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Accuracy of transient elastography in the assessment of chronic hepatitis C-related liver cirrhosis

Abstract

Purpose: Staging liver cirrhosis is essential for the management of chronic hepatitis C (CHC). The current meta-analysis evaluated the accuracy of transient elastography for detecting liver cirrhosis in patients with CHC.

Methods: Either prospective or retrospective studies, including cohort and cross sectional studies, in patients diagnosed with chronic hepatitis C, as assessed by transient elastography, were searched from Medline, Cochrane, EMBASE, and Google Scholar databases until March 3, 2015, using the terms “transient elastography, chronic hepatitis C and liver cirrhosis”. The primary outcome analyzed was the diagnostic performance, which included sensitivity, specificity, diagnostic odds ratio and area under the receiver-operating characteristic (ROC) curve.

Results: Data from 24 articles included in the meta-analysis demonstrated high sensitivity (84%) and specificity (90%) of transient elastography (TE) for assessing liver cirrhosis patients with HCV. Subgroup analysis of patients by underlying diseases revealed a sensitivity and specificity of 91% and 92% (HCV alone), 100% and 75% (HCV-liver transplant), 83.6% and 89.7% (HIV/HCV co-infection) and 97.1% and 90.7% (recurrent CHC after liver transplantation). The pooled diagnostic odds ratio was 61.57 (95% CI, 39.5 - 96.00) and the area under the summary ROC curves was 0.952 ± 0.008 , suggesting high diagnostic accuracy of TE.

Conclusion: Transient elastography can accurately predict liver cirrhosis in patients with hepatitis C, with a sensitivity and specificity of 84% and 90%, respectively. The present results further validate the utility of TE in staging liver cirrhosis in chronic HCV infections.

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Though acute infection with hepatitis C virus (HCV) is sometimes asymptomatic, chronic infection leads to liver cirrhosis and subsequent liver failure. HCV infection is reported to be one of the main factors underlying the increased incidence of hepatocellular carcinoma (HCC) [1]. Moreover, the risk of HCC is highly correlated with the degree of fibrosis. Severe liver fibrosis (Ishak stage ≥ 4) secondary to hepatitis C is associated with a poor prognosis [2], making it crucial to monitor the progression of liver fibrosis in HCV infections.

The treatment guidelines for chronic HCV infection are continuously evolving, and assessing liver injury is key to the decision making process. Liver biopsy is regarded as the gold standard for the evaluation of hepatic fibrosis [3]; however, this procedure is invasive, with the potential for serious complications, including hemorrhage, and is not completely reliable due to the variability in sampling and inter-observer assessments [3,4]. During the past decade, many noninvasive methods have been developed to reduce the need for liver biopsy in staging fibrosis. Transient elastography (TE) is a relatively new, rapid and non-invasive technique to assess liver cirrhosis [5].

TE using the FibroScan has become one of the most widely used noninvasive methods for evaluating patients with chronic hepatitis [6-10]. FibroScan utilizes one-dimensional (1-D) TE, a technique that uses both ultrasound (US) (5 MHz) and low-frequency (50 Hz) elastic waves, whose propagation velocity is directly related to elasticity. TE has been shown to be reproducible (standardized coefficient of variation: 3%), operator-independent and well-correlated (partial correlation coefficient = 0.71, $p < 0.0001$) to fibrosis grade (METAVIR) [5]. It has been proposed as a promising alternative for the detection of cirrhosis in patients with chronic liver disease [11,12]. Furthermore, it has been demonstrated that the fibrosis stage predicted by elastography is similar to that predicted by histological examination of the biopsy specimen [13].

A recent meta-analysis showed excellent diagnostic accuracy of TE in the prediction of cirrhosis; independent of the underlying liver disease [14]. Though the use of TE in patients with significant liver fibrosis in HCV transplant patients has been found to be satisfactory, it cannot replace liver biopsy [15]. In a cohort of patients with chronic hepatitis C (CHC), acoustic radiation force impulse (ARFI) was found to be more accurate than TE for staging of both significant and severe cases of liver fibrosis [16]. These data should be taken into consideration while choosing the diagnostic approach. Recent studies have revealed that higher body mass index and

metabolic syndrome might increase the liver stiffness values [17], thus affecting the accuracy of TE [15,18] and Sandrin *et al.* have demonstrated a direct correlation between liver stiffness measurements and fibrosis in HCV patients [5].

