Original Article

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

Xiao-Xia Geng, Ren-Gang Huang, Jian-Mei Lin, Nan Jiang, Xing-Xiang Yang

Department of Infectious Diseases, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu 610072, Sichuan Province, China

Address for correspondence:
Dr. Xing-Xiang Yang,
32 West Second Section,
First Ring Road,
Chengdu 610072,
Sichuan Province, China.
E-mail: 719525383@qq.com

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

Received: 25.11.2015, Accepted: 27.02.2016

How to cite this article: Geng XX, Huang RG, Lin JM, Jiang N, Yang XX. Transient elastography in clinical detection of liver cirrhosis: A systematic review and meta-analysis. Saudi J Gastroenterol 2016;22:294-303.

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.[4-8]

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

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

DOI: 10.4103/1319-3767.187603

of liver fibrosis are not accurately staged, and it is difficult to perform repeat biopsies due to pain and bleeding and risk of death.[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.[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.[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.[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.[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.[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.[23] A Chi-square-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 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.[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.[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].[15,26-81] Forty-four of the studies were prospective in design. The remaining were

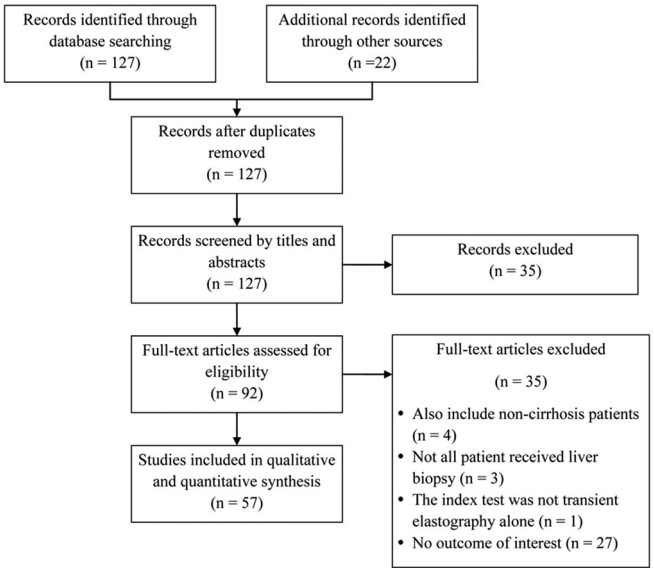

Figure 1: Flow chart of study selection

cross-sectional ($n = 8$), cohort ($n = 4$), or retrospective ($n = 1$) studies. The number of patients in each study ranged from 42 to 1307 with an age range of 30–68 years. The total number of patients with liver cirrhosis was 1870 (range per study; 4–219). In general, there was a higher percentage of males than females across the studies. The investigated liver diseases included autoimmune hepatitis (AIH), alcoholic liver disease (ALD), chronic hepatitis B (CHB), chronic hepatitis C (CHC), chronic liver disease (CLD), hepatitis B virus (HBV), hepatocellular carcinoma (HCC), nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH). Most studies used the METAVIR criteria for determining liver cirrhosis. Other criteria were Batts and Ludwig scoring system, the modified hepatic activity index score, Scheuer classification, Kleiner score, Brunt scoring system, semi-quantitative Chevallier scoring system, and Ishak. The cutoff for transient elastography ranged from 7.9 to 26.5.

Meta-analysis of diagnostic performance

Analysis of the studies indicated that there was a significant heterogeneity with regard to diagnostic sensitivity of transient elastography across the studies ($Q = 175.75$, $I^2 = 68.1\%$, $P < 0.001$); therefore a random-effects model was used for the meta-analysis. The pooled sensitivity of transient elastography for assessing liver cirrhosis was 81% (95% CI: 79%–83%) [Figure 2a].

