Review

Update of liver fibrosis and steatosis with transient elastography (Fibroscan)

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Background: Assessment of liver fibrosis and steatosis is now almost indispensable in most of the chronic liver diseases in order to determine prognosis and need for treatment, and to monitor disease progression and response to treatment. Liver biopsy is limited by its invasiveness and patient acceptability. Transient elastography (TE; Fibroscan) is a non-invasive tool with satisfactory accuracy and reproducibility to estimate liver fibrosis.

Aims & Methods: To review the existing evidence concerning the clinical applications of TE in major liver diseases, including chronic hepatitis B and -C, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, primary biliary cirrhosis and primary sclerosing cholangitis.

Results: As alanine aminotransferase (ALT) is one of the major confounding factors of liver stiffness in chronic hepatitis B, an ALT-based algorithm has been developed and higher liver stiffness measurements (LSM) cut-off values for different stages of liver fibrosis should be used in patients with elevated ALT levels up to five times the upper limit of normal. Furthermore, falsely-high LSM results up to the cirrhotic range may occur during ALT flare. TE is also useful predicting patient prognosis in the development of hepatocellular carcinoma (HCC), portal hypertension, postoperative complications in HCC patients and survival. Unfortunately, failed acquisition of TE is common in obese patients. Furthermore, obese patients may have higher LSM results, even in the same stage of liver fibrosis. To better evaluate NAFLD a new XL probe, with a larger probe with lower ultrasound frequency and deeper penetration, increases the success rate of TE in obese patients. The median LSM value with the XL probe was found to be lower than that by the conventional M probe, hence cut-off values were approximately 1.2 to 1.3 kilopascals lower than those of the M probe, suggesting its adoption. Studies reveal that a novel ultrasonic controlled attenuation parameter is potentially useful to detect and quantify hepatic steatosis non-invasively.

Conclusion: TE is a non-invasive, accurate and reproducible test of liver fibrosis and possibly hepatic steatosis and has been validated in a wide spectrum of liver diseases. TE is also useful to predict patient outcomes.

Keywords: cirrhosis; hepatitis; fatty liver; histology; liver biopsy; liver stiffness measurement.

INTRODUCTION

Liver fibrosis is the natural wound-healing response to parenchymal injury in chronic liver diseases. It may eventually result in liver cirrhosis and its various complications. Accurate staging of liver fibrosis is now essentially indispensable in the decision process for treatment in chronic viral hepatitis, as well as disease prognosis [1, 2]. It is also vital to monitor disease progression and response to treatment.

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LIVER BIOPSY: IS IT STILL A ‘GOLD STANDARD’ ASSESSMENT OF LIVER FIBROSIS?

Liver biopsy has been the ‘gold standard’ for assessing liver fibrosis in the last few decades [3]. However it has numerous limitations, namely its invasive nature, risk of complications, patient discomfort and sampling errors [4]. Complications associated with liver biopsy are rare but can be severe and even life-threatening. Pain and hypotension are the predominant complications for which patients are hospitalized [5]. Clinically significant intraperitoneal hemorrhage is the rarest but most serious bleeding complication of percutaneous liver biopsy, which may happen more often in older-aged patients with cirrhosis or liver cancer [6]. The mortality rate among patients after percutaneous liver biopsy is approximately 1 in 10,000 to 1 in 12,000 [7]. All these problems make it impractical to perform serial biopsies to assess disease progression in routine clinical practice [2].

The diagnostic accuracy of liver biopsy is limited by sampling variability. The average size of biopsy is 15 mm in length, which represents 1/50,000 the size of the entire liver. There is significant variability in the histological assessment of two readings of the same biopsy by the same pathologist and between two pathologists, even among those who are highly specialized [4]. This variability is low for the diagnosis of cirrhosis (kappa coefficient of concordance \( \geq 0.80 \)), moderate for earlier fibrosis stages (kappa 0.70–0.80) but high for the activity grades (kappa 0.40–0.50) [4].

