirrhosis and its complications in patients with chronic liver diseases. Results of a prospective study in 456 patients. Hepatology 2004;40(suppl 1):515A.
36. Coco B, Oliveri F, Colombatto P, et al. Monitoring liver stiffness: a new tool to measure liver fibrosis during therapy. Hepatology 2005;42(suppl 1):435A.
37. Coco B, Oliveri F, Colombatto B, et al. Liver stiffness measured by transient elastography: the influence of biochemical activity. J Hepatol 2006;44(suppl 2):S196A.
38. Corradi F, Piscaglia F, Tame R, et al. Staging of hepatic fibrosis by liver elastometry (FibroScan) in recurrent HCV infection in liver transplant recipients. J Hepatol 2006;44(suppl 2):S59A.
39. De Ledinghen V, Le Bail B, Rebouissoux L, et al. FibroScan® is a new non-invasive method for the diagnosis of liver fibrosis in children: a prospective comparison with FibroSure®, and liver biopsy. Hepatology 2005;42(suppl 1):472A.
40. De Ledinghen V, Beaugrand M, Kelleher TB, et al. Prediction of liver fibrosis in non-alcoholic steatohepatitis (NASH): risk factors and diagnostic potential of liver elasticity using FibroScan. J Hepatol 2006;44(suppl 2):S39A.
41. Foucher J, Vergniol J, Castera L, et al. Fibrosis evaluation in chronic liver diseases: comparison of FibroScan® with liver biopsy, FibroTest®, Forns score, APRI, hyaluronan, prothrombin time, and AST/ALT ratio. J Hepatol 2005;42(suppl 2):78A.
42. Fraquelli M, Rigamonti C, Conte D, et al. Reproducibility of transient elastography (TE) in assessing hepatic fibrosis. Hepatology 2006;44(suppl 1):444A.

