Transient Elastography in Clinical Detection of Liver Cirrhosis: A Systematic Review and Meta-analysis

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ABSTRACT

Background/Aims: Transient elastography is a noninvasive method for measuring liver fibrosis. This meta-analysis assesses the diagnostic performance of transient elastography of detecting liver cirrhosis in patients with liver disease. Patients and Methods: We searched MEDLINE, Cochrane, EMBASE databases until Jan 31, 2015, using the following search terms: elastography and liver cirrhosis. Included studies assessed patients with a diagnosis of liver cirrhosis, with an index test of transient elastography, and with the reference standard being a histopathological exam by liver biopsy. Sensitivity analysis and assessment of risk of bias and publication bias were performed. Results: Fifty-seven studies were included in the meta-analysis with a total of 10,504 patients. The pooled estimate for the sensitivity of transient elastography for detecting liver fibrosis was 81% and the specificity was 88%. The imputed diagnostic odds ratio (DOR) was 26.08 and the area under the receiver-operating characteristic (AUROC) curve was 0.931. Conclusion: Our findings indicate that transient elastography shows good sensitivity, specificity and a high accuracy for detecting liver cirrhosis. Transient elastography can be used as an additional method for the clinical diagnosis of liver fibrosis and cirrhosis.

Key Words: Cirrhosis, liver fibrosis, sensitivity, specificity, transient change to elastography

Liver fibrosis is the result of a number of chronic liver diseases due to a variety of causes including viral infection, alcohol, and fat deposition. Without an appropriate intervention, liver fibrosis can result in deterioration of liver function and hemodynamics and lead to cirrhosis.\(^1\)

Liver fibrosis results from a number of molecular events resulting from liver damage. Chronic liver injury causes inflammation that activates myofibroblasts. The activated myofibroblasts act via a number of cellular pathways to produce collagens and extracellular matrix proteins, which accumulate in the liver.\(^2,3\) The accumulation of extracellular matrix proteins causes liver fibrosis, which disrupts hepatic function and architecture and ultimately results in liver failure.\(^2,3\) Prolonged liver injury leads to increased fibrosis and ultimately chronic liver fibrosis (cirrhosis). Increased fibrosis can increase the risk of hepatocellular carcinoma and hepatic decompensation, both of which are serious complications in patients with end-stage liver disease.\(^4,5\)

Treatment guidelines stress the great clinical importance of estimating the precise degree of liver fibrosis, as this impacts treatment strategies and prognosis in patients with liver disease.\(^6-8\)

Liver biopsy is considered the reference standard for assessing liver fibrosis. However, it is invasive and is limited by risk of complications, sampling error, minor mortality rates, and cost-effectiveness.\(^9-12\) Another limitation is that the biopsy gives a snapshot of the disease and does not give information on whether the disease is progressing, regressing, or static.\(^12\)

Even with adequate liver biopsy samples, 10%–50% of cases
of liver fibrosis are not accurately staged, and it is difficult to perform repeat biopsies due to pain and bleeding and risk of death.\textsuperscript{[10,11,13]}

A number of noninvasive markers have been developed for evaluating liver fibrosis including the use of serum biomarkers, steato-test, Fatty Liver Index, ultrasonography, FibroMeter, and transient elastography.\textsuperscript{[12,14]} Transient elastography is an ultrasound-based method that maps the elastic properties of soft tissue and shows considerable accuracy and reproducibility for detecting cirrhosis.\textsuperscript{[15,16]} It detects changes in elasticity of the liver due to liver fibrosis. Several meta-analyses have found that transient elastography is a reliable tool for detecting liver cirrhosis.\textsuperscript{[14,17‑20]} However, the most recent of these studies was published in 2011. Since then a number of other studies have been published that evaluated transient elastography in HBV. Here we perform a meta-analysis to update the assessment of the diagnostic performance of transient elastography for detecting acute liver fibrosis in patients with liver disease.