THE WORKING PRINCIPLES OF TRANSIENT ELASTOGRAPHY

Transient elastography (TE; Fibroscan\textsuperscript{\textregistered}, Echosens, Paris, France) measures liver stiffness in patients suffering from different chronic liver diseases [8, 9]. An ultrasound transducer probe is mounted on the axis of a vibrator. Vibrations of mild amplitude and low frequency (50 Hz) are transmitted by the transducer, inducing a plastic shear wave that propagates through the underlying tissues. Pulse-echo ultrasound acquisition is used to follow the propagation of the shear wave and to measure its velocity, which is directly related to tissue stiffness (the elastic modulus \( E \) expressed as \( E = 3\rho V^2 \), where \( V \) is the shear velocity and \( \rho \) is the mass density, which is constant for tissues). The stiffer the tissue, the faster the shear wave propagates (Fig. 1). TE measures liver stiffness in a volume that approximates a cylinder 1 cm in diameter and 4 cm in length, between 25 and 65 mm underneath the skin surface. This volume is at least 100 times bigger than a biopsy sample and therefore should be more representative of the liver parenchyma [8].

TE has the advantages of being painless, rapid (usually less than 5 minutes) and easy to perform at the bedside or in the outpatient clinic. The examination is performed on a non-fasting patient lying supine with the right arm placed behind the head to facilitate access to the right upper quadrant of the abdomen. The tip of the probe transducer is placed on the skin between the rib bones at the level of the right lobe of the liver where liver biopsy would be performed. Once the measurement area has been located, the operator presses the button on the probe to start an acquisition. The software determines whether each measurement is successful or not. Results are expressed in kilopascals (kPa) and correspond to the median of 10 validated measurements according to Sandrin et al. [8]. According to the manufacturer, the examination is considered reliable if \( \geq 10 \) valid measurements are acquired, the success rate (number of valid acquisitions divided by the number of attempts) is over 60%, and the ratio of the interquartile range to the median of 10 measurements (IQR/M) is \( \leq 0.3 \) [8].

![Figure 1. Shear wave propagation velocity according to the severity of hepatic fibrosis (Metavir score). The elastic modulus \( E \) expressed as \( E = 3\rho V^2 \), where \( V \) is the shear velocity and \( \rho \) is the mass density (constant for tissues): the stiffer the tissue, the faster the shear wave propagates. Hence, for absent fibrosis (F0), velocity is 1.0 m/s and elasticity is 3.0 kPa, whereas for cirrhosis (F4) velocity is 3.0 m/s and elasticity is 27.0 kPa. Modified from Sandrin et al. [10].](image-url)
ACCURACY OF TRANSIENT ELASTOGRAPHY

Reproducibility of TE is an important feature for its widespread clinical application. The reproducibility of liver stiffness measurement (LSM) was excellent for both inter-observer and intra-observer agreement, with intra-class correlation coefficients (ICC) of 0.98 [10]. However, inter-observer agreement was significantly reduced in patients with lower degrees of liver fibrosis (ICC for F0–1 and F2 were 0.60 and 0.99, respectively), with hepatic steatosis (ICC for steatosis <25% and 25% of hepatocytes 0.98 and 0.90, respectively) and with increased body mass index (BMI; ICC for BMI ≥25 kg/m² and <25 kg/m² were 0.98 and 0.94, respectively).

Using TE to assess liver fibrosis has been widely validated in different liver diseases, including chronic hepatitis C (CHC) [1, 11–12], chronic hepatitis B (CHB) [13–15], co-infection with HIV [16], non-alcoholic fatty liver disease (NAFLD) [17–18], alcoholic liver disease [19], primary biliary cirrhosis, primary sclerosing cholangitis [20] and in the post-liver transplantation setting [21]. In these studies, TE was valid with liver histology being the gold standard. In general, all these studies confirm that TE has good overall accuracy to diagnose advanced fibrosis and cirrhosis, independent of the underlying etiology [22–23]. The remaining controversy is the optimal cut-off values to diagnose advanced fibrosis and cirrhosis, which differ according to particular etiologies. This has significant implications when a clinician interprets TE results. The suggested diagnostic performance and cut-off values for histological cirrhosis (F4) based on published studies are summarized in Table 1.