43. Gaia S, Carenzi S, Brunello F, et al. Is liver stiffness measurement different in patients with NASH or with viral hepatitis? J Hepatol 2007;46(suppl 1):S268A.
44. Ganne-Carrie N, De Ledinghen V, Douvin C, et al. Accuracy of liver stiffness measurement (LSM) for the diagnosis of cirrhosis in patients with chronic liver diseases (CLD): a study in 1345 patients. Hepatology 2005;42(suppl 1):338A.
45. Gomez-Dominguez E, Jimenez-Ridruejo JM, Monteagudo JAM, et al. Efficiency of liver stiffness measurement (FibroScan®) for the follow up of patients with primary biliary cirrhosis. Hepatology 2006;44(suppl 1):633A.
46. Jeon SW, Cho CM, Park YD, et al. Correlation between liver elasticity measured by Fibroscan® and liver fibrosis assessed by histology; preliminary study in Korea. DDW 2006;(Abstract ID: S1610).
47. Khohkar A, Farnan R, MacFarlane C, et al. Liver stiffness and biomarkers: correlation with cirrhosis, portal hypertension and hepatic synthetic function. Hepatology 2005;42(suppl 1):433A.
48. Kim KM, Park SH, Yu ES, et al. Diagnosis of hepatic steatosis and fibrosis by transient elastography in asymptomatic healthy people: a prospective study in potential living related liver donors. J Hepatol 2006;44:S91A.
49. Laharie D, Foucher J, Bernard PH, et al. Assessment of cirrhosis and its severity by FibroScan and biochemical markers in alcoholic patients. DDW 2006;(Abstract ID: M1026).
50. Lewin M, Poujol-Robert A, Boelle PY, et al. Diffusion-weighted MR imaging for the diagnosis of liver fibrosis in patients with chronic hepatitis C. Hepatology 2006;44(suppl 1):280A–281A.
51. Marcellin P, De Ledinghen V, Dhumeaux D, et al. Non-invasive assessment of liver fibrosis in chronic hepatitis B using FibroScan®. Hepatology 2005;42(suppl 1):715A–716A.
52. Marin JC, De la Cruz J, Fernandez I, et al. Prospective comparison between transient elastography (FibroScan), APRI and Forns test for assessing liver fibrosis in patients with histological features of NAFLD. J Hepatol 2007;46(suppl 1):S275A.
53. Miailhes P, Perrot G, Bailly F, et al. Prospective comparison of transient elastography and liver biopsy for the assessment of fibrosis in patients with HIV/HBV co-infection. 14th Conference on Retroviruses and Opportunistic Infections 2007.
54. Nahon P, Ziol M, De Ledinghen V, et al. Assessment of liver fibrosis using liver stiffness measurement (LSM) in patients with alcoholic liver disease. J Hepatol 2007;46(suppl 1): S278A.
55. Nguyen-Khac E, Robert B, Brevet M, et al. Assessment of asymptomatic liver fibrosis in alcohol abuser patients by transient elastography (FibroScan). J Hepatol 2007;46(suppl 1): S280A.
56. Palau R, Mal F, Christidis C, et al. Transient elastography a new non invasive method for assessment of liver fibrosis: results in patients with HCV chronic hepatitis. J Hepatol 2003;38(suppl 2):126A.
57. Pares A, Caballeria L, Lazaro E, et al. Transient elastography: a new and useful non-invasive method for assessing liver damage progression in primary biliary cirrhosis. Hepatology 2005; 42(suppl 1):464A.
58. Rigamonti C, Donato MF, Fraquelli M, et al. Evaluation of liver graft fibrosis by transient elastography (TE). Liver Transpl 2006; 12:C60A.
59. Rigamonti C, Donato F, Fraquelli M, et al. Transient elastography (TE, FibroScan®) in the evaluation of recurrent disease after liver transplantation (LT). Hepatology 2006;44(suppl 1): 195A.
60. Serejo F, Marinho R, Costa A, et al. Transient elastography (FibroScan®) in chronic hepatitis C. Will it modify the assessment and the follow-up of treated patients? Hepatology 2006; 44(suppl 1):322A–323A.
61. Servin-Abad LA, Jeffers LJ, Bejarano P, et al. Correlation between liver histology, laparoscopic gross appearance and elasticity measured with the shear elasticity probe (FibroScan) in patients with chronic liver disease. Hepatology 2006;44(suppl 1):578A.
62. Vergara S, Macías J, Rivero A, et al. Failure of transient elatometry (FibroScan) to differentiate mild from significant liver fibrosis in HIV/HCV-co-infected patients. 14th Conference on Retroviruses and Opportunistic Infections 2007.
63. Beaugrand M, Ziol M, Sandrin L, et al. Liver elasticity measurement by ultrasonic transient elastography: a new non-invasive method for assessment of liver fibrosis in chronic viral hepatitis. Hepatology 2003;38(suppl 1):438A–439A.
64. Swets JA. Measuring the accuracy of diagnostic systems. Science 1988;240:1285–1293.
65. Ebell MH. Probability of cirrhosis in patients with hepatitis C. Am Fam Physician 2003;68:1831–1833.
66. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147: 677–684.
67. Siebert U, Sroczynski G. Effectiveness and cost-effectiveness of initial combination therapy with interferon/peginterferon plus ribavirin in patients with chronic hepatitis C in Germany: a health technology assessment commissioned by the German Federal Ministry of Health and Social Security. Int J Technol Assess Health Care 2005;21:55–65.
68. Sebastiani G, Alberti A. Non invasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. World J Gastroenterol 2006;12:3682–3694.
69. Poynard T, Morra R, Halfon P, et al. Meta-analyses of Fibrotest diagnostic value in chronic liver disease. BMC Gastroenterol 2007;7:40.
70. Poynard T, Munteanu M, Imbert-Bismut F, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. Clin Chem 2004;50:1344–1355.
71. Coco B, Oliveri F, Maina AM, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat 2007;14:360–369.
72. Castera L, Le-Bail B, Foucher J, et al. Prospective analysis of discordance between FibroScan and FibroTest when used in combination as first-line assessment of liver fibrosis in chronic hepatitis C. Hepatology 2005;42(suppl 1):440A.
73. Hui SL, Zhou XH. Evaluation of diagnostic tests without gold standards. Stat Methods Med Res 1998;7:354–370.
74. Ngo Y, Munteanu M, Messous D, et al. A prospective analysis of the prognostic value of biomarkers (FibroTest) in patients with chronic hepatitis C. Clin Chem 2006;52:1887–1896.

Received May 31, 2007. Accepted January 10, 2008.

Address requests for reprints to: Eva Herrmann, PhD, Faculty of Medicine, Internal Medicine-Biomathematics, Saarland University, Kirrbergerstrasse, 66421 Homburg/Saar, Germany. e-mail: eva.herrmann@uniklinik-saarland.de; fax: (49) (0)6841-16-23583.

This study was supported by the Federal Ministry of Education and Research (BMBF) program Kompetenznetz Hepatitis (Hep-Net).

The authors thank Céline Fournier for her assistance in the literature search, for reviewing the manuscript, and for her helpful discussions.

Reference list of above mentioned excluded full paper publications:

1. Fraquelli M, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G, Colombo M. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007;56:968–973.
2. Nguyen-Khac E. [Results and place of FibroScan in non-invasive diagnosis of hepatic fibrosis]. La Revue de Medicine Interne 2007;28:94–102.
3. de Franchis R, Dell'Era A. Non-invasive diagnosis of cirrhosis and the natural history of its complications. Best Pract Res Clin Gastroenterol 2007;21:3–18.
4. De Ledinghen V, Trimoulet P, Mannant PR, Dumas F, Champbenoit P, Baldit C, Foucher J, Faure M, Vergniol J, Castera L, Bertet J, Fleury H, Couzigou P, Bernard PH. Outbreak of hepatitis C virus infection during sclerotherapy of varicose veins: Long-term follow-up of 196 patients (4535 patient-years). J Hepatol 2007;46: 19–25.
5. Carrion JA, Colmenero J, Bataller R, Forns X. Diagnostico no invasivo de la fibrosis hepatica. Gastroenterologia y Hepatologia 2007;30, Suppl.1:106-112.
6. Barreiro P, Labarga P, Martin-Carbonero L, Amor A, Ruiz-Sancho A, Castellares C, Gonzalez-Lahoz J, Soriano V. Sustained virological response following HCV therapy is associated with non-progression of liver fibrosis in HCV/HIV-coinfected patients. Antivir Ther 2006;11:869–877.
7. Takeda T, Yasuda T, Nakayama Y, Nakaya M, Kimura M, Yamashita M, Sawada A, Abo K, Takeda S, Sakaguchi H, Shiomi S, Asai H, Seki S. Usefulness of noninvasive transient elastography for assessment of liver fibrosis stage in chronic hepatitis C. World J Gastroenterol 2006;12:7768–7773.
8. Kelleher TB, Afdhal N. Assessment of liver fibrosis in co-infected patients. J Hepatol 2006;44:S126–S131.
9. Nguyen-Khac E, Capron D. Noninvasive diagnosis of liver fibrosis by ultrasonic transient elastography (Fibroscan). Eur J Gastroenterol Hepatol 2006;18:1321–1325.
10. Maida I, Soriano V, Castellares C, Ramos B, Sotgiu G, Martin-Carbonero L, Barreiro P, Rivas P, Gonzalez-Lahoz J, Nunez M. Liver fibrosis in HIV-infected patients with chronic hepatitis B extensively exposed to antiretroviral therapy with anti-HBV activity. HIV Clin Trials 2006;7:246–250.
11. Sebastiani G, Alberti A. Non invasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. World J Gastroenterol 2006;12:3682–3694.
12. Murtagh J, Foerster V. Transient elastography (FibroScan) for non-invasive assessment of liver fibrosis. Issues Emerg Health Technol 2006;1-4.
13. Guechot J. [Noninvasive assessment of liver fibrosis in patients with chronic hepatitis virus C]. Presse Med 2006;35:1317–1326.
14. Corpechot C, El Naggar A, Poupon R. Gender and Liver: is the liver stiffness weaker in weaker sex? Hepatology 2006;44:513–514.
15. Kawamoto M, Mizuguchi T, Katsuramaki T, Nagayama M, Oshima H, Kawasaki H, Nobuoka T, Kimura Y, Hirata K. Assessment of liver fibrosis by a noninvasive method of transient elastography and biochemical markers. World J Gastroenterol 2006;12:4325–4330.
16. Bosch J. Prediction from a hard liver. J Hepatol 2006;45:174–177.
17. Kazemi F, Kettaneh A, N'kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, Beaugrand M. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006;45:230–235.
18. Verveer C, De Knegt RJ. Non-invasive measurement of liver fibrosis: Application of the FibroScan(R) in hepatology. Scand J Gastroenterol Suppl 2006;85-88.
19. Moreno-Otero R, Trapero-Marugan M, Mendoza J. Liver fibrosis assessment by transient elastography in hepatitis C patients with normal alanine aminotransferase. Gut 2006;55:1055–1056.
20. Lemoine M. [Place and perspectives of diagnosis with FibroScan]. Gastroentérologie Pratique 2006;June 1st.
21. Luo JW, Shao JH, Bai J, Cui LG, Wang JR. [Using non-invasive transient elastography for the assessment of hepatic fibrosis]. Zhonghua Gan Zang Bing Za Zhi 2006;14:395–397.
22. Beaugrand M. [Fibroscan: instructions for use]. Gastroenterol Clin Biol 2006;30:513–514.
23. Masaki N, Imamura M, Kikuchi Y, Oka S. Usefulness of elastometry in evaluating the extents of liver fibrosis in hemophiliacs coinfected with hepatitis C virus and human immunodeficiency virus. Hepatol Res 2006;35:135–139.
24. Maida I, Nunez M, Rios MJ, Martin-Carbonero L, Sotgiu G, Toro C, Rivas P, Barreiro P, Mura MS, Babudieri S, Garcia-Samaniego J, Gonzalez-Lahoz J, Soriano V. Severe liver disease associated with prolonged exposure to antiviral drugs. J Acquir Immune Defic Syndr 2006;42:177–182.
25. Sandrin L, Fournier C, Miette V, Yon S, Hasquenoph JM. [FibroScan: a noninvasive device that measures liver stiffness by transient elastography]. ITBM-RBM 2006;27:25–31.
26. Laharie D, Zerbib F, Adhoute X, Boue-Lahorgue X, Foucher J, Castera L, Rullier A, Bertet J, Amouretti M, De Ledinghen V. Diagnosis of liver fibrosis by transient elastography (FibroScan) and non-invasive methods in Crohn's disease patients treated with methotrexate. Aliment Pharmacol Ther 2006;23:1621–1628.
27. Barreiro P, Martin-Carbonero L, Nunez M, Rivas P, Morente A, Simarro N, Labarga P, Gonzalez-Lahoz J, Soriano V. Predictors of liver fibrosis in HIV-infected patients with chronic hepatitis C virus (HCV) infection: assessment using transient elastometry and the role of HCV genotype 3. Clin Infect Dis 2006;42: 1032–1039.
28. Beaugrand M. How to assess liver fibrosis and for what purpose? J Hepatol 2006;44:444–445.
29. Foucher J, Castera L, Bernard PH, Adhoute X, Laharie D, Bertet J, Couzigou P, De Ledinghen V. Prevalence and factors associated with failure of liver stiffness measurement using FibroScan in a prospective study of 2114 examinations. Eur J Gastroenterol Hepatol 2006;18:411–412.
30. Mendoza J, Gomez-Dominguez E, Moreno-Otero R. [Transient elastography (Fibroscan), a new non-invasive method to evaluate hepatic fibrosis]. Med Clin (Barc) 2006;126:220–222.
31. Castera L, Foucher J, Bertet J, Couzigou P, de L, V. FibroScan and FibroTest to assess liver fibrosis in HCV with normal aminotransferases. Hepatology 2006;43:373–374.
32. Cherry K. Accurate detection of cirrhosis by transient elastography. Nat Clin Pract Gastroenterol Hepatol 2006;3:243–244.
33. Melin P, Dacon A, Gauchet A, Schoeny M, Diebold MD. [Non invasive detection of liver fibrosis- Value of FibroScan in alcohol consulting out-patients]. Alcoologie et Addictologie 2005; 27:191–196.
34. Kelleher TB, Afdhal N. Noninvasive assessment of liver fibrosis. Clin Liver Dis 2005;9:667–683.
35. Blanc JF, Bioulac-Sage P, Balabaud C, Desmouliere A. Investigation of liver fibrosis in clinical practice. Hepatol Res 2005; 32:1–8.
36. Sogni P, Salmon-Ceron D, Podevin P. [Management of cirrhosis complications in HIV patients coinfected with hepatitis B or C virus]. Presse Med 2005;34:1579–1583.
37. Ghany MG, Doo E. Assessment of liver fibrosis: palpate, poke or pulse? Hepatology 2005;42:759–761.
38. Saito H, Tada S, Nakamoto N, Kitamura K, Horikawa H, Kurita S, Saito Y, Iwai H, Ishii H. Efficacy of non-invasive elastometry on staging of hepatic fibrosis. Hepatol Res 2004;29:97–103.