**PATIENTS AND METHODS**

**Search strategy and study selection**

This meta-analysis was performed in accordance with PRISMA guidelines. We searched MEDLINE, Cochrane, EMBASE databases until January 31, 2015, using the search terms elastography and liver cirrhosis.\textsuperscript{[21]} Included studies assessed patients with diagnosed liver cirrhosis, with an index test of transient elastography alone, and with the reference standard being a histopathological exam by liver biopsy. Excluded studies included in the index test real-time elastography, shear wave elastography, acoustic radiation force impulse elastography, supersonic shear imaging, and magnetic resonance elastography. Studies not published in English or Chinese were also excluded, as were letters, comments, editorials, case reports, proceedings, and personal communication. All potential studies were hand searched by two independent reviewers, and a third reviewer was consulted to resolve any uncertainties regarding study eligibility.

**Data extraction**

The following information were extracted from studies that met the inclusion criteria: The name of the first author, year of publication, study design, patient demographics, underlying liver disease, reference standard-based diagnosis of liver cirrhosis, cutoff level of index test, and number of true and false positives as well as, true and false negatives. Similar to study selection, two independent reviewers extracted the data and the third reviewer resolved discrepancies.

**Assessment of risk of bias**

We utilized the Cochrane Risk of Bias Tool to assess the quality of the included studies.\textsuperscript{[22]} The assessment of risk of bias was also performed by two independent reviewers and a third reviewer was consulted for any uncertainties.

**Statistical analysis**

Tables that were 2 × 2 were reconstructed from the original published data. Pooled measures for diagnostic performance, such as sensitivity, specificity, diagnostic odds ratios (DORs) with their corresponding 95% confidence intervals (95% CIs), and area under the receiver-operating characteristic (AUROC) curve were calculated. The DORs combine sensitivity and specificity into one measure for diagnostic performance. A DOR of 1 means that the test has no ability to discriminate between two outcomes. In the context of this study, the higher the DOR, the better the diagnostic accuracy of transient elastography for assessing liver cirrhosis. If more than one cutoff point was presented in the study, maximum value of the Youden’s index (sensitivity + specificity – 1) was used as a criterion for selecting the optimum cutoff point.\textsuperscript{[21]} A Chi-square-based test of homogeneity was performed, and the Cochran’s Q inconsistency index (I²) statistics were determined. If the I² statistic (>50%) indicated heterogeneity existed between studies, a random-effects (DerSimonian–Laird approach) model was calculated. Otherwise, fixed-effects (Mantel–Haenszel approach) models were used. All statistical assessments were two‑sided and a P value < 0.05 was considered to indicate statistical significance. All analyses were performed using Meta‑Disc version 1.4.\textsuperscript{[24]}

Publication bias was assessed by constructing funnel plots for DOR by Egger’s test. The absence of publication bias was indicated by the data points forming a symmetric funnel‑shaped distribution and one‑tailed significance level P < 0.05 (Egger’s test). If publication bias existed, adjusted effect sizes were calculated after considering publication bias using Duval and Tweedie’s “trim and fill” procedure.\textsuperscript{[25]} Publication bias was performed using Comprehensive Meta‑analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

**RESULTS**

**Search results and characteristics of included studies**

Of the initial 147 studies identified, 35 were excluded for not being relevant [Figure 1]. An additional 35 were eliminated for several reasons: assessment of patients without cirrhosis, not all patients received a liver biopsy, the index test was not transient elastography, or the study did not report outcomes of interest.

Fifty-seven studies were included in the meta-analysis with a total of 10,504 patients [Table 1].\textsuperscript{[15,26‑81]} Forty-four of the studies were prospective in design. The remaining were...
The pooled DOR was 39.07 (95% CI: 29.81–51.20), heterogeneity $Q = 135.44$ ($P < 0.001$), and $I^2 = 58.7%$. However, significant heterogeneity existed across the studies, as assessed by inspection of the Forest plot [Figure 2c]. The AUROC curve was 0.931 (with standard error of 0.007 [Figure 2d]). According to the DOR value and the summary AUROC curves, transient elastography has a high accuracy for detecting chronic liver disease.