The accuracy of TE in predicting HCV-induced liver cirrhosis can be modified by many host- and disease-related factors and by the severity of fibrosis [19]. In addition, considerable heterogeneity exists among the studies regarding the clinical diagnostic cut off values for TE [20]. The aim of the present meta-analysis was to evaluate the diagnostic accuracy of TE on the hepatitis c-related liver cirrhosis (F4 stage).

Methods

Search strategy

An updated literature search of the Medline, Cochrane, EMBASE and Google Scholar databases until March 3, 2015 was performed using the terms, “transient elastography, chronic hepatitis C and liver cirrhosis”. The reference lists of relevant studies were also hand-searched. The literature search was performed by two independent reviewers, and where there was uncertainty regarding eligibility, a third reviewer was consulted.

Selection criteria

Both prospective and retrospective studies were included, including cohort and cross sectional studies. The study population was composed of patients diagnosed with CHC, as assessed by TE. Studies including recipients with other underlying liver diseases were also included if the data for HCV-infected patients could be extracted; such as, HIV/HCV co-infection and recurrent hepatitis C after liver transplantation. Only studies with quantitative outcomes were included in the current meta-analysis. Reviews, letters, comments, abstract only articles, editorials, case reports, proceedings and personal communications were excluded from the final analysis. In addition, studies where the primary objective was different from that of the present study, like evaluation of the success rate of Fibroscan or the value of liver stiffness measurement in fibrosis, were also excluded.

Data Extraction

The following data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, reference standard for the

diagnosis of liver cirrhosis, cut-off point of elastography, sensitivity and specificity.

Outcome measures

The primary outcome measure was the diagnostic performance, which included sensitivity, specificity, diagnostic odds ratios with 95% CI, and area under the receiver-operating characteristic curve.

Statistical Analysis

Pooled measures of diagnostic performance, such as sensitivity, specificity, diagnostic odds ratio (DOR) with their corresponding 95% confidence intervals (95% CI), and area under the receiver-operating characteristic (ROC) curve (AUC) were calculated. The DOR combine sensitivity and specificity into one measure of diagnostic performance. In the context of this study, the higher the DOR, the better the diagnostic accuracy of TE for assessing liver cirrhosis in patients with hepatitis C. A typical pattern of “shoulder arm” plot in a ROC space and a strong positive correlation would suggest a threshold effect [21]. A χ^2 -based test of homogeneity was performed, and the Cochran’s Q inconsistency index (I^2) statistics were determined. If the I^2 statistic ($> 50\%$) indicated heterogeneity among studies, a random-effects (DerSimonian-Laird approach) model was used. Otherwise, fixed-effects (Mantel-Haenszel approach) model was used. Planned subgroup analyses were performed according to patients’ disease. All statistical assessments were two-sided and a P value < 0.05 was considered statistically significant. All analyses were performed using Meta-Disc version 1.4 [22]. Publication bias was assessed by constructing funnel plots for DOR using the Egger’s test: the absence of publication bias was indicated by data points forming a symmetric funnel-shaped distribution and a one-tailed significance level of $P > 0.05$. If publication bias was found to exist, adjusted effect sizes were calculated after consideration of publication bias using Duval and Tweedie’s “trim and fill” procedure [23]. Analysis of publication bias was performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Literature search

Of the 360 articles identified through the literature search, 248 non-relevant studies were excluded, and the remaining 112 articles were assessed for full text reviewing. After full text

reviewing, 86 articles were excluded for various reasons, including the absence of quantitative outcome, the details of which are represented in Figure 1. The present meta-analysis comprised of 24 studies, which were included for the following qualitative and quantitative analysis.

Study characteristics

The characteristics of the studies included in the meta-analysis are summarized in Table 1. Of the included 24 studies, 19 of them were prospective studies, two of them were cross-sectional and three were cohort studies. The number of patients in the studies ranged from 51 to 386 (total = 4255; 3576 patients with CHC/HCV, 364 HIV/HCV co-infection, and 315 patients with recurrent hepatitis C after liver transplantation), the majority of which were males. The average age of patients ranged from 42-68 yrs. Most studies used the METAVIR criteria for staging liver cirrhosis (79%) however, Batts and Ludwig (8%) and Scheuer classification (4%) and Ishak scoring (8%) were also used. The cut-off point of TE varied considerably among the studies, ranging from 9.2 to 26.5 kPa.