Supplementary Table 1. QUADAS Questionnaire

Item#	Question
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?
2.	Were selection criteria clearly described?
3.	Is the reference standard likely to correctly classify the target condition?
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? (disease progression bias)
5.	Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis? (partial verification bias)
6.	Did patients receive the same reference standard regardless of the index test result? (differential verification bias)
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? (incorporation bias)
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?
10.	Were the index test results interpreted without knowledge of the results of the reference standard? (test review bias)
11.	Were the reference standard results interpreted without knowledge of the results of the index test? (diagnostic review bias)
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? (clinical review bias)
13.	Were uninterpretable/intermediate test results reported?
14.	Were withdrawals from the study explained?

Supplementary Table 2. Reasons for Exclusion of Full Paper Publications

Author, publication, year	Abstract and article not written in English	Language	No liver biopsy	No data on AUROC, sens, spec	Staging system not comparable with METAVIR	Staging system used	Review/ Editorial	Reference test/ Comment
Fraquelli M Gut 2007 [1]			x					Reproducibility of FS was evaluated
Nguyen-Khac E La Revue de Medecine Interne 2007 [2]							x	
De Franchis R Best Pract Res Clin Gastroenterol 2007 [3]							x	
De Ledinghen V J Hepatol 2007 [4]				x				Outbreak of HCV during sclerotherapy
Carrion JA Gastroenterologia y Hepatologia 2007 [5]	x	Spanish					x	
Barreiro P Antiviral Therapy 2006 [6]			x					Non-invasive assessment of liver fibrosis after antiviral therapy in patients with SVR versus non-response
Kelleher T J Hepatol 2006 [8]							x	
Nguyen-Khac E Eur J Gastroenterol Hepatol 2006 [9]							x	
Maida I HIC Clin Trials 2006 [10]			x					Non-invasive assessment with FS in HIV/HBV patients extensively exposed to antiretroviral therapy
Sebastiani G World J Gatroenterol 2006 [11]							x	
Murtagh J Issues Emerg Health Technol 2006 [12]							x	
Guechot J Presse Med 2006 [13]							x	
Corpechot C Hepatology 2006 [14]			x					Effect of gender on FS in healthy subjects
Kawamoto World J Gastroenterol 2006 [15]					x	Hepatectomy specimen, fibrotic area using NIH image		
Bosch J J Hepatol 2006 [16]							x	
Kazemi F J Hepatol 2006 [17]			x					Liver cirrhosis patients only, assoc. of FS and risk of large esophageal varices
Verveer C Scand J Gastroenterol Suppl 2006 [18]							x	
Moreno-Otero R Gut 2006 [19]			x					Non-invasive assessment of liver fibrosis in HCV-infected patients and normal ALT
Lemoine M Gastroenterologie Pratique 2006 [20]	x	French					x	
Luo JW Zhonghua Gan Zang Bing Za Zhi 2006 [21]	x	Chinese					x	
Beaugrand M Gastroenterol Clin Biol 2006 [22]	x	French					x	
Masaki N Hepatol Res 2006 [23]			x					Non-invasive assessment of liver fibrosis in hemophiliacs with HCV/HIV coinfection, comparison with ultrasound
Maida I J Acquir Immune Defic Syndr 2006 [24]				x				LBP or FS showing more severe liver disease assoc. with prolonged antiretroviral drugs