### Data quality and publication bias

Quality assessment indicated that there was a low risk of bias for the entire set of data [Figure 3a and b]. Only one study had a high risk of bias for data selection. There was a low risk of bias for index test, reference standard, flow and timing.

The results via Egger’s test showed that there was a publication bias for the findings with regard to DOR value ($t = 4.841$, one-tailed, $P < 0.001$ [Figure 4]). Simulation by the “trim and fill” method to look for missing studies based on the random-effects model, the imputed point estimate was changed to 26.08 (95% CI: 19.75–34.44 [Figure 4]).

### DISCUSSION

The meta-analysis evaluated the diagnostic performance of transient elastography in detecting liver cirrhosis. Fifty-seven studies were included with a total of 10,504 patients. Pooled estimates for the sensitivity of transient elastography for detecting liver fibrosis was 81% and the specificity was 88%. The imputed DOR was 26.08 and the AUROC was 0.931. Our findings indicate that transient elastography has good diagnostic performance for detecting liver cirrhosis, and supports its use as an additional method for assessing chronic liver disease. We did not evaluate its diagnostic performance for lower-stage liver fibrosis.

Our findings are similar to several prior meta-analyses that evaluated the diagnostic accuracy of transient elastography for hepatic fibrosis in chronic liver disease. The meta-analysis of Talwalkar et al. included nine studies, they found that for patients with stage IV fibrosis (cirrhosis), the pooled estimate for sensitivity was 87% and for specificity was 91%. For patients with stages II–IV fibrosis, the pooled estimate for sensitivity was 70% and for specificity was 84%. These findings suggest that the degree of liver fibrosis impacts the diagnostic accuracy and that transient elastography has good performance for diagnosis of cirrhosis and lesser performance and ability for lower-stage fibrosis.

The meta-analyses of Tschatzis et al., Stebbing et al., and Friedrich-Rust et al. had similar findings to that of Talwalkar et al. Tschatzis et al. included 40 studies and also found that the sensitivity and specificity were dependent on...
### Table 1: Summary of basic characteristics of selected studies for meta-analysis