Meta-analysis of outcomes

A Spearman rank correlation was performed as a further test for threshold effect. The Spearman correlation coefficient was 0.398 ($P = 0.110$), indicating that factors other than threshold caused the variations in accuracy estimates among the individual studies. There was significant heterogeneity in sensitivity between the studies ($Q = 61.84$, $I^2 = 62.8\%$, $P < 0.001$); therefore a random-effects model was used for the meta-analysis. The pooled sensitivity of TE for assessing liver cirrhosis in patients with hepatitis C was 84% (95% CI: 81% - 86%) (Figure 2A). Homogeneity tests of specificity showed $Q = 92.06$ and $I^2 = 75.0\%$ ($P < 0.001$). Since these results showed significant heterogeneity existed between studies, the random-effects model was used for the pooled specificity. Figure 2B shows the pooled specificity of TE for assessing liver cirrhosis in patients with hepatitis C was 91% (95% CI: 90% - 92%). For all studies, the pooled DOR was 60.11 (95% CI: 38.27 - 94.41), heterogeneity $Q = 64.17$ ($P < 0.001$) and $I^2 = 64.2\%$. Significant heterogeneity existed between studies, as assessed by the Forest plot (Figure 3A). The areas under the summary ROC curves were 0.954 (with standard error of 0.008, Figure 3B). According to the DOR value and the summary ROC curves, TE can accurately assess liver cirrhosis in patients with hepatitis C.

TABLE 1. Summary of basic characteristics of selected studies for meta-analysis

First author (year) [Ref]	Study design	No. of analyzed patients	Underlying liver disease	Fibrosis stage [†] (F0/F1/F2/F3/F4)	Age (years)	Male (%)	Criteria of liver cirrhosis	Cut-off point of TE (kPa)	No. of patients with liver cirrhosis
Ferraioli (2013) [20]	Cross-sectional	195	HCV	50% (F0F1)/24%/10%/16%	45	71%	METAVIR	9.3	32
Ferraioli (2012) [10]	Prospective	130	HCV	6%/48%/18%/10%/18%	46*	70%	METAVIR	9.3	24
Cho (2011) [6]	Prospective	86	HCV	35% (F0F1)/29%/29%/7%	52	47%	Batts and Ludwig	14.7	6
Gaia (2011) [19]	Prospective	77	HCV	4%/45%/29%/5%/17%	46*	55%	METAVIR	11.5	13
Kim (2011) [7]	Prospective	91	HCV	3%/42%/32%/13%/10%	48	48%	Batts and Ludwig	11.0	9
Liu (2011) [29]	Prospective	284	Hemodialysis HCV	29%/36%/21%/9%/5%	47	59%	METAVIR	9.2	14
Rizzo (2011) [16]	Prospective	139	HCV	9%/28%/24%/17%/22%	55	60%	METAVIR	11.0	30
Sporea (2011) [18]	Prospective	266	HCV	2%/12%/49%/25%/12%	50	32%	METAVIR	13.4	31
Cross (2010) [37]	Prospective	187	HCV	3%/49%/15%/12%/21%	49*	59%	Ishak	10.05	39
Sanchez-Conde (2010) [31]	Prospective	100	HIV/HCV co-infection	29%/28%/28%/7%/8%	42*	71%	METAVIR	14	8
Sporea (2010) [40]	Prospective	317	HCV	2%/11%/46%/29%/12%	50	33%	METAVIR	13.3	39
Castera (2009) [41]	Prospective	294	HCV	25% (F0F1)/33%/18%/24%	52	57%	METAVIR	12.5	66
Kirk (2009) [13]	Cohort	192	HCV or HCV-HIV co-infection	24%/39%/8%/4%/25%	49*	35%	METAVIR	12.3	48
Nitta (2009) [42]	Prospective	165	HCV	40% (F0F1)/25%/20%/15%	57*	56%	METAVIR	11.6	24
Arena (2008) [43]	Cross-sectional	150	HCV	23%/21%/19%/18%/19%	51	60%	METAVIR	14.8	29
Harada (2008) [31]	Prospective	56	Recurrent HCV after living donor liver transplantation	39%/23%/16%/13%/9%	63	54%	Scheuer classification	26.5	5
Lupsor (2008) [44]	Prospective	324	HCV	4%/31%/32%/11%/21%	48	35%	METAVIR	11.8	69
Masuzaki (2008) [34]	Prospective	386	HCV	0/8%/15%/21%/57%	68	59%	METAVIR	15.9	219
Obara (2008) [8]	Prospective	51	HCV	18%/29%/24%/12%/20%	58*	55%	METAVIR	17.2	10
Rigamonti (2008) [33]	Prospective	90	Recurrent HCV post liver transplantation	33%(S0S1)/42%(S2S3)/8%(S4)/17%(S5S6) †	54	81%	Ishak	12	15
Carrion (2006) [25]	Cohort	169	Recurrent HCV post liver transplantation	23%/34%/24%/8%/9%	60*	66%	METAVIR	12.50	15
deLedinghen (2006) [32]	Prospective	72	HIV-HCV	39%(F0F1)/31%/7%/24%	42	72%	METAVIR	11.8	17
Castera (2005) [45]	Prospective	183	HCV	0/26%/29%/20%/25%	51	57%	METAVIR	12.5	46
Ziol (2005) [35]	Cross-sectional	251	HCV	0.4%/35%/35%/11%/20%	48	62%	METAVIR	14.60	49