Supplementary Table 2. Continued

Author, publication, year	Abstract and article not written in English	Language	No liver biopsy	No data on AUROC, sens, spec	Staging system not comparable with METAVIR	Staging system used	Review/ Editorial	Reference test/Comment
Sandrin L ITBM-RBM 2006 ([25])	x	French					x	
Laharie D Aliment Pharmacol Ther 2006 ([26])			x					Non-invasive assessment of liver fibrosis in Crohn's pat. treated with methotrexate
Barreiro P Clin Infect Dis 2006 ([27])			x					Predictors of liver fibrosis in HCV/HIV pat. Using FS as reference
Beaugrand M J Hepatol 2006 ([28])							x	
Foucher J Eur J Gastroenterol Hepatol 2006 ([29])			x					Factors ass. with failure of FS measurement
Mendoza J Med Clin (Barc) 2006 ([30])	x	Spanish					x	
Castera L Hepatology 2006 ([31])							x	
Cherry K Nat. Clin Pract Gastroenterol Hepatol 2006 ([32])							x	
Melin P Alcoologie et Addictologie 2005 ([33])				x				LBP only if FS was >13kPa
Kelleher TB Clin Liver Dis 2005 ([34])							x	
Blanc JF Hepatol Res 2005 ([35])							x	
Sogni P Presse Med 2005 ([36])							x	
Ghany M et Hepatology 2005 ([37])							x	
Saito H Hepatol Res 2004 ([38])					x	Inuyama classification		

SVR, sustained virological response; FS, FibroScan; HBV, hepatitis B virus; HCV, hepatitis C virus; LBP, liver biopsy; AUROC, area under the ROC curve; sens, sensitivity; spec, specificity.

Supplementary Table 3. Reasons for Exclusion of Abstract With Liver Biopsy as Reference Test

Author, publication, year	Abstract not written in English	Language	No data on AUROC, sens, spec	Staging system not comparable with METAVIR	Staging system used	Reference test/Comment
Yeshua H EASL 2007			x			Sampling variability of LBP and FS was analyzed
Di Marco V EASL 2007			x			FS to measure liver stiffness in patients with iron overload
Lai L APASL 2007			x			Liver resection (liver cancer, liver secondaries, liver donors)
Tamano M APASL 2007			x			Liver biopsy only in patients with FS-measurement $>$ 9 kPa
Merchante N CROI 2007			x			Liver biopsy only in patient with FS measurement $>$ 7.1 kPa
Cales P AASLD 2006			x			AUROC only for combination of FS with blood scores and ultrasonography criteria
Bureau C AASLD 2006			x			Transjugular liver biopsy, AUROC of FS for prediction of PPG only
Kim J AASLD 2006			x			AUROC only for the prediction of esophageal varices in cirrhotic patients
Farnan R AASLD 2006			x			All patients had biopsy proven cirrhosis. Optimization of diagnosis of cirrhosis comparing clinical, biochemical, and radiological features with FS
Takeda T AASLD 2006			x			27 patients with NAFLD, cut-off for identification of NASH Stage 3 or more (Brunt classification) is given
De Ledinghen V AASLD 2006			x			Liver biopsy before treatment and FS at the end of long-term follow-up. Regression of fibrosis in HCV-responders
Lemoine M AASLD 2006			x			Transjugular liver biopsy, AUROC of FS for prediction of PPG $\geq$ 12 mm Hg only
Fukuzawa Y AASLD 2006			x			Increase of FS-measurement with fibrosis in NASH patients.
Barreiro P CROI 2006			x			Liver biopsy before treatment and FS only at the end of long-term follow-up. Regression of fibrosis in HCV-responders
Castera L AASLD 2005			x			Discordance between FibroScan and FibroTest was analysed
Takeda T AALSD 2005			x			Patients with SVR were compared with patient without SVR
Melin P AASLD 2005			x			Liver biopsy only in patients with FS-measurement $>$ 13 kPa
Christidis C Radiological Society of North America. 88th scientific assembly and annual meeting 2002			x			First technical study, no AUROC available

SVR, sustained virological response; FS, FibroScan; LSM, liver stiffness measurement; HBV, hepatitis B virus; HCV, hepatitis C virus; LBP, liver biopsy; PPG, porto-systemic pressure gradient; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; CPDD, Annual Scientific Meeting of the College on Problems of Drug Dependence; ICAA, International Council on Alcohol and Addictions; APASL, Asian Pacific Association for the Study of Liver Conference; EASL, European Association for the Study of the Liver; AASLD, merican Association for the Study of Liver Diseases; DDW, Digestive Disease Week; CROI, Conference on Retroviral and Opportunistic Infections.