| First author (year) | Study design | Number of analyzed patients | Underlying liver disease | Age (years) | Male (%) | Criteria of liver cirrhosis | Cutoff point of TE (kPa) | Number of patients with liver cirrhosis |
|---------------------|--------------|-----------------------------|--------------------------|-------------|----------|-----------------------------|--------------------------|---------------------------------------|
| Liu (2014)          | Prospective  | 92                          | CHB                      | 39.8        | 77       | Metavir                     | 9.47                     | 29                                    |
| Papatheodoridis (2014) | Prospective  | 113                         | HBeAg-negative CHB       | NA          | NA       | Ishavir                     | 11.2                     | 16                                    |
| Trembling (2014)    | Prospective  | 182                         | CHB                      | 46*         | 71       | Metavir                     | 10.3                     | 36                                    |
| Wong (2014)         | Cohort       | 85                          | CHB                      | 44          | 61       | Metavir                     | 10                       | 22                                    |
| Ferraioli (2013)    | Cross-sectional | 246                     | HBV and HCV              | 45          | 70       | Metavir                     | 9.6                      | 39                                    |
| Goyal (2013)        | Prospective  | 357                         | CHB                      | 30          | 85       | Metavir                     | 8                        | 21                                    |
| Kumar (2013)        | Cross-sectional | 120                     | NAFLD                    | 39          | 75       | Metavir                     | 10.6                     | 10                                    |
| Leung (2013)        | Prospective  | 226                         | CHB carriers             | 49          | 65       | Metavir                     | 11.4                     | 35                                    |
| Ferraioli (2012)    | Prospective  | 130                         | CHC                      | 46*         | 70       | Metavir                     | 9.3                      | 24                                    |
| Wong (2012)         | Prospective  | 193                         | NAFLD                    | 52          | 57       | Metavir                     | 7.9                      | 25                                    |
| Cho (2011)          | Prospective  | 207                         | CHB or CHC               | 44          | 59       | Batt's and Ludwig scoring system | 14.1                    | 15                                    |
| Gaia (2011)         | Prospective  | 259                         | NAFLD, CHB, and CHC      | 46*         | 67       | Metavir                     | 10.5                     | 44                                    |
| Kim (2011)          | Prospective  | 91                          | CHC                      | 48          | 48       | Batt's and Ludwig scoring system | 11.0                    | 9                                     |
| Liu (2011)          | Prospective  | 284                         | Hemodialysis CHC         | 47          | 59       | Metavir                     | 9.2                      | 14                                    |
| Mialilhes (2011)    | Prospective  | 59                          | HIV/HBV coinfection      | 43*         | 83       | Metavir                     | 9.4                      | 12                                    |
| Osakabe (2011)      | Retrospective | 51                          | CHB                      | NA          | NA       | Metavir                     | 16                       | 14                                    |
| Rizzo (2011)        | Prospective  | 139                         | CHC                      | 55          | 60       | Metavir                     | 11.0                     | 30                                    |
| Sporea (2011)       | Prospective  | 266                         | CHC                      | 50          | 32       | Metavir                     | 13.4                     | 31                                    |
| Anastasiou (2010)   | Cross-sectional | 65                          | CLD (CHB, CHC, ALD, AIH, NAFLD) | 50*         | 62       | Metavir                     | 15.25                   | 10                                    |
| Bonnard (2010)      | Cross-sectional | 59                          | HBV-infected             | 35          | 73       | Metavir                     | 11                       | 14                                    |
| Cross (2010)        | Prospective  | 187                         | CHC                      | 49*         | 59       | Ishavir                     | 10.05                   | 39                                    |
| Degos (2010)        | Prospective  | 1307                        | HBV, HCV, and HIV        | 47          | 69       | Metavir                     | 12.9                     | 181                                   |
| Fung (2010)         | Prospective  | 102                         | Active CHB               | 41*         | 62       | Modified hepatic activity index score | 11                      | 4                                     |
| Janssens (2010)     | Prospective  | 49                          | Alcoholic patients       | 53*         | 69       | Metavir                     | 19.6                    | 20                                    |
| Kamphues (2010)     | Prospective  | 94                          | HCV liver transplant patients | 52*         | 65       | Scheuer classification      | 10.5                    | 9                                     |
| Lee (2010)          | Prospective  | 121                         | HBV and HCV              | 43          | 73       | Metavir                     | 11                       | 18                                    |
| Mueller (2010)      | Prospective  | 101                         | ALD                      | 53          | 72       | Kleiner score               | 11.5                    | 26                                    |
| Myers (2010)        | Cohort       | 251                         | CLD                      | 49*         | 15       | Metavir                     | 11.1                     | 11                                    |
| Sanchez-Conde (2010)| Prospective  | 100                         | HIV/HCV coinfection      | 42*         | 71       | Metavir                     | 14                       | 8                                     |
| Sporea (2010)       | Prospective  | 457                         | HBV and HCV              | NA          | NA       | Metavir                     | 13.6                    | 46                                    |
| Wong (2010)         | Prospective  | 246                         | NAFLD                    | 51          | 55       | Kleiner score               | 10.3                    | 25                                    |
| Yoneda (2010)       | Cross-sectional | 54                          | NAFLD                    | 51          | 46       | Metavir                     | 16.0                     | 6                                     |
| Chan (2009)         | Prospective  | 161                         | CHB                      | 45          | 76       | Metavir                     | 13.4                     | 40                                    |
| Kim (2009)          | Prospective  | 91                          | CHB                      | 40          | 73       | Metavir                     | 10.3                     | 39                                    |

Contd...
| First author (year) | Study design | Number of analyzed patients | Underlying liver disease | Age (years) | Male (%) | Criteria of liver cirrhosis | Cutoff point of TE (kPa) | Number of patients with liver cirrhosis |
|---------------------|--------------|----------------------------|--------------------------|-------------|----------|----------------------------|--------------------------|----------------------------------|
| Kim (2009)          | Prospective  | 130                        | Treatment-naive CHB      | 43          | 79       | Metavir                    | 10.1                     | 67                               |
| Kirk (2009)         | Cohort       | 192                        | HCV or HCV-HIV coinfection | 49*         | 35       | Metavir                    | 12.3                     | 48                               |
| Marcellin (2009)    | Prospective  | 173                        | CHB                      | 40          | 67       | Metavir                    | 18.2                     | 28                               |
| Nitta (2009)        | Prospective  | 165                        | CHC                      | 57*         | 56       | Metavir                    | 11.6                     | 24                               |
| Wang (2009)         | Prospective  | 320                        | HBV and HCV              | 51          | 62       | Metavir                    | 12                       | 61                               |
| Chang (2008)        | Prospective  | 120                        | HBV, NAFLD, AIH, NASH, HCV, drug-induced liver injury, HCC, alcoholic hepatitis | 50*         | 58       | Metavir                    | 16                       | 12                               |
| Gomez-Dominguez (2008) | Prospective | 55                         | PBC                      | NA          | NA       | Metavir, Scheuer classification | 15.6                     | 2                                |
| Harada (2008)       | Prospective  | 56                         | Recurrent hepatitis C after living donor liver transplantation | 63          | 54       | Scheuer classification     | 26.5                     | 5                                |
| Masuzaki (2008)     | Prospective  | 386                        | CHC                      | 68          | 59       | Metavir                    | 15.9                     | 219                              |
| Nahon (2008)        | Prospective  | 147                        | ALD                      | 54          | 76       | Brunt scoring system, Semi-quantitative Chevallier scoring system, Chevallier scoring system | 22.7                     | 79                              |
| Nguyen-Khac (2008)  | Prospective  | 103                        | Alcohol abuse patients   | 53          | 74       | Metavir                    | 19.5                     | 33                              |
| Nudo (2008)         | Cross-sectional | 101                   | Patients who required a liver biopsy for diagnostic purposes | 51          | 51       | Batts and Ludwig scoring system | 11.8                     | 20                              |
| Obara (2008)        | Prospective  | 114                        | CLD                      | 56*         | 48       | Metavir                    | 17.2                     | 19                              |
| Wong (2008)         | Prospective  | 100                        | Hepatitis B e Antigen-Negative CHB | 49          | 78       | Metavir                    | 13.4                     | 20                              |
| Wong (2008)         | Prospective  | 133                        | CLD                      | 48          | 70       | Metavir                    | 8.4                      | 35                              |
| Yoneda (2008)       | Prospective  | 97                         | NAFLD                    | 52          | 41       | Metavir                    | 17.5                     | 9                               |
| Coco (2007)         | Prospective  | 228                        | CHB and CHC              | 50*         | 72       | Metavir                    | 14                       | 46                              |
| Kim (2007)          | Cross-sectional | 42                     | Abnormal liver function and/or hepatitis symptoms | 46          | 55       | Metavir                    | 15.1                     | 5                               |
| Carrion (2006)      | Cohort       | 169                        | Hepatitis C recurrence after liver transplantation | 60*         | 66       | Metavir                    | 12.50                    | 15                              |
| Corpechot (2006)    | Prospective  | 95                         | Chronic cholestatic diseases | 57*         | 26       | Metavir                    | 17.3                     | 15                              |
| deLedinghen (2006)  | Prospective  | 72                         | HIV with HCV             | 42          | 72       | Metavir                    | 11.8                     | 17                              |

Contd...
The degree of fibrosis. They found that for F2 stage disease, the sensitivity and specificity were 79% and 78%, respectively, whereas for cirrhosis they were 83% and 89%. Tsokatzis et al. also found that the accuracy of the transient elastography as evaluated by post-test biopsy was 78% for F2 stage disease and 88% for cirrhosis. The meta-analysis of Stebbing et al. included 22 studies with 4430 patients. They found that the sensitivity was 71.9% and the specificity was 82.4% for significant fibrosis (≥F2) and they were 84.5% and 94.7%, respectively, for cirrhosis.

Table 1: Contd...

| First author (year)       | Study design | Number of analyzed patients | Underlying liver disease | Age (years) | Male (%) | Criteria of liver cirrhosis | Cutoff point of TE (kPa) | Number of patients with liver cirrhosis |
|---------------------------|--------------|-----------------------------|--------------------------|-------------|----------|------------------------------|--------------------------|-----------------------------------------|
| Ganne-Carrie (2006)       | Prospective  | 775                         | HCV, HBV, alcohol-related, NASH, hemochromatosis, cholestatic liver disease | 48          | 63       | Metavir                      | 11.7                     | 120                                     |
| Ziol (2005)               | Cross-sectional | 251                        | CHC                      | 48          | 62       | Metavir                      | 14.60                    | 49                                      |

AIH: Autoimmune hepatitis, ALD: Alcoholic liver disease, CHB: Chronic hepatitis B, CHC: Chronic hepatitis C, CLD: Chronic liver disease, HBV: Hepatitis B virus, HCC: Hepatocellular carcinoma, NAFLD: Nonalcoholic fatty liver disease, NASH: Nonalcoholic steatohepatitis, TE: Transient elastography, NA: Not available

Figure 2: Meta-analysis of (a) sensitivity; (b) specificity; (c) diagnostic odds ratio; and (d) summary receiver operating characteristic curve of transient elastography in detecting liver cirrhosis
Friedrich-Rust et al. performed a meta-analysis that assessed the overall performance of transient elastography for diagnosing liver fibrosis and they also analyzed what factors influence the accuracy.\[18\] They included 50 studies and found that the mean AUROC curve varied depending on the severity of the fibrosis; the AUROC for significant fibrosis was 0.84, for severe fibrosis was 0.89, and for cirrhosis was 0.94. Factors that influenced AUROC were underlying liver disease, scoring system used, and country.

Currently, there are a number of different methods available for assessing liver fibrosis. Several serum-based biomarkers are available to diagnose disease severity and include peptides or proteins derived from fibrogenic cells, extracellular matrix components, and biochemical tests.\[12\] Most of these assays have been validated in chronic liver disease resulting from hepatitis C virus (HCV) but have not been validated for other important chronic liver diseases.\[12\] A systematic review that included 172 studies evaluated the diagnostic accuracy of two commonly used biomarker tests, FibrTest and APRI. They found that the AUROCs for use of Fibr and APRI tests in detection of significant fibrosis were 0.79 and 0.77, respectively, and for cirrhosis were 0.86 and 0.84.\[83\] Therefore, similar to transient elastography, the biomarker assays perform better in detecting cirrhosis than less-advanced fibrosis. However, our findings and those of Friedrich-Rust et al. indicate that transient elastography may have a better diagnostic accuracy than these two biomarker tests as determined by AUROC.

Both biomarker assays and transient elastography are fast, simple, and easy to use. Transient elastography is more expensive than biomarker assays and the technology is not widely available.\[12\] Results of biomarker assays can be confounded by not always being specific for the liver, and transient elastography findings can be confounded by the presence of obesity, congestion, acute inflammation, cholestasis, and food intake.\[12\]
There are several limitations to this study that should be considered when interpreting the findings. The underlying liver disease across the studies was heterogeneous, and as found by Friedrich-Rust et al., can affect the results. However, in real-world clinical practice, cirrhosis will result from a number of different causes and knowing the diagnostic accuracy of transient elastography in this mixed patient population is important. As mentioned above, we did not evaluate the diagnostic performance of transient elastography for different levels of liver fibrosis.

**CONCLUSION**

Our findings support earlier work that indicates that transient elastography shows good sensitivity and specificity and a high accuracy for detecting liver cirrhosis. It supports the use and further development of transient elastography for diagnosing liver fibrosis.

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**Conflicts of interest**

There are no conflicts of interest.

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