HCV = hepatitis C virus, HIV = human immunodeficiency virus

* Data are displayed as median

† Fibrosis (staging 0–6) according to the Ishak score

TABLE 2. Subgroup analysis

	Sensitivity			Specificity			Diagnostic odds ratio		
	Effect size	Lower limit	Upper limit	Effect size	Lower limit	Upper limit	Effect size	Lower limit	Upper limit
A. CHC/HCV alone									
Ferraioli (2013)	92.0%	86.7%	95.7%	93.8%	79.2%	99.2%	173.1	37.1	806.9
Ferraioli (2012)	93.4%	86.9%	97.3%	95.8%	78.9%	99.9%	325.3	38.1	2775.4
Cho (2011)	88.8%	79.7%	94.7%	100.0%	54.1%	100.0%	97.8	5.1	1878.7
Gaia (2011)	93.8%	84.8%	98.3%	69.2%	38.6%	90.9%	33.8	7.1	159.5
Kim (2011)	93.9%	86.3%	98.0%	77.8%	40.0%	97.2%	53.9	8.8	330.4
Liu (2011)	95.9%	92.8%	97.9%	100.0%	76.8%	100.0%	654.4	36.7	11662.2
Rizzo (2011)	81.7%	73.1%	88.4%	70.0%	50.6%	85.3%	10.4	4.1	26.0
Sporea (2011)	93.2%	89.2%	96.1%	58.1%	39.1%	75.5%	19.0	7.9	45.5
Cross (2010)	87.8%	81.5%	92.6%	92.3%	79.1%	98.4%	86.7	24.2	310.7
Sporea (2010)	93.2%	89.5%	95.8%	76.9%	60.7%	88.9%	45.4	18.9	109.4
Castera (2009)	95.5%	91.9%	97.8%	83.3%	72.1%	91.4%	106.0	42.8	262.4
Nitta (2009)	78.0%	70.3%	84.5%	91.7%	73.0%	99.0%	39.0	8.7	175.2
Arena (2008)	91.7%	85.3%	96.0%	93.1%	77.2%	99.2%	149.9	31.0	724.2
Lupsor (2008)	90.6%	86.3%	93.9%	87.0%	76.7%	93.9%	64.2	28.3	145.3
Masuzaki (2008)	80.8%	74.0%	86.5%	79.0%	73.0%	84.2%	15.9	9.6	26.3
Obara (2008)	87.8%	73.8%	95.9%	80.0%	44.4%	97.5%	28.8	4.7	176.0
Castera (2005)	91.2%	85.2%	95.4%	87.0%	73.7%	95.1%	69.4	24.5	197.0
Ziol (2005)	96.0%	92.3%	98.3%	85.7%	72.8%	94.1%	145.5	50.0	423.3
Pooled effects	91.0%	89.9%	92.0%	82.9%	80.0%	85.5%	55.5	34.0	90.7
Pooled effects	100.00%	83.20%	100.00%	75.00%	66.40%	82.30%	129.0	7.3	2294.2
B. HIV/HCV coinfection									
Sanchez-Conde (2010)	100.00%	63.10%	100.00%	93.50%	86.30%	97.60%	226.2	11.7	4372.2
Kirk (2009)	75.00%	60.40%	86.40%	86.10%	79.40%	91.30%	18.6	8.3	41.7
deLedinghen (2006)	100.00%	80.50%	100.00%	92.70%	82.40%	98.00%	400.6	20.5	7820.5
Pooled effects	83.60%	73.00%	91.20%	89.70%	85.60%	92.90%	82.3	8.6	788.0
C. Recurrent hepatitis C after liver transplantation									
Harada (2008)	100.00%	47.80%	100.00%	98.00%	89.60%	100.00%	370.3	13.4	10237.5
Rigamonti (2008)	93.30%	68.10%	99.80%	93.30%	85.10%	97.80%	196.0	21.2	1809.0
Carrion (2006)	100.00%	78.20%	100.00%	87.00%	80.70%	91.90%	203.4	11.7	3531.1
Pooled effects	97.10%	85.10%	99.90%	90.70%	86.70%	93.80%	227.7	48.3	1073.1

FIGURE 1. Flow chart for study selection

A. Sensitivity

B. Specificity

FIGURE 2. Meta-analysis of (A) sensitivity and (B) specificity of transient elastography for detecting liver cirrhosis.