Supplementary Table 4. DANA for Each Study

Author. publication. year	METAVIR and other scoring systems F ≥ 2				METAVIR and other scoring systems F ≥ 3			METAVIR and other scoring systems F =4		
	AUROC	AdAUROC[1]	DANA	DANA*	AUROC	DANA	DANA*	AUROC	DANA	DANA*
Sandrin L et al. Ultrasound Med Biol 2003	0.88	0.93	1.99	1.80	0.91	2.12	2.00	0.99	2.31	2.22
Ziol M et al. Hepatology 2005	0.79	0.87	1.78	1.77	0.91	2.15	2.15	0.97	2.31	2.30
Castera L et al. Gastroenterology 2005	0.83	0.89	1.95	1.95	0.90	2.02	2.02	0.95	2.07	2.07
Foucher J et al. Gut 2006	0.80	n/a	n/a	1.98	0.90	n/a	2.19	0.96	n/a	2.24
Coletta C et al. Hepatology[1]	1.00	1.00[2]	1.47	1.36	n/a	1.83	1.74	n/a	n/a	n/a
de Ledinghen V et al. J Acquir Immune Defic Syndr. 2006	0.72	n/a	n/a	1.89	0.91	n/a	2.33	0.97	n/a	2.42
Corpechot C et al. Hepatology 2006	0.92	n/a	n/a	1.88	0.95	n/a	2.06	0.96	n/a	2.23
Carrion J et al. Liver Transpl. 2006	0.90	0.95	2.06	1.76	0.93	2.51	2.22	0.98	2.81	2.55
Gomez-Dominguez E et al. Aliment Pharmacol Ther 2006	0.74	0.83	1.68	1.68	0.72	1.74	1.74	0.94	1.96	1.96
Ganne-Carrie N et al. Hepatology 2006	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.95	n/a	n/a
Erhardt A et al. DMW 2006	n/a	n/a	2.66	2.15	0.91	2.57	2.27	0.94	2.47	2.24
Nahon P et al. Am J Gastroenterol 2006	0.68	0.74	1.93	1.93	0.78	2.21	2.21	0.89	2.28	2.28
Takeda T et al. World J Gastroenterol 2006	0.81	0.86	2.07	1.76	0.88	2.60	2.38	0.88	2.78	2.58
Posthouwer D et al. J Throm Haemost 2007	0.87	0.94	1.81	1.69	0.89	2.20	2.12	n/a	2.53	2.46
Kettaneh A et al J Hepatol 2007	0.79	n/a	n/a	1.68	0.89	n/a	2.09	0.91	n/a	2.41
Marin J et al. EASL 2007	0.83	0.85	2.29	1.82	0.88	2.79	2.38	0.97	3.14	2.75
Blanc P et al. EASL 2007	0.80	n/a	n/a	n/a	0.91	n/a	n/a	0.95	n/a	n/a
Gaia S et al. EASL 2007	0.84	0.87	2.23	2.12	n/a	2.64	2.57	0.90	2.67	2.60
	0.84	0.85	2.39	1.74	0.74	2.46	2.00	0.98	2.69	2.33
Nahon P et al. EASL 2007	n/a	n/a	2.33	2.33	0.96	1.95	1.95	0.90	1.65	1.65
Nguyen-Khac E et al. EASL 2007	n/a	n/a	2.30	1.88	n/a	2.23	1.98	0.94	2.29	2.12
Miailhes P et al. CROI 2007	0.79	n/a	n/a	n/a	0.73	n/a	n/a	n/a	n/a	n/a
Vergara S et al. CROI 2007	0.88	n/a	n/a	n/a	n/a	n/a	n/a	0.95	n/a	n/a
Chang J et al. APASL 2007	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Servin-Abad L et al. AASLD 2006	n/a	n/a	2.08	1.88	0.84	1.82	1.76	0.87	1.86	1.83
Gomez-Dominguez E et al. AASLD 2006	n/a	n/a	n/a	n/a	0.89	n/a	n/a	0.95	n/a	n/a
Baldaia C et al. AASLD 2006	n/a	n/a	n/a	1.59	0.92	n/a	1.88	n/a	n/a	2.09
Serejo F et al. AASLD 2006	0.79	n/a	n/a	n/a	0.96	n/a	n/a	0.98	n/a	n/a
Beaugrand M et al. AASLD 2006	0.84	0.91	1.82	1.68	0.93	2.26	2.18	0.96	2.48	2.41
Rigamonti M et al. AASLD 2006	0.93	n/a	n/a	n/a	0.97	n/a	n/a	n/a	n/a	n/a
Poujol-Robert A et al. AASLD 2006	0.87	0.91	2.12	2.09	0.92	2.49	2.46	n/a	2.61	2.59
Fraquelli M et al. AASLD 2006	0.84	n/a	n/a	n/a	0.87	n/a	n/a	0.90	n/a	n/a
Corradi F et al. EASL 2006	0.94	1.00[2]	1.42	1.42	n/a	2.0	2.0	n/a	2.6	2.6
Kim K et al. EASL 2006	0.77	0.85	1.71	1.71	0.93	1.61	1.61	0.81	1.84	1.83
Coco B et al. EASL 2006	0.85	n/a	n/a	n/a	n/a	n/a	n/a	0.87	n/a	n/a
de Ledinghen V et al. EASL 2006	0.86	n/a	n/a	1.98	n/a	n/a	2.39	n/a	n/a	2.50
Lahaire D et al. DDW 2006	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.96	n/a	n/a
Jeon S et al. DDW 2006	n/a	n/a	2.14	1.78	0.79	1.91	1.76	0.86	2.03	1.93
Castera L et al. DDW 2006	n/a	n/a	n/a	1.79	n/a	n/a	1.90	0.95	n/a	2.05
Rigamonti C et al. Liver Transpl 2006	0.84	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Supplementary Table 4. Continued