Heterogeneity among the studies was also observed for the specificity of transient elastography for detecting liver cirrhosis ($Q = 408.22$ and $I^2 = 86.3\%$ ($P < 0.001$), hence a random-effects model was used. The pooled specificity of transient elastography for assessing liver cirrhosis was 88% (95% CI: 87%–89%) [Figure 2b].

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 supports its use 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.[14,17-20,82] The meta-analysis of Talwalkar *et al.* included nine studies.[17] 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 Tsochatzis *et al.*, Stebbing *et al.*, and Friedrich-Rust *et al.* had similar findings to that of Talwalkar *et al.*[17,18,19,82] Tsochatzis *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	Ishak	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	Batts 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	Batts and Ludwig scoring system	11.0	9
Liu (2011)	Prospective	284	Hemodialysis CHC	47	59	Metavir	9.2	14
Miailhes (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	Ishak	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...

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
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	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	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...

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

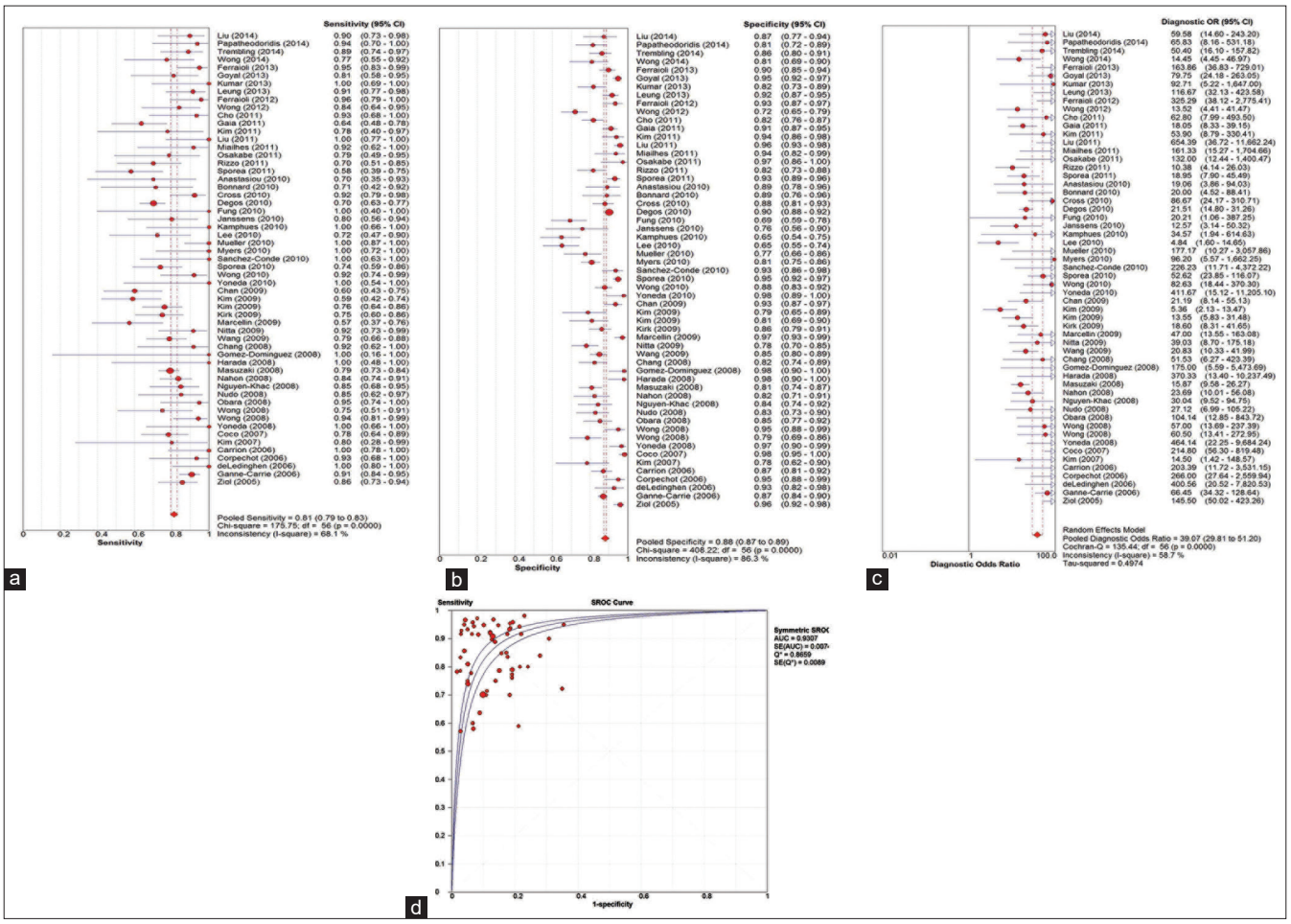

Figure 2: Meta-analysis of (a) sensitivity; (b) specificity; (c) diagnostic odds ratio; and (d) summary receiver operating characteristic curve of transient elastography in detecting liver cirrhosis

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%. Tsochatzis *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.

Figure 3: Summary of quality assessment. (a) Risk of potential bias of individual study; and (b) risk of bias of all included studies

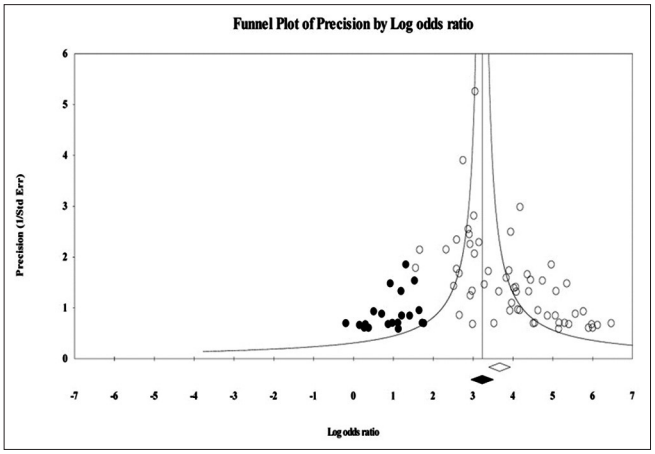

Figure 4: Funnel plots for DOR showing the distribution of published study outcomes (open circles) and simulated outcomes (black circles) estimated by "trim and fill" procedure

Friedrich-Rust *et al*. performed a meta-analysis that assessed the overall performance of transient elastography for diagnosing liver fibrosis and they and 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 077, 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.

Financial support and sponsorship

Scientific Research Foundation from Science and Technology bureau of Chengdu, Sichuan Province.(No. 2014-HM01-00240-SF).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Benvegnù L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: A prospective study on the incidence and hierarchy of major complications. Gut 2004;53:744-9.
2. Seki E, Schwabe RF. Hepatic inflammation and fibrosis: Functional links and key pathways. Hepatology 2015;61:1066-79.
3. Iredale JP. Liver fibrosis: Therapeutic armory 40 years on. Clin Liver Dis 2015;6:1-4.
4. Pungpapong S, Kim WR, Poterucha JJ. Natural history of hepatitis B virus infection: An update for clinicians. Mayo Clin Proc 2007;82:967-75.
5. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, *et al.* Interferon therapy reduces the risk for hepatocellular carcinoma: National surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. Ann Intern Med 1999;131:174-81.
6. Coffin CS, Fung SK, Ma MM, Canadian Association for the Study of the Liver. Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines. Can J Gastroenterol 2012;26:917-38.
7. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167-85.
8. Korean Association for the Study of the Liver. KASL Clinical Practice Guidelines: Management of chronic hepatitis B. Clin Mol Hepatol 2012;18:109-62.
9. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495-500.
10. Castéra L, Nègre I, Samii K, Buffet C. Pain experienced during percutaneous liver biopsy. Hepatology 1999;30:1529-30.
11. Rockey DC. Noninvasive assessment of liver fibrosis and portal hypertension with transient elastography. Gastroenterology 2008;134:8-14.
12. Bedossa P, Patel K, Castera L. Histologic and noninvasive estimates of liver fibrosis. Clin Liver Dis 2015;6:5-8.
13. Afdhal NH, Nunes D. Evaluation of liver fibrosis: A concise review. Am J Gastroenterol 2004;99:1160-74.
14. Kwok R, Tse YK, Wong GL, Ha Y, Lee AU, Ngu MC, *et al.* Systematic review with meta-analysis: Non-invasive assessment of non-alcoholic fatty liver disease – The role of transient elastography and plasma cytokeratin-18 fragments. Aliment Pharmacol Ther 2014;39:254-69.
15. Ganne-Carrié N, Ziol M, de Ledinghen V, Douvin C, Marcellin P, Castera L, *et al.* Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. Hepatology 2006;44:1511-7.
16. Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, *et al.* Diagnosis of cirrhosis by transient elastography (FibroScan): A prospective study. Gut 2006;55:403-8.
17. Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: Systematic review and meta-analysis. Clin Gastroenterol Hepatol 2007;5:1214-20.
18. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, *et al.* Performance of transient elastography for the staging of liver fibrosis: A meta-analysis. Gastroenterology 2008;134:960-74.
19. 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;54:650-9.
20. Chon YE, Choi EH, Song KJ, Park JY, Kim do Y, Han KH, *et al.* Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: A meta-analysis. PLoS One 2012;7:e44930.
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Ann Intern Med 2009;151:W65-94.
22. Higgins JP. Cochrane Collaboration Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011. Available from: http://www.cochrane-handbook.org. [Last updated on 2011 Mar].
23. Schisterman EF, Perkins NJ, Liu A, Bondell H. Optimal cut-point and its corresponding Youden Index to discriminate individuals using pooled blood samples. Epidemiology 2005;16:73-81.
24. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: A software for meta-analysis of test accuracy data. BMC Med Res Methodol 2006;6:31.
25. 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;56:455-63.
26. Anastasiou J, Alisa A, Virtue S, Portmann B, Murray-Lyon I, Williams R. Noninvasive markers of fibrosis and inflammation in clinical practice: Prospective comparison with liver biopsy. Eur J Gastroenterol Hepatol 2010;22:474-80.
27. Bonnard P, Sombié R, Lescure FX, Bougouma A, Guiard-Schmid JB, Poynard T, *et al.* Comparison of elastography, serum marker scores, and histology for the assessment of liver fibrosis in hepatitis B virus (HBV)-infected patients in Burkina Faso. Am J Trop Med Hyg 2010;82:454-8.
28. Carrión JA, Navasa M, Bosch J, Bruguera M, Gilabert 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;12:1791-8.

29. Chan HL, Wong GL, Choi PC, Chan AW, Chim AM, Yiu KK, *et al.* Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat 2009;16:36-44.
30. Chang PE, Lui HF, Chau YP, Lim KH, Yap WM, Tan CK, *et al.* Prospective evaluation of transient elastography for the diagnosis of hepatic fibrosis in Asians: Comparison with liver biopsy and aspartate transaminase platelet ratio index. Aliment Pharmacol Ther 2008;28:51-61.
31. Cho HJ, Seo YS, Lee KG, Hyun JJ, An H, Keum B, *et al.* Serum aminotransferase levels instead of etiology affects the accuracy of transient elastography in chronic viral hepatitis patients. J Gastroenterol Hepatol 2011;26:492-500.
32. Coco B, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P, *et al.* Transient elastography: A new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat 2007;14:360-9.
33. Corpechot C, El Naggar A, Poujol-Robert A, Ziol M, Wendum D, Chazouillères O, *et al.* Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. Hepatology 2006;43:1118-24.
34. Cross TJ, Calvaruso V, Maimone S, Carey I, Chang TP, Pleguezuelo M, *et al.* Prospective comparison of Fibroscan, King's score and liver biopsy for the assessment of cirrhosis in chronic hepatitis C infection. J Viral Hepat 2010;17:546-54.
35. Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, *et al.* Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: A multicenter prospective study (the FIBROSTIC study). J Hepatol 2010;53:1013-21.
36. de Lédinghen V, Douvin C, Kettaneh A, Ziol M, Roulot D, Marcellin P, *et al.* Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. J Acquir Immune Defic Syndr 2006;41:175-9.
37. Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Lissandrin R, Filice G, *et al.* Performance of liver stiffness measurements by transient elastography in chronic hepatitis. World J Gastroenterol 2013;19:49-56.
38. Ferraioli G, Tinelli C, Malfitano A, Dal Bello B, Filice G, Filice C; Liver Fibrosis Study Group, *et al.* 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;199:19-25.
39. Fung J, Lai CL, Chan SC, But D, Seto WK, Cheng C, *et al.* Correlation of liver stiffness and histological features in healthy persons and in patients with occult hepatitis B, chronic active hepatitis B, or hepatitis B cirrhosis. Am J Gastroenterol 2010;105:1116-22.
40. Gaia S, Carenzi S, Barilli AL, Bugianesi E, Smedile A, Brunello F, *et al.* Reliability of transient elastography for the detection of fibrosis in non-alcoholic fatty liver disease and chronic viral hepatitis. J Hepatol 2011;54:64-71.
41. Gómez-Dominguez E, Mendoza J, García-Buey L, Trapero M, Gisbert JP, Jones EA, *et al.* Transient elastography to assess hepatic fibrosis in primary biliary cirrhosis. Aliment Pharmacol Ther 2008;27:441-7.
42. Goyal R, Mallick SR, Mahanta M, Kedia S, Shalimar, Dhingra R, *et al.* Fibroscan can avoid liver biopsy in Indian patients with chronic hepatitis B. J Gastroenterol Hepatol 2013;28:1738-45.
43. Harada N, Soejima Y, Taketomi A, Yoshizumi T, Ikegami T, Yamashita Y, *et al.* Assessment of graft fibrosis by transient elastography in patients with recurrent hepatitis C after living donor liver transplantation. Transplantation 2008;85:69-74.
44. Janssens F, de Suray N, Piessevaux H, Horsmans Y, de Timary P, Stärkel P. Can transient elastography replace liver histology for determination of advanced fibrosis in alcoholic patients: A real-life study. J Clin Gastroenterol 2010;44:575-82.
45. Kamphues C, Lotz K, Röcken C, Berg T, Eurich D, Pratschke J, *et al.* Chances and limitations of non-invasive tests in the assessment of liver fibrosis in liver transplant patients. Clin Transplant 2010;24:652-9.
46. Kim do Y, Kim SU, Ahn SH, Park JY, Lee JM, Park YN, *et al.* Usefulness of FibroScan for detection of early compensated liver cirrhosis in chronic hepatitis B. Dig Dis Sci 2009;54:1758-63.
47. Kim KM, Choi WB, Park SH, Yu E, Lee SG, Lim YS, *et al.* Diagnosis of hepatic steatosis and fibrosis by transient elastography in asymptomatic healthy individuals: A prospective study of living related potential liver donors. J Gastroenterol 2007;42:382-8.
48. Kim SU, Ahn SH, Park JY, Kang W, Kim do Y, Park YN, *et al.* Liver stiffness measurement in combination with noninvasive markers for the improved diagnosis of B-viral liver cirrhosis. J Clin Gastroenterol 2009;43:267-71.
49. Kim SU, Jang HW, Cheong JY, Kim JK, Lee MH, Kim DJ, *et al.* The usefulness of liver stiffness measurement using FibroScan in chronic hepatitis C in South Korea: A multicenter, prospective study. J Gastroenterol Hepatol 2011;26:171-8.
50. Kirk GD, Astemborski J, Mehta SH, Spoler C, Fisher C, Allen D, *et al.* Assessment of liver fibrosis by transient elastography in persons with hepatitis C virus infection or HIV-hepatitis C virus coinfection. Clin Infect Dis 2009;48:963-72.
51. Kumar R, Rastogi A, Sharma MK, Bhatia V, Tyagi P, Sharma P, *et al.* Liver stiffness measurements in patients with different stages of nonalcoholic fatty liver disease: Diagnostic performance and clinicopathological correlation. Dig Dis Sci 2013;58:265-74.
52. Lee MH, Cheong JY, Um SH, Seo YS, Kim DJ, Hwang SG, *et al.* Comparison of surrogate serum markers and transient elastography (Fibroscan) for assessing cirrhosis in patients with chronic viral hepatitis. Dig Dis Sci 2010;55:3552-60.
53. Leung VY, Shen J, Wong VW, Abrigo J, Wong GL, Chim AM, *et al.* Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: Comparison of shear-wave elastography and transient elastography with liver biopsy correlation. Radiology 2013;269:910-8.
54. Liu CH, Liang CC, Huang KW, Liu CJ, Chen SI, Lin JW, *et al.* Transient elastography to assess hepatic fibrosis in hemodialysis chronic hepatitis C patients. Clin J Am Soc Nephrol 2011;6:1057-65.
55. Liu Y, Dong CF, Yang G, Liu J, Yao S, Li HY, *et al.* Optimal linear combination of ARFI, transient elastography and APRI for the assessment of fibrosis in chronic hepatitis B. Liver Int 2015;35:816-25.
56. Marcellin P, Ziol M, Bedossa P, Douvin C, Poupon R, de Lédinghen V, *et al.* Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int 2009;29:242-7.
57. Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T, *et al.* Comparison of liver biopsy and transient elastography based on clinical relevance. Can J Gastroenterol 2008;22:753-7.
58. Miailhes P, Pradat P, Chevallier M, Lacombe K, Bailly F, Cotte L, *et al.* Proficiency of transient elastography compared to liver biopsy for the assessment of fibrosis in HIV/HBV-coinfected patients. J Viral Hepat 2011;18:61-9.
59. Mueller S, Millonig G, Sarovska L, Friedrich S, Reimann FM, Pritsch M, *et al.* Increased liver stiffness in alcoholic liver disease: Differentiating fibrosis from steatohepatitis. World J Gastroenterol 2010;16:966-72.
60. Myers RP, Elkashab M, Ma M, Crotty P, Pomier-Layrargues G. Transient elastography for the noninvasive assessment of liver fibrosis: A multicentre Canadian study. Can J Gastroenterol 2010;24:661-70.
61. Nahon P, Kettaneh A, Tengher-Barna I, Ziol M, de Lédinghen V, Douvin C, *et al.* Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. J Hepatol 2008;49:1062-8.
62. Nguyen-Khac E, Chatelain D, Tramier B, Decrombecque C,

Robert B, Joly JP, *et al.* Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: Prospective comparison with seven non-invasive laboratory tests. Aliment Pharmacol Ther 2008;28:1188-98.
63. Nitta Y, Kawabe N, Hashimoto S, Harata M, Komura N, Kobayashi K, *et al.* Liver stiffness measured by transient elastography correlates with fibrosis area in liver biopsy in patients with chronic hepatitis C. Hepatol Res 2009;39:675-84.
64. Nudo CG, Jeffers LJ, Bejarano PA, Servin-Abad LA, Leibovici Z, De Medina M, *et al.* Correlation of laparoscopic liver biopsy to elasticity measurements (FibroScan) in patients with chronic liver disease. Gastroenterol Hepatol (N Y) 2008;4:862-70.
65. Obara N, Ueno Y, Fukushima K, Nakagome Y, Kakazu E, Kimura O, *et al.* 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.
66. Osakabe K, Ichino N, Nishikawa T, Sugiyama H, Kato M, Kitahara S, *et al.* Reduction of liver stiffness by antiviral therapy in chronic hepatitis B. J Gastroenterol 2011;46:1324-34.
67. Papatheodoridis GV, Manolakopoulos S, Margariti A, Papageorgiou MV, Kranidioti H, Katoglou A, *et al.* The usefulness of transient elastography in the assessment of patients with HBeAg-negative chronic hepatitis B virus infection. J Viral Hepat 2014;21:517-24.
68. Rizzo L, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S, *et al.* 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;106:2112-20.
69. Sánchez-Conde M, Montes-Ramírez ML, Miralles P, Alvarez JM, Bellón JM, Ramírez M, *et al.* 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;17:280-6.
70. Sporea I, Sirli R, Deleanu A, Tudora A, Popescu A, Curescu M, *et al.* Liver stiffness measurements in patients with HBV vs HCV chronic hepatitis: A comparative study. World J Gastroenterol 2010;16:4832-7.
71. Sporea I, Sirli RL, Deleanu A, Iulia R, Tudora A, Dan I, *et al.* What did we learn from the first 3,459 cases of liver stiffness measurement by transient elastography (FibroScan®)? Ultraschall Med 2011;32:40-5.
72. Trembling PM, Lampertico P, Parkes J, Tanwar S, Viganò M, Facchetti F, *et al.* Performance of Enhanced Liver Fibrosis test and comparison with transient elastography in the identification of liver fibrosis in patients with chronic hepatitis B infection. J Viral Hepat 2014;21:430-8.
73. Wang JH, Changchien CS, Hung CH, Eng HL, Tung WC, Kee KM, *et al.* FibroScan and ultrasonography in the prediction of hepatic fibrosis in patients with chronic viral hepatitis. J Gastroenterol 2009;44:439-46.
74. Wong GL, Chan HL, Choi PC, Chan AW, Yu Z, Lai JW, *et al.* Non-invasive algorithm of enhanced liver fibrosis and liver stiffness measurement with transient elastography for advanced liver fibrosis in chronic hepatitis B. Aliment Pharmacol Ther 2014;39:197-208.
75. Wong GL, Wong VW, Choi PC, Chan AW, Chim AM, Yiu KK, *et al.* Evaluation of alanine transaminase and hepatitis B virus DNA to predict liver cirrhosis in hepatitis B e antigen-negative chronic hepatitis B using transient elastography. Am J Gastroenterol 2008;103:3071-81.
76. Wong GL, Wong VW, Choi PC, Chan AW, Chum RH, Chan HK, *et al.* Assessment of fibrosis by transient elastography compared with liver biopsy and morphometry in chronic liver diseases. Clin Gastroenterol Hepatol 2008;6:1027-35.
77. Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, *et al.* Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454-62.
78. Wong VW, Vergniol J, Wong GL, Foucher J, Chan AW, Chermak F, *et al.* Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. Am J Gastroenterol 2012;107:1862-71.
79. Yoneda M, Suzuki K, Kato S, Fujita K, Nozaki Y, Hosono K, *et al.* Nonalcoholic fatty liver disease: US-based acoustic radiation force impulse elastography. Radiology 2010;256:640-7.
80. Yoneda M, Yoneda M, Mawatari H, Fujita K, Endo H, Iida H, *et al.* Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). Dig Liver Dis 2008;40:371-8.
81. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, *et al.* Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48-54.
82. Stebbing J, Farouk L, Panos G, Anderson M, Jiao LR, Mandalia S, *et al.* A meta-analysis of transient elastography for the detection of hepatic fibrosis. J Clin Gastroenterol 2010;44:214-9.
83. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: A systematic review. Ann Intern Med 2013;158:807-20.