A. Diagnostic odds ratio

B. SROC

FIGURE 3. Meta-analysis of (A) diagnostic odds ratio and (D) summary receiver operating characteristic (ROC) curve of transient elastography for detecting liver cirrhosis.

Publication bias

The results from the Egger's test showed that there was a publication bias in the findings with regards to the DOR value ($t = 5.058$, one-tailed, $P < 0.001$, Figure 5; available on request). Simulation using the "trim and fill" method, to look for missing studies based on the random-effects model, resulted in a change in the imputed point estimate from 61.57 (95% CI: 39.5 -96.00) to 47.48 (95%CI: 31.07- 72.54, Figure 5; available on request).

Subgroup analyses

Subgroup analyses were performed according to patients' diseases. The pooled sensitivity and specificity of TE for assessing liver cirrhosis were 91% and 92%, respectively, for patients with CHC/HCV alone; 83.6% and 89.7% for patients with HIV/HCV co-infection and 97.1% and 90.7% for patients with recurrent hepatitis C after liver transplantation. Moreover, the pooled DORs were 55.5, 82.3 and 227.7 for patients with CHC/HCV alone, HIV/HCV co-infection and recurrent hepatitis C after liver transplantation, respectively (Table 2). In addition, the areas under the summary ROC curves are represented in Figure 6 (available on request).

Quality assessment

The studies included in this analysis were assessed with QUADAS-2 [24]. Figure 4 represents the assessed outcomes. Figure 4A showed that there were three studies with unclear patient selection and two studies with unclear index test. Figure 4B showed that, overall, the included studies had low risk of bias.

Discussion

This meta-analysis compared TE to liver biopsy and suggests that TE is an accurate, valuable tool in predicting the stages of liver fibrosis in patients with CHC. The pooled sensitivity and specificity of TE for assessing liver cirrhosis was 84% and 90%, respectively; validating the utility of TE in the diagnosis of liver cirrhosis.

Considering that CHC infection is the most common etiology of liver fibrosis, detecting the precise staging of the liver fibrosis is particularly relevant in the prognosis of liver diseases. Recurrence of hepatitis C after liver transplantation is the main cause of graft loss and re-transplantation [25]. Although systematic reviews on the accuracy of TE in patients with recurrent HCV after liver transplantation [26,27] and other underlying causes [28] are available, this analysis provides an updated review and discusses the diagnostic value of TE to HCV-related cirrhosis in a wider cohort of patients, including patients with liver transplantation and HIV co-infection.

FIGURE 4. Quality assessment

current analysis is in agreement with similar reviews, where TE has been found to perform better than the surrogate serum markers (direct and indirect) and showed good discrimination for significant fibrosis [27]. TE has been shown to be superior to APRI in assessing the severity of hepatic fibrosis [29] in CHC patients, including those with recurrent hepatitis C after liver transplantation [30]. Furthermore, previously published reports indicate that TE outperformed other noninvasive indexes in predicting liver fibrosis in HIV/HCV co-infected patients and may be useful for discriminating between mild and no fibrosis [31,32]. Likewise, reports have shown the reliability of TE in predicting

significant fibrosis when compared with the traditional liver biopsy [20,33-35]. Results from a recent systematic review indicated that TE had summary sensitivities and specificities greater than 80% when compared with liver biopsy [36]; results which are comparable with our own results (84 and 91%, respectively, Figure 1). Despite these clinical advantages, certain limitations to TE have also been reported, including the development of ascites and obesity [17].

Quality assessment of the included studies showed good reliability and a low risk of bias (Figure 4); however, significant heterogeneity seen among the studies was a major limitation of this meta-analysis. Furthermore, the criteria for diagnostic reference and the modalities varied considerably among the studies, seriously limiting the interpretation of the overall efficacy of TE. Another limitation of the current analysis is that the cut-off points for TE varied across studies, as there are no validated optimal stiffness cut-offs for individual fibrosis stages [14,20]. As seen in our analysis (9.2 -26.5 kPa; Table 1), a wide range exists in the cut-off and they overlap within and between stages [14]; hence, it is important that stiffness cut-offs for various stages and underlying etiologies be validated before the adoption of TE in clinical practice.

The degree of liver stiffness is reported to be associated with increased risk of decompensated cirrhosis, liver cancer and death in patients with chronic liver diseases, thus making it useful in risk stratification [37]; however, TE measures liver stiffness and not fibrosis, and hence factors that predict liver fibrosis, like aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, may not be an accurate measure of TE and may lead to skewed results [6,38]. Cho *et al.* [6] suggested avoiding TE in patients with elevated ALT levels to guarantee the predictive accuracy of TE. In addition to the above limitations, the diagnostic accuracy of meta-analyses conducted on aggregate data may include duplicates that are likely to bias the pooled estimates. Duplicate observations published through different studies may have been missed, especially when the means of identifying them vary [39]. Meta-analyses of individual patient data are ideal in overcoming these limitations and should be used to validate the diagnostic accuracy of TE, rather than aggregate data meta-analysis. Future studies are warranted to further validate the accuracy and reliability of TE.

In summary, the current analysis indicates that TE is a valuable tool for the diagnosis of liver cirrhosis in patients with hepatitis C. Its validity in predicting hepatic cirrhosis should be explored further in larger cohorts and using individual patient data-meta-analysis.

References

- Kim MN, Kim BK, Han KH. Hepatocellular carcinoma in patients with chronic hepatitis C virus infection in the Asia-Pacific region. *J Gastroenterol*. 2013 Jun;48(6):681-8.
- Lawson A, Hagan S, Rye K, Taguri N, Ratib S, Zaitoun AM, Neal KR, Ryder SD, Irving WL; Trent HCV Study Group. The natural history of hepatitis C with severe hepatic fibrosis. *J Hepatol*. 2007 Jul;47(1):37-45.
- Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology*. 2003 Dec;38:1449-57.
- Rousselet MC, Michalak S, Dupré F, Croué A, Bedossa P, Saint-André JP, Calès P; Hepatitis Network 49. Sources of variability in histological scoring of chronic viral hepatitis. *Hepatology*. 2005 Feb;41:257-64.
- Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poulet B, Kazemi F, Beaugrand M, Palau R. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol*. 2003 Dec;29:1705-13.
- Cho HJ, Seo YS, Lee KG, Hyun JJ, An H, Keum B, Kim JH, Yim HJ, Jeon YT, Lee HS, Chun HJ, Um SH, Kim CD, Ryu HS. Serum aminotransferase levels instead of etiology affects the accuracy of transient elastography in chronic viral hepatitis patients. *J Gastroenterol Hepatol*. 2011 Mar;26:492-500.
- Kim SU, Jang HW, Cheong JY, Kim JK, Lee MH, Kim DJ, Yang JM, Cho SW, Lee KS, Choi EH, Park YN, Han KH. The usefulness of liver stiffness measurement using FibroScan in chronic hepatitis C in South Korea: a multicenter, prospective study. *J Gastroenterol Hepatol*. 2011 Jan;26:171-8.
- Obara N, Ueno Y, Fukushima K, Nakagome Y, Kakazu E, Kimura O, Wakui Y, Kido O, Ninomiya M, Kogure T, Inoue J, Kondo Y, Shiina M, Iwasaki T, Yamamoto T, Shimosegawa T. Transient elastography for measurement of liver stiffness measurement can detect early significant hepatic fibrosis in Japanese patients with viral and nonviral liver diseases. *J Gastroenterol*. 2008;43:720-8.
- Beckebaum S, Iacob S, Klein CG, Dechêne A, Varghese J, Baba HA, Sotiropoulos GC, Paul A, Gerken G, Cicinnati VR. Assessment of allograft fibrosis by transient elastography and noninvasive biomarker scoring systems in liver transplant patients. *Transplantation*. 2010 Apr 27;89:983-93.
- Ferraioli G, Tinelli C, Malfitano A, Dal Bello B, Filice G, Filice C; Liver Fibrosis Study Group, Above E, Barbarini G, Brunetti E, Calderon W, Di Gregorio M, Lissandrin R, Ludovisi S, Maiocchi L, Michelone G, Mondelli M, Patruno SF, Perretti A, Poma G, Sacchi P, Zaramella M, Zicchetti M. Performance of real-time strain elastography, transient elastography, and aspartate-to-platelet ratio index in the assessment of fibrosis in chronic hepatitis C. *AJR Am J Roentgenol*. 2012 Jul;199:19-25.
- Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, Bertet J, Couzigou P, de Ledinghen V. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut*. 2006 Mar;55:403-8.
- Gómez-Domínguez E, Mendoza J, Rubio S, Moreno-Monteaudo JA, García-Buey L, Moreno-Otero R. Transient elastography: a valid alternative to biopsy in patients with chronic liver disease. *Aliment Pharmacol Ther*. 2006 Aug 1;24:513-8.
- Kirk GD, Astemborski J, Mehta SH, Spoler C, Fisher C, Allen D, Higgins Y, Moore RD, Afdhal N, Torbenson M, Sulkowski M, Thomas DL. Assessment of liver fibrosis by transient elastography in persons with hepatitis C virus infection or HIV-hepatitis C virus coinfection. *Clin Infect Dis*. 2009 Apr 1;48:963-72.
- Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol*. 2011 Apr;54:650-9.
- Kamphues C, Lotz K, Röcken C, Berg T, Eurich D, Pratschke J, Neuhaus P, Neumann UP. Chances and limitations of non-invasive tests in the assessment of liver fibrosis in liver transplant patients. *Clin Transplant*. 2010 Sep-Oct;24:652-9.
- Rizzo L, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S, Fatuzzo F, Montineri A, Mazzola A, L'abbate L, Nunnari G, Bronte F, Di Marco V, Craxi A, Cammà C. Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. *Am J Gastroenterol*. 2011 Dec;106:2112-20.
- Roulot D, Czernichow S, Le Clésiau H, Costes JL, Vergnaud AC, Beaugrand M. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. *J Hepatol*. 2008 Apr;48:606-13.
- Sporea I, Sirli RL, Deleanu A, Iulia R, Tudora A, Dan I, Popescu A. What did we learn from the first 3,459 cases of liver stiffness measurement by transient elastography (FibroScan(R))?. *Ultraschall Med*. 2011 Feb;32:40-5.
- Gaia S, Carenzi S, Barilli AL, Bugianesi E, Smedile A, Brunello F, Marzano A, Rizzetto M. Reliability of transient elastography for the detection of fibrosis in non-alcoholic fatty liver disease and chronic viral hepatitis. *J Hepatol*. 2011 Jan;54:64-71.
- Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Lissandrin R, Filice G, Filice C, Above E, Barbarini G, Brunetti E, Calderon W, Di Gregorio M, Gulminetti R, Lanzarini P, Ludovisi S, Maiocchi L, Malfitano A, Michelone G, Minoli L, Mondelli M, Novati S, Patruno SF, Perretti A, Poma G, Sacchi P, Zanaboni D, Zaramella M. Performance of liver stiffness measurements by transient elastography in chronic hepatitis. *World J Gastroenterol*. 2013 Jan 7;19:49-56.
- Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med*. 1993 Jul 30;12:1293-316.

22. Zamora J, Abaira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol*. 2006 Jul 12;6:31.
23. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000 Jun;56:455-63.
24. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011 Oct 18;155:529-36.
25. Carrión JA, Navasa M, Bosch J, Bruguera M, Gilibert R, Forns X. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. *Liver Transpl*. 2006 Dec;12:1791-8.
26. Adebajo CO, Talwalkar JA, Poterucha JJ, Kim WR, Charlton MR. Ultrasound-based transient elastography for the detection of hepatic fibrosis in patients with recurrent hepatitis C virus after liver transplantation: a systematic review and meta-analysis. *Liver Transpl*. 2012 Mar;18:323-31.
27. Cholongitas E, Tsochatzis E, Goulis J, Burroughs AK. Noninvasive tests for evaluation of fibrosis in HCV recurrence after liver transplantation: a systematic review. *Transpl Int*. 2010 Sep;23:861-70.
28. Chon YE, Choi EH, Song KJ, Park JY, Kim do Y, Han KH, Chon CY, Ahn SH, Kim SU. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta-analysis. *PLoS One*. 2012;7:e44930.
29. Liu CH, Liang CC, Huang KW, Liu CJ, Chen SI, Lin JW, Hung PH, Tsai HB, Lai MY, Chen PJ, Chen JH, Chen DS, Kao JH. Transient elastography to assess hepatic fibrosis in hemodialysis chronic hepatitis C patients. *Clin J Am Soc Nephrol*. 2011 May;6:1057-65.
30. Harada N, Soejima Y, Takeromi A, Yoshizumi T, Ikegami T, Yamashita Y, Itoh S, Kuroda Y, Maehara Y. Assessment of graft fibrosis by transient elastography in patients with recurrent hepatitis C after living donor liver transplantation. *Transplantation*. 2008 Jan 15;85:69-74.
31. Sánchez-Conde M, Montes-Ramírez ML, Miralles P, Alvarez JM, Bellón JM, Ramírez M, Arribas JR, Gutiérrez I, López JC, Cosín J, Alvarez E, González J, Berenguer J. Comparison of transient elastography and liver biopsy for the assessment of liver fibrosis in HIV/hepatitis C virus-coinfected patients and correlation with noninvasive serum markers. *J Viral Hepat*. 2010 Apr;17:280-6.
32. de Lédinghen V, Douvin C, Kettaneh A, Ziol M, Roulot D, Marcellin P, Dhumeaux D, Beaugrand M. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. *J Acquir Immune Defic Syndr*. 2006 Feb 1;41:175-9.
33. Rigamonti C, Donato MF, Fraquelli M, Agnelli F, Ronchi G, Casazza G, Rossi G, Colombo M. Transient elastography predicts fibrosis progression in patients with recurrent hepatitis C after liver transplantation. *Gut*. 2008 Jun;57:821-7.
34. Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T, Goto T, Yoshida H, Kanai F, Sugiooka Y, Ikeda H, Shiina S, Kawabe T, Omata M. Comparison of liver biopsy and transient elastography based on clinical relevance. *Can J Gastroenterol*. 2008 Sep;22:753-7.
35. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, de Lédinghen V, Marcellin P, Dhumeaux D, Trinchet JC, Beaugrand M. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology*. 2005 Jan;41:48-54.
36. Steadman R, Myers RP, Leggett L, Lorenzetti D, Noseworthy T, Rose S, Sutherland L, Clement F. A health technology assessment of transient elastography in adult liver disease. *Can J Gastroenterol*. 2013 Mar;27:149-58.
37. Singh S, Fujii LL, Murad MH, Wang Z, Asrani SK, Ehman RL, Kamath PS, Talwalkar JA. Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2013 Dec;11(12):1573-84.
38. Cross TJ, Calvaruso V, Maimone S, Carey I, Chang TP, Pleguezuelo M, Manousou P, Quaglia A, Grillo F, Dhillon AP, Dusheiko GM, Burroughs AK, Harrison PM. Prospective comparison of Fibroscan, King's score and liver biopsy for the assessment of cirrhosis in chronic hepatitis C infection. *J Viral Hepat*. 2010 Aug;17:546-54.
39. Pambrun E, Bouteloup V, Thiébaud R, Asselineau J, de Lédinghen V, Perez P; Steering Committee of the Transient Elastography Individual Patient Data meta-analysis Study (TE IPD Study). On the validity of meta-analyses: exhaustivity must be warranted, exclusion of duplicate patients too. *J Clin Epidemiol*. 2010 Mar;63:342-3.
40. Sporea I, Sirli R, Deleanu A, Tudora A, Popescu A, Curescu M, Bota S. Liver stiffness measurements in patients with HBV vs HCV chronic hepatitis: a comparative study. *World J Gastroenterol*. 2010 Oct 14;16:4832-7.
41. Castera L, Le BB, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, Couzigou P, de Lédinghen V. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. *J Hepatol*. 2009 Jan;50:59-68.
42. Nitta Y, Kawabe N, Hashimoto S, Harata M, Komura N, Kobayashi K, Arima Y, Shimazaki H, Nakano T, Murao M, Ichino N, Osakabe K, Aoki H, Hosoe Y, Sugiyama H, Nishikawa T, Yoshioka K. Liver stiffness measured by transient elastography correlates with fibrosis area in liver biopsy in patients with chronic hepatitis C. *Hepatol Res*. 2009 Jul;39:675-84.
43. Arena U, Vizzutti F, Abbrades JG, Corti G, Stasi C, Moscarella S, Milani S, Lorefice E, Petrarca A, Romanelli RG, Laffi G,

- Bosch J, Marra F, Pinzani M. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. *Gut*. 2008 Sep;57:1288–93.
44. Lupsor M, Badea R, Stefanescu H, Grigorescu M, Sparchez Z, Serban A, Branda H, Iancu S, Maniu A. Analysis of histopathological changes that influence liver stiffness in chronic hepatitis C. Results from a cohort of 324 patients. *J Gastrointest Liver Dis*. 2008 Jun;17:155–63.
45. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Ledinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*. 2005 Feb;128:343–50.