Author. publication. year	METAVIR and other scoring systems F ≥ 2				METAVIR and other scoring systems F ≥ 3			METAVIR and other scoring systems F =4		
	AUROC	AdAUROC[1]	DANA	DANA*	AUROC	DANA	DANA*	AUROC	DANA	DANA*
Khokhar A et al. AASLD 2005	n/a	n/a	n/a	n/a	0.92	n/a	n/a	n/a	n/a	n/a
Coco B et al. AASLD 2005	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.95	n/a	n/a
Castera L et al. AASLD 2005	0.82	n/a	n/a	1.98	0.90	n/a	2.01	0.93	n/a	2.04
Pares A et al. AASLD 2005	0.80	0.90	1.55	1.55	0.86	1.97	1.97	0.93	2.45	2.45
Ganne-Carrie N et al. AASLD 2005	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.93	n/a	n/a
de Ledinghen V et al. AASLD 2005	0.91	n/a	n/a	2.18	n/a	n/a	2.21	0.88	n/a	2.11
Barrault C et al. AASLD 2005	n/a	n/a	n/a	n/a	0.80	n/a	n/a	n/a	n/a	n/a
Marcellin P et al. AASLD 2005	0.81	0.88	1.87	1.73	0.92	2.16	2.08	0.90	2.39	2.32
Foucher J et al. EASL 2005	0.79	n/a	n/a	1.98	0.89	n/a	2.18	0.95	n/a	2.23
Chanteloup E et al. AASLD 2004	0.79	n/a	n/a	n/a	0.89	n/a	n/a	0.93	n/a	n/a
Palau R et al. AASLD 2003	0.89	n/a	n/a	n/a	n/a	n/a	n/a	0.98	n/a	n/a

AUROC, area under the receiver operating characteristic curve; n/a, not available; AdAUROC, DANA-adjusted AUROC as been proposed for the respective adjustment of AUROC in the context of FibroTest (Ref. 35). We found still a significant heterogeneity $P<.001$ of the DANA-adjusted AUROC; DANA, difference of mean of advanced and mean of non-advanced fibrosis stages; DANA*, difference as DANA but pooling together stage F0 and stage F1 when calculating mean of non-advanced fibrosis stages.

[1]This study was excluded from the analysis of AUROC because of the lack of a suitable standard error.

[2]Here, the theoretically obtained adjusted AUROC was above 1.0.

Supplementary Table 5. Quality Assessment of Included Studies Using QUADAS Questionnaire