CLINICAL APPLICATIONS OF TRANSIENT ELASTOGRAPHY

Pre-treatment assessment of liver fibrosis

The severity of liver fibrosis is the key factor of timing and choice of therapy. This is particularly relevant in chronic viral hepatitis. Current international guidelines recommend antiviral therapy for CHB patients with significant liver fibrosis [24–26]. As TE has been repeatedly shown to have satisfactory accuracy to exclude and diagnose advanced fibrosis and cirrhosis, as mentioned above, more than half of the patients might reach a treatment decision without the need for confirmatory liver biopsies [13]. TE is also found to be more cost-effective than liver biopsy [27]. TE has been incorporated in the international guidelines for CHB and CHC [24–25].

Follow-up assessment of liver fibrosis

A few longitudinal studies have reported that patients responding to treatment had low or decreased liver stiffness

### Table 1. Diagnostic performance and suggested cut-off values of transient elastography for the diagnosis of histological cirrhosis (F4)

| Reference number | No. of biopsies | Prevalence of cirrhosis (F4; %) | Etiologies | Proposed cut-off values (kPa) | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | AUROC |
|------------------|----------------|-------------------------------|------------|----------------------------|----------------|----------------|-----------------------------|-----------------------------|------|
| [10]             | 200            | 12.0                          | All         | 11.0                       | 91             | 95              | 0.8                         | 0.98                        | 0.90 |
| [65]             | 775            | 15.5                          | All         | 14.0                       | 96             | 95              | 0.7                         | 0.93                        | 0.95 |
| [66]             | 354            | 13.3                          | All         | 17.0                       | 96             | 97              | 0.4                         | 0.98                        | 0.96 |
| [67]             | 94             | 17.0                          | All         | 25.0                       | 97             | 96              | 0.4                         | 0.99                        | 0.97 |
| [13]             | 161            | 25.0                          | HBV         | 19.0                       | 96             | 98              | 0.4                         | 0.99                        | 0.98 |
| [15]             | 238            | 23.5                          | HBV         | 25.0                       | 96             | 95              | 0.4                         | 0.98                        | 0.97 |
| [11]             | 173            | 38.5                          | HBV & HBV   | 19.0                       | 96             | 95              | 0.4                         | 0.98                        | 0.97 |
| [16]             | 120            | 17.0                          | HCV         | 22.5                       | 96             | 95              | 0.4                         | 0.98                        | 0.97 |
| [21]             | 94             | 17.0                          | HCV & HCV   | 17.0                       | 95             | 94              | 0.4                         | 0.99                        | 0.97 |
| [70]             | 228            | 17.0                          | HCV         | 25.0                       | 94             | 93              | 0.4                         | 0.99                        | 0.97 |
| [12]             | 251            | 17.0                          | HCV         | 19.0                       | 92             | 96              | 0.4                         | 0.99                        | 0.97 |
| [1]              | 183            | 17.0                          | HCV-HIV     | 17.0                       | 93             | 95              | 0.4                         | 0.99                        | 0.97 |
| [11]             | 141            | 17.0                          | HCV-HIV     | 17.0                       | 93             | 95              | 0.4                         | 0.99                        | 0.97 |
| [16]             | 238            | 17.0                          | HCV-LT      | 17.0                       | 92             | 95              | 0.4                         | 0.99                        | 0.97 |
| [68]             | 173            | 17.0                          | HCV-LT      | 17.0                       | 91             | 95              | 0.4                         | 0.99                        | 0.97 |
| [69]             | 228            | 17.0                          | NAFLD       | 17.0                       | 94             | 93              | 0.4                         | 0.99                        | 0.97 |
| [12]             | 251            | 17.0                          | NAFLD       | 17.0                       | 94             | 93              | 0.4                         | 0.99                        | 0.97 |
| [19]             | 183            | 17.0                          | ALD          | 17.0                       | 93             | 95              | 0.4                         | 0.99                        | 0.97 |
| [20]             | 150            | 17.0                          | PBC & PSC   | 17.0                       | 92             | 95              | 0.4                         | 0.99                        | 0.97 |

Fibroscan for liver fibrosis and steatosis

| ALD = alcoholic liver disease, ALT = alanine aminotransferase, AUROC = area under receiver operating characteristic curves, HBV = hepatitis B virus infection, HIV = human immunodeficiency virus infection, HCV = hepatitis C virus infection, HCV-HIV = hepatitis B virus and human immunodeficiency virus co-infection, HCV-LT = hepatitis C virus infection recurrence after liver transplantation, NAFLD = non-alcoholic fatty liver disease, PBC = primary biliary cirrhosis, PSC = primary sclerosing cholangitis, LR = likelihood ratio, F4 = histological cirrhosis. *Cut-off values proposed for advanced fibrosis (F3 or above).
In a prospective study of 71 CHB patients on antiviral therapy, paired liver biopsy and TE were both performed at baseline and at 1 year following treatment [30]. Although TE remained accurate in distinguishing patients with insignificant disease from those with advanced fibrosis or cirrhosis at both time points, the absolute change in liver stiffness correlated poorly with the change in histological fibrosis stage and resolution of advanced fibrosis could only be assumed with significantly decreased liver stiffness to 5.0 kPa or less after antiviral treatment [30].

Prediction of portal hypertension and variceal bleeding

TE is found useful to identify cirrhotic patients with higher risk of portal hypertension and cut-off values of 17.6 kPa and 21.0 kPa having sensitivity ≥90%, in order to detect patients with hepatic venous pressure gradient (HVPG) above 10–12 mmHg [31–32]. The presence of varices could be excluded with a liver stiffness below 12.5–19.8 kPa [33–34]. Unfortunately, these suggested cut-off values overlap with those for detecting histological cirrhosis in most chronic liver diseases. Hence there seems to be no significant new information provided by TE regarding screening endoscopy for varices among cirrhotic patients.

Prediction of hepatocellular carcinoma

TE is also useful in predicting the risk of other liver-related complications and death. A dose–response relationship between LSM and risk of hepatocellular carcinoma (HCC) was found in both CHB and CHC patients (Table 2). Taking patients with LSM ≤10.0 kPa as reference, the hazard ratios of developing HCC were 17, 21, 26 and 46 in patients with LSM at 10.1–15.0 kPa, 15.1–20.0 kPa, 20.1–25.0 kPa and above 25.0 kPa, respectively, in a prospective cohort of 866 CHC patients [35]. Patients with LSM ≤8.0 kPa acted as the control group; the hazard ratios of developing HCC were 3.1, 4.7, 5.6 and 6.6 in patients with LSM at 8.1–13.0 kPa, 13.1–18.0 kPa, 18.1–23.0 kPa, and above 23.0 kPa, respectively, in another cohort of 1,130 CHB patients [36]. LSM, as well as FibroTest, can also predict 5-year survival of patients with CHC; the prognostic values of LSM remained even after adjustments for treatment response, patient age and degree of necroinflammation [37].

### LIMITATIONS OF TRANSIENT ELASTOGRAPHY

#### Factors affecting accuracy of measurements

Not only liver fibrosis but also other factors contribute to liver stiffness. LSM has been consistently found to be falsely elevated in acute hepatitis, manifested as alanine aminotransferase (ALT) flares [40–41]. Severe hepatic necroinflammation may lead to LSM values well within the cirrhotic range, even in the absence of fibrosis on histology [29, 42–43]. In this setting, LSM tends to decrease considerably after the resolution of acute hepatitis. Therefore, applying TE in this scenario can be misleading and is not recommended until at least 3 months after normalization, or at least until stabilization of ALT levels below five times the upper limit of normal [13, 41] (Fig. 2). An ALT-based algorithm has been developed and higher LSM cut-off values for different stages of liver fibrosis should be used in patients with elevated ALT levels (Fig. 3).

Extrahepatic cholestasis [44], hepatic congestion [45], hepatic amyloidosis [46] and recent food intake (within 60 minutes) [47] were also found to be associated with a falsely high LSM values. Fortunately, the degree of hepatic

| Chronic hepatitis B patients | Chronic hepatitis C patients |
|-----------------------------|-----------------------------|
| LSM | Hazard ratios of HCC | LSM | Hazard ratios of HCC |
| ≤10.0 kPa | Referent | ≤8.0 kPa | Referent |
| 10.1–15.0 kPa | 17 | 8.1–13.0 kPa | 3.1 |
| 15.1–20.0 kPa | 21 | 13.1–18.0 kPa | 4.7 |
| 20.1–25.0 kPa | 26 | 18.1–23.0 kPa | 5.6 |
| > 25.0 kPa | 46 | > 23.0 kPa | 6.6 |

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steatosis does not appear to affect LSM results: therefore TE remains an accurate tool for fibrosis assessment in CHC and NAFLD [11, 18]. Our recent study showed that NAFLD patients with BMI 30 kg/m², the lowest limit of an abnormal BMI in NAFLD, would have higher LSM values by M probe even in the same fibrosis stage [48]. This provocative finding may lead to concern about the M probe’s accuracy in obese patients. The emergence of the XL probe is a possible solution to this issue.

Factors affecting success rate of measurements
It has been noted that unreliable and failed LSMs occur, respectively, at about 3% and 11.6–18.4% in all TE examinations and they are independently associated with BMI > 30 kg/m² in both Caucasians and Chinese [49–50]. The success rate of LSMs with the M probe would be as low as 75% in NAFLD patients with BMI > 30 kg/m² [18]. The low LSM success rate among obese patients is likely related to the thick subcutaneous fat, which hinders the transmission of shear waves and ultrasound waves through the liver parenchyma [50]. Patients with extreme—very high and very low—BMI were recently found to have higher LSM values in an Indian population [51]. Subjects with narrow intercostal space, high-riding liver, hyperinflated lungs, ascites or free peritoneal fluid may also have lower success rate or failed acquisition of LSM [8].

A recent study challenged the validity of the reliability criteria, suggested by the manufacturer, of 1165 patients with chronic liver diseases, who underwent LSM within 3 months of liver biopsy. The investigators found that the number of successful acquisitions, and their success rate, had no influence on the diagnostic accuracy [52]. Furthermore, LSM remained reliable even if the ratio of the interquartile range to the median of 10 measurements (IQR/M) > 0.30, provided that the median LSM was below 7.1 kPa.

These new findings implied that LSM results were more reliable than what had been previously described.

COMBINING TRANSIENT ELASTOGRAPHY WITH SERUM MARKERS
In general, serum markers have modest accuracy for diagnosing advanced liver fibrosis [53–54]. TE has certain advantages over serum markers as it provides a more direct measurement of fibrosis, is less affected by intercurrent health disorders and is theoretically applicable to all chronic liver diseases. On the other hand, its diagnostic performance was particularly affected in patients with elevated serum ALT levels [29]; hence a second non-invasive test, independent of the serum ALT or AST levels, may be a good supplementary test for LSM. Among various serum test formulae, the Forns index [55] and Hui index [53] are composed of clinical parameters other than ALT or AST levels. We demonstrated that a combined LSM-Forns algorithm improved the accuracy to predict advanced liver fibrosis in 238 CHB patients [15]. In this combined algorithm, low LSM or low Forns index could be used to exclude advanced fibrosis with a high sensitivity of 95%. To confirm advanced fibrosis, agreement between high LSM and high Forns index could improve the specificity up to 99–100% [15].
The combination of TE and FibroTest was found to have the best diagnostic performance, compared to either test alone, in patients with CHC [1]. When TE and FibroTest matched (present in 70–80% of cases), results were also concordant, respectively, in 84%, 95% and 94% of patients with liver fibrosis ≥F2, ≥F3 and F = 4 [1]. The combination of LSM and FibroTest allowed exclusion of significant fibrosis (≥F2) in nearly 80% of 100 CHB patients in the inactive carrier stage.

NEW FEATURES OF TRANSIENT ELASTOGRAPHY

S and XL probes

The development of S and XL probes aim to cater for different population groups of various body build types (Fig. 4). The S probe contains a higher frequency ultrasonic transducer and shallower measurements below the skin surface, which suit pediatric subjects and those with small body build [56]. The XL probe contains a lower frequency and a more sensitive transducer, a deeper focal length, larger vibration amplitude and a greater depth of measurements below the skin surface [57]. This probe serves obese subjects with ‘XL’ body builds. Data concerning the validations of these new probes are emerging.

With the XL probe, LSM could be successfully performed in more obese patients compared to the M probe [58]. In our validation study involving 286 patients, LSM using the XL probe documented reliable results in 92% of patients, compared to 80% using the M probe [64]. In another study of 193 NAFLD patients, a cut-off value of 215 dB/m has a sensitivity of 90% to detect S1 steatosis [58]. In order to evaluate hepatic steatosis, the data supports the use of CAP simultaneously with LSM. This would be a promising new tool to monitor the development of NAFLD not only in patients with high BMI, but in ‘metabolically obese’ patients, as recent evidence demonstrated that distribution of fat (not total fat) was associated with NAFLD [63–64].

CONTROLLED ATTENUATION PARAMETER

As obesity is becoming a pandemic and is increasingly encountered worldwide in the last few decades [60], the prevalence of NAFLD has been substantially increased [61]. This makes the estimation of the degree of hepatic steatosis essential. Recently, a novel physical parameter, based on the properties of ultrasonic signals acquired by the Fibroscan machine, has been developed, applying the property that hepatic steatosis affects ultrasound propagation [62]. This novel parameter, ‘controlled attenuation parameter’ (CAP), is measuring ultrasound attenuation at the center frequency (expressed as dB/m) of the M probe. In a recent study of 112 patients with liver biopsy, CAP was found efficient in detecting low grade steatosis [58].

CONCLUSIONS

TE is a non-invasive, accurate and reproducible test of liver fibrosis—and possibly hepatic steatosis—and has been validated in a wide spectrum of liver diseases. TE is also useful in predicting patient outcomes. Further studies should explore the appropriate cut-off values of newer XL and S probes, as well as those of the novel controlled attenuation parameter (CAP).

Conflict of interest: G.W. has served as a speaker for Echosens and an advisory committee member for Otsuka.

REFERENCES

1. Castera L, Vergniol J, Foucher J et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis. C. Gastroenterology 2005; 128:343–50.

2. Wong VW, Wong GL, Choi PC et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut 2010;59:969–74.
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3. Bravo AA, Sheth SG and Chopra S. Liver biopsy. N Engl J Med 2001; 344:495–500.

4. Bedossa P, Dargere D and Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449–57.

5. Janes CH and Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. Ann Intern Med 1993;118:96–98.

6. Piccinino F, Sagnelli E, Pasquale G et al. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. J Hepatol 1986;2:165–73.

7. McGill DB, Rakela J, Zinsmeister AR et al. A 21-year experience with major hemorrhage after percutaneous liver biopsy. Gastroenterology 1990;99:1396–400.

8. Sandrin L, Fourquet B, Hasquenoph JM et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705–13.

9. Wong VW and Chan HL. Transient elastography. J Gastroenterol Hepatol 2010;25:1726–31.

10. Fraquelli M, Rigamonti C, Casazza G et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007;56:968–73.

11. Arena U, Vizzutti F, Abraldes JG et al. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut 2008;57:1288–93.

12. Ziol M, Handra-Luca A, Kettaneh A et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. J Hepatol 2005;43:48–54.

13. Chen HL, Wong GL, Choi PC 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;16:34–46.

14. Marcellin P, Ziol M, Bedossa P et al. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int 2009;29:242–47.

15. Wong GL, Wong VW, Choi PC et al. Development of a non-invasive algorithm with transient elastography (Fibroscan) and serum test formula for advanced liver fibrosis in chronic hepatitis B. Aliment Pharmacol Ther 2010;31:1095–103.

16. de Ledinghen V, Douvin C, Kettaneh A et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-infected patients. J Acquir Immune Defic Syndr 2006;41:175–79.

17. Nobile V, Vizzutti F, Arena U et al. Accuracy and reproducibility of transient elastography for the diagnosis of fibrosis in pediatric non-alcoholic steatohepatitis. Hepatology 2008;48:442–48.

18. Wong VW, Vergniol J, Wong GL et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454–62.

19. Nahon P, Kettaneh A, Tengher-Barna I et al. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. J Hepatol 2008;49:1062–68.

20. Corpechot C, El Naggar A, Pouchol-Robert A et al. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. Hepatology 2006;43:1118–24.

21. Carrion JA, Navasa M, Bosch J et al. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Liver Transpl 2006;12:1791–98.

22. Friedrich-Rust M, Ong MF, Martens S et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960–74.

23. Talwalkar JA, Kurtz DM, Schoenleber SJ et al. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2007;5:1214–20.

24. 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.

25. Liaw YF, Kao JH, Piratvisuth T et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int 2012;6:531–61.

26. Lok AS and McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–62.

27. Carlson JJ, Knowdley KV, Sullivan SD et al. An evaluation of the potential cost-effectiveness of non-invasive testing strategies in the diagnosis of significant liver fibrosis. J Gastroenterol Hepatol 2009;24:786–91.

28. Arima Y, Kawabe N, Hashimoto S et al. Reduction of liver stiffness by interferon treatment in the patients with chronic hepatitis C. Hepatol Res 2010;40:383–92.

29. Wong GL, Wong VW, Choi PC et al. Increased liver stiffness measurement by transient elastography in severe acute exacerbation of chronic hepatitis B. J Gastroenterol Hepatol 2009;24:1002–7.

30. Wong GL, Wong VW, Choi PC et al. On-treatment monitoring of liver fibrosis with transient elastography in chronic hepatitis B patients. Antivir Ther 2011;16:165–72.

31. Bureau C, Metivier S, Peron JM et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. Aliment Pharmacol Ther 2008;27:1261–68.

32. Vizzutti F, Arena U, Romanelli RG et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;45:1290–97.

33. Castera L, Le Bail B, Roudot-Thoraval F et al. 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;50:59–68.

34. Kazemi F, Kettaneh A, N’Kontchou G et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006;45:230–35.

35. Masu数额uki T, Tateishi R, Yoshida H et al. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatol Res 2009;49:1954–61.

36. Jung KS, Kim SU, Ahn SH et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology 2011;53:885–94.

37. Vergniol J, Foucher J, Terrebonne E et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology 2011;140:1970–79.

38. Wong JS, Wong GL, Chan AW et al. Liver stiffness measurement by transient elastography as a predictor on post-hepatectomy outcomes. Ann Surg 2012, Sep 21. [Epub ahead of print].

39. Jung KS, Kim SU, Choi GH et al. Prediction of Recurrence after Curative Resection of Hepatocellular Carcinoma using Liver Stiffness Measurement (FibroScan®). Ann Surg Oncol 2012;19:4278–86.

40. Coco B, Oliveri F, Maina AM et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat 2007;14:360–69.
41. Wong GL, Wong VW, Choi PC 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.

42. Arena U, Vizzutti F, Corti G et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. Hepatology 2008;47:380–84.

43. Sagir A, Erhardt A, Schmitt M et al. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. Hepatology 2008;47:592–95.

44. Millonig G, Friedrich S et al. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. Hepatology 2008;48:1718–23.

45. Millonig G, Friedrich S, Adolf S et al. Liver stiffness is directly influenced by central venous pressure. J Hepatol 2010;52:206–10.

46. Janssens F, Sphar L, Rubbia-Brandt L et al. Hepatic amyloidosis increases liver stiffness measured by transient elastography. Acta Gastroenterol Belg 2010;73:52–54.

47. Mederacke I, Wursthorn K, Kirschner J et al. Identification of chronic hepatitis B patients without significant liver fibrosis by a simple noninvasive predictive model. Gastroenterology 2010;138:1500–6.

48. Rockey DC and Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2008;48:557–67.

49. Hui AY, Chan HL, Choi PC et al. Normal liver stiffness measure (LSM) values are higher in both lean and obese individuals: a population-based study from a developing country. Hepatology 2011;54:303–9.

50. Das K, Sarkar R, Ahmed SM et al. ‘Normal’ liver stiffness measure (LSM) values are higher in both lean and obese individuals: a population-based study from a developing country. Hepatology 2012;55:584–93.

51. Boursier J, Zaraki JP, de Ledinghen V et al. Determination of reliability criteria of liver stiffness evaluation by transient elastography. Hepatology 2012, Aug 16. [Epub ahead of print].

52. Hui AY, Chan HL, Wong VW et al. Identification of chronic hepatitis B patients without significant liver fibrosis by a simple noninvasive predictive model. Am J Gastroenterol 2005;100:616–23.

53. Rockey DC and Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2006;43:5113–20.

54. Forns X, Ampurdanes S, Llovet JM et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology 2002;36:986–92.

55. Forns X, Ampurdanes S, Llovet JM et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology 2002;36:986–92.

56. Engelmann G, Teufel U and Hoffmann GF. Feasibility study and control values of transient elastography in healthy children. Eur J Pediatr 2012;171:1417.

57. de Ledinghen V, Vergniol J, Foucher J et al. Feasibility of liver transient elastography with FibroScan using a new probe for obese patients. Liver Int 2010;30:1043–48.

58. de Ledinghen V, Wong VW, Vergniol J et al. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan®. J Hepatol 2012;56:833–39.

59. Wong VW, Vergniol J, Wong GL et al. Liver Stiffness Measurement using XL Probe in Patients with Nonalcoholic Fatty Liver Disease. Am J Gastroenterol 2012;107:1862–71.

60. Finucane MM, Stevens GA, Cowan MJ et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011;377:557–67.

61. Wang VW, Chu WC, Wong GL et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut 2012;61:409–15.

62. Sasso M, Tengher-Barna I, Ziol M et al. Novel controlled attenuation parameter for noninvasive assessment of steatosis using Fibroscan®: validation in chronic hepatitis C. J Viral Hepat 2012;19:244–53.

63. Kwon YM, Oh SW, Hwang SS et al. Association of nonalcoholic fatty liver disease with components of metabolic syndrome according to body mass index in korean adults. Am J Gastroenterol 2012;107:1852–58.

64. Pagadala MR and McCullough AJ. Editorial: non-alcoholic fatty liver disease and obesity: not all about body mass index. Am J Gastroenterol 2012;107:1859–61.

65. Ganne-Carrie N, Ziol M, de Ledinghen V et al. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. Hepatology 2006;44:1511–17.

66. Foucher J, Chanteloup E, Vergniol J et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55:403–8.

67. Gomez-Dominguez E, Mendoza J, Rubio S et al. Transient elastography: a valid alternative to biopsy in patients with chronic liver disease. Aliment Pharmacol Ther 2006;24:513–18.

68. Vergara S, Macias J, Rivero A et al. The use of transient elastometry for assessing liver fibrosis in patients with HIV and hepatitis C virus coinfection. Clin Infect Dis 2007;45:969–74.

69. Rigamonti C, Donato MF, Fraquelli M et al. Transient elastography predicts fibrosis progression in patients with recurrent hepatitis C after liver transplantation. Gut 2008;57:821–27.

70. Yoneda M, Yoneda M, Fujita K et al. Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD). Gut 2007;56:1330–31.