	Q1 Spectrum composition	Q2 Selection criteria	Q3 Appropriate reference standard	Q4 Disease progression bias	Q5 Partial verification bias	Q6 Differential verification bias
Sandrin L. et al. Ultrasound Med Biol 2003	Yes	No	Yes	Yes	Yes	Yes
Ziol M et al. Hepatology 2005	Yes	Yes	Yes	Yes	Yes	Yes
Castera L et al. Gastroenterology 2005	Yes	Yes	Yes	Yes	Yes	Yes
Foucher J et al. Gut 2005	Yes	Yes	Yes	Yes	No	Yes
Coletta C et al. Hepatology 2005	Yes	Unclear	Yes	Yes	Yes	Yes
de Ledinghen V et al. J Acquir Immune Defic Syndr. 2006	Yes	Yes	Yes	Yes	Yes	Yes
Corpechot C et al. Hepatology 2006	Yes	Yes	Yes	Yes	Yes	Yes
Carrion J et al. Liver Transpl. 2006	Yes	Yes	Yes	Yes	Yes	Yes
Gomez-Dominguez E et al. Aliment Pharmacol Ther 2006	Yes	Yes	Yes	Yes	Yes	Yes
Ganne-Carrie n et al. Hepatology 2006	Yes	Unclear	Yes	Yes	Yes	Yes
Erhardt a et al. DMW 2006	Yes	Yes	Unclear	Yes	Yes	Yes
Nahon P et al. Am J Gastroenterol 2006	Yes	Yes	Yes	Yes	Yes	Yes
Takeda T et al. World J Gasroenterol 2006	Yea	No	Unclear	Yes	No	Yes
Posthouwer D et al. J Throm Haemost 2007	Yes	No	Yes	Yes	No	Yes
Kettaneh A et al. J Hepatol 2007	Yes	Yes	Yes	Yes	Yes	Yes
Marin J et al. EASL 2007	Yes	Unclear	Unclear	Yes	Yes	Yes
Blanc P et al. EASL 2007	Yes	Unclear	Unclear	Yes	Yes	Yes
Gaia s et al. EASL 2007	Yes	Unclear	Unclear	Yes	Yes	Yes
Nahon P et al. EASL 2007	Yes	Unclear	Yes	Yes	Yes	Yes
Nguyen-Khac E et al. EASL 2007	Yes	Unclear	Yes	Yes	Yes	Yes
Miailhes P et al. CROI 2007	Yes	Unclear	Yes	Yes	No	Yes
Vergara S et al. CROI 2007	Yes	Unclear	Unclear	Yes	No	Yes
Chang J et al. APASL 2007	Yes	Yes	Unclear	Yes	Yes	Yes
Servin-Abad L et al. AASLD 2006	Yes	Unclear	Unclear	Yes	Yes	Yes
Gomez-Dominguez E et al. AASLD 2006	Yes	Unclear	Unclear	Yes	Yes	Yes
Baldaia C et al. AASLD 2006	Yes	Unclear	Yes	Yes	Yes	Yes
Serejo F et al. AASLD 2006	Yes	No	Yes	Yes	No	Yes
Beaugrand M et al. AASLD 2006	Yes	Yes	Yes	Yes	Yes	Yes
Rigamonti M et al. AASLD 2006	Yes	Unclear	Yes	Yes	Yes	Yes
Poujol-Robert A et al. AASLD 2006	Yes	Unclear	Unclear	Yes	Yes	Yes
Fraquelli M et al. AASLD 2006	Yes	Unclear	Unclear	Yes	Yes	Yes
Corradi F et al. EASL 2006	Yes	No	Unclear	Yes	No	Yes
Kim K et al. EASL 2006	Yes	Yes	Yes	Yes	Yes	Yes
Coco B et al. EASL 2006	Yes	Yes	Unclear	Yes	No	Yes
de Ledinghen V et al. EASL 2006	Yes	Yes	Unclear	Yes	Yes	Yes
Laharie D et al. DDW 2006	Yes	No	Unclear	Yes	No	Yes
Jeon S et al. DDW 2006	Yes	Unclear	Unclear	Yes	No	Yes
Castera L et al. DDW 2006	Yes	Yes	Yes	Yes	No	Yes
Rigamonti C et al. Liver Transplantation 2006	Yes	No	Unclear	Yes	Yes	Yes
Khokhar A et al. AASLD 2005	Yes	Yes	Unclear	Yes	Yes	Yes
Coco B et al. AASLD 2005	Yes	Yes	Yes	Yes	No	Yes
Castera L et al. AASLD 2005	Yes	Unclear	Yes	Yes	Yes	Yes
Pares A et al. AASLD 2005	Yes	Unclear	Unclear	Yes	Yes	Yes
Ganne-Carrie N et al. AASLD 2005	Yes	Yes	Yes	Yes	Yes	Yes
De Ledinghen V et al. AASLD 2005	Yes	Yes	Yes	Yes	No	Yes
Barrault C et al. AASLD 2005	Yes	Unclear	Yes	Yes	Yes	Yes
Marcellin P et al. AASLD 2005	Yes	Unclear	Yes	Yes	Yes	Yes
Foucher et al. EASL 2005	Yes	Yes	Unclear	Yes	Yes	Yes
Chanteloup et al. AASLD 2004	Yes	No	Unclear	Yes	Unclear	Yes
Palau et al. EASL 2003	Yes	Unclear	Yes	Yes	Yes	Yes

EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; DDW, Digestive Disease Week; APASL, Asian Pacific Association for the Study of the Liver; CROI, Conference on Retroviral and Opportunistic Infections.

Supplementary Table 5. Continued

Q7 Incorporation bias	Q8 Test execution details	Q9 Reference execution details	Q10 Test review bias	Q11 Diagnostic review bias	Q12 Clinical review bias	Q13 Uninterpretables results	Q14 Withdrawals
Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
Yes	Yes	No	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Unclear	Yes	Unclear	Yes	No	Yes
Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	No	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Yes	Unclear	Yes	Unclear	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes
Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes